

# Modulatory Effect of Cortical Activation on the Lemniscal Auditory Thalamus of the Guinea Pig

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In the present study, we investigated the point-to-point modulatory effects from the auditory cortex to the thalamus in the guinea pig. Corticofugal modulation on thalamic neurons was studied by electrical activation of the auditory cortex. The modulation effect was sampled along the frontal or sagittal planes of the auditory thalamus, focusing on the ventral division (MGv) of the medial geniculate body (MGB). Electrical activation was targeted at the anterior and dorsocaudal auditory fields, to which the MGv projects and from which it assumptively receives reciprocal projections. Of the 101 MGv neurons examined by activation of the auditory cortex through passing pulse trains of 100–200  $\mu$ A current into one after another of the three implanted electrodes (101 neurons  $\times$  3 stimulation sites = 303 cases), 208 cases showed a facilitatory effect, 85 showed no effect, and only 10 cases (7 neurons) showed an inhibitory effect. Among the cases of facilitation, 63 cases showed a facilitatory effect >100%, and 145 cases showed a facilitatory effect from 20–100%. The corticofugal modulatory effect on the MGv of the guinea pig showed a widespread, strong facilitatory effect and very little inhibitory effect. The MGv neurons showed the greatest facilitations to stimulation by the cortical sites, with the closest correspondence in BF. Six of seven neurons showed an elevation of the rate-frequency functions when the auditory cortex was activated. The comparative results of the corticofugal modulatory effects on the MGv of the guinea pig and the cat, together with anatomical findings, hint that the strong facilitatory effect is generated through the strong corticothalamic direct connection and that the weak inhibitory effect might be mainly generated via the interneurons of the MGv. The temporal firing pattern of neuronal response to auditory stimulus was also modulated by cortical stimulation. The mean first-spike latency increased significantly from  $15.7 \pm 5.3$  ms with only noise-burst stimulus to  $18.3 \pm 4.9$  ms ( $n = 5$ ,  $P < 0.01$ , paired *t*-test), while the auditory cortex was activated with a train of 10 pulses. Taking these results together with those of previous experiments conducted on the cat, we speculate that the relatively weaker inhibitory effect compared with that in the cat could be due to the smaller number of interneurons in the guinea pig MGB. The corticofugal modulation of the firing pattern of the thalamic neurons might enable single neurons to encode more auditory information using not only the firing rate but also the firing pattern.

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## INTRODUCTION

The auditory cortex receives projections from the thalamus, and in turn, projects to the thalamus and also to the inferior colliculus (Andersen et al. 1980; Herbert et al. 1991; Liu et al. 1995a; Montero 1991; Ojima 1994; Winer et al. 1998). Corticofugal projection to the thalamus and the inferior colliculus has been suggested as performing the following: 1) a gating or gain control function in the transmission of information from the periphery to the cortex (Crick 1984; Harth et al. 1987; He 1997; Murphy and Sillito 1987; Villa et al. 1991); and 2) a sharpening of the tuning curves of the frequency and temporal features of the auditory information in the auditory system (Gao and Suga 1998, 2000; Jen et al. 1998, 2001; Suga et al. 1997, 2000; Sun et al. 1989, 1996; Yan and Suga 1996, 1998, 1999; Zhang et al. 1997; Zhang and Suga 1997, 2000; Zhou and Jen 2000).

Earlier investigators adopted a cooling technique to inactivate the cortex and compare the neuronal responses to auditory stimuli (Orman and Humphrey 1981; Ryogo and Weinberger 1976; Villa et al. 1991). However, this methodology has the following two weak points: 1) it is difficult to selectively inactivate a small region of the cortex by cooling; and 2) the effects of cortical cooling on thalamic activity may be difficult to observe in an anesthetized animal, which may already have depressed cortical activity to some degree. Most of the recent studies adopt electrical stimulation to selectively activate the defined auditory cortex (Chowdhury and Suga 2000; He 1997; Jen et al. 2001; Ma and Suga 2001a; Sakai and Suga 2001; Yan and Suga 1996, 1998; Zhang and Suga 2000; Zhou and Jen 2000). Investigators have used a very wide range of electrical stimulation current, from 100 nA to 1 mA, to activate the cortex (Chowdhury and Suga 2000; Edeline et al. 1994b; He 1997; Jen et al. 2001; Ma and Suga 2001a,b; Sakai and Suga 2001; Suga et al. 2000; Weinberger et al. 1995; Xiao and Suga 2002; Yan and Suga 1996, 1998; Zhang and Suga 2000; Zhou and Jen 2000). This fundamental parameter, which will largely affect data interpretation, urgently needs to be standardized. The present study examined the parameter for cortical activation in the guinea pig.

A mainly corticofugal facilitatory effect has been observed in the ventral nucleus (MGv) of the medial geniculate body

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(MGB) (He 1997), which has been recognized as the recipient of the most direct ascending auditory pathway, as the nucleus with the most clear-cut cochleotopic representation, as the nucleus that projects to the primary auditory cortex (AI), and as the major recipient of the direct corticothalamic projection (Andersen et al. 1980; Burton and Jones 1976; Imig and Morel 1983; Jones 1985; Merzenich et al. 1982; Sousa-Pinto 1973; Winer and Larue 1987). Previous study has suggested that the observed corticofugal inhibitory effect on the cat MGv was caused by the interneurons in the cat thalamus, which count for 24–27% of the total neuron population. A comparative study on the guinea pig, in which the interneurons count only for <1% of the total, would provide information about the source of the inhibitory effect. The comparative results would also offer hints as to its functional significance. The suggested study may also provide a reference to a recent study which investigated the strong inhibitory corticofugal effect on the nonlemniscal MGB of the guinea pig (He and Fukunishi 1998).

In the present study, we investigated the point-to-point influence from the auditory cortex to the thalamus in the guinea pig. Corticofugal modulation on the thalamic neurons was studied by electrical activation of auditory cortex. Stimulation electrodes were implanted in a defined area of the auditory cortex. The modulation effect was sampled along the frontal or sagittal planes of the auditory thalamus. This report examines the modulatory effect of the thalamic neurons on not only their onset responses to sound stimuli, but also their firing pattern.

## METHODS

### *Animal preparation*

Fifteen guinea pigs of both sexes, weighing 450–546 g, with clean external ears, served as subjects, with normal auditory thresholds estimated from the cortical unit responses. Anesthesia was induced and maintained with ketamine/xylazine (40 and 10 mg/kg initially, 10 and 2.5 mg/kg/h, im) during the surgical preparation and recording. Atropine sulfate (0.05 mg/kg, sc) was given 15 min before anesthesia and at regular intervals (0.01 mg/kg/h, sc) during the recording, to inhibit tracheal secretion. The preparation of the guinea pig is similar to that of the cat and another recent study in the guinea pig, as has been described before (He 1997, 2001). Briefly, the subject was mounted in a stereotaxic device following the induction of anesthesia. A midline incision was made in the scalp, and craniotomies were performed to enable us to map the auditory cortex and implant stimulation electrodes into it, and to vertically access the MGB in the left hemisphere. The dura mater was removed at a position vertically above the auditory thalamus. Before the right ear was freed from the ear bar, the head was fixed with two stainless steel bolts to an extended arm of the stereotaxic frame using acrylic resin so that the subject's head remained fixed to the stereotaxic device without displacement. These procedures were approved by the Animal Subjects Ethics Sub-Committee of The Hong Kong Polytechnic University.

