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LEARNING-INDUCED PHYSIOLOGICAL PLASTICITY IN THE THALAMO-CORTICAL SENSORY SYSTEMS: A CRITICAL EVALUATION OF RECEPTIVE FIELD PLASTICITY, MAP CHANGES AND THEIR POTENTIAL MECHANISMS

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Abstract—The goal of this review is to give a detailed description of the main results obtained in the field of learning-induced plasticity. The review is focused on receptive field and map changes observed in the auditory, somatosensory and visual thalamo-cortical systems as a result of an associative training performed in waking animals.

Receptive field (RF) plasticity, 2DG and map changes obtained in the auditory and somatosensory system are reviewed. In the visual system, as there is no RF and map analysis during learning per se, the evidence presented are from increased neuronal responsiveness, and from the effects of perceptual learning in human and non human primates.

Across sensory modalities, the re-tuning of neurons to a significant stimulus or map reorganizations in favour of the significant stimuli were observed at the thalamic and/or cortical level.

The analysis of the literature in each sensory modality indicates that relationships between learning-induced sensory plasticity and behavioural performance can, or cannot, be found depending on the tasks that were used.

The involvement (i) of Hebbian synaptic plasticity in the described neuronal changes and (ii) of neuromodulators as ''gating'' factors of the neuronal changes, is evaluated. The weakness of the Hebbian schema to explain learning-induced changes and the need to better define what the word ''learning'' means are stressed.

It is suggested that future research should focus on the dynamic of information processing in sensory systems, and the concept of ''effective connectivity'' should be useful in that matter.

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ABBREVIATIONS

BF	Best frequency	dLGN	Dorsal part of the lateral geniculate nucleus
CS	Conditioned stimulus	vLGN	Ventral part of the lateral geniculate nucleus
CS +	Reinforced conditioned stimulus (discrimination training)	LC	Locus coeruleus
		MGB	Medial geniculate body
CS −	Unreinforced conditioned stimulus (discrimination training)	MGd	Dorsal division of the medial geniculate body
		MGm	Medial division of the medial geniculate body
DMS	Delay-matching to sample task	MGv	Ventral division of the medial geniculate body
EEG	Electroencephalogram	MRF	Mesencephalic reticular formation
US	Unconditioned stimulus	NBM	Nucleus basalis magnocellularis
MU	Multi-Units activity	POm	Posterior thalamic complex
RF	Receptive field	VPL	Lateral division of the ventral posterior nucleus
SDT	Signal detection theory	VPM	Medial division of the ventral posterior nucleus
SU	Single unit activity	RE	Reticular nucleus of the thalamus
AI	Primary auditory cortical field	ACh	Acetylcholine
AAF	Anterior auditory cortical field	2DG	2-Deoxyglucose
AII	Secondary auditory cortical field	NE	Norepinephrine
LGN	Lateral geniculate nucleus	NMDA	N-methyl-d-aspartate

1. INTRODUCTION AND AIMS

Over the last decade an increasing number of studies have shown that sensory systems reorganize in adult animals, and a special emphasis has been made on the reorganizations taking place in sensory neocortices. These reorganizations were described under a large variety of circumstances, that will be briefly presented below, from the more artificial ones to the more natural ones (see Table 1). A first set of situations comes from experiments where researchers control the firing rate of the neuron while presenting a particular sensory stimulus. These manipulations of the neuron level of discharge are achieved by applying either pulses of current or pharmacological agents at the vicinity of the recorded neurons. Such studies are usually performed to determine the neuronal mechanisms underlying the plasticity observed either during epigenesis (Frégnac *et al*., 1988, 1992) or in the adult cortex (Cruikshank and Weinberger, 1996a). A second set of studies concerns the reorganizations that are described after peripheral deafferentations, denervations, or after modifications of the peripheral epithelium. Lastly, behavioural training is the third and most natural situation where sensory maps and sensory receptive fields were found to be modified.

Several articles have previously reviewed the cortical plasticity occurring during these different situations (Cruikshank and Weinberger, 1996b; Frégnac and Shulz, 1994; Gilbert, 1993; Kaas, 1991; Rauschecker, 1991; Weinberger, 1995a,b). However, because these different types of plasticity were discussed within the same articles, the readers could have assumed that the same conceptual framework

Table 1. Types of experiments leading to sensory plasticity in adult animals. The type of experiments covered in the present review are listed under item 3, Associative training

	Type of plasticity tested	State of the animal during:	
		Induction of plasticity	Expression of plasticity
1. Manipulation of the neurons firing rate	RF plasticity (Frégnac *et al*., 1988, 1992; Cruikshank and Weinberger, 1996a; McLean and Palmer, 1998)	Anaesthetized	Anaesthetized
2. Peripheral alterations	RF and map changes		
2.1. Deafferentation	(Merzenich *et al*., 1983a; Robertson and Irvine, 1989; Kaas *et al*., 1990; Rasmusson, 1996a,b)	Awake	Anaesthetized
2.2. Denervation	(Merzenich *et al*., 1983b)		
2.3. Syndactyly	(Allard *et al*., 1990; Clark *et al*., 1988)		
2.4. Whisker-pairing	(Diamond *et al*., 1993, 1994)		
3. Associative training			
3.1. Sensory–sensory association	RF plasticity and map changes (Delacour *et al*., 1987, 1990; Cahill *et al*., 1996)	Awake	Awake
3.2. Classical conditioning	RF plasticity[a]	Awake	Awake[b]
3.3. Instrumental conditioning	RF and changes (Bakin *et al*., 1996; Jenkins *et al*., 1990)	Awake/awake	Awake/anaesthetized
3.4. Perceptual learning	Map changes (Recanzone *et al*., 1992a,b,c,d, 1993)	Awake	Anaesthetized

[a]Receptive fields (RF) plasticity was described in the following experiments: Bakin and Weinberger (1990); Diamond and Weinberger (1986); Diamond and Weinberger, 1989; Edeline and Weinberger (1991a); Edeline and Weinberger, 1991b, 1992, 1993); Edeline *et al*. (1993); Lennartz and Weinberger (1992); Ohl and Scheich (1996); Weinberger *et al*. (1993). Map changes were described in the following experiments: Gonzalez-Lima and Scheich (1984); Gonzalez-Lima and Scheich, 1986a); Siucinska and Kossut (1996).
[b]In the two experiments (Lennartz and Weinberger, 1992; Weinberger *et al*., 1993), RF plasticity induced in waking animals was tested in anaesthetized animals.

can be applied, and that the mechanisms underlying these different forms of plasticity are similar. However, the fact that different situations trigger receptive field or map changes does not guarantee that the mechanisms are the same.

