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Learning-Induced Receptive Field Plasticity in the Primary Auditory Cortex

Norman M. Weinberger

Center for the Neurobiology of Learning and Memory and Department of Psychobiology, University of California, Irvine, California 92697-3800

Primary sensory cortex in the adult is modified by learning. The primary auditory cortex is retuned when a tone is paired with a behaviorally relevant reinforcer. Frequency receptive fields are shifted toward or to the frequency of the signal stimulus, yielding enhanced processing and representation of important frequencies. Receptive field plasticity constitutes "physiological memory" because, like much memory, it is associative, highly specific, rapidly-induced, and retained indefinitely, at least for months. The basal forebrain cholinergic system may be a substrate because its paired activation is sufficient to induce receptive field plasticity in the absence of actual behavioral learning experiences. © 1997 Academic Press

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Contrary to traditional assumptions and beliefs, primary sensory cortex is highly plastic in the adult animal. Moreover, the induction and maintenance of plasticity in primary sensory cortical fields do not require damage to a sensory system with subsequent recovery or reorganization. Rather, relatively simple moment-to-moment learning experiences involve substantial, highly specific, rapidly induced, very long term modification of neuronal receptive fields (RFs). That is, primary sensory cortices are not only concerned with sensation, but also actually *store* modality specific experiences.

This article concerns the primary auditory cortex (ACx) because this region of the brain provides the most current knowledge of the characteristics and mechanisms of sensory cortical plasticity in learning. It focuses on learning-induced receptive field plasticity in the ACx and its possible mechanisms, particularly the basal forebrain cholinergic system. More detailed reviews of auditory cortical plasticity in particular, and adult sensory cortical plasticity and learning in general, are available (1–2).

CONCEPTUAL CHALLENGES

Before summarizing the findings, it will be helpful to consider conceptual arguments against learning-induced primary sensory cortical plasticity in the adult. These positions challenge the concept that the *processing of information* in the primary sensory cortex of the adult is strongly *modified simply by learning about that information*. The assumptions underlying these arguments are still held explicitly, more often implicitly, by many workers. Some derive from the fact that understanding the role of learning in sensory systems requires the synthesis of two traditionally noninteracting fields within neuroscience, sensory neurophysiology, and the neurobiology of learning, so that misunderstandings may be more prevalent than in less complex situations.

First, there is the "common sense" view, based on personal experiences that our perceptions seem to be immediate and veridical. As it is assumed that such experiences reflect the functional organization of primary sensory cortex, it is concluded that learning effects cannot intervene. As stated by one worker, "If learning modifies sensory cortex, then one would not know what is real." There are at least two reasons to reject this position. First, the method of "introspection" upon which it is based was thoroughly tried and discarded by psychology as inadequate and misleading, almost a century ago (3). Second, the field of perception long ago established the constructive nature of perception, based on prior learning experiences (4).

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Second, there is the "critical periods" view, based on reports that processes such as ocular dominance plasticity in the visual cortex, due to early restricted visual experience, are limited to a developmental phase of life (5). However, sensory deprivation-based effects have been established in the adult (6). And as will be seen, learning effects are common and are marked in the adult.

Third, the responses of sensory cortical neurons are usually precise and stable, which is often assumed to support a fixed coding of sensory stimuli and by implication is thought to be incompatible with learning effects. However, most sensory neurophysiological data have been obtained in subjects under anesthesia, a state designed to preclude the induction of learning effects. Moreover, it is now established that the receptive fields of sensory cortical neurons in behaving animals are quite stable until a relevant learning experience occurs, at which point the cells develop a new receptive field that itself exhibits stability in the absence of further relevant learning experiences.

EMPIRICAL BACKGROUND

Turning now to the empirical background, the vast majority of the literature on learning effects in primary sensory cortex involves the use of Pavlovian (classical) conditioning procedures, in which a neutral sensory stimulus (the conditioned stimulus, CS) is paired with an immediately subsequent biologically significant stimulus, such as food or shock (the unconditioned stimulus, US). It has long been known that a variety of different associations are formed in conditioning, including a rapidly acquired association between the CS and the US (7–8). This contrasts with the narrow outdated view that the learning in classical conditioning is an association between the CS and a single specific conditioned response (CR). The former constitutes stimulus–stimulus (S-S) learning, whereas the latter exemplifies stimulus–response (S-R) learning. S-S learning develops more rapidly than S-R learning (9–11). For example, subjects first learn that a tone (CS) signals a puff of air to the eye (US) (i.e., S-S learning) and later learn to blink that eye (make a conditioned response) to the tone (i.e., S-R learning).

