Plasticity of the cochleotopic (frequency) map in specialized and nonspecialized auditory cortices

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Auditory conditioning (associative learning) causes reorganization of the cochleotopic (frequency) maps of the primary auditory cortex (AI) and the inferior colliculus. Focal electric stimulation of the AI also evokes basically the same cortical and collicular reorganization as that caused by conditioning. Therefore, part of the neural mechanism for the plasticity of the central auditory system caused by conditioning can be explored by focal electric stimulation of the AI. The reorganization is due to shifts in best frequencies (BFs) together with shifts in frequency-tuning curves of single neurons. In the AI of the Mongolian gerbil (*Meriones unguiculatus*) and the posterior division of the AI of the mustached bat (*Pteronotus parnellii*), focal electric stimulation evokes BF shifts of cortical auditory neurons located within a 0.7-mm distance along the frequency axis. The amount and direction of BF shift differ depending on the relationship in BF between stimulated and recorded neurons, and between the gerbil and mustached bat. Comparison in BF shift between different mammalian species and between different cortical areas of a single species indicates that BF shift toward the BF of electrically stimulated cortical neurons (centripetal BF shift) is common in the AI, whereas BF shift away from the BF of electrically stimulated cortical neurons (centrifugal BF shift) is special. Therefore, we propose a hypothesis that reorganization, and accordingly organization, of cortical auditory areas caused by associative learning can be quite different between specialized and nonspecialized (ordinary) areas of the auditory cortex.

bat | gerbil | hearing | reorganization of cortex | tonotopic map

In the big brown bat (*Eptesicus fuscus*), auditory responses, frequency-tuning curves, best frequencies (BFs), and the frequency (cochleotopic) map in the inferior colliculus (IC) change according to acoustic signals frequently heard by the animal (1, 2) and also by auditory conditioning, i.e., associative learning (2, 3). Inactivation of the primary auditory cortex (AI) during the conditioning abolishes these collicular changes. Therefore, the corticofugal (descending) auditory system plays an essential role in the plasticity of the IC (2, 3). The conditioning evokes not only collicular changes, but also changes in the AI. Cortical changes are almost the same as collicular changes in amount but different in time course (3). Focal electric stimulation of the AI also evokes the same changes in the IC (1, 4) and AI (4, 5) as those evoked by repetitive acoustic stimuli or auditory conditioning. The cortical and collicular changes evoked by the electric stimulation are augmented by electric stimulation of the cholinergic basal forebrain (4) or by acetylcholine applied to the AI, as expected (6). These findings indicate that BF shifts evoked by focal electric stimulation are directly related to a normal function: reorganization of the central auditory system caused by associative learning. Therefore, the mechanism for plasticity of the auditory cortex caused by associative learning can be studied by focal electric stimulation of the auditory cortex.

The AI differs in shape and frequency representation among species. In the AI of the Mongolian gerbil (*Meriones unguiculatus*), iso-BF contour lines are long and 1- to 10-kHz sounds are somewhat over-represented (Fig. 1*A*; ref. 7). In the AI of the mustached bat (*Pteronotus parnellii rubiginosus*) from Panama, the Doppler-shifted constant frequency (DSCF) area shows the prominent over-representation of ≈61-kHz sounds, and the anterior and posterior divisions of the AI (AIa and AIp, respectively) show some over-representation of 92- to 95-kHz sound and 20- to 30-kHz sound (Fig. 1*B*; ref. 8). In the AI of the big brown bat, 20- to 40-kHz sounds are somewhat over-represented (Fig. 1*C*; refs. 9 and 10).

Focal electric stimulation of the AI evokes reorganization of the frequency map of the AI, which is quite different between the big brown bat and the mustached bat. In the AI and IC of the big brown bat, the BFs, together with frequency-tuning curves, shift toward the frequency of repetitively delivered tone bursts (1, 2), the frequency of a conditioned tone burst paired with electric leg-stimulation (2, 3), or the BF of electrically stimulated cortical neurons (1, 4, 5). In other words, reorganization of the frequency map is due to "centripetal" BF shift. However, in the mustached bat, DSCF neurons in the ventral nucleus of the medial geniculate body (MGB) and in the central nucleus of the IC show BF shifts away from the BF of electrically stimulated cortical DSCF neurons. In other words, reorganization of the frequency map is due to "centrifugal" BF shift (11). The FM–FM area of the auditory cortex of the mustached bat has no frequency axis but has an echo-delay axis for systematic representation of target range (12, 13). Focal electric stimulation of the cortical FM–FM area evokes centrifugal shift of best delays of subcortical FM–FM neurons (14). The DSCF and FM–FM areas both are large relative to the remaining portion of the auditory cortex and are specialized for the representation (processing) of certain types of biosonar information. Therefore, there are three alternative explanations for the difference in BF shift between the two species of bats: the difference may be due to a difference in species, the specialization of the DSCF area, or both.

