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Plasticity of temporal information processing in the primary auditory cortex

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Abstract

Neurons in the rat primary auditory cortex (A1) generally cannot respond to tone sequences faster than 12 pulses per second (pps). To test whether experience can modify this maximum following rate in adult rats, trains of brief tones with random carrier frequency but fixed repetition rate were paired with electrical stimulation of the nucleus basalis (NB) 300 to 400 times per day for 20–25 days. Pairing NB stimulation with 5-pps stimuli markedly decreased the cortical response to rapidly presented stimuli, whereas pairing with 15-pps stimuli significantly increased the maximum cortical following rate. In contrast, pairing with fixed carrier frequency 15-pps trains did not significantly increase the mean maximum following rate. Thus this protocol elicits extensive cortical remodeling of temporal response properties and demonstrates that simple differences in spectral and temporal features of the sensory input can drive very different cortical reorganizations.

Most studies of cortical plasticity have documented changes evoked by spatially or spectrally specific stimuli[1−7]. In one such experiment, we demonstrated that pairing NB activation with tonal stimulation in a non-behaving rat can greatly expand the representation of a given tone frequency in A1 and cause large-scale remodeling of the spectral selectivity of A1 receptive fields (frequency–intensity tuning curves)[8] (see also refs [9, 10] from others). The NB neurons, located in the basal forebrain, send cholinergic and GABAergic projections to the entire cortical mantle[11] (Fig. 1**a**). Pairing NB stimulation with sound stimulation failed to produce significant cortical reorganizations when the acetylcholine-containing cells in the NB were immunolesioned[8]. Together, these studies support the long-standing view that the cholinergic projection from the NB is a primary modulatory input that enables experience-dependent cortical plasticity.

Here we used NB activation to explore the principles governing the plasticity of cortical dynamics as they apply to the representation of the temporal features of rapid, successive stimulus events. One method of describing the capacity of cortical neurons to respond to successive inputs is to derive a 'repetition-rate transfer function' (RRTF), in which the neural discharge rate is defined as a function of the stimulus repetition rate. Depending upon the type of stimulus modulation used, RRTFs derived for neurons in the primary visual, auditory or somatosensory cortices are low-pass (responding only to stimuli below a certain rate) or band-pass (responding best to rates over a limited range)[12−19]. In the primary visual and auditory

cortical areas, most neurons respond maximally to repeated stimuli when they are presented at 7–12 pps, responding progressively more poorly at higher repetition rates.

Because the RRTFs of cortical neurons reflect sequences of excitatory and inhibitory cortical circuit events that are set in motion when the cortex is abruptly engaged by a stimulus[12,17, 18,20–25], one might predict that this elemental input sampling/recovery property of cortical circuits is immutable. However, a large body of evidence has indicated that temporal response properties of cortical neurons can be substantially altered by experience. For instance, the visual cortex of visually deprived animals responds poorly to stimuli repeated at rates above 5 pps[26,27]. Furthermore, psychophysical studies show that training can improve the ability to discriminate differences in rate, stimulus duration or interval separating successively presented stimuli, consistent with progressive improvements in cortical processing of temporal information[28–32]. For example, with practice, subjects are able to detect brief auditory or visual stimuli that are followed at progressively shorter times by intense masking stimuli, consistent with a several-fold training-induced decrease in cortical integration time[33,34]. Monkeys trained to detect changes in amplitude modulation rate show sharper and stronger cortical responses to the trained modulation rate[35], and this strengthening of cortical responses strongly correlates with improved task performance.

Such changes in temporal properties of cortical responses could result from plasticity of synaptic, intrinsic or network time constants. For example, plasticity of excitatory synapses onto inhibitory neurons[36–38] and of inhibitory synapses themselves[39] may shape the responses of cortical neurons to rapidly successive stimuli *in vivo*[40,41]. Additionally, presynaptic release probability contributes to the cortical response to successive inputs and shows experience-dependent plasticity[42,43]. Together these experiments indicate that the capacity of the cortex to respond to successive events in time is shaped by a succession of excitatory and inhibitory processes, whose dynamics can be modified by experience.

