Behavioral/Systems/Cognitive

Differential Dynamic Plasticity of A1 Receptive Fields during Multiple Spectral Tasks

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Auditory experience leads to myriad changes in processing in the central auditory system. We recently described task-related plasticity characterized by rapid modulation of spectro-temporal receptive fields (STRFs) in ferret primary auditory cortex (A1) during tone detection. We conjectured that each acoustic task may have its own "signature" STRF changes, dependent on the salient cues that the animal must attend to perform the task. To discover whether other acoustic tasks could elicit changes in STRF shape, we recorded from A1 in ferrets also trained on a frequency discrimination task. Overall, we found a distinct pattern of STRF change, characterized by an expected selective enhancement at target tone frequency but also by an equally selective depression at reference tone frequency. When single-tone detection and frequency discrimination tasks were performed sequentially, neurons responded differentially to identical tones, reflecting distinct predictive values of stimuli in the two behavioral contexts. All results were observed in multiunit as well as single-unit recordings. Our findings provide additional evidence for the presence of adaptive neuronal responses in A1 that can swiftly change to reflect both sensory content and the changing behavioral meaning of incoming acoustic stimuli.

Key words: **auditory; cortex; attention; plasticity; STRF; behavior**

Introduction

Listening is an active process in which our experience, goals, and expectations shape our percepts in complex ways (Handel, 1989). In active listening, our ears receive an acoustical kaleidoscope of overlapping and changing sounds, and our auditory system performs an extraordinary real-time acoustic scene analysis of this complex input and detects, discriminates, and identifies salient acoustic stimuli and sound sources (Handel, 1989; Bregman, 1990; Darwin and Carlyon, 1995; Alain and Arnott, 2000). We have recently developed an animal model to better understand the neural basis of active listening and the neural correlates of acoustic salience and initiated a series of physiological studies on behaving ferrets trained on multiple acoustic tasks, including spectral detection and discrimination. In previous work (Fritz et al., 2003, 2005a,b), we described a form of adaptive receptive field plasticity in primary auditory cortex (A1) that could be rapidly induced as the ferret performed a tone detection task. In the present study, we report another variety of selective and rapid receptive field plasticity in A1 neurons, which occurs during performance of a two-tone frequency discrimination task.

Although compatible with previous studies of cortical plasticity after frequency discrimination training (Edeline and Weinberger, 1993; Blake et al., 2002), our findings of receptive field changes during two-tone discrimination in this study offer a fundamentally new perspective. We monitored single-unit plasticity in three novel contexts. (1) The first was simultaneous with animal behavior. In previous studies, receptive field plasticity was monitored (a) either before or after training rather than during training [with one exception (Ohl and Scheich, 1996)], (b) without voluntary behavioral responses (i.e., instead using autonomic measures of conditioning), or (c) in anesthetized animals. Here, we shall demonstrate a form of task-dependent receptive field plasticity (i.e., absent in naive animals with no behavioral training) that occurs quite swiftly, on the order of minutes, and can be monitored while the animal performs the task. (2) The second was during generalized cognitive behaviors with arbitrarily selected tonal frequencies. In contrast, previous studies that used trained animals in a frequency discrimination paradigm involved extended training on specific frequencies that induced long-term perceptual learning (Recanzone et al., 1993; Blake et al., 2002; Brown et al., 2004; Irvine et al., 2004). (3) The third was during a series of different behavioral tasks. A comparison of single-unit cortical receptive field plasticity in A1 during performance of multiple auditory behavioral tasks has not been reported previously. In our multitask experiments, we shall show that the identical tone stimulus can take on different meanings during tone detection and two-tone discrimination, and that these different behavioral meanings lead to differential receptive field effects. Consequently, these results demonstrate highly specific task-dependent rules of plasticity in A1 neurons and the ability of single A1 neurons to change response fields in different behavioral contexts.

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The combination of such task-dependent, adaptive neural plasticity and the resultant possibility that neurons and networks may multiplex for different perceptual tasks may be an important mechanism in A1 underlying active listening and a general principle of cortical processing during attentive behavior in other sensory systems (Iriki et al., 1996; Alain and Arnott, 2000; Iwamura et al., 2001; Fritz et al., 2003, 2005a,b; Mazer and Gallant, 2003; Boynton, 2004; Li et al., 2004; Maravita and Iriki, 2004; McMains and Somers, 2004; Petkov et al., 2004; Reynolds and Chelazzi, 2004; Brechmann and Scheich, 2005).

Materials and Methods

Three adult female ferrets were used in these experiments. Two were behaviorally trained, and one was a behaviorally naive control. All experimental procedures used in this study were approved by the University of Maryland Animal Care and Use Committee and were in accord with National Institutes of Health guidelines.

Behavioral paradigm and training. Two ferrets were trained on both a tone detection task and tone frequency discrimination task using conditioned avoidance procedures (Heffner and Heffner, 1995; Fritz et al., 2003, 2005a,b). One of the two ferrets had also been a subject in a previous set of behavioral physiology studies of tone detection (Fritz et al., 2003). Animals trained on the behavioral tasks were placed on a water schedule in which water intake was restricted to water reward during task performance 5 d/week (on weekends, the ferrets received water *ad libitum*). Animal condition was carefully monitored on a daily basis, and weight was maintained above 80% of maximal weight.

For the tone detection task, as described previously (Fritz et al., 2003), ferrets licked water from a spout while listening to a sequence of broadband reference stimuli (each 1.25 s in duration) until they heard a narrowband tonal target (also 1.25 s in duration). When presented with a tone, the animals were trained to stop licking to avoid a mild shock to the tongue. A trial run consisted of a sequence of reference stimuli (sequence length randomly ranged from one to six stimuli), followed by a tonal target [except on catch trials in which seven reference temporally orthogonal ripple combination (TORC) stimuli were presented with no tonal target]. Target likelihood was equiprobable at any point in a trial run (e.g., after a reference stimulus, the likelihood that the next stimulus was a target was fixed at ~22%).

The frequency discrimination behavioral paradigm (Fig. 1) was similar in basic structure to the tone detection task.

As in the tone detection paradigm, ferrets were trained in a modified conditioned avoidance paradigm to lick water from a spout during the presentation of reference sounds and to refrain from licking after the presentation of target sounds (Heffner and Heffner, 1995). In the tone discrimination task, each reference sound consisted of a combination of (1) a broadband noise-like stimulus (1 s in duration) with a spectro-temporally modulated envelope called a TORC (Klein et al., 2000), followed by (2) a short (250 ms) pure tone at a specific frequency (f_R) that occurred at the end of the TORC. As in the tone detect task, the particular TORC component in each reference sound was chosen from a set of 30 different TORCs that were specifically designed to serve during physiological experiments to characterize the spectro-temporal receptive field (STRF) of the cell under study using the reverse-correlation method. In the frequency discrimination task, target sounds were a similar TORC-tone combination, except that the target tone component had a different frequency (f_T) than the reference tone component (f_R). In a given behavioral block (typically of 40–120 trial runs), the f_R and the f_T were typically held constant (similarly, in a given behavioral block in the tone detection task, the target frequency was also held constant). The target tone (f_T) frequency could be higher or lower than the reference frequency (f_R) and differed from the reference frequency by 0.25–2.5 octaves.

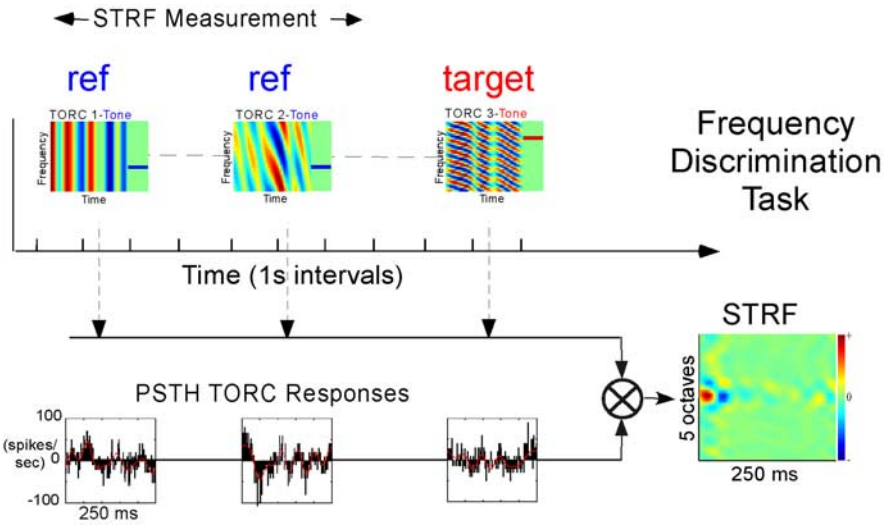

Figure 1. Experimental design: stimulus sequence for discrimination task. Two types of stimuli were used: broadband noise-like stimuli known as TORCs and pure tones. Reference and target sounds consisted of TORC-tone combinations in which the reference or target tones were of relatively short duration (250 ms) and occurred at the end of each 1 s TORC. On a given trial during a behavioral session, a random number of reference TORC tones (1–6 reference signals) was followed by a target TORC tone (except on control "catch" trials in which 7 reference TORC tones were presented with no target). The panels illustrate spectrograms of three such reference TORC tones (blue stripe denotes the reference tone) and of the following target TORC tone (red stripe denotes target tone). Responses to the TORC portions of each reference stimulus were collected in peristimulus time histograms (PSTH) that were cross-correlated with the TORC spectrograms to estimate the STRF (see Materials and Methods).

