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PLASTICITY AND PERCEPTION IN PRIMARY AUDITORY CORTEX

By Hania Köver

DISSERTATION

**Submitted in partial satisfaction
of the requirements for the degree of**

DOCTOR OF PHILOSOPHY IN NEUROSCIENCE

**In the Graduate Division of the
University of California, Berkeley**

Committee in Charge:
Professor Shaowen Bao, Chair
Professor Frederic Theunissen
Professor Yang Dan
Professor Keith Johnson

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Abstract
Plasticity and Perception in Primary Auditory Cortex
by Hania Köver
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During an early epoch of development, the brain is highly adaptive to the stimulus environment. Repeatedly exposing young animals to a particular tone, for example, leads to an enlarged representation of that tone in primary auditory cortex. While the neural effects of simple, single-frequency tonal environments are well characterized, the principles that guide plasticity in complex tone environments, as well as the perceptual consequences of cortical plasticity, remain unclear. To address these questions, this dissertation documents the neural and perceptual effects of simple and complex manipulations to the early acoustic environment.

First, I show that rearing rat pups in a multi-tone environment leads to complex primary cortical representational changes that are related to the statistical relationships between experienced sounds. Specifically, tones that occur together within short temporal sequences tend to be represented by the same groups of neurons, whereas tones that occur separately are represented separately. This suggests that the development of primary auditory cortical response properties is sensitive to higher-order statistical relationships between sounds.

The observed neural changes are accompanied by perceptual changes. Discrimination ability for sounds that never occur together within temporal sequences is improved. Heightened perceptual sensitivity is correlated with heightened neuronal response contrasts. These results suggest that early experience-dependent neural changes can mediate perceptual changes that may be related to statistical learning.

Finally, I develop and experimentally test a model of the relationship between cortical sensory representations and perception. The model suggests that cortical stimulus representations may function as the neural representation of previously encountered stimulus probabilities, and makes predictions about how changes in these representations should affect perception within a statistical inference framework. Preliminary behavioral results support the model predictions, suggesting that one function of early experience-dependent plasticity may be to internalize stimulus distributions to shape future perception and behavior.

THIS THESIS IS DEDICATED TO MY PARENTS
INKE KÖVER AND MARCIN ZACHARIASIEWICZ

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Chapter 1

Introduction:

Sensory Representations and Perception

Sensory Coding and Perception

A central goal of systems neuroscience is to determine how sensory stimuli are represented and ultimately “perceived” by the brain. When we hear a sound, for example, the physical sound wave is transformed by the ear into a neural signal that propagates through the nervous system. In mammals, millions of neurons across multiple, hierarchically-organized sensory areas respond to a single stimulus, and at each stage of processing the stimulus is represented in different ways. Ultimately, the computations that occur are thought to allow us hear (“perceive”), identify, discriminate, locate or remember (the list goes on) a stimulus in question. *How* this occurs, namely the full set of principles underlying stimulus encoding and decoding, is still unclear.

In addition to the complexity of neuronal stimulus representations, they are not static: rather, they change dynamically across the lifespan in response to changing stimulus statistics, task demands, perceptual learning, and nervous system injury (Merzenich et al., 1983a; Merzenich et al., 1983b; Kaas et al., 1990; Recanzone et al., 1990; Allard et al., 1991; Recanzone et al., 1992b; Recanzone et al., 1993; Schoups et al., 2001; Zhang et al., 2001; Fritz et al., 2003; Polley et al., 2006). The ways in which stimulus representations can change are diverse: the number of neurons responding to a stimulus can increase (Recanzone et al., 1992a; Recanzone et al., 1993; Polley et al., 1999; Zhang et al., 2001; Han et al., 2007) or decrease (Logothetis et al., 1995; Kobatake et al., 1998; Polley et al., 1999; Miyashita and Hayashi, 2000; Ghose et al., 2002; Atiani et al., 2009); the strength of responses can change (Ghose, 2004; Atiani et al., 2009; Insanally et al., 2009); the timing of neural responses can be altered (Kilgard and Merzenich, 1998; Bao et al., 2004; Russo et al., 2005; Kim and Bao, 2009); and neuronal tuning curves can change shape (Recanzone et al., 1993; Schoups et al., 2001; Han et al., 2007). Interpretations of the functional relevance of these changes vary widely (Field, 1994; Weinberger, 2004; Bieszczad and Weinberger, 2010; Girshick et al., 2011; Reed et al., 2011), reflecting the lack of unifying framework as to the goals of sensory coding.

The Efficient Coding Hypothesis

Interpretations about the goals of sensory coding can be divided into two major groups. One approach, known as the efficient coding hypothesis (Barlow, 1961; Field, 1994; Barlow, 2001; Simoncelli, 2003; Singh and Theunissen, 2003), proposes that the goal of sensory coding is to represent the sensory world as efficiently as possible, and that this can be achieved by making use of patterns in the environment (Attneave, 1954; Barlow, 2001; Singh and Theunissen, 2003). Initially this idea was based on principles of information transmission, which emphasized that exploiting statistical regularities in a signal allowed for more economical representation and communication (Shannon, 1949; Barlow, 1961). It has since been recognized that economical transmission is only one of many concerns of the mammalian brain, and more recent formulations have focused on the perceptual and cognitive benefits of making environmental regularities explicit (Barlow, 2001).

The efficient coding hypothesis has been very successful in accounting for stimulus representations in early sensory areas. For example, receptive fields in early visual (Dan et al., 1996; Olshausen and Field, 1996; Schwartz and Simoncelli, 2001; Girshick et al., 2011) and auditory (Lewicki, 2002; Smith and Lewicki, 2006) areas are well matched to the statistics of natural images and sounds, respectively. In addition, neuronal firing properties across sensory systems appear to be optimized to efficiently represent stimulus statistics (Schwartz and Simoncelli, 2001; Niven et al., 2007). Despite these successes, a number of authors have pointed out that indiscriminately representing environmental stimuli regardless of their behavioral relevance may not be optimal, and that additional constraints may guide sensory coding (Machens et al., 2005; Salinas, 2006; Kim and Bao, 2009). On a broader level, very few studies have directly considered the perceptual consequences of stimulus representations that reflect environmental stimulus statistics. This dissertation addresses this problem from a theoretical (Chapter 3) and experimental (Chapters 2 and 4) perspective. My results suggest that representing environmental stimulus statistics may directly lead to adaptive perceptual changes.

Another outstanding question regarding efficient coding concerns the extent to which sensory representations are optimized for the environment on developmental, as opposed to evolutionary time scales. While peripheral coding strategies are often conserved across species and time (Lewicki, 2002; Neuhofer et al., 2008), cortical stimulus representations are highly plastic and can change to match the statistics of the environment. This is particularly true in an early “critical period,” when even passive exposure to stimuli drawn from different frequency distributions can result in long-lasting changes in stimulus representations (Blakemore and Cooper, 1970; Zhang et al., 2001; Han et al., 2007). Natural, biologically relevant stimuli contain complex structures such as temporal dependencies between stimuli (Singh and Theunissen, 2003), and it is not known to what extent these higher-order statistics affect sensory representations during the critical period. Chapter 2 addresses this question by looking at how complex auditory sequences affect the development of frequency representations in primary auditory cortex.

Decoding Sensory Representations

The efficient coding hypothesis focuses mainly on the *encoding* side of sensory processing, by asking how neurons can effectively represent the sensory environment. The second major approach to understanding sensory coding takes the reverse approach and asks how *decoding* sensory representations can result in advantageous behaviors and perception (Metzner and Juranek, 1997; Salinas, 2006; Wang, 2007). According to this view, sensory representations are optimized to solve perceptual tasks, and their variety and complexity is related to the range of tasks that need to be solved (Metzner and Juranek, 1997). For example, *discriminating* between two similar stimuli may require neurons with steep tuning curve slopes at relevant stimulus transitions (Seung and Sompolinsky, 1993; Schoups et al., 2001), (Butts and Goldman, 2006; Han et al., 2007; Navalpakkam and Itti, 2007) whereas *identifying* stimuli favors neurons tuned to the stimulus in question (Butts and Goldman, 2006). Likewise, rapidly firing neurons may

solve the task of faithfully representing sounds at the level of the auditory nerve, whereas temporally invariant representations may be better at representing abstract perceptual properties of sounds (Wang, 2007).

The decoding approach to sensory coding implicitly assumes that there could be as many encoding goals as there are tasks to solve, and the staggering variety of proposed coding strategies illustrates this point (Gilbert et al., 2001). Nevertheless, there is likely to be a common decoding strategy across sensory modalities and tasks, and discovering computationally and biologically plausible mechanisms has been the subject of much theoretical research (Seung and Sompolinsky, 1993; Jazayeri and Movshon, 2006; Rolls and Treves, 2010; Fischer and Pena, 2011; Girshick et al., 2011). A major outstanding question concerns which response parameters convey meaningful information: suggested candidates vary as widely as neuronal firing rates, spike timing, correlations between neurons and neuronal oscillations (Rolls and Treves, 2010). Additionally, authors disagree on whether perception is mediated by populations of neurons (Pouget et al., 2000), small efficient circuits (Reed et al., 2011), or even single cells (Britten et al., 1996; Houweling and Brecht, 2008). Finally, while many computational models of perception have been proposed, several authors have noted the importance of creating biologically plausible models that could actually be implemented by the brain (Jazayeri and Movshon, 2006).

In this dissertation, I focus on the idea that populations of neurons represent sensory stimuli through stimulus-dependent changes in firing rate. Chapter 3 explores how experience-dependent changes in such population representations might affect stimulus decoding. My theoretical (Chapter 3) and preliminary experimental results (Chapter 4) suggest that enlarged sensory representations may provide a neuronal mechanism for biasing perception towards previously experienced stimuli. While the model in its described form is based on a maximum-likelihood estimation algorithm, more recently several authors have proposed biologically plausible versions (Fischer and Pena, 2011; Girshick et al., 2011) that lead to similar conclusions.

A Synthesis

Sensory representations are likely optimized both for efficient encoding of environmental statistics and behaviorally advantageous decoding. In fact, in many cases these may actually be the same thing. Psychophysical studies in humans have shown that perception can often be described as optimal statistical inference, in the sense that it takes into account the distributions of previously encountered stimuli (Knill and Richards, 1996; Kersten, 1999; Ernst and Banks, 2002; Kording and Wolpert, 2004; Feldman et al., 2009). In young infants, the ability to internalize statistical patterns may play a critical role in learning adaptive behaviors, such as the ability to segment words from a continuous speech stream (Saffran et al., 1996), or to discriminate between phonemic units (Saffran et al., 1996).

Prior experience with stimuli can affect perception both on short-term scales, such as over the course of an experiment (Ernst and Banks, 2002; Kording and Wolpert, 2004), or on long-term scales, such as over the course of a lifetime (Feldman et al., 2009). As an example of the latter, native English speakers, but not native Japanese speakers, perceive an exaggerated difference between the speech sounds /la/ and /ra/, a phenomenon that can be attributed to differences in language-specific statistical distributions of these speech sounds (Feldman et al., 2009). On a broader level, it has been argued that all behaviors learned through associative learning require knowledge of statistical dependencies between sensory events and reinforcers (Barlow, 2001). Representations that make explicit these statistical relationships may therefore naturally lead to advantageous behaviors.

This dissertation explores the relationships between environmental stimulus statistics, sensory representations, and perception. Chapter 2 investigates the neuronal and perceptual effects of rearing young rat pups in complex acoustic environments with different higher-order statistics. The results add to the existing literature by showing that the developing rat auditory cortex is shaped by higher-order conditional probabilities of sounds in sequences. In addition, we find that perceptual discrimination behavior in adult rats is altered by the developmental sound exposure, indicating that encoding environmental stimulus statistics can have downstream perceptual decoding effects. With a few exceptions, most previous studies of efficient coding have not directly investigated such decoding effects, and so this Chapter makes a contribution to tying together the two different approaches to sensory coding.

Finally, Chapter 3 presents a decoding model that makes the theoretical prediction that enlarged stimulus representations should lead to perceptual biases towards over-represented stimuli. The preliminary results presented in Chapter 4 confirm the model predictions, suggesting that one function of experience-dependent plasticity may be to mediate perceptual biases towards previously encountered stimuli.

Together, my results contribute to our understanding of how the sensory environment affects neural tuning and perception, and offer new insights into the fundamental principles underlying sensory coding.

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Chapter 2

**Learning Higher-Order Stimulus Probabilities
in the Developing Auditory Cortex**

Abstract

Sensory perception is believed to be a process of statistical inference, in which incoming sensory information is integrated with expectations based on previously encountered stimulus probabilities. In the present study, we investigated whether neurons in the developing primary auditory cortex of rats adapt their response properties to higher-order conditional probabilities between stimuli in the environment, and whether this in turn affects auditory perception in adult rats. Our results provide evidence that the development of tonal frequency-intensity receptive fields, as well as frequency discrimination ability, are shaped by conditional probabilities between sounds played in sequences. These observations are consistent with previous reports that the tuning properties of primary cortical neurons are well matched to environmental stimulus statistics, and provide evidence that this phenomenon may be at least partly experience-dependent. Further, our results suggest a mechanism by which higher-order stimulus probabilities may be encoded in sensory cortex to influence sensory perception.

Introduction

Perceiving a sensory stimulus involves both processing incoming information conveyed by our sensory receptors, as well as incorporating expectations drawn from experience (Knill and Richards, 1996; Barlow, 2001). Recent reports have shown that sensory perception across a range of modalities and species is influenced by environmental stimulus distributions (Han et al., 2007; Feldman et al., 2009; Fischer and Pena, 2011; Girshick et al., 2011), as well as higher-order stimulus statistics such as the temporal dependencies between stimuli (Saffran et al., 1996; Hauser et al., 2001; Fiser and Aslin, 2002; Toro and Trobalon, 2005). How environmental stimulus statistics are encoded by neurons and combined with sensory information to bias perception is currently unclear. In the case of simple stimulus distributions, stimulus probabilities may be encoded in primary sensory cortices through experience-dependent plasticity mechanisms^{11,12}. Sound representation in the primary auditory cortex of the rat, for example, is profoundly influenced by both the spectral and temporal characteristics of the early acoustic environment (Zhang et al., 2001; Chang and Merzenich, 2003; de Villers-Sidani et al., 2007; Kim and Bao, 2009). Repeated exposure to a sound not only increases cortical representation of that sound but also alters auditory perception (Han et al., 2007), indicating that stimulus distribution plays a critical role in shaping neural and perceptual processes. (Wiesel and Hubel, 1963; Simons and Land, 1987; Zhang et al., 2001; Kim and Bao, 2009).

Higher-order stimulus probabilities, such as the temporal dependencies between stimuli, also influence perception in humans and model animals (Saffran et al., 1996; Hauser et al., 2001; Fiser and Aslin, 2002). Rodents, including rats, are sensitive to higher-order stimulus statistics (Toro and Trobalon, 2005), and their own vocalizations exhibit complex statistical structure (Holy and Guo, 2005). Most notably, rodent pup and adult calls are repeated in bouts (Liu et al., 2003; Holy and Guo, 2005; Kim and Bao, 2009), resulting in high sequential conditional probabilities for calls of the same type, and low sequential conditional probabilities for calls of different types (Holy and Guo, 2005). It is not known whether such higher-order structure of sounds experienced during early life affects perception or cortical acoustic representation in rats.

