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Induction of a physiological memory in the cerebral cortex by stimulation of the nucleus basalis

(receptive field plasticity/auditory cortex/associative learning)

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ABSTRACT **Auditory cortical receptive field plasticity produced during behavioral learning may be considered to constitute "physiological memory" because it has major characteristics of behavioral memory: associativity, specificity, rapid acquisition, and long-term retention. To investigate basal forebrain mechanisms in receptive field plasticity, we paired a tone with stimulation of the nucleus basalis, the main subcortical source of cortical acetylcholine, in the adult guinea pig. Nucleus basalis stimulation produced electroencephalogram desynchronization that was blocked by systemic and cortical atropine. Paired tone/nucleus basalis stimulation, but not unpaired stimulation, induced receptive field plasticity similar to that produced by behavioral learning. Thus paired activation of the nucleus basalis is sufficient to induce receptive field plasticity, possibly via cholinergic actions in the cortex.**

The cerebral neocortex is generally acknowledged to be a major repository of memories. However, little is known about the mechanisms by which information is stored in the neocortex. A considerable body of evidence has implicated the cholinergic system, including behavioral studies of memory and memory dysfunction (1–5), and related neuroplasticity at the levels of neural circuits and cells (6–13). For example, blockade of cholinergic function, either by pharmacological means or by lesions of the nucleus basalis (14–17) (NB; the major source of cortical acetylcholine (ACh) (18–22), can impair the acquisition of memories.

While demonstrations of impaired memory following interference with cholinergic system function are important, the induction of cortical memory by direct activation of the cholinergic system would considerably strengthen the cholinergic hypothesis and provide a more direct approach to understanding the mechanisms by which normal learning situations produce the cortical storage of experience. Unfortunately there are currently no means by which any neurobiological measure can reveal the actual "contents" (detailed experience-based information) of memories.

However, there is a cortical neurophysiological phenomenon that bears striking similarities to memory—learning-induced receptive field (RF) plasticity. Classical conditioning (tone-shock pairing) specifically "retunes" frequency RFs in the primary auditory cortex to favor the processing of the frequency of the tone conditioned stimulus (CS+). Neuronal discharges to the CS+ frequency increase, in contrast to responses to other frequencies, including that of the pretraining best frequency (BF; the frequency that elicits the greatest response), which decrease. These coordinated and opposing changes can produce a shift of frequency tuning toward or even to the CS+ frequency, so that it becomes the new BF of a cortical cell (23).

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The characteristics of learning-induced RF plasticity have proven to be strikingly similar to the characteristics of at least some forms of memory. RF plasticity is (*i*) associative (requires stimulus pairing), (*ii*) highly specific (can be limited to the CS+ frequency ± 0.05 octaves), (*iii*) discriminative (facilitation of the CS+ frequency but depression of a nonreinforced CS− frequency), (*iv*) develops very rapidly (five trials or less), and (*v*) is long lasting (retained for 8 weeks, the longest interval studied) (24–27). Therefore, we refer to it as "physiological memory," to distinguish it from the actual contents of behaviorally delineated memory.

This learning-induced RF plasticity involves specific cortical mechanisms, as the major subcortical source of frequency-specific input to the auditory cortex, the ventral medial geniculate nucleus of the thalamus, fails to develop long-term RF plasticity (28). We proposed a model in which the convergence in the auditory cortex of acoustic frequency information and acetylcholine acting at muscarinic receptors is sufficient to induce RF plasticity during learning (29). This model has been supported by subsequent findings that RF plasticity can be produced by direct application of muscarinic agonists to the auditory cortex, that this plasticity is blocked by atropine (30), and that neurons in the NB develop learning-induced discharge plasticity before such plasticity develops in the auditory cortex (31). The similarities of RF plasticity to memory, and the findings that both RF plasticity and memory storage involve the cholinergic system, led us to investigate the hypothesis that activation of the NB cholinergic system is *sufficient* to induce RF plasticity similar to that induced by normal learning experiences. We approached this problem by pairing a tone with electrical stimulation of the NB. Failure to obtain RF plasticity would constitute evidence against the hypothesis.

