Modulatory Effects of Regional Cortical Activation on the Onset Responses of the Cat Medial Geniculate Neurons

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He, Jufang. Modulatory effects of regional cortical activation on the onset responses of the cat medial geniculate neurons. J. Neurophysiol. 77: 896–908, 1997. Corticofugal modulation on activity of the medial geniculate body (MGB) was examined by locally activating the primary auditory cortex (AI) and looking for effects on the onset responses of MGB neurons to acoustic stimuli. Of 103 MGB neurons recorded from 13 hemispheres of 11 animals, 91 neurons (88%) showed either a facilitatory or inhibitory effect or both; of these neurons, 72 showed facilitatory effects and 25 inhibitory effects. The average facilitatory effect was large, with a mean increase of 62.4%. Small inhibitory effects (mean: \(-16.2\%\) ) were obtained from a few neurons (6 of 103) when a pure tone stimulus was used, whereas the effect became larger and more frequent when a noise burst stimulus was used (mean: \(-27.3\%, n = 22\) of 27 neurons). Activation of an AI site having the same best frequency (BF) as the MGB neuron being recorded from produced mainly a facilitatory effect on MGB neuronal responses to pure tones. Activation of AI at a site neighboring the BF site produced inhibitory effects on the MGB response when noise burst stimuli were used. We found that the effective stimulation sites in AI that could modulate MGB activity formed patchlike maps with a diameter of 1.13 ± 0.09 (SE) mm (range 0.6–1.9 mm, \(n = 15\) ) being larger than the patches of thalamocortical terminal fields. Examining the effects of sound intensities, of 18 neurons tested 9 neurons showed a larger effect for low-sound-intensity stimuli and small or no effects for high-sound-intensity stimuli. Five neurons showed high sound intensity effectiveness and four were non-intensity specific. Most low-sound-intensity effective neurons were monotonic rate-intensity function neurons. The AI cortical modulatory effect was frequency specific, because 15 of 27 neurons showed a larger facilitatory effect when a BF stimulus was used rather than a stimulus of any other frequency. The corticothalamocortical connection between the recording site in MGB and the most effective stimulation site in AI was confirmed by injecting wheat germ agglutinin–horseradish peroxidase tracer at the stimulation site and producing a small lesion in the recording site. The results suggest that 1) the large facilitation effects obtained by AI activation at the region that directly projected to the MGB could be the result mainly of the direct projection terminals to the MGB relay neurons; 2) the large size patches of the effective stimulation site in AI could be due to widely ramifying corticothalamocortical projections; and 3) the corticofugal projection selectively gates auditory information mainly by a facilitatory effect, although there is also an inhibitory effect that depends on the sound stimulus used.

INTRODUCTION

The thalamus relays sensory information from the periphery to the cortex, and in turn receives much stronger reciprocal projections back from the cortex (Andersen et al. 1980; Liu et al. 1995; Montero 1991; Ojima 1994; Sherman and Koch 1986). Corticofugal feedback to the thalamus has been suggested as performing a gating or gain control function in the transmission of information from the periphery to the cortex (Crick 1984; Harth et al. 1987; Murphy and Sillito 1987; Sillito et al. 1994; Villa et al. 1991).

Previous investigators have observed mostly inhibitory effects on the medial geniculate body (MGB) neurons caused by activation of the auditory cortex (Amato et al. 1969; Watanabe et al. 1966). Aitkin and Dunlop (1969) reported an antidromic effect and intrinsic inhibition in the MGB caused by cortical stimulation. Both corticofugal facilitation and inhibitory effects on the MGB neuronal responses to sound stimuli were demonstrated when the primary auditory cortex (AI) was cooled (Ryogo and Weinberger 1976; Villa et al. 1991), and a clear facilitatory effect was reported by Orman and Humphrey (1981). However, there are two weak points in studying the corticofugal modulation by cooling the cortex. First, it is difficult to selectively inactivate a small region of the cortex by cooling. Second, 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. It may be better in this case to test the role of corticofugal feedback to the cortex in a positive rather than negative manner, by activating the cortex through electrical stimulation rather than depressing it through cooling.

