

Basal forebrain stimulation changes cortical sensitivities to complex sound

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Experience affects how brains respond to sound. Here, we examined how the sensitivity and selectivity of auditory cortical neuronal responses were affected in adult rats by the repeated presentation of a complex sound that was paired with basal forebrain stimulation. The auditory cortical region that was responsive to complex sound was 2–5 five times greater in area in paired-stimulation rats than in naive rats. Magnitudes of neuronal responses evoked by complex sounds were also

greatly increased by associative pairing, as were the percentages of neurons that responded selectively to the specific spectrotemporal features that were paired with stimulation. These findings demonstrate that feature selectivity within the auditory cortex can be flexibly altered in adult mammals through appropriate intensive training. *NeuroReport* 12:2283–2287 © 2001 Lippincott Williams & Wilkins.

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INTRODUCTION

Current theories suggest that cholinergic and GABAergic neurons projecting from the basal forebrain (in particular, the nucleus basalis) mediate experience-induced changes in auditory cortical responses [1,2]. Support for these theories comes primarily from experiments showing that the response characteristics of auditory cortex can be altered by repeatedly pairing sounds with basal forebrain stimulation [3–6]; that experience-induced plasticity can be blocked by lesioning the basal forebrain [5,7] or blocking cholinergic effects [3]; and that basal forebrain neurons can be associatively conditioned to respond to tones [8].

Researchers studying auditory cortical plasticity have typically examined changes in responses to short-duration pure tones. Many cortical neurons, however, respond most strongly to sounds with more complex spectrotemporal features [9,10]. Mammals with damaged auditory cortices can often discriminate pure tones, but not frequency-modulated sounds [11]. These data suggest that the adaptability of cortical neurons might be more fully characterized by examining how cortical responses are affected by experience with spectrally dynamic sound.

Here, we show that pairing basal forebrain stimulation with the presentation of complex sound dramatically changes spectrotemporal response sensitivity and selectivity in rat auditory cortex.

MATERIALS AND METHODS

Preparation and recording techniques have been extensively described in previous studies [5,6,12]. Briefly, platinum bipolar stimulating electrodes were chronically

implanted in the right nucleus basalis (7 mm below the cortical surface, 3.3 mm lateral and 2.3 mm posterior to bregma) of barbiturate-anesthetized rats (female, Sprague-Dawley, ~300 g, $n=6$) using techniques approved under UCSF Animal Care Facility protocols. After ≥ 2 weeks of recovery, periodic trains of rising frequency sweeps (1 s, 25 ms rise/fall, 2–16 kHz, ~50 dB, broadcast via a free-field speaker) were paired with electrical stimulation of the nucleus basalis (a 150 μ A, 100 Hz train of capacitively coupled, 0.1 ms, biphasic pulses was delivered during the last 200 ms of sound presentation). Sweep trains paired with electrical stimulation occurred randomly every 8–40 s, 400–500 times a day, for 10–20 days. Pairing basal forebrain stimulation with the presentation of tonal stimuli is known to produce much larger changes in auditory cortical responses that are selective for the paired tone than do either the presentation of tonal stimuli without stimulation, or than does basal forebrain stimulation in the absence of sound stimuli [3,5,13–15].

In one group of rats (Group 1: $n=2$), stimulation was paired with a 10 sweep/s upswing train (sweep rate 20 octaves/s, 2 octave spacing, 45% overlap; see Fig. 3a). In a second group of rats (Group 2: $n=4$), stimulation was again paired with a 10 sweep/s upswing train. However, rats in Group 2 also experienced an equal number of 6 sweep/s downswing trains (sweep rate 12 octaves/s; see Fig. 3b) that were presented without stimulation. Presentations of paired and non-paired stimuli were randomly interleaved. Bandlimited, uniform noise (see Fig. 3c) was presented simultaneously with the sweep trains presented to Group 2, so that at any point within a sweep train there

was always energy at all frequencies between 2 and 16 kHz. The sweep trains that were presented to these two groups of rats have previously been described as moving auditory gratings [9].

Twenty-four to forty-eight hours after their last stimulation session, each rat was anesthetized with sodium pentobarbital (50 mg/kg) and the right auditory cortex (ipsilateral to the site of stimulation) was surgically exposed. Multiple unit or single unit extracellular recordings were then collected using tungsten microelectrodes, 1–2 M Ω , at a cortical target depth centered at about 800 μ m (approximate layer 5). Sounds were presented monoaurally to the left ear (i.e. contralateral to the cortical recording site) via a calibrated headset speaker connected to a sound tube introduced into the external auditory meatus.