### *Acoustic stimulus*

Acoustic stimuli were generated digitally by a MALab system (Kaiser Instruments, Irvine, CA), which was controlled by a Macintosh computer (He 1997; Semple and Kitzes 1993). Acoustic stimuli were delivered to the subject via a dynamic earphone (Bayer DT-48) mounted in a pyramid-shaped container. The sound pressure level (SPL) of the earphone was calibrated over a frequency range of 100 Hz to 35 kHz under computer control by using a condenser microphone (Brüel and Kjær ¼ in.). The subject was placed in a double-

walled soundproof room (NAP, Clayton, Australia). Repeated noise bursts and pure tones with 1-s or longer intervals and 5-ms rise/fall time were used to examine the neuronal responses.

### *Recording*

Platinum or tungsten microelectrodes with impedances of 9–12 M $\Omega$  (Frederick Haer, Brunswick) were advanced by a stepping-motor microdrive, which was controlled outside the soundproof room. The time of spike occurrence relative to stimulus delivery was stored in the same computer used as the stimulus controller by the MALab software. The computer automatically created raster displays and peristimulus time histograms (PSTHs) of the responses, together with frequency response functions (responses to pure tones plotted as a function of frequency).

For each subject, the frequency tonotopicity of the auditory cortex was mapped to identify the electrical stimulation sites for the later experimental sessions. To characterize the auditory cortex, we used 50-ms tone pips (5-ms rise/fall time, >400-ms interval) and most often recorded spikes from cell clusters rather than single cells.

The MGB was accessed vertically from the top of the brain in the stereotaxically positioned subject. The penetrations were made according to a guinea pig brain atlas (Rapisarda and Bacchelli 1977). The vertical coordinate of the electrode was determined at a point slightly above the cortical surface at the first penetration. A single electrode was used for each experiment, so that the depth coordinates could be kept consistent for different penetrations during the experiment. This technique enabled us to reconstruct the physiological map of the whole sagittal or frontal auditory thalamic plane containing many penetrations and to superimpose it with the Nissl-stained histological sections.

The best frequency (BF) of the MGB neuron was defined as the frequency which produced a measurable neural response at the lowest possible sound intensity. Pure tones with frequencies near the BF of the MGB neuron, noise bursts, and clicks were used as testing acoustic stimuli.

We isolated single units in the thalamus during our recording by an amplitude and time window discriminator. Multi-unit recordings of three or fewer units were used in some cases and were not distinguished from single-unit ones.

### *Electrical stimulation*

After a rough mapping of the auditory cortex, three electrodes were implanted into the auditory cortex targeting at the anterior (A, 38 stimulation electrodes over 14 roughly mapped cortex) and the dorso-caudal (DC, 4 stimulation electrodes) fields. The stimulation electrodes were in a row and each was separated by about 0.5–1.0 mm from its neighbors.

To activate the auditory cortex, we used bi-phasic current pulse trains of 200-Hz frequency and 30 pulses (each composed of a 0.1-ms negative pulse followed by a positive pulse of the same duration). Pulse trains of electrical current of 50–1000  $\mu$ A, delivered via an isolator, were applied to the auditory cortex ipsilateral to the recording thalamus through the bi-polar electrodes with a low impedance of 35–40 k $\Omega$ . A sound stimulus was delivered to the contralateral ear of the recording hemisphere after the end of the cortical stimulation and following a delay interval. The interval between the electrical stimulation and acoustic stimulus was examined as a parameter on a few neurons and was set to 100 ms as a standard for most neurons. The responses of the thalamic neurons to pure tones and noise bursts were compared with and without cortical activation. Since it has been suggested that the excitation of the corticothalamic fibers results in responses that have long time constants of seconds in some conditions (McCormick and von Krosigk 1992), we set the interval between different experimental/control conditions to 10 s to allow the neuron to recover from its modulated state.

### Data collection and analysis

Before and after the experimental conditions which included a sequential activation of the three stimulation electrodes in the cortex with a pseudo-random order, the responses of the thalamic neurons to a certain acoustic stimulus were examined. The neuronal responses in the experimental conditions were compared with those in the control condition, i.e., without electrical activation of the cortex. We used a control protocol which included either E−/E− (repeating the same test in the condition without cortical activation) or E+/E+ (with cortical activation) to test the stability of the neuron. The neuron was terminated or paused from recording when its response showed over a 15% change during the control protocol. To exclude artifacts as a result of fluctuations in neuronal responsiveness over time due to uncontrolled variables, we tested replicability for many neurons when the order of the E+ (with cortical activation) and E− (without cortical activation) conditions were reversed. When we tested the cortical modulatory effect on the frequency response function of the MGB neuron, the presentation orders of both stimulus frequencies and conditions (E− or E+) were pseudo-randomly chosen.

### Anatomical confirmation

A small lesion was made by passing a current (1.0  $\mu\text{A}$ , 15 s) through the high-impedance recording electrode at the last recording site in the MGB. Nine animals were used for the purpose of anatomical confirmation.

After the last recording session of one subject, 2% biocytin in 0.5 M KCl and 0.05 M Tris-HCl buffer (pH 7.6) was injected into a stimulation site of facilitatory effect in cortex to confirm the direct connection between the stimulation and recording sites. The subject was allowed to recover from anesthesia after sealing the craniotomy openings and suturing the incision for 24 h after the injection of biocytin.

All subjects were deeply anesthetized with pentobarbital sodium and perfused transcardially with 0.9% saline followed by a mixture of 0.4% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M phosphate buffer (pH 7.3). The brains were dissected free and stored overnight in 0.1 M phosphate buffer containing 30% sucrose. The thalami were cut transversally using a freezing microtome. For the subject with biocytin injection, anterogradely labeled terminal fields in every fourth section (50  $\mu\text{m}$  thick) of the MGB were visualized after the reactions of the ABC reagent (vector; 4 h) and the standard diaminobenzidine (DAB; Sigma) at room temperature.

All sections of the eight subjects were stained using the Nissl method. For the subject into which biocytin was injected, half of the sections were stained using the Nissl method and the remaining ones were processed to visualize the labeled terminal fields. The Nissl sections were superimposed on the physiology map, using the electrode penetration tracks and the lesion for guidance. There was some shrinkage of the sections after the Nissl procedure. Enlargements of 10–13% of the Nissl images were made to match them to the physiology maps.