METHODS

Subjects and Preparation. Adult male Sprague–Dawley rats (366–516 g, 2.5–4.5 months old), while under sodium pentobarbital anesthesia (55 mg/kg, i.p.), had a pedestal of dental acrylic attached to the calvaria and a stimulating electrode implanted in the left basal forebrain. (For a complete description of methods, see ref. 23). Several days after recovery, the experimental protocol was conducted while subjects were under urethane anesthesia (4.24 mg/kg, i.p.; ethyl carbamate, Sigma). The subject was affixed to a metal frame via the pedestal. A craniotomy was performed over the left auditory cortex and the dura mater was removed. A Parlyene-C insulated tungsten microelectrode (≈1.0 MΩ; Microprobe, Clarks-

Abbreviations: NB, nucleus basalis; RF, receptive field; CS, conditioned stimulus; BF, best frequency; EEG, electroencephalogram.

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burg, MD) was lowered into the middle or deep cortical layers (mean depth = 498 microns, range 397–787 microns). The entire apparatus was contained within an acoustic chamber. Heart rate and respiration were monitored continuously. All procedures were performed in accordance with University of California Irvine Animal Research Committee and National Institutes of Health animal welfare guidelines.

Stimulation, Recording, and RF Determination. Pure tone bursts were generated by a computer-controlled system and delivered to the ear contralateral to the recording site via a calibrated speaker located at the entrance to the ear canal. The RF was defined as the responses to a frequency tone sequence (11 frequencies, 50-ms tone duration, 550-ms intertone interval, 5-ms rise/fall time, repeated 20 times) delivered at a single mid-level intensity (mean level = 46 dB, range = 30–60 dB). Frequencies were selected to minimally span the particular cell's RF, and thus varied across recording sites. Thus, computation of group RF changes required normalization across frequencies (see *Results* for details).

Neuronal activity was amplified (Dagan Instruments, Minneapolis) and filtered for recording of unit cluster activity (0.3–3.0 kHz), voltage discriminated (>3:1 signal/noise ratio), and waveforms were continually monitored. The electroencephalogram (EEG; 0.3–300 Hz) was recorded from the same microelectrode and written out on a Grass Instruments (Quincy, MA) model 7 polygraph. The computer also controlled a Grass Instruments S88 stimulator connected to the NB electrode via stimulus isolation units. A computer stored the times of occurrence of acoustic stimuli, NB stimulation, and action potentials for use in quantitative data analysis.

Data Analysis. Frequency RFs were quantified by determining the average discharge during a temporal window set to minimally frame the auditory response to each frequency. A typical window was 40 ms in duration beginning 10 ms after tone onset. Selected windows did not differ between paired and unpaired groups (Unpaired t test, $P > 0.05$). Tone-evoked activity was calculated by subtracting the average discharge obtained during a pretone period (500 ms) from the average discharge obtained during the window.

For each subject, the response magnitudes of RFs were normalized by calculating a percent of total spikes measure for each tone:

$$\%\text{ of total spikes tone ``x'' } = \frac{[\text{average rate of tone ``x''}]}{[\text{total average rate of all tones}]} \times 100.$$

RF difference functions were calculated by subtracting the percent of total spike RF of the preperiod from the same measure for each of the posttreatment periods.

The effectiveness of NB control over the EEG was quantified by measuring the amplitude of the EEG prior to and after the onset of a NB stimulus train:

$$\text{NB stimulation effect} = \frac{\text{EEG amplitude 2 s before onset of NB stimulation}}{\text{EEG amplitude 2 s after onset of NB stimulation}}.$$

Values >1 indicate that NB stimulation produced reduced EEG amplitude (desynchrony). Measurements were made directly from the polygraph write-out and were converted to microvolts by dividing by the known amplitude of a 100-μV calibration pulse.

