

Cortical Map Plasticity Improves Learning but Is Not Necessary for Improved Performance

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SUMMARY

Cortical map plasticity is believed to be a key substrate of perceptual and skill learning. In the current study, we quantified changes in perceptual ability after pairing tones with stimulation of the cholinergic nucleus basalis to induce auditory cortex map plasticity outside of a behavioral context. Our results provide evidence that cortical map plasticity can enhance perceptual learning. However, auditory cortex map plasticity fades over weeks even though tone discrimination performance remains stable. This observation is consistent with recent reports that cortical map expansions associated with perceptual and motor learning are followed by a period of map renormalization without a decrement in performance. Our results indicate that cortical map plasticity enhances perceptual learning, but is not necessary to maintain improved discriminative ability.

INTRODUCTION

Cortical map expansions have been observed in the sensory and motor cortices of highly trained animal and human subjects. The enlarged region of the map invariably corresponds to the trained sensory input or motor output (Bieszczad and Weinberger, 2010; Conner et al., 2003, 2010; Doyon and Benali, 2005; Fahle, 2009; Gilbert et al., 2001; Irvine and Rajan, 1996; Irvine et al., 2001; Polley et al., 2006; Recanzone et al., 1992a, 1992b, 1993; Roelfsema et al., 2010; Rutkowski and Weinberger, 2005). Both learning and map expansions are blocked by cholinergic lesions and antagonists (Conner et al., 2003). Some of the most compelling evidence that map plasticity is responsible for perceptual and skill learning comes from studies showing that the magnitude of cortical map expansion is correlated with the amount of learning (Bieszczad and Weinberger, 2010; Polley et al., 2006; Recanzone et al., 1993; Rutkowski and Weinberger, 2005). However, other studies have failed to find a correlation between map plasticity and performance (Brown et al., 2004; Molina-Luna et al., 2008; Talwar and Gerstein, 2001; Yotsumoto et al., 2008).

Recent reports provide anatomical and physiological evidence that cortical plasticity develops during early learning but then renormalizes after further behavioral training (Ma

et al., 2010; Molina-Luna et al., 2008; Takahashi et al., 2010; Yang et al., 2009; Yotsumoto et al., 2008). Rats trained to perform a skilled reaching task develop motor cortex map expansions after 3 days of training. However, after 8 days of training, map expansions subside though behavioral performance remains stable (Molina-Luna et al., 2008). Similar renormalization occurs in the human visual cortex after learning an orientation discrimination task. Plasticity develops during initial learning, but is eliminated 4 weeks after training begins (Yotsumoto et al., 2008). These results indicate that map plasticity may be most important during the early phases of learning. Given that map plasticity is not always associated with skilled movement or discrimination, there are two possible roles for cortical plasticity. Map plasticity could either be an epiphenomenon with little functional importance, or it could be a critical but transient stage in perceptual and skill learning. The best method to distinguish between these two possibilities is to generate map plasticity using a method that is independent of learning and then test the behavioral consequences. A finding that map plasticity has no effect on learning would suggest map plasticity is an epiphenomenon; the finding that map plasticity improves learning would indicate that map plasticity is indeed functionally relevant, even if unnecessary for continued task performance.

Nucleus basalis stimulation (NBS) can be used to create cortical plasticity outside of a behavioral context. NBS during tone presentation leads to stimulus-specific map expansions in both primary and secondary auditory cortex (Bakin and Weinberger, 1996; Froemke et al., 2007; Kilgard and Merzenich, 1998; Puckett et al., 2007). Plasticity has also been observed in the inferior colliculus and auditory thalamus after NBS-tone pairing, apparently due to the influence of cortical feedback connections onto these subcortical stations (Ma and Suga, 2003; Zhang and Yan, 2008). Although nucleus basalis is active during both aversive and appetitive behavioral tasks, NBS is motivationally neutral (Miasnikov et al., 2008). Previous studies have demonstrated that NBS-tone pairing causes map expansions that are similar to the plasticity seen after tone discrimination learning (Bakin and Weinberger, 1996; Bjordahl et al., 1998; Kilgard and Merzenich, 1998). NBS and tone exposure must occur within a few seconds of each other for stimulus-specific map plasticity to occur (Kilgard and Merzenich, 1998; Metherate and Ashe, 1991). Passive exposure to tones without NBS does not result in map reorganization (Bakin and Weinberger, 1996; Bao et al., 2001; Recanzone et al., 1993).

In the current study, we used NBS paired with tones to determine the functional consequence of auditory cortex map

plasticity. In the first experiment, we used NBS-tone pairing to cause auditory cortex map expansions before discrimination learning. In the second experiment, we used NBS-tone pairing in animals that had already learned to perform the discrimination task. We performed neurophysiological recordings in all groups of animals to measure cortical map plasticity after NBS-tone pairing and behavioral training.

RESULTS

Map Expansion after NBS-Tone Pairing Is Long Lasting

For our study, it was important that the map expansions caused by NBS-tone pairing last long enough to evaluate the behavioral consequences of map plasticity. We have previously reported that 20 days of NBS-tone pairing results in map expansions in the primary auditory cortex (A1) that last at least 48 hr after the end of pairing (Kilgard and Merzenich, 1998). To determine the stability of this plasticity, we recorded from rats 1, 10, 20, or 100 days after 20 days of NBS paired with a 19 kHz tone and compared A1 responses to experimentally naive rats (823 A1 recording sites in 21 experimental rats compared to 372 A1 recording sites in 5 naive rats). We found that map expansions endured for >20 days but <100 days after the end of NBS-tone pairing (Figure 1; $p < 0.05$). These results indicate that the map plasticity induced by NBS-tone pairing is frequency specific and long lasting.

