Modulation of thalamic auditory neurons by the primary auditory cortex

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Tang J, Yang W, Suga N. Modulation of thalamic auditory neurons by the primary auditory cortex. J Neurophysiol 108: 935–942, 2012. First published May 2, 2012; doi:10.1152/jn.00251.2012.—The central auditory system consists of the lemniscal and nonlemniscal pathways or systems, which are anatomically and physiologically different from each other. In the thalamus, the ventral division of the medial geniculate body (MGBv) belongs to the lemniscal system, whereas its medial (MGBm) and dorsal (MGBd) divisions belong to the nonlemniscal system. Leminiscal neurons are sharply frequency-tuned and provide highly frequency-specific information to the primary auditory cortex (AI), whereas nonlemniscal neurons are generally broadly frequency-tuned and project widely to cortical auditory areas including AI. These two systems are presumably different not only in auditory signal processing, but also in eliciting cortical plastic changes. Electric stimulation of narrowly frequency-tuned MGBv neurons evokes the shift of the frequency-tuning curves of AI neurons toward the tuning curves of the stimulated MGBv neurons (tonic-specific plasticity). In contrast, electric stimulation of broadly frequency-tuned MGBm neurons augments the auditory responses of AI neurons and broadens their frequency-tuning curves (non-specific plasticity). In our current studies, we found that electric stimulation of AI evoked tone-specific plastic changes of the MGBv neurons, whereas it degraded the frequency tuning of MGBm neurons by inhibiting their auditory responses. AI apparently modulates the lemniscal and nonlemniscal thalamic neurons in quite different ways. High MGBm activity presumably makes AI neurons less favorable for fine auditory signal processing, whereas high MGBv activity makes AI neurons more suitable for fine processing of specific auditory signals and reduces MGBm activity.

corticofugal modulation; frequency tuning; medial geniculate body; non-specific plasticity; tone-specific plasticity


MATERIALS AND METHODS

Materials, surgery, acoustic stimulation, electric stimulation, recording of action potentials, and data acquisition and processing were the same as described in Ma and Suga (2001, 2009), although the sites of electric stimulation and recording auditory responses (action potential) were respectively AI and the MGB instead of the MGB and AI. Therefore, only the essential portions of the methods are described below. The Animal Studies Committee of Washington University in St. Louis approved all experimental procedures.

Sixteen adult big brown bats (Eptesicus fuscus) were used for the current experiments. Under neuroleptanalgesia (4.08 mg/kg body wt; Innovar), a 1.5-cm-long metal post was glued on the dorsal surface of the bat’s skull. Physiological experiments were started 3–4 days after the surgery. The awake 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 toward a loudspeaker located 74 cm away. Several holes (~100 μm in diameter) were made in the skull covering AI. A reference tungsten-wire electrode with a ~15-μm tip diameter was placed on the cortical surface at one of these holes. A recording tungsten-wire electrode with...
a ~7-μm tip diameter was inserted into AI through the other holes for recording neural responses to tone bursts at 300- to 700-μm depths, and the approximate center of AI (tuned to 25–30 kHz) and the posterior edge of AI were located. Then, a pair of tungsten-wire electrodes that were separated by ~110 μm horizontally and 50–150 μm vertically at their tips was inserted at the center for electric stimulation. After recording the auditory responses and measuring the BF and frequency-tuning curves of AI neurons, this pair of electrodes was connected to the constant current stimulus isolator for electric stimulation. A four-electrode assembly (Ma and Suga 2009; NeuroNexus Technologies, Ann Arbor, MI) was inserted at the posterior edge of AI into the MGBm (1.3–1.5 mm lateral to the midline) or MGBv (1.8–2.1 mm lateral to the midline) through the hippocampus for recording the auditory responses of MGB neurons so that we first observed the responses of cortical auditory neurons, regular spontaneous discharges of hippocampus neurons, and then the auditory responses of MGBm neurons (1.1–1.3 mm below the hippocampus) or MGBv neurons (0.8–1.0 mm below it). An electrode of the four-electrode assembly that did not record auditory responses was used as a reference electrode. The effects of the cortical electric stimulation on the auditory response and frequency tuning of broadly tuned MGBm or sharply tuned MGBv neuron were then studied.