Primary sensory cortices alter the way they respond to the conditioned stimulus during S-S association, when subjects learn that the CS signals a forthcoming unconditioned stimulus.

Previous research, beginning in the 1950s with evoked-field potentials and continuing into the 1980s with the recording of neuronal discharges, revealed that responses to the CS in primary sensory cortex usually are increased during Pavlovian conditioning. This facilitation is due to the association between the CS and the US because it requires forward pairing (the CS must precede the US) and because arousal and other nonassociative effects had been ruled out (12). Therefore, it has long been known that learning modifies the responses of primary sensory cortex to sensory stimuli that acquire behavioral importance.

RECEPTIVE FIELD ANALYSIS

These findings provide the basis for asking a critical question. "Does learning *specifically* modify the processing of information about the conditioned stimulus or does it *generally* increase responses to similar stimuli?" There is a very important, but subtle, difference between a learning-induced *general increase in responsivity* and a learning-induced *specific modification of information processing.* If learning generally increases responses to acoustic stimuli, then responses to the conditioned stimulus would be increased but responses to other sounds, i.e., to tones that were not used as the CS, also would be increased. In contrast, if learning specifically alters the processing of information about the CS, then increases in response would be restricted mainly to the conditioned stimulus, while responses to non-CS stimuli would be less enhanced, perhaps even decreased. In this case, primary sensory cortex *would actually code the acquired behavioral importance of a stimulus, by increasing its magnitude of response to that stimulus* and perhaps increasing its representation across the cortical field.

This issue cannot be resolved in standard learning experiments, because both specific informational and general excitability mechanisms would produce response facilitation to the CS. However, it can be resolved by the use of receptive field analysis. Figure 1 illustrates the two possibilities.

The use of receptive field analysis in a hybrid learning–sensory physiology design provides a way to distinguish between a learning-induced general increase in responsivity and a modification of information that is specific to the conditioned stimulus. The novel type of experimental design is to "sandwich" a conditioning protocol between two auditory neurophysiology protocols, for the same cells. First, the cell's frequency receptive field is determined. Second, the animal is trained using a tonal frequency that is not the pretraining best frequency (BF, peak of the tuning

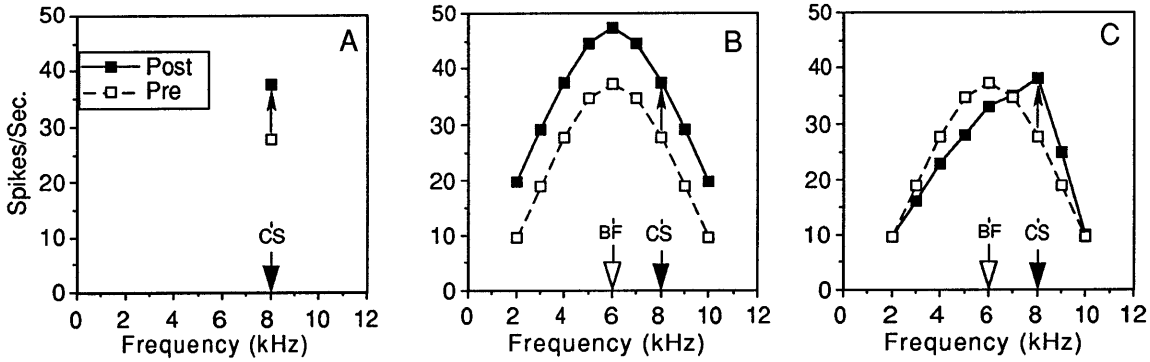

FIG. 1. The application of receptive field analysis to learning. (A) A standard conditioning result in which responses to the CS frequency (e.g., 8 kHz) are increased due to learning (Pre vs. Post). The increased response could be due either to a general increase in response across the receptive field (B) or to a CS-specific change in which response to the CS is increased while responses to other frequencies are increased less, unchanged, or decreased (C). The latter is a shift of tuning to favor CS processing (1).

curve), to determine if learning actually shifts tuning. Third, the frequency RF is determined again after training (and for several retention periods thereafter if desired). The question is whether learning produces a *shift* in receptive fields (a CS-specific effect) or does not change tuning but simply increases the magnitude of response across the RF (a general effect).