Protocol. The subjects were divided into two groups, paired ($n = 8$) or unpaired ($n = 5$). At the start of the session, the NB was stimulated to determine the current level that would produce consistent cortical EEG desynchrony (32). The average current level was 270 μA, range, 150–500 μA (biphasic 0.2 ms square waves, 200 Hz, for a total train duration of 500 ms). This stimulation was not aversive because the subjects were anesthetized and exhibited no cardiac responses to stimulation, and the same stimulation parameters applied to waking subjects did not produce any behavioral or autonomic responses (N.M.W., T. Bjordahl, and M. Dimyan, unpublished observations).

Next, the RF was determined several times to insure stability. Then, a frequency that was not the BF was selected as the CS during training. Paired subjects received forty trials of tone paired with NB stimulation (CS = 1.0 s, NB stimulation = 500 ms, CS–NB interval = 750 ms, for a CS–NB overlap of 250 ms, mean intertrial intervals CS–CS onset = 40 s, range = 20–60 s). Unpaired subjects received 40 (intermixed) trials each of the CS and NB stimulation (all parameters identical except mean CS–NB interval = 20 s). RFs were obtained immediately after the last training trial, and at intervals of 10, 20, and 30 min posttraining. Major features of the protocol are illustrated in Fig. 2*A*.

To determine whether or not the EEG desynchrony induced by NB stimulation involved muscarinic receptors, the following procedure was performed. After the completion of the protocol, some subjects received additional trains of NB stimulation before and after either systemic injections ($n = 4$, 0.25–2.5 mg/kg) or direct cortical application ($n = 2$, 100–500 μM) of atropine sulfate. Ratios of EEG amplitude were calculated as described above for NB stimulation and values obtained postatropine were compared with values obtained immediately prior to atropine administration.

Marking lesions were made at the NB electrode and the brains were processed for routine frozen section histology and stained with cresyl violet.

RESULTS

EEG Desynchronization by NB Stimulation. All electrode placements were histologically verified to be in the NB, globus pallidus, or entopeduncular nucleus, all of which contain cholinergic cells that project to the cerebral cortex (33–35). Typical records of NB-induced EEG desynchrony are presented in Fig. 1*A*. The average current was not significantly different between paired and unpaired groups (df = 10, $t = 0.386$, $P > 0.05$). Further, there was no significant difference between groups in the amount of NB-induced EEG desynchrony (df = 473, unpaired t test, $t = -1.413$, $P > 0.05$). Therefore, prior to training, there was no difference in the effectiveness of the NB stimulation between groups.

The cholinergic nature of the NB activation was evident from blockade of EEG desynchronization by the administration of atropine sulfate, both systemically and directly to the auditory cortex (Fig. 1*B*). Prior to atropine administration, NB stimulation produced desynchrony in each case (all individual one-sample t tests, $P < 0.05$; single group t test, testing mean = 1, $t(29) = 9.912$, $P < 0.0001$). In each case, EEG desynchrony was blocked following atropine administration (all individual one-sample t tests, $P > 0.05$; single group t test, $t(29) = 0.789$, $P > 0.05$). The direct cortical blockade of NB-elicited desynchronization indicates that atropine had local effects in the auditory cortex. Nonspecific injection effects were controlled by injections of saline following NB stimulation in three additional control subjects. In no case did saline injections reduce NB-induced desynchrony (all individual one-sample t tests for pre and post-saline injection $P \leq 0.01$, indicating desynchronization, and group statistics preinjection $t(15) = 7.214$, $P < 0.001$, postinjection $t(15) = 6.185$, $P < 0.01$).