Results

In this study, NB activation was paired with temporally modulated acoustic stimuli to investigate plasticity of the cortical representation of time-varying information. Stimulating electrodes were chronically implanted in the right NB of 15 adult rats. After recovery, animals were placed in a sound-attenuation chamber, and trains of six tone bursts were paired with NB stimulation during daily sessions. Tone trains and NB stimulation occurred randomly every 8–40 seconds, repeated three- to four-hundred times per day for 20–25 days. Rats were unanesthetized and unrestrained throughout this procedure. The train repetition rate for each rat was fixed at 5, 7.5 or 15 pps. The tonal (carrier) frequency was varied randomly trial by trial. The seven carrier frequencies that were used extended across most of the frequency range represented in the primary auditory cortex (A1) of the rat. Twenty-four hours after the last pairing session, each animal was anesthetized, and the responses of A1 neurons were recorded from 30–60 microelectrode penetrations distributed evenly across A1. Frequency–intensity tuning curves and RRTFs were derived to characterize the spectral and temporal response properties of neurons in every penetration.

In naïve animals, at repetition rates up to about 9 pps, each brief tone generally evoked the same number of spikes from A1 neurons as did the first tone in the train (Fig. 1). At repetition rates from 9 to 14 pps, the number of spikes per tone fell off rapidly, and only neurons at rare sites responded at all to rates above 15 pps. In experimental rats, exposure to 15-pps stimuli at variable carrier frequencies paired with NB stimulation markedly altered the temporal responses of cortical neurons recorded all across A1. Although no specific response peak emerged at 15 pps, the cut-off rate of low-pass RRTFs in A1 rose significantly in most sampled neurons. In striking contrast to control rats, the average neuron in these samples responded

strongly to repetition rates between 10 and 20 pps (Fig. 2**a**). This increase in the neural response to 15-pps trains after pairing was highly significant ($p < 0.0001$; Fig. 2**c**). The high-rate slope of the average RRTF shifted up, reflecting a strong response improvement across a broad range of higher modulation frequencies (Fig. 2**a** and **c**).

To determine whether or not NB-induced temporal plasticity is specific to the repetition rate of the paired acoustic stimulus, 5-pps trains were paired with NB activation. The normalized response evoked by stimuli repeated at 5 pps was increased significantly ($p < 0.01$), resulting in RRTFs with bandpass characteristics (response maxima near 5 pps). The 5-pps pairing resulted in two distinct classes of cortical responsiveness to faster rates. In three of four animals, the entire RRTF was shifted leftward, causing significantly lower maximum following rates (Fig. 2**b** and **c**). In the remaining animal, 75% of sites showed strong facilitation to both 5- and 10-pps stimuli, but poor responses to stimuli repeated at 7.5 pps (data not shown). Thus NB-induced plasticity reliably increased the strength of the cortical response to stimuli presented at the paired rate, even though the RRTF plasticity took two different forms.

Pairing 7.5-pps stimuli at randomly varied carrier frequency with NB stimulation selectively strengthened the cortical response to stimuli repeated at rates near 7.5 pps. The mean RRTF again took a bandpass form, with a substantially stronger-than-normal response to modulated stimuli emerging at the paired stimulus rate (Fig. 2**c**). The normalized response of 1.2 indicates that 20% more spikes were evoked on average by each tone in the context of a 7-pps train compared to the same tone in isolation.

As reported previously, pairing tones at 15 pps with a constant carrier frequency of 9 kHz markedly enlarged the region of A1 representing 9 kHz in every animal[8]. Surprisingly, pairing NB stimulation with trains of 9-kHz tones repeated at 15 pps did not cause the rightward shift in the mean RRTF that resulted from pairing NB stimulation with multiple-frequency trains repeated at 15 pps. No significant alteration in the mean response to the paired repetition rate (15 pps) was detected in the population RRTF analysis (0.27 versus 0.28, $p > 0.5$; one-way ANOVA). Although it is unclear how topographic map reorganization and temporal plasticity are related, it is interesting to note that pairing random-frequency 15-pps trains with NB stimulation significantly increased the maximum stimulus following rate of cortical neurons, but did not systematically alter the A1 frequency map.