ASSOCIATIVELY-INDUCED RECEPTIVE FIELD PLASTICITY IN THE PRIMARY AUDITORY CORTEX

The first study on the effects of learning on RFs in a primary sensory cortex was reported in 1990 (13). (A previous experiment reported a different form of RF plasticity in secondary auditory cortical fields during classical conditioning (14). Adult guinea pigs, bearing microelectrodes that were chronically implanted in infragranular layers of primary auditory cortex, were trained by presenting a tone followed by brief footshock. The training was relatively brief, only 10–30 pairings (trials), within a period of about 15–40 min. Behaviorally, subjects rapidly (5–10 trials) acquired typical signs of conditioned fear which persisted for the duration of training. RFs for frequency were obtained again, immediately and 24 hr after training.

After conditioning, RFs were altered in a highly specific manner. Responses to the frequency of the CS (and sometimes immediately adjacent frequencies) were increased, whereas responses to the BF were usually reduced; responses to other non-CS frequencies were often reduced if close to the BF or were unchanged if far from the CS frequency. The opposing changes between the CS frequency and the BF were usually large enough to shift frequency tuning toward or even to the frequency of the conditioned stimulus, which then became the new BF. An example of CS-specific RF plasticity is provided in Fig. 2.

Learning-induced RF plasticity is associative, that is, it requires forward pairing of the tone and footshock. Control subjects that received sensitization training (unpaired tone and shock) developed a general increase in response to all frequencies; there was no CS specificity (13, 15). (Habituation, i.e., the simple repetition of a single tone, produces a frequency-specific decrease in response at the repeated frequency (16)). Figure 3 summarizes the differences between pre and posttraining receptive fields for classical conditioning, sensitization training, and habituation. Note the specific increase of response to the frequency of the CS in conditioning (Fig. 3A), the lack of specificity in sensitization (Fig. 3B), and the specific decrease at the repeated frequency in habituation (Fig. 3C).

Subsequent studies have shown that RF plasticity is highly discriminative. In two-tone training experiments, responses to the CS+ (paired with the US) increased, whereas responses to the CS− (another tone that was not followed by the US) did not change (Fig. 4) (17). Furthermore, RF plasticity develops rapidly, within only five training trials (Fig. 5) (18). Moreover, this plasticity lasts indefinitely, as tested at retention intervals as long as 2 months (Fig. 6) (19). Additionally, it is not limited to classical conditioning but also develops during instrumental conditioning, when a subject learns to make a response to avoid shock (20). Finally, RF plasticity in learning is highly robust across brain states. Thus, RF plasticity that is induced in