Cortical regions sensitive to dynamic broadband sound were mapped in treated and naive rats ($n=10$) using a search stimulus composed of a single FM sweep followed by a burst of noise. Cortical sites responsive to this sound were monitored during the presentation of 450 tonal stimuli (25 ms, 3 ms rise fall, 300 ms period) varying in frequency and intensity, as well as 30 FM sweep trains varying in direction, rate of modulation (4–24 octaves/s), and rate of repetition (2–24 sweeps/s); each sweep train was presented four times for each recording site.

Spike discharges were amplified and converted to digital signals for later analysis.

RESULTS

Measurements were obtained from 821 recording sites in the auditory cortex; 448 penetration samples were from control rats; 373 were from treated rats. Measurements of cortical responses to sweep trains were made in six control rats (136 recordings), and in all treated rats. Measurements from treated rats included 213 samples from the two rats that experienced basal forebrain stimulation paired with sweeps alone (Group 1), and 235 from three rats that experienced stimulation paired with sweeps presented with noise (Group 2); recordings from a fourth rat in Group 2 were limited because of complications during surgery.

The cortical area responding to complex sound was much larger in treated than in naive rats (Fig. 1). The average area in treated rats ($n=5$) was 7.8 ± 2.2 mm² (mean \pm s.d.) compared to 2.8 ± 0.9 mm² in naive rats ($n=10$). Responsive cortex in treated rats was probably larger than indicated by our measurements because neurons at the borders of the cortical region from which recordings could be made (i.e. determined by the position and size of the craniotomy) often responded strongly to complex sounds. These increases in responsive area were much greater than those reported after months of training with sounds [15], or after pairing basal forebrain stimulation with the presentation of pure tones [5]. No obvious differences in the areas of responsive cortex were noted between treated rats in experimental groups 1 and 2.

Post-stimulus time histograms generated by averaging responses across recordings showed that periodic trains of FM sweeps evoked substantially more spikes, for longer periods of time, in treated rats than in naive rats (Fig. 2, Fig. 3). In treated rats, cortical neurons would often continue to fire at periodic intervals during and after the

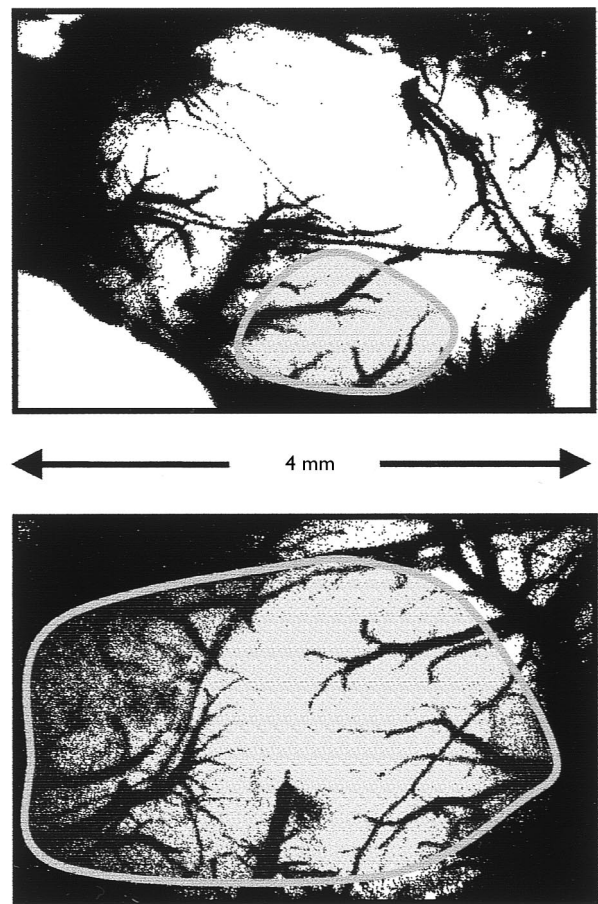


Fig. 1. The cortical area responding to complex sound was much smaller in naive rats (top) than in treated rats (bottom).

presentation of a periodic FM sound. These post-stimulus oscillatory responses were rarely observed in recordings from naive rats. Late responses to sound onsets (occurring 50–120 ms after the initial onset response) and responses to the offsets of sweep trains were also more prevalent in treated rats (Fig. 2, Fig. 3c). While few neurons in naive rats responded periodically to trains faster than 10 sweeps/s, many neurons in treated rats responded strongly to rates as high as 12 sweeps/s (Fig. 2). These induced changes in cortical responses were generally similar in groups 1 and 2.