NBS-Tone Pairing Improves Tone Discrimination Learning

The goal of Experiment 1 was to evaluate the effect of map plasticity on tone discrimination learning. Learning to discriminate tones involves learning both the procedures required to perform the task as well as the required sensory discrimination. We wanted to test the effects of auditory cortex map plasticity on sensory discrimination rather than on procedural learning. Fifteen rats were trained to perform the go/no-go task using two highly distinct broadband sounds so that they would learn the procedural requirements of the task before NBS-tone pairing began. Rats were rewarded with a sugar pellet for pressing a lever after presentation of a target stimulus (5 Hz train of 25 ms duration, 65 dB SPL intensity white noise bursts, 1025 ms total duration), but were negatively reinforced with a 6–8 s “timeout” (lights extinguished and sound presentation delayed) for pressing after presentation of a distracter (complex irregular noise stimulus, 1025 ms duration, 60 dB SPL intensity). Rats learned this easy broadband discrimination within 3 days, and there were no differences in the performance of any of the experimental groups [average d' for all rats 2.4 ± 0.21 , $F(2,12) = 1.46$, $p = 0.27$]. Thus, any difference in discrimination ability observed after NBS-tone pairing can be attributed to the plasticity caused by NBS-tone pairing rather than differences in procedural learning.

After mastering the broadband go/no-go task, the rats were placed on full feed with no behavioral testing for 20 days. NBS-tone pairing occurred for 3 hr each day during this 20 day period. The rats were randomly assigned to one of three groups. Rats in all three groups heard 300 low-frequency (2 kHz) tones and 300 high-frequency (19 kHz) tones each day. For rats in the Low Group, the low tones were paired with NBS (Figure 2A,

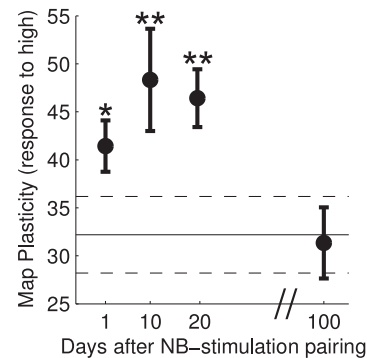


Figure 1. Repeatedly Pairing NBS with a High-Frequency Tone Significantly Increases the Percent of A1 Neurons that Respond to High-Frequency Tones for 20 Days

The methods of inducing and quantifying map plasticity are identical to Kilgard and Merzenich (1998). * $p < 0.05$; ** $p < 0.01$; all stars indicate statistical results of a t test of whether percent of cortex responding to high tones was significantly different from naive controls. Error bars indicate standard error of the mean (SEM). Solid and dashed lines indicate mean and SEM of the percent of A1 neurons in naive controls that responded to high-frequency tones.

red). For rats in the High Group, the high tones were paired with NBS (Figure 2A, blue). Rats in the Control Group heard both tones but did not experience any stimulation (Figure 2A, green). Because all three groups of animals heard the same tones, any differences in learning can be attributed to differences in NBS-tone pairing. We predicted that the exaggerated representation of low-frequency tones in the Low Group would improve learning on a low-frequency tone discrimination task. After the 20 day period of NBS-tone pairing, every rat was trained to discriminate the 1.8 kHz target (5 Hz train of 25 ms duration, 65 dB SPL tone pip, 1025 ms total duration) from distracter tone trains that were 0.5, 1.0, and 2.4 octaves above the target stimulus. All other task parameters were identical to the broadband task above.

As predicted, the Low Group learned the task faster than the other groups. The Low Group reached a d' of 0.5 on the 1 octave discrimination within 3 days of training, whereas the High and Control Groups took >8 days to reach the same level of performance [Figure 2B, days to reach $d' = 0.5$, Low: 2.8 ± 0.8 , High: 8.2 ± 2.3 , Control: 10.0 ± 2.6 , analysis of variance (ANOVA) $F(2,14) = 4.14$, $p = 0.043$]. The Low Group performed significantly better than the other two groups on the final 2 days of training on the easy frequency discrimination task [d' discrimination of all three distracter tones by Low, High, and Control groups, $F(2,14) = 4.94$, $p = 0.027$, repeated-measures ANOVA] (see Table S1 available online). After 6 days of training, the Control Group was unable to discriminate the target tone from any of the three distracter tones (Figure 2E). In contrast, the Low Group was able to discriminate all three distracters from the target (Figure 2C). This result confirms our prediction that an exaggerated representation of low-frequency tones would improve learning of a low-frequency discrimination task.

The High Group was not able to discriminate the target from the two lowest distracters (0.5 and 1.0 octave higher), but was able to discriminate the target from the highest distracter

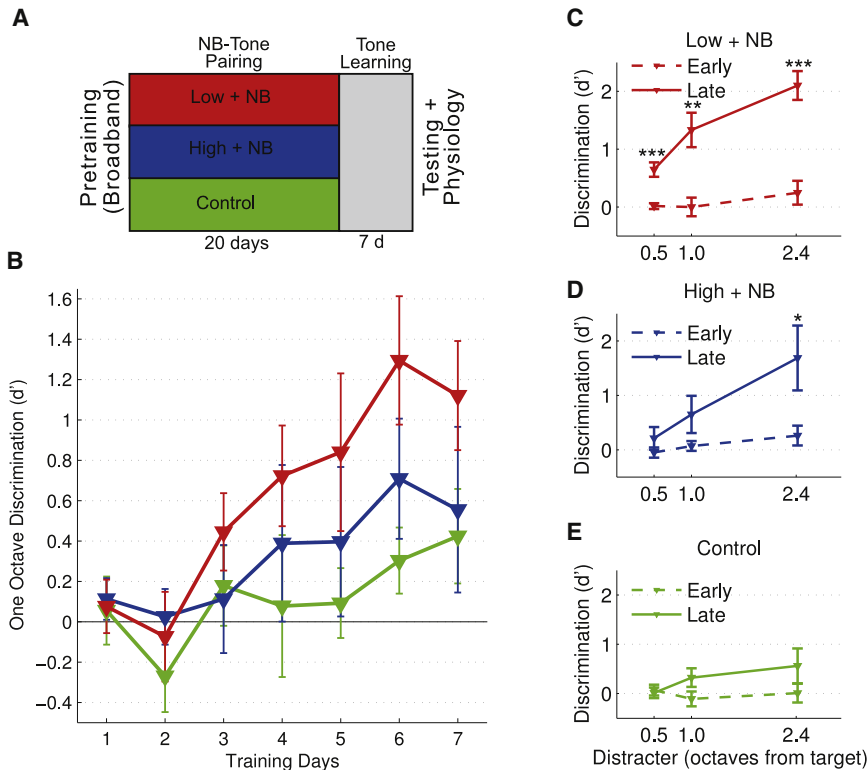


Figure 2. NBS-Induced Plasticity before Tone Discrimination Training Improves Learning

(A) Training timeline. Rats did not begin tone frequency discrimination training until after NBS-tone pairing was completed.