A first particularity of the present review will be to focus on a detailed description of receptive field (RF) and map changes occurring following associative training, i.e. the plasticity that is observed when an awake animal learns the association between two events and modifies its behaviour as a function of the learned association. In all but one of the experiments reviewed here, a behavioural index attested to the acquisition about a significant specific stimulus or about a specific situation. The only exception (Section 4.1) concerns the sensory–sensory training used by some authors where no overt behaviour was quantified. These experiments were included in the present review since sensory–sensory protocols performed in awake animals are clearly considered as associative learning in psychology (see for reviews Mackintosh, 1974; Rescorla, 1980). Therefore, I insist on the fact that what is reviewed here is not the field of experience-dependent plasticity. Experience-dependent changes can occur in sensory systems without any specific association: for example, map reorganizations are observed after deafferentations or denervations (for review see Kaas *et al*., 1983), or during natural behaviour such as nursing behaviour (Xerri *et al*., 1994). The fact that experience-induced reorganizations occur in waking animals does not mean that there is a learning process involved in the observed plasticity.

The willingness to review only the plasticity occurring after associative training will have two main consequences. First, it is clear that only a limited aspect of the field of adult sensory plasticity will be discussed. The other aspects of the field will not be ignored; they will be used when appropriate to discuss the potential mechanisms of learning-induced sensory plasticity. Second, I will not consider here results using the most advanced techniques available to map sensory areas, since, at the present time (through January 1998), the results obtained with these techniques do not involve learning situations. For example, although optical imaging of intrinsic signals was recently used to test potential map reorganizations in experience-induced plasticity (Das and Gilbert, 1995; Godecke and Bonhoeffer, 1996), there are yet no results concerning the effects of associative training using such techniques.

It is important to consider that in all cases, the reorganizations described here, at both the RF and map level, involved a dimension that was already present at the sensory periphery. For example, the RF plasticity involved changes in selectivity for pure tone frequency, a dimension that is already present at the cochlea level. Similarly, the maps that were tested were first-order topographic maps (somatotopic or tonotopic), which means that there is a topographic correspondence between the peripheral receptors and the neighbouring columns of neurons in the cortex.* As a consequence, simple relationships exist between RF and maps, and it is possible to consider that RF plasticity reflects local signs of map reorganizations. In all cases here, the use of the word "plasticity" will refer to the fact that effects induced by associative training will be maintained a certain amount of time after the situation of induction. Therefore, modulations of RF induced from one trial to another by experimental protocols used

*This correspondence does not exist for non-topographic coding, such as the orientation map in the primary visual cortex (V1): a stimulus of a given orientation evokes the recruitment of multiple columns spatially dispersed in V1 (see for review Frégnac and Bienenstock, 1998).

in attention studies will not be discussed here. Although this field of research points out that fast and selective modulations of information processing exist in behaving animals engaged in attentional task, the transient nature of the effects suggests that they involve processes and mechanisms different from those involved in learning (for review see Fuster, 1995).

For the sake of clarity, the descriptions of the receptive field and/or of the map changes are grouped by sensory modality; data from human studies will be used when available and appropriate. The putative mechanisms of these learning-induced reorganizations will be discussed across sensory modalities.* Finally, another particularity of the present review compared with previous ones will be to describe changes induced by associative training not only at the cortical level but within the whole thalamo-cortical system. As will be discussed below, the anatomical interconnections between cortical and thalamic level (including the reticular nucleus of the thalamus) are so important that it is almost useless to describe the cortical plasticity without looking at its potential thalamic contribution.

2. ORGANIZATION OF THE THALAMO-CORTICAL SYSTEM

The present paper cannot pretend to give an accurate description of the detailed anatomy of the thalamo-cortical system, which is developed in several reviews either across sensory modalities (Jones, 1985; Merzenich *et al*., 1984; Sherman and Guillery, 1996) or within a given sensory modality [auditory: Weinberger and Diamond (1987); Winer (1992); somatosensory: Diamond and Armstrong-James (1992); Kossut (1992); visual: Sherman and Koch (1986); Crick and Koch (1998)]. However, it is crucial to briefly present the major aspects of thalamo-cortical anatomy because (i) in some cases the effects observed after training were different according to the locus of recordings, and (ii) specific predictions were made concerning the involvement of anatomical divisions in the induction of learning-induced plasticity (Weinberger *et al*., 1990a,b). Efforts will be made to point general considerations across sensory modalities, even if some examples are taken from the organization of the auditory system.

2.1. The Thalamo-Cortico-Thalamic Loop

In the visual, somatosensory and auditory systems, it has long been recognized that the connections between cortex and thalamus form a loop where the topographic organization is preserved (see Jones, 1985). That is, the projections from the retina, and from the lower somatosensory and auditory relays, preserved the topographic organization of the periphery, and in turn, the cortico-thalamic projections match the topographic projections coming in the sensory thalamus. The anatomical complexity of this thalamo-cortical loop (which was sometimes underestimated, see Koch, 1987) causes difficulties for understanding how the thalamo-cortical loop processes information (see Sherman and Guillery, 1996). A first reason is that several thalamic nuclei (and sometimes several anatomical divisions within each nucleus) and several cortical areas are involved in processing the information for each sensory modality. The fact that some of these nuclei and cortical areas form distinct pathways comes from the early work of Graybiel (1972a,b, 1973) who provided a schema for identifying functional pathways. In the visual, somatosensory and auditory system, it is possible to delineate a lemniscal (primary) pathway where the neurons show the greatest selectivity for the physical parameters of the stimuli, and a non-lemniscal (secondary) pathway where the neurons show less selectivity for the parameters of the stimuli. This leads to a situation where several parallel thalamo-cortical loops exist and interact with each other either via cortico-cortical connections, or via the divergence of the cortico-thalamic projections. Even if it was recently speculated that the strength of these thalamo-cortical loops may not be as strong as it is usually supposed (Crick and Koch, 1998), it is clear that their organizations (across species and sensory modalities) constrain the way by which sensory information is processed. Before drawing general conclusions, it seems appropriate to briefly mention the structure and connections involved in the three sensory modalities.