Spontaneous activity was higher in treated than in naive rats (Fig. 2). Quantitative estimates of spontaneous activity were made based on the number of spikes that occurred in the first 10 ms after stimulus onset. In naive rats, spontaneous activity was low; the mean number of spikes in the first 10 ms was 0.11 ± 0.08 ($n=136$). In rats from Group 1, the mean number of spikes in the first 10 ms was 1.16 ± 0.13 ($n=213$), and in rats from Group 2, it was 1.66 ± 0.23 ($n=235$); over 10 times as high as in naive rats.

Cortical responses to the 10 sweep/s upswing train paired with stimulation were more temporally precise in Group 1 rats than in Group 2 rats (Fig. 3a). In Group 1 rats, responses to individual sweeps within the 10 sweep/s

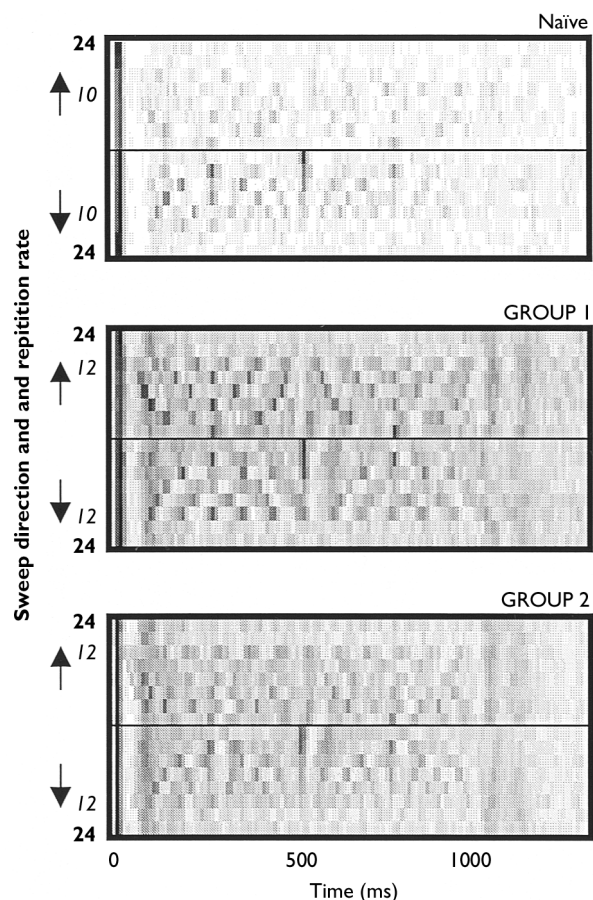


Fig. 2. Magnitudes of cortical responses evoked by sweep trains were greatly increased in treated rats from Group 1 (middle) and Group 2 (bottom) relative to responses in naive rats (top). Images show averaged post-stimulus time histograms of responses from all recordings to 16 different sweep trains (presented 4 times each). The x-axis shows time in 10 ms bins; darker levels indicate higher peaks in the PSTH (i.e. more spikes). Each row along the y-axis (16 total) corresponds to a particular sweep train. The upper half of each image shows responses to upsweep trains (upwards arrow) produced at rates of, from top to bottom: 24, 18, 12, 10, 8, 6, 4 and 2 sweeps/s. The lower half of each image shows responses to downsweep trains (downwards arrow) produced at rates of, from top to bottom: 2, 4, 6, 8, 10, 12, 18 and 24 sweeps/s. PSTH images from cortical neurons in treated rats show: (1) an increased sensitivity to upsweeps (note darker bins above the midline); (2) stronger responses to sound onsets and offsets (indicated by dark vertical bands after 0 and 1000 ms, respectively); (3) an increased ability to respond periodically at faster rates (maximum responding rate is italicized); and (4) increased spontaneous activity.

train were comparable to responses evoked by the onset of the train (Fig. 3a, row 3). Rats in Group 2 that were exposed to 6 sweep/s downsweep trains, unpaired with stimulation, showed greater responding to these sounds than naive rats, as did rats in Group 2 that had never previously experienced these sounds (Fig. 3b). Similarly, cortical neurons in rats from both groups showed enhanced responses to the onset and offset of bandlimited uniform noise relative to naive rats.