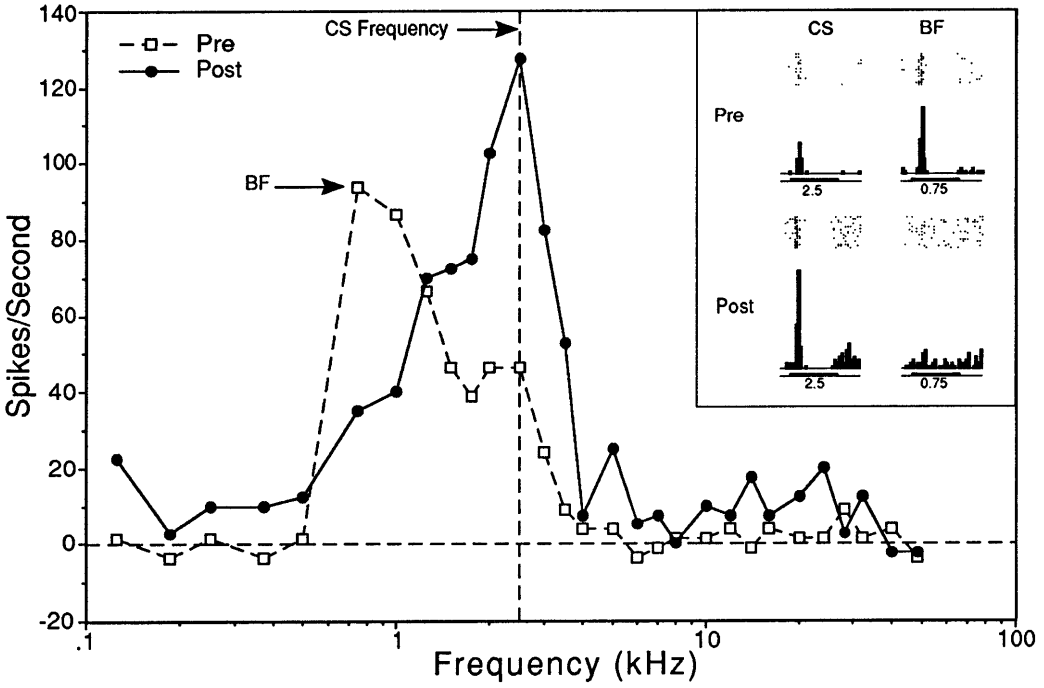

FIG. 2. An example of a learning-induced shift of tuning in a single neuron. Before learning, the best frequency (BF) was 0.75 kHz. The subject was trained with a CS of 2.5 kHz. After training at this frequency, the receptive field was shifted so that the new best frequency became the frequency of the CS. The insets show rasters and poststimulus time histograms for these two frequencies pre and postconditioning (1).

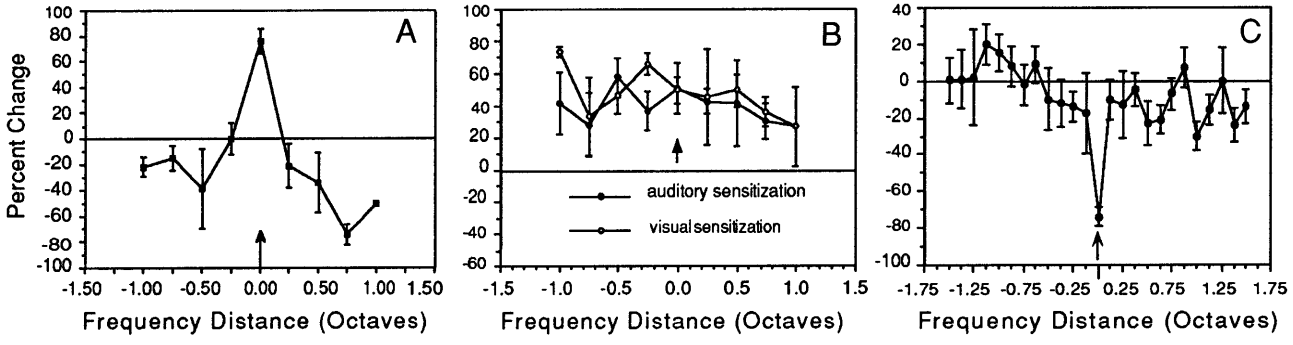

FIG. 3. Group average differences in frequency tuning curves (posttraining minus pretraining) for neurons in the primary auditory cortex, for three types of training: classical conditioning (tone followed by shock), sensitization control training (tone and shock unpaired; also shown are data for cross-modality control, i.e., light and shock unpaired), habituation (tone presented alone). The data are normalized to the frequency of the training tone and expressed as magnitude of change as a function of octave distance from the training frequency. (A) Conditioning—Note the increase in response only at the frequency of the conditioned stimulus, with no change at ±0.25 octaves and decreased responses at more distant frequencies. (B) Sensitization—Note the broad increase with no specific effect at the frequency of the "CS." Also, the same broad increase in frequency RFs was seen even when a light was presented randomly with shock ("CS" frequency is arbitrary in this nontone protocol), showing that sensitization simply produces a general increase in response regardless of the modality of the "CS" stimulus. If data had been obtained only for the "CS" frequency in auditory sensitization, one would have falsely concluded that sensitization training produces the same type of effect (increased response to the CS) as does genuine conditioning. (C) Habituation—Simply repeatedly presenting a tone produces a frequency specific change in RFs that is opposite to the effects of conditioning, i.e., a frequency-specific decrease. Error bars are ±SD (1).

