

Spectral Features Control Temporal Plasticity in Auditory Cortex

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Abstract

Cortical responses are adjusted and optimized throughout life to meet changing behavioral demands and to compensate for peripheral damage. The cholinergic nucleus basalis (NB) gates cortical plasticity and focuses learning on behaviorally meaningful stimuli. By systematically varying the acoustic parameters of the sound paired with NB activation, we have previously shown that tone frequency and amplitude modulation rate alter the topography and selectivity of frequency tuning in primary auditory cortex. This result suggests that network-level rules operate in the cortex to guide reorganization based on specific features of the sensory input associated with NB activity. This report summarizes recent evidence that temporal response properties of cortical neurons are influenced by the spectral characteristics of sounds associated with cholinergic modulation. For example, repeated pairing of a spectrally complex (ripple) stimulus decreased the minimum response latency for the ripple, but lengthened the minimum latency for tones. Pairing a rapid train of tones with NB activation only increased the maximum following rate of cortical neurons when the carrier frequency of each train was randomly varied. These results suggest that spectral and temporal parameters of acoustic experiences interact to shape spectrotemporal selectivity in the cortex. Additional experiments with more complex stimuli are needed to clarify how the cortex learns natural sounds such as speech.

Mechanisms of Experience-Dependent Cortical Plasticity

Experiments conducted over the last twenty years have documented that cortical representations are continually shaped by experience [Weinberger, 1993, Merzenich et al., 1996, Katz and Shatz, 1996, Gilbert, 1998, Buonomano and Merzenich, 1998, Edeline, 1999]. Extensive behavioral training on discrimination tasks that engage a limited region of the sensory epithelium increases the number of cortical neurons that respond to task-dependent stimuli [Jenkins et al., 1990, Recanzone et al., 1992, Recanzone et al., 1993]. The correlation between cortical map reorganization and practice-induced improvement in individual animals suggests that cortical plasticity contributes significantly to perceptual learning. These and related experiments in humans clearly demonstrate that cortical networks are continually optimized to meet changing behavioral needs [Karni and Bertini, 1997].

A more detailed understanding of how sensory experience leads to different forms of cortical reorganization will have important theoretical and clinical implications. Although the cellular and synaptic mechanisms that underlie neural plasticity have been extensively studied, the operating principles that allow networks of millions of neurons to organize themselves and generate useful behavior remain poorly defined [Buonomano and Merzenich, 1998]. A better understanding of how specific input patterns control network organization is needed to clarify how synaptic plasticity mechanisms contribute to learning in large populations of neurons. New insight into the relationship between sensory experience and cortical reorganization will prove useful in the design of therapies to enhance recovery from brain injury or damage to peripheral structures.

Cholinergic Contribution to Cortical Plasticity

Recanzone and colleagues elegantly demonstrated that passive sensory stimulation is insufficient to generate lasting cortical reorganization [Recanzone et al., 1992, Recanzone et al., 1993]. With repeated exposure, behaviorally meaningful stimuli are able to reshape both the topography and selectivity of cortical neurons. Several lines of evidence suggest that cholinergic neurons in nucleus basalis (NB)

contribute to cortical plasticity by marking which sensory events are behaviorally important and initiating plasticity mechanisms to sharpen their cortical representation [Hasselmo, 1995].

NB neurons receive their inputs from the amygdala and other limbic structures and project diffusely from the basal forebrain to the entire cerebral cortex [Mesulam et al., 1983] (Figure 1). Lesions of NB disrupt both cortical map plasticity and learning [Juliano et al., 1991, Webster et al., 1991, McGaughy et al., 2000]. Recordings in awake animals have shown that NB neurons 1) respond vigorously to both aversive and rewarding stimuli, 2) learn to respond to stimuli that predict rewards, and 3) habituate when animals become satiated [Richardson and DeLong, 1991]. Finally, pairing a tone with electrical activation of NB causes cortical neurons to increase their response to the paired stimulus [Hars et al., 1993, Bakin and Weinberger, 1996, Bjordahl et al., 1998, Kilgard and Merzenich, 1998a].