(B) Mean \pm SEM performance of each group on the 1 octave discrimination task during the first 7 days after NBS-tone pairing.

(C–E) Mean \pm SEM discrimination performance for each group during the first 2 days (Early, dashed lines) and last 2 days (Late, solid lines) of the easy frequency discrimination task. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; all stars indicate statistical results of a t test of whether discrimination performance was significantly above chance ($d' = 0$). Error bars in all figures indicate SEM. See also Table S1.

(2.4 octaves higher; Figure 2D). The highest distracter was only 1 octave below the 19 kHz tone that was paired with NBS. We analyzed physiological data in the untrained rats that experienced NBS paired with 19 kHz tones (Figure 1) and found that the pairing caused an increased cortical response to the 2.4 octave distracter (45 ± 3 versus 32 ± 3 percent cortex, $p = 0.029$). An exaggerated representation of high tones is the most likely reason that the High Group was able to learn to reject the 2.4 octave distracter more quickly than the Control Group.

The results of Experiment 1 demonstrate that NBS-tone pairing before training can enhance tone frequency discrimination learning. This supports the hypothesis that map plasticity is a key substrate of improved discrimination learning.

NBS-Tone Pairing Does Not Improve Behavior in Well-Trained Rats

In Experiment 2 we tested whether NBS-low tone pairing could improve discrimination in rats that had already learned to discriminate low-frequency tones. Twelve rats were trained to perform the low-frequency discrimination task for 10 days and then tested on the same task for 10 additional days (Figure 3A). After mastering the frequency discrimination task (Figure 3B), rats were placed on full feed with no behavioral testing for 20 days. For 3 hr each day, rats were exposed to 300 low-frequency (2 kHz) tones. For rats in the Pretrained Low Group, the low tone was paired with NBS (Figure 3A, red). Rats in the Pretrained Control Group did not experience any stimulation (Figure 3A, green).

to induce further cortical plasticity or the additional map plasticity was not sufficient to influence discrimination abilities.

Although NBS-low tone pairing did not improve behavior in the Pretrained Low group, it was still possible that NBS-high tone pairing could impair low tone discrimination. Previous studies have shown that map expansions in one frequency region are often accompanied by map contractions in another frequency region. We analyzed physiological data in untrained rats that experienced NBS-tone pairing with 19 kHz tones (Figure 1) and found that pairing caused a 20% decrease in the response to a 2 kHz tone 1–20 days after NBS-tone pairing (percent of cortex responding to a 2 kHz 60 dB SPL tone, $\text{exp} = 37.6207 \pm 2.6711$ versus controls: 45 ± 2.0033 , $p = 0.035$, one-tailed t test). This map contraction may be extensive enough to disrupt behavioral performance. To test this possibility, another group of six rats (Pretrained High Group) was pretrained to perform the low-frequency discrimination task, and then exposed to NBS paired with high tones for 20 days (Figure 3A, blue). We did not include a group that experienced passive exposure to high tones, because many previous studies have shown that in adults passive tone exposure does not lead to map reorganization or changes in learning (Bakin and Weinberger, 1996; Bao et al., 2001; Han et al., 2007; Recanzone et al., 1993; Zhang et al., 2001). During the first 3 days after NBS-tone pairing, the Pretrained High group was significantly worse than either the Pretrained Low or Pretrained Control group [Figure 3C, d' discrimination of 0.38 to 1.0 octave distracters, $F(2,16) = 3.65$, $p = 0.049$, repeated-measures ANOVA; Table S2]. Although we did not directly measure map plasticity in any of the Pretrained groups

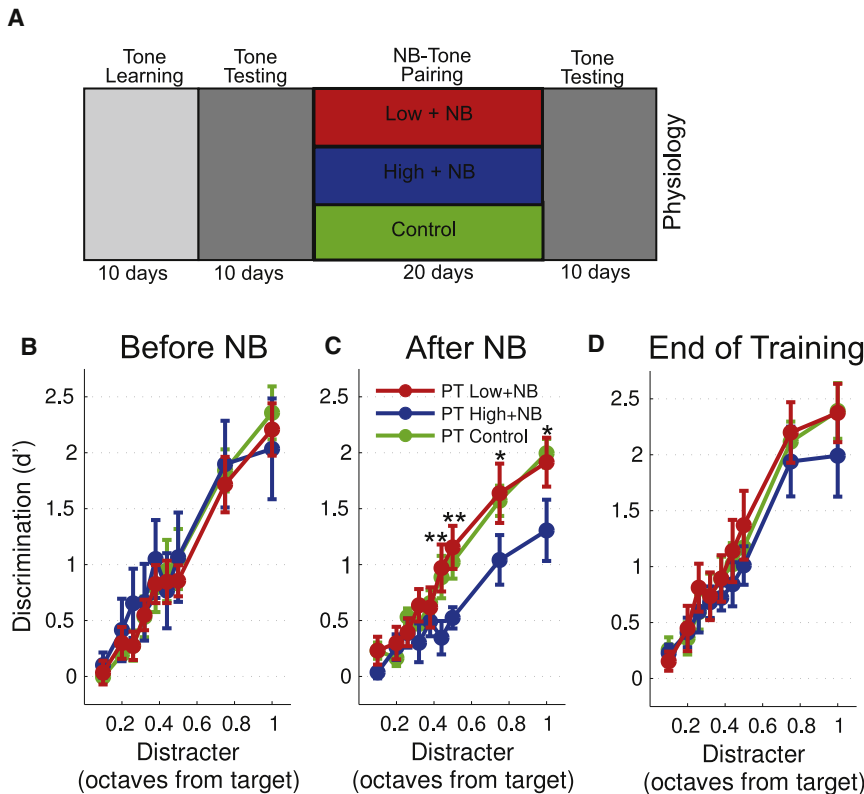


Figure 3. NBS-Induced High-Frequency Map Plasticity after Pretraining Transiently Degrades Low-Frequency Discrimination Performance

(A) Training timeline for Pretrained Groups of animals. All rats learned to perform the low-frequency discrimination task before NBS pairing began.