Discussion

Paired NB and sensory stimulation provides a simple model system for studying the rules that operate in the cortex to transform sensory input structure and schedules into distributed cortical response patterns. Previous studies focusing on the plasticity of the cortical representation of spectral information have demonstrated that cholinergic modulation is sufficient to shift A1 tuning curves toward the frequency paired with NB stimulation[8–10,44,45]. In this study, we used NB activation to explore temporal information processing, and we showed that the temporal response properties of A1 neurons can be altered markedly to refine or degrade the capacity of the cortex to respond to rapid successive input events. We also showed that this plasticity has a large capacity to exaggerate the representation of specific, heavily presented sensory input rates. Finally, we demonstrated that A1 neuronal networks can generate spectrally and temporally selective responses and that these networks can reorganize topographic representations of tone frequency with no evident change in the representation of temporal information, or vice versa, all as an apparent function of the spectrotemporal structures and schedules of sensory inputs.

This striking capacity for learning-based revision of the basic integration/segmentation times of the cortical processing machinery could result from plasticity of synaptic time constants, of

intrinsic temporal characteristics and/or of network dynamics[12,17,21,42,46]. Paired-pulse facilitation and slow inhibitory potentials, for example, almost certainly are important in the cortical recovery of responsiveness following any brief stimulation[12,23,24,40–42,47]. NB-induced plasticity will provide a powerful experimental approach for relating the cortical representation of temporal information to changes in basic cortical dynamics that shape the cortical responses to time-varying stimuli.

Methods

PREPARATION

Platinum bipolar stimulating electrodes were lowered 7 mm below the cortical surface, 3.3 mm lateral and 2.3 mm posterior to bregma in barbiturate-anesthetized female rats (~300 g) and cemented into place using sterile techniques approved under UCSF Animal Care Facility protocols. After two weeks of recovery, trains of six 25-ms tones were paired with 200 ms of NB electrical stimulation in a sound-shielded, calibrated test chamber (five days per week). The frequency of the tone was either one of seven frequencies (1.3, 2, 3, 5, 9, 14 or 19 kHz) or was fixed (9 kHz). Tone amplitude was 20–30 dB above the minimum rat hearing threshold[48]. In experiments using multiple carrier frequencies, the frequency of the tones within each train was constant, whereas the frequencies used from train to train were randomly varied. The tone pips in stimulus trains were presented in a given rat at 5, 7.5 or 15 pps. Electrical stimulation began with the onset of the fourth tone. The stimulating current level (70–150 µA) was the minimum necessary to desynchronize the EEG during slow-wave sleep for 1–2 seconds. Stimulation consisted of 100-pps capacitatively coupled biphasic pulses of 0.1-ms duration. Several microdialysis studies have shown that this stimulation protocol results in the release of cortical acetylcholine[49,50]. Either cholinergic antagonists or lesions of the cholinergic cells in the NB with 192 immunoglobulin G-saporin are sufficient to block this plasticity generated by NB stimulation[8,9]. Tonal and electrical stimuli did not evoke any observable behavioral responses (that is, they did not cause rats to stop grooming, or if sleeping, to awaken).

ELECTROPHYSIOLOGY

Twenty-four hours after the last pairing, animals were anesthetized with sodium pentobarbital, the right auditory cortex was surgically exposed, and neural responses were recorded with pary-lene-coated tungsten microelectrodes (FHC #070-02-01, 2 MΩ). Because we used barbiturate anesthesia, the modulation of responses recorded in this study may not be identical to the responses of awake animals. Penetration sites were chosen to evenly sample the cortical surface while avoiding blood vessels. To minimize the possibility of experimenter bias or response variability due to variable recording depth, at every penetration site the electrode was lowered to ~550 µm below the pial surface (layers 4/5), which yielded vigorous driven responses. Frequency/intensity response areas were reconstructed in detail by presenting 45 pure tone frequencies (50-ms duration, 3-ms ramps) at each of 15 sound intensities to the contralateral ear at a rate of 2 stimuli per s. The evoked spikes of a neuron or a small cluster of 2–5 neurons were collected at each site. Primary auditory cortex was defined on the basis of the short latency (8–20 ms) of its evoked neuronal spike responses and its continuous tonotopy. (Best frequency increases from posterior to anterior.) Responsive sites that had clearly discontinuous best frequencies, along with long-latency responses, high thresholds or very broad tuning were considered to be non-A1 sample sites and were not included in these sample data.