The ventral nucleus of the MGB (MGv) has been established as the recipient of the most direct ascending auditory pathway, as the nucleus with the most clear-cut cochleotopic representation, and as the nucleus that projects to AI (Burton and Jones 1976; Jones 1985; Sousa-Pinto 1973). Thalamocortical and corticothalamic pathways are roughly reciprocally connected (Andersen et al. 1980; Berson and Graybiel 1983; Colwell 1975; Merzenich et al. 1982), although there are some discontinuities between them (Winer and Larue 1987). Corticothalamic fibers terminate mainly on distal dendrites of the thalamic relay neurons (Liu et al. 1995). Intracellular recording by McCormick and von Krosigk (1992) showed that delivery of two or more electrical stimuli to corticothalamic fibers at a high frequency causes a slow excitatory potential that lasts for seconds. These morphological and physiological results suggest that the corticofugal modulation has a long time constant. Because antidromic effects on thalamic neurons caused by AI activation have short latencies, these effects could be avoided by the use of...
Corticofugal modulation of the auditory thalamus

METHOS

Animal preparation

Eleven cats of both sexes weighing 2.4–3.6 kg with clean external ears served as subjects, with normal auditory thresholds estimated from cortical unit responses. Anesthesia was initially induced with pentobarbital sodium (Nembutal, Abott, 40 mg/kg ip) and maintained by supplemental doses (~5 mg⋅kg⁻¹⋅h⁻¹ sc) during the surgical preparation. An injection of atropine sulphate (0.05 mg/kg sc) was given 15 min before anesthesia. The animal was mounted in a stereotaxic device after the induction of anesthesia. A midline incision was made in the scalp and a craniotomy was performed to enable access to the ectosylvian gyrus and also to provide vertical access to MGB in each hemisphere (13 hemispheres in total). The craniotomy opening was usually ~3.0 × 5.0 mm² where located above the auditory thalamus and 10.0 × 10.0 mm² above AI. The dura mater was removed from above AI and at the position vertically above the auditory thalamus. A brass block for head fixation was attached to the top of the skull 2–3 cm anterior to the craniotomy with the use of stainless steel bolts and acrylic resin. Both ears were then freed from the ear bars after the acrylic resin set, so the animal’s head could be fixed by the brass block without any movement.

Anesthesia during recording was maintained at the same level as during surgery. Atropine sulphate (0.01 mg⋅kg⁻¹⋅h⁻¹ sc) was given at regular intervals to reduce any respiratory difficulties. Body temperature was maintained between 37.5 and 38.5°C by the use of a thermistor-controlled heating pad attached to the animal’s abdomen. Ringer solution with 5% glucose was given (100 ml⋅kg⁻¹⋅day⁻¹ iv). The use of animal was approved by the Laboratory Animal Care Committee at RIKEN.

Acoustic stimulus

Acoustic stimuli were generated digitally by a MALab system (Kaiser Instruments, Irvine, CA) that was controlled by a Macintosh computer (Semple and Kitzes 1993). Acoustic stimuli were delivered via a dynamic earphone (Bayer DT-48) mounted in a probe. A tube on the probe conducted the acoustic stimulus to the contralateral ear. The pinnae were left intact. Before recording, tympanic sound pressure levels (SPLs, expressed in dB re 20 mPa) were calibrated over a frequency range of 100 Hz to 35 kHz under computer control with the use of a condenser microphone (Briel and Kjaer, 1/4 in.). The earphones could produce acoustic stimuli of high intensity to ~80 dB SPL for low frequencies ranging from 0.1 to 25.0 kHz, but only low intensities of ~50 dB SPL for high frequencies in the range of 25.0–35.0 kHz. The cat was placed in the stereotaxic apparatus, with the ear bars removed but the head fixed by the brass block, in a double-walled soundproof room (IAC, New York). Acoustic calibrations for both ears were stored in a computer file for use in controlling the attenuators used to obtain the desired SPLs.

Recording

Platinum or tungsten microelectrodes with impedances of 9–12 MΩ (Frederick Haer, Brunswick, ME) were advanced by a step-
FIG. 2. Neuronal responses of neuron 32tl04 to acoustic stimuli (pure tones of 12 kHz, 50 ms in duration, 65 dB SPL) are shown in the raster display under 3 conditions: in control, during AI activation, and in control after AI activation. The BF of the neuron was 12 kHz and that of the electrical stimulation site in AI was 11.5 kHz. Each stimulus was repeated for 20 trials. Digits in the top right corner of each raster: number of onset responses that had latencies <40 ms. Conventions same as in Fig. 1. Asterisk: $P < 0.0001$. n.s.: $P = 0.344$.