In the present study, we exposed litters of rat pups to sequences of tone pips that differed only in terms of the higher-order conditional probabilities between tone pips. We then performed neurophysiological recordings to assess changes in neuronal response properties, as well as behavioral testing to measure changes in perceptual ability.

Results

To probe the sensitivity of the developing auditory cortex to higher-order stimulus probabilities, we exposed three groups of rat pups to sequences of tone pips that differed

only in terms of the conditional probabilities between tone pips within a sequence (Figure 2.1A). All groups experienced sequences of six tones repeated at an ethological rate (Kim and Bao, 2009) of 6 Hz, with 1 s intervals between sequences. The temporal structure of sequences approximated rat vocalization patterns, which are characterized by bouts of calls repeated at around 6Hz (Kim and Bao, 2009). The overall spectral distribution was the same for all groups: all tones were drawn from a uniform distribution between 4 kHz and 32 kHz (Figure 2.1A). Across groups, however, different constraints were placed on the spectral composition of individual sequences. For the single-frequency group, sequences were made up of the same tone repeated six times. For the full-range group, tones within a sequence were drawn from the entire breadth of the tone distribution, resulting in a broad spectral range (3 octaves). For the half-range group, tones within a sequence were drawn from either the higher or lower half of the frequency range, resulting in two categories of sounds with high conditional probabilities, and a low conditional probability “boundary” at 11.314 kHz (Figure 2.1A). The half-range group sequences had an intermediate spectral range (1.5 octaves). Animals were continuously exposed to the tone sequences from postnatal day 9 (p9) to p35, and subsequently mapped between p35 to p52. Naïve control animals were maintained in a normal animal room, and mapped at matching ages.

Sound exposure did not lead to gross changes in the tonotopic organization of primary auditory cortex (Figure 2.1B). The distribution of characteristic frequencies (CFs; white stars in Figure 2.1C) was not different between groups (four-conditions by sixteen-frequencies ANOVA: no main effect of condition $F_{3,224}=0$; $p < 1$ and no interaction $F_{45,224}=1.31$; $p<0.1023$; data not shown). However, inspection of individual receptive fields revealed striking changes in receptive field bandwidth and shape (Figure 2.1C). The receptive field bandwidth at 60dB was significantly different between the groups (one-way ANOVA, $F_{3,14}=10.02$; $p<0.0009$). A *posthoc* t-test showed that receptive fields in the full-range condition were significantly broader than in the control group ($p=0.025$), whereas those in the single-frequency condition were significantly narrower ($p=0.0021$) (Figure 2.1D.). The bandwidth differences were present regardless of whether we measured tuning bandwidth at a fixed intensity level (e.g. 60dB as shown in Figure 2.1D), or relative to threshold (e.g. bandwidth 20 dB above threshold, one-way ANOVA, $F_{3,14}=12.53$; $p<0.0003$, data not shown). These results indicate that the receptive field bandwidth of cortical neurons is shaped by the spectral range of tones with high conditional probabilities within sequences, but not the overall spectral distribution of the stimulus ensembles.

Receptive field bandwidth was not different between the half-range condition and the control condition ($p=0.96$). Since the spectral range of the half-range sequences (1.5 octaves) approximately matched the tuning bandwidth of naïve auditory cortical neurons (1.45 +/- 0.16, 95% confidence interval), adaptation to the spectral range should lead to shifting, rather than broadening or narrowing, of receptive fields. We examined the

distribution of the frequency-intensity response area on each side of the low-conditional-probability-boundary frequency (11.314 kHz). Receptive fields in the half-range condition shifted to preferentially respond to the lower or higher portion of the frequency range, with fewer neurons responding equally well to both sides (Figure 2.1C). We quantified this effect using a category selectivity index (CSI), defined as the sum of the receptive field responses in the higher half of the frequency range divided by the sum of responses in the full frequency range. A four-condition by five-CSI bins ANOVA showed no main effect of condition, and a significant interaction ($F_{3,12}=2.71$, $p=0.0047$). *Posthoc* analysis revealed that in the half-range group, significantly fewer receptive fields had CSI values between 0.4 and 0.6 (Figure 2.2A; $p=0.039$). These results, together with the narrower tuning bandwidth seen in the single-frequency group, suggest that pairs of sounds with low conditional probabilities within sequences tend to be represented by separate populations of cortical neurons.

The shift in receptive fields but not CFs in the half-range group suggests that changes in frequency selectivity occurred at the flanks, but not at the threshold of receptive fields. Comparison of frequencies at the center-of-mass of the receptive fields (white triangle in Figure 2.1B), which are sensitive to shifts in the flanks of receptive fields, confirmed that significantly fewer neurons in the half-range group had receptive fields centered at the boundary frequency (Figure 2.2B; four-condition by sixteen-frequency bins ANOVA, no main effect of condition and significant interaction $F_{45,224}=1.47$, $p<0.036$; *posthoc* t-test for bin centered at 11.3 kHz, half-range condition versus control $p<0.0054$). We compared tuning curve slopes at the receptive field flanks to determine whether they were altered by the receptive field shifts. Because tuning curve slopes at any given frequency vary depending on a particular neuron's best frequency (Figure 2.3A), any effects will likely be washed out by this peak-dependent variability. Therefore, we grouped neurons by the peaks of their tuning curves. Neurons tuned to the boundary frequency (Figure 2.3B, peak F – boundary F = 0) and neurons tuned to frequencies far away from the boundary frequency did not show changes in slope. However, neurons tuned to frequencies flanking the boundary frequency had significantly steeper slopes at the boundary frequency in the half-range group relative to all other groups (Figure 2.3B, four-condition by nine-CF bins ANOVA: main effect of condition $F_{3,1014}=4.37$, $p<0.0046$ and significant interaction $F_{24,1014}=1.77$, $p<0.0127$; *posthoc* t-test shows that half-range group neurons with tuning curve peaks 0.5-1.3 octaves below and 0.2-0.5 octaves above the boundary have steeper slopes at the boundary). Slopes at other, non-boundary frequency locations were not significantly different between the groups (Figure 2.3C).

Neurons are most sensitive to stimulus differences at the slopes of tuning curves, and experimental (Schoups et al., 2001; Han et al., 2007) and theoretical (Butts and Goldman, 2006) evidence suggests that the steepness of tuning curves may be related to performance in tasks involving fine stimulus discriminations. We therefore examined how the steeper tuning curve slopes observed in the half-range group impacted perception

using a frequency discrimination task. The behavioral examination consisted of two phases: a procedure-learning phase, followed by a perceptual-testing phase. In the first phase, the rats were trained to detect the transition from repetitive tone pips of the standard frequency ($f_s, f_s, f_s...$) to tones of alternating standard and target frequencies ($f_s, f_t, f_s, f_t...$; Figure 2.4A) The f_t was either 1 octave below or above f_s . The center of the two frequencies was randomly chosen from a range of 4 to 32 kHz. The detection of the large 1-octave frequency difference was perceptually unchallenging; the animals learned the task procedure in a period of 3 days. On the fourth day, all animals underwent the second phase of perceptual testing (3 days), in which their perceptual discrimination ability was examined with smaller frequency differences of 0.5, 0.3, and 0.1 octaves. For each animal, we chose the frequency difference that gave a mean performance level between 60% and 85% for optimal quantification of performance improvement and impairment.

There was no overall difference in discrimination ability between conditions (four-conditions by three-frequency differences ANOVA: main effect of condition $F_{3,99}=2.07$, $p<0.1096$, data not shown). In all groups, perceptual discrimination at threshold was better at higher frequencies relative to lower frequencies (Figure 2.4B-E). In the half-range group, there was an additional effect of enhanced perceptual discrimination across the probability boundary relative to flanking frequencies (Figure 2.4C), an effect that was not present for the naïve control (Figure 2.4A), single-frequency (Figure 2.4B) or the full-range (Figure 2.4D) groups.

Discussion

These results demonstrate that the developing primary auditory cortex is sensitive to the higher-order statistics of the sensory input. Specifically, stimuli with high conditional probabilities within 6-Hz sequences tended to be represented together, whereas stimuli with low conditional probabilities were represented separately. This was manifested by broader frequency tuning in the full-range group, narrower tuning in the single-frequency group, and preferentially selective receptive fields in the half-range group. Furthermore, in the half-range group, the stimulus boundary was represented by steeper tuning curve slopes. Correspondingly, perceptual sensitivity was elevated at the low-probability boundary compared to the neighboring frequencies, forming a perceptual boundary.

Developing auditory cortex is sensitive to the stimulus statistics on the spectral and temporal domains (Zhang et al., 2001; Chang and Merzenich, 2003; de Villers-Sidani et al., 2007; Han et al., 2007; Kim and Bao, 2009). Our results suggest that the developing auditory cortex can compute joint stimulus probabilities over hundreds of milliseconds, consistent with the prolonged temporal integration window of cortical neurons (Bao et al., 2004; Chang et al., 2005). Rodent vocalizations occur in bouts on similar time scales (Holy and Guo, 2005; Kim and Bao, 2009). Our results suggest that early experience of

those vocalizations could lead to similar cortical representations and reduced perceptual contrast of the individual calls despite their substantial trial-by-trial variability (Holy and Guo, 2005). By contrast, functionally different call types that do not occur in the same bout may be represented by distinct populations of neurons, resulting in perceptual boundaries and categorical perception of the calls.

Theoretical considerations and empirical observations have suggested that statistical inference is involved in almost every aspect of the brain function, from sensory perception and motor control to language acquisition and decision making (Knill and Richards, 1996; Saffran et al., 1996; Kording and Wolpert, 2004). Representing probability structures is essential for statistical inference. Previous studies have suggested that long-term prior probability distributions of sensory stimuli may be stored in the size of their representations in the sensory cortex. Here we show that higher-order probability distributions may also be stored in the sensory cortex, where they can be integrated with sensory information and shape sensory perception

Methods

Acoustic rearing of young rat pups. All procedures used in this study were approved by the UC Berkeley Animal Care and Use Committee. Three groups of Sprague Dawley rat pups (single-frequency, half-range, full-range) were placed with their mothers in an anechoic sound-attenuation chamber from p9 to p35. This time period comprises the critical period for experience-dependent plasticity in primary auditory cortex (AI), including changes in frequency tuning, neuronal tuning bandwidth, and complex sound selectivity. All groups heard 1 s long trains of six tone pips (100 msec, 60dB SPL), with one train occurring every 2 s (Figure 2.1A). For all groups, tones were drawn from a uniform distribution spanning 4 – 32 kHz, with constraints placed only on the sequential conditional probabilities of sounds within a sequence. For the full-range group, tones within a single sequence were drawn from the entire breadth of the distribution (Figure 2.1A). For the single-sequence group, sequences were made up of the same tone repeated 6 times (Figure 2.1A). For the half-range group, tones within a sequence were *either* higher or lower than the “boundary frequency” 11.314 kHz (Figure 2.1A). After sound exposure, rats were moved to a regular animal room environment until they were mapped. A control litter was reared in a regular animal room environment.

Electrophysiological recording procedure. The primary auditory cortex (AI) of sound-reared (single-sequence n = 4; half-range n = 4; full-range n = 6) and naive control rats (n = 4) were mapped at comparable ages from p35 – p52. Rats were preanesthetized with buprenorphine (0.05 mg/kg, s.c.) a half hour before they were anesthetized with sodium pentobarbital (50 mg/kg, followed by 10-20 mg/kg supplements as needed). Atropine sulfate (0.1 mg/kg) and dexamethasone (1 mg/kg) were administered once every 6 h. The head was secured in a custom head-holder that left ears unobstructed, and the cisterna

magna was drained of CSF. The right auditory cortex was exposed through a craniotomy and duratomy and was kept under a layer of silicone oil to prevent desiccation. Sound stimuli were delivered to the left ear through a custom-made speaker that had been calibrated to have <3% harmonic distortion and flat output in the entire frequency range.

Cortical responses were recorded with tungsten microelectrodes (FHC). Recording sites were chosen to evenly and densely map primary auditory cortex while avoiding surface blood vessels and were marked on an amplified digital image of the cortex. Microelectrodes were lowered orthogonally into the cortex to a depth of 500 – 600 μm where responses to noise bursts could be found. Multiunit responses to 25 ms tone pips of 51 frequencies (1-32 kHz, 0.1 octave spacing, 5 ms cosine-squared ramps) and eight sound pressure levels (0-70 dB SPL, 10-dB steps) were recorded to reconstruct the frequency-intensity receptive field.

Electrophysiological data analysis. The characteristic frequency (CF), center-of-mass frequency, tuning bandwidth and threshold of each neuron were determined using an automated algorithm, which involves smoothing and thresholding of the receptive field. The characteristic frequency (CF) was defined as the frequency at which responses are evoked at threshold: the lowest sound pressure level that activates the neuron. Bandwidth was measured both at an absolute intensity level of 60dB (bandwidth at 60dB), and relative to threshold (bandwidth 20dB above threshold).

The category response index (CRI) for each receptive field was calculated as the total response (number of spikes) to any frequency-intensity combination in the “high” category (above 11.314 kHz) divided by the total response to frequencies in the “low” category (below 11.314 kHz). Because the majority of receptive fields yielded values of either 0 or 1 (i.e. they were not crossing the boundary at all), this analysis was restricted to neurons with CFs within a 1 octave range of the boundary.

To quantify changes in tuning curve slope at the boundary frequency, tuning curves at 60dB were fitted with a cubic spline interpolation (MATLAB, Mathworks). The squared sum of errors of the fitting averaged less than 0.01. Neurons were divided into bins based on the difference between their characteristic frequency and the boundary frequency, and the absolute value of the tuning curve derivatives was plotted against CF.

Behavioral testing. Behavioral training and testing began when the pups were two months old. Animals were food-deprived to reach a 10% body-weight reduction before training was started. Training took place in a wire cage located in an anechoic sound-attenuation chamber. On automatic initiation of a trial, tone pips of 100-ms duration and of a standard frequency were played 5 times per s through a calibrated speaker. After a random duration of 5-35 s, tone pips of a target frequency were played in the place of every other standard tone pip. Rats were trained to detect the frequency difference and

make a nose-poke in a nosing hole within 3 s after the first target tone, which was scored as a hit and rewarded with a food pellet. The false alarm rate was determined as the percentage responses when the target frequency was the same as the standard frequency (10% of trials). In each training day, animals were allowed to achieve 250-300 hits. All animals underwent 3 d of initial training with a large difference between the target and standard frequencies ($\Delta f = 1$ octave). Rapid procedure learning occurred in this phase of training. In the subsequent testing phase (3 d), we tested perceptual discrimination of smaller Δf s of 0.5, 0.3, 0.2 and 0.1 octaves, randomly intermixed within each block. The larger Δf values were included to motivate the animals, and often lead to saturated performance levels of greater than 85%. Consequently, for each animal the data from the Δf level that led to performance between 60 and 85% was included in the analysis. Animals that did not learn the task within the 3 days and had a false alarm rate of more than 30% were not included in testing.

Statistical testing. Unless stated otherwise, statistical significance was determined using ANOVA and post-hoc two tailed t-tests (MATLAB, Mathworks).