To determine the RRTF for each site, six tones (25 ms with 5-ms ramps, 70 dB SPL) were presented twelve times at each of sixteen repetition rates. To minimize adaptation effects, repetition rates were randomly interleaved, and two seconds of silence separated each train. The two-second interval between trains allowed the response strength to 0.5-pps trains to be

approximated. RRTFs were defined using the tone frequency of the seven presented during the pairing period that was closest to the best frequency of each site. To reduce the variability resulting from different numbers of neurons included in different 'multi-unit' responses recorded in this study, response amplitude was normalized using the number of spikes evoked at each site to an isolated tone. The normalized RRTF was defined as the average number of spikes evoked for each of the last five tones in the train divided by the number of spikes evoked by the first tone in the train. Thus, a normalized spike rate of one indicates that, at the given repetition rate, each of the tones in the train, on average, evoked the same number of spikes as the first tone. Values greater than one indicate facilitation; values less than one indicate response adaptation. Only spikes occurring from 5–40 ms after each tone onset were used to calculate the RRTF. The RRTF data could not be viewed on-line and were analyzed only after each experiment was completed. All analyses were automatized and therefore were not subject to experimenter bias or error. The effect of NB pairing on mean RRTF across all conditions was determined with analysis of variance; pairwise comparisons were analyzed by Fisher's PLSD (protected least significant differences) test.
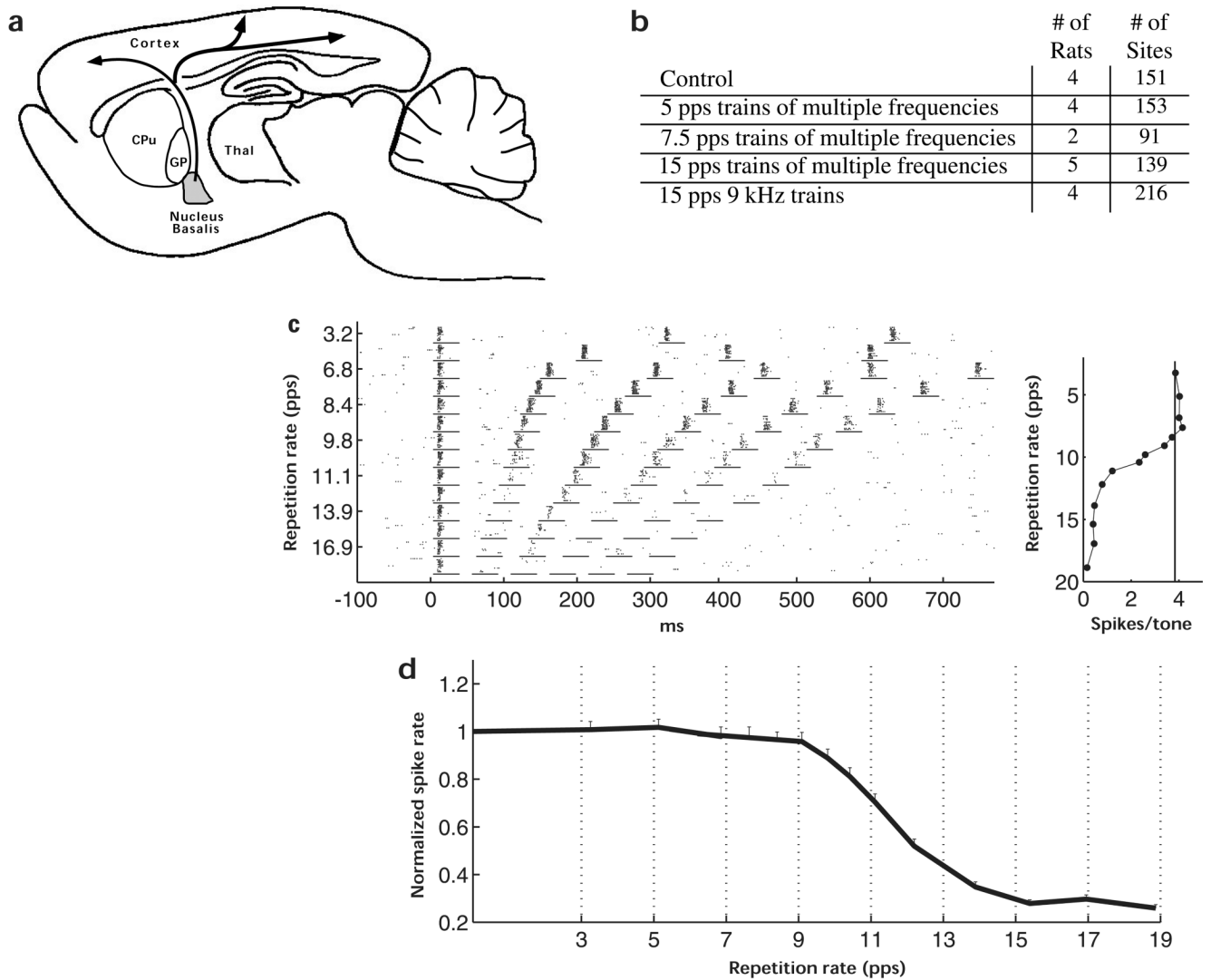
Acknowledgments

