

Development/Plasticity/Repair

Modifying the Adult Rat Tonotopic Map with Sound Exposure Produces Frequency Discrimination Deficits That Are Recovered with Training

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Frequency discrimination learning is often accompanied by an expansion of the functional region corresponding to the target frequency within the auditory cortex. Although the perceptual significance of this plastic functional reorganization remains debated, greater cortical representation is generally thought to improve perception for a stimulus. Recently, the ability to expand functional representations through passive sound experience has been demonstrated in adult rats, suggesting that it may be possible to design passive sound exposures to enhance specific perceptual abilities in adulthood. To test this hypothesis, we exposed adult female Long–Evans rats to 2 weeks of moderate-intensity broadband white noise followed by 1 week of 7 kHz tone pips, a paradigm that results in the functional over-representation of 7 kHz within the adult tonotopic map. We then tested the ability of exposed rats to identify 7 kHz among distractor tones on an adaptive tone discrimination task. Contrary to our expectations, we found that map expansion impaired frequency discrimination and delayed perceptual learning. Rats exposed to noise followed by 15 kHz tone pips were not impaired at the same task. Exposed rats also exhibited changes in auditory cortical responses consistent with reduced discriminability of the exposure tone. Encouragingly, these deficits were completely recovered with training. Our results provide strong evidence that map expansion alone does not imply improved perception. Rather, plastic changes in frequency representation induced by bottom-up processes can worsen perceptual faculties, but because of the very nature of plasticity these changes are inherently reversible.

Key words: auditory cortex; cortical reorganization; frequency discrimination; passive sound exposure; perceptual learning; tonotopic map

Significance Statement

The potent ability of our acoustic environment to shape cortical sensory representations throughout life has led to a growing interest in harnessing both passive sound experience and operant perceptual learning to enhance mature cortical function. We use sound exposure to induce targeted expansions in the adult rat tonotopic map and find that these bottom-up changes unexpectedly impair performance on an adaptive tone discrimination task. Encouragingly, however, we also show that training promotes the recovery of electrophysiological measures of reduced neural discriminability following sound exposure. These results provide support for future neuroplasticity-based treatments that take into account both the sensory statistics of our external environment and perceptual training strategies to improve learning and memory in the adult auditory system.

Introduction

Statistical variations in the sensory environment can have profound effects on cortical sensory representations long after tradi-

tional developmental windows have closed. In the acoustic domain, prolonged exposure to moderate-intensity sounds may elicit experience-dependent plasticity in the mature auditory cortex under conditions such as environmental enrichment with varied stimuli (Engineer et al., 2004), or persistent exposure to uninformative (Noreña et al., 2006; Zhou et al., 2008; Pienkowski

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and Eggermont, 2009) or disruptive (Zheng, 2012; Zhou and Merzenich, 2012; Kamal et al., 2013) sounds. The resulting effects on the adult tonotopic map can be broad or precise, as illustrated by passive exposure to broadband white noise, which disrupts frequency-tuning in a nonspecific manner but can induce the highly specific expansion of a selected isofrequency band if followed by a subsequent exposure to pure tones (Zhou et al., 2011; Thomas et al., 2019a). These findings reveal the possibility that passive sound exposures could be designed to elicit targeted plastic changes in the auditory cortex in adulthood.

In frequency discrimination training, learning is often associated with an increase in the cortical representation of the frequency region corresponding to the rewarded sound (Polley et al., 2006; Keuroghlian and Knudsen, 2007; McGann, 2015; Voss et al., 2016). And although greater representation is generally thought to confer improved perception (Merzenich et al., 1984; Pantev et al., 1998; Rutkowski and Weinberger, 2005; Wiestler and Diedrichsen, 2013), artificially inducing tonotopic map expansion for a specific frequency has not always been found to improve discrimination for that frequency. While map expansion induced by pairing passive tone exposure with nucleus basalis stimulation enhanced discrimination for the paired tone in adult rats (Reed et al., 2011; Froemke et al., 2013), expansion by direct cortical microstimulation with a weak electric current did not alter frequency-discrimination performance (Talwar and Gerstein, 2001), and rats with expanded frequency representation due to tone exposure during the critical period were worse at discriminating those frequencies as adults (Han et al., 2007). The diverging results of these studies suggest that although map expansion may be a shared phenotype, its mechanism of induction determines whether or not it will carry perceptual significance.

Here, we attempted to improve frequency discrimination learning by enhancing the representation of a specific frequency in the primary auditory cortex (A1) of adult rats using passive sound exposure. We exposed young-adult Long–Evans rats to 2 weeks of moderate-intensity white noise followed by 1 week of 7 kHz tone pip clouds to increase the functional representation of 7 kHz within A1 similar to Zhou et al. (2011) and our previous work (Thomas et al., 2019a). We then trained exposed and non-exposed rats on an adaptive tone discrimination task in which the target tone was 7 kHz. Although we had hypothesized that the induced early overrepresentation of the target tone would improve the behavioral performance of exposed animals, we found that it actually impaired discrimination for the exposure frequency and delayed perceptual learning. Rats exposed to noise followed by 15 kHz tone pip clouds were not impaired at the same task. We also investigated the electrophysiological response properties of A1 neurons of exposed animals before and after training and found evidence of reduced neural discriminability for the target tone that was completely recovered with training. Our results confirm that map expansion alone does not imply improved perception. Rather, changes in frequency representation induced by passive sound experience can worsen perceptual faculties, but because of the very nature of plasticity these changes are inherently reversible.

Materials and Methods

Experimental groups. Six groups of female young adult Long–Evans rats (3.5–6 months) were used for this experiment: three untrained (UT) and three trained (T). Of the untrained groups, one was housed in a standard acoustic environment (Naive-UT, $N = 10$). The other two were passively exposed to white noise for 2 weeks followed by 7 kHz (7 kHz-UT, $N = 6$) or 15 kHz (15 kHz-UT, $N = 5$) tone pip clouds for 1 week. The three

trained groups underwent the same exposures before starting training. The groups were Naive-T ($N = 10$), 7 kHz-T ($N = 10$), and 15 kHz-T ($N = 8$). A seventh group of rats was used to examine whether the effects of passive sound exposure persisted for the duration of training (7 kHz-UT+12weeks, $N = 4$). This group was exposed to white noise for 2 weeks followed by 7 kHz tone pip clouds for 1 week and then returned to a standard acoustic environment for 12 weeks. All experimental procedures were approved by the Montreal Neurological Institute Animal Care Committee and follow the guidelines of the Canadian Council on Animal Care.

Exposure conditions. Rats were housed in pairs in cages within sound-attenuated chambers [background sound level 40 dB sound pressure level (SPL)] under a 12 h light/dark cycle with unlimited access to water. Those undergoing training were lightly food restricted. The weights of all rats were monitored to ensure that training and noise exposure conditions did not result in >20% bodyweight reduction. Sound-exposed rats were passively exposed 24 h/d to moderate intensity (70 dB SPL) broadband white noise for 2 weeks followed by 1 week of tone pip clouds. The tone pip clouds consisted of 50 ms tones (5 ms onset and offset ramps) of random frequencies within a 0.25 octaves range centered on either 7.6 kHz (ranging from 7 to 8.3 kHz) or 15 kHz (ranging from 13.8 to 16.4 kHz) and delivered in trains of 5 pulses/s. The interval between each train of tones was a random duration generated from a normal distribution with a mean of 2.5 s. The stimuli were generated using custom MATLAB scripts (The MathWorks) and played through an Ultralite-mk3 Hybrid Interface (MOTU) with sampling at 192 kHz. The stimuli were amplified to a free-field sound level calibrated so that the intensity of the white noise measured in the center of the chamber was 70 dB SPL (root mean square) and the intensity of the tone pips was 65 dB SPL.