## RESULTS

The present report focuses on the lemniscal MGB, i.e., the MGv. Electrical activation was targeted at auditory fields A (38/42 electrodes) and DC (4/42 electrodes), to which the MGv projects and from which it assumptively receives reciprocal projections (Redies et al. 1989). As a general exploration of either the facilitatory or the inhibitory modulatory effects, we used the following standard electrical stimulation parameters: a 30-pulse train in 200 Hz of 100–200  $\mu\text{A}$  and a 100-ms interval between electrical stimulation and the acoustic stimulus of a

60-dB noise-burst. Of the 101 MGv neurons examined by activation of the auditory cortex through passing current pulse trains into one after another of the three implanted electrodes (101 neurons  $\times$  3 stimulation sites = 303 cases), 208 cases showed a facilitatory effect, 85 showed no effect, and only 10 cases (7 neurons) showed an inhibitory effect. Among the cases of facilitation, 63 cases showed a facilitatory effect  $>100\%$ , and 145 cases showed a facilitatory effect from 20–100%. The neuron in Fig. 1 increased its spike number by 94, 105, and 58% with the activation of sites X, Y, and Z in the auditory cortex, respectively.

### Current intensity of electrical stimulation

Twelve MGv neurons were tested at various levels of electrical stimulation. The effect of cortical stimulation on thalamic neurons depends on the stimulation current. Electrical stimulation of the cortex started to show a modulatory effect on thalamic neurons with a current intensity of 50–150  $\mu\text{A}$ , depending on the site of stimulation and the recorded neuron. The effect was augmented when we increased the current intensity of the stimulation to 200–500  $\mu\text{A}$  and was reversed in many cases as the current was further increased.

The neuron in Fig. 2A showed no corticofugal effect when the stimulation current was 75  $\mu\text{A}$  and a facilitatory effect when the stimulation current was increased to 100  $\mu\text{A}$  as shown in Fig. 1. This facilitatory effect was magnified when the current was

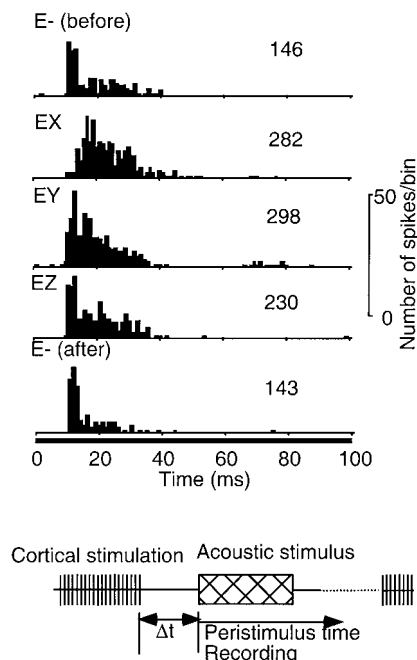


FIG. 1. Modulatory effect of cortical stimulation on an ventral division of the medial geniculate (MGv) neuron. Peri-stimulus time histograms (PSTHs) shows neuronal responses to a noise burst without cortical stimulation (E−), or with cortical stimulation on site X (EX), on site Y (EY), and on site Z (EZ). Controls were made before (E−before) and after (E−after) the conditions. Only onsets of 100 ms of the responses were shown in the PSTHs in 1-ms bins. The stimulus was repeated over 20 times at 1.0-s intervals. The inter-condition interval was set at 10 s. The time interval between the electrical stimulation and the acoustic stimulus was 100 ms. The total number of spikes of the onset responses was shown above each PSTH. The experimental paradigm is shown in the inset below the PSTHs. The conventions apply to Figs. 2, 3, 4, 5, and 6.

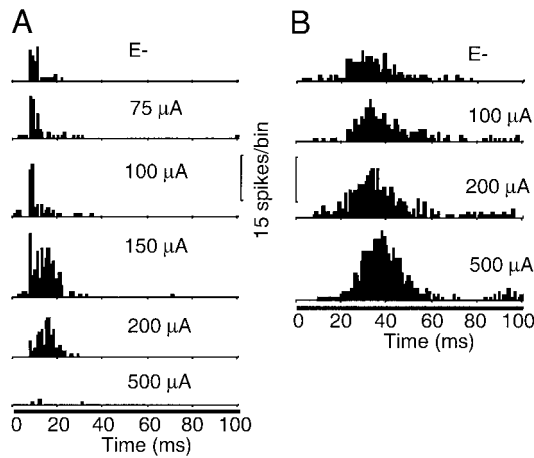


FIG. 2. PSTHs of onset responses to noise bursts of 2 medial geniculate body (MGB) neurons with the auditory cortex activated at varied current intensity. Both neurons were located in the MGv. The current of the electrical stimulation is shown from low to high. The order of the current was randomly selected during the experiment.

increased to 150  $\mu\text{A}$ , but weakened when the current was further increased to 200  $\mu\text{A}$ . Furthermore, this modulatory effect became inhibitory when the current was increased to 500  $\mu\text{A}$  (Fig. 3A). The neuron in Fig. 2B showed a magnified facilitatory effect as the stimulation current increased.

#### Number of stimulation pulses

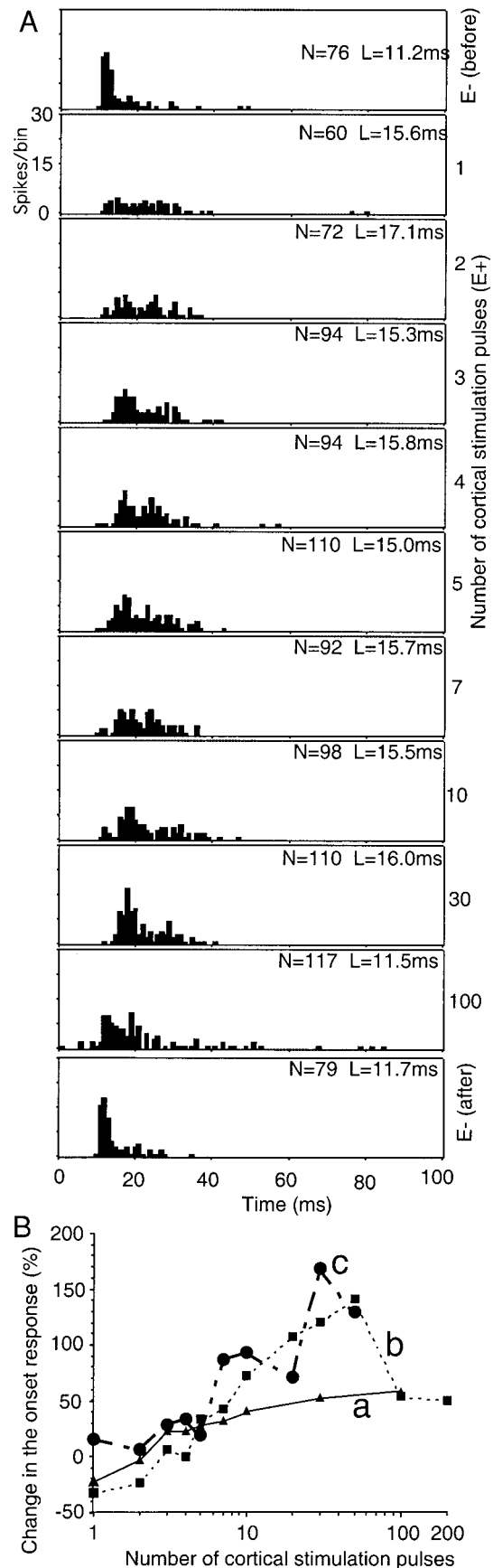
In the present study, we used a pulse train rather than a single pulse as the electrical stimulus. Figure 3A shows an example in which the neuron showed a stronger facilitatory effect for the larger number of stimulation pulses. A phenomenon whereby the general facilitatory effect becomes inhibitory for a single pulse, which was reported on the thalamic slice by McCormick and von Krosigk (1992), was observed in two of three neurons examined (neurons a and b in Fig. 3B).