FIG. 3. Neuronal responses (neuron 29tl18) to pure tones of different frequencies at a sound intensity of 30 dB SPL. A: PSTHs summed over 20 trials showing neuronal responses to pure tones near the neuron’s BF. Left: responses to pure tones in the control condition. Right: responses when a neighboring frequency site in AI was electrically activated. The electrical pulses were the same as shown in Fig. 1 but the intensity was $-500 \mu A$. B: frequency-response functions plotted in terms of spike number of the ON responses shown in A from 0 to 50 ms post-onset time for 2 conditions, E− and E+. C: reproducibility of the modulatory effect in frequency-response functions shown in B. The order of sampling points was reversed from that in B. Asterisk: $P < 0.05$. 

ping motor microdriver that was controlled outside the soundproof room. After being amplified and filtered, neural signals were fed through a window discriminator and passed to an oscilloscope and an audio monitor. The time of spike occurrence relative to stimulus delivery was stored in the same computer used as the stimulus controller with the use of the MALab software package. The computer automatically created raster displays and peristimulus time histograms of the responses together with frequency-response functions (responses to pure tones plotted as a function of frequency).

The frequency tonotopicity of AI for each hemisphere was mapped by 14 penetrations, on average, to identify the electrical stimulation sites for the later experimental sessions. The iso-frequency contours (IFCs) were generated roughly by eye from these data. To characterize AI, we used 50-ms tone pips (rise-fall room. After being amplified and filtered, neural signals were fed through a window discriminator and passed to an oscilloscope and an audio monitor. The time of spike occurrence relative to stimulus delivery was stored in the same computer used as the stimulus controller with the use of the MALab software package. The computer automatically created raster displays and peristimulus time histograms of the responses together with frequency-response functions (responses to pure tones plotted as a function of frequency).

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The MGB was accessed vertically from the top of the brain in the stereotactically positioned animal. The penetrations were made according to a cat brain atlas (Berman and Jones 1982). The depth in the thalamus was roughly known by the use of the lateral geniculate nucleus, which shows responses to light stimuli, as a
reference. Because we selected the MGv as the target region, frequency-tuned neurons with short latencies of <20 ms to sound stimuli were studied in the present experiments.

The BF of the MGB neuron was defined as the frequency that produced a measurable neural response at the lowest possible sound intensity. Because low-frequency IFCs of cat AI were located inside the posterior ectosylvian sulcus, where it was difficult to accurately characterize units by electrical stimulation in most cases, we studied neurons tuned to high frequencies (7–30 kHz) in MGB and with AI modulation from high-frequency sites.

Pure tones with frequencies near the BF of the MGB neuron, noise bursts, and clicks were used as testing acoustic stimuli.

**Electrical stimulation**

We used electrical current pulse trains of 99 pulses with pulse widths of 0.1 ms and frequencies of 300 Hz to activate the auditory cortex. Electrical current pulses of 100–500 μA delivered by an isolator were applied to AI by a monopolar low-impedance electrode (glass-shielded tungsten microelectrode with its tip exposed). Sound stimuli were delivered after the end of AI electrical stimulation after a delay interval. Responses of the MGB neurons to pure tones and noise bursts were compared before and during AI activation. Because it has been suggested that the corticothalamic synapses have long time constants of seconds in some conditions (McCormick and von Krosigk 1992), we set the interval between different experimental trials to 10 s to allow the neuron to recover from habituation and from its modulated state.

After the BF of an MGB neuron was determined, the stimulation site in AI was manually selected along the IFC of the same BF and also surrounding cortical areas, with reference to the tonotopic map.

**Anatomic confirmation**

A small lesion (1.0 μA, 10 s) was made by passing current through the recording electrode (9–12 MΩ) at the last recording site in the MGB.

After the last recording session, 0.05–0.10 ml of 2% wheat germ agglutinin–horseradish peroxidase (WGA-HRP) in 0.05 M tris(hydroxymethyl)aminomethane buffer (pH 8.6) was injected into the most effective facilitation stimulation site in AI to confirm the direct connection between the stimulation and recording sites. The animal was allowed to recover from anesthesia after the craniotomy openings were sealed and the incision was sutured. Antibiotics (Penicillin, Tomiyama Chemical, 100 mg·kg–1·h–1 im) and analgesics (Menamin, Toko Medical, 10 mg/day im) were administered during the 48-h survival period. The animals 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 brain stems were cut transversely with the use of a freezing microtome. Retrogradely labeled cells and anterogradely labeled terminal fields in the MGB in every fourth section (50 μm thick) were visualized by the tetramethylbenzidine reaction (He et al. 1994; Mesulam 1976).

Seven animals were used for the purpose of anatomic confirmation.

