

Cortical network reorganization guided by sensory input features

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Abstract. Sensory experience alters the functional organization of cortical networks. Previous studies using behavioral training motivated by aversive or rewarding stimuli have demonstrated that cortical plasticity is specific to salient inputs in the sensory environment. Sensory experience associated with electrical activation of the basal forebrain (BasF) generates similar input specific plasticity. By directly engaging plasticity mechanisms and avoiding extensive behavioral training, BasF stimulation makes it possible to efficiently explore how specific sensory features contribute to cortical plasticity. This review summarizes our observations that cortical networks employ a variety of strategies to improve the representation of the sensory environment. Different combinations of receptive-field, temporal, and spectro-temporal plasticity were generated in primary auditory cortex neurons depending on the pitch, modulation rate, and order of sounds paired with BasF stimulation. Simple tones led to map expansion, while modulated tones altered the maximum cortical following rate. Exposure to complex acoustic sequences led to the development of combination-sensitive responses. This remodeling of cortical response characteristics may reflect changes in intrinsic cellular mechanisms, synaptic efficacy, and local neuronal connectivity. The intricate relationship between the pattern of sensory activation and cortical plasticity suggests that network-level rules alter the functional organization of the cortex to generate the most behaviorally useful representation of the sensory environment.

1 Introduction

The most important function of nervous systems is to learn and adapt to novel situations. Understanding how networks of neurons self-organize in response to chang-

ing environmental demands remains one of the greatest challenges in contemporary neuroscience. Studies in invertebrates have established that relatively sophisticated behavior (including associative memory) can be implemented using simple synaptic plasticity rules (Glanzman 1995). However, the operating principles that allow networks of millions of neurons to restructure themselves to facilitate complex and adaptive behaviors remain poorly defined (Buonomano and Merzenich 1998a).

Experiments in mammalian sensory cortex have shown that large populations of neurons can be substantially reorganized when required to learn novel stimuli and adapt to changing situations. The expression and implementation of this representational plasticity depends on the statistics of specific input patterns and the context in which the information is experienced. Functional reorganization of the cortex could result from any combination of cell intrinsic (i.e., spike initiation threshold, oscillatory ionic conductances), synaptic [i.e., long-term potentiation (LTP) or depression (LTD), paired-pulse facilitation (PPF) or depression (PPD)], or circuit (i.e., local connectivity) changes. Understanding how learning rules at each of these three levels interact to give rise to behaviorally useful plasticity will require a concerted effort by experimentalists, theoreticians, and modelers.

In the following brief report, we summarize our finding that manipulation of sensory experience results in systematic changes in the functional organization of adult primary auditory cortex (A1). For the purpose of this review, acoustic experience can be simply thought of as the spatial and temporal pattern of input delivered to the cortical network via topographically organized receptors on the cochlea. Electrical activation of an important neuromodulatory center was used to gate neural plasticity mechanisms in order to examine how different input patterns direct cortical plasticity in the absence of behavior. Our observations confirm and extend previous findings of cortical remodeling generated by behavioral training.

Differential sensory experience led to profound and systematic changes in (i) topographic organization of A1,

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(ii) receptive-field size (contraction or expansion), (iii) response latency (increase or decrease), (iv) maximum temporal following rate (increase or decrease), and (v) spectrotemporal sensitivity of A1 neurons. The systematic relationship between sensory features and cortical plasticity suggests that evolution has selected for a repertoire of synaptic, intrinsic, and network-level learning rules that give rise to the most appropriate cortical organization for any given environment.

Cortical plasticity has been documented using many different tasks, modalities, and species. The results of these studies have had a profound impact on how we view the brain. Unfortunately, direct comparisons of these results are complicated by the differences in parameters such as behavioral response, task difficulty, task goal, motivation, and duration of training. These important differences make it difficult to discern which parameters account for the different forms of cortical plasticity that have been reported.

One common finding of these studies is that cortical plasticity tends to be specific to the sensory stimuli encountered during training. Another important observation is that experience-dependent plasticity is gated by behavioral state, apparently as a function of the neuromodulatory influences on the cortex (Ahissar and Ahissar 1994; Ahissar and Hochstein 1993; Ahissar et al. 1992, 1998; Recanzone et al. 1992c, 1993). Direct experimental control of the ascending modulatory inputs which stimulate plasticity provides a way to efficiently explore how the structure and schedule of sensory input guides network reorganization without the uncontrolled variables often associated with behavioral training.

Activation of the cholinergic nucleus basalis, located in the basal forebrain (BasF), was used to gate cortical plasticity in each of the experiments described here. Using this technique, we have been able to generate distinct forms of cortical reorganization with only one independent variable: sensory experience. Systematic manipulation of sensory experience is easier in the auditory modality than in vision or somatosensation. Acoustic features such as tone frequency, variability, and modulation rate can also be compared with analogous stimulus dimensions in other modalities. For example, a train of constant-frequency tone pulses generates a pattern of activation in auditory cortex that is similar to the pattern of activation in somatosensory cortex in response to a series of taps presented at a constant skin location. Many of the sensory input patterns used in our studies were designed to mimic the stimuli experienced during perceptual learning paradigms previously shown to improve acuity or discrimination ability (Recanzone et al. 1992b, 1993).