Selectivity to sweep direction was determined on the basis of measurements of the firing rate. Recordings were

considered to show evidence of directional selectivity if, for the two sweep trains that produced maximal responding: (1) sweeps in both trains were modulated in the same direction; and (2) the number of spikes evoked by sweeps produced at the same rate, but modulated in the opposite direction, was $\geq 80\%$ less than the number evoked by sweeps modulated in the preferred direction. Neuronal response samples that did not meet these criteria were considered to be from non-selective neurons.

Directional selectivity was dramatically altered in treated rats. The percentage of recordings showing selectivity for downsweeps decreased from 44% in naive rats to 14% in treated rats (19% in Group 1; 10% in Group 2). The percentage of recordings showing selectivity for upsweeps increased from 13% in naive rats to 17% in treated rats (22% in Group 1; 12% in Group 2). Overall, the percentage of recordings that showed responses to trains of upsweeps that were as good as, or better than, responses to downsweeps increased from 56% in naive rats to 86% in treated rats (81% in Group 1; 90% in Group 2); these changes in directional selectivity can also be seen in Fig. 2.

It is important to note that because the area of responsive cortex increased in treated rats, equal percentages of recordings in naive and treated rats do not represent equal numbers of directionally selective neurons. For example, if 10% of neurons in both naive and treated rats responded best to upsweeps, this would correspond to an average cortical area of about 0.28 mm^2 in naive rats and about 0.78 mm^2 in treated rats (i.e. encompassing more than twice as many neurons). Thus, an increase of 30% in the percentage of recordings showing sensitivity to upsweeps indicates a very large increase in the number of cortical neurons sensitive to upsweeps.

DISCUSSION

Based on past studies of experience- and stimulation-induced auditory cortical plasticity, it could be predicted that when basal forebrain stimulation is repeatedly paired with the presentation of periodic FM sounds, cortical sensitivities to features of those sounds would be substantially changed. Because researchers have focused almost exclusively on changes in cortical responses to short-duration pure tones induced by experience or behavioral training with such tones, it has been unclear how spectrotemporal sensitivities in cortex might be affected by learning-based exposure to more complex sounds, a situation that is much more likely to naturally occur. Our results suggest that cortical responses to sound can be powerfully, positively changed by experience with periodic FM sounds. Those changes result in strong increases in the area of origin, magnitude and temporal coordination of distributed responses evoked by that stimulus. They result in a substantial change in the specificity of response for stimuli like the complex stimulus that was associatively paired in this experiment. They also result in the generation of feature selectivity that confers substantial response generalization, i.e., that enables the cortex to respond to other related high-rate or spectro-temporally dynamic stimuli.

Increases in spiking activity and persistence, in spontaneous activity, in sensitivity to sound onsets and offsets, and in the phase-locking and temporal coordination of