**Data collection and analysis**

Responses of MGB neurons to acoustic stimuli were tested with and without AI activation, with the use of pure tones at or near their BF as well as other acoustic stimuli. We used a control protocol that included either E−/E− (repetition of the same test in the condition without AI activation) or E+/E+ (with AI activation) to test the stability of the neuron. The neuron was terminated or paused from recording when its response showed >15% change during the control protocol. To exclude artifacts due to fluctuations in neuronal responsiveness over time due to uncontrollable variables, for most neurons we tested replicability when the order of the E+ (with AI activation) and E− (without AI 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 pseudorandomly chosen (see legend to Fig. 1 for an example).

Unpaired, one-tailed t-tests were performed between the ON responses with and without AI activation. Neuronal responses to each repeated trial of the stimulus were considered as individual measures.

**RESULTS**

The data presented here are from 103 MGB neurons recorded from 13 hemispheres in 11 cats. Responses of 88% of the neurons (91 of 103) were modulated by local activation of AI. We tested the AI modulatory effects on MGB responses to pure tones for all neurons and to noise bursts for 27 neurons. Five neurons that showed modulatory effects to pure tones and/or noise bursts were also tested with the use of a click sound, but for these we could observe no effect on their responses of AI activation.

A facilitatory cortical effect was seen in 72 of 91 neurons and an inhibitory effect in 26 neurons. However, a small portion (12 of 103) of neurons showed no effect of AI activation.

**Facilitatory and inhibitory effects**

With the use of pure tones as acoustic stimuli, we observed mostly facilitatory effects. Neurons showed a sig-
significant increase of 62.4 ± 8.5% (mean ± SE; maximum: 362.5%, n = 72) (paired, 1-tailed t-test, P < 0.0001) in their maximum response to sound stimuli when AI was activated at the most effective facilitatory site. Figure 1 shows a typical example of an MGB neuron, 33tl02. The neuron was tuned to 29 kHz. A site in AI with the same BF was activated by −300 µA at a depth of 1.500 µm, approximately in layers 5 and 6. No change in spontaneous firing rate was observed in this neuron. The onset responses to pure tones are shown in the figure. Compared with the controls, the neuron showed a great increase in spike number (180.7% at its BF and >100% at the neighboring frequencies; unpaired, 1-tailed t-test, P < 0.05), when AI was activated. The frequency-response function, defined as the neural responses when stimulus frequency was varied while intensity was kept constant, showed a significant elevation with AI activation as opposed to without AI activation.

We tested the neuronal responses to acoustic stimuli after tens of repeated trials of AI electrical stimulation, with neurons allowed to recover for 10 s after AI activation. Figure 2 shows the responses of neuron 32tl04 to pure tone stimuli before, during, and after AI activation. The neuron showed a significant facilitatory effect (increasing onset responses by 108%, P < 0.0001) in responding to pure tones when AI was activated, and recovered 10 s after AI activation back to its original level before activation.

We obtained inhibitory effects from 25 neurons. They showed a 25.5 ± 4.8% (mean ± SE, P < 0.005) decrease in the maximal responses to pure tones or noise burst stimuli. Only 6 of 103 neurons showed inhibitory effects on neuronal responses to pure tones, and these effects were relatively small (16.2%, not significant), whereas 22 of 27 neurons tested with the use of noise bursts showed larger inhibitory effects (27.3%, P < 0.001) on their responses. Figure 3 shows neuron 34tl18 with BF = 7.5 kHz, an example of an inhibitory effect on neuronal responses to pure tones caused by AI activation. The poststimulus time histograms show a decrease in the onset responses to pure tones of 7.5 and 8.0 kHz when a site of BF = 9 kHz in AI was activated. There was a 15.8% (not significant) decrease in the onsets to its BF. The change was confirmed by reversing the order of each stimulus and control, as shown in Fig. 3C.

AI stimulation current and delay interval between AI stimulation and acoustic stimulus

We tested the activation effect of pulse trains to AI of various current strengths from 50 µA to 1 mA. A 50-µA current showed no effect or very small effect and a 1-mA

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**FIG. 5.** A: recording site in MGB, #37. An electrical microlesion was made after measurement of the corticofugal modulation on a neuron of BF = 15.5 kHz in the ventral nucleus of MGB (MGv). B: resulting labeling in MGB of a wheat germ agglutinin–horseradish peroxidase (WGA-HRP) injection in an effective stimulation site in AI. Retrograde labeled neurons and anterograde labeled terminal fields were visualized by TMB reaction. The BF of the WGA-HRP injection site in AI was about the same as for the MGB site. Arrows in A and B: same blood vessels. Arrowheads in A and B: diameters of the lesion sites.
current activated too large a region, e.g., it showed an inhibitory effect on the MGv neuronal response to sound stimuli whereas a facilitatory effect was obtained for 100 and 300 μA pulse trains at the same site in AI. A stimulus of 800 μA also demonstrated an opposite effect to that of 100 and 300 μA. Three hundred and 500 μA showed greater effect than 100 μA. Possibly, larger currents of 800 μA and 1 mA might have spread to adjacent regions with different BFs and activated too large an area in AI and/or the other auditory fields. Because the present study aimed to investigate the point-to-point effect of the corticothalamic modulation, we most often adopted pulse trains of 300 μA as the AI activation current.