In this brief review, we summarize published work and report unpublished findings from experiments that employ chronic NB stimulation to investigate how experience shapes cortical plasticity. These results suggest that specific features of the acoustic environment systematically alter cortical response properties. In the first half, we will review how different classes of tonal stimuli paired with identical NB activation lead to very different forms of receptive field plasticity. In the second half, we will describe recent experiments that indicate that temporal response properties of cortical neurons are controlled by spectral features of acoustic stimuli.

Methods and Materials

Many of the experiments described in this review have been published elsewhere and the methods are explained in detail in those publications (e.g. [Kilgard et al., (In Press), Kilgard and Merzenich, 1998a, Kilgard and Merzenich, 1998b, Kilgard and Merzenich, 1999]). Previously unpublished electrophysiological results were obtained using the same methodologies and equipment, and are described only briefly below.

To stimulate cortical plasticity, bipolar electrodes were permanently implanted into NB of adult rats using sterile stereotaxic techniques. Brief pulses of current delivery have been shown to activate these neurons and trigger release of acetylcholine in the cerebral cortex [Jimenez-Capdeville et al., 1997]. After recovery, acoustic stimuli were paired with NB activation several hundred times per day for one

month. The efficacy of NB activation was monitored daily in every animal by quantifying NB-induced EEG desynchronization during slow wave sleep. Acoustic and electrical stimuli did not evoke any observable behavioral responses (i.e. did not cause rats to stop grooming, or awaken, if sleeping).

Twenty-four hours after the last pairing session, rats were barbiturate anesthetized and responses from the primary auditory cortex were quantified in detail using standard microelectrode mapping techniques. The distributed cortical response was assembled from data collected from up to 70 recording sites. To document how acoustic experience alters information processing in the auditory cortex, we compare responses from groups of rats that differ only in the acoustic stimuli that were associated with identical NB activation. Cortical responses are also compared with responses from experimentally naïve rats.

Responses to pure tones (as a function of frequency and intensity), tone trains (as a function of repetition rate), and spectral gratings, or “ripples” (as a function of ripple density and phase) were compared between groups of animals that had each heard one (or a small subset) of these sounds repeatedly associated with NB activation. Ripples are broadband sounds with a sinusoidal power spectrum. The density of a ripple is proportional to the number of spectral peaks. Shifting the phase of a ripple by 180 degrees inverts the power spectrum such that all the peaks become valleys. The intensity difference between the spectral peaks and valleys for all the ripples used in this study were 40dB. Ripple stimuli were constructed from 310 tones separated by 100Hz (1-32 kHz, random phase).

Sensory Experience Directs Receptive Field Plasticity

Learning-induced map reorganizations in both the somatosensory and auditory cortex are specific to the region of the sensory epithelium engaged during training [Bakin and Weinberger, 1990, Recanzone et al., 1992, Recanzone et al., 1993, Ohl and Scheich, 1996]. These results demonstrate that the observed cortical plasticity is task dependent, but do not indicate to what extent this plasticity is controlled by sensory experience and to what extent it is controlled by other task-related factors (e.g. selective attention).

To determine whether similar plasticity effects could be generated in the absence of a behavioral task, cortical maps were reconstructed in rats that received identical NB stimulation paired with a 4, 9, or 19 kHz tone several hundred times per day for a month. The resulting reorganizations of the frequency map in primary auditory cortex were specific to the paired tone frequency [Kilgard and Merzenich,

1998a]. This result indicates that enduring and large-scale cortical reorganization can result from passive hearing given sufficient activation of NB neurons.