**Acoustic stimulation.** For the measurement of the frequency-threshold or -response curve and the BF of a MGBm, MGBv, or AI neuron, a 4.0-ms tone burst, including a 0.5-ms rise-decay time, was delivered to the animal from a leaf tweeter (Model EAS-10 TH-800; Panasonic) at a rate of 4/s. Its frequency and amplitude were varied manually or computer-controlled (TDT System 3; Tucker-Davis Technologies). Before the experiments, the sound amplitude was calibrated with a Bruel & Kjæl 1/4-in. calibrated microphone (Model #4135; Copenhagen, Denmark) placed at the location of the bat’s ears and was expressed in decibels in sound-pressure level (dB SPL) referencing to 20-Pa root-mean-square.

The frequency-threshold (tuning) curve of a MGB or an AI neuron was first audiovisually measured. Then, the tone burst was randomly changed in amplitude in 5-dB steps from 0 to 100 dB SPL and in frequency in 0.5-kHz steps between ±5.0 kHz of the BF if the tuning curve was narrow but between ±10 kHz of the BF if it was broad by TDT System 3. The frequency-amplitude scan was repeated 10 times to obtain 10 responses at each frequency-amplitude combination. It took 7 or 14 min to complete the 10 scans. A frequency-threshold curve of a neuron was obtained from its responses to the frequency-amplitude scans. The frequency-response curve of the neuron could be obtained by counting the number of action potentials at 30 dB above the minimum threshold (MT) of the neuron as a function of frequency. However, the frequency-response curves based on 50 responses at a given frequency were obtained with the frequency scan at 30 dB above the MT delivered 50 times.

**Action potentials of AI and MGB neurons.** Action potentials recorded usually originated from a few neurons. Therefore, we used an amplitude-window-discriminator software (Tucker-Davis Technologies) to select action potentials of a single neuron. At the beginning of data acquisition, the waveform of an action potential was stored and displayed on the monitor screen. The data acquisition was continued as long as other action potentials obtained during data acquisition matched with this action potential (i.e., template). Since the electrode placements and recording action potentials were exactly the same as those in Ma and Suga’s experiments (2009), the recording sites in the MGB were not anatomically studied in our current experiments.

**Electric stimulation.** An electric stimulator (S88; Grass Technologies) and a constant current isolator (A360; WPI) were used for focal electric stimulation of AI. A 1.5×2-mm train of four monophasic electric pulses (100-nA constant current, 0.2-ms duration, 2.0-ms interval) was delivered to AI neurons at a rate of 10/s for 30 min through the paired tungsten-wire electrodes as described above. The bat showed no behavioral response at all to such weak electric stimulation.

**Data acquisition and processing.** Data obtained from the MGB before and after the focal electric stimulation of AI were stored on a computer hard drive and were used for offline data processing that included plotting frequency-threshold and -response curves and measuring the BF, MT, and quality factor, Q-30 dB, which was the BF divided by the tuning width at 30 dB above the MT of a given neuron. The frequency-threshold curves of the thalamic neurons could be classified into either sharply tuned or multipeaked broadly tuned according to both their shapes and Q-30 dB. We calculated a Q-30 dB instead of a Q-10 dB because the Q-10 dB was related to the tuning width only at the tip portion of a tuning curve and did not appropriately represent the difference in sharpness between broadly tuned and sharply tuned frequency-tuning curves. The broadly tuned neuron had a Q-30 dB <6.5, and the sharply tuned neuron had a Q-30 dB >6.5, as described in RESULTS. The paired t-test was used to test the difference between the responses obtained before and after the electric stimulation and also between the broadly tuned and sharply tuned thalamic neurons.