To determine the optimal delay interval (see Fig. 1, inset, for definition) between AI electrical stimulation and the acoustic stimulus, we tested the modulatory effect of AI activation at different delays, with the results shown in Fig. 4. Neuron 41tl02 in Fig. 4 showed facilitatory effects of >50% (P < 0.05) for delay intervals of <200 ms. The most effective delay intervals were between 20 and 130 ms (P < 0.005). Neuron 41tl02 showed significant facilitatory effects for delay intervals of <100 ms (P < 0.05). Neurons 35tl02 and 39tl105 showed facilitatory effects of >20% (P < 0.05) for delay intervals of 50 and 100 ms. In the present study, we selected 50 and 100 ms as the delay intervals between the electrical stimulation and acoustic stimulus.

Anatomic confirmation of the recording site in MGB and the projections in MGB from the stimulation site of AI

We could confirm the recording site for five of seven cats. Most of our recording neurons were located in the MGv. We confirmed that neurons with low BF are located laterally and those with high BF medially in the MGv (Aitkin and Webster 1972).

Figure 5 shows an example of a recording site (BF = 15.5 kHz) and the connection from the corresponding AI stimulation site (same BF). The tracer WGA-HRP labels anterograde fibers and retrograde neurons in MGB. We obtained a facilitatory effect (25.2%, P < 0.05) in the MGB

![Diagram](http://jn.physiology.org/Downloaded-from)
neuronal response to auditory stimulus by AI activation at the WGA-HRP injection site. As shown in Fig. 5, the recording site was located in the terminal field and surrounded by retrogradely labeled neurons.

**Topography of AI modulatory effect on MGv neurons**

Activation of AI at the same BF site showed a facilitatory effect on MGv neuronal responses to pure tones. Activation at the neighboring IFCs in AI showed small effects or no effect. Weak inhibitory effects on MGv neuronal responses to pure tones were observed only in a few neurons (6 of 103).

We were able to successfully record neuronal responses to acoustic stimuli of 13 MGv neurons while changing the activation site in AI, and thereby to obtain the spatial topographies of AI modulatory effects. The effective stimulation sites in AI were of the same BFs as the MGB neurons and formed patches with a mean diameter of 1.13 ± 0.09 mm (data obtained from 15 patches varied from 0.6 to 1.9 mm).

Figure 6 shows three AI modulation topographies, for MGv neurons 33tl09, 35tl04, and 31tl12. The BF of neuron 33tl09 was 17.5 kHz. The most effective stimulation site in AI had the same BF. However, the effect was nonhomogeneous along the IFC. The topography shows that two patches of 1.1 and 1.7 mm diam are located roughly along an IFC that had the same BF as the MGB neuron, with a distance of ~1.4 mm between two centers. The raster displays in Fig. 6 show a big difference only to a pure tone at its BF, not to other frequencies, nor in the background firing during either control or AI activation conditions. Neuron 35tl04 showed a similar pattern to that of neuron 33tl09, two patches in AI of 1.0 and 1.9 mm diam with a distance of 1.9 mm between them. There was an additional site in the anterior auditory field that showed a facilitatory effect for neuron 35tl04 (data not discussed). Neuron 31tl12 showed only one patch of 1.1 mm diam.

**AI modulatory effect vs. sound intensity**

Activation at the BF site of AI shows nonhomogeneous effects on MGv neuronal responses to pure tones at different sound intensities. Figure 7 shows AI modulation of neuronal responses (neuron 35tl01) to pure tones of varied sound intensity, A: neuronal responses plotted in terms of spike number for 2 conditions, showing changes when AI was activated in comparison with the control. Inset: 2 tuning frequency curves at 30 and 50 dB SPL, showing that the BF of the neuron was 16.5 kHz. The neuron shows a large facilitatory effect to low-intensity sound, but not to high-intensity sound, and therefore was classified as a low-sound-intensity effective (LIE) neuron. B: raster displays comparing neuronal responses to pure tones of 20 and 70 dB SPL for 2 conditions, E− and E+. The effective cortical activation site in AI had a BF of 16 kHz, and the stimulation current was −500 μA. Pure tones were 16.5 kHz. Single asterisk: \( P < 0.05 \). Double asterisk: \( P < 0.005 \).
sound intensities. Figure 7 shows AI modulatory effects on neuronal responses to pure tones of varied sound intensities of an MGv neuron, 35t101. The neuron showed the largest effect (88% increase in spike number, \( P < 0.001 \)) for a pure tone of 10 dB SPL and a small effect (\(<10\%\), not significant) for a pure tone of 70 dB SPL. As shown in the curve of the number of spikes for the control condition (E−), this was a monotonic neuron. With electrical stimulation, the curve of number of spikes showed a saturating nonlinearity for high-intensity acoustic stimuli.