All ferrets were initially trained on the tone detection task with a seven-octave range of random target-tone frequencies (from 125 Hz to 16 kHz) until they reached behavioral criterion and learned to respond correctly to any target tone in this range. They were then trained on frequency discrimination to behavioral criterion. As in the tone detection task, during training on the frequency discrimination task, pairs of reference and target tone frequencies were randomly selected (with >0.25 octave separation), across a range of seven octaves in different behavioral sessions. The ferrets learned to respond correctly to any (target) TORC tone (f_T) that differed in tone frequency from the reference TORC tone (f_R). As indicated above, the ferrets were trained to respond to any target tone frequency (f_T) that differed from reference tones (f_R). However, in any given behavioral block of trials, f_R was fixed. In most experiments f_T was also constant during a given behavioral block (of 40–120 trial runs lasting 20–60 min) within a physiological recording session. Thus, soon after the onset of a given behavioral block, the ferret quickly learned the relevant tonal reference and target frequency for the rest of the test block. Although there was usually only one target tone frequency in a given behavioral session, in some training and in a few physiological experiments (9 of 59, 15.3%), several target-tone frequencies (two to six) were presented in one behavioral block. In such cases, the animals discriminated between the differing tonal component frequencies of the target TORC tones versus the single frequency of the reference TORC tone and hence avoided any f_R that differed in frequency from f_T. Also, in some physiological experiments (4 of 59, 6.8%), the target frequency f_T was changed between successive behavioral blocks (while holding f_R constant throughout), and, in others (5 of 59, 8.5%), the frequencies of f_T and f_R were reversed in successive behavioral blocks so that the same neuronal STRF could be successively probed with different salient combinations of target and reference frequencies.

The ferrets were initially trained on the tone detection task and then on tone discrimination. They were trained daily (50–150 trials per session) in a sound-attenuated test box until they reached behavioral criterion

(see below). Their performance level was maintained at or above behavioral criterion throughout behavioral physiology recordings. Initial training to criterion on both tasks in the free-running test box took ~10 weeks for each ferret. During the last 2 weeks in this time period, the ferrets were trained to switch readily between the two tasks in successive behavioral blocks in the same session.

After reaching criterion, a head post was surgically implanted. After 2 weeks of recovery, the ferrets were retrained on a head-fixed variant of the same task in daily sessions over an additional period of 2 weeks. There were several changes in this task variant: (1) the ferrets were restrained in a horizontal Lucite holder rather than being able to move freely about a testing cage in which they could approach or withdraw from a water spout; (2) the head was fixed in place with a secured head post; (3) tongue movement was monitored by interruption of a photobeam placed between the mouth and the lick plate; and (4) tail shock (enough to elicit a small tail flick) rather than mild tongue shock resulted after "misses," behavioral errors in which the animal licked after a "warning" or target sound.

The naive ferret had no previous behavioral training of any kind. It was surgically implanted with a head post and then, after 2 weeks of recovery, was gradually habituated to head restraint in the horizontal Lucite holder (over an additional period of 2 weeks). The "passive" and "active" task acoustic stimuli, which were presented to the naive control ferret, were identical to the acoustic stimuli that were presented to the two behavioral ferrets. The naive ferret was given *ad libitum* water outside the recording chamber and received neither water nor tail shocks during control experiments.

Behavioral performance measures. The discrimination rate (DR) for a given behavioral block or session was defined as the product of hit rate and safe rate (Heffner and Heffner, 1995) and was the principal measure used to measure ferret performance in the two acoustic tasks. Specifically, in our study, a hit was defined as having occurred when the animal was licking for an interval (400 ms before target) before the onset of the target stimulus and completely stopped licking for an equal duration (400 ms) interval (from 300 to 700 ms after target) after the offset of the target stimulus. A miss occurred when the ferret licked both before and after a target stimulus. A false-positive response occurred when the animal was licking before but ceased licking after the presentation of a reference stimulus. In a safe response, the animal licked both before and also after the presentation of the reference stimulus. Behavioral criterion was defined as consistent performance on the tone detection or discrimination task for two sessions with >80% hit rate accuracy and >80% safe rate (leading to an overall performance discrimination rate between target and reference that was >0.65).

In addition to the DR, we developed another measure of task performance, lick rate discrimination (LRD), which was a useful parallel performance measure to analyze ferret behavior. To derive the LRD for the tone discrimination task, we first computed the average lick rates during the 1.25 s duration of all TORC-tone reference stimuli and also of all TORC-tone target stimuli over the entire time course (i.e., including all stimuli in all trials) of a given behavioral block. We then computed the average lick rates for a 300 ms interval immediately after stimulus offset (this interval corresponds to the "decision time" in which the ferret must decide whether to continue poststimulus licking and risk possible shock). We took the ratio of (lick rate during stimulus)/(poststimulus lick-rate) to derive differential lick rates (DLR) for reference (DLR_{ref}) and target (DLR_{tar}) stimuli. If a ferret was performing well, the DLR_{ref} should be ~1, whereas the DLR_{tar} should be significantly >1. Our criterion for good behavioral performance (used to separate sessions with good and poor behavioral performance in Fig. 3*e*,*f*) was that $LRD = (DLR_{tar})/(DLR_{ref}) > 2$.

Surgery. To secure stability for electrophysiological recording, a stainless steel head post was surgically implanted on the skull. The ferrets were anesthetized with Nembutal (40 mg/kg), and deep anesthesia was maintained throughout the surgery. Using sterile procedure, the skull was surgically exposed and the head post was mounted using dental cement, leaving clear access to primary auditory cortex in both hemispheres. Antibiotics and postsurgery analgesics were administered as needed after surgery.

Neurophysiological recording. Experiments were conducted in a double-walled, sound-attenuation chamber. Small craniotomies (~1–2 mm in diameter) were made over primary auditory cortex before recording sessions that lasted 6–8 h. Physiological recordings were acquired using tungsten microelectrodes (4–8 MΩ; the relatively high resistance enabled better single-unit isolation).

We used multiple criteria for acceptable single-unit recordings from A1: (1) clear, short-latency auditory response to pure tone stimuli; (2) rapidly measurable on-line multiunit STRF with only a few TORC repetitions (suggesting a large linear component in the neuronal response); (3) at least one unit in the multiunit cluster whose spike waveform had an amplitude more than five times the baseline noise level; (4) stability of the recording (persistence of the same waveform throughout the recording for at least one unit), and (5) >150 μm distance from any other previous recording. If these criteria were met, then responses were recorded and then stored, filtered, and spike sorted off-line. A typical recording yielded one to four simultaneously active single units. Spike sorting of the neural traces was done off-line using manually traced, user-defined templates (constructed with multiple amplitude time windows) for each spike shape. The window thresholds were chosen such that variances from the different sorted classes did not overlap at those chosen points, as shown in the examples in Figure 6. The variance of each sorted class of units was then estimated as shown in the examples in Figure 6, which was always well within the threshold windows chosen in the sorting. In addition, we always used two other criteria for the sorted spike classes: (1) the interspike intervals for each class were exponential with a minimum 1 ms spike latency, and the distribution peak was always >2 ms; and (2) the spike rate remained approximately stable throughout the recording time.

For each suitable isolated unit, we first measured the STRF using TORC stimuli while the animal was in a behaviorally passive resting state, in which there were no task demands, there was no water flow in the reward waterspout, and no target or reference tones were presented. Then, a series of STRF measurements ensued while the animal performed a sequence of discrimination or detection tasks, alternating with additional STRF measurements in the passive state between successive acoustic tasks. The reference and target-tone frequencies (f_R and f_T) were chosen as suitable probes after inspection of the initial passive STRF of the cell and were usually positioned at or near specific excitatory or inhibitory regions of interest in the receptive field. By successively selecting different f_R and/or f_T or by switching between different tasks while maintaining one of the same tone frequencies, we could monitor any changes in multiple locations of the STRF and view them within a few minutes of their occurrence.

Both single-unit and multiunit STRFs were computed for each recording. Multiunit records were constructed from responses to all spikes with amplitudes above a low threshold level [4 SDs (4σ) above baseline noise]. Multiunit records were used because it was often possible (because of the greater spike number in multiunit records compared with single-unit records) to obtain a clear STRF with only one repetition of the 30 TORCs rather than the five or more repetitions, which were often necessary to construct clear STRFs with single-unit records.

Physiological data from the two trained animals was pooled for additional analysis and compared with responses in the naive animal. Evidence for the location of recordings in primary auditory cortex was based on the presence of distinctive A1 physiological characteristics (such as latency and tuning) and the position of the neural recording relative to the cortical tonotopic map in ferret A1 (Shamma et al., 1993; Nelken et al., 2004; Bizley et al., 2005).

Stimuli. As mentioned above, during training and active physiological measurements in the tone discrimination task, the acoustic stimuli were TORC-tone combinations, which were 1.25 s in duration and consisted of 1.0 s broadband stimuli called TORCs (Klein et al., 2000), followed by 0.25 s pure tones. In the tone detection task, the acoustic stimuli were either TORCs or tones (each 1.25 s in duration). Passive STRF measurements interleaved between tasks used TORC stimuli that were longer in duration (3 s), which allowed for more rapid STRF measurements. Each of the 30 TORCs was a broadband noise with a dynamic spectral profile that was the superposition of the envelopes of six moving ripples. A single ripple has a sinusoidal spectral profile, with peaks equally spaced at 0

(flat) to 1.4 peaks per octave; the envelope drifted temporally up or down the logarithmic frequency axis at a constant velocity of up to 24 Hz (Kowalski et al., 1996; Klein et al., 2000; Depireux et al., 2001; Miller et al., 2002). During physiological recording, the computer-generated stimuli were delivered through an inserted earphone in the contralateral ear that was calibrated *in situ* at the beginning of each experiment. The amplitude of tone and TORC stimuli was set at 5 dB below neuronal best amplitude at best frequency (BF) during physiological recording. In terms of single-unit recordings, it took ~20 min to present sufficient number of repetitions (5–10) of the 30 TORC stimuli to measure each passive STRF. It took approximately the same amount of time to measure each active STRF for single-unit recordings. However, it was sometimes possible, particularly with multiunit recordings, to measure the STRFs (passive and active) much more rapidly, after only one repetition of all 30 TORC stimuli (corresponding to ~2 min resolution).

STRF estimation and analysis. STRFs were measured using the reverse-correlation method (Klein et al., 2000). This method was used with both sorted single-unit or multiunit neural responses. The TORC stimuli were specially designed to have their autocorrelation approach an impulse function both spectrally and temporally, thus formally approximating a white-noise stimulus (Klein et al., 2000). Hence, no normalization by the stimulus autocorrelation was required to complete the reverse-correlation process for the STRF measurement.