**RESULTS**

The BFs of cortical (AI) neurons recorded ranged from 24.0 to 54.0 kHz (mean ± SD: 36.0 ± 9.3 kHz, n = 51). On the other hand, those of MGB neurons recorded ranged from 20.0 to 55.0 kHz (38.0 ± 9.5 kHz, n = 51). Corticofugal modulation was different depending on the sharpness of the frequency-threshold curves of thalamic auditory neurons. Figure 1 displays the frequency-threshold curves of two cortical neurons (AI and B1) and the response areas (receptive fields) of a MGBm (A2–4) and a MGBv (B2–4) neuron. The cortical neurons were tuned to either 26.0 or 27.0 kHz. Their Q-30 dB were either 7.4 or 9.0. The MGBm neuron in Fig. 1A2 was broadly tuned and multipeaked. Its BF and Q-30 dB were respectively 23.0 kHz and 1.3. On the other hand, the MGBv neuron in Fig. 1B2 was sharply tuned to 29.0 kHz, and its Q-30 dB was 11.6. The broadly tuned MGBm neuron was medially located, whereas the sharply tuned MGBv neuron was located laterally.

When the cortical neuron (Fig. 1A1) was electrically stimulated, the responses of the broadly tuned MGBm neuron (Fig. 1A2) to tone bursts were suppressed, its response area was reduced, its threshold became higher, and its Q-30 dB reduced from 1.3 to 1.1 (Fig. 1A7). That is, the response properties of the neuron were “degraded.” The effects of the cortical stimulation disappeared ~60 min after the onset of the electric stimulation (A4). Such suppression of the responses of a thalamic neuron occurred over many frequencies even if the BF of the electrically stimulated cortical neurons was different as much as 24 kHz from that of the thalamic neuron. Therefore, the suppression was not specific to the BF of the stimulated cortical neurons. Such nonspecific suppression or inhibition was observed in all 34 broadly tuned MGBm neurons studied.

When the cortical neuron (Fig. 1B1) was electrically stimulated, the response area of the MGBv neuron sharply tuned to 29.0 kHz (Fig. 1B2) shifted its response area toward the BF of the stimulated neuron so that the BF of the neuron changed from 29.0 to 28.0 kHz. The width of the response area (tuning curve) of this thalamic neuron slightly widened (Fig. 1B3) so its Q-30 dB changed from 11.6 to 9.3. The shifted BF returned to the control BF ~60 min after the onset of the electric stimulation (Fig. 1B4). The BF shift, i.e., tuning shift was generally based on a decrease in response by inhibition at the BF of the recorded neuron in the control condition and an
increase in response (facilitation) at the frequencies at or near the BF of the stimulated cortical neuron (Ma and Suga 2004; Xiao and Suga 2002, 2004, 2005). Such a BF shift evoked by AI stimulation was observed in 15 sharply tuned neurons out of the 17 studied. The BF shift is also elicited by auditory fear conditioning and has been known as a tone-specific plastic change (Suga and Ma 2003 for review). In the following, the nonspecific suppression and BF shift evoked by the cortical stimulation are further documented with the frequency-threshold and -response curves obtained from thalamic neurons.

In Fig. 2, A1 and B1 show the frequency-threshold and -response curves of a cortical neuron, respectively. Its BF was 42.0 kHz. Electric stimulation of this neuron evoked nonspecific suppression of a MGBm neuron broadly tuned to 36.0 kHz with a Q-30 dB of 2.9 (Fig. 2, A2 and B2, open circles). That is, the frequency-threshold curve of the thalamic neuron became 30 dB higher (Fig. 2A2, closed circles), and the responses to tone bursts became 57% less at the BF (Fig. 2B2, closed circles). The suppression of the response occurred at many different frequencies so that it was nonspecific to frequencies. The amount of the decrease in the response over the 10-kHz band with the BF at its center was 51%. The BF did not shift. These changes in the curves and responses reverted to the control condition 60 min after the onset of the cortical electric stimulation (Fig. 2, A2 and B2, dashed lines).