Training procedure. Rats were trained in wire cages within sound-attenuated chambers. Behavior was shaped in two parts: pretraining and training. During pretraining, rats learned to poke their nose in a nose-poke (Lafayette Instrument) to obtain a food reward of chocolate flavored sucrose pellets (45 mg; BioServ). Rats received a pellet if they poked within 5 s of stimulus presentation, which was a 7 kHz tone. Rats graduated from pretraining after three consecutive sessions in which they poked within 5 s of the tone at a rate significantly greater than chance. This stage lasted ~2 weeks. Following pretraining, rats were either housed in a standard acoustic environment or exposed to sound for 3 weeks. After this period, the training program of interest began. Rats were trained on an adaptive go/no-go tone discrimination task in which the 7 kHz pure tone target stimulus was presented in 20% of trials. The nontarget tone started as 7 kHz + ½ octave at the beginning of each session and became 0.025 octaves closer to the target tone as the task level increased. For a given trial, the rat's behavior was scored according to the combination of behavioral state (go or no-go) and stimulus property (target or nontarget). Go responses within 5 s of a target were scored as a hit; a failure to respond was scored as a miss. A go response within 5 s of a nontarget stimulus was scored as a false-positive; the absence of a response was scored as a withhold. Go responses outside of these time windows were scored as false alarms and initiated a 5 s timeout period during which no stimuli were presented. A hit triggered the delivery of a chocolate pellet and an increase in task level. A miss or false-positive initiated a decrease in task level and a 5 s timeout. A withhold did not produce any consequences. The stimulus target recognition index, d' (Macmillan and Creelman, 1990), was calculated for each training session from the hit rate (hits/hits + misses) and the false-positive rate (false-positives/false-positives + withholds). Tones were 50 ms in duration (5 ms ramps) with 4–6 s between presentations and delivered in a free-field manner through a calibrated speaker at 60 dB SPL. Sound presentation and response recording were performed with custom MATLAB scripts and Arduino hardware.

Training evaluation. Of a total of 32 trained rats, four (one Naive-T, two 7 kHz-T, and one 15 kHz-T) did not successfully relearn how to poke in response to the tone after this period. This was not found to be related to exposure group ($\chi^2 = 0.32$, $p = 0.8508$, $df = 2$). These rats were not included in analyses. The rest of the animals were trained for ~12 weeks and completed between 60 and 71 training sessions. For analyses, we focused on the first 60 sessions for which we had an equal number of data points per rat, although most rats completed >60 sessions in total. We

did not include a small number of training sessions in which rats were considered to be unmotivated. Unmotivated sessions were identified as having a hit rate <60% after a rat had obtained a $d' \geq 1$ at least once (typically after 4–5 weeks of training). At this point in the training, rats were very familiar with the task and a low hit rate indicated that there was either a technical error with the hardware (e.g., pellets were not being released) or they were not hungry enough to be motivated by the food reward. The number of unmotivated sessions was not different between the three groups (combined mean = 2.0 ± 2.0 sessions, one-way ANOVA $F_{(2,25)} = 1.36, p = 0.2747$). For both pretraining and training, rats were trained for 1 h/d ~6 times/week. The rate of training also did not differ between the three groups (combined mean = 5.47 ± 0.46 sessions/week, one-way ANOVA $F_{(2,25)} = 0.701, p = 0.5057$).

Electrophysiological recordings. Rats underwent electrophysiological recordings the day after exposure or training ended. Untrained rats were 3.5 months old at the time of recordings, trained rats were 2 months old at the beginning of training and 6 months old at the time of recordings, and 7 kHz-UT+12weeks rats were 6 months old at the time of recordings. Electrophysiological recordings of the left auditory cortex were performed in a shielded soundproof recording chamber. Rats were premedicated with dexamethasone (0.2 mg/kg, i.m.) to minimize brain edema. Anesthesia was induced with ketamine/xylazine/acepromazine (63/13/1.5 mg/kg, i.p.) followed by continuous delivery of isoflurane 1% in oxygen via endotracheal intubation and mechanical ventilation. Heart rate and blood oxygen saturation were monitored with a pulse oximeter. Body temperature was monitored with a rectal probe and maintained at 37°C with a homeothermic blanket system. Rats were held by the orbits in a custom designed head holder leaving the ears unobstructed. The cisterna magna was drained of CSF to further minimize cerebral edema. To access the auditory cortex, the left temporalis muscle was reflected, the skull over the auditory cortex was removed, and the dura was resected. Once exposed, the cortex was maintained under a thin layer of silicone oil to prevent desiccation. Acoustic stimuli were delivered in a free-field manner to the right ear through a calibrated speaker. Cortical responses were recorded with a 64-channel tungsten microelectrode array [Tucker-Davis Technologies (TDT)] lowered orthogonally into the cortex to a depth of 600–900 μm (layers 4/5). The electrode wires (33 μm diameter) were arranged in an 8×8 grid orthogonal to the cortex spaced 375 μm apart with row separation of 500 μm . To maximize recording density, neural responses were consecutively recorded from multiple overlapping electrode positions within each rat. The stereotaxic location of each position relative to the first was noted to accurately reconstruct auditory maps during offline analysis. Extracellular multiunit responses were obtained, amplified, and filtered (0.3–5 kHz) using a TDT RZ2 processor. The TDT OpenEx software package was used to generate acoustic stimuli, monitor cortical activity online and store data for offline analysis.

Tonotopic map reconstruction. Frequency-intensity receptive fields were constructed using neural responses to frequency-intensity combinations of pure tones. Sixty-six frequencies (0.75–70 kHz; 0.1 octave increments; 25 ms duration; 5 ms ramps) were presented at eight sound intensities (0–70 dB SPL; 10 dB increments) at a rate of 1 tone/s with three repetitions and in pseudorandom presentation order. The onset latency for each cortical site was defined as the time in ms when the peristimulus time histogram (PSTH) first exceeded the mean baseline firing rate by 2.5 SD. The period of time between the onset latency and the time when the PSTH returned to <2.5 SD of the mean baseline firing rate was defined as the response duration. Receptive fields were generated from the average firing rate at each frequency and intensity combination over the response duration. The characteristic frequency (CF) and threshold of a cortical site were defined, respectively, as the frequency and intensity at the tip of the V-shaped tuning curve. For flat-peaked tuning curves or tuning curves with multiple peaks, the CF was defined as the frequency that elicited the strongest firing rate at the lowest threshold. The best frequency (BF) was defined as the frequency that elicited the strongest firing rate over the response duration when presented at 60 dB. The latency, response duration, CF, BF, and threshold were first determined by an automated custom MATLAB routine and then manually verified by an experimenter blind to the identity of the experimental groups. The receptive field bandwidth (BW) at each intensity was com-

puted by estimating 2σ from the Gaussian fit to the tuning curve using a standard 50 ms response window starting 8 ms after stimulus onset (Han et al., 2007; Montgomery and Wehr, 2010). We determined goodness of fit with corrected r^2 and, for BW analyses, only retained sites where r^2 was >0.25 and the mean of the function, μ , was within the range of presented frequencies. Cortical sites were identified as belonging to the primary auditory field (A1) based on published functional characteristics of each field (Polley et al., 2007). These were reversal of CF tonotopic gradients, onset latencies, threshold, and PSTH morphologies. Only responses recorded from full A1 maps were included in analyses. A full A1 map was defined by having low, medium, and high-frequency regions and by the detection of a reversal of the tonotopic gradient on the rostral border of A1 and the detection of non-auditory sites on the caudal and medial borders of A1. To generate A1 maps, Voronoi tessellation was performed using custom MATLAB scripts to create tessellated polygons with electrode penetration sites at their centers. To verify that an individual isofrequency region was not oversampled for any experimental group, we investigated the distribution of distances between each penetration site and its nearest neighbor. Of all sites, 92.70% (1550/1672 sites) had a nearest neighbor distance of 312.5 μm . We confirmed that this proportion did not differ between groups for frequency bins centered on 1.25, 2.5, 3.5, 5, 7, 10, 14, 20, 28, and 48 kHz by performing Kruskal–Wallis tests for each bin and correcting for multiple comparisons by evaluating at the Bonferroni adjusted α level of 0.005. No test was significant for any CF ($\chi^2 \leq 11.71, p \geq 0.0687, df = 6, n = 50$ rats. 7 kHz bin: $\chi^2 = 3.18, p = 0.7859$. 14 kHz bin: $\chi^2 = 2.23, p = 0.8979$) or BF bin ($\chi^2 \leq 12.65, p \geq 0.0489, df = 6, n = 50$ rats. 7 kHz bin: $\chi^2 = 4.26, p = 0.6417$. 14 kHz bin: $\chi^2 = 4.64, p = 0.5904$).

Spatial overlap analysis. To estimate the number of cortical sites that robustly responded to a given frequency, we first smoothed and normalized the frequency-intensity receptive field for each site by applying a median filter and dividing by the maximum response. We then selected a response threshold of >0.5 to indicate whether a site was robustly responsive at a given frequency-intensity combination. A strict response threshold was necessary to separate neural responses to the target and nontarget frequencies, which are relatively close tonotopically. Finally, the amount of spatial overlap between A1 sites that responded to the target and nontarget frequencies was computed by dividing the number of A1 sites that robustly responded to both frequencies by the total number of A1 sites.