Appendix 2.1: Figures

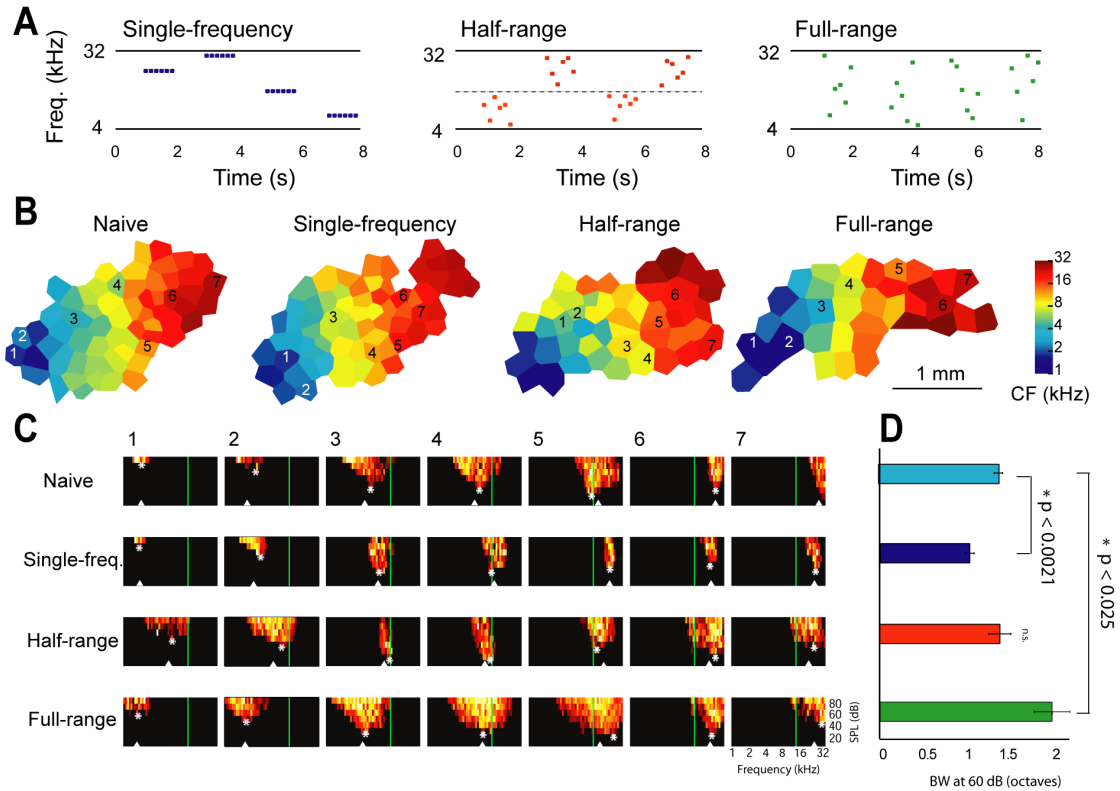


Figure 2.1. Influences of higher-order stimulus statistics on spectral selectivity of primary auditory cortical neurons. **A.** Schematics of the acoustic environments that the animals experienced. The three acoustic environments had the same logarithmically uniform frequency distribution and the same temporal presentation rates, but differed in the conditional probabilities of the tonal frequencies within sequences. **B.** Representative cortical maps. The sound exposure did not alter the tonotopic characteristic frequency distribution. **C.** Representative frequency-intensity receptive fields. The corresponding locations are marked on the tonotopic maps in B. The green vertical lines mark the low conditional probability boundary experienced by the half-range group. Stars denote the characteristic frequency (CF) and triangles denote the center-of-mass frequency. **D.** Tuning bandwidth at 60 dB SPL. Frequency tuning bandwidth became narrow in the single-frequency group and broader for the full-range group.

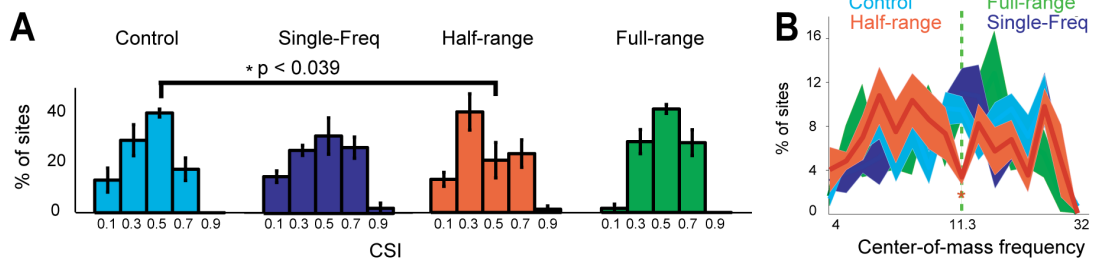


Figure 2.2. Selective representation of low and high tones in the half-range condition. **A.** Distribution the category selectivity index. Fewer neurons in the half-range group had receptive fields equally straddling the probability boundary, i.e., with CSI near 0.5. **B.** Distributions of center-of-mass frequency. Fewer neurons in the half-range group had center-of-mass frequency near the low-conditional-probability-boundary (dashed line). Shown are group mean and SEM.

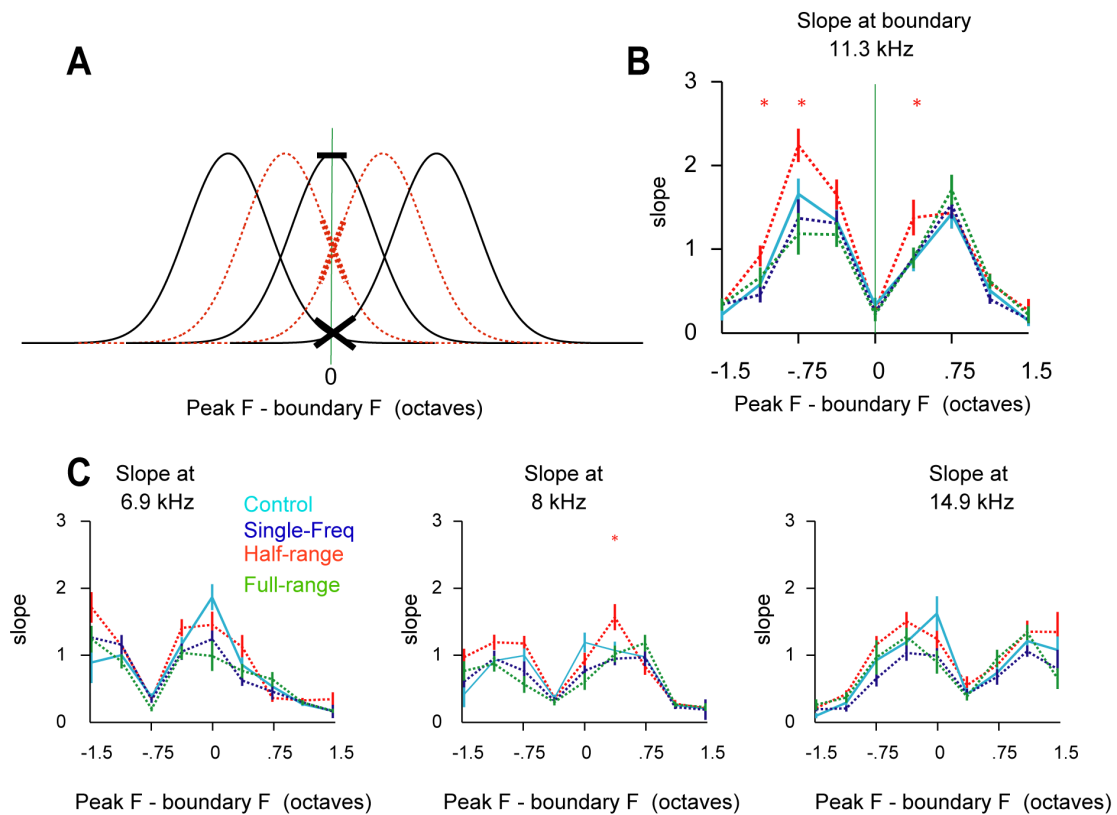


Figure 2.3. Steeper tuning curve slopes in the half-range group at the low conditional probability boundary (11.3 kHz). **A.** Schematic of the dependency of tuning curve slope on tuning curve peak. Neurons with tuning curve peaks flanking the low conditional probability boundary (green) have the steepest slope at the boundary. **B.** Absolute values of tuning curve slopes as a function of neuronal tuning curve peaks relative to the boundary. Tuning curve slopes in the half-range group were steeper than tuning curve slopes in the other groups *only* for neurons tuned to flanking frequencies. **C.** There were no group differences in tuning curve slopes at three other, non-boundary frequency locations. * $p < 0.05$.

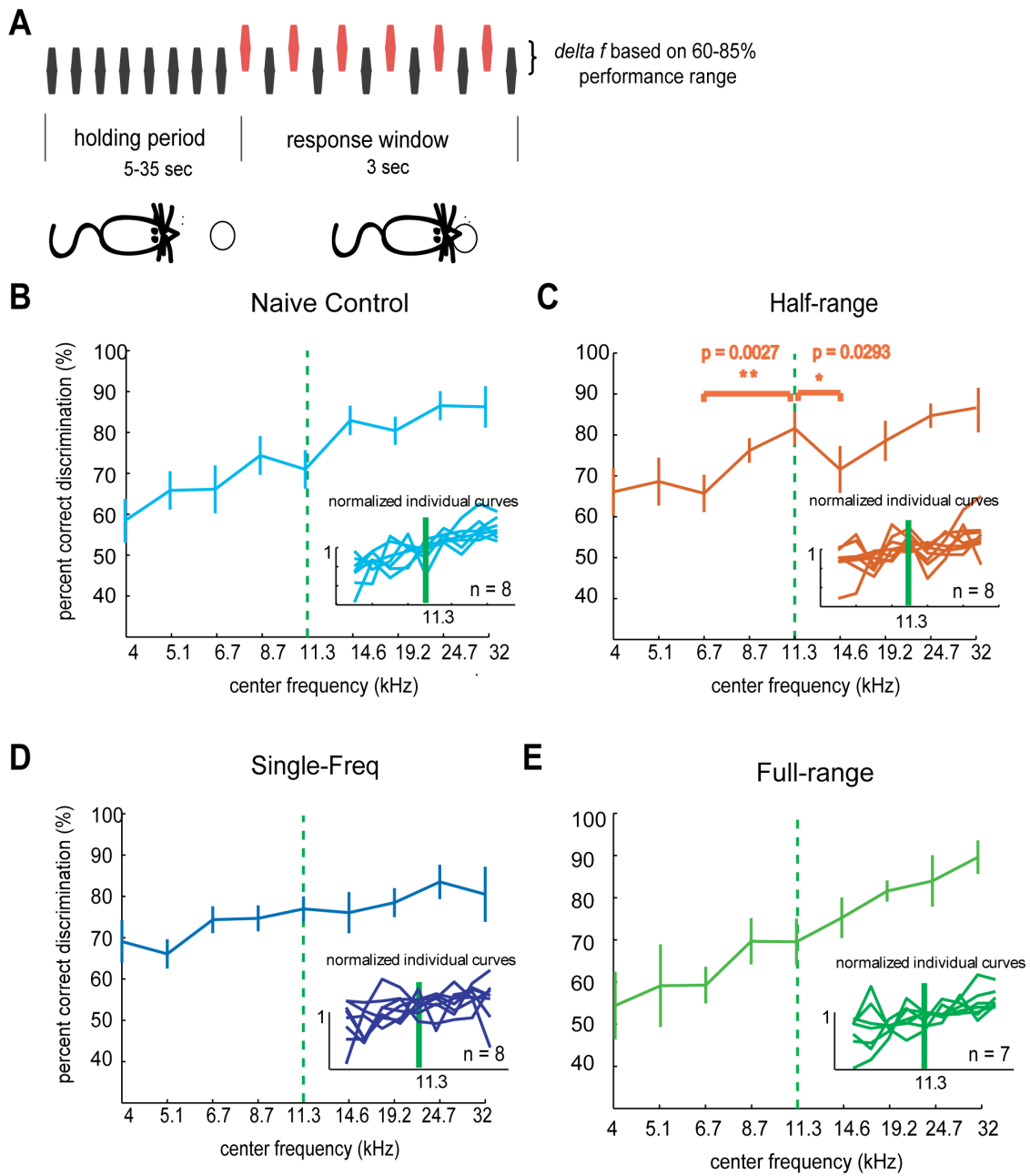


Figure 2.4. Perceptual boundary shaped by conditional stimulus probabilities. **A.** Schematic paradigm of frequency discrimination task. **B-E.** Improved discrimination performance at the low conditional probability boundary (dashed line) compared to neighboring frequencies for the half-range group.

Appendix 2.2: Supplemental Information

Because behavioral data can be variable, we sought to confirm the experience-dependent perceptual changes measured using the discrimination task with another test of perceptual ability. Previous work has shown that pre-pulse inhibition, also known as the startle response, can be used to measure perceptual discrimination ability (Floody and Kilgard, 2007). In our version of the pre-pulse inhibition test, animals were placed in a small plastic chamber with a wire-mesh lid on top of an electric scale (Figure 2.S1A). The voltage output of the electric scale provided a continuous record of activity level. A standard 50 msec pure tone was played at regular intervals (5 Hz). At random intervals (once every 15-30 sec), a loud white noise burst (50msec, 90dB) elicited a startle response, which was measured as a deflection of the voltage signal from baseline (Figure 2.S1A). During *uncued* trials, the noise burst occurred without warning, resulting in a large startle response. During the more frequent *cued* trials, the noise burst was preceded by a target tone of a different frequency, which generally resulted in a reduction of startle amplitude (Figure 2.S1B).

While there was wide variety in startle amplitudes on individual trials and for each animal, the ratio of average cued:uncued amplitudes provided a reliable measure of how well the animal could discriminate the target from the standard tone: high discriminability led to a greater reduction in startle amplitude. In a preliminary experiment, we tested naïve animals and animals reared in the half-range sequences using two different frequency differences between target and standard (0.1 octaves and 0.3 octaves), at three different center frequencies. The center frequencies (6.7kHz, 11.3kHz and 19.0kHz) were chosen to lie in the center of the two half-range distributions (6.7kHz—low sequence; 19.0kHz—high sequence), as well as across the boundary frequency (11.3kHz). A three-way ANOVA (2 groups x 2 frequency differences x 3 center frequencies) revealed a main effect of frequency difference ($F(1,80)=35.9$, $p<0.001$), and no interactions (Figure 2.S1C). *Post hoc* t-tests revealed that the startle reduction ratio was significantly less than 1 for the 0.3 octave frequency difference ($p<2.5*10^{-9}$) but not the 0.1 octave frequency difference. While this result differs slightly from results obtained using the nose-poke discrimination task in which animals can reliably detect a 0.1 octave difference, the difference is most likely due to the reduced number of target tone instances that the animals hear in the startle reduction task (one instance compared to nine instances, compare Figure 2.S1C and Figure 2).