The corticofugal effect on the sharply tuned thalamic neurons was quite different from the above. Figure 3 shows the frequency-threshold (AI) and -response (B1) curves of a cortical neuron tuned to 30.0 kHz. When this neuron was electrically stimulated, the BF of the sharply tuned MGBv neuron (Fig. 3, A2 and B2, open circles) shifted from 34.0 to 32.0 kHz (Fig. 3, A2 and B2, closed circles). That is, the BF shifted toward the BF of the stimulated cortical neuron. The shifted BF reverted to the control BF 60 min after the onset of the electric stimulation (A2 and B2, dashed lines).

The thalamic neurons were classified as either broadly or sharply tuned according to the shapes of their tuning curves and their Q-30 dB. The distributions of the Q-30 dB of the 51 stimulated cortical and 51 recorded thalamic neurons are shown in Fig. 4, A and B, respectively. The Q-30 dB of the 51 cortical neurons, except 4, were unimodally distributed from 5.8 to 14.5 (8.3 ± 2.0). On the other hand, those of the 51 thalamic neurons were bimodally distributed from 1.3 to 12.0. The 1st and 2nd groups, respectively, corresponded to the MGBm and MGBv neurons. Since the distributions crossed over at the Q-30 dB of 6.5, the tuning curves with the Q-30 dB < 6.5 were defined as broadly tuned, and those with the Q-30 dB larger than that were defined as sharply tuned. There were 3 neurons with Q-30 dB between 6.5 and 7.9. One of them was the MGBm neuron, and the remaining two were the MGBv neurons. As described later, this MGBm neuron reduced its response by 27%, increased its MT by 20 dB, and decreased its Q-30 dB by 8% after the cortical electric stimulation, as the typical broadly tuned MGBm neurons. On the other hand, the two MGBv neurons showed a response change < 8%, a MT change < 5 dB, and a Q-30 dB change < 4% after the cortical electric stimulation, as the typical sharply tuned neurons.

The Q-30 dB of the 34 MGBm neurons ranged between 1.3 and 6.5 (3.3 ± 1.4) with a mode at 2.0–2.5, and their BFs ranged from 20.0 to 54.0 kHz (37.0 ± 9.5 kHz). The Q-30 dB of the MGBv neurons ranged from 6.5 to 12.0 (8.7 ± 1.7) with a mode at 7.5–8.0 (Fig. 4B), and their BFs ranged from 26.0 to 55.0 kHz (38.0 ± 9.8 kHz). The BFs were not different between these 34 MGBm and 17 MGBv neurons (P > 0.5). Therefore, the difference in Q-30 dB between these two groups was not due to any difference in BF.

Recording MGBv neurons was much easier than that of MGBm neurons. However, we studied them every three to four neurons because the corticofugal modulation of the sharply tuned MGBv neurons had already been studied in the mus-tached bat (Zhang and Suga 2000) and the house mouse (Zhang and Yan 2008) and because the corticofugal modulation of sharply tuned collicular neurons of the big brown bat had already been known to be BF shifts as in the above two species of animals (Ma and Suga 2001). When broadly tuned and sharply tuned neurons were simultaneously recorded with an
electrode assembly, they were always at the electrodes located medially and laterally, respectively.

After cortical stimulation, the Q-30 dB of the 34 broadly tuned neurons ranged between 1.1 and 5.8 (2.6 ± 1.2). They were significantly smaller than those in the control condition (P < 0.001; Fig. 4C, gray bars). Their BFs ranged between 20.0 and 54.0 kHz (38 ± 9.6 kHz) and were not different from those in the control condition (P > 0.5). After the cortical stimulation, however, the Q-30 dB of the 17 sharply tuned neurons ranged between 6.6 and 13.0 (9.0 ± 1.9). They were not different from those in the control condition (Fig. 4C, white bars). The BFs of 15 neurons out of the 17 shifted after the cortical stimulation. The remaining 2 did not show a BF shift: 1 was BF-matched with the stimulated cortical neurons, and the other had a BF that was 10 kHz higher than that of the stimulated neurons.