Learning-induced cortical plasticity in primates can lead to increased or decreased receptive field size depending upon the nature of the task. Extensive practice at a modulation rate discrimination task, for example, caused receptive fields to expand, while practice on a frequency discrimination task caused receptive fields to contract [Recanzone et al., 1992, Recanzone et al., 1993]. To determine whether the differences in sensory parameters alone could account for the opposite forms of receptive field plasticity, two groups of rats received NB stimulation paired with acoustic stimuli designed to mimic the patterns of input that occurred during the two operant discrimination tasks. Pairing NB stimulation with a 9 kHz tone that was rapidly modulated generated receptive field expansion (Figure 2c&d), while pairing two different frequency tones in random order resulted in receptive field contraction [Kilgard and Merzenich, 1998a]. Both of these experiments also generated cortical map reorganizations that parallel practice-induced plasticity in primates. The observation that NB- and learning-induced plasticity effects were nearly identical in both the direction and scale of receptive field reorganization confirms that given sufficient NB activity cortical plasticity is determined by specific parameters of the sensory environment.

After confirming that the form of plasticity resulting from NB activation parallels natural learning, we systematically varied both the tone repetition rate and the number of carrier frequencies to determine how these acoustic parameters contribute to changes in receptive field size. Cortical responses were reconstructed from 34 rats (>1,700 recording sites) that each heard one of seven sets of tonal stimuli. The analysis revealed that receptive field size consistently increased as repetition rate was increased and decreased when the number of carrier frequencies was increased [Kilgard et al., (In Press)]. These results indicate that systematic rules operate in the cerebral cortex to transform sensory experience into changes in receptive field structure.

Spectral Features Direct Temporal Plasticity

Response Latency. To understand how the cortex learns more complex sounds, such as speech, it is important to document how experience alters the cortical representation of both broadband and time-varying stimuli. The spectral ripple (or “acoustic grating”) is a spectrally complex sound that shares some features in common with human vowels sounds and can be easily varied to examine cortical selectivity within this stimulus class [Schreiner and Calhoun, 1994, Shamma et al., 1995, Versnel and Shamma, 1998, Calhoun and Schreiner, 1998]. Five rats were exposed to a 50dB ripple with a sinusoidal power spectrum (1-32kHz bandwidth with a spectral peak every 6 kHz) paired with NB stimulation [Pandya et al., 2000]. In addition to narrowing A1 tuning curves (Table 1), this stimulus *decreased* the minimum latency of the cortical response to the ripple, while it *increased* the minimum latency in response to tones (compared to naïve controls). Although there was no change in the average strength of response to the paired ripple or any shift in the ripple transfer function (see [Schreiner and Calhoun, 1994]), there was a significant *decrease* in the strength of response to tones. Thus, rather than increasing the number of spikes evoked by the ripple stimulus, the NB-induced cortical reorganization combined a general decrease in the response of cortical neurons to tones with a faster response to the ripple. This relative increase in the response to ripples compared to tones bears some similarity to the timbre-specific enhancement of cortical evoked responses observed in musicians [Pantev et al., 1998, Pantev et al., 2001].

Responses to ripples of various densities and phases, including the paired ripple, were recorded to quantify the expected increase in cortical selectivity for ripple stimuli. Although pairing did not significantly alter the cortical selectivity for ripple density, it did have a profound effect on ripple phase sensitivity. Neurons are defined as phase sensitive if they respond with significantly more spikes to their preferred phase compared to the 180 degree shifted ripple. Forty-four percent of A1 neurons in naïve rats exhibited phase sensitive responses to ripples with a density of one cycle per 6 kHz. After pairing, only half as many A1 neurons (22%) were phase sensitive at this density. Phase sensitivity at all other densities (one cycle per 1.5, 3, 6, 12, 24, and 48 kHz) was unaffected. While unexpected, this result

supports the need for a systematic exploration of the cortical learning rules that operate on complex acoustic stimuli. The decrease in phase sensitivity specifically for ripples with a density of one cycles per 6 kHz may be related to perceptual generalization [Kuhl, 1999, Guenther et al., 1999, Tremblay et al., 1997]. Additional experiments are needed to evaluate this hypothesis.