Statistical analyses. Statistical results appear in parentheses with test name, statistic, and number of data points per level of nested data. Where data are not shown in figures or extended data figures, mean \pm SD are reported in the text. Linear mixed-effects models (Reed and Kaas, 2010; Aarts et al., 2014) were used to analyze data collected through nested experimental designs. For these models, recording position nested within rat ID were included as random effects. Analyses were conducted using MATLAB and JMP Pro 13 (SAS Institute). The fixed-effect test results are reported with the degrees of freedom denominator approximated for normal data using the Kenward–Roger adjustment. All tests were evaluated at an α level of 0.05 unless otherwise noted. Additional descriptive statistics and ANOVA summary tables are reported in Table 1-1, available at <https://doi.org/10.1523/JNEUROSCI.1445-19.2019.t1-1>, Table 2-1, available at <https://doi.org/10.1523/JNEUROSCI.1445-19.2019.t2-1>, Table 2-2, available at <https://doi.org/10.1523/JNEUROSCI.1445-19.2019.t2-2>, Table 3-1, available at <https://doi.org/10.1523/JNEUROSCI.1445-19.2019.t3-1>, and Table 5-1, available at <https://doi.org/10.1523/JNEUROSCI.1445-19.2019.t5-1>.

Results

We attempted to improve frequency discrimination learning in adult rats by enhancing the functional representation of 7 kHz in A1 with passive sound exposure. Two-month-old female Long–Evans rats were exposed to 2 weeks of moderate-intensity (70 dB SPL) white noise followed by 1 week of 7 kHz tone pip clouds. We then trained exposed and non-exposed rats on an adaptive go/no-go tone discrimination task that tested their ability to identify a 7 kHz target tone among distractor (nontarget) tones. The nontarget tones were $\frac{1}{2}$ octave higher than the target at the beginning of each training

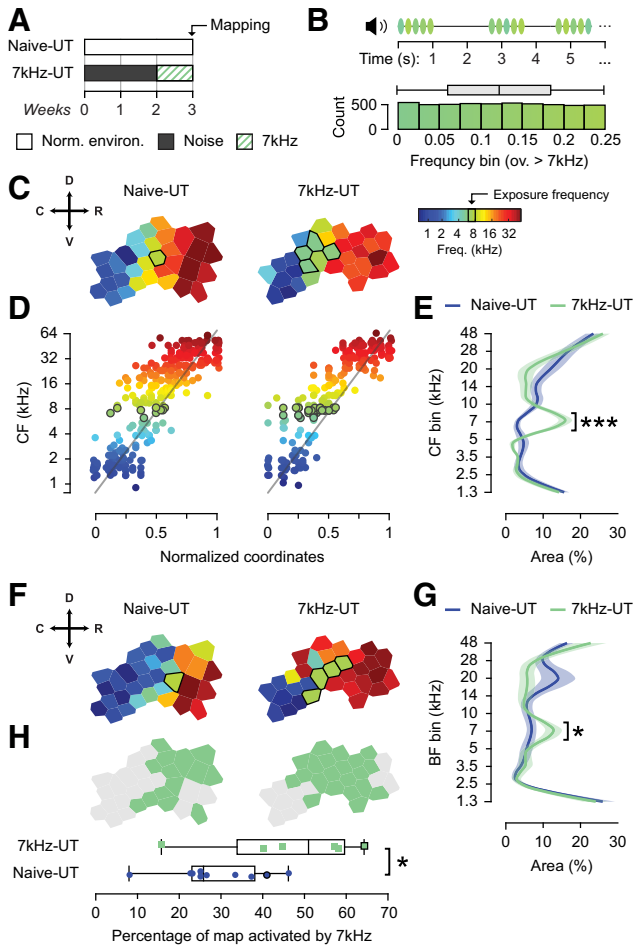


Figure 1. Passive sound exposure increases cortical representation of the 7 kHz frequency region. **A**, Experimental timelines for each group. **B**, Depiction of the 7 kHz tone pip cloud exposure stimulus. The clouds consisted of 50 ms tones of random frequencies between 7 kHz and 7 kHz + 0.25 octaves and delivered in trains of 5 pulses/s. The histogram shows the even distribution of tones within this range for a sample of ~60 min. **C**, Representative A1 CF maps from each exposure group. **D**, CFs from all animals plotted against a normalized tonotopic axis. The gray line represents a perfect tonotopic gradient. **E**, Percentage of A1 area with CFs in 10 frequency bins. **F**, A1 BF at 60 dB maps from the same animals as in **C**. **G**, Percentage of A1 area with BFs in 10 frequency bins. **H**, Top, A1 maps from the same animals as in **C** and **F** showing sites that robustly respond (green) or not (gray) to 7 kHz at 60 dB SPL. Bottom, Box plot of the percentage of A1 area that robustly responds to 7 kHz at 60 dB SPL. Outlined points indicate the animals from the representative maps in **C**, **F**, and **H**. Outlined sites in **C**, **D**, and **F** have CFs of 7 kHz ± 0.25 octaves. Shading in **E** and **G** represents SEM. ****p* < 0.0001, **p* < 0.05, *ov.* = octaves. Number of animals, recording positions, and cortical sites per group: Naive-UT 10, 21, 277; 7 kHz-UT 6, 14, 228. Descriptive statistics may be found in Table 1-1, available at <https://doi.org/10.1523/JNEUROSCI.1445-19.2019.t1-1>.

session and became progressively closer to the target tone in 0.025 octave increments as task level increased, up to a maximum of 20 levels, following a one-up/one-down staircase procedure.

Passive sound exposure induces map expansion of the 7 kHz frequency region

We first verified that sound exposure led to expansion of the 7 kHz frequency region in the adult tonotopic map before behavioral training. Tone pip clouds that included an even distribution of frequencies between 7 and 7 kHz + 0.25 octaves were chosen to increase the representation of the target tone and nearby frequencies corresponding to levels 11–20 of training (Fig. 1A,B). In untrained rats housed in a standard acoustic environment (Naive-UT, *N* = 10) and in untrained rats that underwent sound

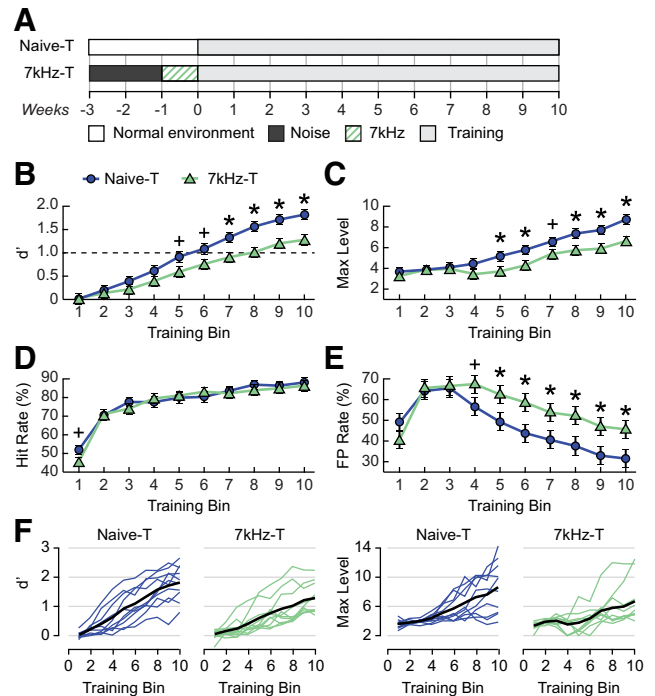


Figure 2. Sound-exposed animals exhibit impaired perceptual learning. **A**, Experimental timelines for each group. **B**, Mean *d'* reached over 10 training bins (6 sessions per bin) in an adaptive tone discrimination task where the frequency of the target tone was 7 kHz. **C**, Mean maximum level reached over 10 training bins. **D**, Mean hit rate over the course of 10 training bins. **E**, Mean FP rate over 10 training bins. **F**, Individual rats' performance for *d'* and maximum level over 10 training bins. The bold line represents the group mean as plotted in **B** and **C**. **p* < 0.05, +*p* < 0.09. Error bars represent SEM. Number of animals and training sessions per group: 10,600. Descriptive statistics and statistic summary tables may be found in Table 2-1, available at <https://doi.org/10.1523/JNEUROSCI.1445-19.2019.t2-1>, and Table 2-2, available at <https://doi.org/10.1523/JNEUROSCI.1445-19.2019.t2-2>.

exposure (7 kHz-UT, *N* = 6), we reconstructed CF and BF tonotopic maps using *in vivo* extracellular responses to presentations of tone pips of various frequencies and intensities under isoflurane anesthesia. We were interested in assessing both CF and BF as CF describes tuning at threshold intensities, which vary per neuron, and BF describes tuning at 60 dB, which was the intensity of the training stimuli. After binning CF and BF values into 10 frequency bins with centers at ~1.25, 2.5, 3.5, 5, 7, 10, 14, 20, 28, and 48 kHz, we observed a significantly greater percentage of map area in the 7 kHz bin for the 7 kHz-UT group in both CF (unpaired *t* test: $t_{(14)} = 7.44, p < 0.0001, n = 16$ rats; Fig. 1C–E) and BF maps (unpaired *t* test: $t_{(14)} = 2.47, p = 0.0272, n = 16$ rats; Fig. 1F, G). The percentage of map area robustly activated (see Materials and Methods, Spatial overlap analysis) by 7 kHz at 60 dB SPL was also significantly greater for the 7 kHz-UT group (unpaired *t* test: $t_{(14)} = 2.52, p = 0.0246, n = 16$ rats; Fig. 1H).