Although these preliminary results showed no statistically significant main effect of group, nor an interaction between center frequency and group, there was a trend for enhanced perceptual discrimination ability at the boundary frequency in the half-range group (Figure 2.S1C). We therefore re-ran the experiment with a new set of age-matched animals using only the 0.3 octave frequency difference to increase power. There was an almost significant interaction between group and center frequency ($p=0.06$). *Post-hoc*

paired t-tests revealed that in the half-range group but not naïve controls, startle reduction was greater (smaller startle reduction ratio) at the boundary relative to category centers (low range center vs. boundary: $p < 0.04$, high range center vs. boundary $p < 0.06$ Figure 2.S1D). These results confirm that rats in the half-range group have elevated perceptual sensitivity at the boundary, and are consistent with the results obtained using the nose-poke discrimination task.

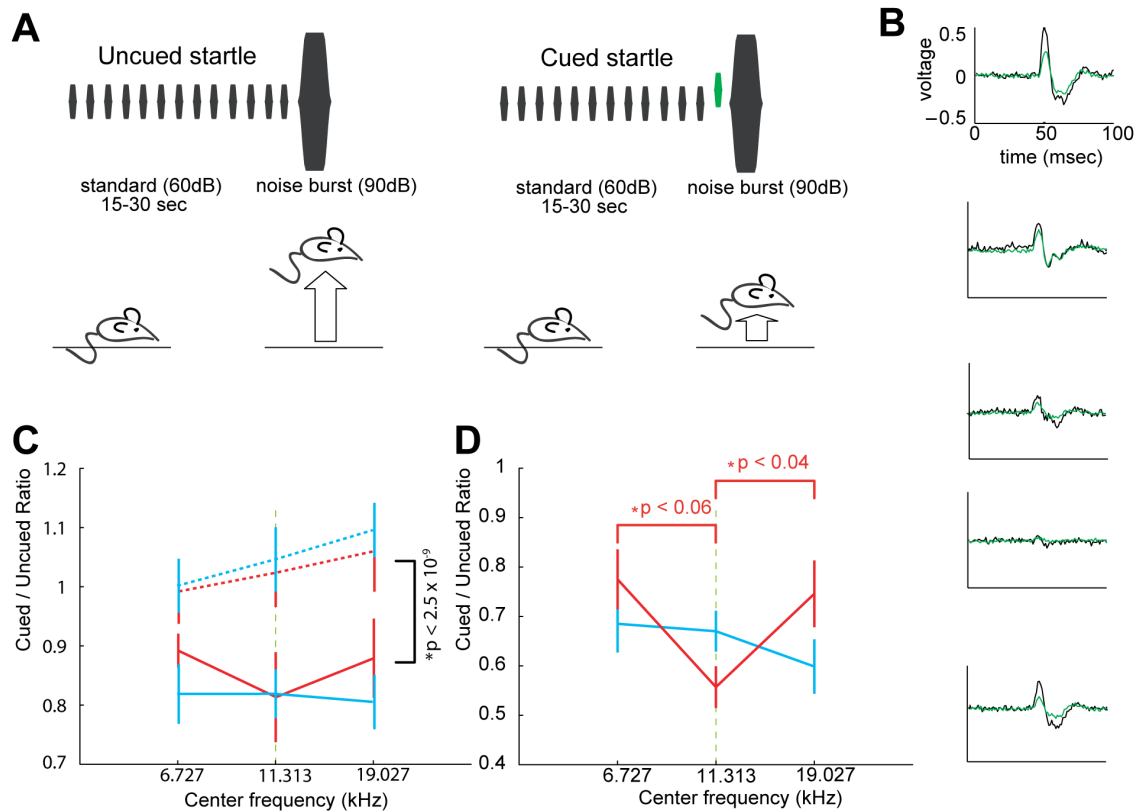


Figure 2.S1: Pre-pulse inhibition test for discrimination ability. **A.** Schematic of the experimental set-up. During the uncued trials, animals startle upon hearing an infrequent noise burst. On cued trials, a target tone (green) cues the animal to expect an impending noise burst, leading to a reduction in the startle amplitude. **B.** Example average startle waveforms for five different animals and days. Despite large overall variations in startle amplitudes, the cued amplitude (green) tends to be smaller than the uncued amplitude (black). **C.** Ratio of cued/uncued startle amplitudes using frequency differences of 0.1 octaves (dashed line) and 0.3 octaves (solid line) in naïve control (cyan) and half-range exposed animals. Trend for improved discriminability (increased startle reduction) at boundary frequency in half-range exposed animals. **D.** Improved discriminability at boundary relative to category centers in half-range exposed animals.

Supplementary Methods

Subjects. During preliminary testing (Figure 2.S1C), the subjects were 9 adult naïve Sprague-Dawley rats, and 6 adult Sprague-Dawley rats that had been exposed to half-range sequences during the critical period. Data was collected over 2 sessions for naïve controls, and 4 sessions for half-range exposed animals (1 session per day). In the second experiment (Figure 2.S1D), the subjects were 6 naïve controls and 6 half-range exposed animals tested for one session only. Except during tests, animals were housed in groups of two with free access to food and water.

Startle Test. During testing, animals were housed individually in a small plastic container with a wire-mesh lid, positioned directly below a speaker and on top of an electric scale. The entire startle apparatus was placed inside an anechoic sound attenuation chamber. Each session consisted of a total of 100 noise burst trials, divided evenly across the two frequency differences (0.1 and 0.3 octaves), the three frequencies of interest (6.7kHz, 11.3kHz and 19.0kHz), and cued vs. uncued trials. Cued trials were more frequent than uncued trials, with an overall ratio of 5 cued trials for every 2 uncued trials. A standard frequency was played at 5 Hz, and at random intervals (15-30 seconds), were interrupted by a large noise burst (50msec, 90dB) that elicited a startle. Cued noise bursts were preceded by a target tone that was either 0.1 octaves or 0.3octaves higher than the standard.

Data Analysis. Startle amplitudes were calculated by averaging across all trials of a given type, and subtracting the maximum and minimum of the average waveform. Cued amplitude values were divided by uncued amplitude values for each trial type. Statistical significance was determined using 3 frequency x 2 groups x 2 frequency differences ANOVA, and *post-hoc* t-tests.

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Chapter 3

**Cortical Plasticity as a Mechanism for
Storing Bayesian Priors in Sensory Perception**

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Abstract

Human perception of ambiguous sensory signals is biased by prior experiences. It is not known how such prior information is encoded, retrieved and combined with sensory information by neurons. Previous authors have suggested dynamic encoding mechanisms for prior information, whereby top-down modulation of firing patterns on a trial-by-trial basis creates short-term representations of priors. Although such a mechanism may well account for perceptual bias arising in the short-term, it does not account for the often irreversible and robust changes in perception that result from long-term, developmental experience. Based on the finding that more frequently experienced stimuli gain greater representations in sensory cortices during development, we reasoned that prior information could be stored in the size of cortical sensory representations. For the case of auditory perception, we use a computational model to show that prior information about sound frequency distributions may be stored in the size of primary auditory cortex frequency representations, read-out by elevated baseline activity in all neurons and combined with sensory-evoked activity to generate a percept that conforms to Bayesian integration theory. Our results suggest an alternative neural mechanism for experience-induced long-term perceptual bias in the context of auditory perception. They make the testable prediction that the extent of such perceptual prior bias is modulated by both the degree of cortical reorganization and the magnitude of spontaneous activity in primary auditory cortex. Given that cortical over-representation of frequently experienced stimuli, as well as perceptual bias towards such stimuli is a common phenomenon across sensory modalities, our model may generalize to sensory perception, rather than being specific to auditory perception.

Introduction

Natural stimuli are variable and often mixed with noise. Our perception of these stimuli is thus derived from ambiguous sensory inputs. Psychophysical experiments in humans and primates indicate that this ambiguity is partly compensated for by incorporating information about the probabilities of previously experienced stimuli directly into the percept in a Bayesian manner (Kording and Wolpert, 2004; Stocker, 2006; Feldman and Griffiths, 2007). However, it is not known how this prior information is encoded, retrieved and combined with sensory information by neurons (Kording and Wolpert, 2006; Ma et al., 2006).

Previous theoretical investigations of Bayesian inference were often based on homogeneous stimulus representations—i.e., all possible values of stimulus parameters are evenly represented (Ma et al., 2006). In such a representational system, prior information is typically modeled as the activation of a sub-population of neurons by top-down influences or cross-modal interactions (Basso and Wurtz, 1997; Ma et al., 2006). This population activity may be linearly combined with sensory-driven activity for optimal integration of information (Ma et al., 2006). These prior storage and integration processes are believed to occur in higher-level/multi-sensory cortical areas, but not in low-level sensory cortices.

Although such a mechanism of dynamic prior information encoding and integration may underlie perceptual bias arising in the short-term and in a context-dependent manner (Kording and Wolpert, 2004), it does not account for the often irreversible, robust and context-independent changes in perception that result from long-term, developmental experience (Kuhl et al., 1992; Han et al., 2007). Extensive experience of native speech sounds, for instance, warps the perceptual space so that speech sound variants near a frequently heard prototype are perceived as being more similar to the prototype than they actually are (Kuhl, 1991; Kuhl et al., 1992). Such a phenomenon, also known as the perceptual magnet effect, has been interpreted as an example of Bayesian inference in language perception (Feldman and Griffiths, 2007), and has been correlated with experience-altered stimulus representations in the sensory cortices (Guenther FH, 1996; Han et al., 2007).

Cortical stimulus representations are not homogeneous. Sensory experience during early development results in robust changes in primary cortical sensory representations that persist into adulthood. A very consistent finding is that more frequently experienced stimuli gain greater representations in primary sensory cortices (Han et al., 2007). The influences of inhomogeneous representations on sensory perception have not been fully explored. We reasoned that the sizes of cortical stimulus representations carry long-term prior information (Barlow, 2001), and could play an important role in Bayesian inference in sensory perception. Using a computational model of auditory perception, we investigated the effect of increasing cortical frequency representations on the perception of pure tones. The results indicate that prior information stored in primary auditory cortex

frequency representations can be read-out by locally generated neuronal activity and combined with sensory-evoked activity to generate a percept that conforms to Bayesian integration theory.

Results

Convergence of maximum-likelihood estimate at the input stimulus

We first examined model auditory perception with normal levels of baseline activity for both the naïve and 7kHz-over-represented model AIs. The maximum likelihood estimate or ‘percept’ converged at the input frequency for both naïve and 7kHz-over-represented model AIs (Figure 3.2A, Figure 3.3A-B), even for the under-represented frequencies that no neurons were tuned to. This is not surprising because primary auditory cortical neurons are broadly tuned, and responsive to those frequencies. Thus, the maximum-likelihood estimate of sensory input from population responses is insensitive to inhomogeneity of sensory representations, and always converges on the input stimulus.

Readout of prior information by nonselectively elevated population activity

We reasoned that the readout of long-term, context-independent priors should not depend on specific patterns of population activity driven by higher-level inferences. Rather, if information about prior stimulus distributions is encoded in the size of primary cortical representations, it should be retrieved by a non-selective increase in the activity in all neurons. Although such activity may be triggered or enhanced by task-related top-down influences or neuromodulatory activity (for example in situations where sensory information is ambiguous) (Basso and Wurtz, 1997; Yu and Dayan, 2005), it need not contain specific prior information itself. To test this idea, we increased the baseline activity of all neurons to their maximum response magnitude, and examined the stimulus likelihood distribution in the absence of stimulus-evoked activity (Figure 3.2B). The likelihood function of the naïve model AI was flat with no peaks (data not shown), whereas that of the 7kHz-over-represented model AI showed a peak near the over-represented frequency (Figure 3.2B). This peaked likelihood function may be regarded as an internal representation of the prior probability distribution of the stimulus. In calculating the likelihood function here, we assumed that the maximum-likelihood decoder was unaware that the elevated activity was not sensory driven. This is not different from the treatment of top-down prior-related or cross-modal activity in other models of Bayesian inference (Ma et al., 2006) (see Discussion).

Bayesian Integration of prior and sensory information

It has recently been shown that Bayesian integration of probability distributions represented in neuronal population codes such as the one used in our model may be achieved by simple summation of population activities (Ma et al., 2006). Stimulus-

evoked and spontaneous activity in primary sensory cortices summates linearly (Arieli et al., 1996). When we decoded the summed population response (consisting of the linear superposition of elevated baseline activity and 4-kHz-evoked activity (Ma et al., 2006)), the peak of the likelihood function was shifted towards 7kHz for the 7kHz-over-represented model (Figure 3.2C, right). Such a shift was observed for frequencies near 7kHz in the 7-kHz-overrepresented (Figure 3.3D), but not the naïve (Figure 3.3C), model AI. This perceptual bias is consistent with Bayesian integration of prior information and noisy auditory input (Feldman and Griffiths, 2007), and may explain the impaired discrimination ability for frequencies near over-represented frequencies which has been recently reported (Han et al., 2007).

Decoding variability

The relative decoding variability at the over-represented frequency range behaves differently with and without the elevated baseline activity. With an increased baseline, although overall variability is increased, it is relatively lower for the over-represented frequencies than for the neighboring frequencies (Figure 3.3D). This is consistent with human psychophysical studies showing that extensively experienced native speech sounds are perceived with less variability than novel foreign speech sounds (Iverson et al., 2003).

Influences of neuronal population size and activity levels on perceptual bias

Some parameters of the model AI, such as the total number of neurons and the magnitude of the elevated spontaneous firing rate, were arbitrarily chosen. We therefore systematically varied these parameters to explore their influence on the observed characteristic perceptual shift (Figure 4). The slope of the input-output function in the over-represented frequency range was used as a measure of perceptual shift magnitude—smaller slopes indicate greater prior bias (Figure 3.3D). When the magnitudes of the stimulus-evoked responses were fixed, increasing the level of baseline activity led to smaller input-output slopes, indicative of stronger prior biases (Figure 4A). Similarly, when the ratio of baseline to evoked responses was set at 1, increasing overall activity also resulted in stronger prior biases (Figure 4C). Increasing baseline activity led to higher decoding variability (Figure 4B), whereas increasing both baseline and sensory-evoked activity reduced decoding variability (Figure 4D). Increasing neuronal population size reduced this variability. Thus, higher baseline-to-evoked activity ratio in a larger population of neurons would produce more reliable and robust prior biases. Optimal integration of prior and sensory information may be achieved by adjusting the levels of baseline activity in a task-dependent manner (e.g., higher baseline activity when the stimulus is more ambiguous).

Discussion

Earlier studies have suggested that dynamic prior information may be encoded by the activity of a subset of primary cortical neurons in a homogeneous representational system. The specific pattern of activity is driven by inputs outside of primary sensory cortex that carry prior information derived from high-level inference. Thus the encoding of the prior is separate from its integration with sensory information and must be mediated by different neural circuits. The specific brain substrates and mechanisms for prior encoding and retrieval are unknown. The present study considered the possibility of storing long-term prior information in the size of sensory representations. A novel finding is that in the context of auditory perception, long-term priors about sound frequency distributions can be retrieved by *non-selective* increase in the activity of *all* neurons in primary auditory cortex. In the model, the same cortical circuit performs both the encoding and integration of the prior. The increase in overall activity could be driven by a general top-down signal without specific prior information.