References

1. Bakin JS, Weinberger NM. Classical conditioning induces CS-specific receptive field plasticity in the auditory cortex of the guinea pig. Brain Res 1990;536:271–286. [PubMed: 2085753]

2. Bakin JS, South DA, Weinberger NM. Induction of receptive field plasticity in the auditory cortex of the guinea pig during instrumental avoidance conditioning. Behav. Neurosci 1996;110:905–913. [PubMed: 8918994]

3. Recanzone GH, Merzenich MM, Jenkins WM. Frequency discrimination training engaging a restricted skin surface results in an emergence of a cutaneous response zone in cortical area 3a. J. Neurophysiol 1992;67:1057–1070. [PubMed: 1597697]

4. Recanzone GH, Merzenich MM, Jenkins WM, Grajski KA, Dinse HR. Topographic reorganization of the hand representation in cortical area 3b owl monkeys trained in a frequency-discrimination task. J. Neurophysiol 1992;67:1031–1056. [PubMed: 1597696]

5. Recanzone GH, Schreiner CE, Merzenich MM. Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. J. Neurosci 1993;13:87–103. [PubMed: 8423485]

6. Weinberger NM. Learning-induced changes of auditory receptive fields. Curr. Opin. Neurobiol 1993;3:570–577. [PubMed: 8219724]

7. Xerri C, Coq JO, Merzenich MM, Jenkins WM. Experience-induced plasticity of cutaneous maps in the primary somatosensory cortex of adult monkeys and rats. J. Physiol. (Paris) 1996;90:277–287. [PubMed: 9116682]

8. Kilgard MP, Merzenich MM. Cortical map reorganization enabled by nucleus basalis activity. Science 1998;279:1714–1718. [see comments]. [PubMed: 9497289]

9. Bakin JS, Weinberger NM. Induction of a physiological memory in the cerebral cortex by stimulation of the nucleus basalis. Proc. Natl. Acad. Sci. USA 1996;93:11219–11224. [see comments]. [PubMed: 8855336]

10. Bjordahl TS, Dimyan MA, Weinberger NM. Induction of long-term receptive field plasticity in the auditory cortex of the waking guinea pig by stimulation of the nucleus basalis. Behav. Neurosci 1998;112:467–479. [PubMed: 9676965]

11. Mesulam MM, Mufson EJ, Wainer BH, Levey AI. Central cholinergic pathways in the rat: an overview based on an alternative nomenclature (Ch1–Ch6). Neuroscience 1983;10:1185–1201. [PubMed: 6320048]

12. De Ribaupierre F, Goldstein MH Jr, Yeni-Komshian G. Cortical coding of repetitive acoustic pulses. Brain Res 1972;48:205–225. [PubMed: 4645205]

13. Tolhurst DJ, Movshon JA. Spatial and temporal contrast sensitivity of striate cortical neurones. Nature 1975;257:674–675. [PubMed: 1186842]

14. Movshon JA, Thompson ID, Tolhurst DJ. Spatial and temporal contrast sensitivity of neurones in areas 17 and 18 of the cat's visual cortex. J. Physiol. (Lond.) 1978;283:101–120. [PubMed: 722570]

15. Schreiner CE, Urbas JV. Representation of amplitude modulation in the auditory cortex of the cat. II. Comparison between cortical fields. Hear. Res 1988;32:49–63. [PubMed: 3350774]

16. Schreiner, CE.; Langer, G. Auditory Function. Edelman, G.; Gall, E.; Cowan, M., editors. New York: John Wiley; 1986. p. 337-362.