2 Cholinergic modulation of experience-dependent plasticity as a global gating mechanism

Cholinergic input to the cerebral cortex from the BasF plays a significant role in learning and memory as evidenced by anatomical, neurophysiological, pharmacological, and lesion studies (Hasselmo 1995; Rasmusson

2000). BasF cholinergic neurons receive their inputs from the amygdala and other limbic structures, project to the entire cerebral cortex, and are thus uniquely suited to modulate learning and plasticity (Mesulam et al. 1983). These neurons respond to any arousing stimulus and can learn to respond to novel stimuli associated with either rewarding or aversive stimuli (Baxter and Chiba 1999; Everitt and Robbins 1997; Richardson and DeLong 1991; Sarter and Bruno 1997; Sarter et al. 2001). Lesion studies further support role of cholinergic modulation in inducing experience-dependent cortical plasticity. Even the robust topographic reorganizations that follow peripheral denervation and digit amputation can be blocked by BasF lesions (Juliano et al. 1991; Webster et al. 1991).

The cholinergic system has been shown to influence cellular excitability and receptive field plasticity in somatosensory (Baskerville et al. 1997; Sachdev et al. 1998; Tremblay et al. 1990; Verdier and Dykes 2001; Zhu and Waite 1998), visual (Bear and Singer 1986; Sillito and Kemp 1983), olfactory (Saar et al. 2001), and auditory (Bakin and Weinberger 1996; Kilgard and Merzenich 1998a,b; Kilgard et al. 2001a,b; Mercado et al. 2001a) modalities. Plasticity of unit discharges in the cortex is dependent upon the activation of muscarinic receptors (Bandrowski et al. 2001; Metherate and Ashe 1991; Miasnikov et al. 2001) which suppresses intracortical synaptic activity and enhances thalamocortical inputs (Gil et al. 1997; Hsieh et al. 2000). Several studies using short-term conditioning procedures have documented that pairing BasF stimulation with sensory input causes facilitated cortical responses to the paired stimulus and shifts in neural tuning (Bakin and Weinberger 1996; Bjordahl et al. 1998; Edeline et al. 1994a,b; Metherate and Ashe 1991, 1993). Collectively, these studies indicate that acetylcholine regulates local plasticity mechanisms to generate functional reorganization of cortical networks.

3 Experimental approach and methodology

In perceptual learning experiments, extensive training (often thousands of trials) is usually required to improve discrimination ability and perceptual acuity (Ahissar 2001; Goldstone 1998). Our plasticity experiments were designed to mimic the time course of perceptual learning. Electrical stimulation of the BasF was paired with the presentation of an auditory stimulus hundreds of times each day for a month in adult rats implanted with a chronic stimulating electrode. Stimulation was nonaversive, and animals were unrestrained and unanesthetized during all pairing sessions. After thousands of BasF–acoustic stimulus pairings, a detailed map of multiunit response properties is reconstructed from up to one hundred microelectrode penetrations in A1 from each animal. Tuning curves were derived at each site from the responses to pure tones (as a function of frequency and intensity). In a series of experiments exploring the potential for temporal plasticity, repetition-rate transfer functions were also determined at each site by recording cortical responses to tones trains presented at various rates. In the experiments on cortical coding of complex

acoustic sequences, we quantified the response to fifteen variations of the sequence paired with BasF stimulation. In all of these experiments, responses from groups of animals that heard different sounds paired with BasF stimulation were compared with one another and with naïve rats. Because identical stimulation parameters were used in every experiment, each experimental group differed only in their acoustic exposure. Therefore, we can attribute differences in cortical selectivity to experience-dependent plasticity. More detailed descriptions of the experimental techniques (such as chronic implantation, stimulus generation, and recording techniques) can be found in previous publications (Kilgard and Merzenich 1998a,b; Kilgard et al. 2001a,b).

4 Features of sensory input direct receptive-field size and structure

In the auditory system, receptive fields are described by tuning curves that quantify neural selectivity for tones over a limited range of frequency and intensity. Several investigators have demonstrated that these receptive fields can be altered by learning (Recanzone 2000; Scheich et al. 1997; Weinberger 1995). Receptive fields were increased by some tasks, and decreased by others. These opposite effects on receptive-field size may have been caused by differences in the sensory stimuli used in the studies. One goal of our studies was to determine what acoustic features, if any, could be manipulated to significantly increase or decrease frequency selectivity of A1 neurons.

In our first set of experiments on receptive-field plasticity, the sensory input was distributed across the receptor surface (i.e., spatially variable) to simulate the effects of training on a frequency discrimination task (Recanzone et al. 1993). Five animals heard two different randomly interleaved tones several hundred times per day paired with BasF activation, while another group of five animals heard seven randomly interleaved tones on the same schedule paired with the same BasF activation. In the second set of experiments, the temporally modulated tones with a fixed carrier frequency (i.e., spatially invariant) were paired with BasF stimulation to simulate the effects of training on a modulation rate task (Recanzone et al. 1992a). Four animals heard a train of 9-kHz tones presented at 15 Hz paired with BasF activation. These experiments generated opposite changes in receptive-field size (Kilgard and Merzenich 1998a; Kilgard et al. 2001a). As in monkeys trained on a frequency discrimination task, spatially variable stimuli caused receptive fields in rat A1 to contract by 25% compared to naïve controls (Fig. 1, arrow a). In contrast, rat A1 receptive fields were increased by 60% when temporally modulated, but spatially invariant tones were paired with BasF stimulation, just like in monkeys trained on an analogous task (Kilgard et al. 2001a) (Fig. 1, arrow c).