Passive and behavior STRFs were derived from responses to all TORCs presented during the "reference" phase of the stimuli (Fig. 1). It is worth emphasizing that, although the animal behaved in anticipation of the specific target, all of the spike measurements to derive the STRF were made only during the presentation of the reference TORC portions. Precisely the same TORC-tone stimuli were used for control studies in the naive, untrained animal. They were presented passively, with no behavioral responses from the naive ferret.

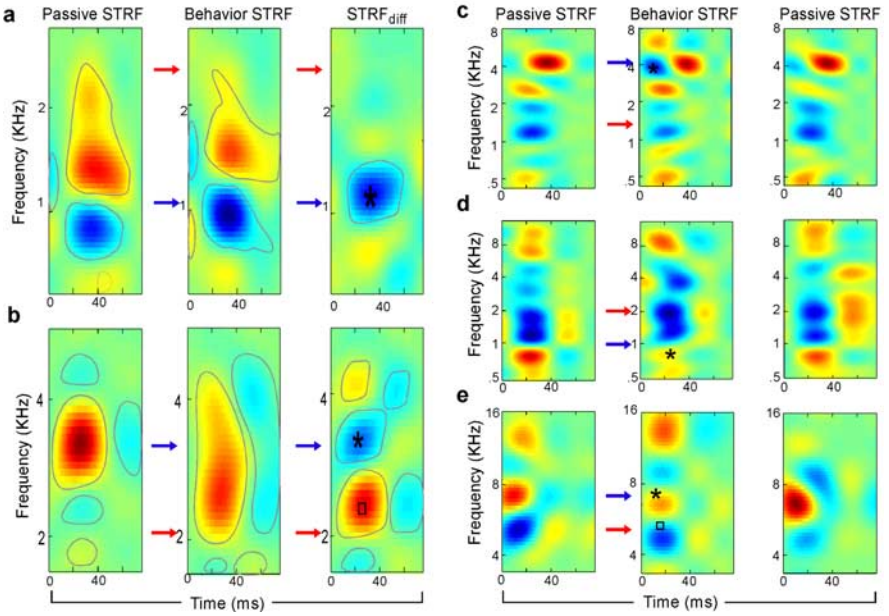

Figure 2. STRFs from five single units (***a–e***) in A1 illustrate receptive field changes observed during performance of the frequency discrimination task. ***a***, Comparison of a prebehavior passive STRF (left) and a behavioral STRF (middle). Each panel depicts an STRF with a "rainbow" color scale ranging from red to green to blue, representing increased-to-suppressed firing about the (green) mean. The STRF in each panel was normalized, and all STRFs were then depicted on the same color scale for each unit. The contours in ***a*** demarcate the excitatory (red) and inhibitory (blue) regions with statistically significant fluctuations (level of 2.5σ) from the mean (as explained in Materials and Methods). We do not draw these contours in subsequent STRFs to avoid cluttering the figures. However, all excitatory and inhibitory features of the STRF or STRF$_{diff}$ discussed subsequently are statistically significant by this criterion. The blue arrows indicate the frequency of the reference tone; the red arrows indicate the frequency of the target tone during the discrimination task. The difference between the normalized passive and behavior STRF is shown in the right (STRF$_{diff}$). An asterisk marks the location of maximal change near f_R (within $\pm$0.125 octaves from the reference) ($\Delta A_{ref} = -95\%$). No significant changes occurred at target in this unit. ***b***, Same as in ***a***, except that both ΔA_{ref} (−57%) and ΔA_{tar} (61%) are significant in this unit. A square marks the maximal change near target as defined in Results. ***c***, ***d***, Examples of STRF depression induced at the reference tone frequencies ($\Delta A_{ref} = -69$ and -55%; blue arrows), with small or insignificant effects at the target tone (red arrows). Postbehavior STRFs reverted to their original prebehavior shapes. ***e***, Example of STRF depression near f_R ($\Delta A_{ref} = -63\%$; blue arrow) and facilitation near f_T ($\Delta A_{tar} = 61\%$; red arrow). In this case, the postbehavior STRF did not revert to its original shape but showed a persistent enhancement at the target tone frequency (e.g., an additional decrease in the lower inhibitory sideband) and a rebound to higher than original levels of the excitatory region at reference tone frequency.

Response variance (σ) was estimated using a bootstrap procedure (Efron and Tibshirani, 1998; Depireux et al., 2001), and an overall signal-to-noise ratio (SNR) was computed for each STRF (Klein et al., 2000). Most SNRs were >1, and those with an SNR <0.2 were excluded from additional analysis. Each STRF plot is therefore associated with a particular variance (σ). Excitatory (positive) and inhibitory (negative) fluctuations from the (zero) mean of the STRF were deemed significant only if they exceeded a level of 2.5σ. Contours were drawn at this level to demarcate significant excitatory and inhibitory features.

These analyses and criteria also apply in determining the significant changes between two STRFs. To quantify the effect of the behavioral tasks on STRF shape, we first independently normalized the passive and behavior STRFs by the Euclidean norm and calculated the difference between the two STRFs (Fig. 2*a*, STRF$_{diff}$). Thus, a significant STRF change refers to a suppressive or facilitative region in the STRF$_{diff}$ that exceeds the 2.5σ criterion. We then extracted two measures from the STRF$_{diff}$: (1) ΔA_{ref} (denoted by an asterisk), which is the local maximum difference within a $\pm$0.125 octave vicinity around the reference frequency (f_R) and (2) ΔA_{tar} (denoted by a square), which is the local maximum difference within a $\pm$0.125 octave vicinity around the target f_T. The values of these two measures are indicated in the figure legend. The values of ΔA_{ref} and ΔA_{tar} were reported as percentages relative to the maximum value of the passive STRF. In the multiple-target tests, we reported the largest change among the target frequencies used. In subsequent figures, the location of these two maxima (ΔA_{ref} and ΔA_{tar}) will be indicated on the plot of the behavioral STRF. We use the term "depression" to refer to a local, significantly decreased STRF shape change at either reference or target frequencies and the term "facilitation" to refer to a local, significantly increased STRF change at either reference or target frequencies. The use of the terms depression and facilitation in this paper are in fact descriptions of changes in the shape of the STRF (changes in relative neuronal firing likelihood for different spectro-temporal conditions) rather than a description of synaptic mechanisms that may give rise to these changes, which could be the result of a combination of changes in excitatory and/or inhibitory synaptic inputs to A1 neurons (Wehr and Zador, 2003; Tan et al., 2004).

We note that the observed plastic changes in STRFs induced by behavior were well above any "noise" of spontaneous receptive field variations. Analysis of consecutive pairs of passive recordings collected over the time course of the naive control experiments confirmed that intrinsic STRF variability or measurement variations cannot explain the reported task-induced changes in the receptive fields.

The smooth distributions of the (ΔA_{ref}, ΔA_{tar}) changes shown in Figure 3 were derived from the histograms as follows. (1) We assumed that, for each cell, the resulting ΔA_{ref} and ΔA_{tar} were each Gaussian distributed with a mean and variance computed using the bootstrap method. Assuming that the two measures were independent, the joint two-dimensional (2-D) probability was the product of the marginal Gaussians. (2) We assumed that the probability that the ΔA_{ref} and ΔA_{tar} fell

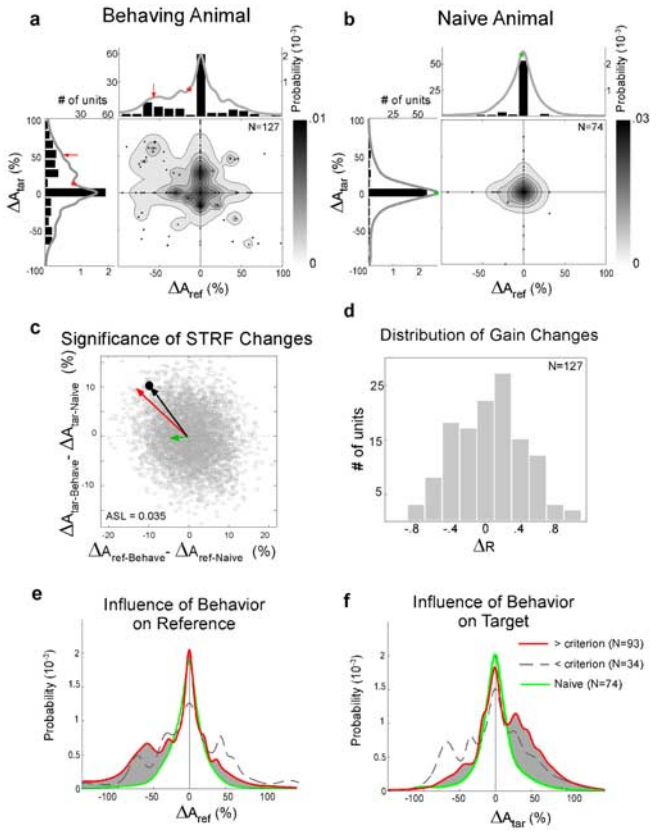

Figure 3. Overall summary scatter plot and smoothed distribution of local STRF changes (ΔA_{ref} vs ΔA_{tar}) from a population of 74 single units recorded in the naive control and also from all 127 neurons recorded during discrimination behavioral sessions (including a comparison of STRF changes in high and low performance behavioral sessions). ***a***, Scatter plot and superimposed distribution from neurons recorded in the behaving animals. The smoothed distribution is computed by first replacing each point with a 2-D Gaussian with unit area and the variances of the ΔA estimates. All Gaussians are then summed to produce the total smoothed gray-color surface shown (gray bar range on the right). Contour plots at 10% steps are also shown. Note that the distribution is skewed toward the top left quadrant, indicating tendency toward negative ΔA_{ref} and positive ΔA_{tar} STRF changes. The side graphs indicate the corresponding 1-D histograms of ΔA_{ref} and ΔA_{tar}. The smooth plots are the marginal distributions obtained from the contours in the middle panel. The red asterisk indicates the overall mean of each distribution, with a mean value of −18% for ΔA_{ref} and +13% for ΔA_{tar}. The red arrows indicate the mean value of the distribution of negative ΔA_{ref} values (mean of −65%) and positive ΔA_{tar} values (mean of +53%). ***b***, Scatter plot and superimposed distribution from the naive animal. All other details are as in ***a***. The distribution of changes from neurons recorded in the naive ferret appears approximately circular as would be expected from random variations in the STRF. ***c***, Establishing the significance of the difference between the distributions of STRF changes in ***a*** and ***b*** above. The light gray points are difference vectors between randomly selected behaving and naive distributions (for details, see Results). The red vector is the net vectorial sum of all points in the behaving distribution in ***a***. The green vector is the vectorial sum of all points in the naive distribution in ***b***; it is relatively small because of the smaller and more highly random direction of STRF changes in this distribution. The black vector is the difference between the gray and green vectors above; its tip is represented by the large black circle that lies at the edge of the random distribution, indicating a highly significant difference between the behaving and naive distributions of STRF changes. ***d***, The distribution of gain changes (percentage change in spike rate) between passive and active state for all 127 single units. The histogram indicates that fluctuations in gain are variable and mostly symmetric around 0. ***e***, Graphs of three distributions of ΔA_{ref} derived from populations of neurons in the naive (green line), poor performance (LRD <2; black dashed line), and good performance (LRD >2; red line) conditions (see Materials and Methods). This figure demonstrates a negative correlation between behavioral performance and amplitude of adaptive change at reference frequency (ΔA_{ref}). ***f***, Similar set of graphs showing a positive correlation between behavioral performance and amplitude of adaptive change at target frequency (ΔA_{tar}).

