Learning-induced changes of auditory receptive fields

Norman M. Weinberger

University of California, Irvine, USA

Classical conditioning specifically modifies receptive fields in primary and secondary auditory cortical areas to favor the frequency of a tone signal over other frequencies, including tuning shifts toward, or to, this frequency. This plasticity of receptive fields is associative and highly specific, can develop very rapidly, can be expressed under anesthesia and can be maintained indefinitely. Muscarinic receptors in the cortex may be involved. Non-lemniscal thalamic nuclei also develop receptive field plasticity that may contribute to cortical plasticity.

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Introduction

Receptive field (RF) plasticity is well established for sensory deprivation in the developing visual and adult somatosensory cortices. Learning has long been studied in the adult auditory cortex. Responses to an acoustic conditioned stimulus (CS) that is followed by an unconditioned stimulus (US), such as food or shock (a 'training trial'), are generally enhanced when repeated CS-US pairing (classical conditioning) produces behavioral evidence of learning [1]. Further investigation of RF plasticity was recently initiated to clarify how the processing of an acoustic CS is modified when it acquires behavioral significance.

Enhanced responses to the CS could reflect either a general increase in neuronal excitability or a specific enhancement in the processing of a behaviorally significant stimulus. Comparison of RFs determined before and after training can distinguish between these alternatives [2]. If the facilitation is caused by a general increase in neural excitability, then responses to other (non-CS) frequencies should also be increased. In contrast, if the increased response reflects a specific modification in the processing of information about the acquired relationship between the CS and the US, then responses to other frequencies would not be increased to the same extent, and might exhibit no change or even decreased responses. This brief article reviews recent work on learning-induced modifications of RFs in the auditory system. Response modifications during training trials themselves are beyond the scope of this review.

Learning-induced receptive field plasticity in the auditory cortex

The auditory cortex consists of multiple fields, some of which have a spatially organized frequency map that reflects the organization of the cochlea ('primary' or 'tonotopic' fields), while others lack this organization ('secondary' or 'non-tonotopic fields') [3]. RF analysis was first used in work on secondary fields in the cat [4]. RFs were determined in infragranular cells before and after three types of training: sensitization (CS/US unpaired), conditioning (CS/US paired) and extinction (CS alone). Behaviorally, classical conditioning, but not sensitization ('secondary' or 'non-tonotopic fields') [3], RF analysis was first used in work on secondary fields in the cat [4]. RFs were determined in infragranular cells before and after three types of training: sensitization (CS/US unpaired), conditioning (CS/US paired) and extinction (CS alone). Behaviorally, classical conditioning, but not sensitization, caused pupillary dilation conditioned responses (CR), which verified the establishment of a CS-US association. Conditioning, but not sensitization training, modified RFs. RF plasticity was usually highly specific to the frequency of the CS and was maintained unless the animal subsequently underwent extinction training, in which case the modifications were diminished or abolished.

Analysis of pupillary behavior during RF determination compared with acquired pupillary dilation during training trials, provided no evidence that arousal was elicited by the CS frequency or other tones. This was attributed to the very different types of acoustic context between training (single tone, 1.3 min⁻¹) and RF determination (16–30 frequencies, 30–60 per minute) [5]. Overall, these findings indicate that associative learning produces CS-specific modification of receptive fields.

Traditionally, learning and memory have been attributed to secondary sensory cortex and association cortex but...
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not to primary sensory cortex. Thus it may not be surpris-
ing that learning-induced RF plasticity develops in sec-
ondary auditory cortical fields. To clarify this issue, RFs
were obtained from infragranular cells in primary tono-
topic fields in the guinea pig [6]. The CS frequency was
never the best frequency (BF) — the frequency that is
the peak of the pre-training tuning curve — to enable
determination of the extent to which conditioning shifts
frequency tuning. Conditioning (one session consisting
of 30 trials) produced behavioral CR in 4-5 trials, typi-
cal for aversive, or 'fear', conditioning [7]. Highly specific
modifications of RFs developed immediately after training
and were maintained at a 24 hour retention test in most
typical cases. Typically, responses to the CS frequency increased,
and responses to the BF and many other frequencies de-
creased or showed little change, shifting tuning toward,
or to, the CS frequency which became the new BF. The
RF plasticity was highly specific to the frequency of the
CS (Figs. 1a(i-iii) and Fig. 1b(i)).