Of five neurons tested with this parameter, four showed a facilitatory effect in the standard parameter condition, and one showed an inhibitory effect. All five neurons showed a stronger modulatory effect for a larger number of stimulation pulses, while the number of pulses was  $<50$ . As a result, 30 pulses were used as the standard parameter in the examination of the majority of neurons in the present study.

#### Interval between electrical stimulation and acoustic stimulus

The time interval between the pulse train of electrical stimulation and the acoustic stimulus is a critical parameter in the present study. We examined this parameter in three neurons

FIG. 3. Effect of the number of pulses in the electrical stimulation on the MGB neuronal response to acoustic stimulus. A: PSTHs show neuronal responses to noise bursts of 60-dB sound pressure level (SPL), while the auditory cortex was activated by electrical stimulation with a varied number of pulses. E- means control either before or after the experimental conditions; N, the total number of onset responses; L, the mean first-spike latency. B: change of the spike number as a function of the pulse number of the electrical stimulation. The pulse number of the electrical stimulation was changed from 1 to 200. The changes in the responses to noise bursts of 3 neurons (a, b, and c) are illustrated as a function of the pulse number of the electrical stimulation. Stimulation current was 200  $\mu\text{A}$ .



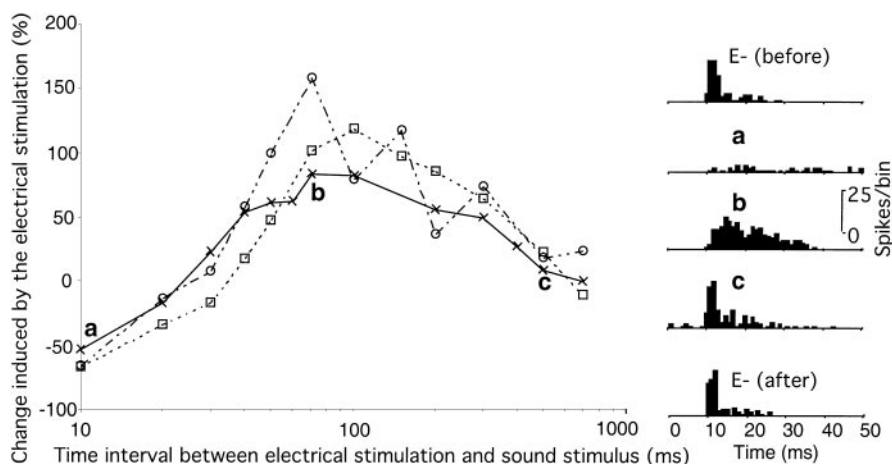


FIG. 4. Change of the spike number as a function of the interval (rate-interval function) between the end of the cortical stimulation and the onset of the sound stimulus. The interval between the offset of the electrical stimulation and the onset of the sound stimulus was changed as a parameter to test the modulatory effect on the neuronal response of 3 thalamic neurons to noise-burst stimuli. A train of 30 electrical pulses at 200 Hz and lasting for 150 ms was applied to the cortex, and noise bursts were used as the sound stimuli. Three sampling points indicated by a, b, and c in the rate-interval function (solid curve) are shown in PSTHs, together with their controls (before and after the experimental conditions). Stimulation current was 200  $\mu$ A.

which received a large modulatory effect from cortical activation. Figure 4 showed the modulatory effects of three neurons as functions of the interval between the electrical current and the acoustic stimulus.

These neurons showed the strongest facilitatory effect for an interval between 70 and 100 ms, and a decreased effect for the intervals greater and smaller than this interval range. It was confirmed from all three facilitatory neurons defined under most intervals >50 ms that the effect became inhibitory for intervals shorter than 30 ms. As a result, 100 ms was chosen as the standard interval between electrical stimulation and the acoustic stimulus.

*Corticofugal facilitatory effect on MGv*

As mentioned above, with the standard parameters, cortical activation caused a mainly facilitatory effect on the MGv neurons. This facilitatory effect was widespread: 208 cases over 303 cases that were recorded from randomly sampled recording MGB planes and with randomly sampled activation sites in fields A and DC.

Figure 5 shows an example in which the corticofugal modulation was widespread. Cortical activation in any of three sites in the auditory cortex (X: BF = 16 kHz; Y: BF = 21 kHz on the border of the fields A and DC; and Z: BF  $\approx$  14 kHz in the