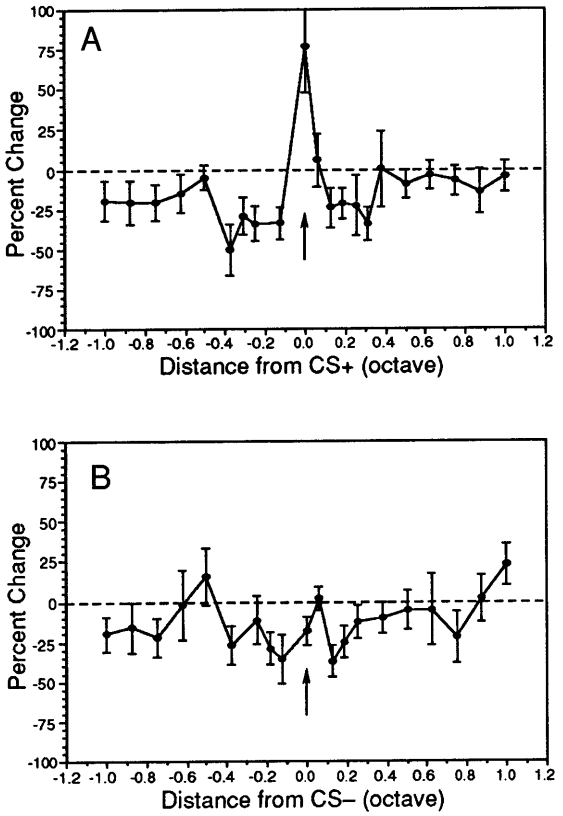

FIG. 4. Frequency-specific changes in tuning in two-tone discrimination training. Normalized group average differences in frequency tuning curves (posttraining minus pretraining) for neurons in the primary auditory cortex, for the CS+ (tone followed by shock), and for the CS− (another tone presented randomly during training, without shock). Subjects developed discriminative behavior (heart rate conditioning). (A) Changes in tuning to the CS+ stimulus; note the specific increase at the frequency of the CS+. (B) Change in tuning to the CS− stimulus; note the absence of specific increased response to the CS− (17).