RF Plasticity. Pairing produced CS-specific RF plasticity, similar to that observed previously in awake animals following behavioral training (23–27). In particular, conditioning could cause a long-lasting increase in response to the CS frequency

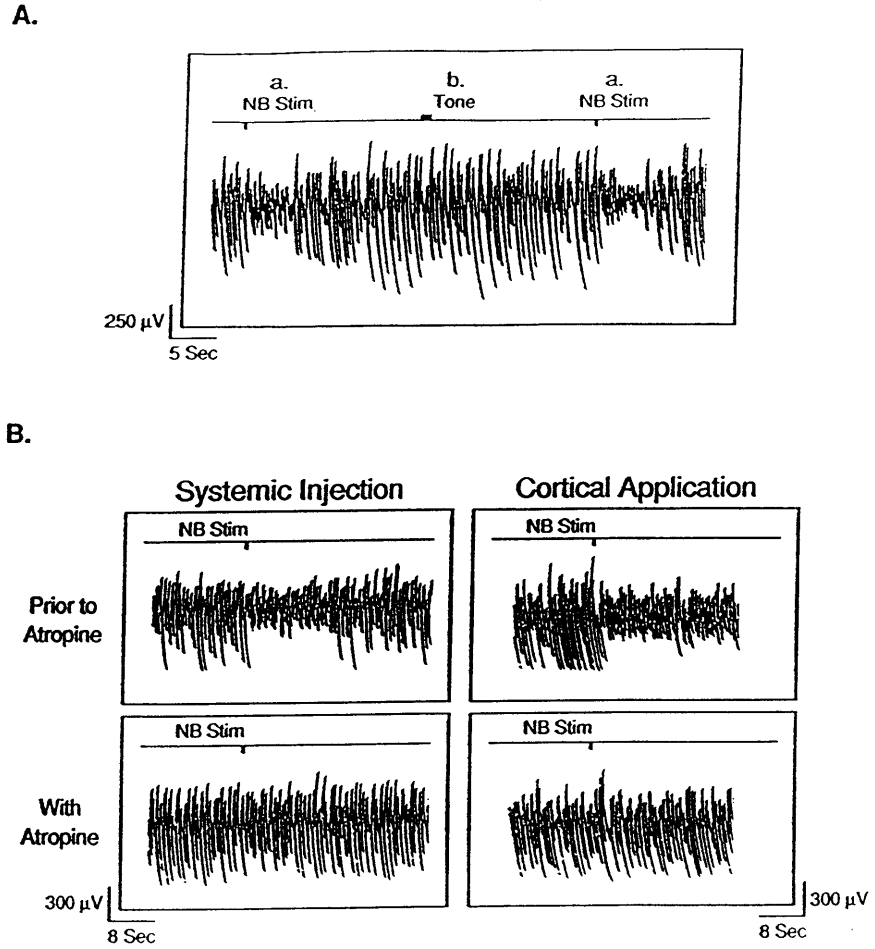

FIG. 1. (*A*) NB stimulation produces EEG desynchrony. Prior to NB stimulation, the EEG was characterized by large amplitude slow wave potentials. NB stimulation [down marks on time line (*a* and *a'*): 250 μA, 200 Hz for 500 ms] produced a bout of EEG desynchrony lasting ≈6 s. Presentation of a tone (*b*, upmark on time line: 16.6 kHz, 60 dB, for 1 s) had no effect on the EEG state. (*B*) Atropine blocked the EEG desynchrony induced by NB stimulation (bottom row traces) when administered either systemically (15 min following 25 mg/kg atropine sulfate, *Left*) or locally to the cortical surface (60 min following 300 μM atropine, *Right*).

and decrease in response to the BF. Examples are presented in Fig. 2. In a case illustrated (Fig. 2*B*), the BF was 6.0 kHz prior to conditioning, with decreasing responsiveness to lower and higher frequencies. The CS was selected to be 4.0 kHz, a frequency with a reduced response in the RF. Following conditioning, the RF had changed, and was characterized by a smooth increase in response magnitude building to the BF of 6.0 kHz (Fig. 2*C*). The contribution of each frequency to the overall RF is quantified in the tuning curves (Fig. 2*D*). Subtracting the pre-RF from the post-RF revealed that the largest increase was at the frequency of the CS and that the largest decrease was at the frequency of the BF (Fig. 2*E*).

