samples treated as above or at 1100°C for >32 hours showed no trace of crystalline silicate by XRD and have very weak luminescence (in contrast to the films), and the optimal stoichiometry coincides with Gd₅Ga₃O₁₂. However, x-ray photoemission spectroscopy (XPS) and energy-dispersive x-ray analysis confirmed the presence of SiO₂ in the sample. The measured percentage of SiO₂ in the sample was higher than that expected from the deposition stoichiometry, which suggests that SiO₂ is on the surfaces of the particles of Gd₅Ga₃O₁₂. XPS measurements also ruled out the presence of residual carbon in the sample. Consistent with these results, pure Gd₂O₃, Ga₂O₃ and Gd₅Ga₃O₁₂ thin films made on an LaAlO₃ substrate using the same procedures showed no PL in the same spectral region.

It is well known that both oxidized porous silicon (p-Si) (9, 10) and properly prepared silicon oxide (11–13) show blue photoluminescence at 420 to 490 nm.

Two models have been proposed to explain the blue PL from p-Si. The first model (10), used to explain the photoluminescence in SiO₂, connects the blue emission in p-Si directly to the defect states of SiO₂. In the second model [the extended quantum confinement (EQC) model], the PL arises from charge recombination processes across the broadened band gap of nanocrystalline Si (14). In our blue PL samples, the EQC model can be excluded because there is no pure Si in the sample. There are two possible origins for the blue PL in Gd₅Ga₃O₁₂/SiO₂. First, it is possible that Si may have substituted into the tetrahedral sites of Ga and functions as the activator in the host lattice of Gd₅Ga₃O₁₂. This notion is less likely because we are not aware of any report of Si-activated phosphors. It is more likely that nanocrystalline or amorphous SiO₂ or interfacial silicate (therefore not detectable by XRD) is finely dispersed into the Gd₅Ga₃O₁₂ matrix and possibly coated on the surface of Gd₅Ga₃O₁₂ grains, which are on the order of 100 nm as observed by atomic force microscopy. These interfaces may form the specific local electron states that give rise to the observed blue emission. Consistent with this notion, etching of the Gd₅Ga₃O₁₂/SiO₂ films with dilute hydrofluoric acid (which does not substantially affect the Gd₅Ga₃O₁₂ host) dramatically reduces photoluminescence in comparison to that in the untreated films. Additional experimental and theoretical investigations are needed to more fully understand the mechanism of luminescence in this material. Given the high PL efficiency and compatibility of the synthesis methods with Si wafer processing, this material may find applications in optoelectronics and imaging technologies.

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Cortical Map Reorganization Enabled by Nucleus Basalis Activity

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Little is known about the mechanisms that allow the cortex to selectively improve the neural representations of behaviorally important stimuli while ignoring irrelevant stimuli. Diffuse neuromodulatory systems may facilitate cortical plasticity by acting as teachers to mark important stimuli. This study demonstrates that episodic electrical stimulation of the nucleus basalis, paired with an auditory stimulus, results in a massive progressive reorganization of the primary auditory cortex in the adult rat. Receptive field sizes can be narrowed, broadened, or left unaltered depending on specific parameters of the acoustic stimulus paired with nucleus basalis activation. This differential plasticity parallels the receptive field remodeling that results from different types of behavioral training. This result suggests that input characteristics may be able to drive appropriate alterations of receptive fields independently of explicit knowledge of the task. These findings also suggest that the basal forebrain plays an active instructional role in representational plasticity.

The mammalian cerebral cortex is a highly sophisticated self-organizing system (1). The statistics of sensory inputs from the external world are not sufficient to guide cortical self-organization, because the behavioral importance of inputs is not strongly correlated with their frequency of occurrence. The behavioral value of stimuli has been shown to...
regulate learning in experiments conducted over more than a century (2). Recently, behavioral relevance has been shown to directly modulate representational plasticity in cortical learning models (3, 4). The cholinergic nucleus basalis (NB) has been implicated in this modulation of learning and memory. The NB is uniquely positioned to provide the cortex with information about the behavioral importance of particular stimuli, because it receives inputs from limbic and paralimbic structures and sends projections to the entire cortex (5). NB neurons are activated as a function of the behavioral significance of stimuli (6). Several forms of learning and memory are impaired by cholinergic antagonists and by NB lesions (7). Even the highly robust cortical map reorganization that follows peripheral denervation is blocked by NB lesions.