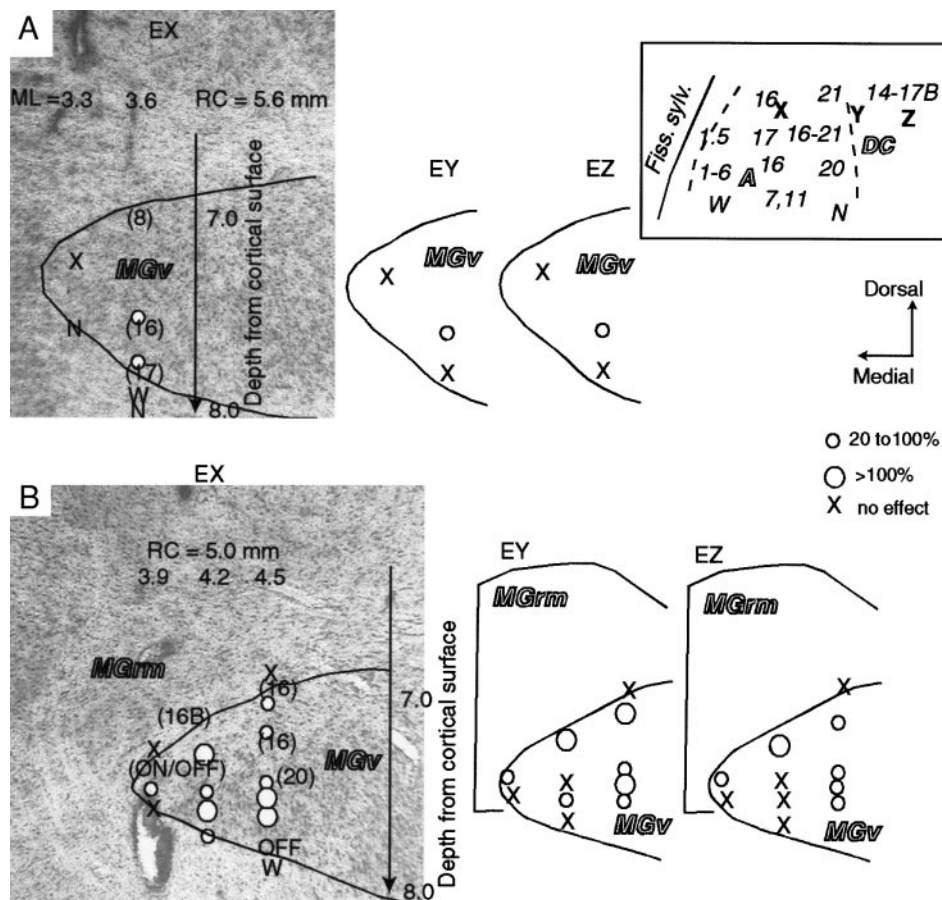
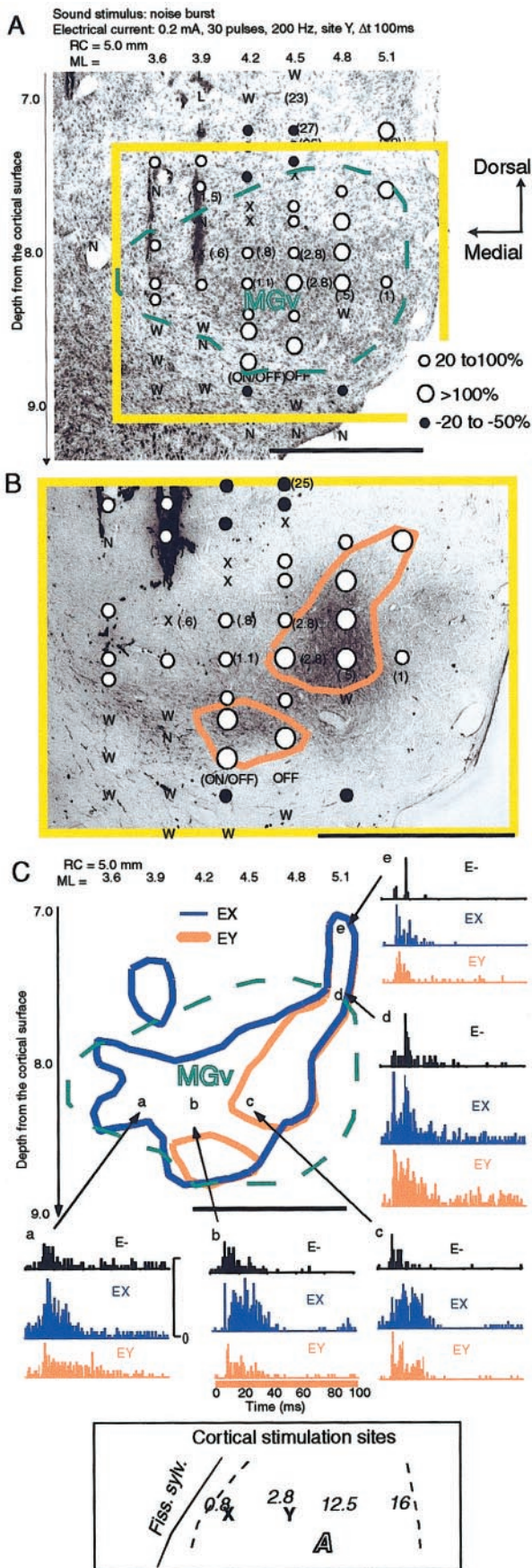


FIG. 5. The topography of the modulatory effect of the activated cortex on neurons in different sites of the MGB. Corticofugal modulatory effects on the thalamic neurons were examined from 5 penetrations in 2 frontal planes: A, where the rostrocaudal coordinate of Rapisarda and Bacchelli's coordinates (Rapisarda and Bacchelli 1977), RC = 5.6 mm, and B, where RC = 5.0 mm, while the auditory cortex was activated at 3 different sites (X, Y, and Z). The physiological maps were superimposed on the Nissl-stained section of the recording plane. The mediolateral coordinate is shown above the map and the depth coordinate is shown on the left. The depth coordinate was with reference to the first penetration and was kept the same during the whole mapping process. Open circles indicate facilitatory effects and the letter "X" indicates no effects. W represents a weak auditory response; ON-OFF represents an ON-OFF response; N, no response to noise burst; numbers in parentheses, best frequencies. Stimulation sites (X, Y, and Z) in the auditory cortex are shown in the inset of the figure. Numbers in the inset indicate the best frequencies; a number followed with a B, broad tuning; W, weak response; N, no response; A, anterior auditory field; DC, dorsocaudal auditory field.



field DC) showed facilitatory effects on the majority of the neurons in the MGv recorded from the two planes shown in the figure, although the patterns of the facilitated areas caused by different cortical sites were different.

In Fig. 6, the modulatory effects of activating cortical field A (a site with BF = 2.8 kHz) on MGv neuronal responses to acoustic stimuli are shown. Only facilitatory effects were detected in the MGv as defined with the Nissl-stained section. There were a few sites where no modulatory effect was observed while the above site of the cortex was activated. No inhibitory effect was obtained in the MGv of this sampled plane.

The regions showing the strongest facilitatory effects had a BF at around 0.5–2.8 kHz, which was comparable to the BF of the stimulation site in the cortex (Fig. 6A). These regions received strong projections from the stimulation site (Fig. 6B).

Unlike the modulation observed in the MGv of the cat and bat, activation of a site in the auditory cortex has a facilitatory effect on a widespread region of the MGv. There was a large overlap between the activation of site X (BF < 1.0 kHz) and site Y (BF = 2.8 kHz) (Fig. 6C). However, the activation of the low frequency site in the auditory cortex tended to cause a facilitatory effect centered at low frequency region in the MGv (Fig. 6C). The region of facilitation caused by cortical activation of site X was larger than that caused by cortical activation of site Y in the sampled plane (note: the situation might be reversed/different in other planes). The facilitatory regions caused by activation of site X, as compared with that caused by site Y, was found more toward the medial part of the MGB, where tonotopically lower frequencies lie.

#### Effect on tuning curve

We examined the corticofugal effect on the frequency selectivity of thalamic neurons. Six of seven neurons showed an elevation of rate-frequency functions when the auditory cortex was activated (Fig. 7). Elevation of rate-frequency functions at both 0 and 50 dB SPL were obtained (Fig. 7A).