CS specific RF plasticity, consisting of an increase in response to the frequency of the CS and a decrease in response to the pretraining BF and other frequencies, was found in six of eight subjects. In three of the six cases, these opposing changes were sufficient to produce a shift of tuning so that the frequency of the CS became the new BF after training (Fig. 2 *F* and *G*). Like classical conditioning, NB induced RF plasticity is also associative, as specific increases or shifts of tuning toward the frequency of the CS did not develop in unpaired subjects (Fig. 2 *H* and *I*).

To directly compare the effect of paired or unpaired training on the specificity of changes in tuning curves, we computed group RF difference functions (posttraining RF minus pretraining RF) for each period (Immediate, 10, 20, and 30 min). Because (as noted in *Methods*) subjects had different absolute frequencies, each difference function was normalized to the nearest one-third octave centered on the CS frequency, and then average group difference functions were calculated (23). The associative effects were determined by subtracting the unpaired group RF difference function for each time period from the paired group RF difference function for the corresponding period. The results are presented in Fig. 3*A*. Note that the associative effect is a maximal increase at the frequency of the CS, with no change or mainly a decrease at frequencies ±0.33 octaves. This CS-specific RF plasticity was observed immediately after training and was present at all later time points, although reduced at the 30 min retention interval.

A statistical comparison of the magnitude of change at the CS frequency relative to the BF for paired versus the nonpaired treatments was achieved by determining changes in the ratio of responses to the CS frequency and the posttraining BF. The change in CS/BF ratio was calculated as follows for each posttime period using the percent of total spikes values of the respective tones:

$$\Delta\text{CS/BF} = \frac{[(\text{post-CS/post-BF}) - (\text{pre-CS/pre-BF})]}{(\text{pre-CS/pre-BF})} \times 100.$$

Ratios were determined for each posttreatment period and the pretreatment ratio was subtracted from each of these. Increases in ΔCS/BF indicate a relative increase in the magni-