In the visual system, coming to terms with the enormous connectivity of the visual thalamo-cortical loop still represents a major challenge and there is little doubt that years of experiments are still necessary. First, the dorsal lateral geniculate nucleus, which provides the major thalamic input to areas 17, 18 and 19 (and probably a more diffuse input to other visual areas), can logically be considered as the lemniscal line of the visual pathway. Second, it is known from the work of Graybiel (Graybiel, 1970, 1972a,b) that the cat lateral posterior complex (including the lateral posterior and the pulvinar nuclei) furnishes a "non specific" input to areas 17 and 18 and to several other visual areas (see for details Jones, 1985). Thus, the lateral posterior complex can be considered as the non-lemniscal visual pathway. An important contribution toward understanding this non-lemniscal pathway was made by Updyke (1977) when he showed that the cat areas 17, 18 and 19 projected visuotopically to the lateral posterior nucleus and that the cat area 19 projects, again visuotopically, to the pulvinar nucleus (Updyke, 1977). In their principles, these projections exist in other species, but generalizations are difficult given that the lateral posterior nuclei and the pulvinar are organized in a very different way across species. For example, monkeys are usually said to have a single lateral posterior nucleus and at least four pulvinar nuclei, whereas the cat is said to have three or more lateral posterior nuclei and a single

*This review will deliberately avoid referring to in vitro studies. Although they might provide better control of the experimental conditions, specifically for the level of pre and postsynaptic activity, their relevance to clarifying the neuronal mechanisms of learning-induced sensory plasticity is still a matter of speculation as no RF and no map can be tested.

pulvinar nucleus.* In addition, the large number of visual cortical areas in the monkey cerebral cortex, organized in a hierarchical system (with ten distinct levels according to Felleman and Van Essen, 1991), leads to a situation where it is difficult to propose an organizational plan of the thalamo-cortical connections that remains valid across species. Rather than concentrating on the detailed connectivity, it might be more important to consider the distribution of these connections across cortical layers. It has been known for a long time (see for review, Gilbert, 1983) that the terminals from the dorsal geniculate, the lemniscal pathway, reach preferentially layer IV of the primary visual cortex, the exact laminar distribution being a function of the species and of the type of geniculate cells. In contrast, the terminals from the lateral posterior complex, the non-lemniscal pathway, predominantly reach layer I of almost all visual cortical areas. However, there is quite an important proportion of terminals in layer IV in several non primary areas, specially in area 19. Another distinction between the lemniscal and non-lemniscal line comes from the fact that the corticofugal fibres to the lateral geniculate arising in areas 17–18 come from layer VI cells (Gilbert and Kelly, 1975), while corticofugal fibres to the lateral posterior complex arising from the same cortical areas come from layer V cells.

In the auditory system, the situation of the thalamo-cortical loop is schematically summarized in Fig. 1 on the basis of the anatomical data obtained from cats (see for details Winer, 1992). In this modality too, the number of cortical areas and the number of divisions within the auditory thalamus fluctuate across species, leading to difficulties in drawing a general schema. Traditionally, the ventral division of the auditory thalamus (MGv) is considered as the lemniscal component of the auditory pathway based upon anatomical (Morest, 1964, 1965; Morest and Winer, 1986) and physiological criteria (Aitkin and Webster, 1972; Calford, 1983; Imig and Morel, 1985). The medial division of the auditory thalamus (MGm) is considered as the non-lemniscal part based upon anatomical (Winer and Morest, 1983b) and physiological criteria (Aitkin, 1973; Calford, 1983; Rouiller *et al*., 1989). The status of the dorsal division (MGd) was not always clear, mainly since it is composed of different subdivisions. This heterogeneity within the MGd was noted in anatomical studies (Clerici and Coleman, 1990; Clerici *et al*., 1990; Winer and Morest, 1983a, 1984) and physiological studies: a topographic organization was described in the deep dorsal division (Andersen *et al*., 1980; Calford, 1983; Calford and Aitkin, 1983), while cells unresponsive to tonal stimuli were described in the suprageniculate or in the superficial dorsal (Calford, 1983; Calford and Aitkin, 1983). In the cat and all the other species, the primary, tonotopic field (AI) receives from and projects to the tonotopic part of the medial geniculate (MGv). Another tonotopic field (AAF) exists in many species and receives its afferences both from the posterior nucleus and partially from some aspects of the dorsal division. The secondary, non-tonotopic fields (AII for example) receive from and project to the dorsal part of the medial geniculate (MGd). The medial part of the medial geniculate (MGm) sends projections to both the tonotopic and non-tonotopic cortical fields, and it receives corticofugal influence from all the cortical fields. The layer specificity of these connections are clearly different: the projections from MGv and MGd neurons reach layer IV of the tonotopic and non-tonotopic fields, while the projections from MGm mainly reach layer I.

In the somatosensory system, the existence of a somatotopic organization within the ventral posterior nucleus stems from the earliest single unit studies (Jones and Friedman, 1982; Mountcastle and Henneman, 1952; Poggio and Mountcastle, 1960; Welker, 1974). All these studies have shown that the contralateral limbs, trunk and tail are represented in the lateral division (VPL) and the head, face and intraoral structures in the medial division (VPM). In this modality, species differences also cause difficulties for the proposal of a general organization. In monkeys the lemniscal pathway seems to be relayed in the VP by clusters of large cells, the "rods" which receive a dense projection from the trigeminal and dorsal column nuclei (Rausell *et al*., 1992; Rausell and Jones, 1991a,b). The "rods" are densely labelled by the calcium binding protein parvalbumin, and they seem to project in patchy pattern to layer IV providing a precise cortical somatotopic organization (mostly in area 3b and 3a, but also in area 1 and 2). In contrast the "matrix" of small VP cells surrounding the rods is distinguished from the rods by several histochemical markers, including the absence of parvalbumin. This matrix, receiving weak projections from the trigeminal and dorsal columns nuclei, is considered as the non-lemniscal pathway. It projects to the primary somatosensory cortex with very little projections in layer IV. In rodents, a large part of the VPM is divided into elongated cell clusters referred to as "barreloids" (Van der Loos, 1976), and the space between barreloids is free of neurons. Neurons in barreloids project in a dense patchy pattern to the barrels in layer IV of primary somatosensory cortex, and thus can be considered as the lemniscal pathway. Based upon anatomical and physiological considerations, Diamond and Armstrong-James (1992) have proposed that in rat the rostral sector of the thalamic posterior complex (POm) should be considered as the non-lemniscal somatosensory pathway. The rationale is that (i) the cortical projections of the POm neurons avoid the layer IV barrels and reach the septa separating the barrels from each other (Chmielowska *et al*., 1989; Koralek *et al*., 1988); (ii) POm in the rat receives only a weak input from the principal trigeminal nucleus, and (iii) it receives cortical afferences from layer V neurons, whereas VPM neurons receive their cortical afferences from layer VI neurons.