The aim of the present research is to determine which of these three is the case, which type of BF shift (centripetal or centrifugal) is commonly present in different mammalian species, and whether BF shift is different between different cortical areas of a single species. Among mammalian species, the Mongolian gerbil has been well-studied in terms of the frequency map in the AI and may be considered to be a species that is not particularly specialized in acoustic communication. Therefore, we first studied whether focal cortical electric stimulation evoked centripetal or centrifugal BF shift for reorganization of the AI of the gerbil. Unlike the DSCF area, the AIp of the mustached bat is not specialized in frequency representation and appears to be comparable to the AI of other mammalian species, such as gerbils and cats. Therefore, we studied whether focal electric stimula-

Abbreviations: AC_r, recorded auditory cortical neuron; AI, primary auditory cortex; BF, best frequency; IC, inferior colliculus; PST, peri-stimulus-time; AC_s, stimulated auditory cortical neuron; AIp, posterior division of AI; DSCF, Doppler-shifted constant frequency; MGB, medial geniculate body; PSTC, PST-cumulative; b.w., body weight.

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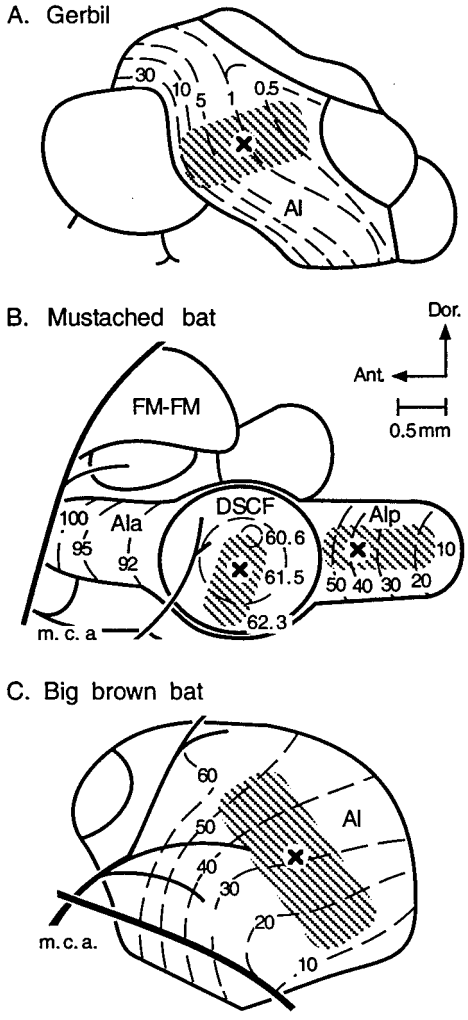

Fig. 1. Cochleotopic (frequency) maps in the AIs of the Mongolian gerbil (*A*), mustached bat (*B*), and big brown bat (*C*). Iso-BF contour lines in the AI are shown by dashed lines. There are non-AI areas around the AI. The mean BFs of electrically stimulated cortical neurons are indicated by Xs. Almost all neurons studied in the gerbil and big brown bat were recorded from the shaded areas. In *B*, the DSCF area is a part of the AI. The areas anterior and posterior to the DSCF area are, respectively, called the AIa and AIp. The ''FM–FM'' area has an echo delay axis instead of a frequency axis. The frequency maps in *A*, *B*, and *C* are, respectively, based on Thomas *et al.* (7), Suga (24), and both Dear *et al.* (9) and Shen *et al.* (10). m.c.a., medial cerebral artery. The 0.5-mm scale applies for all three auditory cortices.

tion of the AIp evoked centripetal or centrifugal BF shift for reorganization of the AIp. We found that centripetal BF shift underlies reorganization of the nonspecialized AI and that centrifugal BF shift underlies reorganization of a specialized AI.

Materials and Methods

Sixteen adult Mongolian gerbils (*Meriones unguiculatus*; 69.1 ± 2.0 g b.w.), and eight adult mustached bats (*Pteronotus parnellii rubiginosus*; 18.4 ± 1.2 g b.w.) from Trinidad were used for the present experiments. Under anesthesia (ketamine 40 mg/kg b.w. plus Meditomidine 0.26 mg/kg b.w. for gerbils) or neuroleptanalgesia (Innovar 4.08 mg/kg b.w. for bats), the dorsal surface of the animal's skull was exposed and a 1.8-cm long metal post was glued onto the skull. Four days after the surgery, a gerbil lightly anesthetized with ketamine plus Meditomidine or an awake bat was placed in a polyethylene-foam body-mold suspended by an elastic band at the center of a soundproof, echo-attenuated room maintained at 30–32°C. The head was immobilized by fixing the post on the skull to a metal rod with set-screws and was adjusted to face directly at a tweeter (for gerbils) or a condenser loudspeaker (for bats) located 74-cm away. (The protocol of our research was approved by the animal studies committee of Washington University, St. Louis).