Sound-exposed animals demonstrate impaired perceptual learning

Next, we evaluated the behavioral performance of non-exposed (Naive-T, *N* = 10) and exposed (7 kHz-T, *N* = 10) rats on the adaptive tone discrimination task (Fig. 2A). Contrary to our initial hypothesis, we found that the 7 kHz-T group was worse than Naive-T on several measures of behavioral performance. The sensitivity index *d'* was used to estimate detection accuracy for the target tone during each session, and a threshold of $d' \geq 1$ was used to indicate successful detection. We calculated the average *d'* for training bins of 6 sessions per bin, representing ~1 week of

training each. Over 10 bins comprising 60 1 h training sessions, the discrimination performance of both groups improved steadily. However, Naive-T rats obtained a bin with $d' \geq 1$ on average 2.66 bins before 7 kHz-T rats, corresponding to ~16 training sessions (Naive-T mean = 5.78 ± 1.79 bins, 7 kHz-T mean = 8.44 ± 2.60 bins, unpaired t test: $t_{(16)} = 2.53, p = 0.0221, n = 18$ rats; 1 rat from each group was not included because they did not have any bin where average $d' \geq 1$). When comparing performance between the two groups, we found that d' was significantly higher for the Naive-T group toward the end of training, from bins 7–10 (two-way repeated-measures ANOVA with Group and Bin as factors, Interaction: $F_{(9,1162)} = 8.48, p < 0.0001$; Bins 7–10: all $F_{(1,23,57)} \geq 5.44, all p \leq 0.0285, n = 20$ rats; Fig. 2B). The Naive-T group also reached a higher maximum level per session for bins 5, 6, 8, 9, and 10 of training (two-way repeated-measures ANOVA with Group and Bin as factors, Interaction: $F_{(9,1162)} = 4.73, p < 0.0001$; Bins 5, 6, 8–10: all $F_{(1,30,86)} \geq 5.38, all p \leq 0.0271, n = 20$ rats; Fig. 2C). d' is calculated from the hit rate and false-positive (FP) rate from each training session. We found that differences in d' between the two groups were driven entirely by FP rate, because hit rate was not significantly different for any bin (two-way repeated-measures ANOVA with Group and Bin as factors, Interaction: $F_{(9,1162)} = 1.92, p = 0.0462$. Simple main effects tests did not yield a significant difference for any bin: all $F_{(1,37,34)} \leq 3.49, p \geq 0.0697, n = 20$ rats; Fig. 2D). The average FP rate of the 7 kHz-T group was significantly higher than that of Naive-T for bins 5–10 (two-way repeated-measures ANOVA with Group and Bin as factors, Interaction: $F_{(9,1162)} = 10.67, p < 0.0001$; Bins 5–10: all $F_{(1,24,19)} \geq 4.44, all p \leq 0.0457, n = 20$ rats; Fig. 2E). Despite responding to the target tone at the same rate as Naive-T rats, these findings reveal that 7 kHz-T rats were unable to suppress their response to the nontarget tones, demonstrating a deficit in their ability to properly discriminate these sounds from 7 kHz.

Training recovers electrophysiological measures of reduced discriminability induced by sound exposure

We reconstructed A1 maps from Naive-T and 7 kHz-T rats at the end of behavioral training and compared these to the maps of untrained animals (Fig. 3A). In line with previous studies, we observed an increase in CF area dedicated to the 7 kHz target frequency for trained rats (Fig. 3B,E, top). For the Naive-T group, this percentage area was significantly greater than that of Naive-UT ($p = 0.0016$), while for 7 kHz-T it was greater but the difference approached significance ($p = 0.0677$). The increase for both groups was less than that of 7 kHz-UT, which remained significantly higher than Naive-UT ($p < 0.0001$; one-way ANOVA $F_{(3,29)} = 10.71, p < 0.0001$, followed by Dunnett’s test, $n = 33$ rats). The percentage area dedicated to the CF bin containing the nontarget frequency for training level 1 did not significantly change with either exposure or training (one-way ANOVA $F_{(3,29)} = 2.53, p = 0.0763, n = 33$ rats). On the other hand, we did not observe a training effect on BF area for either the target (one-way ANOVA $F_{(3,29)} = 1.52, p = 0.2290, n = 33$ rats) or nontarget frequency (one-way ANOVA $F_{(3,29)} = 1.23, p = 0.3168, n = 33$ rats; Fig. 3C,E, bottom). These results show that perceptual learning during training led to an overrepresentation of the target tone within A1 when measured with CF, but not BF.

We also noted earlier that sound exposure led to a greater proportion of A1 robustly responding to the target frequency at 60 dB regardless of CF. We next decided to investigate the proportion of map area that responded to either the target or nontarget frequency at the full range of stimulus intensities in trained

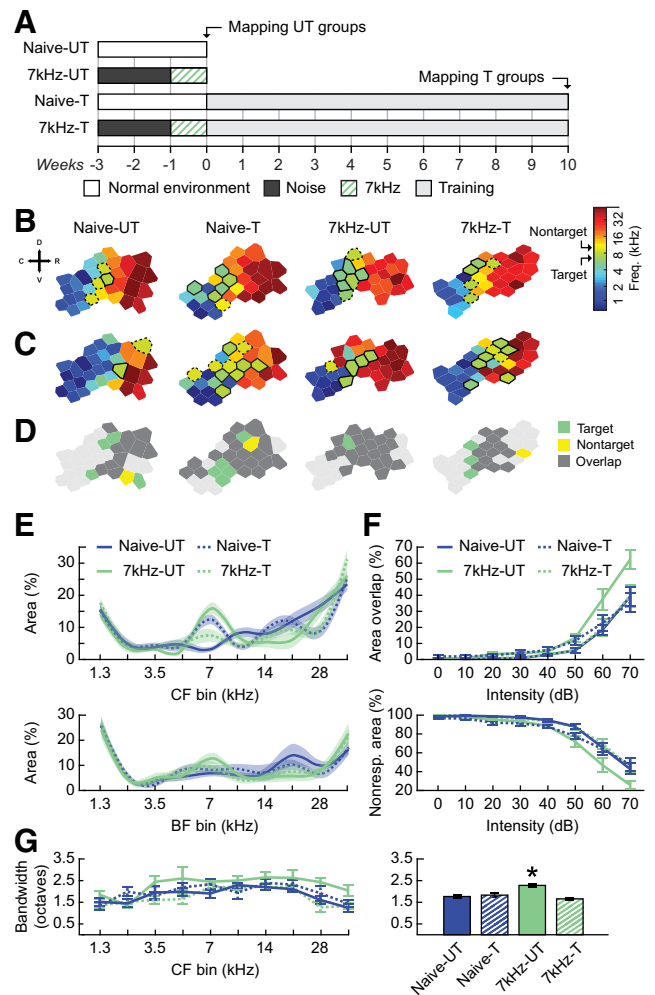


Figure 3. Training recovers typical neuronal responses to the exposure frequency. **A**, Experimental timelines for each group. **B**, Representative A1 CF maps from each exposure group. Bold outlined sites have CFs of 7 kHz $\pm 1/4$ octave representing the target/exposure frequency, dotted outlined sites have CFs of $9.9 \pm 1/4$ octave representing the nontarget frequency. **C**, A1 BF at 60 dB maps from the same animals as in **B**. Bold and dotted outlined sites have BFs corresponding to the target or nontarget frequencies, respectively. **D**, A1 maps showing sites that robustly respond to the target frequency (green), nontarget frequency (yellow), or both (dark gray) at 60 dB. **E**, Percentage of A1 area with CFs (top) or BFs (bottom) in 10 frequency bins. **F**, Top, Percentage overlap of A1 area that robustly responds to both the target and nontarget frequency at all sampled intensities. Bottom, Percentage of A1 area that does not respond to either the target or nontarget frequency. **G**, Comparison of tuning curve bandwidths at 60 dB. Left, Average bandwidth per CF bin. Right, Average bandwidth for all sites. Error bars and shading represent SEM. * $p < 0.05$. Number of animals, recording positions, and cortical sites per group: Naive-UT 10, 21, 277; Naive-T 8, 18, 265; 7 kHz-UT 6, 14, 228; 7 kHz-T 9, 22, 319. Descriptive statistics and statistic summary tables may be found in Table 1-1, available at <https://doi.org/10.1523/JNEUROSCI.1445-19.2019.t1-1>, and Table 3-1, available at <https://doi.org/10.1523/JNEUROSCI.1445-19.2019.t3-1>.