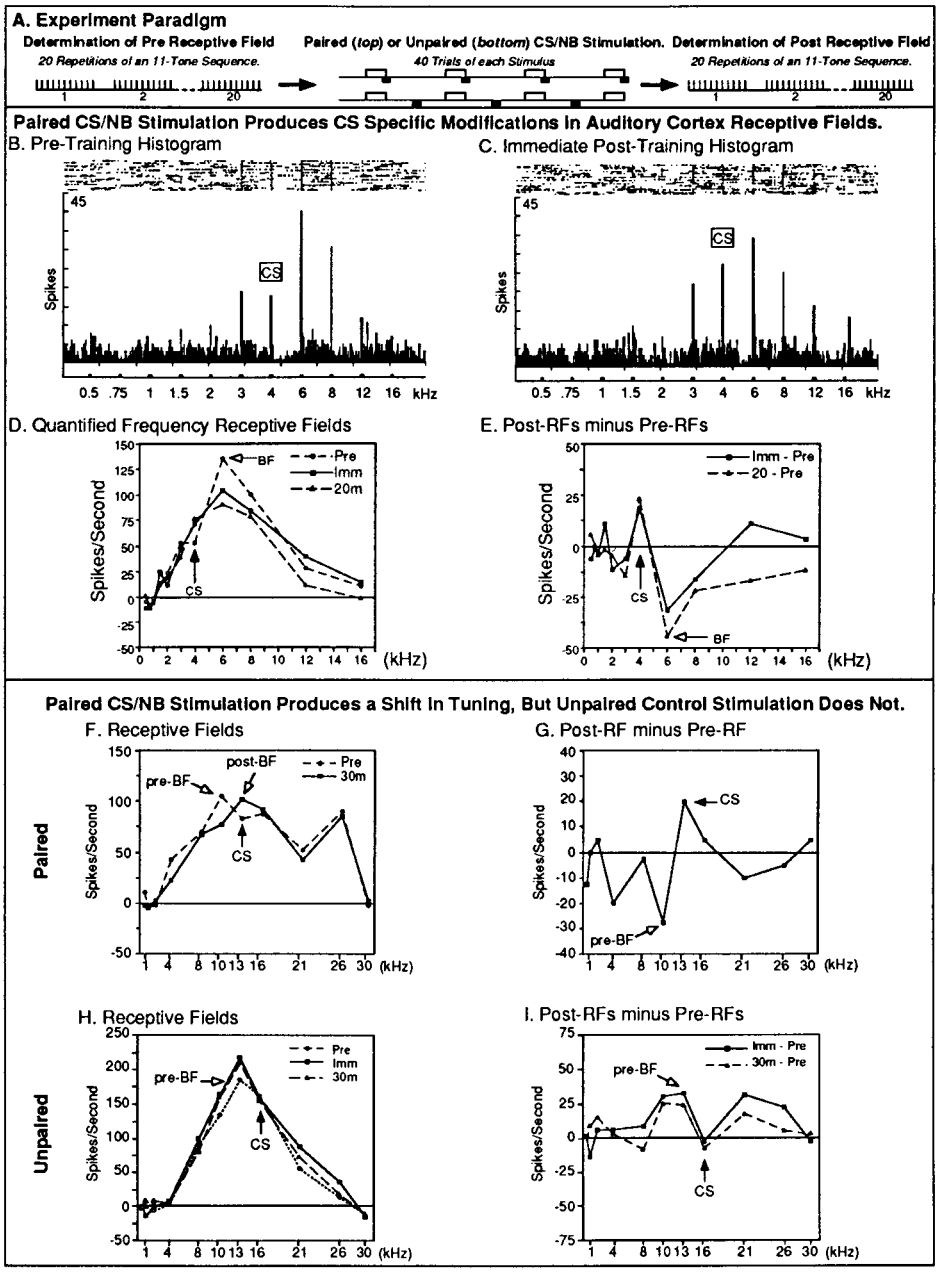

FIG. 2. Paired CS/NB stimulation produces CS-specific modification of auditory cortex RF. (*A*) A summary of the experimental protocol. (*B*) Prepairing peristimulus histogram (PSTH). (*C*) Immediate postpairing PSTH. (*D*) Quantified RFs for prepairing (Pre), immediate (Imm), and 20 min (20 m) postpairing. (*E*) Corresponding RF difference functions (post- minus pre-RFs) reveal that pairing produced an increase in response that was highly specific to the frequency of the CS (filled arrowhead); it was the only frequency that showed a consistent increase in the RFs. In addition, there was a decrease in response to the prepairing BF (6.0 kHz, open arrowhead) and its adjacent higher frequency. (*F*) RF from another subject in the paired group, showing an example of a CS-specific shift in tuning. Prior to pairing (Pre) the BF was 10.0 kHz (open arrowhead). Thirty minutes after pairing (30 m), the BF had shifted to the frequency of the CS, 13.3 kHz (filled arrowhead). (*G*) The RF difference function for the date shown in *F* shows the specific increase in response to the frequency of the CS, and decreases in response to other frequencies, including the pretraining BF. (*H*) Unpaired CS/NB stimulation does not produce CS-specific plasticity. Prior to training, the pre-BF was 13.0 kHz (open arrowhead). Tuning was unchanged following 40 trials of unpaired CS (16.0 kHz, filled arrowhead) and NB stimulation; shown are RFs immediately (Imm) and 30 min (30 m) after training. (*I*) The RF difference functions for the RFs shown in *H* show a slight increase to non-CS frequencies, with no change in response to the CS frequency (filled arrowhead) immediately and 30 min posttraining.

tude of response to the CS frequency after treatment while decreases indicate the converse.