Changes in the Q-30 dB of the individual thalamic neurons elicited by cortical electric stimulation are plotted in Fig. 5A as a function of the Q-30 dB of the stimulated cortical neurons. The cortical stimulation broadened the frequency-threshold
The most prominent and easily detectable change evoked by the cortical stimulation was that in the magnitude of a response (number of spikes) to a tone-burst stimulation. The percent change in the responses in a 10-kHz band with the BF of a given neuron at its center was counted before and after the cortical stimulation, and the percent change in response was calculated. The changes ranged between −8 and −76% (−34 ± 16%, n = 34) for the broadly tuned MGBm neurons and between −15 and +27% (+2.1 ± 14%, n = 17) for the sharply tuned MGBv neurons (Fig. 5B). The difference in the response change between the two groups of thalamic neurons was not related to the BFs (P > 0.5) but to the sharpness of the tuning curves. It was clear that the broadly tuned MGBm neurons were corticofugally inhibited, whereas the sharply tuned MGBv neurons were not. This was the second difference in corticofugal modulation between the MGBm and MGBv neurons. The third difference was the change in MT. That is, the change in a MT was between 0 and 30 dB (18.5 ± 6.9 dB, n = 34) for the broadly tuned MGBm neurons and between −15 and +5 dB (−2.3 ± 5.8 dB, n = 17) for the sharply tuned MGBv ones (Fig. 5C). This difference was statistically significant (P < 0.01). The cortical stimulation increased the thresholds of the MGBm neurons but tended to decrease the thresholds of the MGBv neurons.

The fourth difference in corticofugal modulation between the MGBm and MGBv neurons was a tuning shift, i.e., a BF shift. In Fig. 5D, the BF shifts of thalamic neurons are plotted as a function of the BF differences between the recorded thalamic and stimulated cortical neurons. It has been known that BF shifts depend on the difference in BF between the recorded and stimulated auditory neurons (Suga and Ma 2003 for review). In the big brown bat, they were rarely observed when the difference is >10 kHz and when the electric stimulation pulse is weak, 0.2 ms, 100 nA (Ma and Suga 2001). Therefore, the BF shift that might be elicited by cortical stimulation was particularly examined for the thalamic neurons with a BF within a range of ±10 kHz of the BFs of the stimulated cortical neurons. In the MGBm, the BF increased 1.0 kHz in 5 neurons and decreased 1.0 kHz in 3 neurons. The BF did not change in the remaining 26 neurons (Fig. 5D, closed circles). We could not find any systematic BF shift of the MGBm neurons as the function of the BF difference between the stimulated and recorded neurons. On the contrary, the BFs of the MGBv neurons systematically shifted as a function of the difference in BF between the stimulated and recorded neurons. The correlation coefficient (r) was 0.9 for ±6.0 kHz BF differences. The amount of the BF shift became smaller at BF differences >6.0, as reported by Ma and Suga (2001) and Yan and Suga (1998).