In order for optimal Bayesian integration of prior and sensory information to occur, our model requires that the relative contributions of prior-related and sensory-evoked activity be modulated by task conditions on a trial-by-trial basis. In other words, although the prior is long-term, optimal Bayesian inference requires that the extent to which it is used in generating a sensory percept depend on task demand and stimulus uncertainty. Our simulation shows that this could be accomplished by changing overall levels of activity. Higher levels of overall activity increase the contribution of prior information to sensory perception and increase prior bias. Thus our results suggest that in situations where auditory input is ambiguous, the overall level of activity in all primary auditory cortex neurons should increase. Although dynamic prior encoding also calls for a higher level of prior-related activity when the sensory input is ambiguous, such activity occurs only in a subset of neurons.

Elevated neuronal activity is not the only way that a prior stored in the size of sensory representations could be read out. Another possibility, recently proposed in unpublished work (Simoncelli, 2009), is that the decoder is unaware of the change in sensory representations: such a scheme leads to the same degree of prior bias as our simulation. The major difference between these two schemes is that in our simulation the degree of bias is adjustable and dependent on task conditions rather than being a fixed and inbuilt property of the decoder. Recent experimental work has suggested that the degree of bias for long-term priors may be dependent on task conditions (Feldman et al., 2009).

Different levels of intrinsic, “baseline” activity in primary sensory cortices have been shown to profoundly influence neuronal responses to sensory stimuli (Arieli et al., 1996; Fiser et al., 2004), sensory perception (Ress and Heeger, 2003) and motor behaviors (Fox et al., 2007). In our model, the level of internally driven activity depends on the uncertainty of auditory input. It remains to be determined how this sensory uncertainty is encoded and used to optimize performance. Task-related uncertainty has been shown to

modulate baseline activity (Basso and Wurtz, 1997), possibly by activation of neuromodulatory systems, thereby influencing the extent to which behavioral responses depend on internal prior information versus external sensory information sources (Yu and Dayan, 2005). Another possibility is that the background noise that characterizes ambiguous sensory situations nonspecifically activates auditory cortex to achieve the same end as elevated spontaneous activity. However, unlike elevated spontaneous activity, noise activates neurons in different regions of auditory cortex differentially (Schreiner et al., 2000) and its effects can therefore not be directly inferred from this study.

Maximum-likelihood estimation is an unbiased feature decoding method. With a sufficient number of neurons, as well as the knowledge of which part of the neuronal activity is due to the input stimulus, its decoding result always converges on the input stimulus (Figure 3.3). In earlier studies of Bayesian integration, top-down prior-related activity and cross-modal sensory activity were linearly combined with, and not distinguished from, stimulus driven activity (Ma et al., 2006). Perceptual biases arise out of this treatment of prior-encoding or cross-modal activity. We treated spontaneous activity similarly in our simulation – the decoder does not distinguish it from stimulus driven activity.

Elevating spontaneous activity results in greater decoding variability in our simulations (Figure 3.3). Thus, stimulus-decoding performance is decreased. However, the increase in spontaneous activity in our model is caused by task demand when the sensory input is ambiguous, and cannot be resolved by simple (optimal) stimulus decoding. It enables integration of prior information to optimally resolve stimulus ambiguity. Furthermore, decoding variability decreases rapidly when more neurons are included in the model (Figure 4), and therefore may not pose a problem for the real brain.

Although our model is based on tonal frequency representations in primary auditory cortex, it should generalize to any stimulus dimension represented by populations of plastic sensory neurons. Over-representation of frequently experienced stimuli is a common feature of primary sensory cortex independent of modality, and occurs for sound intensity (Polley et al., 2006), sweep direction (Insanally et al., 2009), spectral bandwidth [25] and temporal rate (Kim and Bao, 2009) in primary auditory cortex, line orientation (Sengpiel et al., 1999) in primary visual cortex, and whisker representation in primary somatosensory cortex (Kossut, 1998), to name a few examples. Maximum likelihood estimation has also been used to model sensory perception in multiple modalities (Seung and Sompolinsky, 1993; Jazayeri and Movshon, 2006). Although there are not many explicitly documented examples of perceptual bias towards long-term priors outside of the auditory system, recent work in the visual system has shown that subjects perform a line orientation discrimination task in a way that suggests bias towards line orientations that occur more frequently in the environment (Girshick et al., 2010). Our model may therefore generalize to sensory perception in general, rather than the specific case of auditory perception.

In summary, we have shown that long-term prior information in auditory perception may be stored in the sizes of primary auditory cortex frequency representations and be read out by non-selective increases in baseline activity. Such increase in baseline activity may be controlled by task demand through top-down influences, and when combined with stimulus-driven activity, allow Bayesian integration of prior and sensory information. Our model makes two unique testable predictions independent of sensory modality that distinguish it from other models of dynamic Bayesian integration: 1) percepts of ambiguous stimuli are biased toward stimuli with larger sensory representations; 2) ambiguous sensory input leads to a *non-selective* increase in baseline activity of all coding neurons.

Methods

Modeling frequency representations in AI. We modeled primary auditory cortex (AI) frequency representations with 800 independent Poisson-firing neurons. The parameters of the model were chosen based on properties of the primary auditory cortical neurons documented in the literature and our unpublished results. In particular, our experimental finding that the firing rates of neurons in auditory cortex exhibit significant variability, with a mean Fano factor value of 0.98 +/- 0.21 (Kim, 2008), led us to model neuronal firing as a Poisson process. Each neuron had a Gaussian-shaped response-frequency tuning curve as:

$$T_i(f) = \alpha e^{-\frac{(\text{frequency} - \mu)^2}{2\sigma(f)^2}} + \delta \quad (1)$$

where μ is the characteristic frequency, α is the maximum response magnitude, 2σ is the tuning bandwidth and δ is the baseline spontaneous firing rate. The distributions of tuning bandwidths (2σ) and maximum response magnitudes (α) are approximately lognormal, and based directly on our experimental observations. Lognormal distribution is characterized by two parameters—the mean and standard deviation of the logarithm of the investigated response property. The baseline spontaneous firing magnitudes exhibit an exponential distribution, which is characterized by a population mean. The tuning bandwidths, maximum response magnitudes and baseline spontaneous firing magnitudes of the model AI neurons were independently and randomly drawn from the corresponding distributions. The parameters of the distributions are listed in Table 1.

To replicate frequency representations seen in AI of naïve animals and animals with extensive prior experience of a specific tone (7 kHz) (Han et al., 2007), model characteristic frequencies (CFs) were either uniformly distributed on a logarithmic scale in the range of 1-32 kHz (naïve) or skewed such that more neurons were tuned to 7kHz (7-kHz-over-represented) (Figure 3.1). For the 7kHz-over-represented AI, CFs from 5 to 10 kHz were shifted to have a Gaussian distribution centered at 7kHz and with a standard deviation of 0.1 octave (Figure 3.1). Consistent with our experimental findings the

bandwidths of neurons in the over-represented range were slightly smaller (Table 1) (Han et al., 2007).

Modeling frequency perception. We modeled auditory perception by decoding the simulated population response to an input frequency using the maximum-likelihood decoding method (Seung and Sompolinsky, 1993; Han et al., 2007; Kim, 2008). Assume that, when stimulated with a tone of frequency f , the i th neuron of the model AI responds with $Rstim_i$ spikes. As the model neurons fire spikes in a Poisson-random fashion, $Rstim_i$ is a Poisson-random number with a mean of $T_i(f)$, where T_i is the neuron's response-frequency tuning curve. The probability of the neuron responding to f with $Rstim_i$ is

$$P(Rstim_i | f) = \frac{T_i(f)^{Rstim_i}}{Rstim_i!} e^{-T_i(f)} \quad (2)$$

The stimulus likelihood distribution derived from the population response \mathbf{Rstim} of all N model neurons (1, 2, ... N) is:

$$L(f | \mathbf{Rstim}) = P(\mathbf{Rstim} | f) = \prod_{i=1}^N P(Rstim_i | f) = \prod_{i=1}^N \frac{T_i(f)^{Rstim_i}}{Rstim_i!} e^{-T_i(f)} \quad (3)$$

When given the population response to an unknown frequency f , we can calculate the maximum-likelihood estimate of f , denoted as F , by maximizing the following log-likelihood function (Seung and Sompolinsky, 1993; Jazayeri and Movshon, 2006), using a sequential quadratic programming method (Powell, 1977),

$$\begin{aligned} \ln L(F) &= \sum_{i=1}^N \ln L_i(F) = \sum_{i=1}^N \ln P(R_i | F) = \sum_{i=1}^N \ln \left(\frac{T_i(F)^{R_i}}{R_i!} e^{-T_i(F)} \right) \\ &= \sum_{i=1}^N R_i \ln T_i(F) - \sum_{i=1}^N T_i(F) - \sum_{i=1}^N \ln(R_i!) \end{aligned} \quad (4)$$

where R_i is the response of the i th neuron and in this case refers to $Rstim_i$ (however, see below).

Modeling Bayesian integration. According to Bayesian integration theory, frequency perception depends both on prior-based expectation and sensory input (Kersten D, 2004; Kording and Wolpert, 2004; Feldman and Griffiths, 2007). In order to return an optimal stimulus estimate, the probability distributions representing each quantity should be combined according to Bayes' rule (Kording and Wolpert, 2004). The stimulus probability derived from the sensory stimulus-evoked responses \mathbf{Rstim} is the frequency

likelihood $L(f | \mathbf{Rstim}) = P(\mathbf{Rstim} | f)$. Here we explore the idea that prior probability is read out from the frequency representation by elevated spontaneous activity \mathbf{Rspont} across the whole population of neurons: $L(f | \mathbf{Rspont}) = P(\mathbf{Rspont} | f)$. It is important to distinguish $Rspont$ from δ , as in contrast to δ , which is part of the neuron's tuning curve and used in the maximum likelihood algorithm, $Rspont$ represents elevated spontaneous activity that the maximum likelihood decoder is not aware of.

We therefore modeled Bayesian integration of sensory input and prior-based expectation by calculating the stimulus likelihood function derived from the linear superposition of stimulus-evoked activity and elevated spontaneous activity (\mathbf{Rspont} and \mathbf{Rstim})(Figure 3.2C).

$$L(f | \mathbf{Rstim} + \mathbf{Rspont}) = P(\mathbf{Rstim} + \mathbf{Rspont} | f) \propto L(f | \mathbf{Rstim})L(f | \mathbf{Rspont})e^{-\sum_{i=1}^N T_i(f)} \quad (5)$$

When the frequency representation is homogeneous, equation 5 may be simplified as,

$$L(f | \mathbf{Rstim} + \mathbf{Rspont}) \propto L(f | \mathbf{Rstim})L(f | \mathbf{Rspont}). \quad (6)$$

which is in the form of Bayes rule. With inhomogeneous frequency representations, there is a small deviation from Bayes rule caused by an additional term, $e^{-\sum_{i=1}^N T_i(f)}$ (see equation 5).

Appendix 3.1: Figures

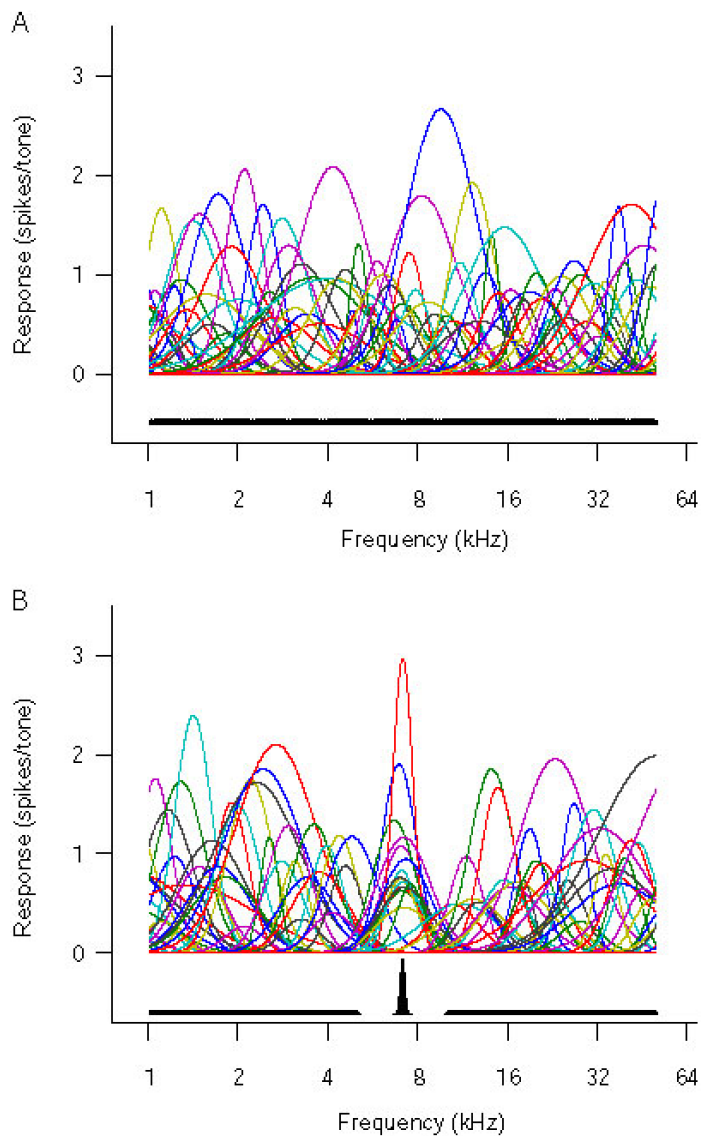


Figure 3.1. Modeling tonal frequency representations in the primary auditory cortex. Representative tuning curves of the naïve (A.) and the 7-kHz-over-represented (B.) model AI. The histograms in the lower part of the graphs show distributions of CFs.

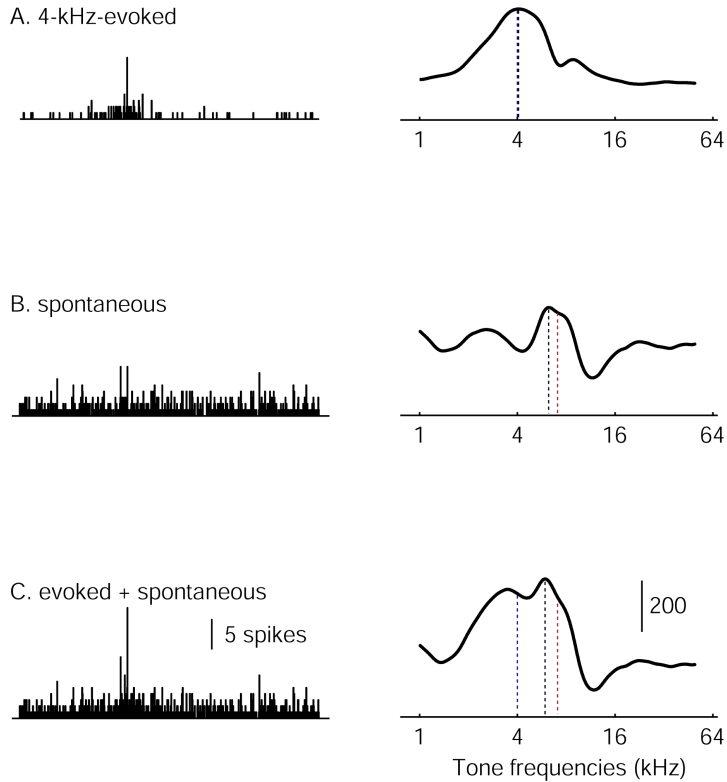


Figure 3.2. Neuronal population activity and derived log-likelihood functions. Left panels show population activity of the model 7-kHz-over-represented AI, and the right panels show stimulus log-likelihood functions. **A.** Response of the model to a 4-kHz tone pip **B.** Elevated baseline activity in the absence of a stimulus **C.** Summed spontaneous and 4-kHz-evoked activity). Each bar in the left panels represents the firing rate of a model neuron. The neurons are arranged by characteristic frequency, with low frequency-tuned neurons on the left and high frequency-tuned neurons on the right. Blue dotted lines in the right panels show the input frequency, red dotted lines show the over-represented frequency, and the black dotted lines mark the peaks of the log-likelihood functions.