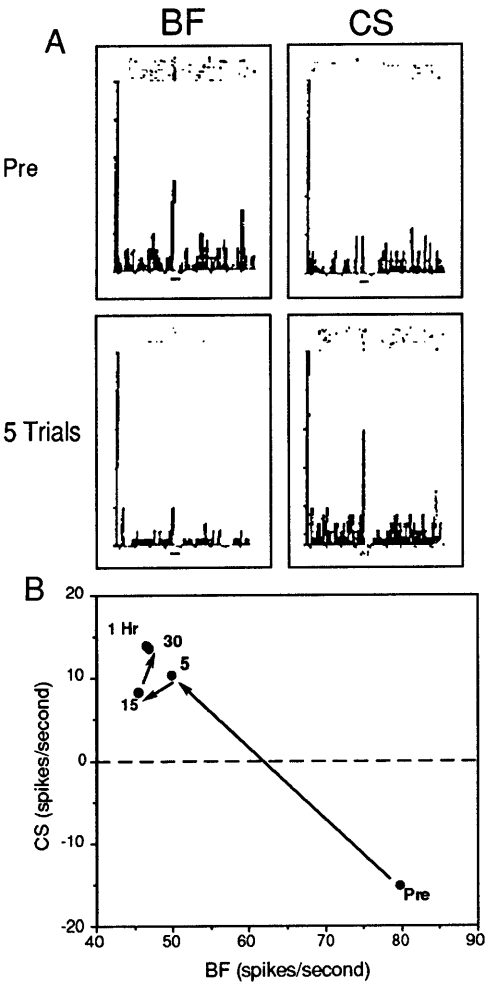

FIG. 5. Rapid development of CS specific receptive field plasticity. RFs were obtained before conditioning (tone → shock) and after 5, 15, and 30 trials and 1 hr posttraining. (A) Poststimulus time histograms for responses to the pretraining best frequency (BF) and to the frequency of the CS, before (pre) and after only five trials of conditioning (5 trials). Note the pretraining the response to the BF was large and excitatory whereas the response to the CS frequency was actually inhibition compared to pretone activity. In contrast, after five training trials, responses to the BF were greatly reduced whereas strong excitatory responses were present for the CS frequency. (B) Vector diagrams illustrating the development of changes of response to the pretraining BF and the CS frequency. The rate of discharge (spikes / sec) for these two frequencies is shown for each of the receptive fields: pretraining, 5, 15, and 30 trials, and 1 hr posttraining, with arrows connecting successive time periods. Note the opposite changes for the BF and CS after 5 trials with minimal variation after 15 and 30 trials and no change from 30 trials to the 1-hr retention test. Note that the pretraining response to the CS frequency was suppressive but became excitatory after only 5 trials (18).

waking, behaving animals can be expressed subsequently while they are under general anesthesia (19).

This last finding also is pertinent to an obvious problem. It might be thought that presentation of the frequency of the CS during posttraining RF determination produces arousal and that increased responses to the CS frequency are therefore attributable to this increased arousal. However, putative CS-evoked arousal cannot occur in subjects under deep barbiturate anesthesia, yet RF plasticity is evident in this state. There are also other grounds to rule out putative arousal. First, the latency of cortical EEG arousal is longer than the latency of the evoked tuned discharges in the ACx. Second, responses to non-CS frequencies presented within a few hundred milliseconds of the CS

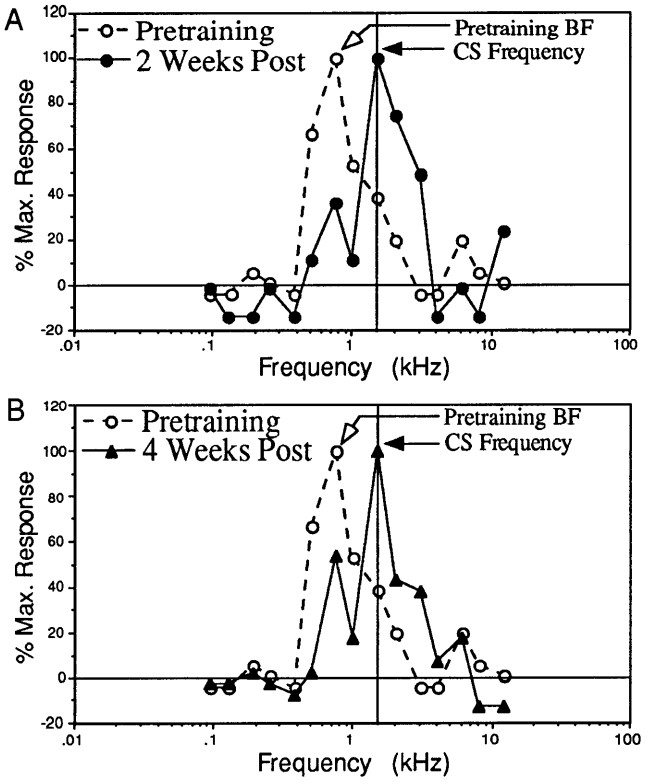

FIG. 6. Very long term retention of CS-specific receptive field plasticity. The BF was 0.75 kHz before conditioning and the CS was selected to be 1.5 kHz. After conditioning, the tuning was shifted so that the CS frequency became the new BF. Shown here are retention data for 2 weeks (1) and 4 weeks (2) posttraining. Pretraining data are repeated in each panel for clarity. Note the stability of the learning-induced shift in tuning to the CS frequency (19).

frequency are decreased, but arousal lasts longer. Third, direct measures of arousal reveal no such changes during RF determination in waking animals (21).