17. Eggermont JJ, Smith GM. Synchrony between single-unit activity and local field potentials in relation to periodicity coding in primary auditory cortex. J. Neurophysiol 1995;73:227–245. [PubMed: 7714568]

18. Gaese BH, Ostwald J. Temporal coding of amplitude and frequency modulation in the rat auditory cortex. Eur. J. Neurosci 1995;7:438–450. [PubMed: 7773441]

19. Hawken MJ, Shapley RM, Grosof DH. Temporal-frequency selectivity in monkey visual cortex. Vis. Neurosci 1996;13:477–492. [PubMed: 8782375]

20. De Ribaupierre F, Goldstein MHJ, Yeni-Komshian G. Intracellular study of the cat's primary auditory cortex. Brain Res 1972;48:185–204. [PubMed: 4345594]

21. Kenmochi M, Eggermont JJ. Autonomous cortical rhythms affect temporal modulation transfer functions. Neuroreport 1997;8:1589–1593. [PubMed: 9189897]

22. Chance FS, Nelson SB, Abbott LF. Synaptic depression and the temporal response characteristics of V1 cells. J. Neurosci 1998;18:4785–4799. [PubMed: 9614252]

23. Brosch M, Schreiner CE. Time course of forward masking tuning curves in cat primary auditory cortex. J. Neurophysiol 1997;77:923–943. [PubMed: 9065859]

24. Schreiner CE, Mendelson J, Raggio MW, Brosch M, Krueger K. Temporal processing in cat primary auditory cortex. Acta Otolaryngol. Suppl. (Stockh.) 1997;532:54–60. [PubMed: 9442845]

25. Cartling B. Control of computational dynamics of coupled integrate-and-fire neurons. Biol. Cybern 1997;76:383–395. [PubMed: 9237364]

26. Beaulieu C, Cynader M. Effect of the richness of the environment on neurons in cat visual cortex. II. Spatial and temporal frequency characteristics. Dev. Brain Res 1990;53:82–88. [PubMed: 2350884]

27. Pizzorusso T, Fagiolini M, Porciatti V, Maffei L. Temporal aspects of contrast visual evoked potentials in the pigmented rat: effect of dark rearing. Vision Res 1997;37:389–395. [PubMed: 9156170]

28. Woodrow H. The effect of practice upon time-order errors in the comparison of temporal intervals. Psychol. Rev 1935;42:127–152.

29. Neisser U, Hirst W. Effect of practice on the identification of auditory sequences. Percept. Psychophys 1974;15:391–398.

30. Recanzone GH, Jenkins WM, Hradek GT, Merzenich MM. Progressive improvement in discriminative abilities in adult owl monkeys performing a tactile frequency discrimination task. J. Neurophysiol 1992;67:1015–1030. [PubMed: 1597695]

31. Nagarajan SS, Blake DT, Wright BA, Byl N, Merzenich MM. Practice-related improvements in somatosensory interval discrimination are temporally specific but generalize across skin location, hemisphere, and modality. J. Neurosci 1998;18:1559–1570. [PubMed: 9454861]

32. Wright BA, Buonomano DV, Mahncke HW, Merzenich MM. Learning and generalization of auditory temporal-interval discrimination in humans. J. Neurosci 1997;17:3956–3963. [PubMed: 9133413]

33. Ahissar M, Hochstein S. Attentional control of early perceptual learning. Proc. Natl. Acad. Sci. USA 1993;90:5718–5722. [PubMed: 8516322]

34. Merzenich MM, et al. Temporal processing deficits of language-learning impaired children ameliorated by training. Science 1996;271:77–81. [see comments]. [PubMed: 8539603]

35. Recanzone GH, Merzenich MM, Schreiner CE. Changes in the distributed temporal response properties of SI cortical neurons reflect improvements in performance on a temporally based tactile discrimination task. J. Neurophysiol 1992;67:1071–1091. [PubMed: 1597698]

36. Charpier S, Behrends JC, Triller A, Faber DS, Korn H. "Latent" inhibitory connections become functional during activity-dependent plasticity. Proc. Natl. Acad. Sci. USA 1995;92:117–120. [PubMed: 7816799]

37. Grabauskas G, Bradley RM. Tetanic stimulation induces short-term potentiation of inhibitory synaptic activity in the rostral nucleus of the solitary tract. J. Neurophysiol 1998;79:595–604. [PubMed: 9463424]

38. Hollrigel GS, Morris RJ, Soltesz I. Enhanced bursts of IPSCs in dentate granule cells in mice with regionally inhibited long-term potentiation. Proc. R. Soc. Lond. B Biol. Sci 1998;265:63–69.