Two neurons showed a sharpening of the rate-frequency function at a relatively low sound intensity as shown in Fig. 7, B and C. Providing stimulation at the cortical site of BF = 11

FIG. 6. Topography of the modulatory effect of the auditory cortex on neurons in different sites of the MGB. *A*: electrical stimulation of site Y in the auditory cortex (BF = 2.8 kHz) caused different modulatory effects in different sites of the MGB. The modulatory effect was mapped as shown in *A*, where the open circles indicate facilitatory effects, the closed ones indicate inhibitory effects, and the letter X indicates no effects. The physiological topography was superimposed on the Nissl-stained section of the recording plane. *B*: an enlarged topography of the marked square in *A* was superimposed on a biocytin-labeled section, where the labeling showed the terminal fields of the corticofugal projection from the injection site (site Y) of the cortex. *C*: the most effective regions in the MGB that responded to electrical stimulation on sites Y and X (BF < 1.0 kHz) of the auditory cortex are circled with different colors. Illustrative contours are used to circle the neighboring sites where the modulatory effect was >100%. The ventral division of the MGB is circled with a dotted line. Five groups of the PSTHs to noise bursts are sampled, and these are marked with a, b, c, d, and e. The PSTHs show neuronal responses to noise bursts under controlled conditions (E-), with cortical stimulation at site X (EX), and at site Y (EY). The locations of the stimulation sites are indicated by X and Y in the roughly mapped auditory cortex, as shown in the inset below *C*. The mediolateral coordinate is shown above the map and the depth coordinate is shown on the left. The depth coordinate was with reference to the first penetration and was kept the same during the whole mapping process.

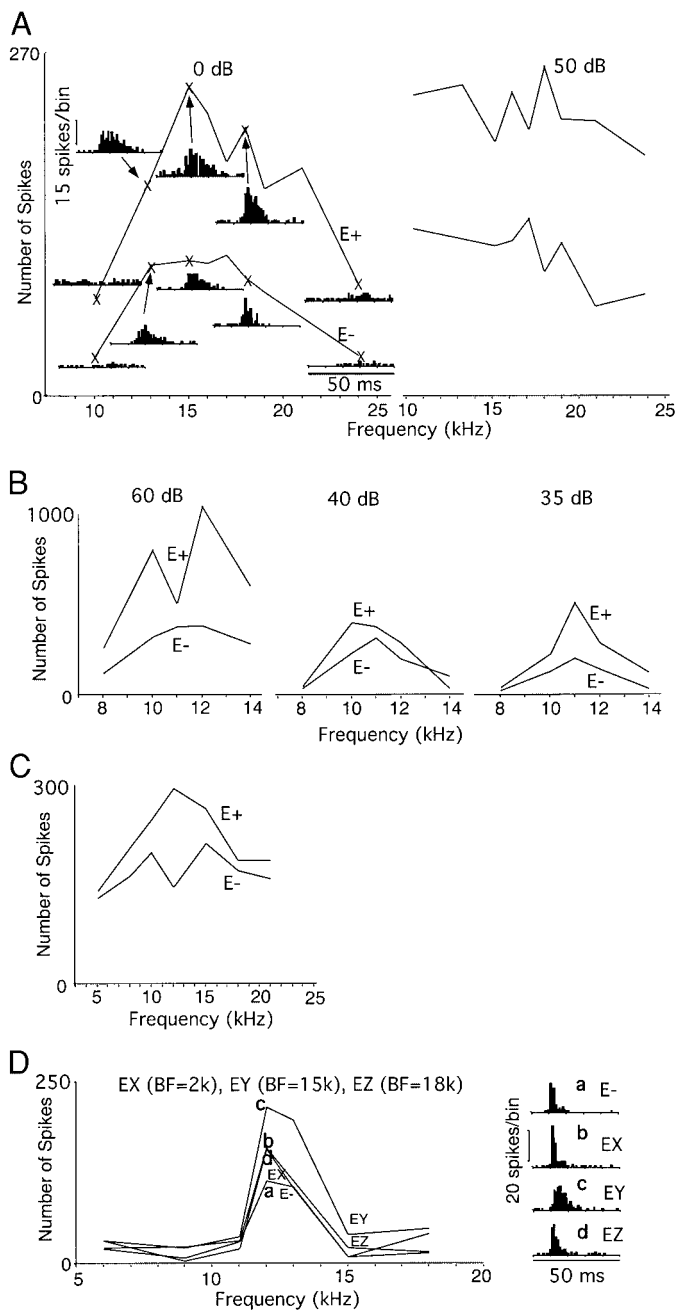


FIG. 7. Effect of electrical stimulation on the frequency-response function. A, B, C, D: effect of electrical stimulation on the response-frequency function of 4 MGv neurons. ON responses to pure tone stimuli are illustrated as a function of the frequency in various sound intensities. The curves indicated with E- illustrate response-frequency functions without cortical activation and those marked with E+ or EX, EY, EZ indicate response-frequency functions while the auditory cortex was activated. The order of frequencies and the conditions were made pseudorandom, e.g., E-, 15 kHz; E+, 24 kHz; E+, 13 kHz; E-, 17 kHz; and others. The PSTHs of 5 paired sampling points from the control and experimental curves indicate the neuronal responses to the pure tone of varied frequencies and with electrical activation of the auditory cortex (A). The changes of the responses are illustrated as functions of the frequency for 2 sound intensities: 0 and 50 dB SPL in A, for 3 sound intensities: 60, 40, and 35 dB SPL in B, for 1 sound intensity (60 dB SPL) in C, and for 1 sound intensity (0 dB SPL) but with the cortex activated in 3 different sites: X, Y and Z in D. In D, the PSTHs at the best frequency in various conditions are shown to the right of the response-frequency function.

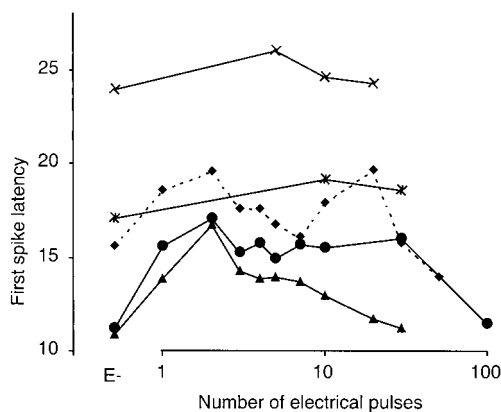


FIG. 8. Changes of the first spike latency caused by the cortical electrical stimulation with a varied number of pulses. Each curve indicates a single neuron. The response latencies to noise burst only were indicated with E-.

kHz, we obtained a stronger facilitatory effect for a pure-tone stimulus of 11 kHz at 35 dB SPL and smaller or no facilitatory effect for other frequencies (Fig. 7B). The neuron in Fig. 7C showed a much stronger facilitatory effect for a pure-tone stimulus of 12 kHz and a lesser effect on other frequencies, showing an obvious frequency selectivity.

The modulation on the tuning curve depended on the site of stimulation. The neuron in Fig. 7D tuned to 12 kHz in the frequency-rate function without cortical activation. Activation of the cortex at various sites did not change its best frequency, but altered the modulation-frequency functions and the elevation. Figure 7D shows that the greatest facilitation occurs at or near BF when the BF at the cortical site corresponds most closely with the BF at the MGv site.