The absence of these modifications in subjects trained in
a sensitization control paradigm (CS and US unpaired)
indicated that the RF plasticity is associative. It is interest-
ing to note that sensitization training increased responses
generally, across the RF (Fig. 1b(ii)). Putative differenti-
al arousal effects during RF determination could not ac-
count for the specific findings and in any event were not
observed [6]. Further investigation revealed that these
general increases are independent of the CS modality.

Visual sensitization training (light/shock unpaired) pro-
duces the same effects on acoustic RFs as does auditory
sensitization training (tone/shock unpaired) (Fig. 1b(ii))
[8].

Specific RF plasticity also develops in habituation. Follow-
ing response decrements to the repetition of a single tone
for several hundred trials, post-repetition, RFs showed
an enduring highly specific decreased response to the
habituated frequency relative to other frequencies (Fig.
1b(iii)) [9].

Highly specific RF plasticity also develops in primary au-
ditory cortex in two-tone — CS+ (reinforced), CS- (not
reinforced) — discrimination training. Responses to the
CS+ frequency increased whereas responses to the fre-
cquency of the CS-, the pretraining BF and other non-
CS+ frequencies generally decreased, both in an easy
task and in a more difficult task. Tuning shifts were re-
tained or stronger at a 1 hour retention test. In contrast,
good behavioral discrimination (cardiac CR) developed only
for the easy task [10]. Thus, RF plasticity neither de-
pends upon nor guarantees the behavioral expression of
learning. (For concordant discrimination findings using
partial RFs, see [11].)

That RF plasticity includes increased response to the
CS(+) frequency and decreased response to the BF and other frequenc-
es, raises the question of whether the modifi-
cations are sequential or simultaneous, i.e.,
are they ‘cooperative’? A time-sampling study, with RFs
determined after 5, 15 and 30 trials of conditioning and
at a retention period of 1 hour indicated that these op-
posite changes at the CS frequency and the BF develop
simultaneously. It is interesting to note that RF plastic-
ity was present after only 5 trials of training; if not fully
developed at this time, it continued to develop with ad-
tional conditioning trials and was maintained at the 1
hour retention test [12**].

Long term retention and the ability of learning-induced
RF plasticity to be expressed under anesthesia were as-
essed by conditioning guinea pigs in the waking state
(30 trials given in a single session) but the RFs were de-
termined while they were deeply anesthetized (pentobar-
bital or ketamine), on the day before training and from
1 hour to 8 hours after training [13**]. CS-specific RF
plasticity was present at the first post-training retention
period and for as long as 8 weeks following training, the
longest period tested. That RF plasticity is expressed in
the anesthetized state provides yet another indication that
it is not the result of arousal to the CS frequency during
RF determination [13**].

The rules governing tuning shifts have not yet been com-
pletely delineated. It appears, however, that there must
be some pre-training excitatory response to the CS fre-
cquency and that the shifts to the CS frequency can be as
great as 1 octave ([4,13**]; NM Weinberger, unpublished
data).

A very recent study using a novel paradigm for discrim-
ination conditioning reports opposite effects on RFs in
the primary auditory cortex of the gerbil. Responses to
the CS+ were decreased relative to responses to CS- fre-
cquencies (all other frequencies including the BF), so that
the CS frequency lies at a local minimum of the post-train-
ing RF ([14**]; F Ohl, C Simonis, H Scheich, Soc Neurosci
Abst 1992, 18:841; F Ohl, H Scheich, unpublished data).
The authors point out that this effect provides for ‘lateral
contrast enhancement’ (Fig. 2).