within a bin of 5% around any specific value was computed by summing over contributions from all STRFs. This gave the smooth distributions shown that represent the mean of the probability of (ΔA_{ref}, ΔA_{tar}) having any particular range of values. To obtain the smooth one-dimensional (1-D) distribution for ΔA_{ref} and ΔA_{tar}, we use the same approach described above but using only the marginal distributions of each one of these measures.

The change in response gain was measured using the TORC portion of the reference stimulus responses in the passive and behaving conditions. We used a measure ΔR to relate the spike rate (in spikes per second) in the passive condition to that of the behavior condition. ΔR is defined as (behavior spike rate − passive spike rate)/(behavior spike rate + passive spike rate). Using this metric, we could then explore whether there was any correlation between gain changes and shape changes in the STRF from passive to behavior states (Fig. 3*d*). We used a Spearman's rank correlation test (Lindgren, 1993) to measure the correlation between changes in rate (ΔR) and changes in STRF shape (ΔA_{ref} and ΔA_{tar}) for each unit. This is a nonparametric statistical test to examine whether the two variables are correlated.

Results

Effects of frequency discrimination behavior on single-unit STRFs

Recordings were made in the primary auditory cortex of two trained ferrets and one naive ferret. Location in A1 was based on position of the recording site in the brain and physiological characteristics of the recording, such as response latency and frequency tuning. STRF measurements and other tests were completed for 127 isolated single units in the two trained animals and in 74 single units in the naive animal. In the trained ferrets, the STRFs changed between the passive and behavioral states in 96 of 127 (76%) of all cases. However, in contrast, in the naive control, only 28% of the neurons (21 of 74) showed any significant change at either reference or target.

Details of the STRF changes in the trained animals depended on the specific frequencies of the reference and target tones and on the shape of the initial STRF. In general, the reference and target tones had opposite effects on the STRF during the discrimination task. The reference tone tended to depress the STRF at its frequency, whereas the target tone facilitated the STRF at its frequency.

The phenomenon of depression at the reference-tone frequency is illustrated in Figure 2*a*. The initial passive STRF had a single sideband of inhibition (0.8 kHz) below a prominent excitatory field centered at 1.2 kHz. When the reference frequency was placed just above the inhibitory area (f_R = 1 kHz) during behavior, the inhibitory sideband enlarged and almost doubled in strength, and its high frequency border moved upward, displacing the excitatory field. In this case, the target (f_T = 2.7 kHz) did not induce any significant change in STRF shape.

In Figure 2*b*, both the reference and target tones induced STRF changes at their frequencies. At the reference frequency, placed in the middle of the initially strong excitatory region centered at 3 kHz, the field was selectively suppressed during behavior. The target induced an opposite (facilitative) effect at f_T = 2 kHz. The net result was that the STRF BF shifted downward in frequency toward the target f_T. The $STRF_{diff}$ clearly displays these changes with STRF depression at f_R and facilitation at f_T. Figure 2*c–e* illustrates STRFs from three more units in the passive prebehavior, active behavior, and passive postbehavior phases. In all, the reference induced a depressive effect in the STRF during behavior, creating an inhibitory region in which none existed before (Fig. 2*c*) or weakened the nearby preexisting excitatory field (Fig. 2*d*,*e*). The target exerted its strongest facilitative influence in Figure 2*b* and also in Figure 2*e*, in which it significantly weakened

and downwardly displaced the inhibitory sideband at 5 kHz. Finally, note that two of the STRFs (Fig. 2*c*,*d*) reverted to their original prebehavior STRF shapes once the behavior ceased. However, the induced changes in the third cell (Fig. 2*e*) persisted in an intermediate form after behavior, which increased the net contrast between responses at the target and reference frequencies (i.e., the postbehavior passive STRF showed further enhancement of the initial facilitative effect at target frequency but a reversal of the initial inhibition at reference frequency, leading to rebound enhancement of the original excitatory field at the reference frequency).

Distribution of changes

A 2-D summary of results from all units sampled in the trained ferrets is shown in Figure 3*a* (middle panel). For each unit, the percentage change in the STRF at the reference (ΔA_{ref}) is plotted against the change at the target (ΔA_{tar}). If all STRF changes were as described in Figure 2 (i.e., depression at the reference and potentiation at the target), we would expect all points in the plot to lie in the top left quadrant or on the two bordering axis segments (i.e., a significant change at only one of the two tones). Although a minority of neurons showed no significant changes, either at target or reference (31 of 127, 24%), of all STRFs that did change significantly (96 of 127, 76%), ~60% (58 of 96) satisfied this prediction. However, there was considerable scatter in the data, and there were points in each quadrant as shown in Figure 3*a*. To clarify and quantify this trend, we computed a smoothed surface that reflects the local density of the points. Specifically, each point was represented by a 2-D Gaussian with unit area and a variance as measured directly from the data (for details, see Materials and Methods). The normalized sum of all these smooth 2-D Gaussians is shown as a grayscale plot (with 10% contours) and superimposed on all of the points (Fig. 3*a*). To highlight behavior-dependent STRF changes compared with random variability, we constructed a similar surface plot (Fig. 3*b*) from 74 units from control experiments in a naive animal using exactly the same discrimination task stimulus paradigm but without water reward, shock, or any behavioral demands. As mentioned above, in the naive control, only 28% of the neurons (21 of 74) showed any significant change at either reference or target compared with 76% of A1 neurons in the behaving animals.

These trends are clarified in the 1-D plots of ΔA_{ref} and ΔA_{tar} on the side panels of Figure 3, *a* and *b*. The histograms and distributions in Figure 3*a* are significantly skewed for the behavior data. In the case of the reference tone, the distribution of the behavioral ΔA_{ref} data is significantly skewed toward negative values with overall mean of −18% (indicated by the red asterisk). In the naive animal (Fig. 3*b*), the reference distribution is quite symmetric with an overall mean of −5% (indicated by the green asterisk). The reference distribution in the naive case is also very slightly skewed toward the left. The distribution of target tone ΔA_{tar} for the behavioral data is skewed toward positive values with an overall mean of +13%, whereas in the naive case, the distribution is very Gaussian with an overall mean of −0.1%.

By comparing the contour plots from Figure 3, *a* and *b*, we note several important features in these cross sections. (1) The amplitude of STRF changes (ΔA) in the behaving animals was significantly larger than in the naive animal. (2) Furthermore, during behavior, the spread was largest toward the top left quadrant; approximately one-third of the cells in this quadrant (33% or 19 of 58) showed significant changes at both reference and target frequencies. The remainder of STRFs in this quadrant fell along the *x*- or *y*-axes and exhibited either depression at reference (29% or 17 of 58) or facilitation at target (38% or 22 of 58). (3) The naive distribution is mostly circular, symmetric, and centered at the origin as we would have expected from purely random and independent variations of the STRF amplitudes at the reference and target tones. However, as mentioned above, we note the presence of a weak bias leading to a slight elongation of the cross-section along the reference and target axes. This slight bias may indicate the presence of a very small degree of depression and potentiation of the STRF at the reference and target frequencies, respectively, even in the naive animal. This result is intriguing because it may be related to recent studies of the "oddball effect" (Ulanovsky et al., 2003). We consider this possibility further in Discussion. However, the behavioral effects (an overall depression) at the reference frequency shown in Figure 3*a* cannot be fully explained by sensory adaptation because exactly the same stimuli were presented to the naive animal in control experiments and had a much slighter effect (Figs. 3, 4). In fact, of the behavior units that showed a negative change at reference ($\Delta A_{ref} < -10\%$), the mean change reached −65% (Fig. 3*a*, red arrow). Similarly, of the behavior units that showed a positive change at target ($\Delta A_{tar} > 10\%$), the mean change was +53% (Fig. 3*a*, left).

To examine the validity of the claim that the behaving and naive distributions are statistically different, we tested the null hypothesis that the two groups were drawn from the same underlying probability distribution. Using a permutation test, we combined all of the observations ($n = 201$) from both distributions together and randomly chose a sample of size of $n = 127$ without replacement (representing the "behaving" distribution), whereas the remaining sample of size of $n = 74$ represented the "naive" distribution. We then computed the difference between the vector sum of each distribution and repeated this process 5000 times. The resulting (5000) difference vectors are represented in Figure 3*c* by their light gray endpoints. Also superimposed on this figure is the red vector that represents the net vector sum of all points in the behaving distribution in Figure 3*a*. The relatively much smaller green vector is the vector sum of all points in the naive distribution in Figure 3*b*. The black vector is the difference between the red and green vectors. The question we seek to answer is whether this black difference vector (also indicated by its endpoint, the large black circle) is significantly larger than those generated by the randomly sampled distribution (light gray circles). As the illustration shows, the large black circle lies on the periphery of the distribution (in fact, outside the 96.5% percentile of the light gray circles derived from the randomly sampled data), and hence we can reject the null hypothesis with a significance level of 3.5%, which is considered "more than reasonably strong evidence" that the two distributions are different (Efron and Tibshirani, 1998). Note also that, as expected, the direction of the net changes (as represented by the black vector) is in the top left quadrant, thus indicating average depression at reference and facilitation at target.