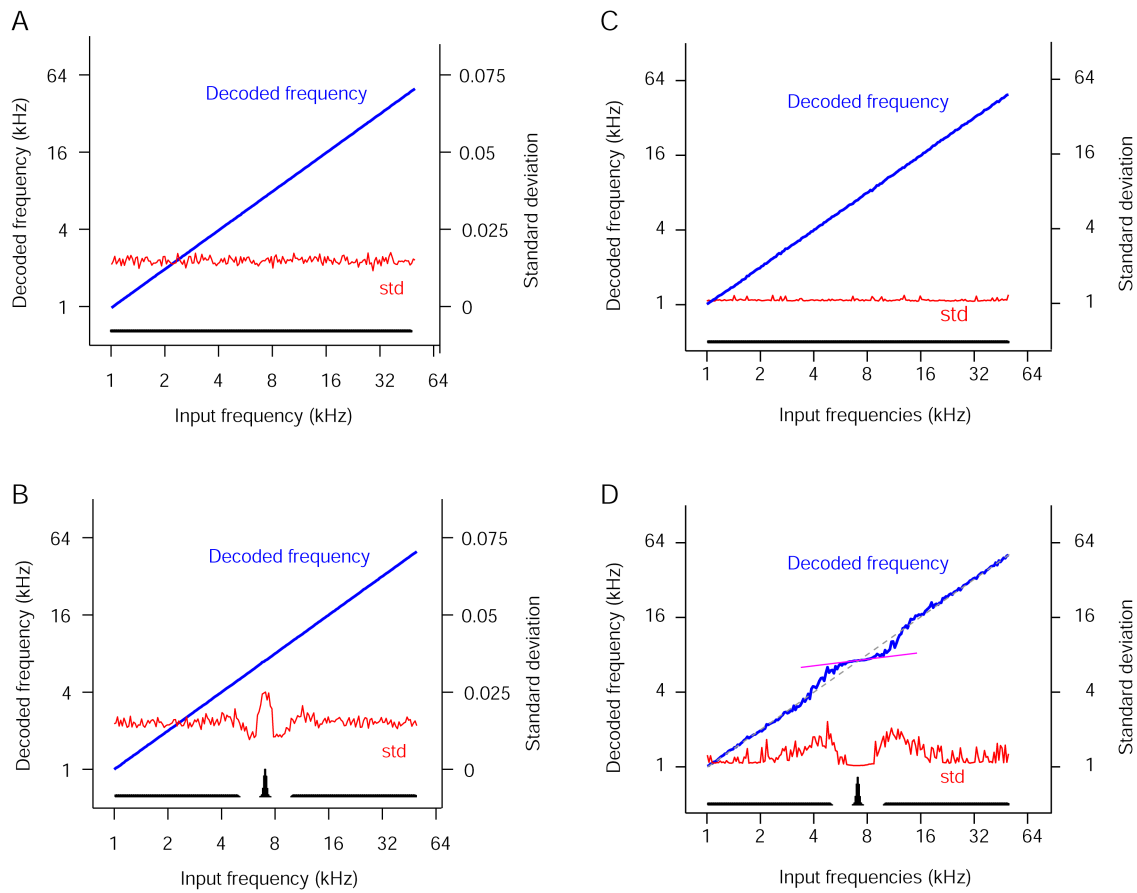


Figure 3.3. Decoded frequency as a function of input frequency. Both the naïve model AI (**A** and **C**) and 7-kHz-over-represented AI (**B** and **D**) were examined with (**C** and **D**) and without (**A** and **B**) elevated baseline activity. In addition, standard deviation of the decoded frequencies (red) was used to measure the output variability. When baseline activity was elevated in the 7-kHz-over-represented AI, the decoded frequencies show shifts characteristic of Bayesian prior bias (**D**). The pink line shows the slope of the input-output curve at the over-represented frequency. The slope is a measure of the prior bias.

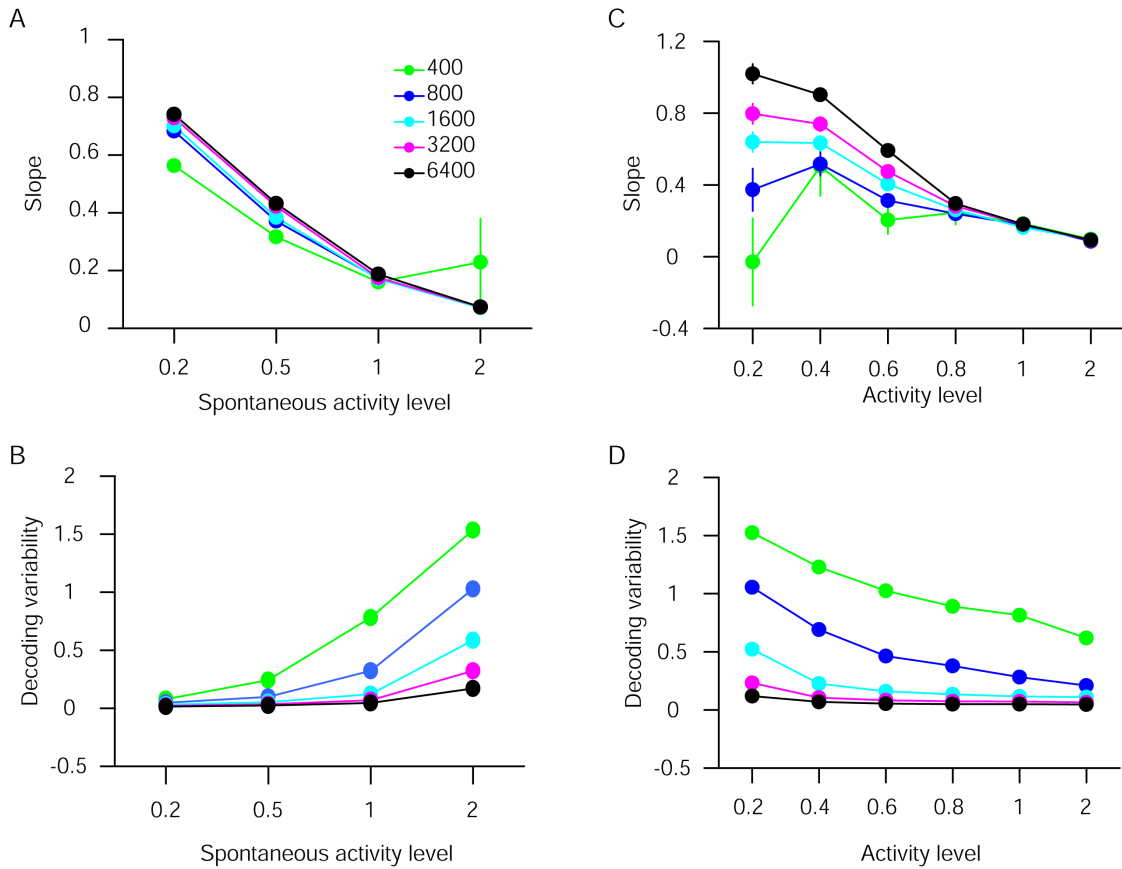


Figure 3.4. Influence of neuronal population size, baseline activity level, and overall activity level on sensory decoding. (**A** and **C**) Slopes of the input-output function (see the pink line in Figure 3.3D), showing the degree of prior bias. (**B** and **D**) Standard deviation of the decoded frequencies, which measures the decoding variability. In **A** and **B**, sensory-evoked activity level was fixed and the neuronal population size (color-coded) and baseline activity level were systematically varied. Baseline activity level refers to the multiplicative factor. For example, baseline activity level of 2 indicates doubling of activity. In **C** and **D**, the ratio of baseline activity to maximum evoked response magnitude was set at 1, and activity was systematically varied together. Error bars represent SEM, and are mostly masked by the data symbols.

Table 3.1. Distribution parameters of neuronal response properties.

Properties	Groups	Mean	SD
Log-bandwidth	Control	-0.7528	0.4727
	7-kHz, BFs of 7 kHz \pm 0.3 octave	-0.8723	0.2837
	7-kHz, other BFs	-0.6359	0.4583
Log-response magnitude	Control	-0.1815	0.5562
	7-kHz	-0.1774	0.5711
Baseline Spontaneous firing magnitude	Control	0.0388	N/A
	7-kHz	0.0374	N/A

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Chapter 4

Perceptual Consequences of Cortical Plasticity

Abstract

Perception has been described as a process of statistical inference, in which noisy sensory information is combined with prior knowledge to generate a best guess about the environment. An appealing hypothesis is that prior knowledge is stored in brain regions where sensory experience induces long-term changes in neural coding. Consistent with this hypothesis, our preliminary data shows that over-representation of a tone experienced during the critical period is correlated with a perceptual bias towards the over-represented tone. Increasing the ambiguity of the stimulus through the addition of noise exaggerates the bias towards the experienced tone. Animal perceptual behavior is qualitatively in line with that of an optimal statistical estimator combining sensory information with prior information learned during the critical period.

Introduction

Our perception of the world is constructed from uncertain sensory inputs. Because we often receive ambiguous information about the environment, we can only infer about external events (Geisler and Kersten, 2002). For example, an image appearing on the retina could either be a small object nearby, or a larger one further away; the geometrical information alone is not enough to know the object's size or distance.

We can improve our estimation by incorporating expectations based on experience. In the example above, prior knowledge about the object's size can help us make a better distance judgment. According to a statistical theory known as Bayesian inference (Geisler and Kersten, 2002), an optimal stimulus estimate takes into account both sensory information and prior knowledge.

Psychophysical experiments in humans and other animals show that perceptual biases observed across a range of sensory and motor tasks can be explained using the Bayesian inference framework (Knill and Richards, 1996; Geisler et al., 2001; Kording and Wolpert, 2004; Feldman et al., 2009; Fischer and Pena, 2011; Girshick et al., 2011). This suggests that subjects have internal representations of previously encountered stimulus probability distributions—the Bayesian prior—and are able to combine them with sensory information in a statistically optimal manner. Theoretical work (Kover and Bao, 2010) presented in Chapter 3 (see also (Simoncelli, 2009; Ganguli and Simoncelli, 2010)) suggests that the prior may be stored in brain regions where sensory experience induces long-term changes in neural coding. Such changes occur in primary sensory cortices, where stimulus representations are highly adaptive to the sensory environment, and more frequently experienced stimuli become over-represented at the expense of less frequently experienced ones (Zhang et al., 2001; de Villers-Sidani et al., 2007; Han et al., 2007).

Recent experimental work supports the idea that inhomogeneities in neural stimulus representations can account for perceptual biases observed in visual orientation perception (Girshick et al., 2011), and auditory sound localization (Fischer and Pena, 2011). However, these studies leave open whether the priors in question are innate or learned—in other words, the result of evolutionary, or developmental shaping of neural stimulus representations. More broadly speaking, although the psychophysical evidence for Bayesian inference in perception has been steadily growing, very little is known about the physiological mechanisms by which statistical priors are learned (Fiser et al., 2010).

In the present study, we directly test the hypothesis that manipulating stimulus probabilities during the early “critical period” of plasticity leads to perceptual bias towards cortically over-represented frequencies. Our preliminary results indicate that exposing rat pups to 7kHz tone trains during early development leads to systematic perceptual biases towards the exposed tone. Increasing the ambiguity of the stimulus

through the addition of noise exacerbates the bias towards the experienced tone. Perceptual changes were accompanied by changes in frequency representation in primary auditory cortex. The behavioral data is qualitatively in line with that of an optimal Bayesian estimator performing a categorization task in the presence of a prior learned during the critical period.

Results

Early experience leads to a perceptual bias

We exposed a litter of rat pups to 7kHz tone pips from postnatal day 9 (p9) to p30, which encompasses the entire critical period. Following sound rearing, animals were maintained in normal animal housing conditions. Naïve control animals were raised entirely in normal animal housing conditions, with no additional tone exposure. When animals reached two months of age, we trained them to differentially respond to two target frequencies, 7.5kHz and 15kHz, by making a nose poke in one of two nose-poke holes (Figure 4.1A). The majority of tone-exposed and naïve control animals learned this task over the course of 25-30 days of training (Figure 4.1B), with no differences in learning rate between the two groups. Animals in both groups showed biases towards the right nose-poke hole (see Supplementary Figure 4.S1), but did not differ in performance for the 7.5kHz or 15kHz components of the task.

Following the training phase, we determined the psychometric frequency-perception functions for both groups by adding 5 intermediate test frequencies that were logarithmically spaced along the frequency axis. Test frequency probe trials were unrewarded and only occurred on 15% of trials. In the tone-exposed animals psychometric functions were systematically shifted towards the rearing frequency relative to naïve controls (Figure 4.1C; 2 group x 7 frequency ANOVA, main effect of group $F(6,84)=48.52, p<0.001$). *Post hoc* t-tests demonstrated that performance between groups did not differ for the endpoints (7.5kHz and 15kHz), but that perception of intermediate probe tones was biased towards 7.5kHz (Figure 4.1C). This trend was mirrored in the reaction time data (Supplemental Figure 4.1), which showed a trend for a rightward shift in the maximal point of uncertainty (longest reaction time) in tone-exposed relative to control animals.

Noise exacerbates perceptual bias

According to the Bayesian inference framework, reliance on prior knowledge should increase as uncertainty about the stimulus increases. To test this prediction, we conducted additional testing (Figure 4.1A) during which we added uniform white noise to all stimuli. In the tone-exposed animals, addition of noise led to a trend for increased bias towards 7.5kHz relative to both naïve controls and reared animals without noise (not

significant). In naïve controls, addition of noise led to a trend for biases towards both task endpoints (not significant) (Figure 4.1C).

Perceptual bias towards cortically over-represented frequencies

Previous studies (Simoncelli, 2009; Fischer, 2010; Kover and Bao, 2010; Fischer and Pena, 2011; Girshick et al., 2011) (see also Chapter 3) have suggested that enlarged cortical representations of experienced stimuli may function as a mechanism for biasing perception towards these stimuli. To confirm that experienced frequencies were over-represented in our subjects, we mapped primary auditory cortex of tone-exposed and control animals that participated in the task. Consistent with previous findings (Zhang et al., 2001; Han et al., 2007), tone-exposed animals had a larger representation of 7kHz compared to controls (Figure 4.2). We found no evidence of task-related over-representation of 7.5 or 15kHz in naïve or tone-exposed animals.