39. Fischer TM, Blazis DE, Priver NA, Carew TJ. Metaplasticity at identified inhibitory synapses in Aplysia. Nature 1997;389:860–865. [see comments]. [PubMed: 9349819]

40. Buonomano DV, Hickmott PW, Merzenich MM. Context-sensitive synaptic plasticity and temporal-to-spatial transformations in hippocampal slices. Proc. Natl. Acad. Sci. USA 1997;94:10403–10408. [PubMed: 9294223]

41. Buonomano DV, Merzenich MM. Temporal information transformed into a spatial code by a neural network with realistic properties. Science 1995;267:1028–1030. [PubMed: 7863330]

42. Markram H, Tsodyks M. Redistribution of synaptic efficacy between neocortical pyramidal neurons. Nature 1996;382:807–810. [see comments]. [PubMed: 8752273]

43. Tsodyks MV, Markram H. The neural code between neocortical pyramidal neurons depends on neurotransmitter release probability [published erratum appears in *Proc. Natl. Acad. Sci. USA* **94**, 5495, 1997]. Proc. Natl. Acad. Sci. USA 1997;94:719–723. [PubMed: 9012851]

44. Metherate R, Weinberger NM. Acetylcholine produces stimulus-specific receptive field alterations in cat auditory cortex. Brain Res 1989;480:372–377. [PubMed: 2713663]

45. McKenna TM, Ashe JH, Weinberger NM. Cholinergic modulation of frequency receptive fields in auditory cortex: I. Frequency-specific effects of muscarinic agonists. Synapse 1989;4:30–43. [PubMed: 2672402]

46. Dinse HR, et al. Low-frequency oscillations of visual, auditory and somatosensory cortical neurons evoked by sensory stimulation. Int. J. Psychophysiol 1997;26:205–227. [PubMed: 9203004]

47. Abbott LF, Varela JA, Sen K, Nelson SB. Synaptic depression and cortical gain control. Science 1997;275:220–224. [see comments]. [PubMed: 8985017]

48. Kelly JB, Masterton B. Auditory sensitivity of the albino rat. J. Comp. Physiol. Psychol 1977;91:930–936. [PubMed: 893752]

49. Jimenez-Capdeville ME, Dykes RW, Myasnikov AA. Differential control of cortical activity by the basal forebrain in rats: a role for both cholinergic and inhibitory influences. J. Comp. Neurol 1997;381:53–67. [PubMed: 9087419]

50. Rasmusson DD, Clow K, Szerb JC. Frequency-dependent increase in cortical acetylcholine release evoked by stimulation of the nucleus basalis magnocellularis in the rat. Brain Res 1992;594:150–154. [PubMed: 1467935]

a

b

	# of Rats	# of Sites
Control	4	151
5 pps trains of multiple frequencies	4	153
7.5 pps trains of multiple frequencies	2	91
15 pps trains of multiple frequencies	5	139
15 pps 9 kHz trains	4	216