There are striking differences between the training meth-
ods of this study and previous studies that might be
responsible for the different findings. In the example
above, discrimination conditioning and RF determina-
tion were highly similar: one of the several frequencies
used to obtain the RF was paired with shock; also brief
tones were presented repeatedly at rates greatly exceed-
ing those used in standard training situations. An advan-
tage of this novel procedure is that it minimizes contex-
tual differences between training and RF determi-
nation [5] while a possible disadvantage is that subjects may
not acquire frequency discriminations under these con-
ditions. No behavioral data were reported, precluding infer-
ences about what the subjects learned. The authors point
out that previous RF studies measured the tuning only to
‘onset’ responses whereas they analyzed discharges dur-
ing the entire 250 ms duration of the tones. Therefore,
to some extent, RF plasticity could consist of facilitated
responses to short-latency discharges followed by relative
suppression of longer latency discharges at the frequency of
the CS.

Implications for frequency maps

Frequency-specific RF plasticity has implications for the
representation of frequency across primary auditory cor-
Fig. 1. The effects of learning upon receptive fields in the primary auditory cortex of the waking guinea pig. (a) An example of CS-specific receptive field modification produced by classical conditioning. In the case illustrated, the CS frequency became the best frequency (BF). (i) Pre-conditioning the BF was 9.5 kHz (open arrowhead) and the CS was selected to be 9.0 kHz (closed arrowhead) for conditioning, which produced behavioral conditioned responses to this frequency (not shown). (ii) One hour post-conditioning, the CS frequency became the BF due to increased response to this frequency and decreased response to the pre-conditioning BF and other frequencies. (iii) The receptive field difference function (post minus pre-RFs) shows that conditioning produces the maximal increase at the CS frequency and maximal decrease at the pre-training best frequency. Open circles show no systematic effect on spontaneous activity. Modified from [6]. (b) Group receptive field mean (± standard error) difference functions (treatment minus control) for three types of training. (i) Conditioning produces increased response at the frequency of the conditioned stimulus and decreases at most other frequencies starting at 0.25 octaves from the CS frequency (side-band suppression). (ii) Sensitization training produces a broad, non-specific increase in response across the auditory receptive field, both for auditory and visual sensitization training. Modified from [8]. (iii) Habituation produces a frequency-specific decrease for a frequency which developed a decrement in response due to repeated presentation alone. Note the high degree of specificity; frequencies 0.125 octaves from the repeated frequency were little affected. Modified from [9].
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Specific learning-induced effects in frequency representation within which discriminations were made occurred. Owl monkeys trained over several months in frequency receptive fields (FRF) from a unit in primary auditory cortex to the conditioned frequency but to frequencies neighboring the CS frequency; this retuning is highly specific, associative and not transient [21-24]. CS-specific increased metabolic activity has also been reported for an appetitively rewarded acoustic localization task in layer IV of the auditory cortex of the rat [20].

Receptive field plasticity in the medial geniculate nucleus

RF plasticity in learning has also been studied in the medial geniculate nucleus, which consists of three major nuclei that project to auditory cortical fields. The ventral medial geniculate nucleus (MGv) is thelemniscal thalamic auditory nucleus, containing narrowly-tuned cells and providing tonotopically-organized input to the middle layers of primary tonotopic fields of the auditory cortex. During classical conditioning, its neurons do not develop changed responses to the CS [21-24]. Receptive fields obtained from the MGv before and after cardiac conditioning in the guinea pig revealed only restricted, highly transient modifications of RFs [25].

The magnocellular medial geniculate nucleus (MGM) is the non-lemniscal auditory input, containing broadly tuned cells and providing non-tonotopic input to the upper layers of all auditory cortical fields, primary and non-primary. During classical conditioning, its neurons very quickly develop increased responses to the CS [21-24,26]. Following classical conditioning, but not sensitization training, RFs in the MGM are modified to favor the CS frequency; this retuning is highly specific, associative and not transient [11,24,27**]. In fact, RF plasticity in the MGM is present after a 45 day retention interval [28]. This plasticity can also be expressed with animals under general anesthesia [29]. Because their RFs are tuned much more broadly than are those of auditory cortical cells, it seems unlikely that the cortical RF plasticity is simply 'projected' from the MGM. Further detailed experiments are required to elucidate the functional relationships between the MGM and the auditory cortex.