Electric stimuli were delivered to the AI through a pair of tungsten-wire microelectrodes, the tips of which were 6–8 μm in diameter and were separated by 150 μm, one proximal to the other. Before the electric stimulation, the responses of cortical neurons to tone burst stimuli were first recorded with these tungsten-wire microelectrodes at five loci in the AI, and their BFs and minimum thresholds were audiovisually measured. Then one of these cortical loci was selected for electric stimulation. The tungsten-wire microelectrodes were inserted to a depth of 1,300–1,500 μm (i.e., cortical layer V) in the gerbil and 600–700 μm (i.e., cortical layer V) in the mustached bat. The electric stimulation was a 6-ms long train of four monophasic electric pulses (100 nA, 0.2-ms duration, 2.0-ms interval). The train was delivered at a rate of 10/s for 30 min (hereafter, ES_{ar}). The train of the electric pulses was estimated to stimulate neurons within a 60-μm radius around the electrode tip (14). Therefore, electric stimulation of the AI was quite focal. The bat showed no behavioral response at all to such a weak electric stimulation delivered to the AI.

BF shifts evoked by focal electric stimulation at the peripheral region of the AI may be different from those at the central region of the AI. For the comparison in BF shift between the auditory cortices of different species of mammals, therefore, electric stimulation and recording of neural responses were mostly performed in the central region of the AI (Fig. 1, shaded areas).

To study the effects of focal electric stimulation of the AI on the auditory responses of single cortical neurons of the homolateral AI, the responses of a single cortical neuron to tone bursts were recorded with a tungsten-wire microelectrode (6- to 8-μm tip diameter). To avoid contamination of action potentials discharged by more than one neuron, a time-amplitude window discriminator (BAK Electronic, Rockville, MD; model DLS-1) was used. The BF and minimum threshold of the single neuron were first measured audiovisually. Then, a computer-controlled frequency scan was delivered, which consisted of 22 time blocks, each 200-ms long. The frequency of the tone burst was shifted from block to block in steps of a given frequency (0.04–0.5 kHz) across the BF of the neuron. The step size was determined according to the sharpness of the frequency-tuning curve of the neuron: the narrower the curve, the smaller the step size. The amplitude of tone bursts in the scan was set at 10 dB above the minimum threshold of the neuron. An identical frequency scan was repeated 50 times, and the responses of the neuron were displayed as an array of peri-stimulus-time (PST) histograms or PST cumulative (PSTC) histograms as a function of frequency (see Figs. 2 and 4).

The acquisition of PST or PSTC histograms was continued as long as action potentials visually matched the template of an action potential of the neuron stored on the screen of a digital storage oscilloscope at the beginning of the data acquisition. Data were stored on a computer hard drive and were analyzed off-line. Data analysis included plotting and comparing PST or PSTC histograms displaying responses to 50 identical acoustic stimuli and frequency-response curves based on the arrays of PSTC histograms for frequency scans obtained before and after the electric stimulation. The magnitude of auditory response at each frequency was expressed by the number of impulses per 50 identical stimuli after subtracting background discharges counted in the last block of the frequency scan.

The following criteria were applied to detect a shift in the BF of a neuron caused by electric stimulation: If a shifted BF and frequency-response curve did not shift back by more than 50%

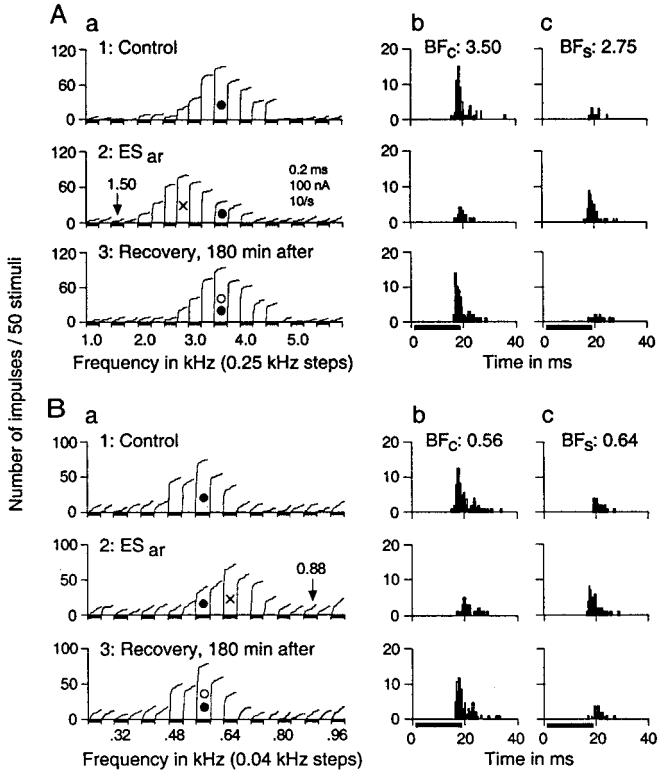

Fig. 2. Changes in the frequency-response curves (*a*) and responses (*b* and *c*) of two cortical neurons (*A* and *B*) evoked by focal electric stimulation (ES_{ar}) of the AI of the gerbil. (*a* in *A* and *B*) Arrays of PSTC histograms displaying the responses to tone bursts at different frequencies. (*b* and *c* in *A* and B) PST histograms displaying the responses to the tone bursts at the BFs, in the control (BF_c, 3.50 kHz in *A* and 0.56 kHz in *B*) or shifted condition (BF_s, 2.75 kHz in *A* and 0.64 kHz in *B*. The 1, 2, and 3 show the responses in the control, shifted, and recovery conditions, respectively. The BF of the stimulated cortical neuron is indicated by the arrow in *a*2. The filled circles, X's, and open circles in *a* indicate the BFs in the control, shifted, and recovery conditions, respectively. The horizontal bars at the bottom of *b* and *c* represent 20-ms long tone bursts. The amplitude of tone bursts was fixed at 10 dB above minimum threshold of a given neuron.