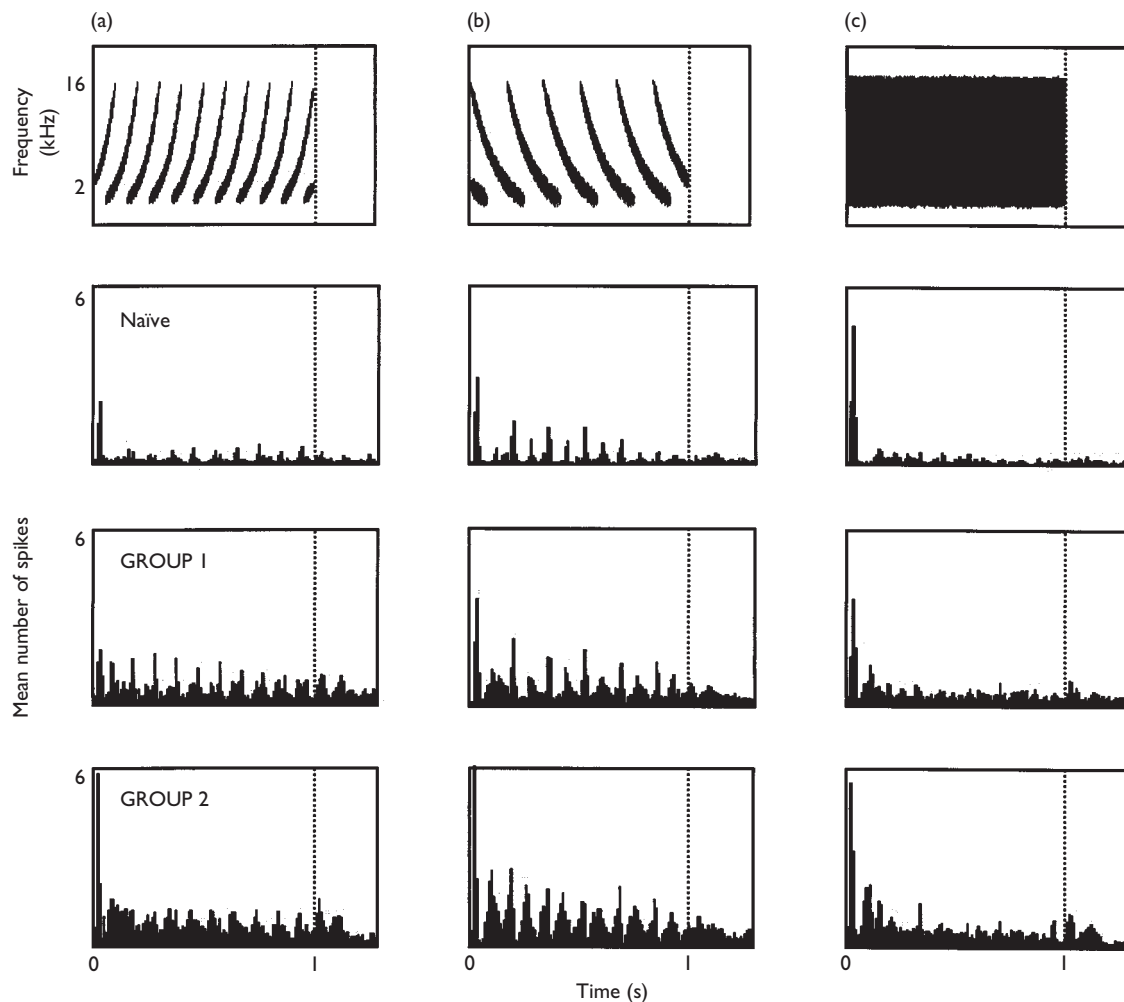


Fig. 3. Cortical responses evoked by periodic trains of FM sweeps (row 1) were less in number and persistence in naive rats (row 2) than in treated rats from Group 1 (row 3) and Group 2 (row 4); row 1 shows spectrograms of sounds and rows 2-4 show post-stimulus time histograms generated by averaging responses across all recordings (4 stimulus presentations each, summed in 10 ms bins) from each group. (a) Responses to the 10 sweep/s upsweep train paired with stimulation. Responses occurring after the offset of a sweep train (marked by the dotted line) were more prevalent in treated rats. (b) Responses to the 6 sweep/s downsweep train presented to rats in Group 2, but not paired with stimulation; rats in Group 1 had never previously experienced this sweep train. (c) Responses to bandlimited uniform noise, presented simultaneously with all sounds experienced by rats in Group 2 during the stimulation phase; this sound was novel for rats in Group 1.

responses to successive stimulus events in treated rats suggest that cortical neurons in these rats come to be generally more excitable than neurons in naive rats. Similar changes in excitability can be produced by behavioral training (for review see [16]), or by applying neuromodulatory chemicals to cortex (for review see [17]). Simulations with self-organizing neural networks suggest that stimulation-induced increases in cortical excitability could hasten cortical reorganization and broaden tuning [18]. At the same time, it is important to note that global changes in excitability cannot account for the large-scale changes in cortical sensitivities and selectivity to spectrotemporal features of the sounds paired with stimulation. Similarly, changes in either spectral or temporal sensitivities alone cannot account for the powerful increase in responses evoked by trains of upsweeps, because trains of downsweeps had identical (but sequentially reversed) spectral and temporal properties.

CONCLUSION

Pairing basal forebrain stimulation with the presentation of broadband periodic sounds for as little as 2 weeks radically changed how fully developed cortex in rats responded to paired, and spectrotemporally related, complex sounds. These results suggest that mammalian sensory cortex remains highly adaptable after maturation, and that it may be possible to flexibly adjust how cortical networks process sensory information through external control of neuromodulatory systems.

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