The dorsal medial geniculate nucleus (MGd) projects to secondary cortical fields. It has been little studied during conditioning, but there is some evidence of conditioning and discrimination effects in this nucleus [24]. During conditioning, frequency-specific RF plasticity develops, is associative and is retained in the MGd of the guinea pig [30]. Its relation to RF plasticity in secondary auditory cortex has not been studied.

Frequency specific metabolic changes have also been found for conditioning [20,31-34] and habituation [35] throughout the subcortical auditory system. These findings contrast with the lack of neurophysiological plasticity during training [21-24] and also minimal and transient...
plasticity of RFs [25] in the MGv, which might be expected to reflect the plasticity of lower auditory structures. However, many metabolic studies use hundreds of training trials. If RF plasticity develops rapidly in the auditory cortex but more slowly in the subcortical lemniscal auditory system, then this plasticity would not be detected in the MGv during the smaller number of trials used in neurophysiological studies [21–25]. Understanding the relationships between metabolic effects and neurophysiological findings of RF plasticity will benefit from greater similarity of experimental paradigms.

**Possible role of cholinergic mechanisms in learning-induced RF plasticity in the auditory cortex**

Studies of acetylcholine (ACh) support the notion that it has a role in learning-induced RF plasticity in the auditory cortex. Iontophoretic application of muscarinic agonists produces atropine-sensitive modification of tuning of RFs that endures well beyond the period of ACh application [36]. Similar effects are found for the application of anticholinesterases, indicating that endogenous ACh can modify frequency receptive fields [37]. Pairing one tone with iontophoretic application of muscarinic agonists produces pairing-specific tuning shifts of RFs and these are blocked by atropine [38].

Stimulation of the nucleus basalis (NB), the major source of neocortical acetylcholine, can modulate various evoked responses in the auditory cortex that endure after cessation of application and are blocked by atropine. These include facilitation of field potentials, cellular discharges and excitatory postsynaptic potentials (EPSPs) elicited by medial geniculate stimulation [39,40], and specific facilitation of neuronal discharges to paired tones in anesthetized and in waking rats ([41••]; E Hennevin, J-M Edeline, B Hars, C Maho, abstract 40, Fifth Conference on the Neurobiology of Learning and Memory, Irvine, October 1992; J-M Edeline, B Hars, C Maho, E Hennevin, unpublished data).

**A model of learning-induced receptive field plasticity**

A model, consistent with many findings reviewed here and elsewhere, suggests that CS-specific receptive field plasticity is produced by the convergence of three systems in the auditory cortex: auditory lemniscal, from the MGv; auditory non-lemniscal from the MGm; and cholinergic from the NB. The three systems interact during con-
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Iliebbian rules applied to receptive field plasticity during conditioning and habituation

<table>
<thead>
<tr>
<th>Pre-synaptic input active?</th>
<th>Postsynaptic cell depolarized?</th>
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<tbody>
<tr>
<td>Yes</td>
<td>Strengthen  (CS, conditioning)</td>
</tr>
<tr>
<td>No</td>
<td>Weaken (CS, habituation)</td>
</tr>
</tbody>
</table>

Yes No
1 2
3 4

Various frequency inputs converge on cell. CS frequency

Conditioning: During each trial (CS-US), the CS frequency is the only active frequency input, and the US depolarizes the cell. Therefore, CS synapses are strengthened (1) and non-CS synapses are weakened (2).

Habituation: During each trial ('CS' alone), the CS frequency is the only active frequency input, but the absence of the US results in a lack of postsynaptic depolarization. Therefore, CS synapses are weakened (3) but non-CS synapses are unchanged (4).

Fig. 4. Application of extended Hebbian Rules to RF plasticity for classical conditioning and habituation. Simple combinations of presynaptic and postsynaptic elements, each of which can be in an active or non-active state might account for the effects of conditioning on CS and non-CS synaptic strengths and for the effects of habituation on the repeated and non-repeated stimuli.