Many studies using acute preparations have shown that electrical stimulation of the NB (8) or local administration of acetylcholine (ACh) (9) can modulate stimulus-evoked single-unit responses. The variability across studies in the direction, magnitude, and duration of the modulation has made it difficult to relate these effects to long-term cortical map plasticity (10).

To clarify the role of the NB in representational plasticity, we investigated the consequences of long-term pairing of tones with episodic NB stimulation. A stimulating electrode was implanted in the right NB of 21 adult rats. After recovery, animals were placed in a sound attenuation chamber and a pure tone was paired with brief trial-by-trial epochs of NB stimulation during daily sessions (11). The tone paired with NB stimulation occurred randomly every 8 to 40 s. Pairing was repeated 300 to 500 times per day for 20 to 25 days. The rats were anesthetized and unrestrained throughout this procedure.

Twenty-four hours after the last session, each animal was anesthetized and a detailed map of the primary auditory cortex (A1) was generated from 70 to 110 microelectrode penetrations (12). During this cortical mapping phase, experimenters were blind to the tone frequency that had been paired with NB stimulation. The frequency-intensity response characteristics of sampled neurons were documented in every penetration by presentation of 45 pure tone frequencies at 15 sound intensities. Tuning curves were defined by a blind experienced observer (13).

Figure 1A illustrates the organization of A1 in a representative naïve rat. The color of each polygon denotes each penetration’s best frequency (BF), which is the frequency that evoked a neuronal response at the lowest stimulus intensity. The frequency representation is complete and regular in control rats. Each frequency is represented by a band of neurons that extends roughly dorsoventrally across A1. The 9-kHz isofrequency band, for example, is shaded light blue in Fig. 1A, and penetrations with a BF within a third of an octave of 9 kHz are hatched with white. Figure 1B shows the tips of the tuning curves recorded in every penetration. The tip of the “V” marks the BF; the width of the “V” denotes the range of frequencies to which the neurons at the site responded at 10 dB above threshold. In naïve rats, BFs were evenly distributed across the entire hearing range of the rat, in accordance with the well-known tonotopic organization of A1 (14).

Pairing a specific tonal stimulus with NB stimulation resulted in remodeling of cortical area A1 in all 21 experimental rats. In the representative example shown in Fig. 1C, a 50-dB 9-kHz tone was paired with NB

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**Fig. 1.** (A, C, E, and G) Representative maps of A1 that show the effects of pairing 9-kHz tones with electrical stimulation of the NB. (A) Representative map from an experimentally naïve rat demonstrating the normal orderly progression of BFs recorded in the rat A1. Each polygon represents one electrode penetration. The color of each polygon indicates the BF in kilohertz. The polygons (Voronoi tessellations) were generated so that every point on the cortical surface was assumed to have the characteristics of the closest sampled penetration. Hatched polygons designate sites with BFs within one-third of an octave of 9 kHz, illustrating a typical isofrequency band. Penetrations that were either not responsive to tones (O) or did not meet the criteria of A1 responses (X) were used to determine the borders of A1. (C) Map of A1 after pairing a 250-ms 9-kHz tone with NB stimulation. (E) Map of A1 after pairing a train of six 9-kHz tones with NB stimulation. (G) Map of A1 after pairing both 9- and 19-kHz tones with NB stimulation. The expansion of the 9-kHz isofrequency band is shown in (C), (E), and (G). Scale bar, 200 μm. (B, D, F, and H) Distribution of tuning curve tips at every A1 penetration from each map, which indicate the BF, threshold, and receptive field width 10 dB above the threshold for neurons recorded at each penetration. Threshold as a function of frequency (in kilohertz) matches previously defined behavioral thresholds. Solid vertical lines mark the frequency paired with NB stimulation. Dotted vertical lines mark frequencies presented as often as, but not paired with, stimulation.
stimulation approximately 300 times per day over a period of 20 days. This treatment produced a clear expansion of the region of the cortex that represented frequencies near 9 kHz (Fig. 1C). Figure 1D illustrates the clustering of tuning curve BFs near the frequency that was paired with NB stimulation. After pairing, neurons from 20 of the penetrations into the conditioned map shown in Fig. 1C had BFs within a third of an octave of 9 kHz, compared to only 6 kHz in the equivalently sampled control map. The increase in 9-kHz representation resulted in a clear decrease in the area of A1 that responded to lower frequencies. In the control map, 22 penetrations had BFs less than 5 kHz, compared to only 4 penetrations in the conditioned map. It should be noted that the decrease in low frequency responses is not a consistent finding. In other examples, the low-frequency responses appeared unaltered and the representation of higher frequencies was decreased.