Of 18 neurons tested for this purpose, 9 neurons showed a larger effect for low-sound-intensity stimuli, and small or no effects for high-sound-intensity stimuli. These were named low-sound-intensity effective (LIE) neurons. Five neurons showed larger effects for acoustic stimuli of higher intensity than for that of lower intensity, and were named high-sound-intensity effective (HIE) neurons. The remaining four neurons were non-intensity specific (NIS), showing effects over a wide range of sound intensities or a complicated pattern to sound intensity. The effect-intensity functions (modulatory effects plotted as % change in neuronal responses as a function of SPL) of 18 neurons are summarized in Fig. 8.

Of nine LIE neurons, eight had monotonic rate-intensity functions (discharge rate plotted as a function of SPL) (Clarey et al. 1992; Phillips 1987). The determination of the monotonicity was based on the rate-intensity functions under the E− condition. Neurons of other types showed both monotonic and nonmonotonic functions of SPL. Figure 9 shows examples of rate-intensity functions for HIE and NIS neurons under both the E+ and E− conditions. Neurons 35t104 and 34t106 were classified as monotonic neurons and 34t105 as nonmonotonic neurons.

Influence on the frequency-response function

As shown in Fig. 1, AI activation modulates the frequency-response function of MGB neurons. The influence on the frequency-response function depended on the acoustic stimulus intensity, as shown in the example in Fig. 10. In this case there were only elevations in the frequency-response functions when AI was activated (Fig. 10A). The facilitatory effect (difference in spike number) as a function of stimulus frequency was defined as the gain/stimulus-frequency function. The gain/stimulus-frequency functions for different stimulus intensities are shown in Fig. 10B. When the stimulus intensity was >30 dB, AI activation enhanced responses to the BF to a much greater extent than it enhanced responses to other frequencies. We named neurons such as this “BF-enhanced neurons.”

Of 27 neurons for which the gain/stimulus-frequency function was measured, 15 showed larger effects at their BF for at least one tested sound intensity, whereas 12 showed no BF specific enhancement. Figure 11 gives an example, that of neuron 31t115, which showed non-BF specificity in its gain/stimulus-frequency function. The raster displays show significant increases (\( P < 0.05 \)) in the responses to pure tones for all frequencies tested when AI was activated. Of the 15 BF-enhanced neurons, 7 showed selectivity for their BF in the gain/stimulus-frequency function for all sound intensities tested, as in the example shown in Fig. 10, and the remaining ones showed gain/stimulus-frequency functions whose characteristics were intensity dependent, i.e., they showed BF-specific enhancement at some sound intensities but not at others.

Modulation of neuronal response to noise burst

We tested the corticofugal modulatory effects of 27 MGB neurons with the use of noise bursts as acoustic stimuli, and usually obtained a facilitatory effect when activating the AI site having the same BF. Inhibitory effects on MGB neurons were obtained from 22 neurons by activating AI at the neighboring IFCs to their BF locations, as the example in Fig. 12A shows. There were two cases in which inhibition was

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**Fig. 8.** Changes in responses of 18 neurons to pure tones of varied sound intensity. According to the patterns of changes in their responses as a function of sound intensity, neurons were classified as LIE, high-sound-intensity effective (HIE), or non-intensity specific (NIS). Neurons were divided into monotonic and nonmonotonic rate-intensity function neurons, which is indicated by an m or n, respectively, after the neurons’ designations.
facilitatory or inhibitory. Usually (72 of 91) facilitatory effects were found, with the use of either pure tones or noise bursts as stimuli, and the facilitatory effects were large, on average causing a 62.4% enhancement in firing rate. We obtained inhibitory effects from about one fourth (25 of 103) of the effective neurons. Of these, only six neurons showed inhibitory effects when pure tone stimuli were used, and these effects were small. Inhibitory modulatory effects from A1 were more common and more potent when noise burst stimuli were used. Of 27 MGB units, 22 showed inhibitory cortical modulation in their responses to noise bursts. Of 103 neurons, 12 showed no effect on their responses to sound stimuli by regional A1 activation.