To address the question of behavior-related gain changes in the STRF as the ferret moved between passive and active states, we measured the percentage change in spike rate from passive to behavior conditions. The distribution in Figure 3*d* shows the range of variability in gain from all 127 single units (depicted in Fig. 3*a*). This distribution is not statistically different from a Gaussian function with 0 mean, indicating that there is no systematic trend in changes of response gain between behavioral states. From this result, we confirm that the normalization of the STRF was an important step in our preceding analyses. It reduced the effects of an overall change in cell responsiveness throughout the passive/active/passive test sequence (e.g., because of fluctuat-

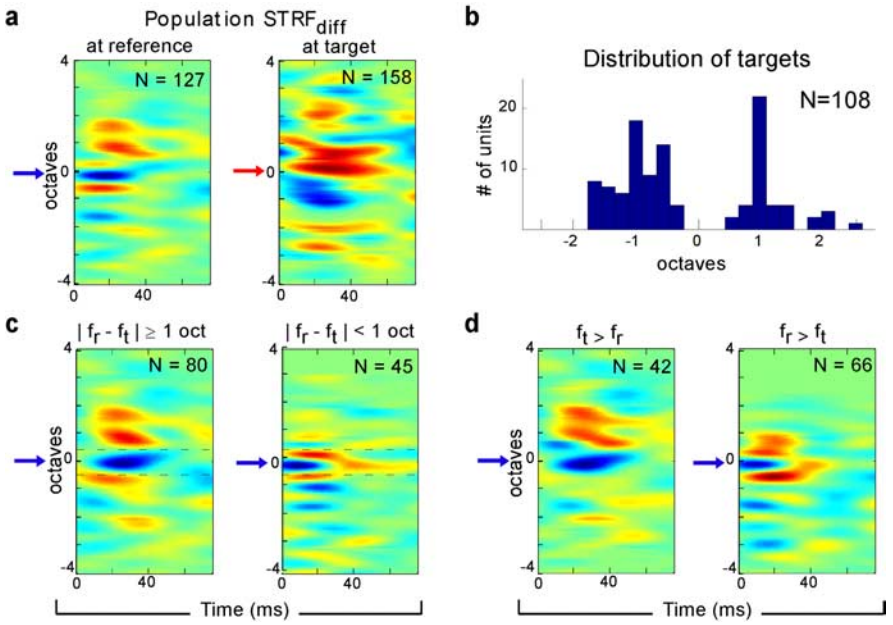

Figure 4. Average change in the STRF for all frequency discrimination experiments. ***a***, The left panel illustrates the average plastic change in STRF as a function of log frequency away from the reference frequency (centered at 0 and marked by the blue arrow). The plot is generated by summing the $STRF_{diff}$ from all cells with any significant change. A relatively strong (blue) suppressed area emerges at the frequency of the reference tone, surrounded by two facilitated (red) sidebands. The right panel is the average plastic change in STRF as a function of log frequency away from the target frequency (centered at 0 and marked by the red arrow). Note that the disparity in unit numbers (127 vs 158) between the two panels, which reflects those cases ($n = 19$) in which multiple target tones were used. ***b***, Distribution of target tone frequencies relative to the reference tone frequency (marked as 0 on the *x*-axis) used in all experiments with only a single target tone frequency (108 neurons). In this distribution, there were twice as many tests with targets below reference frequency than with targets above reference frequency. ***c***, Left, Average STRF changes around the reference tone in experiments in which reference and target tones were far apart ($f_R - f_T >= 1$ octave). Right, Average STRF changes around reference tone frequency from experiments in which reference and target tone frequencies were relatively close ($f_R - f_T < 1$ octave). The depression around the reference tone frequency is significantly wider when the target frequency is farther away. The dashed lines are positioned 0.5 octaves above and below the reference frequency. ***d***, Left, Average STRF changes around the reference tone frequency in experiments in which the reference tone frequency was below the target frequency. The excitatory sideband below the depression vanishes. Right, Average STRF changes from experiments in which target frequency was below reference frequency. In this case, as predicted, there is now an excitatory sideband below the depression centered at the reference frequency. This sideband now is stronger than the excitatory sideband above the reference frequency, which has decreased in amplitude but has not vanished.

ing levels of arousal), focusing instead on the changes in the shape of the STRF.

We also tested for any correlation between the changes in spike rate (ΔR) and the observed change in STRF shape at the reference and target location (the magnitude values of ΔA_{ref} and ΔA_{tar}). Using a Spearman's correlation test, we observed almost no correlation between ΔR and ΔA_{ref} (the correlation value was $r_s = 0.14$). A *t* test of the pairwise differences between these two distributions verified that there was no significant correlation between the two ($p > 0.89$). Similarly, we also observed no correspondence between ΔR and ΔA_{tar}, with a correlation value $r_s = 0.03$ (*t* test, $p > 0.8$).

To determine whether there was a correlation between behavioral performance and the amplitude of STRF shape changes in the tone discrimination task, we used a behavioral criterion (LRD >2) to divide the physiological behavior sessions into two categories of good and poor performance (see Materials and Methods). When we compared the distributions of ΔA_{ref} and ΔA_{tar} for the naive recordings and for good and poor performance behavioral sessions (Fig. 3*e*,*f*), we found a striking correlation of behavior with ΔA. The naive and poor performance group distributions were similar, being approximately symmetrical around the *y*-axis (although the variance was greater for the poor performance behavioral neurons). This near symmetry was reflected in the population means that were very close to 0 for both the naive ($n = 74$) and the poor performance ($n = 34$) groups (ΔA_{ref} was −4.1% for the naive and −1.6% for the poor performance group; ΔA_{tar} was −0.2% for the naive and −2.1% for the poor performance group). In contrast, the population means for A1 neurons recorded during good behavioral performance sessions ($n = 93$) were much higher (ΔA_{ref} was −18.4%; ΔA_{tar} was +14.5%). Moreover, as shown in Figure 3*e*, the distribution of ΔA_{ref} for good performance was highly skewed to the left, and the distribution of ΔA_{tar} was highly skewed to the right (Fig. 3*f*). The difference between the naive distribution and the good performance distribution is shaded in gray.

Average population STRF changes

Another way of summarizing our results, which is less parametric but more inclusive, is to compute the average STRF change, depicted in Figure 4. Specifically, the left panel of Figure 4*a* depicts the average STRF change around the reference tone derived by first aligning the $STRF_{diff}$ from all units with any significant change and then taking the average. The resultant pattern demonstrates that, on average, the reference induced a strong depression of the STRF near f_R, but that there were also two relatively strong excitatory flanking sidebands nearby. Applying the same procedure around the target yields the pattern depicted in the right panel of Figure 4*a*. Here, the opposite effects occurred: the target induced a broad positive change on the STRFs, with an unexpected but apparently a strong suppressive sideband below.

Target–reference interactions

The pattern of average STRF changes arising from frequency discrimination, depicted in Figure 4*a*, are more complex and relatively irregular than the average STRF changes described previously in the tone detection task (Fritz et al., 2003, 2005a,b). This may be, in part, because of the possible mutual influences and interactions of the reference and target tones on the STRF during task performance. To explore such possible interactive effects, we sorted the $STRF_{diff}$ according to the reference and target frequency separations used in behavioral physiology sessions. The distribution of the frequencies of single targets tested around reference frequencies is shown in Figure 4*b* (in some sessions, multiple target frequencies were used for a given reference frequency; these cases are not included in Fig. 4*b*). In the majority of cases, the target frequencies were set at 0.25–2 octaves away from the reference frequency. When the tone frequencies were relatively far apart [$f_R - f_T \geq 1$ octave (Fig. 4*c*, left)] and hence there was presumably less interaction with the target tone, the reference induced a comparatively broad depression of the average $STRF_{diff}$ of approximately ±0.5 octave at its widest point (as

indicated by the dashed lines). However, when the two tones were more closely spaced [$f_R - f_T < 1$ octave (Fig. 4*c*, right)], the induced depression was half as wide (±0.25 octave), presumably because the net suppressive effect at the reference frequency was being "compressed" by the net facilitatory effects from the adjacent target frequencies. To further highlight this source of variability, we computed STRF changes averaged only from responses sorted according to whether the target frequency was above or below the reference frequency (Fig. 4*d*). When the target frequency was above reference frequency [$f_T > f_R$ (left panel)], the average STRF changes simplified considerably, becoming a one-sided potentiation above the localized depression. When the target frequency was below the reference frequency ($f_R > f_T$), a stronger facilitation below reference frequency reappeared. The fact that some facilitation still remained above the reference frequency in these cases (in which $f_R > f_T$) suggests that this facilitation may arise from the reference itself, perhaps a sideband effect analogous to the inhibitory sidebands seen with the potentiation induced by the detection of a tone (Fritz et al., 2003).

STRF changes in multiple tasks

We recorded responses from 52 neurons during a sequence of two or more behavioral tasks or task conditions, alternating with passive conditions. For these units, we computed the corresponding sequence of behavioral STRFs alternating with passive STRFs. In most cases, we observed a series of different STRF changes during such sequences that correlated with the specific stimuli used and the nature of the behavioral tasks. Two such examples are shown in Figure 5. In the first (Fig. 5*a*), two discrimination tasks were conducted with the same reference frequency but different target frequencies. An initial passive STRF exhibited two equally strong excitatory fields (first panel). When the animal discriminated between a reference ($f_R = 250$ Hz) and a target ($f_T = 500$ Hz), the excitatory region centered at f_R vanished (second panel) but reappeared in the subsequent passive STRF (third panel). When the discrimination task was repeated at the same reference, it depressed the 250 Hz excitatory field again (fourth panel), only to reappear in the final passive STRF (fifth panel). In contrast, the target facilitated its corresponding excitatory field centered at 500 Hz in the first test, and the STRF change persisted afterward (second panel). When f_T was moved to 1 kHz in the second test (fourth panel), it also facilitated its STRF region by almost eliminating the inhibition observable in the two passive conditions; however, the inhibition rebounded strongly in the final passive STRF (fifth panel).