When a single unmodulated tone was used as the daily conditioning stimulus, significantly less receptive-field broadening (20%) was observed (Fig. 1, arrow d). Interestingly, this broadening of the excitatory receptive field was prevented when two unpaired background

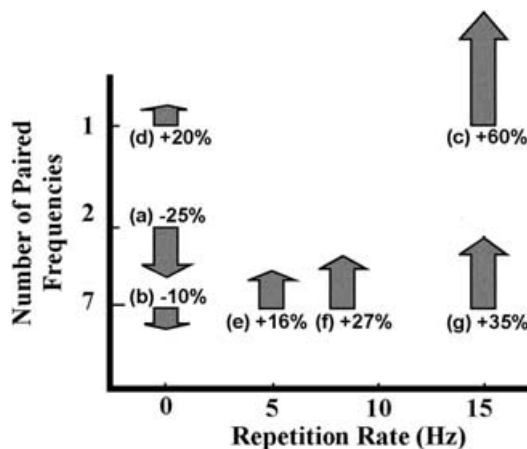


Fig. 1. Receptive-field size is systematically related to spectral and temporal acoustic features that co-occur with basal forebrain (BasF) stimulation. This schematic shows the relationship between the degree of receptive-field expansion or contraction and the acoustic features of carrier-frequency variability and repetition rate. This summary represents data from a total of 43 experimental rats and over 2100 cortical recording sites. Each arrow represents a different experimental group: *upward arrows* indicate receptive-field expansion, while *downward arrows* indicate contraction. The length of each arrow is proportional to the observed receptive-field plasticity. The percentage difference between each experimental group and the mean bandwidth (at 10 dB above threshold) in controls is indicated by each arrow. In agreement with training-induced plasticity in monkeys, receptive-field size is increased by stimuli with a high degree of temporal modulation and little spatial (spectral) variability (c) and reduced by stimuli with more spatial variability and no temporal modulation (a, b). Intermediate receptive-field plasticity was generated by stimuli that combined these features [i.e., a single, unmodulated tone (d) or modulated tones of different frequencies (e–g)]. Adapted from Kilgard et al. (2001a)

tones of different frequency were randomly interleaved with the paired tone (see Fig. 3 of Kilgard et al. 2001a). This finding demonstrates that environmental context and competition play an important role in shaping receptive-field size (Moucha et al. 2001).

Few stimuli encountered in natural environments are either spatially invariant or perfectly repetitive – natural sensory inputs are more likely to be both spatially and temporally modulated. Spectrally diverse tone trains modulated at 5, 7.5, or 15 Hz in three separate groups of rats (Kilgard and Merzenich 1998b; Kilgard et al. 2001a) generated receptive-field expansion that was clearly influenced by repetition rate (Fig. 1, arrows e–g). This result supports our working model that receptive-field size is systematically determined by both temporal and spatial modulation. As repetition rate approaches zero, this stimulus set would be equivalent to the unmodulated tones of different carrier frequency which decreased receptive-field size (Fig. 1, arrow b).

Our finding that receptive-field plasticity is a systematic function of spatial and temporal input statistics suggests that cortical plasticity mechanisms may be designed to make trade-offs between spatial and temporal precision in order to optimize information processing of behaviorally important stimuli. The summary schematic in Fig. 1 relates the magnitude and direction of receptive-field plasticity with the acoustic features of tone frequency variability and repetition rate.

We have also begun to probe how experience with broadband sounds alters receptive-field size and structure. To accomplish this objective, we paired BasF stimulation and a sound with a sinusoidal power spectrum. This ‘ripple’ stimulus is analogous to a visual grating, which elicits a complex spatial activation pattern on the peripheral sensory receptor surface (Calhoun and Schreiner 1998; Schreiner and Calhoun 1994; Shamma et al. 1995). Despite its broadband nature, the ripple stimulus resulted in a narrowing of the mean receptive-field size compared to naïve controls (1.3 vs 1.53 octaves, $p < 0.0005$; Kilgard et al. 2001b).

Hebbian correlation-based learning rules are likely to play a critical role in the relationship between sensory experience and receptive-field size. When reinforced sensory inputs are distributed across the receptor surface (Fig. 1, arrows a and b), the different inputs may stimulate competition that results in sharper frequency tuning. In contrast, modulated spatially invariant inputs may generate more synchronous activity that results in decreased frequency selectivity (Fig. 1, arrow c). These input-specific alterations in receptive-field size likely involve changes in network connectivity, but changes in cellular excitability or synaptic dynamics may also be important. Collectively, these results confirm the hypothesis that receptive-field size is systematically related to temporal and spectral acoustic features that are associated with BasF activity. The finding that input characteristics alone can drive alterations of receptive-field properties independent of explicit knowledge of the task indicates that evolution may have shaped local plasticity rules to generate functional organization that is matched to sensory environments.