rats (Fig. 3D,F, top). We computed the amount of spatial overlap between these two regions at all intensities for each group and compared them to the spatial overlap exhibited by the 7 kHz-UT group. We found that the average overlap for the 7 kHz-UT group was significantly greater or approaching significance for all comparisons at 60 and 70 dB than all of the other groups ($p \leq 0.0580$) except Naive-T ($p = 0.1306$; two-way repeated-measures ANOVA with Group and Intensity as factors, Interaction: $F_{(21,203)} = 2.51, p = 0.0005$; Intensities 60 and 70 dB: both $F_{(3,195.2)} \geq 7.16, both p \leq 0.0001$, followed by Dunnett’s Test, $n = 33$ rats; Fig. 3F, top). The percentage map area that was not responsive to

either tone also differed between groups at high intensities. 7 kHz-UT rats had less cortical area that did not respond to either the target or nontarget tone at 50, 60, and 70 dB. This was significant or approaching significance ($p \leq 0.0725$) for all comparisons except Naive-T at 50 dB and 60 dB (both $p \geq 0.1263$; two-way repeated-measures ANOVA with Group and Intensity as factors, Interaction: $F_{(21,203)} = 2.38$, $p = 0.0010$; Intensities 50–70 dB: all $F_{(3,171.5)} \geq 5.45$, all $p \leq 0.0013$, followed by Dunnett's Test, $n = 33$ rats; Fig. 3F, bottom).

In addition to population measures, the tuning bandwidth of individual neurons can provide an estimate of A1 response specificity, with more broadly tuned neurons indicating a less-specific response. We extracted the tuning bandwidth at 60 dB from each cortical site and compared the average bandwidth in 10 BF bins. We determined that the relationship between bandwidth and frequency bin did not differ between groups, however, the 7 kHz-UT group exhibited significantly broader overall bandwidths than all other groups (all $p \leq 0.0469$; mixed-effects two-way ANOVA with Group and BF Bin as factors, Interaction: $F_{(27,672)} = 0.69$, $p = 0.8779$; Main effect of Group: $F_{(3,672)} = 10.61$, $p < 0.0001$; followed by Tukey's test, $n = 712$ observations within 33 rats; Fig. 3G). This non-frequency-specific broadening of receptive fields was likely a consequence of white noise exposure, and not 7 kHz tone pip exposure, because rats exposed to broadband white noise have been shown to exhibit wider receptive field bandwidths for at least 2 weeks following noise exposure (Zhou et al., 2011).

Reduced neural discriminability persists for at least 12 weeks following sound exposure

The above results show that immediately after sound exposure, the 7 kHz-UT group exhibited a considerable increase in map area robustly responding to both the target and nontarget tones that could contribute to reduced discriminability. This effect did not persist in the 7 kHz-T group, however, which suggests that it was reversed with either training or time. To investigate this further, we exposed a third group of rats (7 kHz-UT+12weeks, $N = 4$) to the same stimuli as above but waited 12 weeks, the average duration of training, before performing electrophysiological recordings (Fig. 4A). After this period, expansion of the 7 kHz frequency region persisted in both CF (unpaired t test: $t_{(12)} = 3.54$, $p = 0.0041$, $n = 14$ rats; Fig. 4B,E, left) and BF maps (unpaired t test: $t_{(12)} = 2.52$, $p = 0.0267$, $n = 14$ rats; Fig. 4C,E, right) compared with Naive-UT. The 7 kHz-UT+12weeks group also exhibited spatial overlap that was significantly greater than that of Naive-UT animals at 60 and 70 dB (two-way repeated-measures ANOVA with Group and Intensity as factors, Interaction: $F_{(7,84)} = 2.62$, $p = 0.0169$; Intensities 60 and 70 dB: both $F_{(1,87.57)} \geq 7.46$, both $p \leq 0.0076$, $n = 14$ rats; Fig. 4D,F, top), and reduced map area that did not respond to either the target or nontarget frequency at 60 dB (two-way repeated-measures ANOVA with Group and Intensity as factors, Interaction: $F_{(7,84)} = 3.37$, $p = 0.0032$; Intensity 60 dB: $F_{(1,69.96)} = 21.20$, $p < 0.0001$, $n = 14$ rats; Fig. 4F, bottom). Finally, the 7 kHz-UT+12weeks group showed incomplete recovery of typical receptive field bandwidths as their average bandwidths were not significantly different from the Naive-UT or 7 kHz-UT group (both $p \geq 0.2695$, mixed-effects two-way ANOVA with Group and BF Bin as factors, Interaction: $F_{(18,360.1)} = 1.29$, $p = 0.1916$; main effect of Group: $F_{(2,48.89)} = 4.21$, $p = 0.0206$; followed by Tukey's test, $n = 409$ observations within 20 rats; Table 1-1, available at <https://doi.org/10.1523/JNEUROSCI.1445-19.2019.t1-1>). We concluded that sound exposure resulted in a long-lasting reduc-

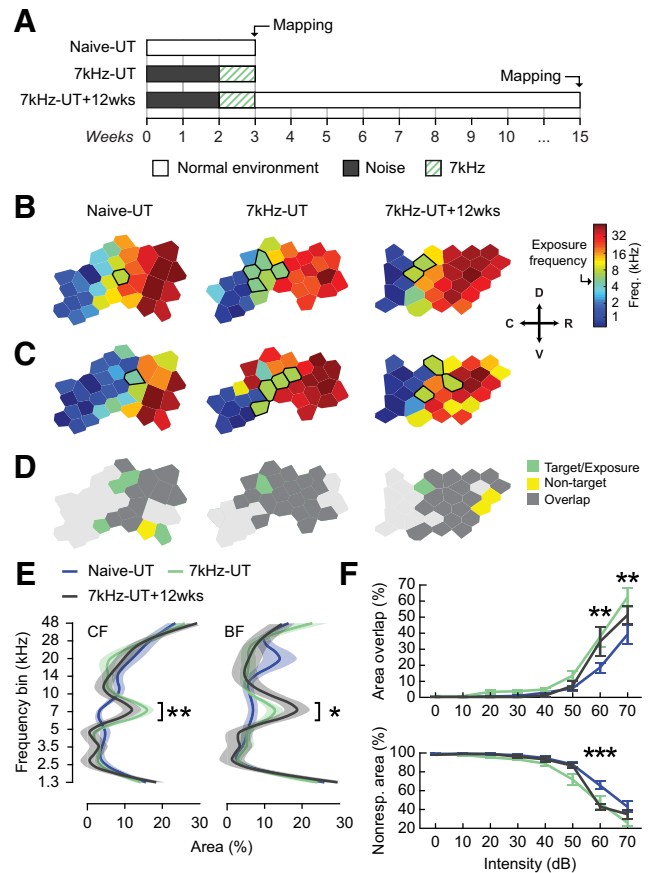


Figure 4. Increased cortical representation and reduced discriminability of the 7 kHz frequency region persists for at least 12 weeks. **A**, Experimental timelines for each group. 7 kHz-UT+12weeks rats were recorded 12 weeks after exposure ended, which was the average duration of training. **B**, Representative A1 CF maps from each exposure group. **C**, A1 BF maps from the same animals as in **B**. **D**, A1 maps showing sites that robustly respond to the target/exposure frequency (green), nontarget frequency (yellow), or both (dark gray) at 60 dB. **E**, Percentage of A1 area with CFs (left) or BFs (right) in 10 frequency bins. **F**, Top, Percentage overlap of A1 area that robustly responds to both the target and nontarget frequency at all sampled intensities. Bottom, Percentage of A1 area that did not respond to either the target or nontarget frequency. Outlined sites in **B** and **C** have CFs or BFs of 7 kHz $\pm 1/4$ octave. Error bars and shading represent SEM. Data from Naive-UT and 7 kHz-UT is the same as in Figure 1. **** $p < 0.0001$, ** $p < 0.01$, * $p < 0.05$ for the comparison between Naive-UT and 7 kHz-UT+12weeks. Number of animals, recording positions, and cortical sites per group: Naive-UT 10, 21, 277; 7 kHz-UT 6, 14, 228; 7 kHz-UT+12weeks 4, 8, 108. Descriptive statistics may be found in Table 1-1, available at <https://doi.org/10.1523/JNEUROSCI.1445-19.2019.t1-1>.

tion in population discriminability of the target and nontarget frequencies that was slightly diminished with time, but completely reversed through training.