An understanding of the role of learning in primary sensory cortex depends critically on obtaining behavioral evidence that learning has actually taken place; it is insufficient merely to execute a conditioning protocol because this does not guarantee that learning actually developed in a given situation. Learning is a whole organism property and is not to be confused with neural plasticity, which is presumed to be a substrate of learning. Sensory neurophysiological data separately assay the extent to which neural plasticity develops and these can be compared with behavioral results. Bearing these two levels of inquiry in mind, it has been found that discriminative RF plasticity in the ACx develops both during an easy two-tone discrimination, when a subject exhibits behavioral learning, and also in a two-tone discrimination task that is too difficult for behavioral discrimination learning (17). The fact that RF plasticity develops below behavioral threshold shows that it is more sensitive and more probable than behavioral learning. The absence of adequate behavioral measures of learning, particularly combined with unproven highly complex discrimination protocols, can produce uninterpretable findings (22).

PLASTICITY OF SPATIAL REPRESENTATION

Based on the shift in tuning toward or to the frequency of the CS at the level of individual RFs, it was predicted that the entire frequency representation in primary auditory cortex should be modified so that the representation of the CS frequency is increased relative to other frequencies (23). This prediction was confirmed subsequently in a study of frequency discrimination training in the owl monkey (24).

While receptive field studies have provided the most detailed information regarding the specificity and long-term retention of learning effects in the auditory cortex, metabolic studies also have shown facilitated processing and increased representation of the conditioned stimulus in both animals and humans, in both aversive and appetitive tasks (25–27). Also, learning effects in the auditory cortex are not confined to a single type of memory as the same cells can participate in both working (short term) and reference (a type of long-term) memory (28).

MECHANISMS OF LEARNING-INDUCED RF PLASTICITY

The locus of RF plasticity in the ACx is thought to involve the convergent action of subcortical systems in the ACx, rather than being directly ''projected'' from a subcortical site. This conclusion is based on three factors. First, the ventral medial geniculate nucleus (MGv), the lemniscal tonotopic auditory thalamic input to the ACx, does not develop plasticity. Therefore, it apparently provides precise and unchanged tonal frequency input to the ACx. Second, the nonlemniscal magnocellular medial geniculate nucleus (MGm) does develop RF plasticity but its tuning curves are far too broad and multipeaked to explain the ACx plasticity. However, its projections to layer I of the ACx may

contribute to plasticity. Third, the basal forebrain cholinergic system can produce long-term changes in tuning (1–2).

The nucleus basalis (NB) is the major subcortical source of cortical acetylcholine (ACh) (29–31). Direct application of muscarinic agonists and blockers to the ACx produces lasting modification of frequency tuning (32–33). Stimulation of the nucleus basalis can produce atropine-sensitive long-lasting facilitation of evoked responses in the ACx at both the extracellular and the intracellular levels (34–38). Further, pairing a tone with iontophoretic application of muscarinic agonists to the ACx produces pairing-specific, atropine-sensitive, modification of RFs that includes shifts of tuning to or toward the frequency of the paired tone (39).

Based on these and other considerations, it had been hypothesized that initial neural association of the CS and US occurs in the magnocellular medial geniculate nucleus and that this activates the NB via the central nucleus of the amygdala. The subsequent engagement of muscarinic receptors in the ACx is thought to be sufficient to produce long lasting RF plasticity (1, 23). Subsequent findings are consistent with this hypothesis. For example, acoustic stimuli that signal the occurrence of a reinforcing stimulus affect the discharges in cells of the NB (40). Of particular relevance, cells in the NB develop increased discharges to the CS+ during tone–shock conditioning before the development of neuronal plasticity in the ACx, and thus could be causal to the RF plasticity in the ACx (41).

To determine directly if NB activation is sufficient for the induction of RF plasticity, a tone was paired with direct electrical microstimulation of the NB, in place of a standard peripheral sensory US. The effects of this pairing treatment were assayed by determining frequency RFs before and at several times after pairing, in rats under urethane anesthesia. Effective stimulation of the NB was established by obtaining desynchronization of the auditory cortical EEG, and muscarinic involvement was established by blocking EEG effects with atropine applied directly to the ACx. This treatment did induce CS-specific RF plasticity. The effects were maintained. Control subjects receiving random presentation of tone and NB stimulation did not show this specific facilitation of the CS frequency, showing the effect is associative (Fig. 7). Therefore, appropriately paired activation of the NB is *sufficient* to induce associative receptive field plasticity in the auditory cortex (42).