Prior to pairing, the average CS/BF ratio of the paired subjects was not significantly different from the average CS/BF ratio of the unpaired subjects (Mann–Whitney test, $U = 6$, $P > 0.05$), indicating that prior to treatment the CS frequency was equally effective for both groups. Therefore within group analyses could be performed. For the paired group, the ΔCS/BF was significantly increased immediately after pairing (Wilcoxin test, $P = 0.01$) and this effect was maintained at 10 ($P = 0.01$) and 20 ($P = 0.01$) min posttraining, but not at 30 min ($P > 0.05$). In contrast, the ΔCS/BF of unpaired subjects did not change significantly at any time period (Wilcoxin test, all P values > 0.05). Group comparisons for each post-treatment period are presented in Fig. 3*B*. Statistical comparisons of the differences between the paired and unpaired groups showed significant differences immediately (Mann–Whitney test, $P < 0.05$), 10 min ($P < 0.05$), and 20 min ($P < 0.01$) posttreatment.

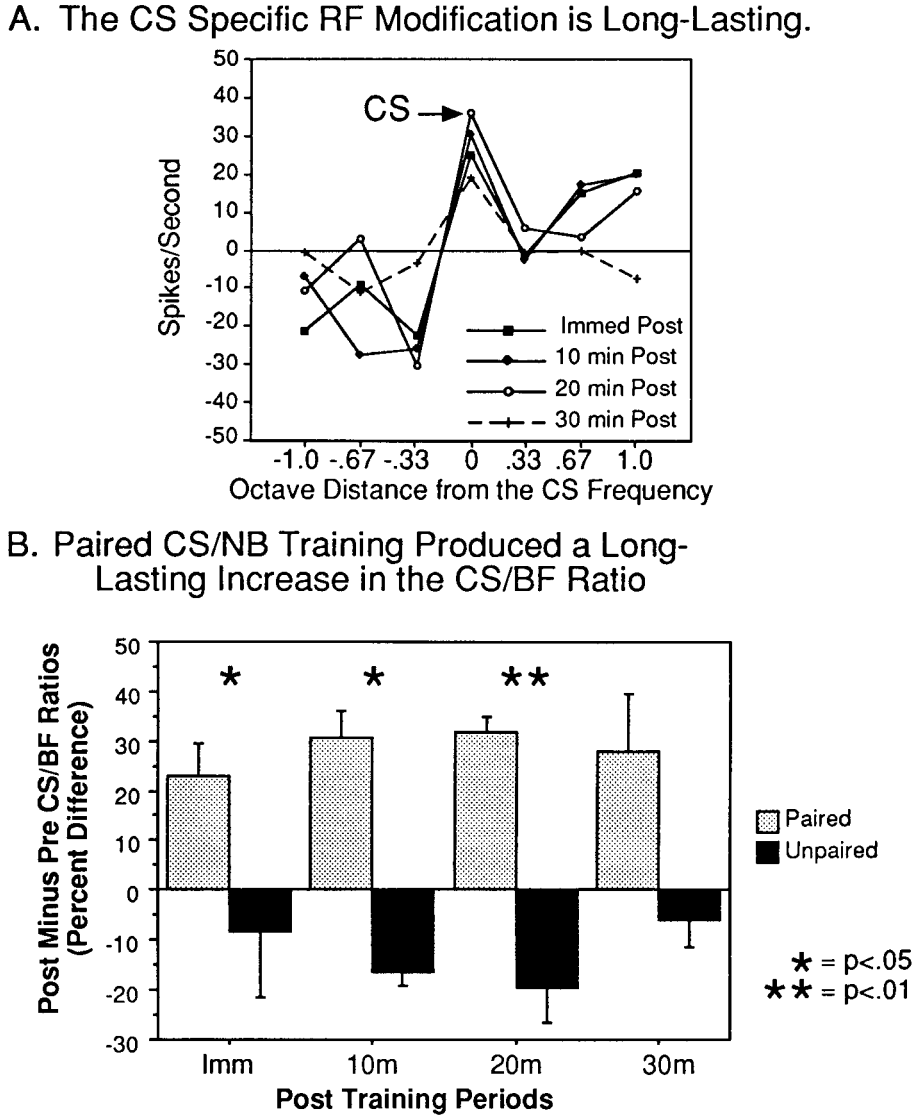

FIG. 3. Group summaries. (*A*) Pairing-induced CS specific RF plasticity. The difference between pairing and unpairing is given in normalized RF difference functions centered on the CS frequency (filled arrowhead). The average difference function for the unpaired group was subtracted from the average difference function for the paired group. This revealed that immediately after treatment paired CS/NB stimulation produced an increase in response that was limited to the CS frequency, with decreases or no change within one-third of an octave of the CS frequency. This pattern of CS-specific RF modification due to pairing was retained for all postintervals tested, the effect being reduced at the 30 minute retention period. (*B*) Paired versus unpaired groups. Paired, but not unpaired training, produced a long-lasting increase in the mean CS/BF ratio (mean ± SE). The CS/BF ratio increased ≈20-30% at each period (immediate, 10, 20, and 30 min) following paired CS/NB stimulation. In contrast, the CS/BF ratio did not exhibit an increase at any time period following unpaired CS-NB training. The difference between paired and unpaired groups was statistically significant immediately and at 10 and 20 min posttreatment.

DISCUSSION

This study asked whether pairing a tone with stimulation of the NB is *sufficient* to induce a predicted modification of frequency RFs in the primary auditory cortex. The predicted plasticity was observed. Responses to the frequency of the paired tone (CS) increased while responses to other frequencies, including the pretraining BF, decreased. These opposing changes could produce a shift in tuning so that the frequency