Modulation on temporal firing pattern

The corticofugal pathway modulated not only the number of spikes but also the temporal firing pattern, as reflected from the PSTHs in Fig. 1. Cortical activation prolonged the first spike latency and broadened the firing pattern over the time domain, as shown in Fig. 3A. The mean latency of the first spike was prolonged from 11.2 ms without cortical stimulation to 17.1 ms when the cortex was activated by a single pulse and to 16.0 ms with 30 pulses. The prolongation of the first spike latency during electrical stimulation was observed in all five neurons tested using the number of the electrical pulses as a parameter (Fig. 8). The mean first-spike latency increased significantly from  $15.7 \pm 5.3$  ms with only noise-burst stimulus to  $18.3 \pm 4.9$  ms ( $P < 0.005$ , paired *t*-test), while the auditory cortex was activated with a train of 10 pulses, and to a maximum of  $19.8 \pm 3.7$  ms with a varied number of stimulation pulses ( $P = 0.01$ , paired *t*-test).

DISCUSSION

Similar to in other animals, cortical activation caused both facilitatory and inhibitory effects on neuronal responses of auditory thalamic neurons in the guinea pig. After anatomical confirmation, it became clear that the modulatory effects on the MGv neurons are mostly facilitatory (208/218), although there were a few inhibitory examples (10/218). Of the 303 cases examined in the MGv neurons, 218 (71.9%) were modulated by cortical activation, indicating a widespread corticothalamic

modulation. Among the cases of facilitation, 63 cases showed a facilitatory effect of >100%, and 145 cases showed a facilitatory effect from 20–100%.

#### *Parameters of electrical stimulation*

In studying the corticofugal modulation, most recent investigators have shifted to using electrical current to activate the auditory cortex, rather than cooling the anesthetized brain, which has already been depressed to some degree (He 1997; Jen et al. 1998, 2001; Ma and Suga 2001a,b; Sun et al. 1989; Villa et al. 1991; Yan and Suga 1996, 1998; Zhang and Suga 2000; Zhou and Jen 2000). Inserting a time interval between the electrical stimulation and the sound stimulus can rule out the antidromic responses of the thalamic neurons to cortical stimulation, which has a short latency of 0.3–3 ms (Aitkin and Dunlop 1969; He 1997; Serkov et al. 1976).

The current used in the electrical stimulation of the cortex and thalamus of the *in vivo* and brain slice varies from 100 nA to hundreds of  $\mu\text{A}$  or even 1 mA in previous reports (5–8 V to a pair of tip-exposed insulated wires, which is about 100–200  $\mu\text{A}$ , Watanabe et al. 1966; >50–100  $\mu\text{A}$  for the corticothalamic and >10–20  $\mu\text{A}$  for the optic tract, McCormick and von Krosigk 1992; 150  $\mu\text{A}$ , 0.5 ms pulses, Cruikshank et al. 1992; 49–145  $\mu\text{A}$ , Edeline et al. 1994a,b; 300–600  $\mu\text{A}$ , Weinberger et al. 1995; 100–500  $\mu\text{A}$ , He 1997; 400  $\mu\text{A}$ –1 mA, Chung and Ferster 1998; 17–480  $\mu\text{A}$ , Sun et al. 1989; 5–50  $\mu\text{A}$ , Jen and Zhang 1999; Jen et al. 1998, 2001; Zhou and Jen 2000; 100 nA, Chowdhury and Suga 2000; Xiao and Suga 2002; Yan and Suga 1996). With a train of bi-phasic pulses of 0.1 ms each in 100 Hz in most cases, we found that the current threshold to evoke a corticofugal modulatory effect on the auditory thalamus was between 50 and 100  $\mu\text{A}$  for most guinea pig neurons. This range is equivalent to that obtained in the brain slice study of the rat (McCormick and von Krosigk 1992). Although their major results were obtained from the current range of 240–480  $\mu\text{A}$ , Sun et al. (1989) showed that the current threshold could be smaller than 40  $\mu\text{A}$ . The smaller but effective current (from 5–50  $\mu\text{A}$ ) needed in the bat's auditory system could be due to the small size of the animal (Jen et al. 1998, 2001; Zhou and Jen 2000). However, a careful calibration is recommended for experiments using 100 nA as the stimulation current (Xiao and Suga 2002; Yan and Suga 1996).

Corticothalamic fibers terminate on the distal part of the dendrite (Liu et al. 1995a) and are speculated to cause an excitatory response on the thalamic relay neurons that have a long time constant (He 1997; McCormick and von Krosigk 1992). The effective time interval between the electrical stimulation and the acoustic stimulus peaked at 60–100 ms and lasted for over 500 ms. The long effective time period of the corticofugal modulation could be explained by the morphological structure of the corticofugal fibers, the synapses of which are mediated with an NMDA receptor (Liu et al. 1995a; McCormick and von Krosigk 1992).

The number of electrical stimulation pulses is another important parameter in corticofugal modulation. Although a train of pulses caused a facilitatory effect, a single pulse in the auditory cortex could cause an inhibitory effect on the MGv neuronal response to acoustic stimulus (Fig. 4A). This finding is consistent with previous results on thalamic slices (McCormick and von Krosigk 1992; Scharfman et al. 1990). That the

greater the number of pulses causes the larger modulatory effect can be explained as the cumulative effect of the slow-constant corticofugal modulation on the MGv neurons. The most effective number of pulses was between 30 and 50, which was equivalent to a time period of 150–250 ms at 200 Hz as used in the present study. That the modulatory effect declined when the number of the pulses was >50, i.e., when the electrical stimulation period was >250 ms, might be due to the declining facilitatory effect of the earlier pulses.

#### *Facilitatory effect on MGv neurons*

Comparing the proportion of 74% (72/97) of corticofugal effective neurons showing a facilitatory effect and 26% (25/97) an inhibitory one in the cat MGv (He 1997), the corticofugal effective neurons in the guinea pig MGv showed a higher proportion of corticofugal facilitatory effect (95.4%) and a much lower proportion of corticofugal inhibitory effect (4.6%).

Using the cortical inactivation method, Zhang and Suga (1997) found that the corticofugal system amplifies collicular auditory responses by 1.5 times and thalamic responses by 2.5 times on average. Watanabe et al. (1966) obtained corticofugal modulatory effects from only 20 MGB neurons out of 292. Of these, 6 showed a facilitatory effect and 14 were strongly inhibited by cortical activation. Referring to their data (Fig. 4 of Watanabe et al. 1966), the illustrated neuron was an ON-OFF neuron, which is very often found in the nonlemniscal MGB or on the border of the lemniscal and nonlemniscal MGB (He 2001) and was a burst-firing neuron which was also characterized as a typical nonlemniscal neuron (Hu 1995). Therefore it would be reasonable to speculate that a great proportion of the inhibitory effect neurons reported by Watanabe et al. (1966) were sampled from the nonlemniscal nuclei of the MGB.