of the change, the data were excluded from the analysis. In stable recordings, all BFs and curves shifted by the electric stimulation recovered by more than 50%. This recovery itself helped to prove that the shift was significant and that the shift was not due to recording action potentials from different neurons, which might be caused by animal's movements. BF shifts highly specific to the BF of stimulated cortical neurons (see *Results*) also indicate that these were not due to recording action potentials from different neurons. When a BF shift was small and its significance was not obvious, a weighted average frequency (i.e., BF) was calculated for the summed response to five consecutive frequency scans. Then the mean and SD of the mean of these weighted averages were computed, and a two-tailed paired *t* test was used to determine whether or not the weighted-average frequencies (BFs) obtained before and after the electric stimulation were significantly different for $P < 0.01$.

Results

The effect of focal electric stimulation of the AI was studied on the auditory responses, frequency-response curves, and BFs of 94 homolateral cortical neurons in gerbils and 76 homolateral cortical neurons in mustached bats. As found in the AI of the big brown bat (1, 5) and in the DSCF area of the mustached bat (11), electric stimulation augmented the responses of "matched" cortical neurons tuned to a frequency within ± 0.2 kHz of the BF of electrically stimulated cortical neurons (hereafter "stimulated cortical BF"). Their BFs were not shifted by the stimulation regardless of species of animals and area of the AI. However, the electric stimulation evoked augmentation or suppression of the responses of "unmatched" cortical neurons tuned to a frequency different by more than 0.2 kHz from the stimulated cortical BF. Augmentation and suppression depended on the frequency of an acoustic stimulus, so that their frequency-tuning curves and BFs shifted together in a particular way. The direction and amount of BF shift were different depending on species of animals and areas of the AI, as explained below.

In the AI of the gerbil, frequencies between 0.1 and 43 kHz are systematically mapped, and frequencies from 0.1 to 10 kHz are somewhat over-represented compared to other frequencies (7). Most of our data were obtained by stimulating the neurons located at the approximate center of the AI (Fig. 1*A*, shaded area). The cortical neuron of a gerbil in Fig. 2*A* was tuned to 3.50 kHz (a1). When cortical neurons tuned to 1.50 kHz were electrically stimulated, its response decreased at 3.50 kHz (compare b2 with b1) and increased at 2.75 kHz (compare c2 with c1). Because of such frequency-dependent changes, its frequency-response curve and BF shifted from 3.50 to 2.75 kHz, i.e., toward the stimulated cortical BF (a2). The auditory responses, frequency-response curve and BF affected by the electric stimulation returned to those in the control condition 180 min after the stimulation (a3, b3, and c3). The cortical neuron of a gerbil in Fig. 2*B* was tuned to 0.56 kHz (a1). When cortical neurons tuned to 0.88 kHz were electrically stimulated, its response decreased at 0.56 kHz (compare b2 with b1) and increased at 0.64 kHz (compare c2 with c1). Accordingly, its frequency-response curve and BF shifted from 0.56 to 0.64 kHz, i.e., toward the stimulated cortical BF (a2). The auditory responses, frequency-response curve and BF affected by the electric stimulation returned to those in the control condition 180 min after the electric stimulation (a3, b3, and c3). The BF shifts evoked by the electric stimulation were centripetal in the gerbil AI.