(B) Discrimination performance in all three groups 3 days before tone exposure and NBS.

(C) Discrimination performance in all three groups 3 days after tone exposure and NBS.

(D) Discrimination performance in all three groups during the last 3 days at end of discrimination training. (*), High group performance was significantly different from Control group, $p < 0.05$. (**), High group performance was significantly different from both Pretrained Control and Pretrained Low group, $p < 0.05$, significance was determined by a t test comparing performance of the Pretrained High group to the Pretrained Control or Low group for each set of distracters (0.1–1.0 octaves). Error bars in all figures indicate SEM. See also Table S2.

immediately after NBS-tone pairing, it is likely that NBS-tone pairing with high tones caused a reorganization of the primary auditory cortex so that high-frequency tones were expanded and low-frequency tones contracted. These results suggest that a minimal representation of low-frequency tones may be necessary to perform the low-frequency discrimination task, even in well-trained animals.

Further behavior training restored the Pretrained High group's discrimination performance. After 10 days of training after NBS-tone pairing, the discrimination abilities of the three Pretrained groups were not significantly different from each other [Figure 3D; d' discrimination of 0.38 to 1.0 octave distracters, $F(2,16) = 0.5499$, $p = 0.9249$]. Therefore NBS-high tone pairing transiently impairs discrimination in rats that had already learned to discriminate low-frequency tones.

Map Plasticity Reverses after Long Periods of Training

To evaluate the relationship between map plasticity and tone discrimination ability, we quantified cortical map plasticity in every rat from Experiments 1 and 2 by recording multiunit responses from the primary auditory cortex (1435 A1 recording sites in 33 experimental rats and 455 A1 recording sites in 9 naive rats). We observed map plasticity in every group that we mapped within 20 days of the beginning of training or NBS low-tone pairing. However, we did not observe map plasticity in any of the groups that were mapped >35 days after the beginning of training or NBS low-tone pairing. These results confirm that map plasticity is a transient phenomenon that occurs during the first few weeks of discrimination training.

In naive rats with no behavior training or NBS-tone pairing, the representation of low and high tones is approximately equal (Figure 4A, black square). We quantified map plasticity by measuring the ratio of the A1 surface area responding to a 2 kHz tone and a 19 kHz tone at 60 dB SPL (Figures 4A and S1). To confirm that training alone was sufficient to generate map plasticity, a Behavior Alone group ($n = 6$ rats, 311 A1 sites) was trained to perform the low-frequency discrimination task, but had no NBS-tone pairing (Figure 4B). As expected, these rats exhibited significant low-frequency map plasticity. Fifty percent more neurons responded to low-frequency tones compared to high-frequency tones (Figure 4A, Naive versus Behavior Alone, $p = 0.019$, t test). This result confirms that 20 days of behavior training generated a low-frequency map expansion.

The pretraining procedure for the Pretrained Groups in Experiment 2 was identical to the procedure for the Behavior Alone group, and so all three Pretrained Groups must also have had low-frequency map expansions after 20 days of behavior training (Figures 4B and 4C). Twenty days of additional NBS-tone pairing followed by 10 days of additional behavior testing led to map renormalization in the Pretrained groups so that the organization of these rat's auditory cortex was similar to naive animals (circles in Figure 4A; $p > 0.15$ for all groups, Figure S1). Renormalization occurred in all three groups, even though two groups experienced NBS-tone pairing and the control group experienced no NBS. All three Pretrained groups experienced the same behavior testing during the 10 days before physiology, implying that this 10 day period was sufficient to renormalize map plasticity in all three groups.

Behavioral performance for all three Pretrained groups was not different from the Behavior Alone group immediately before physiology [Figures 4B and 4C; $F(3,21) = 0.6664$, $p = 0.8369$].

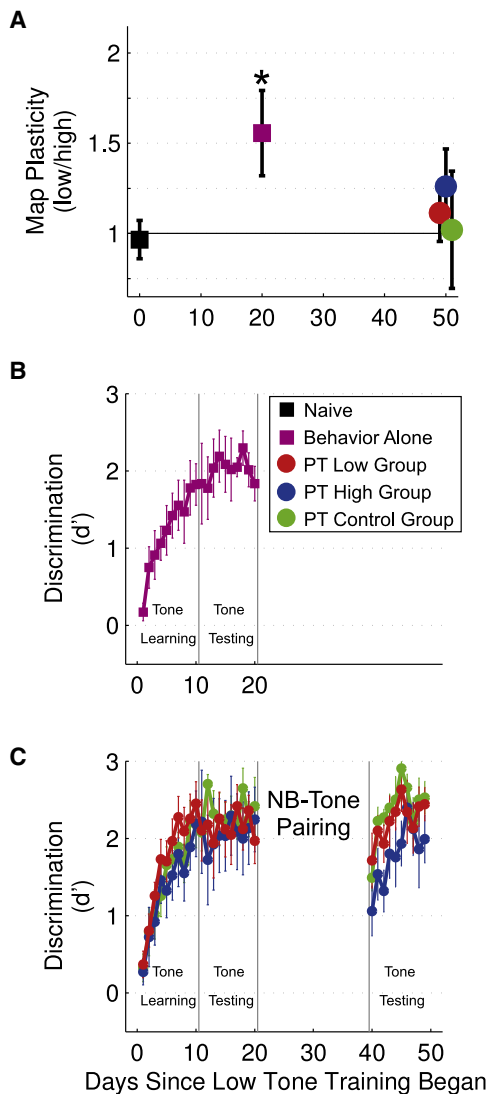


Figure 4. A Brief Period of Training Causes Cortical Map Plasticity, but Longer Periods of Training Renormalize Map Plasticity

(A) Map plasticity was quantified by measuring the ratio of the A1 surface area responding to a 2 kHz tone and a 19 kHz tone at 60 dB SPL. Map plasticity developed after discrimination learning, but renormalized after longer periods of training. The asterisk denotes that the map plasticity ratio for the Behavior Alone group was significantly different than naive controls; $p < 0.05$. See also Figure S1.

(B) Timeline of discrimination performance on the 1 octave task for the Behavior Alone group.

(C) Timeline of discrimination performance on the 1 octave task for all three Pretrained Groups. Error bars in all figures indicate SEM.