Because the tone paired with NB stimulation was well above the threshold, it was important to examine not only the shifts in the tuning curve tips but also the responses of cortical neurons to tones at the conditioned intensity. During pairing, many of the neurons with BFs different from 9 kHz were excited by the auditory stimulus because most rat A1 tuning curves broaden as intensity is increased. In the naïve map, less than 25% of neurons within A1 responded to 9 kHz presented at 50 dB. By contrast, almost 50% of the conditioned cortex responded to the same stimulus.

Figure 2 summarizes the magnitude of representational changes that resulted from pairing one frequency with NB stimulation in 10 animals. Figure 2A represents data from seven naïve controls and illustrates the average percent of the surface of A1 that responded to tones at any combination of frequency and intensity. Figure 2, C and D, shows the percent change relative to controls after pairing NB stimulation with 4-, 9-, or 19-kHz tones, respectively. In each case, the cortical area representing the paired stimulus nearly doubled. These results indicate that the responses of hundreds or thousands of A1 neurons can be altered by pairing tones with NB stimulation in a passively stimulated animal.

In four animals, NB stimulation was paired with a train of six 9-kHz tone pips (25 ms) presented at 15 Hz to test the effects of increasing temporal structure in the auditory stimulus (Fig. 1, E and F). Conditioning with this stimulus unexpec-

![Percent change after 4 kHz paired with NB stim.](image1)

![Percent change after 9 kHz paired with NB stim.](image2)

![Percent change after 19 kHz paired with NB stim.](image3)

**Fig. 2.** (A) Percent of the surface of A1 that responds to pure tones at each combination of tone frequency and intensity. The average of seven experimentally naïve animals is shown. (B through D) Percent change in the percent of the primary auditory cortex responding to tones after 1 month of 4-, 9-, or 19-kHz tones paired with NB stimulation (n = 4, 4, and 2, respectively). Each group showed a significant increase over controls in the percent responding to the conditioned frequency at 50 dB above the minimum threshold (P < 0.005, two-tailed t test). The percent of A1 responding is the sum of the areas of all of the Voronoi tessellations that responded to the particular frequency and intensity combination of interest, divided by the total area of A1. The function is highly reproducible across naïve controls with an average standard error across frequencies of less than 3%. Tesselation was chosen to derive area measurements from discretely sampled points by assuming that each location on the cortical surface had the characteristics of the closest sampled penetration.

![Distribution of receptive field width BW10 for every A1 penetration for each of the four classes of experiments.](image4)

**Fig. 3.** (A) Percent of the surface of A1 that responds to pure tones of any combination of tone frequency and intensity. The average of seven experimentally naïve animals is shown. (B) Percent change in the percent of A1 responding after 1 week of pairing 9-kHz tone pip trains (15 Hz) with NB stimulation. There was a significant increase in the response to 9 kHz at 50 dB above the minimum threshold as compared to controls (t test; n = 2, P < 0.05). (C) Percent change in the percent of A1 responding after 1 month of pairing 9-kHz tone pip trains (15 Hz) with NB stimulation. There was a significant increase in the response to 9 kHz at 50 dB above the minimum threshold as compared to controls (n = 4, P < 0.0001). (D) Distribution of receptive field width BW10 for every A1 penetration for each of the four classes of experiments. Pairing one frequency with NB stimulation did not significantly effect the BW10 distribution relative to naïve animals, whereas pairing two frequencies (4 and 14, or 9 and 19 kHz) or a 15-Hz train of stimuli caused receptive field width to be decreased and increased, respectively. The same effect is present in the distributions of BW20 to BW40. The dashed vertical line marks the mean of each distribution. Single units were sorted from the multi-unit data derived from the four naïve animals (15 units) and from four train-conditioned animals (33 units). The mean BW10 for single units was also increased by 15-Hz train conditioning (0.91 versus 1.38 octaves, P < 0.005). This widening of tuning curves acclives with the BF shifts to generate the large increase in the percent of A1 responding after train conditioning.
edly resulted in even greater cortical reor-
ganization than conditioning with a 250-ms
tone (P < 0.01, Fig. 3C). In the example shown,
the 9-kHz isofrequency band was increased from roughly 250 μm wide in
a naïve A1 to more than 1 mm wide. After
pairing, over 85% of A1 responded to 9 kHz
at 50 dB. Additionally, 50% of A1 penetra-
tions had best frequencies within one-third
of an octave of 9 kHz, compared to less than
15% in the control animals. The extent of
cortical map reorganization generated by
NB activation is substantially larger than
the reorganization that is typically observed
after several months of operant training
(15–17).