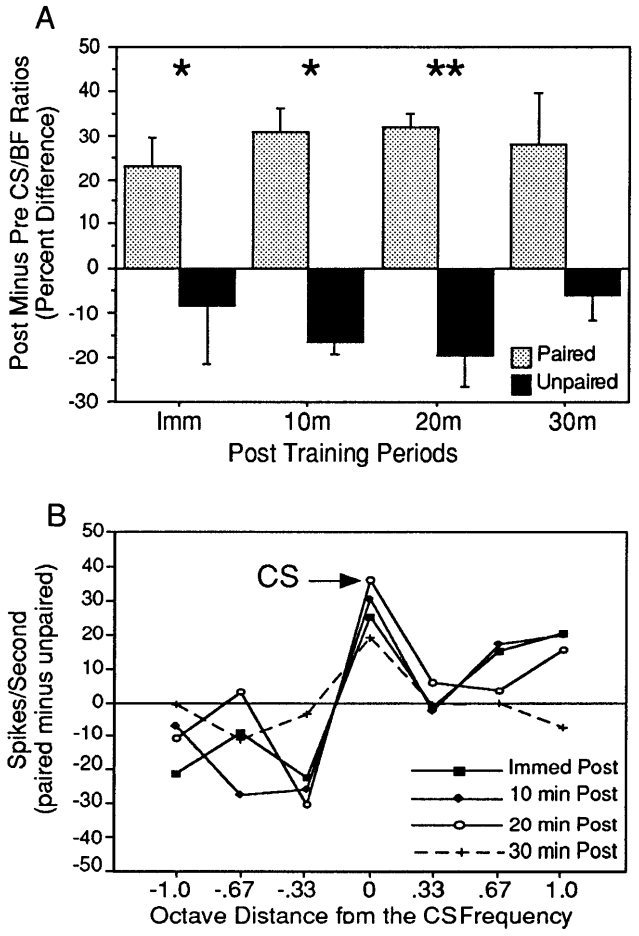

FIG. 7. CS-specific receptive field plasticity induced by pairing a tone with microstimulation of the nucleus basalis. (A) Comparison of changed response to the conditioned group (paired) and the sensitization control group (unpaired). The effects were quantified by computing the ratio of magnitude of discharges to the pretraining BF and to the frequency of the CS (CS/BF ratio) before training and to these same frequencies at various retention intervals. Paired training, but not unpaired training, produced a long lasting increase in the mean CS/BF ratio (mean ± SE). The CS/BF ratio increased approximately 20–30% at each period (immediate, 10, 20, 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. (B) Pairing produces CS specific increase in response across receptive fields. 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. Compared to unpaired controls, 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-min retention period (42).

CONCLUSIONS

In summary, receptive field plasticity develops in the primary ACx during learning. Tuning is shifted to facilitate responses to the frequency of a behaviorally important tone during classical conditioning. Moreover, such learning effects develop across species, tasks, and types of reinforcement. RF plasticity has the characteristics of major forms of memory; it is associative, highly specific to the frequency of the important stimulus, discriminative, rapidly induced, and retained indefinitely. Thus, it has been termed ''physiological memory'' (42).

The delineation of mechanisms of learning-induced receptive field plasticity is under current investigation. The basal forebrain cholinergic system has been implicated. In particular, its activation is sufficient to induce RF plasticity provided that it is paired with a tonal stimulus. This suggests that normal behavioral learning engages this cholinergic system to enable the induction of receptive field plasticity in the auditory cortex.

Many avenues of investigation remain open. These include determination of the existence and characteristics of RF plasticity in the granular and supragranular layers of the cortex, in addition to the known effects in infragranular layers. For example, the primary auditory cortex may hold different types of information or representation within different laminar zones. The detailed circuit and cellular bases of receptive field plasticity also remain an important goal. Finally, the findings call for a broader, more dynamic conception of primary sensory cortex than is reflected in traditional accounts of sensory cortical function.

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