5 Topographic reorganization of primary auditory cortex

Sensory cortices for touch, vision, and audition all represent their sensory receptor surfaces using topographic maps (Kaas 1997). In A1, the organization is based on tonotopic coordinates arranged systematically as a (roughly logarithmic) function of frequency (Fig. 2A, B). A number of studies have demonstrated that these maps are not static in adults and can undergo progressive remodeling in an experience-dependent manner following certain types of sensory experience, behavioral training, or peripheral injury (Buonomano and Merzenich 1998a; Das 1997; Edeline 1999; Gilbert 1998; Kaas 2000; Merzenich and Jenkins 1993; Merzenich et al. 1990, 1996a; Recanzone et al. 1992b, 1993; Xerri et al. 1999). When electrical activation of the BasF is repeatedly paired with a specific tonal stimulus, A1 is reorganized such that the cortical zone responding to the paired tone is increased (Kilgard and Merzenich 1998a). This cortical-map reorganization induced by BasF stimulation is greater in magnitude than the expansion that results from behavioral training (Recanzone et al. 1993). An example of a topographic map reorganization after sensory experience with 9 kHz tone trains is shown in Fig. 2C and D. Pairing other tone frequencies (4 or 19 kHz) resulted in an expansion of the region of A1 responding to the paired

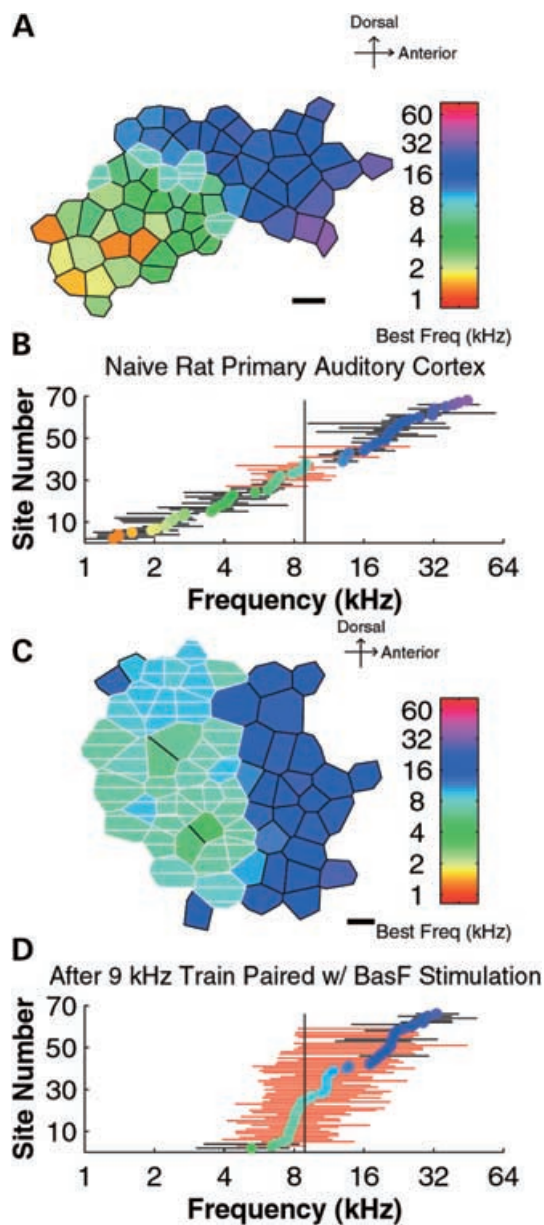


Fig. 2A–D. Topographic organization and reorganization of tone-frequency preference in rat primary auditory cortex. **A** Representative map from an experimentally naïve rat demonstrating the normal orderly progression of best frequency. **B** Every A1 receptive field for the naïve control rat in **A** is shown to illustrate the systematic progression of tone frequency and typical receptive-field sizes. **C** Representative map from one experimental rat of a frequency-specific map expansion following 4 weeks of sensory experience with 9-kHz tone trains modulated at 15 Hz paired with BasF activation. **D** Every A1 receptive-field site for the experimental rat in **C** is shown to illustrate the increased receptive-field size and shift toward 9 kHz in the experimental group. Each *polygon* in **A** and **C** represents one microelectrode penetration (scale bar = 0.25 mm). The color of each polygon indicates the best frequency in kilohertz. Sites with a best frequency within a third of an octave of 9 kHz are indicated by *white hatching*. In **B** and **D**, each *line* indicates the width of each receptive field 10 dB above threshold, and the *colored dots* represent the best frequency at each site. Tuning curves that include 9 kHz are colored red. Adapted from Kilgard and Merzenich (1998a)

tone. This finding is consistent with the regional specificity of behaviorally induced map reorganizations (Recanzone 2000; Xerri et al. 1994).