Besides the conclusion that within each sensory modality important species differences exist, the scheme proposed by some authors (Weinberger and Diamond, 1987; Weinberger *et al*., 1990a,b; Diamond and Armstrong-James, 1992; Crick and Koch, 1998) seems relevant. The lemniscal line pro-

* In rodents, lagomorphs, ungulates, there is no pulvinar and the lateral posterior nucleus has one or two divisions (Jones, 1985).

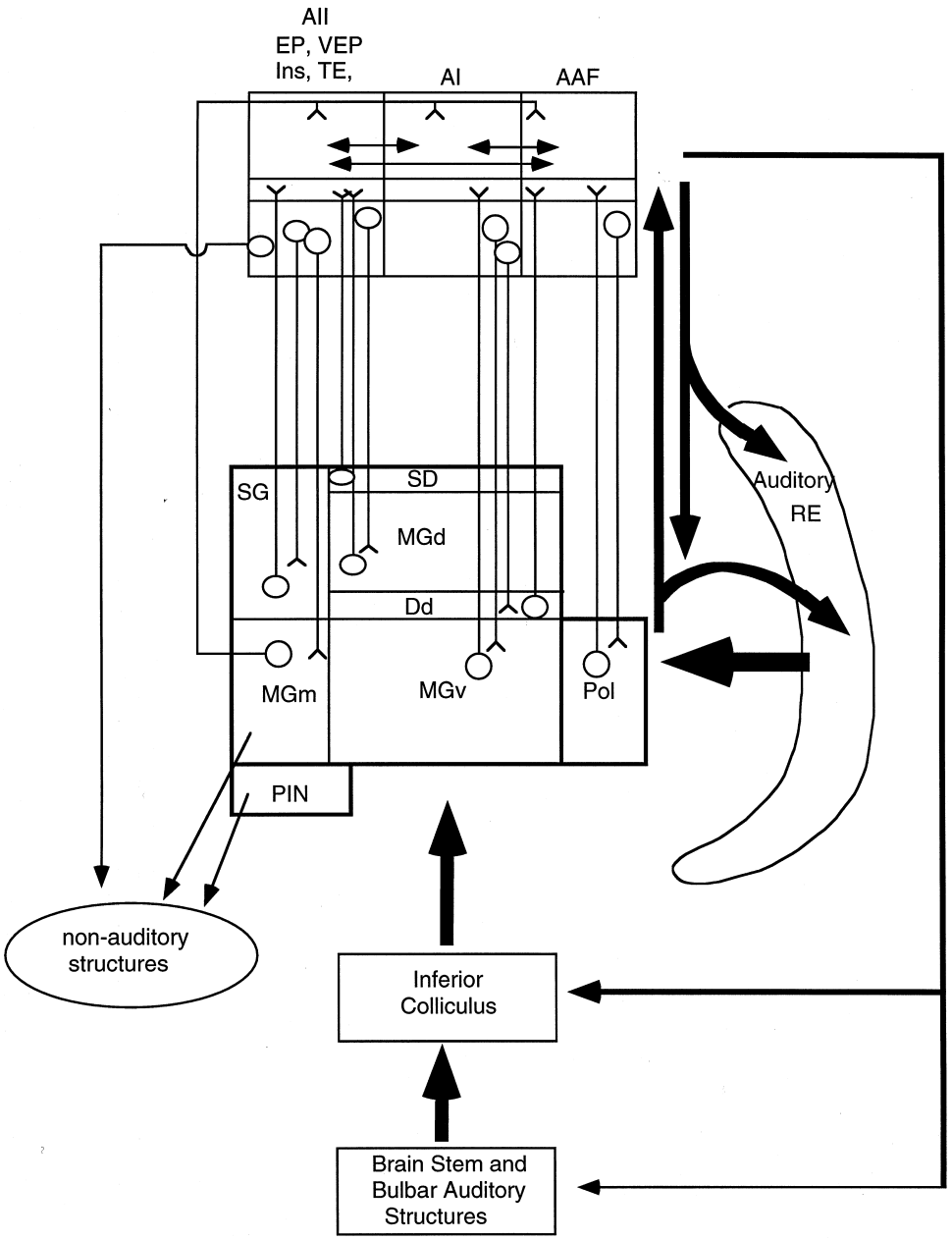

Fig. 1. The thalamo-cortical loop in the auditory system. This schematic representation illustrates the complexity of the thalamo-cortical loops formed by the different divisions of the auditory thalamus, the different fields of the auditory cortex and the auditory sector of the reticular nucleus. The bidirectional connections between the different divisions of the auditory thalamus (SG, SD, MGd, Dd, MGv, MGm, PIN) and the cortical fields are detailed. On the right side of the figure, the thick arrows depict the connections between the RE and the thalamus and the corticofugal projections on the RE. The subthalamic corticofugal projections toward the inferior colliculus and the cochlear nucleus are shown on the extreme right side. Projections to non-auditory structures (shown on the left side) come from the non-primary cortical fields and non-tonotopic parts of the auditory thalamus. Although some particularities exist in the visual and somatosensory thalamo-cortical system, a similar architecture can be found in these two modalities.

jects mainly to layer IV of primary sensory cortices, while the non-lemniscal line mainly projects to layer I. This does not mean that the non-lemniscal line cannot project to layer IV; it does project to layer IV in non-primary cortices. Another key feature is that the lemniscal line seems to receive corticofugal influences from layer VI neurons, while the non-lemniscal line receives from layer V neurons. Thus, the lemniscal and non-lemniscal lines can be distinguished based on (i) their dominant laminar projection to the cortical areas and (ii) the dominant projections they receive from the different cortical layers. As neuro-

modulatory influences (specially the monoaminergic) predominantly reach the sensory cortices in layer I, it is quite relevant to view the influence of the non-lemniscal line as a modulatory influence (Crick and Koch, 1998). Obviously the influence of the extensive corticocortical connections (see for review in the visual system Salin and Bullier, 1995) complicates this scheme, but to what extent these connections attenuate the strength of the thalamo-cortical loops remains a matter of speculation.