The observation that the Pretrained rats with map renormalization discriminated tones as well as rats with map plasticity (Behavior Alone) indicates that map plasticity is not necessary to accurately perform the low-frequency discrimination task. These results are consistent with previous reports that map plasticity occurs during learning and that map renormalization occurs even when training continues (Ma et al., 2010; Molina-Luna et al., 2008; Takahashi et al., 2010; Yotsumoto et al., 2008).

We observed a similar pattern of plasticity development and subsequent renormalization in rats from Experiment 1 that received NBS-tone pairing before learning. The High and Control groups experienced either NBS-tone pairing with high tones or tone exposure without NBS respectively before learning to perform the low-frequency discrimination task (Figure 2A). These two groups showed a similar learning curve to the Behavior Alone Group (Figures 4B and 5B). Low-frequency map plasticity developed in both of these groups after tone discrimination learning (Figure 5A; Naive versus High, $p = 0.026$; Naive versus Control, $p = 0.029$, t tests). This result confirms that low-frequency map plasticity develops during discrimination learning, and indicates that previous NBS-high tone pairing does not interfere with the development of low-frequency map plasticity.

By the end of Experiment 1, the Low Group did not have low-frequency map plasticity (red triangle in Figure 5A; $p = 0.2715$). This demonstrates that 17 days of discrimination training (Figure 5C) was sufficient to renormalize the low-frequency plasticity caused by 20 days of NBS low-tone pairing (Kilgard and Merzenich, 1998). Behavioral performance before mapping was not different between the Low, High, and Control groups [$F(2,12) = 1.7479$, $p = 0.2157$]. These results again confirm the finding that map plasticity is not necessary to accurately discriminate tones. Collectively, these results indicate that map plasticity renormalizes at approximately the same rate whether generated by behavior training or NBS-tone pairing.

DISCUSSION

Summary

In this study, we used NBS-tone pairing to create cortical map plasticity outside of a behavioral context. We trained several groups of animals to perform a low-frequency discrimination task and documented the effects of NBS-tone pairing on learning and discrimination performance. We found that pairing NBS with a low-frequency tone before training began was sufficient to enhance learning of a low-frequency discrimination task. This result supports our initial hypothesis that cortical map plasticity is not an epiphenomenon, and that plasticity is able to improve discrimination learning. In well-trained animals, pairing NBS with a low tone did not improve discrimination performance, but pairing NBS with a high tone did temporarily worsen discrimination performance. Physiological recordings demonstrated that cortical map plasticity developed during learning but subsequently renormalized. Collectively, our results indicate that cortical map expansion improves learning but is not necessary for good performance of a learned discrimination task. These and other recent findings suggest that the current model of cortical map plasticity needs to be reconsidered.

Expansion-Renormalization Model of Plasticity and Learning

There are several problems with the hypothesis that large scale cortical map reorganization is directly responsible for discrimination abilities. If encoding each individual skill required reorganization of an entire cortical field, subjects would be unable to learn new skills while maintaining earlier skills. Additionally, requiring large cohorts of neurons to be active to

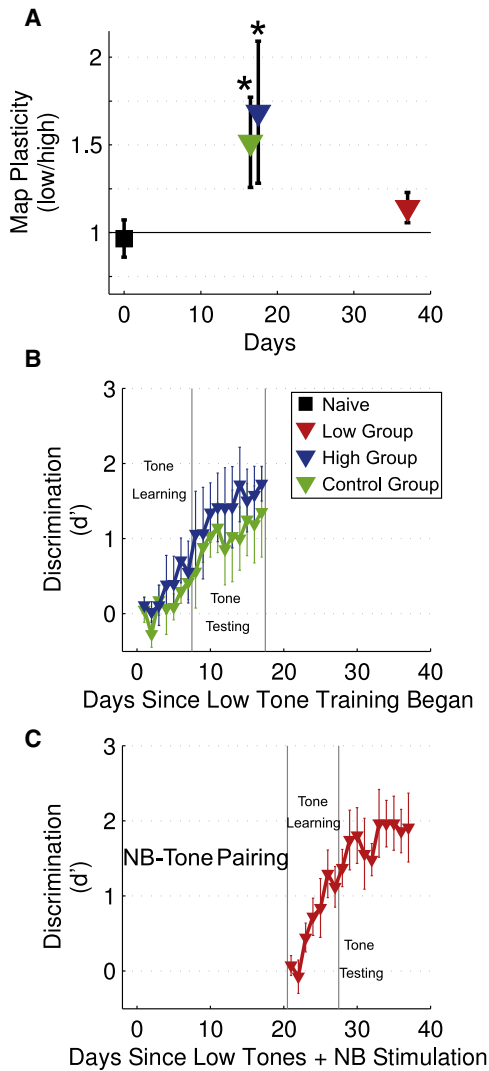


Figure 5. Plasticity Caused by NBS-Tone Pairing Renormalizes with Further Training

(A) Map plasticity was quantified in naive controls as well as the three groups of rats that learned the discrimination task after NBS-tone pairing (see Figure 2). Map plasticity developed in the two groups of rats that experienced low-tone discrimination learning (High Group, blue; Control Group, green), but renormalized in the group that experienced NBS-low tone pairing before low-tone discrimination learning (Low Group, red). The x axis corresponds to the days since low-tone training began for the High and Control groups (same as B), and corresponds to the days since NBS began for the low group (same as C). See also Figure S1.

(B) Discrimination learning curve for the High and Control groups.

(C) Discrimination learning curve for Low Group. There were no differences in discrimination abilities between the Low, High, and Control groups immediately before physiology. Error bars in all figures indicate SEM.

perform a discrimination task would not be the most metabolically efficient method of performing learned skills. We propose that map expansion is a transient phenomenon that serves to expand the pool of neurons that respond to behaviorally relevant stimuli so that neural mechanisms can select the most efficient circuitry to accomplish the task.