Despite considerable experimental and theoretical interest in receptive field plasticity and map reorganization as examples of the network consequences of Hebbian plasticity (Grajski and Merzenich 1990; Mercado et al. 2001b; Pearson et al. 1987), other forms of cortical plasticity are possible. Since most natural stimuli are spatiotemporally complex, studies that employ only the simplest sensory stimuli may underestimate the number of ways cortical networks can improve their representations of important sensory stimuli. For example, pairing BasF stimulation with a modulated, spatially invariant stimulus increased cortical response strength (measured in spikes per tone) that was not observed after pairing any of the other stimulus sets tested to date with the same BasF stimulation. It is not yet clear if the increased response strength was a consequence of map expansion coupled with decreased frequency selectivity or represents some independent plasticity mechanism. Understanding the functional integration of map reorganization with other forms of plasticity will provide a more complete view of neural mechanisms for perceptual learning and may offer significant new insights into the coding strategies used in sensory cortex.

6 Features of sensory input direct temporal plasticity

While spectral information is represented as a topographically organized place code, temporal information is coded in the firing pattern of A1 neurons. The observation that cortical topography can be substantially reorganized suggests that temporal response properties may also be altered by learning. This hypothesis is supported by psychophysical studies showing that temporal processing

ability improves with training (Merzenich et al. 1996b; Nagarajan et al. 1998; Wright et al. 1997). The neurobiological basis of these improvements is not yet clear (Buonomano and Karmarkar 2002). We have recently demonstrated that both the maximum following rate and response latency of A1 neurons can be altered by experience. Once again, the observed changes were specific to both spectral and temporal features of the paired sounds paired with BasF stimulation.

6.1 Plasticity of cortical following rate

A1 neurons typically do not respond to individual stimuli presented at rates greater than 12 Hz (Kilgard and Merzenich 1999). To determine whether the low-pass cutoff of A1 neurons can be changed, we measured the maximum following rate after pairing tones modulated at 15 Hz with BasF activation. The first attempt to generate temporal plasticity by pairing 9-kHz tones modulated at 15 Hz did not significantly alter the maximum cortical following rate (Kilgard et al. 2001a), despite the dramatic cortical map reorganization (Fig. 2C) and receptive-field broadening (Fig. 1, arrow c; Fig. 2D) described in Sects. 4 and 5. In an attempt to isolate temporal plasticity from map expansion, 15-Hz tone trains with seven different carrier frequencies were paired with BasF stimulation. Distributing the 15-Hz trains across A1 prevented map expansion and generated a substantial increase in the maximum cortical following rate (Kilgard and Merzenich 1998b; Fig. 3). Thus, it appears that the cortex adopts a map-expansion strategy (as in Fig. 2C) to better code the stimulus if the tone frequency is constant, and changes its temporal following characteristics to better respond to the modulation common to both stimulus sets only when map expansion is unavailable.

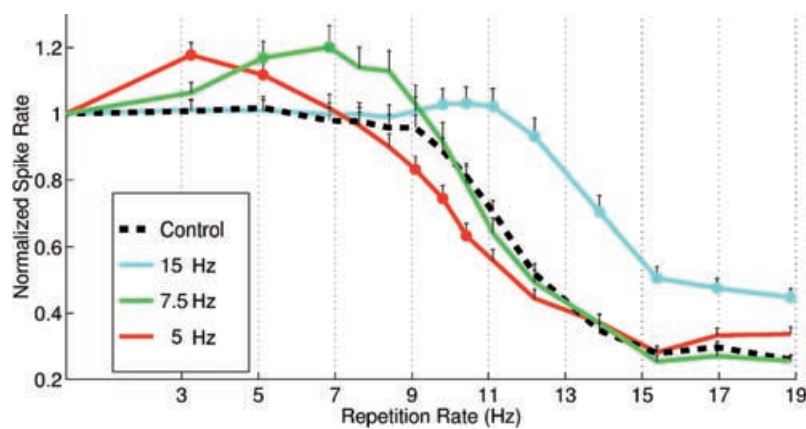


Fig. 3. Sensory experience can modify the cortical representation of time-varying information. The maximum cortical following rate can be increased or decreased depending on the repetition rate and spectral characteristics of the sensory input paired with BasF activation. The graph shows repetition-rate transfer functions for recordings from animals that received identical BasF stimulation paired with 5-, 7.5-, or 15-Hz tone trains of carrier frequencies that varied from train to train, and for recordings from naïve controls. The transfer function of each site was normalized using the number of

spikes evoked by the first tone in each train. These data were collected from a total of 15 rats and over 500 cortical recording sites. Error bars indicate standard error. The rates that were significantly different from controls are marked with dots (one-way ANOVA, Fischer's projected least-significant difference, $p < 0.05$). Plasticity of the cortical following rate was not observed when the carrier frequency was not varied (data not shown). Adapted from Kilgard and Merzenich (1998b)

Cellular plasticity studies provide a potential mechanistic explanation for the lack of temporal plasticity when carrier frequency was constant. The development of LTP is often associated with increased PPD (Markram and Tsodyks 1996). If synapses are strengthened by increasing release probability, rapidly repeated stimuli lead to greater vesicle depletion (Tsodyks and Markram 1997). It is reasonable to expect that LTP is involved in the topographic remodeling and increased response strength that result from pairing 15-Hz tone trains with a 9-kHz carrier. If LTP is responsible for greater PPD which limits the maximum cortical following rate, the representational strategy adopted by cortical neurons may be determined by the mechanics of synaptic plasticity.