Fig. 3 shows the amount and direction of BF shifts of the 94 cortical neurons studied in the gerbil as a function of the difference in BF between paired stimulated and recorded cortical neurons. The BFs of stimulated and recorded cortical neurons respectively ranged between 0.8 and 2.0 kHz (mean ± SD: 1.25 ± 0.30 kHz, $n = 94$) and between 0.20 and 41.0 kHz (5.02 ± 1.38 kHz, $n = 94$). As shown in Fig. 3*A*, BF shift evoked by the electric stimulation occurred for neurons whose BFs were between 0.8 kHz lower and 20.5 kHz higher than the stimulated cortical BF. Almost all BF shifts occurred on the high-frequency side of the stimulated cortical BF and were downward, i.e., toward the stimulated cortical BF. The most noticeable downward BF shifts observed were 2.3 and 2.4 kHz, which, respectively, occurred at approximately 3 and 6 kHz above the stimulated cortical BF. The regression line for the BF shifts for 4.0–28.0 kHz BF differences has a slope of 0.07 and intersects the abscissa at 28.2 kHz (Fig. 3*A*), which corresponds to a ≈0.55-mm distance rostral to the stimulated cortical neurons along the cortical frequency axis. The regression line for BF shifts for −0.4 to +4.0 kHz BF differences has a slope of −0.56 and intersects the abscissa at 0.0 kHz (Fig. 3 *A* and *B*). For BF differences between −1.0 and 0.0 kHz, eight neurons showed small, but significant BF shift: upward shift (centripetal shift) in six neurons and downward shift (centrifugal shift) in two neurons. The upward BF shifts occurred at approximately −0.4 kHz BF difference. The downward BF shifts occurred at a −0.9 kHz BF difference. For BF differences between −0.8 and −0.4 kHz, the regression line has a slope of 0.59 and intersects the abscissa at −0.69 kHz, which corresponds to a 0.53-mm distance caudal to the stimulated cortical neurons along the cortical frequency axis (Fig. 3*B*). Therefore, in the gerbil BF shifts evoked by electric

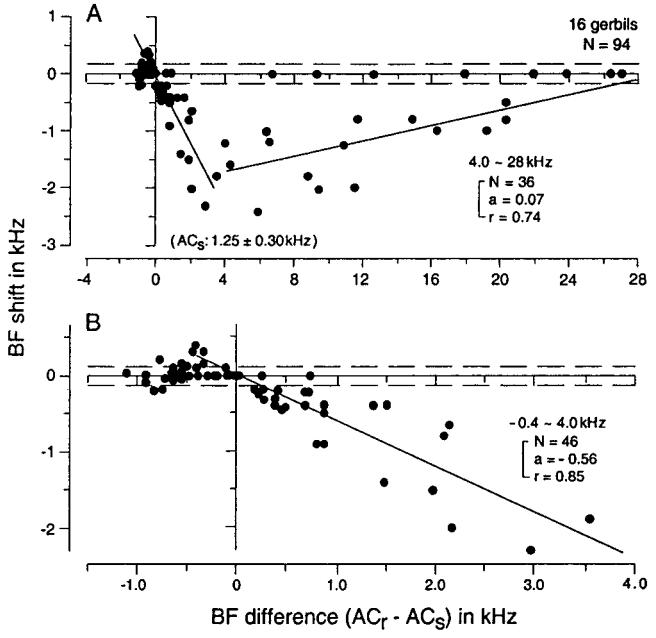

Fig. 3. Shifts in the BFs of 94 cortical neurons in the gerbil evoked by ES_{ar} as a function of difference in BF between recorded (AC_r) and stimulated cortical auditory neurons (AC_s). The BFs of AC_s ranged between 0.8 and 2.0 (1.25 ± 0.30) kHz. The data between −1.0 and +4.0 kHz BF differences in *A* are replotted on the expanded abscissa in *B*. The solid oblique lines are regression lines for data points (N) in given ranges of BF differences. a, slope; *r*, correlation coefficient. The horizontal dashed lines indicate one SD. The major BF shifts were centripetal, i.e., toward the BF of AC_s.

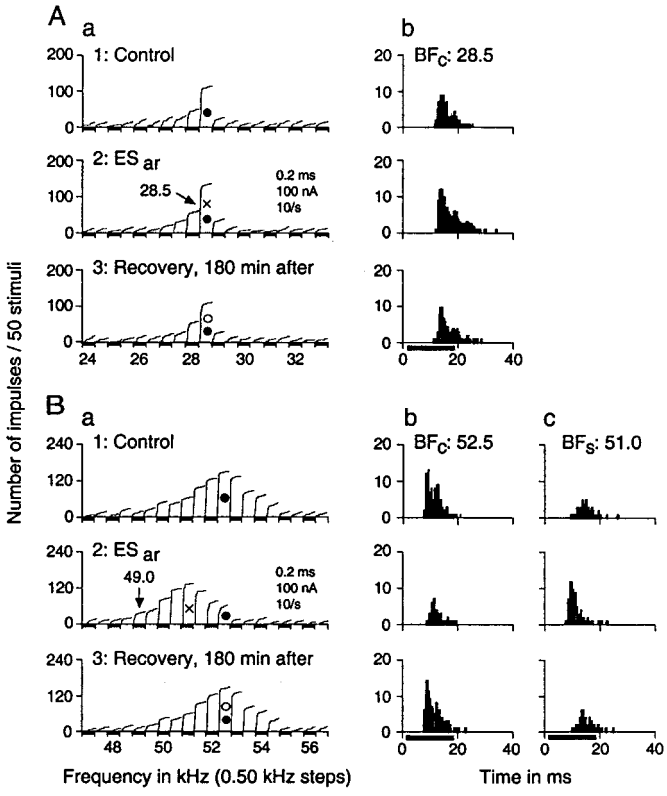

Fig. 4. Changes in the frequency-response curves (*a*) and responses (*b* and *c*) of two cortical neurons (*A* and *B*) evoked by ES_{ar} of the posterior division of the primary auditory cortex (AIp) of the mustached bat. (*a*) Arrays of PSTC histograms displaying the responses to tone bursts at different frequencies. (*b* and *c*) PST histograms displaying the responses to the tone bursts at the BFs in the control (BF_c: 28.5 kHz in *A* and 52.5 kHz in *B*) or shifted condition (BF_s: 51.0 kHz in *B*), respectively. See Fig. 2 for symbols and other explanations.

stimulation are predominantly centripetal and asymmetrical, occurring over 1.08 mm along the cortical frequency axis.