c

d

Fig. 1.
Response of rat auditory cortex neurons to repeated stimuli. **(a)** Schematic diagram of the projection of nucleus basalis to the neocortex. **(b)** Number of rats and penetrations for each experimental condition. **(c)** Dot rasters and repetition-rate transfer function (RRTF) of primary auditory cortex (A1) neurons from a naïve (control) rat. Each dot represents a single action potential. The short horizontal lines indicate the spike-collection windows that were used to generate the RRTF. The RRTF quantifies the generally low-pass nature of the responses of A1 cortical neurons to these pulsed stimuli in the rat. The solid vertical line in the RRTF shows the average number of spikes evoked by the first tone in the train. **(d)** Mean normalized RRTF for all penetrations recorded from normal (control) rats. Error bars indicate standard errors.
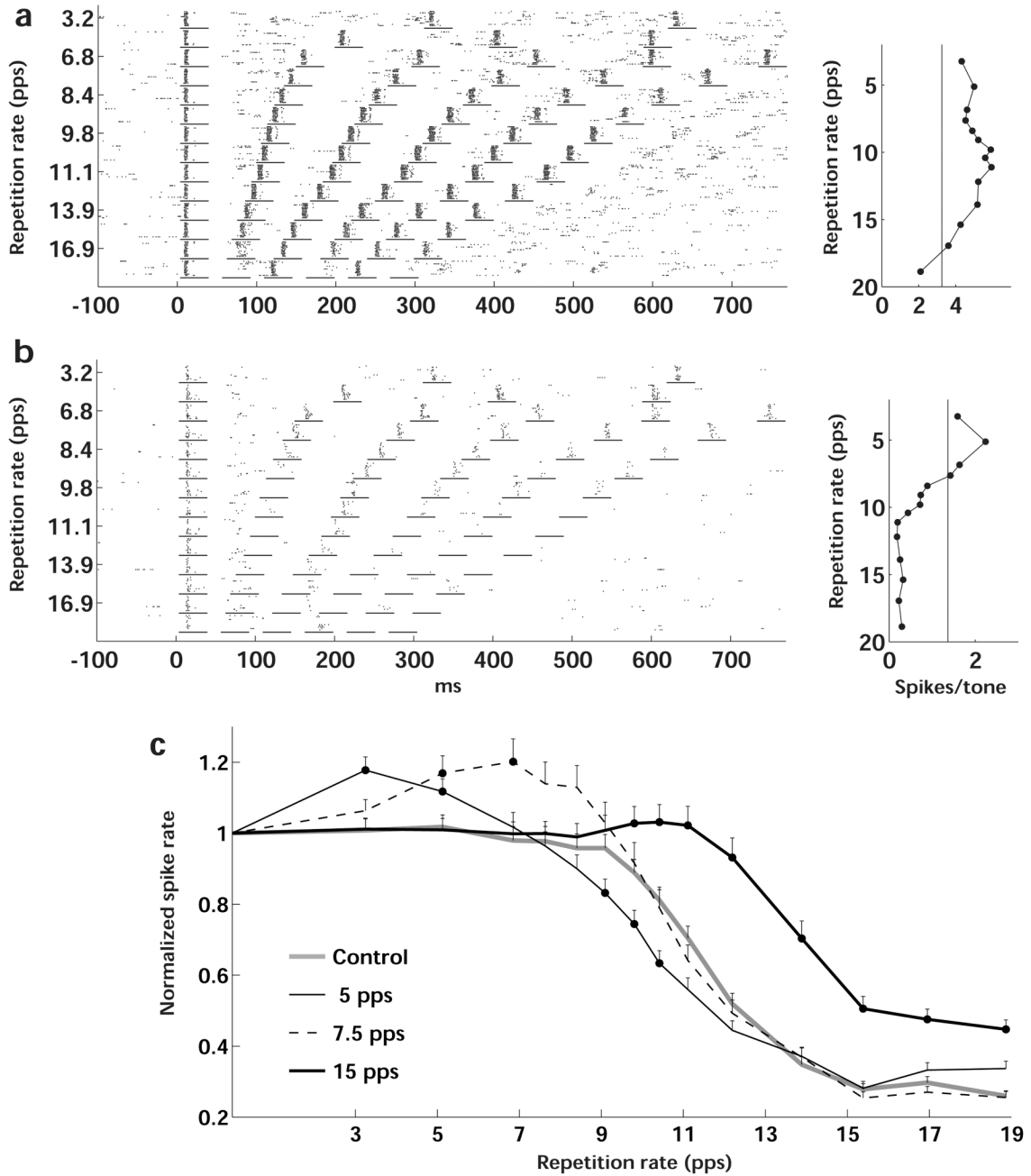
Fig. 2.
Temporal response plasticity induced by nucleus basalis stimulation. **(a)** Response to repeated tones after pairing NB stimulation with 15-pps trains applied at 7 different carrier frequencies. The maximum following rate and the range over which strong stimulus-by-stimulus responses were evoked was increased all across A1 in this sample, compared to controls. **(b)** Response to repeated tones after pairing NB stimulation with 5-pps trains of tones at a randomly varied carrier frequency. The maximum following rate was significantly decreased compared to controls. **(c)** Mean normalized RRTFs for penetrations recorded from animals that received NB stimulation paired with 5-, 7.5- or 15-pps trains of tone (carrier) frequencies that varied from train to train, compared to control RRTFs. The RRTF of each site was normalized using

the number of spikes evoked by the first tone in each train. Error bars indicate standard error. The rates that were significantly different from controls are marked with dots (one-way ANOVA, Fisher's PLSD, $p < 0.05$).