Cortical Following Rate. Cortical neurons generally do not respond to individual stimuli presented at rates faster than 12 Hz [Phillips et al., 1989, Eggermont, 1994, Brosch and Schreiner, 1997, Kilgard and Merzenich, 1999]. We have used NB stimulation to determine 1) whether temporal properties of cortical neurons can be altered by sensory experience, and 2) what stimulus features influence the development of temporal plasticity.

Specifically, we tested whether the maximum cortical following rate could be increased by pairing NB activation with tones modulated at 15 Hz. Pairing 9 kHz tone trains did not significantly alter the maximum following rate, despite dramatic receptive field plasticity (Figure 2). In striking contrast, the maximum following rate was increased when NB stimulation was paired with 15 Hz tone trains whose carrier frequency was randomly selected (Figure 3) [Kilgard et al., (In Press)]. This result indicates that the temporal coding strategy used by the cortex is shaped by *spectral* features of the acoustic stimulus. It appears that the cortex adopts a map expansion strategy to improve the neural representation of the stimulus if tone frequency is constant, and changes its temporal characteristics only when this strategy is unavailable. The specificity of the temporal plasticity was established in two additional experiments in which 5 and 7.5 Hz trains of random carrier frequency lead to a decreased cortical following rate [Kilgard and Merzenich, 1998b]. Collectively, these experiments demonstrate that the maximum cortical following rate can be increased or decreased depending on both temporal and spectral features of the acoustic experience associated with NB activity.

Clinical and Theoretical Implications

A better understanding of the plasticity mechanisms that control the cortical response to repeated sounds may shed new light on conditions such as dyslexia and schizophrenia where the response of cortical neurons to repeated stimuli are abnormal [Nagarajan et al., 1999, Tallal et al., 1998, Cadenhead et al., 2000]. New insight into the relationship between sensory experience and cortical reorganization will prove useful in the design of neuroscience-based rehabilitative therapies to enhance recovery from brain injury or damage to peripheral structures. Some of these insights have already proven useful in designing treatments for children with language-related learning impairments, for individuals suffering from focal hand dystonia, and stroke [Tallal et al., 1998, Wright et al., 2000, Byl and McKenzie, 2000, Nudo and Friel, 1999, Johansson, 2000]. Application of neuroscience-based principles derived from studies of experience-dependent plasticity will be integral in the design of new treatments for tinnitus [Moller, 2000], hearing impairment [Irvine, 2000], and deafness [Klinke et al., 1999].

A more detailed understanding of how specific sensory experiences lead to different forms of cortical reorganization will have also important implications for contemporary theories of neural information processing and learning. Although Hebb's rule and its variants explain experimental findings that correlated spiking of pre- and postsynaptic neurons can result in strengthening or weakening of synaptic connections [Bi and Poo, 2001], they do not specify the behavior of networks composed of thousands to millions of neurons. A comprehensive knowledge of how specific input patterns control network organization and dynamics is needed to clarify how synaptic plasticity mechanisms contribute to learning in large populations of neurons (e.g. [Buonomano and Merzenich, 1995, Markram et al., 1998]). Ongoing studies of experience-dependent cortical plasticity will help to specify the role of sensory experience in refining the distributed cortical response to novel stimuli.

Concluding Remarks

Cortical plasticity appears to be responsible for improvement in a variety of behavioral skills, maintenance of precise sensory representations, compensation for sensory impairments, and recovery from central nervous system damage [Merzenich et al., 1996, King et al., 2000, Rajan and Irvine, 1998, Rauschecker, 1999]. Electrical stimulation of the cholinergic projection to the cortex is sufficient to trigger substantial plasticity in primary auditory cortex. By pairing several classes of sounds with NB stimulation we have shown that acoustic parameters guide both spectral and temporal plasticity. The systematic changes in cortical responses as a function of these acoustic parameters suggest that network-level rules operate in the cortex to transform sensory experience into specific changes in cortical organization. Although the method used to stimulate cortical plasticity in these studies was unnatural, NB-induced plasticity parallels natural learning in both cats and monkeys [Merzenich et al., 1990, Keeling et al., 1994]. Further clarification of the principles that shape experience-dependent cortical plasticity is likely to lead to the development of novel treatments for both neurological and psychiatric disorders. Ongoing experiments with spectrotemporally complex stimuli, including speech, are designed to reveal how cortical neurons learn natural sounds [Kilgard et al., 1999, Moucha et al., 2001, Kraus, 1999].