In the AIp of the mustached bat, frequencies between 6.2 and 57.0 kHz are systematically mapped (8). Almost all of the data were obtained by stimulating and recording neurons located at the central region of the AIp of the mustached bat (Fig. 1*B*, shaded area). The data obtained from the AIp are shown in Figs. 4 and 5. The cortical neuron in Fig. 4*A* was tuned to 28.5 kHz (a1). Electric stimulation of cortical neurons, also tuned to 28.5 kHz, increased the response of the recorded neuron (compare b2 with b1) but did not change its BF (a2). The augmented response returned to that in the control condition 180 min after the electric stimulation (a3 and b3). The cortical neuron in Fig. 4*B* was tuned to 52.5 kHz (a1). Electric stimulation of cortical neurons tuned to 49.0 kHz reduced the response of the neuron at 52.5 kHz (compare b2 with b1) and increased the response at 51.0 kHz (compare c2 with c1), shifting its BF down to 51.0 kHz, i.e., toward the stimulated cortical BF (a2). These changes evoked by the electric stimulation returned to the control condition 180 min after the stimulation (a3, b3, and c3).

In Fig. 5*A*, the amount and direction of BF shifts of the 76 cortical neurons studied in the mustached bat are plotted as a function of the difference in BF between paired stimulated and recorded neurons. The BFs of stimulated and recorded cortical neurons, respectively, ranged between 6.8 and 54.0 kHz (39.4 ± 4.3 kHz, $n = 76$) and between 6.2 and 57.0 kHz (37.2 ± 2.8 kHz, $n = 76$). BF shifts evoked by the electric stimulation were centripetal for BF differences between −31.5 and 10.7 kHz. The most noticeable upward BF shifts were 7.0–7.5 kHz, which occurred at ≈10 kHz below the stimulated cortical BF. The most prominent downward BF shifts were 3.0–3.8 kHz, which occurred at ≈7 kHz above the stimulated cortical BF (Fig. 5*A*). Fig. 5*B* represents the BF shifts for ± 4.0 kHz BF differences. The centripetal BF shifts were somewhat symmetrical, different from those found in the gerbil. The regression line for the BF shifts for 6.5–15.0 kHz BF differences has a slope of 0.40 and intersects the abscissa at 10.7 kHz, which corresponds to a ≈0.34-mm

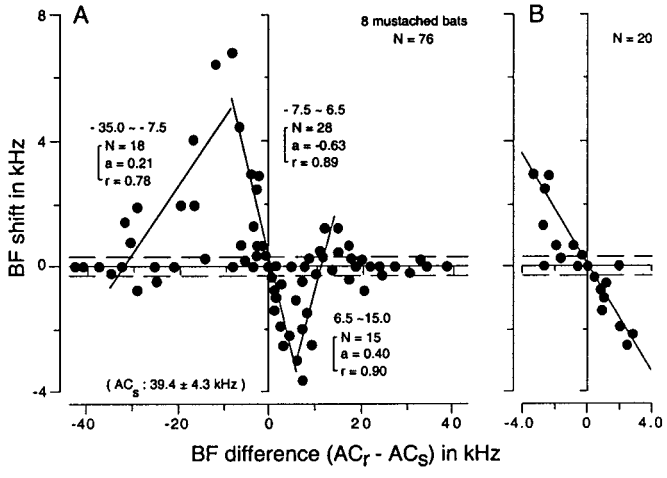

Fig. 5. Shifts in the BFs of 76 cortical neurons in the AIp of the mustached bat evoked by ES_{ar} as a function of difference in BF between AC_r and AC_s. The BFs of AC_s ranged between 6.8 and 54.0 (39.4 ± 4.3) kHz. The data between −4.0 and +4.0 kHz differences are replotted on the expanded abscissa in *B*. The major BF shifts were centripetal, i.e., toward the BF of AC_s. See Fig. 3 for abbreviations and other explanations.