In the second example (Fig. 5*b*), a discrimination task was followed by a detection task. The initial STRF had a strong excitatory field (centered at 1.5 kHz) and a weaker inhibitory sideband (centered at 900 Hz). During the discrimination task (second panel), the reference ($f_R = 1$ kHz) induced a relatively strong inhibitory field at 1 kHz, which persisted afterward during the passive STRF (third panel). During the subsequent detection task (fourth panel), the same 1 kHz tone now played the role of target (rather than the role of reference as in the first task depicted in the second panel), and hence it potentiated the STRF by significantly reducing inhibition at 1 kHz. The inhibitory field rebounded strongly in the final passive STRF. Overall, we were able to record from a total of 45 units in which we were able to study the effects of this sequence of discrimination detection tasks on the STRF.

The average STRF changes around the target frequency are illustrated in Figure 5*c*. They are facilitative during performance of a detection task after the discrimination task (left panel), and the changes are also facilitative when the detection task was performed alone (right panel), with no preceding discrimination tasks (reproduced from Fritz et al., 2003). Note, however, that the facilitation pattern in the first case (left panel) was asymmetric and more complex, perhaps because of the persistence of previ-

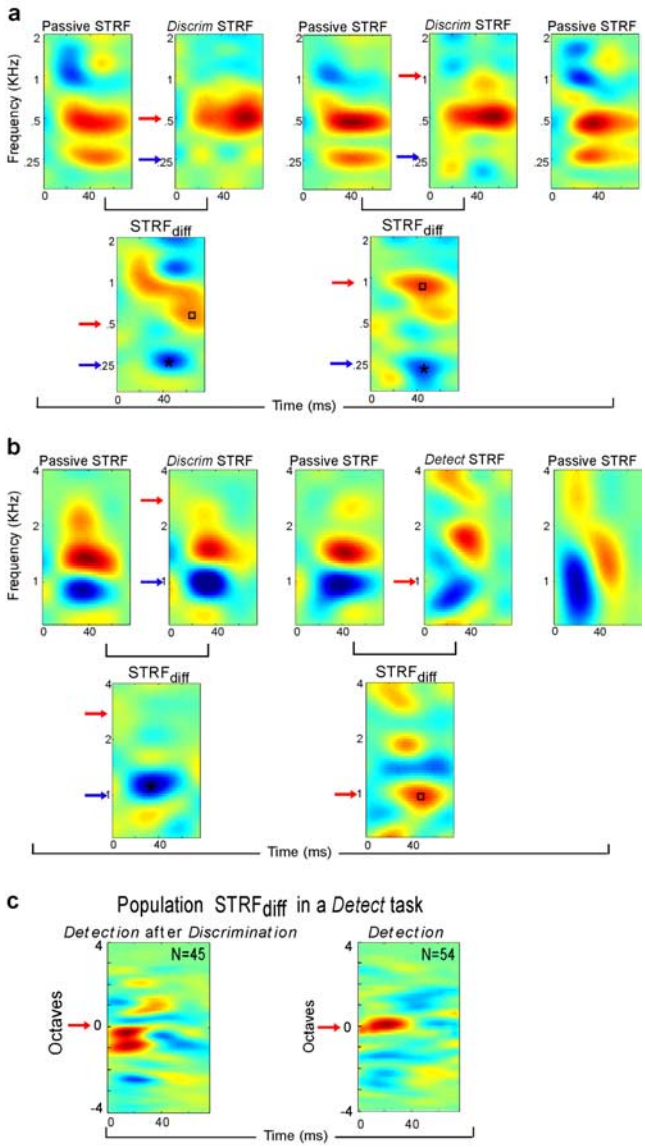

Figure 5. STRF plasticity in a sequence of multiple tasks and behavioral contexts. ***a***, A passive prebehavior STRF (first panel), followed by a discrimination STRF (second panel) in which changes at both target and reference frequencies occurred ($\Delta A_{ref} = -90\%$; $\Delta A_{tar} = 62\%$). The STRF immediately recovered afterward (third panel). Another discrimination test (fourth panel) caused depressive and facilitative STRF changes ($\Delta A_{ref} = -68\%$; $\Delta A_{tar} = 69\%$), which again reverted to the original passive STRF shape afterward. ***b***, Three passive STRFs (first, third, fifth panels) interleaved with discrimination and detection tasks (second, fourth panels). In the two behavioral tasks, the 1 kHz tone played the role of reference tone (in the discrimination task) and target tone (in the detection task). The effect on the STRF was different depending on the behavioral context (as seen in the $STRF_{diff}$ panels below). As a reference tone, the 1 kHz tone (blue arrow) induced a strong depression in the STRF (second panel). As a target tone (red arrow), it facilitated the STRF at 1 kHz (weakening inhibition at 1 kHz). ***c***, Summary of results from performance of the detection task after a frequency discrimination task. Left, The average STRF facilitation induced by target tones during detection tasks, which followed discrimination tasks with the same tone as reference. Note that facilitation for the target frequency in a detection task with a previous discrimination task may be broader than in a single detection task because of the influence of persistent STRF plasticity to the target of the previous discrimination task. Right, The average STRF facilitation at target during a detection task, computed from our previously published single-unit data.

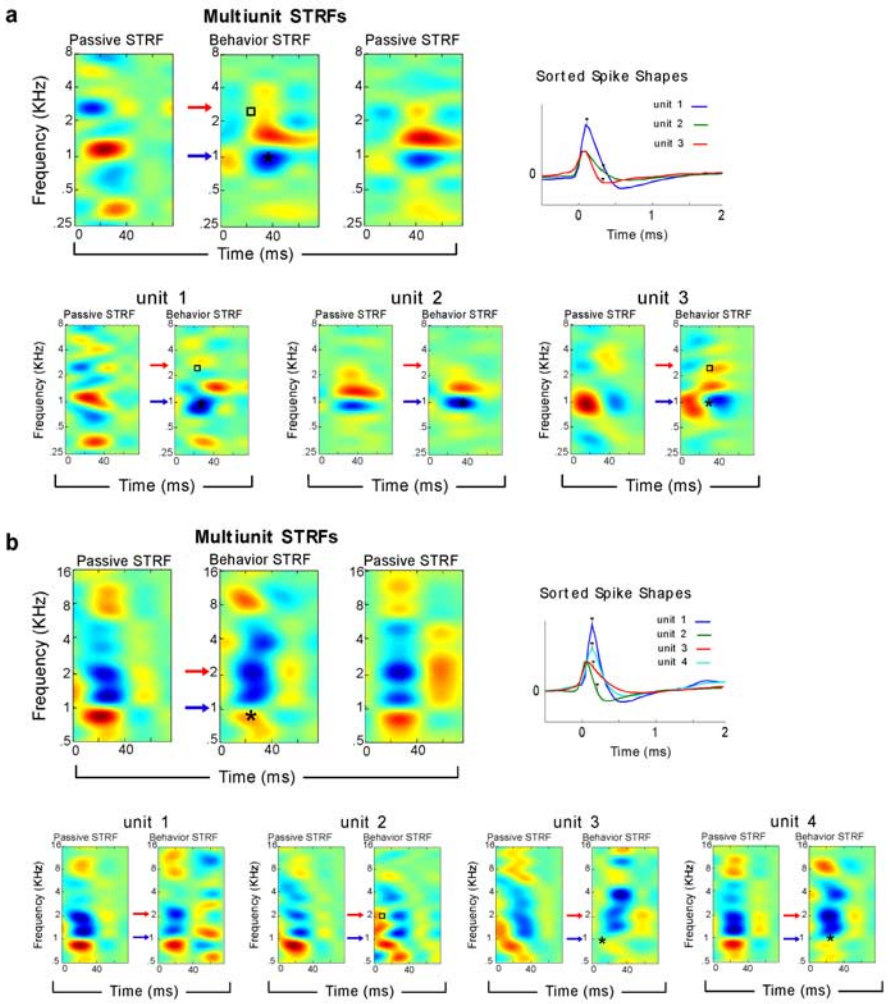

Figure 6. Plasticity and single-unit variability in multiunit STRFs. ***a***, Example of plasticity in a behavioral STRF constructed from multiunit records. The three single units in the panels below were components of the multiunit cluster. The single-unit mean waveforms here (and in ***b***) are clearly distinct, as shown by the nonoverlapping variance bars around each waveform (see Materials and Methods). Multiunit STRFs, The passive STRF (left) changed significantly during frequency discrimination behavior ($\Delta A_{ref} = -128\%$; $\Delta A_{tar} = 69\%$; middle), and the change persisted afterward (right). Single-unit STRFs, STRF changes in three units. In each pair, the passive and behavior STRFs are shown, as well as the locations and type of significant plasticity that occurred in each. Details are the same as in Figure 2. Note that unit 2 in this figure was shown previously in Figure 2*a*. ***b***, Same as in ***a*** above except that there were four single-unit STRFs that were isolated from the multiunit cluster. Multiunit STRFs, A strong depression was induced at the reference tone frequency during the discrimination task, but no significant effects were observed at the target tone frequency (middle). The multiunit STRF reverted to the original shape afterward (see postbehavior passive STRF in the right). Single-unit STRFs, STRF changes in four units that constitute the multiunit cluster. All details are as in ***a*** above. Note that the STRF changes are different in each of the four cells. In the first, no significant changes occurred. In unit 2, only facilitation at target frequency was seen. In the units 3 and 4, only depression at reference frequency occurred.

ous changes in the STRF arising from the complex patterns of plasticity in the preceding discrimination task (as noted previously in Fig. 4).