Impaired perceptual learning is not due to noise exposure

Although not known to elevate hearing thresholds, moderate intensity exposures to continuous or pulsed noise have been shown to degrade listening processes including cortical tuning selectivity (Kamal et al., 2013; Thomas et al., 2019a), gap detection (Jiang et al., 2015), fine pitch discrimination (Zheng, 2012), and temporal rate discrimination (Zhou and Merzenich, 2012). Some of the changes we observed in the 7 kHz-UT group above are consistent with these established measures of degraded listening processes. To test the possibility that perceptual learning deficits in the 7 kHz-T group were driven by noise exposure instead of 7 kHz map expansion we exposed a group of rats to white noise for 2 weeks followed by 15 kHz tone pip clouds for 1 week (15 kHz-T, $n = 8$).

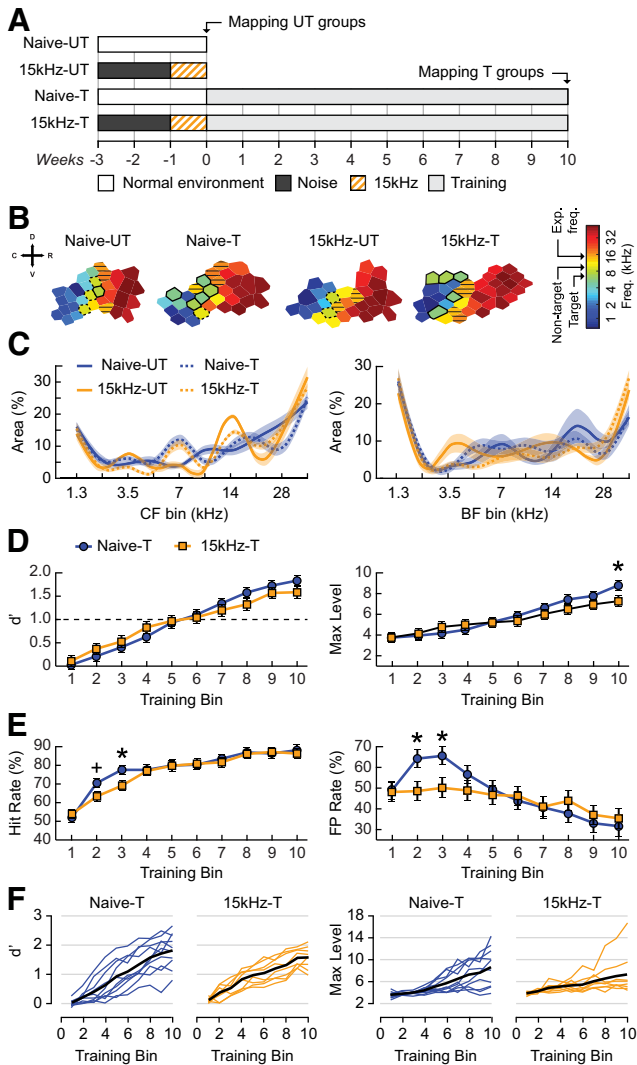


Figure 5. Passive sound exposure increases cortical representation of 15 kHz without impairing 7 kHz tone discrimination. **A**, Experimental timelines for each group. **B**, Representative A1 CF maps from each exposure group. Bold outlined sites have CFs of 7 kHz \pm 1/4 octave representing the target frequency, dotted outlined sites have CFs of 9.9 \pm 1/4 octave representing the nontarget frequency, and striped sites have CFs of 15 kHz \pm 1/4 octave representing the exposure frequency. **C**, Percentage of A1 area with CFs (left) and BF frequencies (right) in 10 frequency bins. **D**, Mean d' (left) and maximum level (right) reached over 10 training bins (6 sessions per bin) in the same adaptive tone discrimination task as in Figure 3. **E**, Mean hit rate (left) and FP rate (right) for the first 10 training bins. **F**, Individual rats' performance for d' and maximum level over 10 training bins. The bold line represents the group mean as plotted in **B** and **C**. Error bars and shading represent SEM. * $p < 0.05$, + $p < 0.09$. Number of animals, recording positions, and cortical sites per group for electrophysiological data: Naive-UT 10, 21, 277; Naive-T 8, 18, 265; 15 kHz-UT 5, 14, 172; 15 kHz-T 8, 20, 332. Number of animals and training sessions per group for behavioral data: Naive-T 10,600; 15 kHz-T 8,480. Descriptive statistics and statistic summary tables may be found in Table 1-1, available at <https://doi.org/10.1523/JNEUROSCI.1445-19.2019.t1-1>, Table 2-1, available at <https://doi.org/10.1523/JNEUROSCI.1445-19.2019.t2-1>, and Table 5-1, available at <https://doi.org/10.1523/JNEUROSCI.1445-19.2019.t5-1>.

The frequencies in the tone pip clouds were evenly distributed between 15 kHz \pm 1/4 octave. We then tested this group on the same adaptive tone discrimination task with 7 kHz as the target tone (Fig. 5A). The frequencies contained in the 15 kHz exposure stimulus were outside the range of trained frequencies, so we did not expect 15 kHz map expansion to have any effect on task performance.

We first verified that 2 weeks of noise followed by 1 week of 15 kHz tone pip clouds would result in increased cortical representation of the 15 kHz frequency region (Fig. 5 B, C, left). There was

a clear expansion of the 15 kHz frequency region in the CF maps of untrained rats exposed to this stimulus (15 kHz-UT, $n = 5$) compared with Naive-UT ($p < 0.0001$). Map expansion persisted throughout training as the 15 kHz-T group also had a greater percentage of map area in the bin containing 15 kHz than Naive-UT ($p = 0.0107$, one-way ANOVA, $F_{(3,27)} = 10.97$, $p < 0.0001$, followed by Dunnett's test, $n = 31$ rats). Next, we investigated the effects of exposure and training on representation of the target and nontarget frequencies (Fig. 5 B, C, left). The 15 kHz-UT group did not differ from Naive-UT in percentage of CF map area corresponding to the target frequency ($p = 0.9973$), although training significantly increased its representation in the 15 kHz-T group compared with Naive-UT ($p = 0.0006$; one-way ANOVA, $F_{(3,27)} = 10.74$, $p < 0.0001$, followed by Dunnett's test, $n = 31$ rats). Of note, both the 15 kHz-UT and 15 kHz-T groups exhibited reduced CF map area dedicated to the nontarget frequency (both $p \leq 0.0075$; one-way ANOVA $F_{(3,27)} = 5.70$, $p = 0.0037$, followed by Dunnett's test, $n = 31$ rats). There was no difference between the BF representation of 15 kHz, the target frequency, or the nontarget frequency in these groups, on the other hand (one-way ANOVAs, all $F_{(3,27)} \geq 0.35$, all $p \leq 0.7894$, $n = 31$ rats; Fig. 5C, right).