Attempts to elucidate the functional role of the cortico-thalamic projections have a long history, but have never been particularly satisfying (see for review Jones, 1985). If one tries to put together the effects observed after cortical inactivation and after cortical stimulation, it is particularly difficult to propose a function for the corticofugal influences. For example, earlier studies reported that weak stimulation of the cortex can either facilitate or inhibit transmission of a subsequent afferent volley through the thalamic relay nuclei. In the three sensory modalities, more recent studies suggest a "gating effect" of the cortico-thalamic fibres. For example, in the somatosensory system, activation of the somatosensory cortex led to excitatory effects in the ventrobasal thalamus both in anaesthetized (Rapisarda *et al*., 1992) and awake animals (Yuan *et al*., 1986); similarly in the auditory system, activation of corticothalamic neurons just before tone presentations often facilitates tone-evoked responses in the MGB, especially at low intensity levels (He, 1997).

However, more subtle effects were recently described by studies aimed at determining the cortical influence on functional properties of thalamic cells. For example, cortical activation or inactivation of the auditory cortex change the properties of MGB cells and can (i) cause shifts of the cell's frequency tuning (Villa *et al*., 1991), (ii) facilitate the responses for a specific range of frequency, (iii) affect selectively long latency activities without modifying the short latency responses (Ryugo and Weinberger, 1976), and (iv) change the "best delay" of echo-delay tuned neurons in the bat (Yan and Suga, 1996; for review, see Suga *et al*., 1997). Similarly in the visual cortex, the results obtained using inactivation procedures suggested that the cortical feedback significantly contributes to length tuning in the lateral geniculate (Murphy and Sillito, 1987), and can help to synchronize the firing of thalamic cells during presentation of a visual stimulus (Sillito *et al*., 1994).

Besides the descriptions of the cortical modulation of functional properties of the thalamic inputs, it seems difficult to draw a more general function for the cortico-thalamic pathway. Perhaps the most elaborate theory remains the hypothesis proposed by Singer in the visual system (Schmielau and Singer, 1977; Singer, 1977). Schmielau and Singer (1977) proposed that the corticofugal pathway facilitates the transmission of signals from binocularly viewed contrasts when these contrasts are presented to precisely corresponding retinal areas, that is when the contrasts are near the fixation plane and thus have only small binocular disparities. In this case, the corticothalamic influences reduce the strength of binocular inhibitions and increase the excitability of relay cells for which the activity pattern from the two eyes are in register. Signals from objects before or behind the fixation plane remain fully subject to binocular inhibition, and may even get actively inhibited by intralaminar lateral inhibitory connections. Thus, the corticothalamic influence can selectively facilitate the transmission of signals from binocularly viewed objects that are near the fixation plane and can be fused into one image. Signals from objects before or behind the fixation plane, which cannot be fused and therefore give rise to double image remain subject to binocular inhibitions in the LGN. These results suggest that the cortico-thalamic pathway favours transmission of binocular information that can be fused and evaluated in terms of disparity depth cues, while it leaves it to the intrinsic LGN circuits to cancel transmission of signals that give rise to disturbing trouble images.

At the present time, there is no direct demonstration of this hypothesis, but it should be possible to propose behavioural experiment to validate this proposed functional role of the corticofugal influence. There is obviously a need for proposing similar functional hypothesis and experimental validations in the other sensory modalities.

2.2. The Role of the Reticular Nucleus in the Thalamo-Cortical Loop

The activity of the thalamo-cortical loop is strongly influenced by the activity of the reticular nucleus (RE) which is part of the ventral thalamus (for reviews see Jones, 1985; Sherman and Guillery, 1996; Guillery *et al*., 1998). Except in its most rostral part, the RE is a fine layer (200–300 μm) of GABAergic cells which surround the dorsal thalamus laterally and ventrally. It receives sensory information from collaterals of the thalamo-cortical fibres, and also from the cortico-thalamic fibres. It projects to the dorsal thalamus, not to the cortex. Within the RE, there are separate sectors related to each sensory modality, and recent anatomical studies show that the topographic projections are preserved within a given sensory modality [somatosensory sector: Cox *et al*. (1996); Crabtree (1992a,b); visual sector: Conley and Diamond (1990); Crabtree (1996); Crabtree and Killackey (1989); auditory sector: Conley *et al*. (1991)]. Depending on the species, the RE represents, or not, the exclusive source of GABAergic inhibitions at the thalamic level. In cats or primates, the percentage of GAD positive neurons (i.e. the number of local interneurons) in the sensory thalamic nuclei ranged 25–30% (Penny *et al*., 1983; Spreafico *et al*., 1983), while in the rat or some bat species this percentage is very low (for example 1% in the rat auditory thalamus,* Winer and Larue, 1988, 1996). Although RE neurons could simply be viewed as local interneurons displaced outside the sensory relays, this is

* This is complicated by the fact that for a given species, different sensory modalities show various percentages of local GAD positive cells (presumed interneurons); see Winer and Larue (1996) for examples.

not acceptable from a developmental point of view since the RE develops in the ventral thalamus which is distinct from the main thalamic nuclei which form the dorsal thalamus (see Jones, 1985).