STRF changes in multiunit clusters

In off-line analysis, it was usually possible to sort one to four single-unit spike waveforms from the multiunit recording trace. Alternatively, after off-line sorting, we could construct a multiunit STRF by pooling spikes from all of the sorted unit clusters. This multiunit STRF sometimes looked very different spectrally and temporally from any of the constituent single-unit STRFs. However, because STRF changes (if they occur) are generally consistent regardless of the shape of the STRFs (i.e., follow a pattern of overall facilitation at target frequency and depression at reference frequency), we conjectured that plasticity in multiunit STRFs would be comparable with that measured in single-unit STRFs. This hypothesis was examined (Fig. 6) for two multiunit clusters from which the two single-unit STRFs in Figure 2, *a* and *d*, were derived. The multiunit cluster in Figure 6*a* consisted of three units with distinct spike shapes. The prebehavior passive multiunit STRF had a strong excitatory region just above 1 kHz and a weaker inhibition at ~2.5 kHz. The constituent neurons that comprised this multiunit cluster (labeled units 1, 2, 3) had approximately similar STRFs, although quite different in detail. During behavior, the reference strongly depressed the STRFs at f_R in all single units as well as in the multiunit cluster. In contrast, the target facilitated the STRFs at f_T only in units 1 and 3 and also in the multiunit STRF (but not in unit 2). It is therefore evident that not all single units in a cluster necessarily show exactly the same pattern of adaptive plasticity, although, in this case, all changes that did occur were in the same direction. This observation is more dramatically illustrated in the multiunit cluster shown in Figure 6*b*, which consisted of four single units. In this case, the reference depressed the STRF locally in the multiunit STRF, whereas the target had no significant local impact. However, in the single-unit STRFs, the plasticity effects were quite varied. In unit 1, the STRF changes during behavior did not reach significance at either target or reference frequency. In unit 2, significant facilitation occurred at the target frequency (an effect not observed in the multiunit STRF), and no significant change occurred at reference frequency (also unlike the multiunit STRF effects). In units 3 and 4, no significant change was observed at target frequency, and depression was seen at the reference frequency (similar to the multiunit STRF). In the presence of all this variability and despite the fact that single-unit STRFs could be quite different from one another and also from the multiunit STRF, most of the observed changes were still consistent (i.e., depression at reference and/or facilitation at target), and hence they could still be manifested in the multiunit STRF.

This correspondence between multiunit and single-unit STRF changes is summarized for all of the cases in the scatter plot of Figure 7*a*. Here the ΔA_{ref} for each multiunit cluster is plotted against the ΔA_{ref} of all constituent single units. The correspondence between the two measures is evidenced by the fact that most points [and the resulting regression (dashed line)] lie near the (ideal) diagonal (solid line).

We also computed a summary of the average depressive and facilitative changes at reference and target frequencies, respectively, from all multiunit recordings. These results are shown in

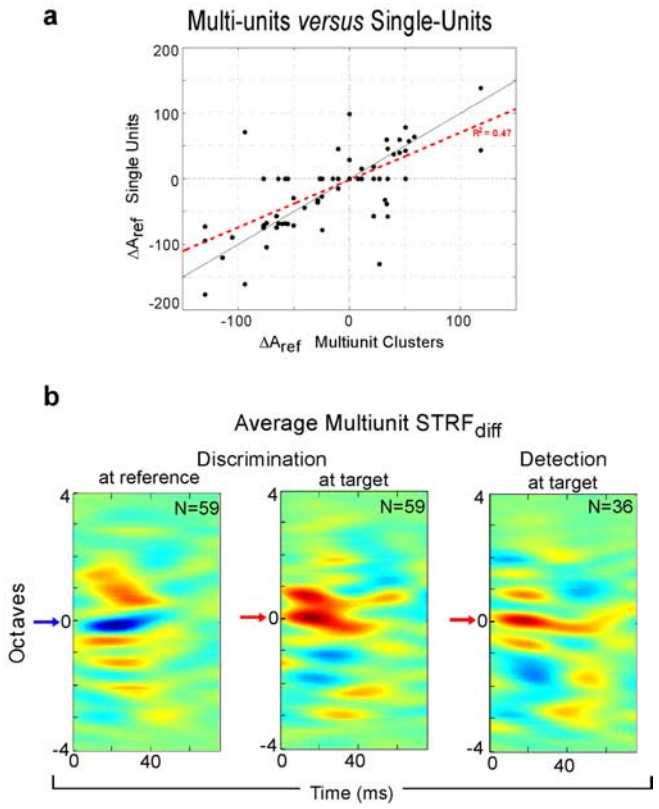

Figure 7. Summary of STRF changes from populations of single units and multiunit clusters. ***a***, A comparison between STRF changes ΔA_{ref} in multiunit clusters versus single units. Each cluster may contain one to four isolated single units. Most points lie near the midline (solid line), indicating that the two changes are reasonably well matched [regression (dashed) line is also shown]. ***b***, The average plasticity effects from all multiunit clusters during discrimination tasks is compared with the average multiunit plasticity effects observed in detection, from a behavioral sequence in which the tone detection task followed the frequency discrimination task. During performance of the discrimination task, a strong depression was induced relative to the reference frequency (left), whereas the opposite effect (facilitation) was seen relative to the target frequency (middle). In detection tasks after frequency discrimination tasks, the multiunit STRFs display a similar pattern of facilitation relative to the target frequency (right). Thus, the facilitatory effects at target frequency are consistent for both detect and discrimination tasks and also consistent for single-unit and multiunit averages (***b***) (see also Fig. 5*c*).

Figure 7*b*, and they resemble the averages computed from single-unit data (Fig. 4), suggesting that it is possible to accumulate reliable evidence of rapid task-dependent plasticity from multiunit recordings.

Because multiunit records have many more spikes than single-unit ones, it is possible to compute clean STRFs from a smaller number of stimulus repetitions (sometimes from as little as one repetition of the set of TORCs) and hence track the history of STRF changes as they occurred. As was found previous in detection tasks (Fritz et al., 2003), STRF changes were already in place during frequency discrimination behavior as soon as the STRF could be reliably measured (sometimes in as little as 2 min, the current maximum temporal resolution possible using the current technique, which corresponds to the time necessary to present one repetition of the complete set of 30 TORCs during behavior). This is evident in the series of gradually constructed multiunit STRFs from one experiment, shown in Figure 8*a*. During performance of the frequency discrimination task, the STRF had already changed significantly after two repetitions (~4 min). There was significant suppression as well as a downward displacement of the excitatory region in which the reference tone frequency had been placed (at 3.2 kHz as indicated by the blue arrow and the dashed line). The multiunit STRF had already stabilized completely by the fourth repetition and remained essentially unchanged during the after six repetitions.

We also observed noticeable decreases in responses to the reference tone (Fig. 8*b*) that corresponded to the STRF change, presumably reflecting the weakening of the excitatory area near the reference tone frequency (3.2 kHz). Figure 8*c* illustrates cumulative decrease in responses to the reference tones in the 12 multiunit clusters that had most negative ΔA_{ref} values. Because target tones were presented considerably less frequently (~¼ as often), we were unable to generate analogous plots for them. In summary, these multiunit recordings provide examples showing that, within the first few minutes of onset of frequency discrimination behavior, there can be a direct change in the neural response to a behaviorally relevant cue corresponding to the observed STRF changes.

Discussion

To study receptive field adaptive plasticity in multiple acoustic tasks, we trained ferrets on both tone discrimination and tone detection tasks (see Appendix) using a modified conditioned avoidance paradigm (Heffner and Heffner, 1995; Fritz et al., 2003, 2005a,b). When a trained animal performed either task, we observed rapid adaptive changes in A1 receptive fields in accordance with task demands. The specific type of change was influenced by the initial shape of the receptive field, the behavioral task, attention to the salient acoustic cues, and was also likely to be modulated by general influences reflecting the animal's state of arousal, motor preparation, and reward expectation (Durif et al., 2003; Brosch et al., 2004). However, we suggest that the overarching principle that characterized these adaptive receptive field changes was that they were consistent overall with (1) identifying the salient task cues, (2) linking them to behavior to achieve the goals of the ongoing task. In simplest terms, these goals were to identify "safe" (reference) sounds during and after which the thirsty animal could drink freely without risk and "warning" (target) sounds after which the animal could avoid shock if it stopped ongoing drinking for a brief interval (400 ms).

The majority of STRFs (~75%) of individual neurons and multiunit clusters changed significantly during performance of either the frequency discrimination (Fig. 3) or the tone detection task (Fritz et al., 2003). In both tasks, STRF changes included selective facilitation at target frequency. In addition, in the frequency discrimination task, the majority of these changes also resulted in a distinctive pattern of selective depression of the STRF at the reference frequency (Figs. 2, 4). These changes were consistent with the behavioral goal of the frequency discrimination task in that they enhanced overall stimulus contrast by sensitizing the neuron to the target warning frequency (after which the animal needed to immediately stop ongoing drinking), while simultaneously suppressing response to the safe reference frequency (after which the animal continued its ongoing drinking).