The six short tones presented at 15 kHz
evoked less than 30% more spikes than did
a single tone, because most rat A1 neurons
do not follow onsets presented faster than
12 to 14 Hz (18). It seems unlikely that the
larger reorganization evoked with stimulus
trains is simply due to an increased cortical response to the stimuli.

Two animals were mapped after only 1
week of conditioning with the 15-Hz stim-
ulus to examine the rate of cortical remod-
eling evoked by NB activation. The 9-kHz
representation was increased by 18% after 1
week of training. This reorganization was
nearly halfway to the 44% increase that was
recorded after a month of conditioning,
indicating that the cortical remodelling gen-
erated by NB stimulation was progressive in
nature (Fig. 3B).

To probe the competitive processes un-
derlying cortical reorganization, five rats
were conditioned with two different ran-
donically interleaved tones that were more
than an octave apart. Two distinct classes of
reorganizations resulted. The tuning curve
tips were either shifted toward a point be-
tween the two conditioned frequencies, so
that both were within the receptive field at
50 dB (n = 3), or shifted toward only one of
the two conditioned frequencies (n = 2, Fig.
1, G and H). The two classes of results may
be the consequence of subtle variations in A1 before NB pairing, which can have large effects when competitive processes are involved.

To document the fact that NB activa-
tion is required for the cortical reorganiza-
tions observed in this study, during four of
our experiments two additional frequencies
were delivered on identical presentation
schedules as the paired tones but were not
paired with NB stimulation. These stimuli,
which never occurred within 8 s of NB
stimulation, did not measurably affect corti-
cal responses or representations (19).

Microdialysis experiments have shown that
electrical stimulation of the NB results in
ACh release in the cortex (20). Addi-
tionally, both the short-term plasticity and
the electroencephalogram (EEG) desynchron-
zation evoked by NB stimulation are
blocked by atropine (21). Thus, the cortical
plasticity demonstrated in this study likely
involves the release of cortical ACh paired
with tones. To test for the necessity of ACh
release in our model, a 19-kHz tone was
paired with electrical stimulation of the NB
in animals with highly specific lesions of
the cholinergic NB neurons (22). No sig-
nificant increase in the 19-kHz representa-
tion was observed in lesioned animals. Even
though ACh release is clearly important for
NB function, it may be too simplistic to
focus exclusively on ACh because only one-
third of NB projection neurons are cholin-
ergic (23). One-third use γ-aminobutyric
acid and the remaining third are uncharac-
terized. Future work is needed to elucidate
the function of concurrent release of these
transmitters in cortical plasticity.

The nature of the auditory stimuli paired
with NB activation had a profound effect on
the selectivity of cortical responses (Fig.
3D). Sharpness of tuning was quantified as
the width of the tuning curve 10 dB above
the threshold (BW10). When a 250-ms tone
was used as the conditioning stimulus, the
average BW10 was not significantly differ-
ent from the average BW10 of control rats
(0.93 versus 1.02 octaves). Condition-
ing with a temporally modulated stimulus (a
train of six short tones of the same frequen-
cy) resulted in a mean cortical response that
was less selective than in controls (1.46
decades, P < 0.0001). Conditioning with
airons that are less selective than in controls (0.70 octaves,
P < 0.0001). Thus, our model results in
receptive fields that are narrowed, broad-
ened, or unaltered depending on specific
parameters of the auditory stimulus paired
with NB stimulation.