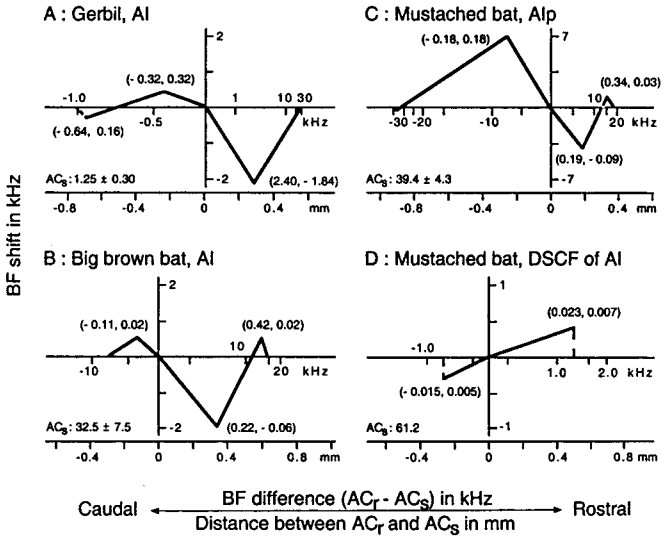

Fig. 6. Difference in BF shift among different mammalian species and between different cortical areas of a single species. BF shifts of cortical neurons along the frequency axis (ordinates) are plotted as a function of difference in BF (kHz) or distance (mm) between AC_r and AC_s. (*A*) AI of the Mongolian gerbil. (*B*) AI of the big brown bat (based on ref. 5). (*C*) AIp of the mustached bat. (*D*) DSCF area of the mustached bat (based on ref. 11). A pair of numbers in parentheses indicates a BF difference and BF shift in octave referring to the mean BF of AC_s. Focal electric stimulation of cortical auditory neurons evokes BF shifts of adjacent cortical neurons toward (centripetal shift; *A*, *B*, and *C*) or away from (centrifugal shift; *D*) the BF of AC_s. See the text.

distance rostral to the stimulated cortical neurons along the cortical frequency axis. The slope of the regression line for BF shifts is −0.63 for BF differences between −7.5 and + 6.5 kHz. The regression line for BF differences between −35.0 and −7.5 kHz has a slope of 0.21 and intersects the abscissa at −31.4 kHz, which corresponds to 0.89-mm caudal to the stimulated cortical neurons along the cortical frequency axis (Fig. 5*A*). It was noticed that small centrifugal BF shifts were evoked for BF differences between 10.7 and 19.2 kHz (Fig. 5*A*). In summary, BF shifts in the mustached bat evoked by focal electric stimulation are predominantly centripetal and nearly symmetrical, occurring over a 1.23-mm distance along the frequency axis of the AIp.

Discussion

BF shifts observed in the AI of the Mongolian gerbil and the AIp of the mustached bat are both centripetal. However, there are a number of differences between them (Fig. 6 *A* and *C*). (*i*) In the gerbil, BF shift is five times larger on the high frequency side of the stimulated cortical BF than on the low frequency side. Therefore, the BF-shift function is centripetal and "high-large-asymmetrical." In the AIp of the mustached bat, however, BF shift is approximately two times larger on the low frequency side of the stimulated cortical BF than on the high frequency side. Therefore, the BF-shift function is also centripetal but "low-large-asymmetrical." (*ii*) The largest BF shift observed is −2.3 kHz (−1.84 octave; 184%) in the gerbil, which occurred at 3.0 kHz (2.40 octave) higher than the stimulated cortical BF (1.25 ± 0.30 kHz), and 7.5 kHz (0.18 octave; 18%) in the mustached bat, which occurred at 7.5 kHz (0.18 octave) lower than the stimulated cortical BF (39.4 ± 4.3 kHz). The absolute amount of BF shift in kilohertz is smaller for the gerbil than for the mustached bat. However, the BF shift in octave or percentage are much larger for the gerbil than for the mustached bat. This is somewhat related to the difference in audible frequency range between these two species of animals: from 0.1 to ≈60 kHz in the gerbil (15) and from ≈6 to 120 kHz in the mustached bat (8). (*iii*) The range of BFs shifted by focal electric stimulation is ≈30 kHz in the AI of the gerbil and ≈40 kHz in the AIp of the mustached bat. This range corresponds to an 1.08-mm distance along the frequency axis of the AI of the gerbil and an 1.23-mm distance in the AIp of the mustached bat.

Fig. 6 shows the BF-shift functions obtained from neurons in the AI of the big brown bat (Fig. 6*B*; ref. 5) and DSCF neurons in the ventral nucleus of the medial geniculate body of the mustached bat (Fig. 6*D*; ref. 11), in addition to those obtained from neurons in the AI of the gerbil (Fig. 6*A*) and the AIp of the mustached bat (Fig. 6*C*). In the big brown bat, BF shifts evoked by focal electric stimulation of the AI are basically the same for the IC (1) and AI (5). In the mustached bat, BF shifts evoked by focal electric stimulation of the DSCF area of the AI are basically the same for DSCF neurons in the IC and MGB (11). Because the corticofugal system forms feedback loops through the MGB and IC (16), it is quite reasonable that the AI, MGB, and IC show basically the same BF shifts for focal cortical electric stimulation. We confirmed this by studying the BF shifts of six DSCF neurons in the AI. Therefore, the BF-shift function for DSCF neurons in the MGB was used for cortical DSCF neurons (Fig. 6*D*). Ketamine blocks *N*-methyl-D-aspartate receptors (17). In our gerbil experiments, the data were obtained from gerbils that were recovering from ketamine anesthesia and were nearly awake. Therefore, the BF shifts observed in the gerbils might be affected only a little by ketamine anesthesia. However, it is extremely unlikely that ketamine either caused frequency-dependent BF shifts or changed their direction. Therefore, the BF-shift function obtained from the ketamine-anesthetized gerbils may be used for a comparison to that obtained from the awake bats.