Our finding that plasticity in multiunit STRFs during performance of these two tasks reliably followed the same pattern observed in the single-unit records will be valuable for future studies and is indicative of the regularity of these adaptive effects across locally diverse groups of cells in A1. Although STRFs of simultaneously recorded units could have strikingly varied patterns of excitatory and inhibitory regions at target and reference frequencies (Fig. 6), local changes were nevertheless consistent with the behavioral meaning of each tone regardless of STRF initial shape. This suggests a widespread process of adaptive modulation that

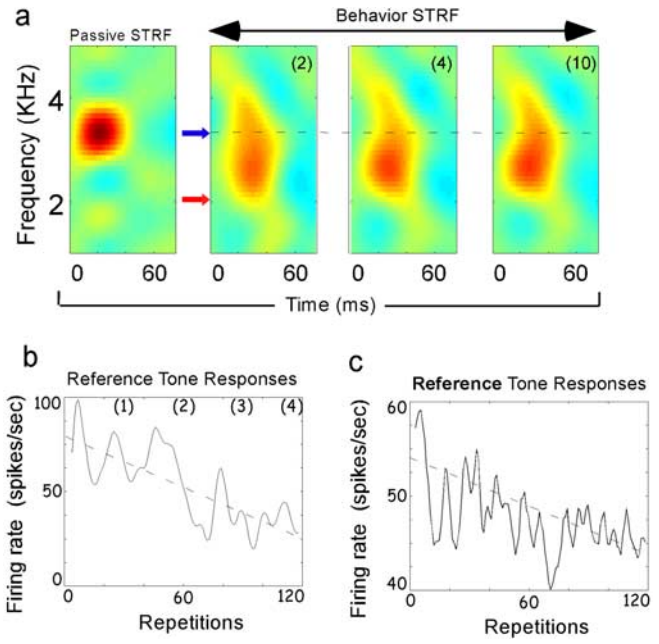

Figure 8. Examples of buildup in STRF plasticity and its relation to responses to reference tone. ***a***, Snapshot sequence of STRFs for a multiunit cluster before (passive STRF) and during the behavior. STRF changes were already evident by the end of the second repetition of the stimulus set (4 min) and were essentially complete by the end of the fourth repetition (8 min). ***b***, Reference tone response of the multiunit cluster decreased, reflecting the fading and downward shift of the excitatory region away from 3.2 kHz in the multiunit behavioral STRFs. The single-unit STRF shown previously (in Fig. 2*b*) was isolated from the multiunit cluster in this figure, and a marked inhibition at the reference frequency can be seen in its $STRF_{diff}$. ***c***, Responses to the reference tones throughout the behavior. Data are accumulated from 12 multiunit clusters that exhibited the strongest suppressive STRF changes at reference tone frequencies. Progression of tone responses is indicated by the dashed lines.

affects a broad variety of STRFs throughout A1. However, there was also a stable group of STRFs that did not apparently change during behavior (~25% of recorded cells), and it is interesting that, even in behaviorally labile STRFs, the plastic changes modulated the strength of preexisting inhibitory or excitatory STRF fields but seldom caused an outright change of synaptic sign at best frequency (observed in only 2 of 127 cases).

Cortical plasticity and frequency discrimination training

Global and local cortical plasticity has been shown after frequency discrimination training. At the global level, some studies (Recanzone et al., 1993; Scheich et al., 1993) have reported enlargement in the cortical representational area activated by the behaviorally relevant frequencies (in owl monkey and gerbil), whereas other studies (Brown et al., 2004; Irvine et al., 2004) have not observed any such changes in cortical magnification nor shown any evidence for map reorganization after extensive behavioral training (in cat). Although changes in tonotopic maps were not measured in this study, because our ferrets were trained to perform equally well at any target or reference frequencies, we predict that there would be virtually no lasting changes in the A1 tonotopic map, because there was no predominant behavioral focus on any single frequency throughout training. At the local level, previous studies have reported several quite different kinds of changes of neuronal activity in the primary auditory cortex after frequency discrimination training (Disterhoft and Olds, 1972; Edeline et al., 1990a,b; Edeline and Weinberger, 1993; Ohl and Scheich, 1996, 1997; Blake et al., 2002). Although the results of these studies were varied, because of many factors such as differing species (guinea pig, gerbil, rat, and owl monkey), experimental designs [changes detected in awake (Disterhoft and Olds, 1972; Edeline et al., 1990a,b; Ohl and Scheich, 1996, 1997) vs anesthetized (Recanzone et al., 1993) animals], and behavioral paradigms (positive reinforcement vs shock avoidance vs shock conditioning), our findings of rapid STRF plasticity (with overall enhancement at target frequency and suppression at reference frequency) during performance of a frequency discrimination task are most compatible with two of the studies above (Edeline and Weinberger, 1993; Blake et al., 2002). Although using very different techniques, common to both studies was (1) behavioral confirmation of learning of the discrimination task and (2) receptive field analysis of task-related changes in A1 during task acquisition. A differential classical conditioning study (Edeline and Weinberger, 1993) was the first to analyze receptive field changes as a result of tone discrimination training. It showed that classical conditioning could selectively induce increased neural responses to the frequency of the positive conditioned stimulus (CS+) and (relatively nonselectively) induce decreased responses to all other frequencies, including that of the negative conditioned stimulus (CS−). This study also contributed another fascinating finding: that difficult tone discrimination training (i.e., differential classical conditioning with closely adjacent CS+ and CS− frequencies) that did not lead to successful behavioral learning still resulted in consistent receptive field changes in A1. In other words, cortical adaptive responses can occur before, or even without, associated behavioral changes. Recently, a long-term study using chronically implanted electrodes in A1 (Blake et al., 2002) followed the neural correlates of instrumental learning of an auditory discrimination task and reported increased neural responses to tones in the target frequency range relative to the standard and nontarget frequencies. A particularly intriguing aspect of this study was the demonstration that the observed neural changes coincided with the onset of behavioral task acquisition (marked by a change in frequency discrimination thresholds from 1 to 1/12 octave). The receptive field changes described in both tone discrimination studies are consistent with our observations; however, the findings of these studies also raise important questions about the relationship between cortical plasticity and behavioral change.

Is there a correlation between task difficulty and the magnitude of induced, adaptive cortical change? In unpublished behavioral studies of behavioral threshold for frequency discrimination in the ferret with reference fixed at either 2 or 6 kHz, we found that trained ferrets are capable of frequency resolution of 1/16 to 1/32 octave. However, in the present study, we never challenged the animals to perform at behavioral threshold. In fact, as shown in Figure 4, we never presented them with frequency discriminations <1/4 octave. In most behavioral physiology sessions, reference and target frequencies were separated by more than one octave, well above behavioral threshold. Thus, even while performing a relatively easy task, there were still systematic STRF changes at the behaviorally relevant frequencies. This result suggests that it may not be necessary to engage the animal in a lengthy process of perceptual learning or to challenge the animal with difficult tasks at perceptual threshold to observe dynamic changes in receptive field properties. Rather, it may be enough to simply focus the animal's vigilance or attention on salient task frequencies to create changes in STRF shape. Of course, had we chosen to challenge the animal with a more difficult frequency discrimination task, it is possible that we would have seen STRF changes of greater magnitude. This conjecture is based on the results of a study that showed that, while monkeys performed a

difficult visual orientation task, neurons in V4 exhibited increased gain and increased orientation selectivity relative to their response selectivity observed during performance of an easier task (Spitzer et al., 1998). Another possible neural outcome of long-term perceptual training on a frequency discrimination task with fixed standard frequency is sharpening in frequency tuning (Recanzone et al., 1993), particularly at the behaviorally relevant frequencies. This result was not observed in the present study, perhaps because the animals were (1) trained on both detection and discrimination tasks and (2) trained on a general version of both tasks (with daily changes in the target and/or reference frequency).

The clear result of our control studies (that used identical discrimination task stimuli but with no accompanying behavior, in recording from A1 in a naive animal) was the absence of major change in neuronal STRFs [compared with the magnitude of STRF changes in the behavioral condition (Fig. 3)]. This result demonstrates that the observed STRF changes, such as suppression at the reference tone, are primarily behaviorally driven and not simply attributable to passive origins such as response adaptation. However, in data from the naive control, there was also a very slight population tendency toward enhanced responses to the rarer sound (target frequency) and depressed responses to the common sound (reference frequency) that may be in keeping with recent observations of A1 stimulus-specific adaptation (Ulanovsky et al., 2003). From an informational viewpoint, it should make no difference to the brain whether the STRF increases or decreases its response to the reference sound, as long as an opposite effect occurs at the target frequency, to enhance the neural contrast disparity between responses to the two frequencies. A speculative explanation for the dominant pattern of behavioral plasticity reported (overall suppression at reference and facilitation for target) is that the auditory system, for voluntary, attentive behavioral tasks, has built on a preexisting set of automatic, preattentive neural mechanisms that are normally used to detect acoustic novelty and show, in miniature, the same response pattern as seen in frequency discrimination behavior.

Conclusion

We have demonstrated that, when ferrets performed a sequence of different acoustic tasks (e.g., multiple discrimination tasks with different reference and target tones, or a series of discrimination and detection tasks) STRFs of single A1 neurons changed in accord with the changing salient cues. Such task-related dynamic plasticity may be a general feature of primary sensory neocortex (Li et al., 2004). We conjecture that, because most A1 sensory neurons participate in multiple behavioral contexts, it is likely that their receptive field properties are continuously being modified (Kisley and Gerstein, 2001; Edeline, 2003) against the basic scaffolding of the synaptic inputs, as the animal enters new acoustic environments and initiates new tasks. Top-down attentional mechanisms may play an important role (Iriki et al., 1996; Alain and Arnott, 2000; Iwamura et al., 2001; Fritz et al., 2003, 2005a,b; Mazer and Gallant, 2003; Boynton, 2004; Li et al., 2004; Maravita and Iriki, 2004; McMains and Somers, 2004; Petkov et al., 2004; Reynolds and Chelazzi, 2004; Brechmann and Scheich, 2005) in identifying salient features of the acoustic or the visual scene, regulating adaptive plasticity, enhancing responses, and reshaping neuronal receptive field properties, enabling A1 neurons to multiplex acoustic inputs for different acoustic tasks.

Appendix

Although we think that the terminology we have chosen to describe the acoustic tasks used in this study is appropriate, it is also important to acknowledge other perspectives. For instance, it may be argued that both the two behavioral paradigms described in this study are, in a sense, discrimination tasks. After all, in the "detection" task (T_1, T_2, T_3 . . . A), the ferret must discriminate a pure tone stimulus (A) from a sequence of broadband noise stimuli (T_1–T_n). Detection, in this view, is a special case of discrimination. Conversely, one might argue that the "frequency discrimination" task (T_1A, T_2A, T_3A . . . T_nB) is in fact is a detection task, because the ferret can perform the task by detecting a change in the tonal frequency (from *A* to *B*) in a sequence of TORC-tone stimuli. However, to detect the change in tone frequency, clearly the ferret must discriminate between the two tones. Each perspective is valuable, but we emphasize that whatever terminology is chosen, it is clear that the two tasks can be distinguished from one another not only by the complexity of the stimuli but also by the differing salient cues to which the animal must attend to perform the tasks correctly. We propose that, in the first "detect" task, the ferret is vigilant for the appearance of any narrow-band sound at any frequency against a background of modulated broadband sounds, whereas in the second frequency discrimination task, the ferret attends to the change in the frequency of the target tone relative to the frequency of the reference tone. However, unlike the detection task, in the frequency discrimination task, the ferret need not attend to the class of TORCs because they carry no direct task-relevant information.

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