Next, we examined the effect of 15 kHz map expansion on training performance (Fig. 5D–F). The average d' learning curve of the 15 kHz-T group was not different from Naive-T (two-way repeated-measures ANOVA with Group and Bin as factors, Interaction: $F_{(9,1044)} = 6.46$, $p < 0.0001$; simple main effects tests did not yield a significant difference for any bin: all $F_{(1,20,62)} \leq 1.93$, all $p \geq 0.1791$, $n = 18$ rats; Fig. 5D, left), although the Naive-T group reached higher maximum levels during training Bin 10 (two-way repeated-measures ANOVA with Group and Bin as factors, Interaction: $F_{(9,1044)} = 3.66$, $p = 0.0002$; Bin 10: $F_{(1,26,40)} = 4.50$, $p = 0.0435$, $n = 18$ rats; Fig. 5D, right). Both groups reached an average $d' > 1$ around Bin 6 of training (Naive-T mean = 5.78 ± 1.79 bins, 15 kHz-T mean = 6.38 ± 2.39 bins, unpaired t test: $t_{(15)} = 0.59$, $p = 0.5650$, $n = 17$ rats; 1 rat from the Naive-T group was not included because it did not have any bin where $d' > 1$). The two groups differed in hit rate and FP rate during the early weeks of training. The 15 kHz-T group had a lower hit rate during Bin 3 of training (two-way repeated-measures ANOVA with Group and Bin as factors, Interaction: $F_{(9,1044)} = 3.06$, $p = 0.0012$; Bin 3: $F_{(1,28,80)} = 5.42$, $p = 0.0271$, $n = 18$ rats; Fig. 5E, left) and a lower FP rate during bins 2 and 3 (two-way repeated-measures ANOVA with Group and Bin as factors, Interaction: $F_{(9,1044)} = 11.36$, $p < 0.0001$. Bins 2–3: both $F_{(1,20,73)} \geq 5.75$, both $p \leq 0.0260$, $n = 18$ rats; Fig. 5E, right). Because hit rate and FP rate decreased proportionally, the resultant d' and maximum level reached during Bins 2 and 3 were not affected.

Finally, we directly compared the performance of all three trained groups over coarse training bins of 20 sessions each corresponding to the early, mid, and late thirds of training (Fig. 6). This comparison revealed that the 15 kHz-T group had performance equivalent to the Naive-T group and superior to the 7 kHz-T group in all stages of training except for maximum level reached during the late stage in which the 15 kHz-T and 7 kHz-T were not significantly different (statistics are reported in figure legend). Because noise exposure is known to affect fine but not coarse frequency discrimination (Zheng, 2012), this could be a result of the rats encountering more fine pitch discriminations during the late stage of training. Together, the above results led us to conclude that noise may have had a negative effect on fine frequency discrimination during late sessions of the adaptive tone discrimination task, but that this could not ac-

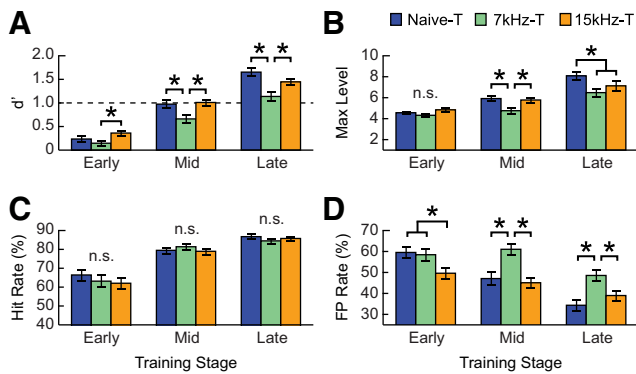


Figure 6. Behavioral performance over coarse training bins. Behavioral performance during early, mid, and late training stages of the adaptive tone discrimination task corresponding to Sessions 1–20, 21–40, and 41–60 respectively. All measures were evaluated by two-way ANOVAs with Group and Training Stage as factors followed by simple main effects tests and Tukey's *post hoc* test. **A**, Mean d' , Interaction: $F_{(4,1671)} = 10.85, p < 0.0001$; Stages: all $F_{(2,1671)} \geq 7.97$, all $p \leq 0.0004$. **B**, Max level, Interaction: $F_{(4,1671)} = 7.86, p < 0.0001$; Stages: all $F_{(2,1671)} \geq 3.01$, all $p \leq 0.0494$. **C**, Hit rate, Interaction: $F_{(4,1671)} = 2.28, p = 0.0585$. **D**, FP rate, Interaction: $F_{(4,1671)} = 13.95, p < 0.0001$; Stages: all $F_{(2,1671)} \geq 15.10$, all $p < 0.0001$. * $p < 0.05$. n.s., Not significant. Error bars represent SEM. Number of animals and training sessions per group: Naive-T 10,600; 7 kHz-T 10,600; 15 kHz-T 8,480.

count entirely for the deficits in perceptual learning demonstrated by the 7 kHz-T group.

Map expansion is related to task performance for high-performing rats only

We investigated the possibility that cortical representation of the target tone was related to behavioral performance by correlating the percentage of A1 sites possessing a CF of 7 kHz \pm 1/4 octave with measures of task performance for all trained animals. Because some animals completed more than 60 training sessions, we used average performance from the last 6 sessions rather than training Bin 10 for correlations. We considered all trained animals together because the percentage of map area dedicated to the target tone was not found to differ between the Naive-T, 7 kHz-T and 15 kHz-T groups. We did not find a significant relationship between map area and average d' , $r = 0.28, p = 0.1798, n = 25$ rats, FP rate, $r = -0.17, p = 0.4123, n = 25$ rats, or hit rate, $r = 0.11, p = 0.5878, n = 25$ rats, for the last six training sessions for all trained groups combined. However, we observed a noticeable divide between rats who were able to reach higher levels during training and those whose performance plateaued at lower levels. We decided to investigate the difference between “high performers” (HPs) and “low performers” (LPs) by dividing them on the basis of average maximum level reached during the last six training sessions (Fig. 7A). The criteria for HPs was an average maximum level >6 , which was chosen to split the rats ($n = 28$) into two equal-sized groups. HPs had a significantly greater average d' during the last six training sessions than LPs (HP mean = 2.05 ± 0.35 , LP mean = 1.29 ± 0.41 , unpaired t test: $t_{(26)} = 5.25, p < 0.0001, n = 28$ rats), as well as a significantly lower average FP rate during the same time frame (HP mean = $23.06 \pm 8.67\%$, LP mean = $51.89 \pm 8.92\%$, unpaired t test: $t_{(26)} = 8.67, p < 0.0001, n = 28$ rats), but did not differ in hit rate (HP mean = $87.87 \pm 6.46\%$, LP mean = $88.67 \pm 6.20\%$, unpaired t test: $t_{(26)} = 0.33, p = 0.7417, n = 28$ rats). Next, we explored whether the percentage of A1 sites dedicated to the target tone would be related to task performance in the HP and LP groups (Fig. 7B). We found evidence of a weak relationship between map expansion and behavioral performance for HPs only, as determined by comparing the

p values obtained from linear correlations. For HPs, the relationship between map expansion and average d' during the last six training sessions approached significance ($p = 0.0515$) and was not significant ($p = 0.0905$) for average FP rate during the last six training sessions. LPs exhibited much higher p values for d' and FP rate (both $p \geq 0.5452$). Hit rate was not related to map expansion for either LPs or HPs (both $p \geq 0.5709$). Interestingly, the average percentage of A1 area with a CF of 7 kHz \pm 1/4 octave did not differ between the two groups (HP mean = $10.19 \pm 5.32\%$, LP mean = $9.67 \pm 5.63\%$, unpaired t test: $t_{(23)} = 0.24, p = 0.8157, n = 25$ rats), suggesting that HP and LP rats may have used different cognitive strategies to advance in training.

Discussion

Perceptual learning has been extensively associated with cortical map expansions in the somatosensory and auditory domains across species (Recanzone et al., 1992, 1993; Feldman and Brecht, 2005; McGann, 2015). Although these findings strongly suggest that map expansion provides some perceptual advantage to the organism, the exact nature of that advantage has remained elusive. Here we induced a similar phenotype to perceptual learning with 3 weeks of passive sound exposure; however, this did not confer a perceptual advantage for discriminating the over-represented frequency. Over more than 60 training sessions, exposed animals displayed a deficit in frequency discrimination and a marked delay in perceptual learning. When comparing the map expansion phenotype between exposed and trained animals, we found that both exposure and training led to CF map expansion but only exposure resulted in BF map expansion. This asymmetry could be indicative of a fundamental difference in the nature of these two types of expansion, possibly explaining why the early over-representation of the target frequency did not confer a task advantage in exposed rats. Map expansion was also accompanied by a greater overlap in population responses to the target and nontarget frequencies at training intensity in exposed animals, very likely contributing to the impaired discrimination of these stimuli. The uncoupling of CF and BF plasticity in trained rats was unexpected, as increased functional representation of the target frequency is well described in both CF and BF maps (Weinberger, 2015). Although shifts in cortical representation for both CF and BF are attributable to thalamocortical plasticity, excitatory/inhibitory balance is more variable at threshold levels (Zhao et al., 2015), suggesting that there is stronger natural variability at the CF than the BF, which could have been highlighted here.