Regarding the anatomy and function of the reticular nucleus, the visual system presents neuroanatomical particularities. First, the LGN itself contains GABAergic interneurons, even in species lacking such neurons in the auditory and somatosensory thalamus (Winer and Larue, 1996). Second, the perigeniculate nucleus seems to be a second "visual" RE located immediately above the LGN. It is unknown whether one should consider that the effects of the visual sector of the RE per se are attenuated or amplified by the fact that it acts in concert with the perigeniculate and with the intrinsic GABAergic neurons of the LGN. But, in any case, this particularity reinforces the role of the inhibitory processes occurring in the visual thalamus compared with the somatosensory and auditory nuclei.

Most of the work carried out on the RE centre on studying its role in generating or participating in rhythmic activities. For example, both in vivo (Steriade *et al*., 1985, 1987) and in vitro (Bal and McCormick, 1993, 1996; Bal *et al*., 1995a,b) studies have indicated that the RE is critically involved in generating spindle activity in the thalamo-cortical system. Very few studies have tried to determine how the RE influences the processing of sensory information in the thalamo-cortical system, and their results are sometimes difficult to reconcile. For example, excitotoxic lesions of the RE led to a large increase of the RF sizes in the medial ventroposterior thalamus (Lee *et al*., 1994), but opposite effects were not observed after activation of the RE: a pharmacological activation of RE neurons led to a significant reduction of the post-stimulus inhibition, with sometimes a facilitation of the excitatory ON or OFF responses of the ventroposterior neurons (Warren and Jones, 1994). In the auditory modality, stimulations of the auditory sector of the RE attenuated click-evoked responses (Shosaku and Sumitomo, 1983), while inhibition of the RE facilitated the phasic ON tone-evoked responses at the thalamic and cortical level (Edeline *et al*., 1997). Therefore, although not sufficiently documented, the activity of RE neurons seems to be able to modulate the way by which information is processed in the thalamo-cortical system. Besides, a hypothetical role in attentional processes (Crick, 1984), it is still unknown how RE neurons can participate in learning-induced plasticity in the thalamo-cortical system.

2.3. The Subthalamic Projections of the Sensory Cortex

It is important to mention that the cortical level also sends corticofugal inputs to subthalamic structures. First, it has long been described that the auditory cortex projects to parts of the inferior colliculus (Diamond *et al*., 1969). Virtually all the cortical fields project to more than one subdivisions of the inferior colliculus (see for review Winer, 1992). It was previously suggested that the connections between auditory cortex, auditory thalamus and the different regions of the inferior collicullus (IC) form a multiple feedback loop system that can influence the animal's behaviour (for a review see Huffman and Henson, 1990). Very few studies have tried to determine how the auditory cortex influences the functional properties of neurons of the IC, but inhibitory effects were reported in some studies (Sun *et al*., 1989)

Second, a corticobulbar pathway was recently described (Weedman and Ryugo, 1996): layer V neurons of the rat primary auditory cortex were found to project until the cochlear nucleus.* The main target of this projection seems to be the granule cells domain located between the dorsal and the ventral cochlear nucleus.

Therefore, based on anatomical studies, it is obvious that the primary cortex is potentially capable of influencing the processing of acoustic information far before the thalamic level. This means that the input reaching the thalamo-cortical system can be modified by the corticofugal projections.

To summarize this brief and incomplete anatomical survey, one can consider that the thalamo-cortical system is made of multiple thalamo-cortical loops that probably influence each other in many ways. The activity of the sensory sectors of the reticular nucleus is able to modulate these loops. Finally, it is possible that the cortical level exerts a control far before the thalamic level, even if it is very difficult to estimate how important this control is.

3. EFFECTS OF LEARNING IN THE AUDITORY SYSTEM

3.1. Overview of Previous Findings

As described in previous reviews, the auditory system is probably the sensory modality that was the most extensively studied during learning protocols. Starting from the 1950s (Beck *et al*., 1958; Galambos *et al*., 1956; Jouvet, 1956) an impressive amount of studies have reported changes in evoked responses during the acquisition of learning tasks in many species (for reviews see Weinberger, 1980, 1984; Weinberger and Diamond, 1987). Most of these studies have used a classical conditioning protocol where a conditioned stimulus (CS) predicts the occurrence of an unconditioned stimulus (US). In most of the cases,* the US was

* Similar observations were recently made in guinea-pigs: labelled cells were found in the dorsal cochlear nucleus after injections of biocytine or BDA in primary auditory cortex (Rodriguez-Nodal *et al*., 1996).

* The only exception is the set of studies that were published by J. Olds and colleagues using an appetitive US.

an aversive event (usually a footshock). Using this protocol, increased evoked responses were detected using evoked potentials (EP), multiunit (MU) or single unit (SU) activity. These initial studies did not necessary include all the appropriate controls required to prove that the effects (i) were associative in nature and (ii) were not due to stimulus inconstancy.

3.1.1. *Controls of Associative Effects and Stimulus Constancy*

First, to determine whether or not the learning-induced changes are associative, it is necessary to compare the effects obtained in animals submitted to associative conditioning with those obtained in animals submitted to pseudo-conditioning where the CS and the US are delivered in a randomized fashion, thus preventing one predicting the occurrence of the other. Comparisons between a situation where the stimulus is not significant (for example, during habituation) and a situation where the stimulus is significant (during conditioning) is not adequate, since it is well-known that the introduction of a nociceptive stimulus in a situation induces an arousal state which modifies the sensory responses (for review see Weinberger, 1982a,b). Although not exactly the equivalent, the use of a discriminative protocol is also a valid control, since it allows to follow the time course of the changes in evoked responses to the stimulus that acquires a predictive value (the reinforced conditioned stimulus, CS+) and to a stimulus that does not (the non-reinforced conditioned stimulus, CS–).