The four BF-shift functions in Fig. 6 show interesting similarities and differences between species and between cortical areas of a single species. (*i*) The BF-shift function and the maximal BF shift in the AI of the big brown bat are very similar to those in the gerbil, although the audible frequency range and the mean BF of electrically stimulated cortical neurons are quite different between these two species: The mean stimulated cortical BF is 1.25 ± 0.30 kHz in the gerbil and 32.5 ± 7.5 kHz in the big brown bat. (*ii*) BF shift is centripetal in both the AI of the big brown bat and the AIp of the mustached bat. The mean BF of electrically stimulated cortical neurons is similar, 32.5 ± 7.5 kHz in the big brown bat and 39.4 ± 4.3 kHz in the mustached bat. However, the BF-shift function is clearly different between these two species of bats. The mean maximal BF shift is −2.0 kHz in the big brown bat, which occurred at 7.25 kHz above the stimulated cortical BF, whereas it is 7.0 kHz in the mustached bat, which occurred at 7.5 kHz below the simulated cortical BF. (*iii*) By contrast, the BF-shift function is quite different between the AIp and DSCF areas of the same species of bat, the mustached bat. It is centripetal in the AIp, but centrifugal in the DSCF area. The mean maximal BF shift is 7.0 kHz (0.18 octave) in the AIp, which occurred at 7.5 kHz below the stimulated cortical BF (39.4 ± 4.3 kHz), whereas it is 0.4 kHz (0.007 octave) in the DSCF area, which occurred around at 1.2 kHz above the stimulated cortical BF (≈61.2 kHz). (*iv*) Although the range and amount of BF shift in kHz is quite different between species and between the cortical areas of a single species, a distance along the cortical frequency axis for centripetal or centrifugal BF shift is similar for the different species and the different areas: 1.08 mm in the AI of the gerbil, 0.90 mm in the AI of the big brown bat, 1.23 mm in the AIp of the mustached bat, and 1.20 mm in the DSCF area of the mustached bat. The train of 0.2-ms long 100 nA electric pulses was estimated to stimulate neurons within a 60-μm radius around the electrode tips (14). Therefore, a 0.9- to 1.2-mm distance along the frequency axis is much longer than the

diameter of 0.12 mm directly affected by the electric current and must be mediated by lateral connections within the AI.

Small centrifugal BF shifts were found at one end of the BF shift function of the AI of the gerbil (Figs. 3 and 6*A*), the AI of the big brown bat (Fig. 6*B*), and the AIp of the mustached bat (Figs. 5*A* and 6*C*). Suga *et al.* (18) hypothesized that centripetal and centrifugal BF shifts, respectively, depend on facilitation and lateral inhibition evoked by focal cortical electric stimulation. According to their interpretation, neural representation of an auditory signal in a nonspecialized auditory cortex is improved mainly by centripetal BF shifts which result in over-representation of a particular value of a parameter characterizing a given acoustic signal. The area for over-representation is bordered with the areas for under-representation of values that are far different from the value characterizing that acoustic signal. On the other hand, a specialized auditory cortex such as the DSCF area over-represents particular values of a parameter in a narrow range in the natural condition. Therefore, improvement of signal processing is performed by mainly increasing the contrast in neural representation, without enhancing over-representation.

As a sensory stimulus is repetitively delivered to an animal or becomes behaviorally important, it evokes reorganization of the sensory cortex, which processes the stimulus. The reorganization thus far found in cats (19–21) and monkeys (22, 23) produces over-representation of the stimulus. Therefore, cortical reorganization by centripetal BF shift must be common, which was found in the AI of the gerbil, the AI of the big brown bat, and the AIp of the mustached bat. On the other hand, cortical reorganization by centrifugal BF shift must be special, which was found in the DSCF and FM–FM areas of the mustached bat. Therefore, we may hypothesize that cortical reorganization according to auditory experience can be quite different between specialized and nonspecialized (i.e., ordinary) cortical auditory areas. This working hypothesis remains to be tested in the auditory cortex of animals other than the mustached bat and also in the somatosensory and visual cortices.

Human infants acquire language through an enormous amount of associative learning by hearing words (nonsense syllables for the infants without associative learning) while seeing, touching, tasting, and/or smelling objects. In mammals, reorganization of the auditory cortex evoked by conditioning (associative learning) greatly depends on both the corticofugal auditory system excited by a conditioned tone and other systems such as the somatosensory cortex excited by an unconditioned electric leg-shock (2, 3) and the cholinergic system (19–21). Our present data suggests that organization and reorganization of the cortical areas specialized for human speech processing may be quite different from those of the AI.

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