**Antidromic and orthodromic responses of MGB neuron by AI activation**

Electrical stimulation of the cortex causes antidromic responses in the thalamic neurons. Aitkin and Dunlop (1969) and Serkov et al. (1976) obtained similar results, both showing that antidromic responses to AI stimulation had latencies of 0.3–3 ms. Only inhibitory effects in the MGB neurons were observed by AI activation of a single electrical shock (Aitkin and Dunlop 1969). According to intracellular studies, a single electrical shock to corticothalamic fibers typically resulted in monosynaptic excitatory postsynaptic potentials in thalamic neurons followed by inhibitory postsynaptic potentials (Deschenes and Hu 1990; Scharfman et al. 1990), and the delivery of two or more electrical stimuli at a high frequency caused a slow excitatory postsynaptic potential that lasted for seconds (McCormick and Krosigk 1992).

In the present study, we presented acoustic stimuli 50–100 ms after the end of AI electrical stimulation by trains of current pulses. No obvious differences were detected in the data whether 50- or 100-ms delays were used (see Fig. 4). It is clear that the results in this report are not due to the antidromic spikes because of the long delay between AI activation and presentation of the sound stimuli. As mentioned in the INTRODUCTION, in the present study we considered the corticofugal modulatory effects on MGB neuronal responses to sound stimulus only during the onset responses.

Previous investigators have mostly observed that cortical activation produces inhibitory effects on MGB neuronal responses to sound stimuli when AI was activated in a small 1-mm region having the same BF at its center. The modulatory effect became significantly inhibitory ($P < 0.05$) when the stimulation electrode shifted horizontally $>1.0$ mm posterior to the BF site.

**Facilitatory and inhibitory effects**

We found that corticofugal modulation produced a large facilitatory effect on MGB neurons (mean: 62.4%, $n = 72$). Because it is possible that we did not find the most effective stimulation site in AI for some neurons, the actual facilitation
FIG. 10. Responses of an MGv neuron, 33H04, to pure tones of different frequencies (frequency-response functions) and sound intensities. A: curves for the E+ and E- conditions. AI was activated by pulse trains of -300 μA at the site of BF = 25 kHz. B: gain/stimulus-frequency functions, defined as the changes in the frequency-response functions of E+ to E-, are shown at sound intensities ranging from 30 to 70 dB SPL. Because the modulatory effects of low-intensity stimuli at 20 dB SPL on frequencies other than the BF were statistically insignificant, the gain/stimulus-frequency curve was ignored for that case. Asterisk: *P < 0.05.

The results here are comparable with those found in the bat (mean: 52%, n = 5) by Teng and Suga (1995). About half of the synapses on thalamic relay neuron are RS terminals (small profiles with rounded vesicles, defined by Guillery 1969; Ralston et al. 1988) (Jones and Powell 1969a; Liu et al. 1995). 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). We therefore speculate that the large facilitatory results in this report are caused by this kind of synapse.

Watanabe et al. (1966) obtained corticofugal modulatory effects for only 20 MGB neurons of 292. Of these, six neurons had facilitatory effects, with a maximum increase of 57% in the number of spikes. That report included one neuron that showed a facilitatory effect when there was a time interval of 40 ms between the electrical stimulation of the cortex and the sound stimulus, and no effect when the time interval was shortened to 20 ms. Aitkin and Dunlop (1969) in the MGB and Tsumoto et al. (1978) in the lateral geniculate nucleus. Pure tones are defined as sound stimuli of a single frequency. Noise bursts consist of many frequency components and they activate most neurons in the MGv. In the present

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together with the anatomic observation by Liu et al., that the inhibitory effect may relate to presynaptic dendrite terminals because it depends on not only the corticofugal activation but also the ascending activation, i.e., the frequency composition of the acoustic stimulus. Further investigation is necessary to clarify the mechanism for producing this kind of inhibitory effects.

**Patch structure in the cortex of the modulatory effect to MGB neurons**

Each region in the thalamus receives reciprocal projections back from the region of cortex to which they project (Andersen et al. 1980; Berson and Graybiel 1983; Colwell 1975; Merzenich et al. 1982). After injecting anterograde and retrograde tracers in the rat auditory cortex, Winer and Larue (1987) found that zones containing many retrogradely labeled neuronal somata were not completely coextensive

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**Fig. 11.** Responses of neuron 31805 to pure tones. A: gain/stimulus-frequency function is shown above the frequency-response functions of E+ and E−. B: raster displays show the neuronal responses to pure tones at 70 dB SPL under both the E+ and E− conditions. Single asterisk: \( P < 0.05 \). Double asterisk: \( P < 0.001 \).