**DISCUSSION**

*Sharpness of the frequency-tuning curves of MGBm neurons.* In general, MGBm neurons are broadly frequency-tuned, whereas MGBv neurons are sharply frequency-tuned in cats (Aitkin 1973; Calford 1983), guinea pigs (Zhang et al. 2008), and big brown bats (Ma and Suga 2009). In the rat thalamic auditory neurons, Bordi and LeDoux (1994) found that the distribution of Q-10 dB overlapped between the MGBm and MGBv neurons and wrote that “Overall, frequency tuning functions were narrower in MGBv than in the other [thalamic auditory] areas, but many cells in MGBm were as narrowly tuned as cells in MGBv”. One might say that some MGBv cells were as broadly tuned as some MGBm cells. A Q-10 dB is inappropriate to express the overall sharpness of the tuning curves of central auditory neurons because their tuning curves are commonly not simple triangular shape and because Q-10 dB is based on the bandwidth of a tuning curve only at its tip portion. Calford (1983) used a scale based on the bandwidth of the tuning curve at 20 dB above the MT. Since auditory neurons commonly respond to tone bursts over 60–80 dB, we calculated a Q-30 dB measuring the bandwidth at 30 dB above the MT. Terms...
In the MGBm and MGBv neurons, respectively. Closed and open circles: the data obtained from total numbers of spikes discharged in a 10-kHz band with the BF of a given neuron at its center. Closed and open circles: the data obtained from the MGBm and MGBv neurons, respectively. In D, the regression line is for the open circles within ±6.0-kHz BF differences ($r^2=0.89$).

such as sharp, narrow, wide, and broad are arbitrary, so someone’s narrow can be another’s broad.

In our current data, the Q-30 dB of the MGBm neurons ranged between 1.3 and 6.5, and those of the MGBv neurons ranged between 6.5 and 12.0. We called the tuning curves with a Q-30 dB < 6.5 broadly tuned and those with a Q-30 dB larger than that sharply tuned. The neurons with a Q-30 dB at or near the boundary can be called either broadly or narrowly tuned by changing the definition.

Corticofugal modulation of MGBm and MGBv neurons. In the guinea pig, most on-responding MGBv neurons are excited by AI stimulation, whereas the great majority of on-responding MGBm neurons are inhibited by it (He 2003; Yu et al. 2004). The corticofugal inhibition of MGBm neurons is evoked through the TRN (Zhang et al. 2008). Unlike the above excitatory or inhibitory corticofugal effect evoked by intense electric stimulation of AI, focal weak electric stimulation of AI evokes both frequency-dependent facilitation and inhibition and BF shifts of neurons in AI (Chowdhury and Suga 2000; Ma and Suga 2001), the MGBv (Zhang et al. 1997; Zhang and Suga 2000; current study), the inferior colliculus central nucleus (ICc; Jen and Zhou 2003; Ma and Suga 2001; Yan and Ehret 2002; Yan and Suga 1998; Zhang et al. 1997; Zhang and Suga 2000), and cochlear nucleus (Luo et al. 2008). When a recorded subcortical or cortical neuron is matched in BF to stimulated cortical neurons, the response of the matched neuron is augmented at its BF and is inhibited at frequencies lower and/or higher than the BF. As a result, its frequency tuning is sharpened. When BF-unmatched, the unmatched neuron is inhibited at its BF and is facilitated at the frequencies at and near the BF of the stimulated neurons. As a result, its frequency tuning shifts, i.e., its BF shifts. All these corticofugal modulations have been studied only in the lemniscal system (Suga and Ma 2003 and Suga 2012 for review). Our current data obtained from the big brown bat indicate that AI stimulation degrades the response properties of broadly tuned MGBm neurons by suppressing their responses to tone bursts, increasing their thresholds and broadening their frequency-tuning curves and that it evokes the BF shift of sharply tuned MGBv neurons. Cortical electric stimulation would activate multiple neural pathways that might evoke the thalamic changes. The most likely pathway for these changes is, however, AI to the MGBv for excitation and AI to the MGBm through the TRN for inhibition, as reported by He et al. (2002) and Zhang et al. (2008). Since AI stimulation evokes the BF shifts of subthalamic auditory neurons (Suga 2012 for review), the BF shifts of MGBv neurons must be partly due to those subthalamic BF shifts.