Early experiments carried out by Sun et al. (1989, 1996) showed the mainly inhibitory effect of cortical electrical activation on the central nucleus of inferior colliculus neurons with an inter-stimulus interval between the electrical stimulation and acoustic stimulus of <5 ms. Their effects could become facilitatory should they prolong the interval between the electrical and acoustic stimuli to over 30 ms.

About half of the synapses on the thalamic relay neuron are RS terminals [small profiles with rounded vesicles, as defined by Guillery (1969) and Ralston et al. (1988)] (Jones and Powell 1969a,b; Liu et al. 1995a). The majority of the RS terminals appear to derive from corticothalamic fibers (Jones and Powell 1969b). This dense synaptic input to thalamic relay neurons is clearly excitatory (Deschênes and Hu 1990; McCormick and von Krosigk 1992). The strong corticofugal facilitatory results obtained in the present and other studies are very likely caused by this corticothalamic direct connection. As discussed above, this connection has a long time constant, which maintains the corticofugal modulation for time periods up to the order of hundreds of milliseconds (He 1997; Liu et al. 1995a; McCormick and von Krosigk 1992).

#### *Differential inhibitory effects on lemniscal MGBs for different animal species*

Morphologically, GABAergic terminals form synapses on every part of the relay neurons, with a higher proportion at the proximal and intermediate parts of the neuron than at the distal

parts (Liu et al. 1995a,b). However, corticothalamic terminals have their main contact on the distal dendrites thereby delivering an accumulative effect, which could be over-counterbalanced by the strong GABAergic inhibition (Bartlett et al. 2000; Golshani et al. 2001; Jones 1985; Liu and Jones 1999; Winer et al. 1999).

The interneurons in the MGB have been thought to be the major source of the cortical inhibitory effect (Winer et al. 1999) and are suggested as the primary candidate causing corticofugal inhibition on the MGv neurons (He 1997). The smaller number of inhibitory modulatory neurons in the guinea pig MGv than in the cat MGv could be explained by the smaller number of interneurons in the guinea pig's MGv than in that of the cat. Anatomical studies have revealed that there are very few interneurons in the rodent MGB: <1% in the rat; <1% in the guinea pig (Arcelli et al. 1997; Winer and Larue 1996), while the interneurons account for 24–27% of the neurons in the cat MGB (Huang et al. 1999; Rinovik et al. 1987; Rouiller et al. 1990).

The smaller number of inhibitory modulatory neurons in the guinea pig MGv would make the guinea pig as compared with the cat less able to effectively select the wanted signals and tune out the unwanted noises.

The interneurons in the bat MGv are comparable with those of the guinea pig (<1%, Winer et al. 1992). However, Winer et al. (1992) found that the spatial distribution of the axonal endings (puncta) immunoreactive for glutamic acid decarboxylase or GABA in the MGv was twice as high as that in the MGd, while the densities of the interneurons in both divisions were comparable. The massive inhibitory puncta in the MGv could be the source of the relatively strong corticofugal inhibitory effect found in the bat (Suga et al. 1997; Zhang et al. 1997), although comparative data about the puncta in the guinea pig MGv is not available. Another cause of the relatively strong inhibitory effect in the bat MGv could be the inferior colliculus. Both strong corticofugal inhibition and facilitation were found in the bat inferior colliculus (Jen and Zhang 1999; Sun et al. 1996, 1989; Yan and Suga 1999).

#### *Spatial selectivity of corticofugal modulation on MGv*

With the standard parameters, cortical activation caused a mainly facilitatory effect on the MGv neurons. This facilitatory effect was widespread: 208 cases of 303 which were recorded from randomly sampled recording MGB planes and with randomly sampled activation sites in fields A and DC. The present study showed that a strong facilitatory effect (>50%) was evoked on the MGv neurons while auditory cortical site with a similar BF was activated. From the BF point of view, the effective modulatory region of a focal site in the auditory cortex spread to a wide MGv region in the guinea pig. As shown in Fig. 6, there was large overlap in the thalamus between corticofugal facilitatory regions (>50%) caused by the activation of two cortical sites with very different BFs (<1.0 and 3.0 kHz).

The tonotopic organization in the MGv is low frequency medially and higher frequency laterally (Imig and Moral 1984, 1985; Redies and Brandner 1991; Redies et al. 1989). The tendency that stimulation of the low BF site in the auditory cortex facilitates a more medial portion of the MGv is consistent with their tonotopic organization and thalamocortical and

corticothalamic projections (Andersen et al. 1980; Imig and Morel 1983; Jones 1985; Sousa-Pinto 1973; Winer and Larue 1987).

Although the corticofugal modulation on some neurons showed some frequency specificity, the modulation on frequency selectivity in the guinea pig MGv was not as good as in other animal species such as the cat and bat (Fig. 6, He 1997; Suga et al. 2000; Yan and Suga 1998; Zhang and Suga 2000; Zhang et al. 1997). From the results in Figs. 6 and 7, the MGv neurons show the greatest facilitation to stimulation by the cortical sites, with the closest correspondence in the BF. This finding is consistent with the previous results on the bat and the cat (He 1997; Sun et al. 1989, 1996; Yan and Suga 1999; Zhang and Suga 1997; Zhang et al. 1997).

#### *Corticofugal modulation on firing pattern*

The temporal firing pattern has been widely believed to encode information in signal transmission. Using an artificial neural network, Middlebrooks and colleagues (1994) demonstrated that a single neuron could tell a sound from a different direction more accurately when they had used information regarding both spike number and spike timing than when they used only information regarding spike number. The neuron carries much more information by using both the temporal and the rate cues than by using the rate cue only (He 1998; He et al. 1997; Middlebrooks et al. 1994).

Data in the present report clearly show that the corticofugal modulation changed the temporal firing pattern of thalamic relay neurons (Figs. 1, 3, and 7). If one applies the same method as Middlebrooks et al. (1994), it would not be difficult to predict that neurons with different temporal firing patterns may indicate different corticofugal modulation. It will be interesting to investigate whether neurons can detect different acoustic stimuli more accurately while corticofugal modulation is activated.

#### *Concluding remarks*

The calibrations of the parameters of the electrical stimulation in the present study provide a basis for future exploration and solidify our previous and ongoing studies. The corticofugal projections showed a widespread, strong facilitatory effect and very little inhibitory effect on the MGv of the guinea pig. The MGv neurons showed the greatest facilitation to stimulation by the cortical sites, with the closest correspondence in BF. The relatively more minor inhibitory effect compared with that in the cat could be due to the smaller number of interneurons in the guinea pig MGB. The present study also found that the corticofugal modulation on the guinea pig's MGv has less frequency/spatial selectivity than that of the cat and bat. The corticofugal projection modifies the firing pattern of the thalamic neuronal response to auditory stimulus, possibly enabling single neurons to encode more auditory information using not only the firing rate but also the firing pattern.

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