We refer to this new conception of map plasticity as the Expansion-Renormalization model. Unlike the earlier conception of map plasticity, large scale map expansion is not the method used to encode discrimination abilities. Rather, cortical plasticity is used to identify the minimum number of neurons that can accomplish any given task. This process involves a map expansion stage and a map renormalization stage. During the first stage of the Expansion-Renormalization model, neuromodulators are repeatedly released at the same time as task specific stimuli (Edeline, 2003; Keuroghlian and Knudsen, 2007; Weinberger, 2007). The resulting map expansion increases the number of neural circuits in multiple brain regions that respond to task stimuli. The map expansion creates a new and heterogeneous population from which later processes can select the most efficient circuitry. As subjects learn the discrimination task, they associate the activity of neural circuits with behavioral responses. In this model, learning results when subjects select the most efficient circuits and preferentially associate these neural responses with the appropriate behavioral response. By the end of learning, discrimination performance relies on responses from a dedicated circuit of neurons rather than requiring large-scale map plasticity to encode the behavioral task. These circuits are likely to be distributed across multiple brain regions (Hernandez et al., 2010; Lemus et al., 2010).

After learning is complete, the map expansion stage is followed by a map renormalization stage that returns the map to its default organization. During this stage of the Expansion-Renormalization model large-scale cortical map expansion is reversed. However, there must still be changes in the brain that are responsible for improved task performance. We propose that the source of this improvement is the efficient circuit that was selected and associated with behavior during initial learning. Consistent with this hypothesis, recent studies indicate that (1), initial learning generates a population of new dendritic spines; (2), this population is then reduced to a small subset; and (3), skilled performance is maintained by this small but stable subset of new dendritic spines (Xu et al., 2009; Yang et al., 2009).

Future studies of plasticity and renormalization should examine the time course of plasticity development and renormalization in multiple brain regions. NBS-tone pairing studies have shown that map expansions develop in multiple stages of the auditory system and that plasticity in these areas are interdependent (Ma and Suga, 2003; Puckett et al., 2007; Zhang and Yan, 2008). However, similar studies have not yet been done in the auditory system after operant discrimination training. In the visual system, there is some evidence that map expansions after training may either develop or renormalize at different rates in secondary versus primary cortical areas (Ghose et al., 2002; Yang and Maunsell, 2004). More studies are necessary to determine whether plasticity develops in multiple brain regions, whether plasticity renormalizes at the same rate in different brain regions, and what factors may inhibit or enhance expansion and renormalization.

Renormalization of Map Expansions

Although the map renormalization stage has been less well-studied than map expansion, several recent studies have reported renormalization after behavior training. In our study,

we found map expansions renormalized 35 days after the beginning of low-frequency discrimination training or NBS pairing with low-frequency tones. Similar map renormalization has now been observed in the auditory, visual, and motor cortex (Ma et al., 2010; Molina-Luna et al., 2008; Takahashi et al., 2010; Yotsumoto et al., 2008). Renormalization has also been observed after the cortical plasticity associated with recovery from stroke and brain injury (Tombari et al., 2004; Ward et al., 2003). These findings indicate that cortical map expansion is not usually the method by which skills are permanently stored in the brain but rather that map expansion is an important mechanism to generate efficient circuitry to perform behaviorally important tasks.

The time required to pass through the map expansion and map renormalization stages is likely to be affected by many factors. Many studies have shown that rates of learning and map expansion are affected by task difficulty and by motivation (Rutkowski and Weinberger, 2005). Demanding tasks are more likely to cause plasticity because they lead to increased neuro-modulator release compared to tasks that are easy to perform (Arnold et al., 2002; Himmelheber et al., 2000). We propose that when subjects are required to perform demanding tasks or are highly motivated, they may transition to the map renormalization stage more slowly than when subjects are required to perform easy tasks.

In some previous studies, map expansions persisted for several months after the beginning of behavior training, implying that these subjects never reached the map renormalization stage (Polley et al., 2006; Recanzone et al., 1992a, 1992b, 1993). In studies with persistent map expansions, subjects were often trained using adaptive tracking so that the difficulty of the task changed on a trial-by-trial basis and subjects never achieved >70% correct performance during a session. This constant adjustment in task difficulty likely caused subjects to be constantly engaged and attentive to the discrimination task. Task difficulty appears to be an important factor for inducing long-term map expansions. When animals performed a frequency discrimination task using adaptive tracking but were held to 85% correct performance (i.e., an easier task) they did not demonstrate map expansions after several months of training (Brown et al., 2004). Because the authors did not record neural responses from any animals after a short period of training, it is unknown whether map expansions developed and then consequently renormalized in these groups or if these animals never developed map expansions at all.

In our study, we found that map expansions developed after 17–20 days of training and that maps renormalized after 35 days. Our rats were presented with the same set of discrimination stimuli during every session regardless of performance. As a result, the task was most challenging during early learning and was less challenging for well-trained animals. By precisely regulating map renormalization based on task demands, the brain appears to maximize learning while minimizing the neural resources devoted to any particular task.

An inability to move from map expansion to renormalization may contribute to clinical disorders. In both chronic pain and tinnitus, the degree of map expansion is highly correlated with the intensity of phantom sensations (Engineer et al., 2011; Karl

et al., 2001; Maihofner et al., 2004; Muhn timer et al., 1998; Tsao et al., 2008; Vartiainen et al., 2009). It is possible that the disturbing nature of these sensations triggers a physiological state that prevents map renormalization and maintains abnormally high excitability. Sensory exposure and discrimination training to renormalize cortical maps has shown promise and provides at least temporary relief for some patients (Flor and Diers, 2009; Moseley, 2004, 2008; Moseley and Wiech, 2009; Moseley et al., 2008; Okamoto et al., 2010; Pleger et al., 2005). A better understanding of the mechanisms responsible for map renormalization could improve treatments for chronic pain and other neurological conditions that are associated with pathological cortical plasticity (Engineer et al., 2011).

The Contribution of Map Expansions to Learning and Plasticity

There is now considerable evidence that cortical plasticity plays an important role in learning. Some of the strongest evidence comes from studies of experimental manipulations that block map expansion and impair learning (Baskerville et al., 1997; Conner et al., 2003, 2005, 2010; Linster et al., 2001; Maalouf et al., 1998; Miasnikov et al., 2001; Ramanathan et al., 2009; Sachdev et al., 1998; Zhu and Waite, 1998). For example, nucleus basalis lesions prevent both map expansions in the motor cortex and learning of new motor skills (Conner et al., 2003, 2010). Studies have shown that drugs or genetic mutations that block plasticity also interfere with learning (Martin et al., 2010; Tzingounis and Nicoll, 2006). These findings imply that cortical plasticity is necessary for learning to take place.