Second, it has long been reported that three main factors can modify stimulus intensity at the cochlea of an awake animal: (i) sound-shadowing by the pinna (Wiener *et al*., 1966), (ii) the action of the middle ear muscles (Baust *et al*., 1964; Carmel and Starr, 1963; Galambos and Rupert, 1959), (iii) masking noise produced by the animal's movements (Baust and Berlucchi, 1964; Irvine and Webster, 1972; Starr, 1964). The use of earphones may control the first factor (the stimulus constancy at the external auditory meatus) but does not control the two other factors. There are two alternatives to circumvent this problem. One possibility is to train the animal under neuromuscular blockage. This strategy was adopted in an earlier study (Buchwald *et al*., 1966) and, until 1989, in all the studies by Weinberger and colleagues. Another possibility is to train the animals in a discriminative training and to analyze only the first tens of milliseconds after tone onset (less than 50 msec). This strategy relies on the fact that the animal's position in relation to the speaker, the animals movements and the tension of its ear muscles have no reason to be systematically different at the time of occurrence of the CS+ and of the CS−. In this case, it is assumed that, when averaged across trials, the stimulus inconstancy is the same at the CS+ and at the CS−. It is also assumed that, during the first 50 msec after tone onset, there is no possibility for a contamination of the recordings by a feedback coming from the animal's conditioned response (CR). This strategy, which had led to polemics in the past (see Gabriel, 1976 vs Disterhoft, 1977), was adopted by several laboratories working on freely moving animals (Disterhoft and Stuart, 1976; Edeline *et al*., 1990a,b; Gabriel *et al*., 1982).

3.1.2. *Neuronal Conditioning at the Thalamic Level*

Using these controls, several laboratories have reported that both at the cortical and the thalamic level, associative modifications of tone-evoked responses occur during learning. However, to draw a realistic picture of these results, several factors have to be examined: first the locus of recordings, i.e. the fact that anatomically distinct areas show differential effects; and second the type of recordings, i.e. MU vs SU activity.

At the thalamic level, the compartmentalization of the learning-induced plasticity was, and is still, controverted. Although studies have demonstrated neuronal conditioning in the auditory thalamus before (for example, Gabriel *et al*., 1975, 1976), the clearest evidence for a compartmentalization comes from the only experiment where the data were analyzed according to the MGB divisions (Ryugo and Weinberger, 1978). In this study, several electrodes were implanted in the different MGB divisions. The results indicated that the only MU recordings which met the criterion for associative changes and for discrimination were from the medial division of the MGB (MGm): within a given animal, showing a behavioural response (pupillary dilatation), the MGm tone-evoked discharges were enhanced while the MGv tone-evoked discharges were not. Other authors have found similar increased MU responses in the MGm using classical conditioning (Buchwald *et al*., 1966; Halas *et al*., 1970), instrumental avoidance task (Gabriel *et al*., 1975, 1976), aversive discriminative task (Edeline *et al*., 1990a,b) and appetitive conditioning (Birt *et al*., 1979; Birt and Olds, 1981; Disterhoft and Olds, 1972; Olds *et al*., 1972). But, increased MU responses were also found in the MGd (Gabriel *et al*., 1982, p. 562) and decreased MU responses were observed in the MGv after overtraining (Gabriel *et al*., 1982, p. 559).

Single unit recordings revealed a more complex picture. In cats, most of the MGm neurons (24/37, 71%) developed discharges plasticity, but 29% of these changes were decreases (Weinberger, 1982a,b; see also Weinberger and Diamond, 1987). In rats, 13/20 of the recorded MGm neurons showed increased evoked responses, while 2/7 MGd neurons showed significant increased discharges (Edeline, 1990). Lastly, the neuronal conditioning is the MGm is robust enough to be maintained during extinction sessions and to exhibit differential responsiveness to a CS+ and a CS− during extinction (Supple and Kapp, 1989). This is of importance if one considers that the MGm is the only part of the thalamus that projects to almost all cortical fields (Winer, 1992)

3.1.3. *Neuronal Conditioning at the Cortical Level*

In the auditory cortex, it seems that there is a large agreement on the fact that increased tone-evoked responses can be observed using MU recordings whatever the species and the learning task

(Disterhoft and Olds, 1972; Disterhoft and Stuart, 1976; Oleson *et al*., 1975; see for review Weinberger and Diamond, 1987).* However, as is the case at the thalamic level, single unit studies revealed a more complex picture. In the cat primary auditory cortex, 62% of the neurons developed response plasticity to the CS during acquisition of the pupillary CR. The response changes emerged quickly; on average they attained statistical criteria after 13 conditioning trials. However, as for the MGm, the direction of the changes was both increases ($n = 6/21$) and decreases ($n = 7/21$; see Weinberger *et al*., 1984a). Using the same protocol, 95% of the neurons exhibited tone-evoked plasticity in the cat secondary auditory cortices (AII/VE, Diamond and Weinberger, 1984). Again, an equivalent number of cells showed increased evoked responses ($n = 11$) and decreased evoked responses ($n = 10$); and this was also the case in rabbit non-primary cortex (increases 47%, decreases 53%, Kraus and Disterhoft, 1982). Interestingly, in this study, the percentage of neurons exhibiting significant changes was the same in conditioned rabbits which did not learn the behavioural responses (the nictitating membrane conditioning) and in rabbits which underwent pseudoconditioning (20% in bad learner vs 19% in pseudoconditioned animals); this percentage was higher (51%) in conditioned rabbits that learned the behavioural response.

The discrepancy between the effects observed with MU recordings (revealing only increased evoked responses) and those reported with SU recordings (revealing both increases and decreases) can be explained by the thoughtful analysis performed by Weinberger *et al*. (1984a) on the data from the primary auditory cortex. The authors pooled together the data coming from their single units to build a "combined MU histogram". This histogram revealed that the tone-evoked discharges were increased during conditioning compared to the sensitization period. Thus, multiunit recordings cannot be considered as representative of the effects occurring at the single cell level because increased discharges are detected even if more neurons actually develop decreased responses than neurons develop increased responses. Also, single unit data suggest that it will be incorrect to conclude that the excitability of single neurons simply increases during learning.

3.2. The Problems of Merging Learning and Sensory Physiology

Whatever the amplitude and the direction of the changes in evoked responses at the CS frequency, and the exact percentage of neurons actually presenting these effects, it is crucial to realize that these experiments did not attack the major question raises by these results: What does this mean about the way by which cortical and thalamic neurons process information, and what does it mean for the messages sent by the auditory neurons toward non-auditory structures? To answer this question, a first approach is to test the neurons' selectivity for a particular dimension of the sensory stimulus, and to determine how learning modifies this selectivity. Such experiments require to perform within the same protocol a sensory physiology experiment and a learning experiment. Although it is legitimate to consider that the fields of sensory physiology and learning are complementary (Weinberger, 1995a), they are difficult to conciliate due to (i) the type of preparations and (ii) the type of protocols that are used in these two fields.