Atzori et al. (2001) have recently found two distinct populations of synaptic connections in acute slices of the auditory cortex. They found that strong connections were likely to exhibit PPD, while weak connections did not. Changes in the proportion of these weak and strong connections could account for the experience-driven changes in cortical following properties. Our observation that exposure to enriched acoustic environments increases response strength but decreases the maximum cortical following rate supports this interpretation (Engineer et al. 2001). Network models of the influence of NMDA on spatial and temporal tuning of thalamocortical circuits suggest that other explanations are also possible (Krukowski and Miller 2001).

To demonstrate that the changes in maximum following rate were specific to the repetition rate of the stimuli paired with BasF stimulation, two additional groups of rats were exposed to 5- and 7.5-Hz trains of random carrier frequency paired with identical BasF activation. These experiments confirmed that the maximum cortical following rate could be increased or decreased depending on the modulation rate paired with BasF activation (Kilgard and Merzenich 1998b; Fig. 3).

6.2 Experience-dependent changes in response latency

Spectral and temporal features in the sensory environment also shape the latency of A1 responses (Recanzone et al. 1992c, 1993). Pairing a slow train of tones with multiple carrier frequencies increased the average onset latency of A1 neurons by more than a millisecond, while pairing a single tone frequency with BasF stimulation (singly or in 15-Hz trains) decreased onset latencies by nearly a millisecond (Kilgard et al. 2001a). Both of these sets of acoustic stimuli significantly delayed the end of the cortical response. Pairing seven different unmodulated tones with BasF stimulation sharpened the population discharge synchronization by increasing onset latency, while decreasing the time to the end of the cortical response. Like the receptive-field and following-rate plasticity described in Sect. 4 and 6.1, changes in the response latency were systematically related to stimulus features, and no changes in response latency were observed when the sounds paired with BasF stimulation were intermediate between stimuli that had opposite latency effects. For example, while a single tone decreased

and seven tones increased onset latency, pairing two different tones had no effect on onset latency. Previous studies have shown that onset latency is correlated with maximum following rate in experimentally naïve animals (Brosch and Schreiner 1997; Kilgard and Merzenich 1999; Schreiner and Raggio 1996; Schreiner et al. 1997). Our finding that onset latency increased as the maximum following rate was decreased (by 5-Hz trains with multiple carrier frequencies) suggests this relationship is functionally important (Kilgard et al. 2001a). Onset latency was not significantly decreased when the maximum following rate was increased (by 15-Hz trains with multiple carrier frequencies), possibly due to the effect of tone frequency variability on onset latency.

When broadband stimuli were paired with BasF activation, the minimum latency of the cortical response to the paired ripple was decreased (12.6 vs 13.3 ms, $p < 0.05$) while the minimum latency in response to tones was increased (15.7 vs 14.4 ms, $p < 0.001$) compared to naïve controls (Kilgard et al. 2001b). Thus, response latencies to different classes of inputs can be differentially altered.

Long-term conditioning with a spectrotemporally complex acoustic sequence resulted in the largest effect on onset latency and response synchronization of any stimulus set paired with BasF stimulation (Kilgard and Merzenich 2002). We decided to examine how the cortex learns a rapid acoustic sequence composed of a high-frequency tone (12 kHz), a low-frequency tone (5 kHz), and a noise burst, because this sequence exhibits spectral transitions present in many natural sounds, but can be easily parameterized to probe the cortical representation and generalization to related stimuli. The average minimum response latency was decreased by 2 ms after conditioning and represents a 35% decrease in cortical processing time if the thalamic volley arrives ~8 ms after tone onset (11.5 vs 13.4 ms, $p < 0.0005$). The average time to peak response was also shortened (14.5 vs 18.2 ms, $p < 0.000001$). Thus, long-term conditioning with a tone–tone–noise sequence substantially increases the temporal coherence of the distributed cortical response. This finding parallels the increased cortical response coherence documented in owl monkey somatosensory cortex following extensive temporal discrimination training (Recanzone et al. 1992c). Cortical synchronization may provide an additional strategy for the nervous system to improve cortical representation of important stimuli. For example, changes in response latency influence the synchronization of cell assemblies involved in perceptual binding of behaviorally relevant features (Singer 1999; Sturm and König 2001). Computational studies implementing spike-timing-dependent plasticity may clarify the relationship between the maximum following rate, latency, and temporal coherence of cortical responses.