In our study, we further tested the relationship between learning and map plasticity by generating a map expansion and then testing its effect on discrimination abilities. We found that creating a map expansion before training increased the rate of learning. This result indicates that map plasticity is able to meaningfully influence behavior. A similar effect was found in the somatosensory system. Short-term somatosensory cortical plasticity temporarily improved tactile discrimination. This effect was enhanced or attenuated by drugs that enhance or attenuate plasticity, respectively (Dinse et al., 2003). Changes to the sensory periphery, such as hearing loss or monocular deprivation, also cause map expansions that can improve discrimination abilities (Lehmann and Lowel, 2008; Steeves et al., 2008). Single tone exposure during development increases the number of auditory cortex neurons tuned to the exposed tone frequency. Discrimination of the exposed tone is impaired and discrimination of tones immediately flanking the exposed tone are enhanced (Han et al., 2007). Taken together, these studies and our own findings support the conclusion that map expansions are not an epiphenomenon and that cortical plasticity is an important component of discrimination learning.

Map expansions and plasticity appear to have less influence on performing previously learned tasks compared to learning a new discrimination task. In our study, naturally occurring map renormalization after long periods of training did not result in a decrement in performance. In addition, using NBS to induce additional map expansions did not improve behavior in well-trained animals. Previous studies have observed that disruption of plasticity mechanisms have smaller effects on the

performance of previously learned tasks compared to new learning (Conner et al., 2003; Fine et al., 1997; Kudoh et al., 2004; Kudoh and Shibuki, 2006; Ridley et al., 1988; Voytko, 1996). For example, lesions of the nucleus basalis do not interfere with performance of a previously learned motor skill (Conner et al., 2003). These results fit with the Expansion-Renormalization model, in which cortical plasticity plays a large role in learning, but becomes less important after learning identified the most efficient discrimination circuits.

Although inducing map expansions did not improve performance in well-trained rats, we did find that NBS-directed map contraction could be used to worsen discrimination performance in well-trained rats. Discrimination abilities were impaired when NBS was paired with high-frequency tones in animals that had already learned to perform the low-frequency discrimination task. The most likely explanation for this result is that NBS high-tone pairing caused a significant decrease in the cortical response to low-frequency tones, suggesting that a minimal representation of low-frequency tones is necessary for discrimination performance. NBS high-tone pairing began shortly after their initial low-frequency discrimination training at a time when the rats had low-frequency map expansions. According to our Expansion-Renormalization model, these rats would still be in the expansion stage. The identification of a small efficient circuit to perform the low-frequency discrimination would not have been complete by the time animals experienced NBS high-tone pairing. The low-frequency map expansion caused by behavior training was likely still important for discrimination performance, and so the decrease in cortical responses to low-frequency tones after NBS high-tone pairing may have worsened behavioral performance. It is possible that NBS pairing would have no impact on discrimination performance in animals that had experienced both map expansions and map renormalization. Future studies using awake recording methods to measure cortical plasticity at all time points during discrimination training and NBS-pairing will help clarify the role of map organization during each stage of learning and performance.

Conclusion

Our results demonstrate that cortical map expansion plays a major role in perceptual learning but is not required to maintain perceptual improvements. These results are consistent with a new understanding of cortical map plasticity in which map expansion is not an end to itself but a means to generate a large and diverse set of neurons that are responsive to behaviorally relevant stimuli so that selective processes can identify the most effective circuitry for accomplishing the necessary task before the exaggerated representation returns to its normal size.

EXPERIMENTAL PROCEDURES

All experimental procedures were approved by the Animal Care and Use committee at the University of Texas at Dallas and conform to guidelines for the Ethical Treatment of Animals (National Institutes of Health).

Behavior Training

Thirty-nine rats in Experiments 1 and 2 were trained to perform a simple go/no-go frequency discrimination task (total of 2610 hr of behavior training). Target or distracter sounds were presented approximately every 10 s. Rats received

a 45 mg sugar pellet when they pressed a lever within 3 s of the target sound presentation. Pressing the lever after a distracter or during silent periods between sound presentations resulted in a timeout period in which all lights in the cage were extinguished and further sound presentations were delayed for 6–8 s. All rats experienced two 1 hr long behavior sessions, 5 days per week. During each 1 hr session, rats performed an average of 271 ± 9 trials. During frequency discrimination, the average Criterion, or response bias (Abdi, 2010), for all groups of rats was neutral ($c = 0.0024 \pm 0.0984$) and there were no significant differences between any experimental groups ($p = 0.1041$).

Broadband Task

Rats in Experiment 1 learned a broadband task before the NBS tone-pairing. The target stimulus was a train of six white noise bursts (25 ms duration, 60 dB SPL intensity, 1–32 kHz frequency range) presented at a rate of 5 Hz, whereas the distracter stimulus was a complex noise stimulus with irregular temporal and spectral features that had the same duration and overall intensity as the target noise-burst train (1025 ms duration, 60 dB SPL intensity, 1–48 kHz frequency spectrum). Animals spent 15 days learning to reliably respond to presentation of the target noise stimulus and then spent 3 days learning to discriminate between the target and distracter noise stimuli. During discrimination, the target stimulus was presented during 50% of trials and the distracter stimulus was presented during the remaining 50% of trials. Animals next moved on to NBS-tone pairing and then frequency discrimination learning (Figure 2A).

Experiment 1: Low-Frequency Discrimination

For the low-frequency discrimination tasks, the target sound was always a train of six tone pips (25 ms duration, 60 dB SPL intensity, 1.78 kHz carrier frequency, presented at a rate of 5 Hz), whereas the distracter sounds differed from the target only in carrier frequency (from 1.9 to 9.5 kHz, or 0.1 to 2.4 octaves above the CS+ stimulus). During Tone Learning for Experiment 1 (Figure 2A, light gray), the distracter tones were 0.5, 1.0, and 2.4 octaves above the target stimulus. The target tone was presented during 60% of trials, whereas distracter tones were equally represented during the remaining 40% of trials during the first 3 days of training for all rats. Thereafter, the target tone was presented during 50% of trials and the distracter tones were equally represented during the remaining 50% of trials. During Tone Testing (10 days after Tone Learning; see Figure 5) the distracter tones were 0.1, 0.26, 0.38, 0.5, 0.75, 1, 1.5, and 2.4 octaves above the target tone. During Tone Testing the target tone was presented during 50% of trials and the distracter tones were equally represented during the remaining 50% of trials.