Corticofugal modulation of auditory thalamus and plasticity elicited by conditioning or pseudoconditioning. Our current findings are presumably related to the plasticity elicited by auditory fear conditioning and the differential gating mechanism, as discussed below. Auditory fear conditioning with paired conditioning tone (CS) and unconditioned leg (US) stimuli elicits the large long-lasting AI and large short-lasting ICc, MGBv, and MGBm BF shifts (Suga and Ma 2003 and Weinberger 2004 for review). Tone-burst stimulation associated with electric stimulation of the basal nucleus evokes the BF shifts of MGBv neurons through AI (Zhang and Yan 2008). Focal electric stimulation of AI evokes BF shifts in not only AI and MGBv, but also subthalamic auditory nuclei (Suga 2012 for review). These BF shifts occur in a specific relation to the BF of the stimulated neurons or the frequency of the conditioning tone. Therefore, they are a tone-specific plastic change. When the CS and US are unpaired for pseudoconditioning, however, AI, MGBv, and ICc neurons show nonspecific augmentation (sensitization), which is quite different from BF shifts (Bakin et al. 1992; Ji and Suga 2008, 2009).

Focal electric stimulation of the MGBv evokes the BF shifts of AI neurons similar to those elicited by conditioning, whereas that of the MGBm evokes the nonspecific augmentation of auditory responses and broadening of the frequency-tuning curves of AI neurons similar to those elicited by pseudoconditioning (Ma and Suga 2009). Our current data indicate that focal electric stimulation of AI degrades MGBm neurons, whereas it evokes the BF shifts of MGBv neurons.

Fig. 5. Changes in the sharpness (Q-30 dB) of the frequency-threshold curves (A), the response magnitudes (B), and the minimum thresholds (C) of thalamic neurons as a function of the sharpness of stimulated cortical (AI) or recorded thalamic (MGB) neurons and the BF shifts of the thalamic neurons as a function of the BF differences (diff.) between the recorded thalamic and stimulated cortical neurons (D). Changes in the response magnitude of the thalamic neurons were calculated with the total numbers of spikes discharged in a 10-kHz band with the BF of a given neuron at its center.
These findings indicate that AI neurons are improved for fine auditory signal processing by the thalamocortical and corticothalamic feedback loop through the lemniscal MGBv neurons and that, at the same time, they suppress the activity of nonlemniscal MGBm neurons and make them inappropriate for fine auditory signal processing. Electric stimulation of AI excites most MGBv neurons and inhibits the great majority of MGBm neurons (Yu et al. 2004) through the TRN (Zhang et al. 2008). ACh depolarizes MGBv neurons but hyperpolarizes MGBm neurons (Mooney et al. 2004). It is possible that a high level of MGBm activity makes AI neurons somewhat similar to nonlemniscal neurons and unfavorable for fine auditory signal processing. Considering all these neural events, Suga (2008) suggested the presence of a differential gating mechanism and also the implication of the corticofugal system, TRN, and neuromodulators to this mechanism.

The US activates the somatosensory system, the ascending reticular activating system (ARAS), and the brain aversion system (BAS). The BAS and ARAS both activate the histaminergic system that broadly releases histamine (HA) in the brain and play an important role in eliciting defensive behaviors and arousal, respectively (Siegel 2002 for review). HA may play an important role in eliciting the nonspecific augmentation and in suppressing the BF shifts (W. Ji and N. Suga, unpublished observations). It has been known that ACh play an essential role in eliciting BF shifts due to cortical electric stimulation (Ma and Suga 2005) and auditory fear conditioning (Weinberger 1998 for review; Ji et al. 2001; Ji and Suga 2003). Thus ACh and HA both are presumably involved in the differential gating mechanism, if it exists.

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS
J.T. and W.Y. performed experiments; J.T., W.Y., and N.S. analyzed data; J.T., W.Y., and N.S. interpreted results of experiments; J.T., W.Y., and N.S. prepared figures; J.T., W.Y., and N.S. drafted manuscript; J.T., W.Y., and N.S. approved final version of manuscript; N.S. conception and design of research; N.S. edited and revised manuscript.

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