Similar increases and decreases in recep-
tive field sizes have been recorded in the
somatosensory and auditory cortices of New
World monkeys that have been trained at
tactile or auditory discrimination, detec-
tion, or time-order judgment tasks (4). A
pure tone discrimination task or a task in-
volving a stimulus that moved across sever-
ally fingers decreased receptive field diame-
ters by approximately 40% (15, 16). In con-
trast, a task that required detection of differ-
ences in the amplitude modulation rate of
tactile stimuli delivered to a con-
stant skin surface increased receptive field
diameters by more than 50% (17).

The mechanisms responsible for remodel-
ing receptive fields in a manner that is
appropriate for the particular task that an
animal practices are not well defined. One
possibility is that top-down instruction from
a higher cortical field with explicit knowl-
edge of the goals of the operant task directs
cortical plasticity. The fact that our single
model, without any behavioral task, can
generate the same receptive field effects as
are induced by extended periods of operant
training suggests that the characteristics of
the stimuli paired with subcortical neuro-
modulatory input are sufficient to deter-
mine the direction of receptive field alter-
ations (24).

Adult cortical plasticity appears to be
responsible for improvements in a variety of
behavioral skills, maintenance of precise
sensory representations, compensation for
damage to sensory systems, and functional
recovery from central nervous system dam-
age (4). Our results suggest that activation
of the NB is sufficient to guide both large-
scale cortical reorganization and receptive
deipel field reorganization to generate representa-
tions that are stable and adapted to an
individual’s environment by labeling which
stimuli are behaviorally important.

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10. Although studies using stimulation of the NB report-
ed mostly facilitation of the response to the paired
stimulus, in several studies using local administration
of ACh to alter receptive field organization the oppo-
site effect was reported. In these studies, ACh most
often caused a significant stimulus-specific de-
crease in cortical responsiveness after the pairing
procedure. The average duration of the plasticity
also varied across studies from less than 10 min to
more than 1 hour.
The OxyR transcription factor is sensitive to oxidation and activates the expression of antioxidant genes in response to hydrogen peroxide in Escherichia coli. Genetic and biochemical studies revealed that OxyR is activated through the formation of a disulfide bond and is deactivated by enzymatic reduction with glutaredoxin 1 (Grx1). The gene encoding Grx1 is regulated by OxyR, thus providing a mechanism for autoregulation. The redox potential of OxyR was determined to be ~185 millivolts, ensuring that OxyR is reduced in the absence of stress. These results represent an example of redox signaling through disulfide bond formation and reduction.

**Activation of the OxyR Transcription Factor by Reversible Disulfide Bond Formation**

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Reactive oxygen species can damage DNA, lipid membranes, and proteins and have been implicated in numerous degenerative diseases (1). As a defense, prokaryotic and eukaryotic cells have developed responses that protect against oxidative damage (2). These antioxidant defense systems have been best characterized in Escherichia coli, in which the OxyR and SoxR transcription factors activate antioxidant genes in response to 

H₂O₂ and to superoxide-generating compounds, respectively. The mechanisms of redox-sensing and the systems that control the redox status of the cell are likely to be coupled. Studies of the thiol-disulfide equilibrium of the cytosol of both prokaryotic and eukaryotic cells indicate that the intracellular environment is reducing, such that protein disulfide bonds rarely occur (3–5). The redox potential of the E. coli cytosol has been estimated to be approximately –0.26 to –0.28 V (4, 5). This reducing environment is maintained by the thioredoxin and the glutaredoxin systems (6, 7).

In response to elevated H₂O₂ concentrations, the OxyR transcription factor rapidly induces the expression of oxyS (a small, nontranslated regulatory RNA), katG (hydrogen peroxidase I), gorA (glutathione reductase), and other activities likely to protect the cell against oxidative stress (2, 8). Purified OxyR is directly sensitive to oxidation. Only the oxidized form of OxyR can activate transcription in vitro, and footprinting experiments indicate that oxidized and reduced OxyR have different conformations (9, 10). Thus, we examined the chemistry of OxyR oxidation and reduction.

No transition metals were detected by inductively-coupled plasma metal ion analysis of two preparations of OxyR (11). We also did not observe any change in OxyR activity after denaturation and renaturation in the presence of the metal chelator des-