Experiment 2: Low-Frequency Discrimination Training in Pretrained Groups

The Pretrained groups learned to perform the frequency discrimination task before tone exposure. The target tone for this group was again a 1.78 kHz tone train and distracter tones ranged from 0.1 to 1.0 octaves above the target. During Tone Learning (Figure 3A, light gray), Pretrained rats spent 20 days learning to reliably respond after presentation of the target, and then spent 10 days learning to respond to target tones and ignore a distracter 1.0 octave above the target. During Tone Testing (Figure 3A, dark gray), the distracter tones were 0.1, 0.2, 0.25, 0.32, 0.38, 0.44, 0.5, 0.7, and 1.0 octaves above the target. The target tone was presented during 50% of trials and the distracter tones were equally represented during the remaining 50% of trials.

NBS-Tone Pairing

NBS-tone pairing was conducted using previously reported methodology (Kilgard and Merzenich, 1998; Puckett et al., 2007). All NBS animals and the Pretrained Control group underwent implantation surgery 2–3 weeks before training. A platinum bipolar stimulating electrode was lowered 7 mm below the cortical surface from a location 2.3 mm posterior and 3.3 mm lateral to bregma in the right hemisphere. Bone screws located ~5 mm posterior to the implant and above the cerebellum were used to monitor EEG activity.

During NBS-tone pairing, the paired sound was presented approximately every 10 s 275–350 times per day for a period of 20 days. Silent intervals (and unpaired stimuli for the Low and High groups) were inserted at random to prevent habituation, and each pairing session lasted ~3.5 hr. Paired sounds were either a 2 kHz or 19 kHz tone (250 ms duration, presented at 50 dB SPL). To prevent Pretrained animals from “rehearsing” the frequency discrimination task during NBS sessions, we chose to pair a single tone during NBS but use

trains of tones during behavior training. Each tone presentation was accompanied by a short train of current pulses delivered to the bipolar stimulating electrode (20 biphasic pulses, 0.1 ms duration at 100 Hz) beginning 50 ms after tone onset. The current amplitude ranged from 120 to 200 μ amps for each animal and was selected to reliably elicit brief EEG desynchronization for 1–3 s whenever the animal was in slow wave sleep. Control rats were trained in the same booths and heard the same tones, but were not connected to the stimulators and EEG activity was not monitored.

Physiology

Physiological experiments were conducted using similar methods to previous publications (Engineer et al., 2008; Puckett et al., 2007). Recordings took place under pentobarbital anesthesia (50 mg/kg). Multiunit responses were recorded using two bipolar parylene-coated tungsten electrodes (250 μ m separation, 2 M Ω m at 1 kHz; FHC Inc., Bowdoinham, ME) that were lowered \sim 550 μ m below the cortical surface (layer IV/V). At each site, a tuning curve consisting of 81 frequencies spanning from 1 to 32 kHz at 16 intensities spanning from 0 to 75 dB SPL was presented (1296 tones, 25 ms duration, 5 ms rise and fall time, 1 repetition of each). In total, we recorded from 6414 cortical sites in 77 animals.

Sites from control and experimental rats for the behavioral experiments were analyzed using an automated tuning curve analysis program. A poststimulus time histogram (PSTH) was constructed from the responses to all tone-intensity combinations using 1 ms width bins. The receptive field area was then calculated using image analysis techniques from a grid of the responses to each frequency-intensity combination during the driven response period (from onset to end of peak latency). For the NBS time course study (Figure 1), the receptive field area of sites from control and experimental rats were identified by hand in a blind, randomized batch by expert observers using customized software. For all sites, receptive field characteristics were calculated based on the identified area of driven activity. The lowest intensity that evoked a reliable neural response was defined as the threshold, and the frequency at which this response occurred was defined as the characteristic frequency (CF). Four bandwidths (BW10–BW40) were calculated as the range of frequencies (in octaves) that evoked reliable responses at 10, 20, 30, and 40 dB above threshold.

As in earlier studies, Voronoi tessellation was used to transform the discretely sampled surface into a continuous map using the assumption that each point on the map has the response characteristics of the nearest recording site (Kilgard and Merzenich, 1998). Because regions with above average sampling density have smaller tessellations, they do not bias estimates of the cortical response. A1 sites were identified on the basis of latency and topography. The percent of the cortical area of A1 responding to each tone was estimated as the sum of the areas of all tessellations from sites in A1 with receptive fields that included the tone, divided by the total area of the field. For the time course study in which animals were mapped after NBS-tone pairing alone, we measured the percentage of A1 cortex that responded to the frequency that was paired with NBS, a 19 kHz, 60 dB SPL tone.

For all behaviorally trained animals, we reported changes in the representation of behaviorally relevant tones by reporting the ratio of the percent of cortex that responded to a 2 kHz, 60 dB SPL tone divided by the percentage of cortex that responded to a 19 kHz, 60 dB SPL tone. In behaviorally trained animals, we commonly observe both a shift in tuning toward behaviorally relevant tones and a decrease in receptive field sizes (Figure S1). The net effect of this plasticity is to cause the cortical response to behaviorally irrelevant tones to decrease whereas the response to behaviorally relevant tones is only slightly increased or unchanged (Figure S1). Therefore a ratio measure provides a reliable indicator of the relative frequency organization of low versus high tones in A1.

Statistics

Discrimination performance was measured using the signal detection theory measure d' during all stages of training (Abdi, 2010; Klein, 2001). Statistical comparisons between three or more groups were done using repeated-measure ANOVA. Tones <0.38 octaves above the target stimulus were excluded from the repeated-measure ANOVA because these sounds were not reliably discriminated from the target stimulus and therefore were not

expected to change significantly after NBS-tone pairing. Statistical comparisons between only two groups and single tone frequencies relative to zero were done using t tests, and t tests were used for all statistical comparisons of physiological measures between two groups. Unless otherwise noted, p -values reported are for two-tailed t tests.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Results, two tables, and one figure and can be found with this article online at doi:10.1016/j.neuron.2011.02.038.

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