7 Development of spatiotemporal combination sensitivity

Spectrotemporal combination sensitivity is a potentially powerful method for representing the conjunction of

different stimulus features (Doupe and Kuhl 1999; Margoliash and Fortune 1992; Suga 1989). Although combination sensitivity is well studied in birds and bats, it is not yet clear whether other species use this method to represent spectrotemporally complex sounds. Short-term plasticity such as PPF combined with dynamic changes in the balance of excitation and inhibition are sufficient to create temporally selective neurons (Buonomano and Merzenich 1995, 1998b). For example, the response of A1 neurons to a tone presented as part of a rapid sequence is often quite different from the response to the same tone presented in isolation (Brosch and Schreiner 1997, 2000; Brosch et al. 1999; Kilgard and Merzenich 1999). Individual neurons in experimentally naïve animals can exhibit adaptation or facilitation depending on the spectral and temporal separation between two tones. To determine if A1 neurons can develop spectrotemporally selective responses to novel stimuli, we paired BasF stimulation with a complex acoustic sequence (high-frequency tone, low-frequency tone, and noise burst separated by 100 ms).

After long-term conditioning with this tone–tone–noise sequence, a large proportion of cortical neurons developed response facilitation that was specific to the order of sequence elements paired with BasF activation (Kilgard and Merzenich 2002). In naïve control animals, A1 neurons generally exhibited little if any facilitation in response to the low-frequency tone (5 kHz) when preceded by the high-frequency tone (12 kHz). In conditioned animals, five times as many A1 sites (25% vs 5%) responded with more spikes to the low tone when preceded by the high tone 100 ms earlier, compared to the response to the low tone alone. In addition, 58% of A1 sites exhibited significant response facilitation to the noise burst when preceded by the two tones, compared to only 35% of sites in naïve controls. Figure 4 gives a representative example of a site illustrating this type of context-dependent facilitation.

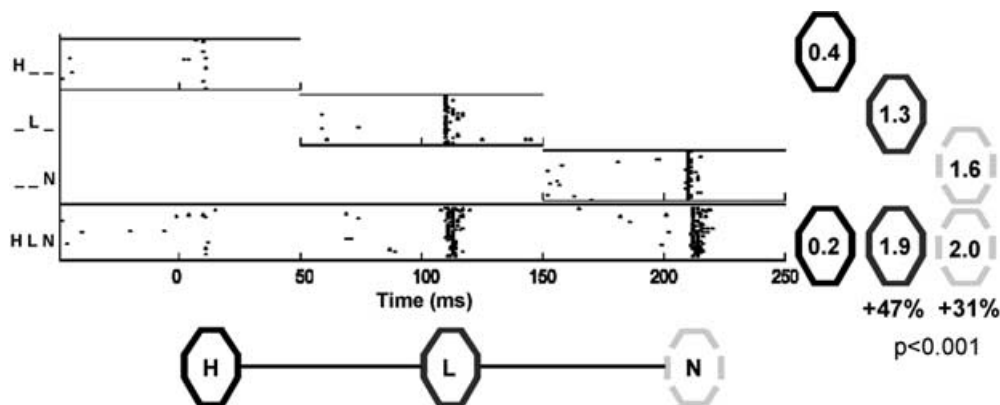


Fig. 4. Example of a cortical site that gave facilitated responses to sounds presented as a rapid series compared to the same sounds presented in isolation. This context-dependent facilitation (a form of combination sensitivity) was specific to the acoustic sequence (12 kHz, 5 kHz, and noise burst presented 100-ms apart) that had been repeatedly paired with BasF stimulation. Each *dot* represents a single spike in response to each sequence element presented in isolation (H, high-frequency tone; L, low-frequency tone; N, noise burst) or in

These results extend our previous work with simple stimuli to demonstrate that cortical networks are capable of using a variety of different strategies to improve the representation of sensory stimuli that co-occur with BasF activity. The nonlinear interactions observed in these neurons after experience with complex acoustic sequences indicates that experience-dependent plasticity can enhance the cortical representation of spectrotemporally complex sounds by creating neural filters which prefer particular spectrotemporal transitions. These filters could provide an efficient mechanism to represent the conjunction of stimulus features that specify the source and meaning of natural sounds.

8 Discussion

It has been known for 40 years that sensory experience modifies cortical circuitry (Hubel and Wiesel 1970; Wiesel and Hubel 1965). The last 10 years of research has led to a great increase in our understanding of the principles that govern plasticity between pairs of neurons. Despite these recent advances, it is far from clear how these local plasticity rules give rise to functional reorganization within large populations of neurons. Our BasF stimulation experiments indicate that spatial and temporal input characteristics shape the receptive-field structure, temporal processing, and spectrotemporal sensitivity of cortical neurons.

The finding that the relationship between sensory input and receptive-field size was so similar – whether plasticity was gated with BasF stimulation or behavioral training – suggests that learning rules exist at the network level to relate sensory experience and functional organization of the cortex. To bridge the gap between cellular- and systems-level studies of learning and memory, it will be necessary to explain how local plasticity rules interact to generate large-scale reorganiza-

sequence. The average number of spikes in response to each sound is shown on the right-hand side of the figure. The response to the low tone produced 47% more spikes when preceded by the high tone. The response to the noise burst was facilitated by 31% when preceded by both the high and low tone in the sequence. The facilitated responses to both the low tone and noise burst were highly significant (*t*-test, $p < 0.001$). The characteristic frequency of this site was 7.3 kHz. Adapted from Kilgard and Merzenich (2002)

tions that are behaviorally useful. Experience-dependent receptive-field expansion and contraction could result from (i) lowering or raising of spike thresholds, (ii) increased or decreased synaptic strength, or (iii) added or reduced number of connections. Cell intrinsic mechanisms (such as spike threshold) are unlikely to contribute to frequency-specific changes in A1 topography, which suggests that synaptic and circuit changes underlie the functional reorganization of cortical maps.