Discussion

Our preliminary results suggest that critical period experience of a sound stimulus in rats leads to a perceptual bias towards the experienced tone, as well as an over-representation of that tone in the primary auditory cortex. These results are consistent with recent reports that inhomogeneities in neuronal stimulus representations may be related to perceptual biases (Fischer and Pena, 2011; Girshick et al., 2011), and add support to the hypothesis that cortical stimulus representations may function as the neural manifestation of Bayesian priors (Simoncelli, 2009; Ganguli and Simoncelli, 2010; Kover and Bao, 2010). Our results go beyond these studies by showing that perceptual biases mirrored in representational inhomogeneities can be acquired on developmental, as opposed to evolutionary time-scales. This suggests that critical period plasticity may be one mechanism by which stimulus distributions are internalized to shape perception and behavior.

Statistical learning plays a critical role during early development, when the neural circuitry to support supervised learning is not yet in place. Human infants are exquisitely sensitive to the statistical distributions of acoustic stimuli (Saffran et al., 1996; Maye et al., 2002), which are thought to directly influence speech sound perception (Kuhl, 2000) in ways that are consistent with statistical inference (Feldman et al., 2009). During the critical period in early development, neuronal plasticity in primary sensory cortices is enhanced, and exposure to different sensory environments leads to dramatic and long-lasting changes in cortical representation. Although it has generally been assumed that these changes serve to improve either sensory processing or sensory perception, very few studies have directly examined this question. Here we provide evidence that one function

of critical period plasticity may be to learn the statistics of sensory stimuli in order to make perceptual judgments that are optimized to the animals' particular environment.

Our preliminary data suggests that even in conditions of relatively low external noise, perception can be biased towards prior experience. Interestingly, our preliminary results in the presence of noise (not significant) suggest that noise alters control and tone-exposed psychometric functions in qualitatively different ways. In naïve controls, noise appears to lead to symmetric biases towards both endpoints on the task, whereas in the tone-exposed animals, we see an asymmetric bias towards the experienced frequency. One possible explanation for this observed trend is that in naïve animals, perception is biased towards two short-term, task-related priors that have been learned over the course of 25-30 days of training. Previous theoretical work relating to speech sound perception has suggested that in the presence of two Gaussian prior categories, increasing stimulus uncertainty could cause perceptual warping towards the center of whichever prior category is more likely (Feldman et al., 2009)—in our case, whichever task endpoint is more likely given the noisily perceived stimulus. By this logic, we would expect that in tone-exposed animals both task-related and early-experience related priors would affect perception, with the early-experience related prior causing the asymmetry of the observed bias. Future work will be necessary to tease apart the respective roles of each type of bias.

If this task does indeed depend on both task-related and early-experience related prior information, an interesting question relates to their respective neural representations. Previous work has shown that enlarged cortical stimulus representations such as the one observed in this study could account for the observed perceptual bias through simple biologically plausible decoding mechanisms such as population vector decoding (Fischer, 2010; Fischer and Pena, 2011; Girshick et al., 2011). However, we found no potential neural candidates for task-related priors. This is consistent with a large body of literature showing that while critical period plasticity produces dramatic and long-lasting changes in cortical representations (de Villers-Sidani et al., 2007), long-term neural effects of adult behavioral training are often subtle or entirely absent in anaesthetized recordings (Ghose et al., 2002). By contrast, studies in awake behaving animals have shown task-related changes in neural tuning curves (Basso and Wurtz, 1998; Platt and Glimcher, 1999; Rickert et al., 2009) that have been proposed to function as neural representations of short-term priors (Ma et al., 2006). During adulthood, statistical priors may be learned by different mechanisms, on different time-scales, or in different brain regions than those addressed in this study. Future work using recording techniques in awake animals will be necessary to gain further insight into this question.

Methods

Acoustic rearing and behavioral testing. All procedures used in this study were approved by the UC Berkeley Animal Care and Use Committee. A litter of Sprague Dawley rat pups was placed with its mother in an anechoic sound-attenuation chamber from p9 to p30. This time period comprises the critical period for experience-dependent plasticity in primary auditory cortex (AI). Trains of tone pips (7kHz, 60dB SPL, 100-ms pip duration, five pips in a train at 5hz, one train every 2 s) were played to the animals 24 h per day. After p30, animals were placed back into normal animal rooms. Behavioral training began at p60. Only females were used in this study. Tone-exposed animals (preliminary data $n = 3$) and control animals raised in the animal room ($n=14$) were food-deprived to reach a 10% body-weight reduction before training started. Training took place in a wire cage located in an anechoic sound-attenuation chamber. On automatic initiation of a trial, tone pips of either 7.5kHz or 15kHz, at 100-ms duration were played 5 times per s through a calibrated speaker located directly overhead. Initially, the animal was given unlimited time to make a nose poke in one of two nose poke holes—over the course of 25-30 days of training the response window was decreased to 10 seconds. For data reported in the main text, 7.5kHz always required a leftward nose-poke to obtain a food-pellet reward, whereas 15kHz required a rightward nosepoke. An additional group of animals ($n=6$) was trained with the nose-poke holes reversed (Supplementary Figure 4S.1). Animals reaching 65% performance or more over the course of 30 days of training were included in the psychometric testing stage. Psychometric testing involved the addition of 5 intermediate frequencies. Intermediate frequency trials were unrewarded and kept at 15% to keep animals motivated. Following 5-7 days of psychometric testing, psychometric testing in the presence of noise began. During this stage, we added 100ms of uniformly sampled white noise (5msec ramp) to all task stimuli. The relative noise:stimulus amplitude ratio was 0.2. Noise testing continued for 5-7 days.

Electrophysiological recording procedure. The primary auditory cortex (AI) of tone-exposed ($n = 3$) and control rats ($n = 4$) were mapped immediately after completion of noise testing. Rats were preanesthetized with buprenorphine (0.05 mg/kg, s.c.) a half hour before they were anesthetized with sodium pentobarbital (50 mg/kg, followed by 10-20 mg/kg supplements as needed). Atropine sulfate (0.1 mg/kg) and dexamethasone (1 mg/kg) were administered once every 6 h. The head was secured in a custom head-holder that left ears unobstructed, and the cisterna magna was drained of CSF. The right auditory cortex was exposed through a craniotomy and duratomy and was kept under a layer of silicone oil to prevent desiccation. Sound stimuli were delivered to the left ear through a custom-made speaker that had been calibrated to have <3% harmonic distortion and flat output in the entire frequency range.

Cortical responses were recorded with tungsten microelectrodes (FHC). Recording sites were chosen to evenly and densely map primary auditory cortex while avoiding surface blood vessels and were marked on an amplified digital image of the cortex. Microelectrodes were lowered orthogonally into the cortex to a depth of 500 – 600 μm where responses to noise bursts could be found. Multiunit responses to 25 ms tone pips of 51 frequencies (1-32 kHz, 0.1 octave spacing, 5 ms cosine-squared ramps) and eight sound pressure levels (0-70 dB SPL, 10-dB steps) were recorded to reconstruct the frequency-intensity receptive field. For each neuron, the characteristic frequency (CF) was determined as the frequency at which responses are evoked at threshold: the lowest sound pressure level that activates the neuron.

Statistical testing. Unless stated otherwise, statistical significance was determined using ANOVA and *post-hoc* two tailed t-tests (MATLAB, Mathworks).

Appendix 4.1: Figures

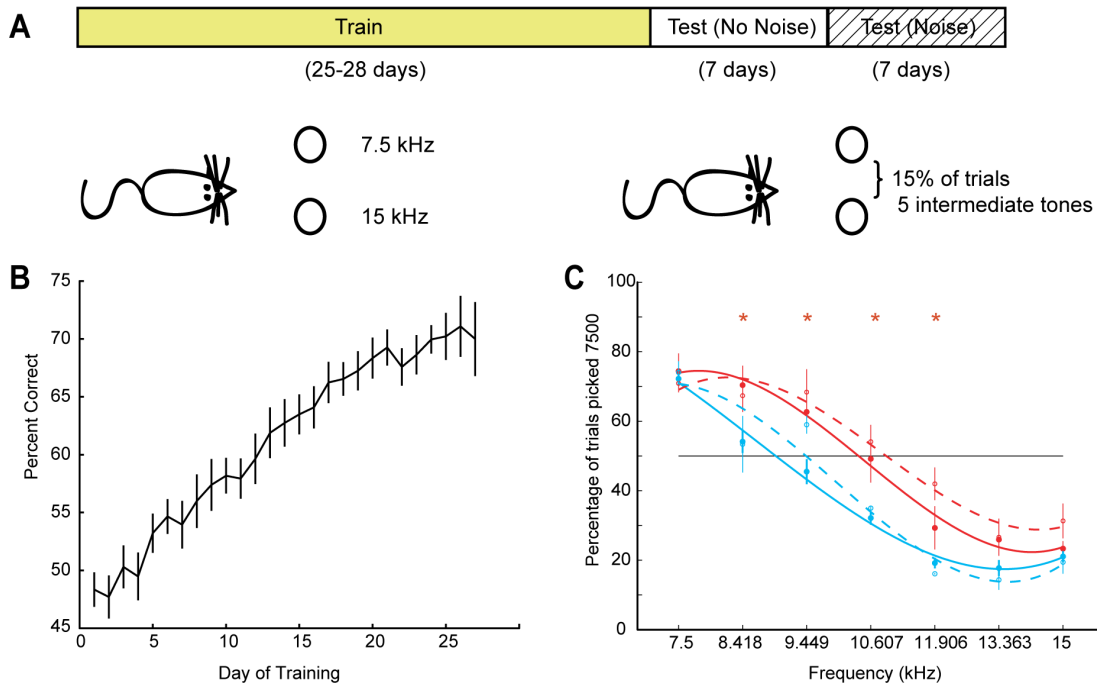


Figure 4.1. Behavioral training procedure and perceptual results. **A.** Naïve control and tone-exposed animals were trained for 25-28 days until they achieved at least 65% performance on the task. Following training, all animals underwent 7 days of psychometric testing with 5 intermediate, unrewarded probe frequencies, followed by 7 days of testing in the presence of background noise. **B.** Learning curves over the course of task training. **C.** Psychometric functions for naïve (cyan) and tone-exposed (red) animals in the absence (solid line) and presence (dotted line) of noise. Perception was systematically shifted towards the experienced frequency (7kHz) in tone-exposed animals. * $p < 0.05$, $n = 3$ tone-exposed, $n = 11$ controls.

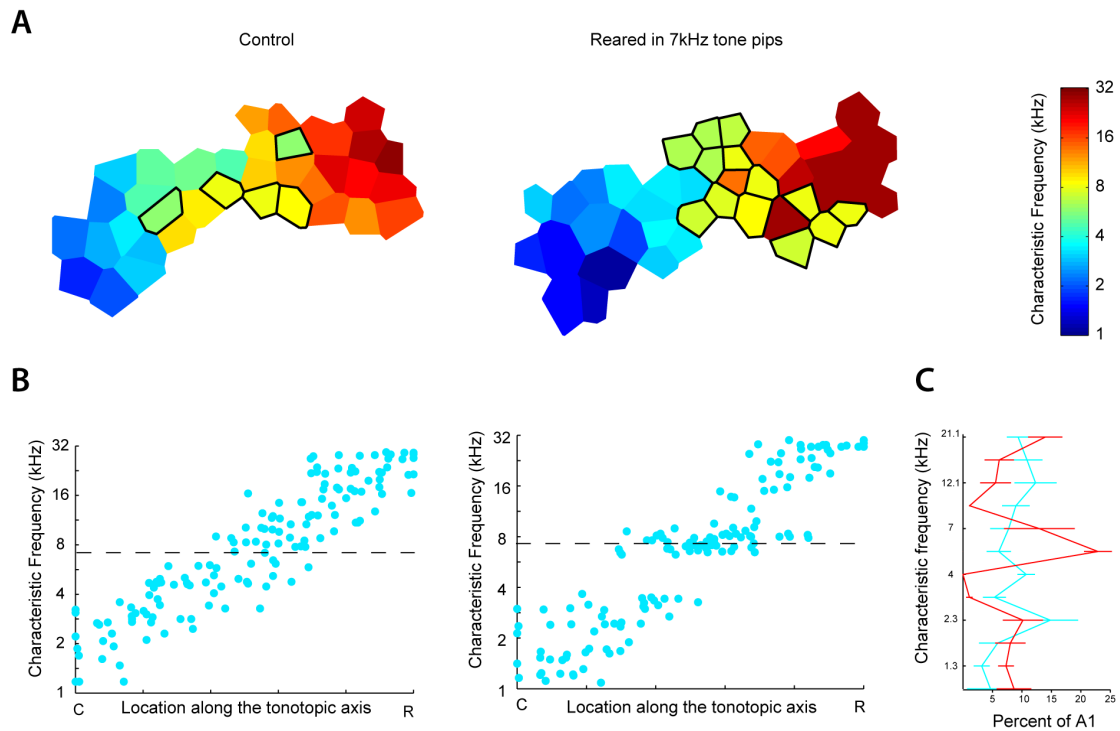
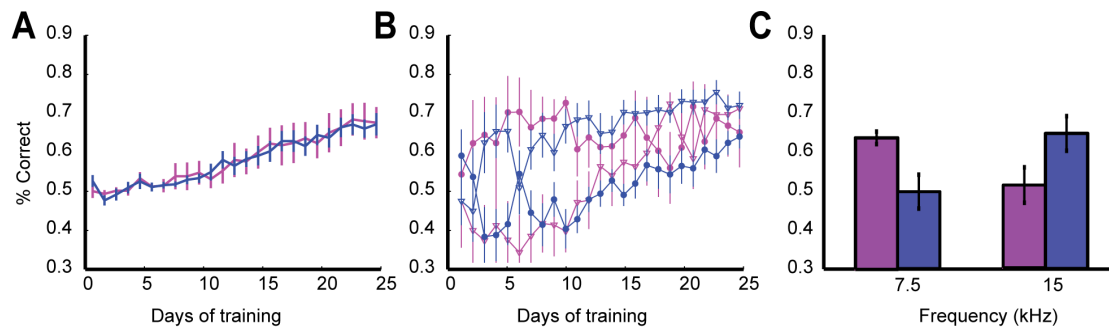
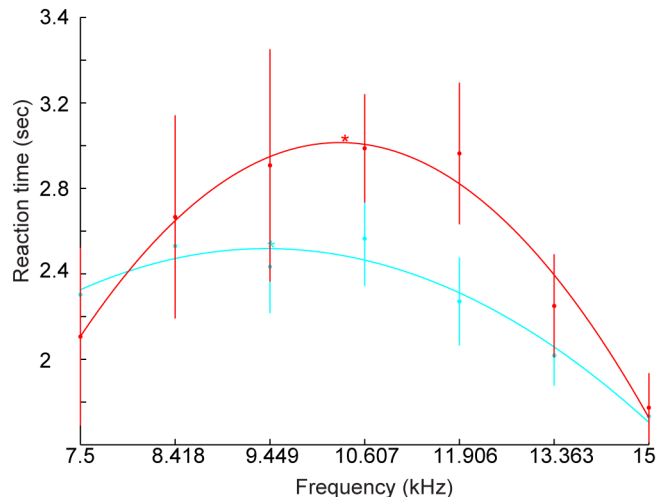


Figure 4.2. Enlarged representation of the experienced frequency. **A.** Representative cortical characteristic frequency maps from a control animal that experienced training and testing, and a 7kHz exposed animal that experienced training and testing. **B.** Distribution of characteristic frequencies as a function of location along the tonotopic axis for control and tone-exposed. **C.** Percent of A1 tuned to different characteristic frequencies. Cyan = control, red = tone-exposed, * $p < 0.05$, $n = 3$ tone-exposed, $n = 4$ control

Appendix 4.2: Supplementary Figures



Supplementary Figure 4.S1. Animals show systematic right-ward poking bias **A.** Training data for two groups of side-counterbalanced animals trained to poke left for 7.5kHz and right for 15kHz (blue) and left for 15kHz and right for 7.5kHz (magenta). There are no overall differences in performance between the groups. **B.** Training data separated by 7.5kHz (filled circles) and 15kHz trials (open triangles). Animals performed better on whichever frequency required a rightward nose poke. **C.** Summary data across all days of training. There was no significant effect of group or frequency, and a highly significant group by frequency interaction, $***p < 0.001$. On the basis of these results, we concluded a rightward poking bias, and only animals who had been trained on the left = 7.5kHz and right = 15kHz task were included for further analysis.