Table 1. Experience with Spectral Ripples Shapes Cortical Responses

	Naïve Controls	After Pairing NB + Ripple	P-Value
Ripple Latency (at paired density and phase)	13.3 ms	12.6 ms	< 0.05
Tone Latency	14.4 ms	15.7 ms	< 0.001
Ripple Response (at paired density and phase)	1.38 spikes	1.22 spikes	N.S.
Tone Response	1.71 spikes	1.47 spikes	< 0.0005
TC Bandwidth * (20dB above threshold)	1.53 octaves	1.30 octaves	< 0.0005
Phase sensitive (at trained density)	44%	22 %	< 0.01

Comparison of primary auditory cortex (A1) responses to tones and ripples. Tone response parameters (minimum response latency, strength of response, and tuning curve bandwidth) were compared between “naïve” controls (n=8 rats; 274 A1 sites) and animals (n=5 rats; 203 A1 sites) that heard a ripple paired with NB activation. Ripple response parameters (minimum response latency, strength of response, and phase sensitivity) were compared between “naïve” controls (n=4 rats; 104 A1 sites) and animals (n=5 rats; 203 A1 sites) that heard a ripple paired with NB activation. P-values are derived from two-tailed t-tests. * Ripple discrimination training in cats also led to narrowing of tuning curves [Keeling et al., 1994].

Figure Legends:

Figure 1. Schematic diagram of the projections to the cerebral cortex, reticular thalamus, and amygdala from the cholinergic nucleus basalis (NB) located in the basal forebrain.

Figure 2. Topographic organization of tone frequency preference in rat primary auditory cortex. A&B) Example of normal organization in naïve animals. C&D) Example of the map reorganization and receptive field plasticity following four weeks of NB stimulation paired with 9 kHz tone trains. Each polygon represents one microelectrode penetration. The color indicates the best frequency for each site. The region of the map that responds selectively to 9 kHz is indicated by white hatching. Scale bar = 0.25 mm. B&D) Every A1 receptive field is shown to illustrate the increased receptive field size and shift toward 9 kHz in the experimental group. Each line indicates the width of each receptive field 10dB above threshold. The color dots represent the best frequency at each site. Receptive fields that include 9 kHz are colored in red. Adapted from “Cortical Map Reorganization Enabled by Nucleus Basalis Activity” (p. 1715) by M. P. Kilgard and M. M. Merzenich, 1998, *Science*, 279, 1714-1718.

Figure 3. Temporal plasticity is sensitive to the spectral characteristics of the auditory stimulus. Pairing 15 Hz trains of 9 kHz tones with NB activation did not increase the maximum cortical following rate. In contrast, pairing 15 Hz tones trains of random carrier frequency led to an increased response to repetition rates above 10 Hz compared to controls (* = $p < 0.01$). All six tones within each tone train were the same, but the carrier frequency varied from train to train. Responses were normalized by dividing by the number of spikes to the first tone. The mean best repetition rate in controls was $6.7 \pm .4$ Hz. After pairing NB activation with 15 Hz train, the mean best repetition rate was $7.4 \pm .3$ Hz for 9 kHz trains (not significantly different from naïve controls), and $9.1 \pm .5$ Hz for trains with random carrier frequency ($p < 0.001$). Adapted from “Sensory Input Directs Spatial and Temporal Plasticity in Primary Auditory Cortex” by M. P. Kilgard, et al. *Journal of Neurophysiology* (in press).

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