Although most studies of cortical plasticity have focused on map reorganization, our results indicate that temporal response properties are equally plastic. The maximum following rate of cortical neurons can be increased or decreased by exposure to fast or slow tone trains paired with BasF activation. The exact mechanisms that limit the maximum following rate of cortical neurons are not yet known. Oscillatory membrane conductances could play an important role in temporal information processing (Silva et al. 1991). PPD and PPF may also alter the maximum following rate of cortical neurons (Buonomano 2000). Finally, cortical following rate is influenced by dynamic cycles of excitation and inhibition (Kenmochi and Eggermont 1997). Although the average A1 repetition-rate transfer function is a simple low-pass filter, relatively few sites exhibit such a simple shape (Kilgard and Merzenich 1999). Most exhibit significant peaks and notches that may reflect the interactions of the stimulus repetition rate with cell intrinsic, local, or global oscillators. Our finding that A1 neurons are able to precisely adjust their maximum following rate indicates that the cellular mechanisms controlling temporal processing are highly regulated.

Our results support earlier behavioral findings that certain forms of training increase cortical response latency, while others decrease it. Increases in onset latency were observed after experience with slow tone trains paired with BasF stimulation, while a single tone rapidly modulated or unmodulated decreased onset latency. Such changes in the temporal coherence of the distributed cortical response as a function of acoustic experience supports a number of theories that spike timing carries important sensory information that may aid in perceptual binding. A decade ago most plasticity mechanisms were thought to be insensitive to millisecond-level timing information. Recent evidence indicates that spike timing plays a critical role in synaptic plasticity, and a few milliseconds can be the difference between LTP and LTD (Bi and Poo 1999; Feldman 2000; Markram and Tsodyks 1996; Yao and Dan 2001; Zhang et al. 1998). Computational studies have suggested that spike-timing-dependent plasticity may balance synaptic strengths within neural networks to make postsynaptic firing more irregular and more sensitive to presynaptic spike timing (Sjostrom et al. 2001; Song and Abbott 2001; Song et al. 2000). In addition, inputs acting in correlated groups are able to out-compete less correlated inputs and develop stronger synapses.

Natural stimuli often generate complex activation patterns distributed across the cortical surface. In many cases no single dimension is sufficient to determine the meaning of natural sounds. Speech perception provides

the clearest example of the important role feature relationships can play in stimulus categorization (Doupe and Kuhl 1999). Although humans can easily extract the statistical regularities found in speech, we do not yet understand how biological networks accomplish the task.

Our demonstration that neurons in primary sensory cortex can develop sensitivities to the spatial and temporal relationships of sensory events provides one potential mechanism for complex relational coding. This type of representational plasticity is considerably more complex to implement than map expansion or temporal plasticity. The development of combination-sensitive responses may require several forms of cellular plasticity, including changes in connectivity, synaptic dynamics, and cell intrinsic properties. Generating a robust representation of complex stimuli using local plasticity rules probably requires some form of global regulation, possibly involving competition based on spike timing. Our finding that exposure to complex spectrotemporal sequences generates both combination sensitivity and increased response coherence suggests that spike-timing-dependent mechanisms may play an important role in rewarding the coordinated activity of neural populations (i.e., cell assemblies).

The use of BasF stimulation to gate cortical plasticity has greatly facilitated our exploration of experience-dependent plasticity. BasF stimulation paired with different sensory stimulation generates plasticity that closely resembles the cortical reorganization resulting from behavioral training using similar stimuli. This finding supports the conclusion that cortical plasticity is determined by the statistics of the sensory input associated with sufficient BasF activation. The systematic relationship between sensory input and functional reorganization suggests that network-level rules govern the expression of local plasticity rules. Numerous additional experimental and theoretical studies are needed to clarify exactly how sensory experience guides plasticity mechanisms to alter the intrinsic properties, synaptic dynamics, and connectivity of individual neurons to generate behaviorally useful changes within large populations of neurons.

Two consequences of behavioral state that have not been specifically manipulated in our studies may also play important roles in guiding cortical plasticity. First, other neuromodulatory systems, including dopamine (Bao et al. 2001), serotonin (Stark and Scheich 1997), and norepinephrine (Manunta and Edeline 1998), may shape plasticity either by influencing the pattern of cortical activation directly or by changing the way that activity engages local plasticity mechanisms. Second, task-specific cognitive influences could alter the pattern of cortical activation or the expression of plasticity rules via top-down projections from 'higher' brain regions (Ahissar and Hochstein 1993; Suga et al. 2000).

Although Hebb's rule and its variants explain the experimental findings that correlated spiking of pre- and postsynaptic neurons can result in strengthening or weakening of synaptic connections (Bi and Poo 2001; Hebb 1949), they do not yet 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.

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