Conclusion

Recent receptive field studies reveal that classical conditioning produces associative, rapidly developing (minutes), enduring (8 weeks) and highly specific modifications of the representation of spectral information in the primary auditory cortex. Cooperativity of facilitation of discharges to a signal frequency and decreased responses to other frequencies is suggested by their simultaneous and very rapid development. Muscarinic and non-muscarinic auditory thalamic processes may be involved. RF plasticity may underlie learning-induced modifications of spatial frequency maps. The occurrence of representational plasticity during learning in the adult challenges pure feature-detection views of primary sensory cortex. Expanded investigation of learning-induced RF plasticity should promote a better understanding of the relationships among sensory, perceptual, learning and memory functions of the auditory cortex in particular, and perhaps of sensory cortex in general [42**].

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest
** of outstanding interest


Explains logic and need for receptive field analyses of learning effects, in the absence of which fallacious conclusions are that associative conditioning and sensitization training produce the same changes in auditory cortex.


Demonstration that discrimination training produces specific RF plasticity shows that RF plasticity develops even when task difficulty results in poor behavioral discrimination.


Time series study in which RF plasticity is evident after only five training trials. Shows simultaneous opposite development of increased responses to CS+, decreased responses to best frequency, suggesting that cooperative processes may be responsible for learning induced tuning changes.


An extensive study of retention of learned induced RF plasticity. Shows indefinite retention up to eight weeks and expression of RF plasticity under general anesthesia; this suggests that auditory cortex in anesthetized subjects may reflect prior learning experiences. For a related rare study of retention of learning induced plasticity see [24].


An important empirical and conceptual paper which reviews both metabolic and recent neurophysiological findings of effects of learning. Demonstrates that auditory cortex contains both feature maps and maps that reflect learning.


First neurophysiological analysis of frequency map subsequent to learning, in owl monkey. Reports increased representation for frequency band used in difficult two-tone discrimination training.


A comprehensive review which explains the technical aspects of the use of metabolic approaches to learning in the auditory system and summarizes findings for several learning paradigms and levels of the auditory system. This work derives from seminal studies, such as that represented by [18], noted both for CS-specific increases in metabolic activity and the distinctive use of novel control groups.


Shows that both broad receptive fields develop CS-specific plasticity in this mid-lateral auditory nucleus that projects to upper lamina of all auditory cortical fields. These findings contrast with the very limited and transient receptive field plasticity in the laminar ventral medial geniculate body which projects topographically to granular layers of tonotopic cortical fields (see [21]).


32. Gonzalez-Lima F, Schreier H: Neural Substrates for Tone-Conditioned Bradycardia Demonstrated with 2-Deoxyglu-
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Tests and supports the hypothesis that ACh acting at muscarinic receptors in the auditory cortex can produce facilitation of auditory input from the medial geniculate, at the level of field potentials, cellular discharges and evoked postsynaptic potentials. This work follows logically from early findings that endogenous ACh, acting at muscarinic receptors in the auditory cortex, can produce return of frequency receptive fields [57], and that pairing cortical application of ACh with a single tone produces frequency specific modifications of receptive fields [38].


12. Weinberger NM, Ashe JR, Erilne J-M: Learning-induced Receptive Field Plasticity in the Auditory Cortex: Specificity of Information Storage. In Neural Bases of Learning and Memory. Edited by Delacour J, Singapore: World Scientific Publishing, 1993, in press. An overview of the use of receptive field analysis in learning. Includes both a review of empirical work, based on initial findings in the cat (see [41] and subsequent studies in the guinea pig, for both classical conditioning (see [6]) and habituation (see [9]) and also a detailed extension of the original model of learning induced receptive field plasticity (see [15]). For additional important aspects of RF plasticity not covered in this recent citation see [4], which shows that RF plasticity transcends the state in which learning occurs and presents the 'functional mosaic' hypothesis that cells have multiple receptive fields, only one of which is expressed in a given situation.

NM Weinberger, Center for the Neurobiology of Learning and Memory, Barney Center, University of California, Irvine, California 92610, USA.