The map expansion-renormalization hypothesis suggests that map expansion improves learning but is not necessary for the maintenance of learned information since representations can renormalize while task performance remains stable (Reed et al., 2011). In line with this, we used an adaptive training paradigm to explicitly target the learning phase of discrimination training as opposed to basic discrimination abilities. Our adaptive task was difficult; even naive rats required an average of 5.78 training bins (~ 35 sessions) to achieve a $d' > 1$ and no rats had plateaued in performance before the end of the experiment resulting in an extremely long learning phase. Our results therefore show that map expansion induced by passive sound exposure is not sufficient to improve perceptual learning. Rather than implying that all map expansions that accompany learning are epiphenomenon, however, our findings support the view that the mode of induction determines whether map expansion will have perceptual significance (Pienkowski and Eggermont, 2011). Based on a small number of studies performed in rodent auditory cortex, techniques that invoke top-down changes through the recruit-

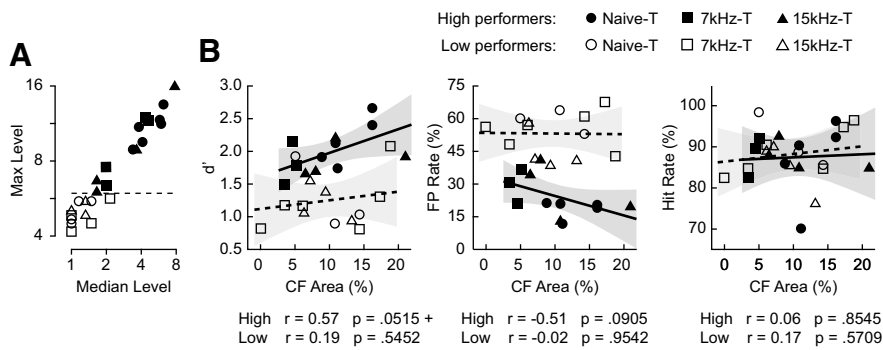


Figure 7. Map expansion is related to training performance for HP rats only. **A**, Average maximum level versus average median level during the last six training sessions. Both axes are on a logarithmic scale. Rats were divided into an equal number of HPs and LPs based on the criteria of maximum level > 6 (dashed line). **B**, Behavioral performance measures d' , FP rate, and hit rate versus percentage A1 area with a CF of 7 kHz ± 0.25 octaves for HPs and LPs. Bold and dashed lines represent the linear fit for HPs and LPs, respectively, whereas shaded areas represent the confidence of fit. Pearson's r , and uncorrected p values are below each graph; $n = 12$ HPs, 13 LPs. Number of animals per group for **A** (including all trained rats) and **B** (including only rats for which full A1 maps were obtained): Naive-T 10, 8; 7 kHz-T 10, 9; 15 kHz-T 8, 8.

ment of neuromodulatory systems produce map expansion that results in perceptual enhancement (Reed et al., 2011; Froemke et al., 2013; Blundon et al., 2017), whereas bottom-up changes resulting from electrical stimulation (Talwar and Gerstein, 2001) or passive sound exposure during development (Han et al., 2007) either do not enhance or impair discrimination for the expanded frequency. In this respect, our methods and findings most closely resemble those of the lattermost study. Han et al., 2007 observed that 7.1 kHz map expansion impaired 2-month-old rats' ability to discriminate the over-represented frequency from tones 0.1 (but not 0.5) octaves apart from it. Interestingly, discrimination for frequencies exactly $\frac{1}{4}$ octave above and below 7.1 kHz was improved, possibly because of a greater number of neurons with tuning curve slopes falling within these frequency bins. This might suggest that the sound-exposed rats in our study had improved discrimination capabilities for frequencies neighboring 7 kHz, including those falling between the target and nontarget frequency. However, the performance of the 7 kHz-T group began to significantly differ from the Naive-T group in training Bin 5, when Naive-T animals reached average maximum levels of 4 or greater corresponding to a 0.425 octave difference from the target frequency. This suggests that map expansion interfered with tone discrimination for relatively coarse frequency comparisons, outweighing any perceptual advantage the rats could have had at higher training levels.

By itself, noise exposure has been shown to have a profoundly disruptive effect on both spectral and temporal auditory cortical responses in the adult brain, which has even led to calls for eliminating white noise therapy as a treatment for tinnitus (Attarha et al., 2018). Adult rats exposed to moderate-intensity broadband white noise for 30 d show impairments in fine frequency discrimination (Zheng, 2012). For this reason, it was important for us to rule out the possibility that deficits in task performance were noise-related. We observed only limited impairment in the performance of 15 kHz-T rats that underwent the same noise exposure and training as 7 kHz-T rats. This led us to conclude that map expansion caused frequency-specific perceptual deficits separate from any deficits introduced by noise alone. We did not test the possibility that 7 kHz tone exposure on its own could have led to perceptual deficits, as this type of exposure has not been shown to produce map expansion when not paired with a plasticity-inducing treatment (Zhou et al., 2011).

Tonotopic map expansion has become a household tool for auditory neuroscientists to validate strategies of enhancing cortical

plasticity (Bieszczad et al., 2015; Blundon et al., 2017). However, a concern is that map expansion may simply be an indicator that plasticity has taken place without giving specific clues as to which mechanism produced it or what consequences it may have for perception. Although we found that noise-induced map expansion impaired frequency discrimination, given the near-ubiquitous and highly reproducible nature of this outcome, it would be strange if it was not adaptive in at least some respect. We found preliminary evidence that at least the highest-performing rats may have used a successful learning strategy that relied on degree of map expansion, illustrating that different learning strategies may exist with respect to this phenomenon.

Related to this, variations in parameters such as methodology, species used, duration of training, and training paradigm, are also likely to influence the relevance of map expansion to training outcomes (Irvine, 2007; Pienkowski and Eggermont, 2011). Map expansion could also improve perceptual acuity for other, yet untested sound features such as detection of the exposure frequency at near-threshold intensities. We recently demonstrated that noise- and tone pip-exposed rats exhibit enhanced sensorimotor gating for the over-represented frequency (Thomas et al., 2019b). However, this is accompanied by electrophysiological evidence of hyperexcitability associated with hyperacusis, including increased spontaneous and tone-evoked firing rates, leading us to conclude that heightened sensorimotor gating was related to maladaptive plastic mechanisms.

The enduring effects of passive sound exposure are another reason to pay attention to the maladaptive aspects of this form of plasticity. Here, we observed that map expansion and accompanying measures of reduced neural discriminability persisted for at least 12 weeks following sound exposure. This is in line with previous studies that showed incomplete recovery of tonotopic reorganization in rats and cats at least 7 weeks (Zhou et al., 2011), 8 weeks (Kamal et al., 2013), and 12 weeks (Pienkowski and Eggermont, 2009) after passive sound exposure. However, Reed et al. (2011) found that map expansion reversed at some point between 20 and 100 d (14.3 weeks) after paired nucleus basalis and tone pip stimulation.

Perhaps the most encouraging aspect of our findings is that despite an early impairment in perceptual learning, training was able to recover physiological and performance deficits in sound-exposed animals. Compared with the 7 kHz-T+12weeks group, trained animals completely recovered both population and neural measures of selectivity for the exposure tone. Furthermore, it is possible that exposed rats could reach identical performance metrics as non-exposed rats given enough time, as they were still improving at the end of training. Auditory training has similarly been shown to enhance recovery from abnormal sensory experiences during development (Merzenich et al., 1996; Guo et al., 2012; Kang et al., 2014) and improve auditory response properties in aged rodents and humans (de Villiers-Sidani et al., 2010; Anderson and Kraus, 2013; Mishra et al., 2014). If properly harnessed, the ability to drive plastic changes in a specific and non-invasive manner through passive sound exposure and targeted training programs therefore has potential neurotherapeutic value. We expect that our results will further inform non-invasive

training strategies that focus on “retuning” the cortical map as a primary means of altering perception, such as those already used in the treatment of tinnitus (Flor et al., 2004; Pienkowski, 2019). Our findings underline the need for future neuroplasticity-based treatments that take advantage of both the sensory statistics of our environment and the brain’s innate capacity to change.

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