of the CS became the new BF. The increased responses to the CS frequency were also highly specific, with no change or decreased responses observed at only a small fraction of an octave from the CS (e.g., Fig. 2*G*). Additionally, this NB-induced RF plasticity is long lasting; with the protocol and stimulation parameters used in this experiment, a statistically significant effect was still present 20 min after pairing. The longest duration of this plasticity remains to be determined. NB-induced RF plasticity is associative because unpaired subjects did not develop RF plasticity. Thus, this CS-specific RF plasticity is highly similar to that obtained during learning (classical conditioning) in the awake, behaving animal (e.g., ref. 23).

The possibility that stimulation of the NB was aversive seems remote, given that the subjects were under deep general anesthesia, they exhibited no cardiac responses to stimulation, and waking subjects exhibit no behavioral responses to the stimulation levels used here. Moreover, it has previously been shown that brain stimulation in waking animals can produce a persistent, nonhabituating cortical activation that is nonaversive, as expected if a cortical arousal system is directly engaged (36). Thus, the fact that NB stimulation effects on the EEG are persistent does not imply that it is aversive.

A model of RF plasticity hypothesizes that the storage of information in the cortex can be achieved by the convergence of sensory information from the environment with the release of acetylcholine acting at muscarinic receptors in the cortex

(29). The results are consistent with this hypothesis because NB stimulation produced both atropine-sensitive EEG desynchronization (indicating that it produced muscarinic effects in the auditory cortex) and associative RF plasticity. Negative RF findings would have provided strong evidence against the hypothesis. However, the present findings do not show whether the RF plasticity is caused by the cortical release of acetylcholine because NB stimulation may have produced two parallel processes, such that the cholinergic effects on the EEG were separate from the processes that produced CS-specific RF plasticity. Therefore, it remains to be determined whether this RF plasticity is mediated by muscarinic receptors in the auditory cortex; separate groups of subjects, receiving either pretraining muscarinic blockers or control substances, will be required to resolve this issue. Nonetheless, association between a sensory stimulus and NB stimulation is sufficient to induce cortical RF plasticity that has the characteristics of memory.

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