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**Fig. 12.** Changes in responses to noise bursts of (A) an MGv neuron, 34tr06, produced by activating different frequency loci in AI and of (B) neuron 34tr09, produced by activating different sites along the isofrequency contour (IFC) in AI. Neuron 34tr06 had a BF of 17 kHz, and neuron 34tr09 had a BF of 18 kHz. Crosses: stimulation sites in AI. IFCs are shown at 5-kHz intervals. Each white bar indicates an increase in response to noise bursts of the MGv neuron when the corresponding site in AI was activated, and each black bar indicates a decrease. Asterisk: \( P < 0.05 \).
with areas of heavy terminal labeling within the MGB, although there was a gross congruence of thalamocortical-corticothalamic projections. Conversely, they found many zones of anterograde labeled terminals without retrogradely labeled somata in the same region. In the visual system, Murphy and Sillito (1996) showed that the terminal fields of corticothalamic axons have a maximum spread of 500–1,500 μm in the lateral geniculate nucleus. This represents a broader arborization than occurs for the axonal terminals of intensity sound, and were classified as LIE neurons. This of corticothalamic axons have been reported numerous times to be <500 μm in various species (de Venecia and McMullen 1994; Hashikawa et al. 1995; Landry and Deschenes 1981; McMullen and de Venecia 1993; Shinoda and Kakei 1989).

A striking finding of the present study is the patchlike pattern of the topography in the corticofugal modulatory effects on the MGB neurons. The size of patches ranged from 600 to 1,900 μm, with an average of 1,130 μm. This is larger than the spread of the terminal projections of thalamocortical neurons, but roughly the same size as terminal projections of the reciprocal corticothalamic neurons. We conjecture that a possible reason why such large functional patches were observed in AI is that they reflect the effects of the widely ramifying corticothalamic projections.

By injecting retrograde tracers into identified excitatory/excitatory or excitatory/inhibitory bands in AI, Middlebrooks and Zook (1983) and Brandner and Redies (1990) have shown that the neuronal populations within the MGv that projected to different classes of binaural bands were strictly segregated from each other. The widths of the excitatory/excitatory and excitatory/inhibitory bands were approximately the same as the diameter of the patches in the present study (Fig. 7 of Imig and Adrien 1977; Middlebrooks et al. 1980). The patch structure in AI of the modulatory effect to MGB neurons obtained in the present study may suggest that the corticothalamic projection preserves the binaural column structure that is present in the thalamocortical projection.

Corticofugal projection selectively affects gains of the auditory input

When activating the AI site having the same BF as the MGB neurons being recorded from, the gains of the MGB neuronal responses to acoustic stimuli are modulated differently depending on the frequency of the stimuli. We obtained greater gains to the BF stimulus than any other frequency stimulus from 15 of 27 neurons for at least one tested sound intensity, showing that the modulation was frequency selective rather than nonspecific (Fig. 10). The selectivity in the gain/stimulus-frequency function also depended on sound intensity.

In the present study, we obtained mostly facilitatory effects on the MGB neuronal responses to pure tones when we activated AI having the same BF. Examples are shown in Figs. 1, 10, and 11, which show only elevations of the frequency-response function. We conclude, therefore, that the modulatory effect of AI on MGB neuronal onset responses to pure tone stimuli is mainly facilitatory when the recording sites are chosen such that AI and MGB have the same BF.

As defined in the Results, we classified neurons into three groups, LIE, HIE, and NIS neurons, depending on whether the corticofugal modulation was strongest for low- or high-intensity sound stimuli, or not affected by stimulus intensity. About half of the neurons showed large facilitatory effects in their responses to low-intensity sound, but not to high-intensity sound, and were classified as LIE neurons. This decreased facilitatory effectiveness at high sound intensities may be the result of a saturating nonlinearity in the monotonic rate-intensity functions of LIE neurons, as is suggested by the example shown in Fig. 7. The selectivity of the facilitatory effect for low sound intensities suggests that in many cases cortical feedback to the MGB acts to make weak sounds appear stronger than they actually are.

Overall, our observations that the facilitatory effects of AI cortex on the MGB are selective for both sound frequency and sound intensity support the notion that the MGB acts as a gate or filter for incoming auditory stimuli, and that AI can control this filter by modulating the gain of transmission through it.

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