Supplementary Figure 4.S2. Reaction times mirror psychometric function data. For tone-exposed animals (red), the longest reaction time (maximal point of uncertainty) is shifted away from 7.5kHz relative to control animals (not significant).

Appendix 4.3: Supplementary Information

The results presented in Chapter 4 show that perceptual biases towards a tone experienced during the critical period are accompanied by an enlarged representation of that tone in primary auditory cortex. To establish a more causal link between the representational change and perceptual bias, we attempted to measure the perceptual effects of artificially inducing cortical plasticity outside of a behavioral context.

To this end, we trained naïve animals on the categorization task described in Chapter 4, tested their perception of intermediate tones, and then exposed them to 20 days of nucleus basalis stimulation paired with one of the two categorization tones. Previous work has shown that this procedure can lead to representational changes similar to those seen after critical period tone exposure (Kilgard and Merzenich, 1998). Following NBS tone pairing, we re-tested performance to observe any perceptual changes, and also mapped primary auditory cortex to assess the neural effects of NBS tone-pairing.

Contrary to previous reports (Kilgard and Merzenich, 1998), we did not observe cortical plasticity in the animals that underwent NBS tone-pairing (Figure 4.S3B). This was despite the fact that we observed decorrelation in the EEG in response to stimulation in four out of five subjects (Figure 4.S4). EEG decorrelation, specifically measured as an increase in power in the gamma frequency band relative to the alpha frequency band, is a hallmark of nucleus basalis activation. We also did not observe any perceptual changes following NBS tone pairing (Figure 4.S3C).

These negative results do not offer any evidence for or against the hypothesis that changes in cortical representation causally result in changes in perceptual bias. Several factors might have contributed to the lack of plasticity seen following NBS tone pairing in this study. First, very recent experimental results (Reed et al., 2011) show that when NBS tone pairing follows prolonged learning and mastery of a frequency-identification task similar to the one used in our study, primary auditory plasticity is not present when measured after completion of NBS tone pairing. Thus, it is possible that the specifics of our experimental design precluded persistent changes in primary auditory cortical representation.

Another possibility is that our chronic stimulating electrodes were not correctly targeting the nucleus basalis. The nucleus basalis is located deep within the basal forebrain, and even minute asymmetries in the positioning of the stereotax could in principle preclude NB activation upon stimulation. Anatomically verifying the location of the stimulating electrodes post experiment would be desirable.

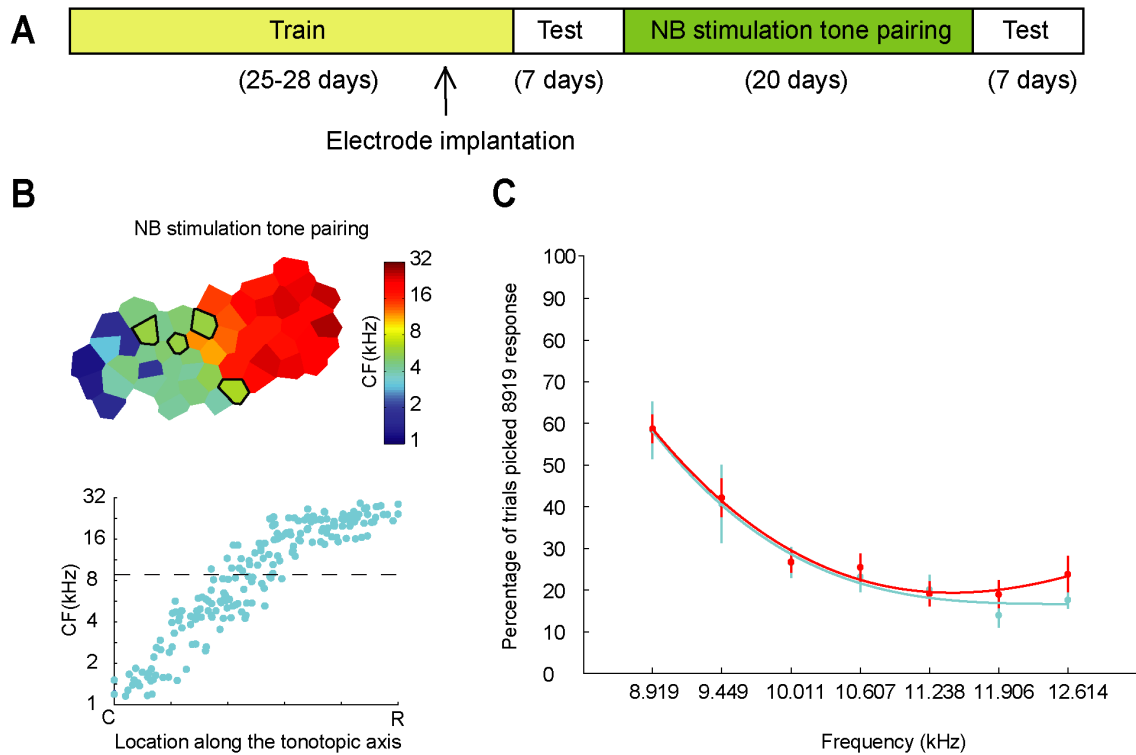


Figure 4.S.3. Nucleus basalis stimulation tone pairing. **A**. Experimental protocol. Naïve animals were trained on the categorization task (8.919kHz versus 12.614kHz), implanted with chronic stimulating electrodes and tested on intermediate frequencies. Following this initial testing, they underwent 20 days of nucleus basalis stimulation paired with 8.919 kHz. Finally, they were re-tested on intermediate frequencies. **B**. Nucleus basalis stimulation did not lead to enlarged representation of the paired tone in primary auditory cortex. Top: representative map from an example subject. Bottom: compiled data for 3 animals. **C**. Psychometric testing data before (cyan) and after (red) stimulation. There were no significant differences between groups, $n = 4$.

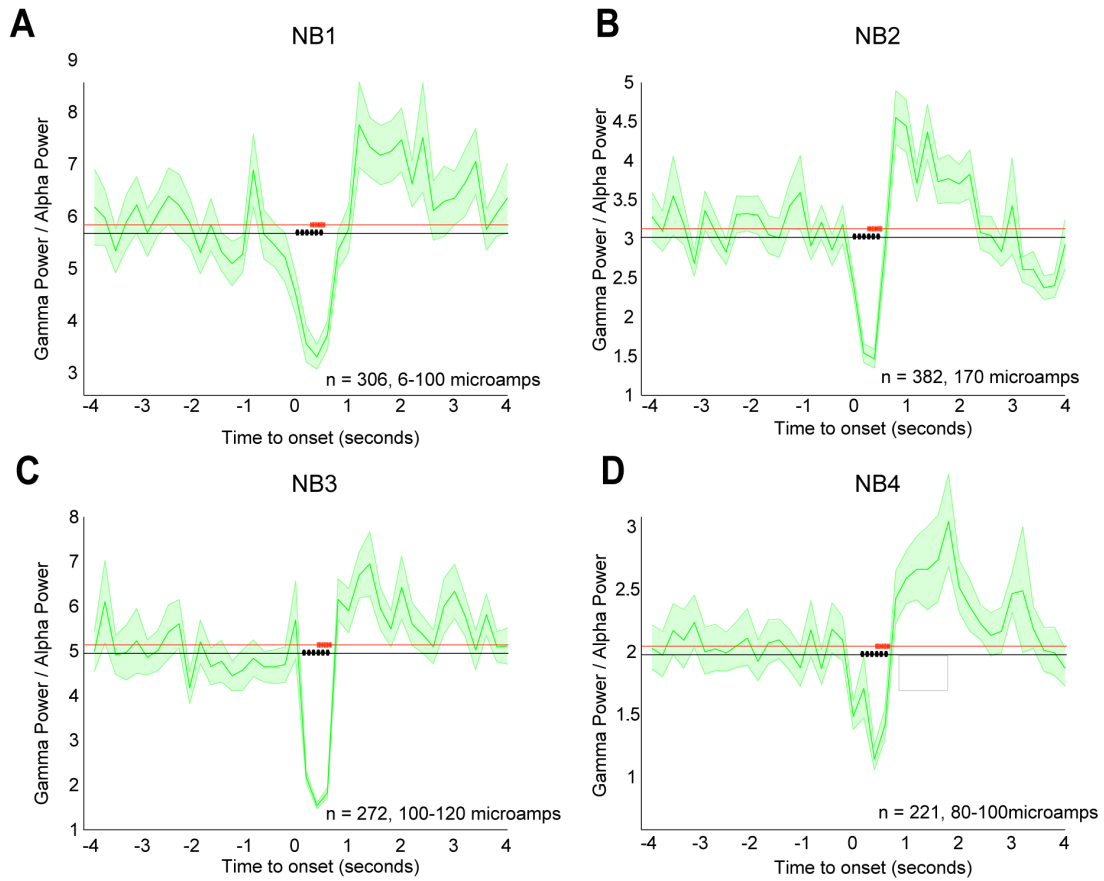


Figure 4.S.4. Nucleus basalis stimulation tone pairing causes desynchronization of the cortical EEG. **A.-D.** Ratio of gamma band power to alpha band power in four subjects undergoing nucleus basalis stimulation. Following the occurrence of the tone (black) and stimulation (red), gamma band power increases relative to alpha band power.

Supplementary Methods

All procedures used in this study were approved by the UC Berkeley Animal Care and Use Committee. Five female Sprague Dawley rats (290-310g; 3-6 months old) were used in this experiment. Behavioral training and electrophysiological procedures were identical to those described earlier in this Chapter, except that 4 out of 5 of the subjects were trained on a 0.5 octave, rather than a 1 octave, categorization task (8.819 kHz versus 12.614 kHz). After 25-30 days of testing, once animals reached at least 65% performance, they were allowed free access to food for 3 days before implantation of chronic NBS electrodes, as described previously in (Bao et al., 2003). Briefly, subjects were kept anesthetized with a continuous stream of 2% isoflurane gas. Stainless steel bipolar stimulating electrodes (SNE-200, Rhodes Medical Instruments, Woodland Hills, CA; 0.55mm separation, 12mm shaft) were stereotaxically implanted into the right nucleus basalis (3.3 mm lateral and 2.3 mm posterior to bregma, 7.0 mm below the cortical surface). Three bone screws were threaded into a burr hole on the skull to anchor the electrode assembly. Leads were attached to the screws over the cerebellum and cortex to monitor cortical EEG during NB stimulation. After a two week recovery period, animals received a few more training days before advancing to psychometric testing. Following 7 days of psychometric testing, we tested for the threshold of current microstimulation (20 biphasic pulses of 0.1msec duration at 100 Hz) necessary to desynchronize cortical EEG during slow-wave sleep. Thresholds varied between 40 μ A and 170 μ A. All subjects received 20 days of pulsed tone pips (6 25msec tone pips; 5 msec on/off ramps; delivered at a rate of 15 pips per second; 65dB sound pressure level) with NB microstimulation (20 biphasic pulses of 0.1 msec duration at 100 Hz, initiated 200 msec after sound onset). Following NBS tone pairing, animals were trained for 1-2 days to ensure task retention, and then tested for intermediate tones as before for 7 days.

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Chapter 5

Conclusions and Opportunities for Future Research

The purpose of this dissertation was to examine the neural and perceptual consequences of manipulating the acoustic environment during the critical period. Previous studies investigating critical period plasticity focused predominantly on the neural effects of simple, single-frequency manipulations, with very little work investigating the perceptual consequences. We sought to add to the existing literature by examining the effects of more complex stimulus environments, as well as downstream perceptual effects.

In Chapter 2, we showed that the development of receptive fields in primary auditory cortex is sensitive to the spectrotemporal relationships between sounds. Specifically, sounds that were played together within one-second sequences tended to be represented by the same population of neurons, whereas sounds that occurred together on longer time-scales (on the order of seconds) were represented separately. This suggests that the relative timing of sound inputs plays an important role in determining the nature of cortical representational change.

An important outstanding question concerns the neural mechanisms underlying this temporal dependence of plasticity. A previous study found that critical period plasticity in rats is enhanced for sounds repeated at 6Hz relative to other modulation rates (Kim and Bao, 2009). This result, together with our finding that sounds within 6Hz sequences are represented together, suggests the existence of a cortical integration window for plasticity on the order of hundreds of milliseconds. Further work investigating the dynamics of neuronal response properties in young animals will be necessary to elucidate this further.

Another outstanding question relates to the locus of the observed neural tuning changes. Recent work suggests that critical period tone exposure leads to representational changes in the primary auditory cortex but not the thalamus (Barkat et al., 2011), implicating the cortex as a primary site of critical period plasticity. Within the cortex, changes in neural tuning could arise from plasticity at thalamocortical or intracortical synapses (Liu et al., 2007). Teasing apart their respective contributions will be an important step in understanding critical-period plasticity at a circuit level.

In Chapters 3 and 4, we propose a model for how changes in cortical sensory representations may affect perception within a statistical inference framework. Our model shows that enlarged stimulus representations may function as the neural representation of a Bayesian prior, and preliminary behavioral results support this idea. However, our current findings are purely correlational—we were not able to establish a causal link between cortical plasticity and perceptual change. Future work that either artificially induces or inhibits primary auditory cortical plasticity will be necessary to establish such causality.

In addition, our model is limited in that it considers only static, spectral priors. As our work in Chapter 2 shows, the temporal dependencies between sounds contain information that not only shapes neural tuning in primary auditory cortex, but also has downstream

perceptual effects. Whether the perceptual changes observed in Chapter 2 can be understood in a similar statistical inference framework as the one proposed in Chapter 3 is an interesting question that requires future theoretical work. More broadly speaking, while we propose that long-term changes in neural representation could be a mechanism of prior bias in contexts where experience induces long-term perceptual biases, we believe it likely that neural priors can be learned on multiple time scales and by different mechanisms. One promising line of research investigates the manifestation of short-term priors in the form of short-term changes in neuronal gain (Basso and Wurtz, 1998; Rickert et al., 2009).

Finally, as expressed in Chapter 1, a more comprehensive characterization of the three-way relationship between the statistics of the early sensory environment, neural tuning in primary sensory cortex, and sensory perception will likely provide important insights into the goals underlying sensory coding. This dissertation has provided a small step in this direction, and we are looking forward to the work to come.

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