First, sensory physiologists describe how single cells code information, and how this information is represented at the map level. This task is easier to do when the state of the brain is controlled (and supposedly stabilized*) by an anaesthetic. In contrast, learning experiments require working with awake animals. In addition, neurobiologists of learning and memory traditionally focused their efforts (i) in looking for animal models of the human amnesic syndrome observed after lesions of the hippocampus and/or associative cortices and (ii) understanding the mechanisms of synaptic plasticity (obviously in vitro preparations provide the more appropriate conditions to reach this goal).

Second, the protocols used in learning experiments require the repetition of one stimulus (two in the case of a discrimination) with a low rate of repetition (1 stimulus/minute or less) to increase the probability that the CS, and not the context, is associated with the US. In contrast, in sensory physiology the protocols are often designed to determine the neuron's selectivity for several dimensions of the sensory stimulus, thus leading to presentation of a large amount of stimuli in the shortest amount of time (the rate of presentation is function of the sensory modality that is studied).

Therefore, to perform a learning experiment and a sensory physiology experiment within the same study, it was necessary to design new types of protocols. In the following studies, the experiments were carried out in awake animals, and the dimension that was studied was the frequency selectivity. At any level of the auditory system, the frequency receptive field (RF) describes the capacity of the neurons to respond for a limited range of frequencies at a given tonal intensity. The protocol that was used (Fig. 2) involved the determination of the frequency RF before and after a learning session, with the implicit assumption that the effects induced during learning will produce detectable changes in the post-training RF when compared with the pretraining RF. Given that increased responses at the CS frequency were often observed during conditioning, two different results could have been obtained on a theoretical ground after this protocol (see Weinberger, 1995b): either the changes at the CS frequency reflect a general modification of the neurons RF, or the changes at the CS frequency are specific to this frequency and, in that case, the selec-

* In a particularly interesting study, Oleson *et al*. (1975) observed that a differential effect obtained in the auditory cortex during discrimination training was maintained 8 days after training. Long-lasting retention was also observed in another study (Edeline *et al*., 1990a).

* But the electroencephalogram (EEG) is not recorded very often in sensory physiology experiments.

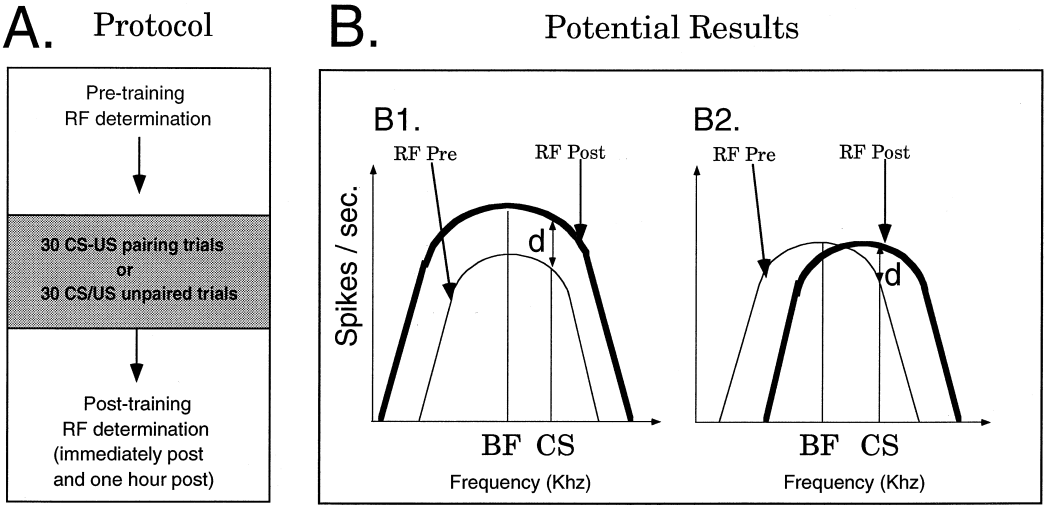

Fig. 2. Protocol used to test RF plasticity during a learning experiment. (A) The protocol consists of three phases. First, the RF of the recorded cell was determined by presenting 10–15 pure tone frequencies at 3–10 intensities. At a given intensity, each tone was repeated 10 or 20 times with an intertone interval of 1 sec, which led to a RF determination which lasted between 15 and 30 min. In the second phase (shaded area) one of the frequencies utilized to test the RF is used as conditioned stimulus (CS) during a classical conditioning protocol in which it predicts the occurrence of the unconditioned stimulus (US). For pseudo-conditioned animals, this learning phase was replaced by 30 CS/US unpaired presentations. Third, the RF was redetermined by presenting the tones of different frequencies and intensities in exactly the same order as before learning. When possible, several post-training RF determinations were made (immediately after, 1 hr after, and up to 24 hr post-training). (B) The two extreme potential results that could be expected from such a protocol are represented in B1 and B2. (B1) General increase in excitability. The RF obtained after training (thick curve) is enlarged compared with the pre-training RF (thin curve). This enlargement is the consequence of increased responses for all the frequencies tested. Therefore, after training the increased response at the CS frequency (labelled "d") is not specific for the CS frequency. Note that in this case the pre-training best frequency (BF) remains at the same frequency after training. (B2) Tuning change. The same increased response "d" is observed at the CS frequency. Such an increased response does not exist at the pre-training BF. Potentially, if the increased response at the CS is strong enough, the CS can become the new best frequency of the neuron. This differential effect can lead to "re-tune" the neuron to the CS frequency.

tivity of the neurons shifts to or toward the CS frequency.

3.3. Receptive Field Plasticity in the Auditory Cortex and Thalamus

3.3.1. *Description of the RF Plasticity in the Auditory Cortex*

Using this strategy, the first data were obtained in the cat secondary areas AII and VE. Three major results came from these earlier reports (Diamond and Weinberger, 1986, 1989). First, in the absence of any behavioural training, the RF showed stability which was important since RFs are not often tested in awake animals. This stability was observed both for normally tuned cells (see Fig. 6 in Diamond and Weinberger, 1989) and for very broadly tuned cells responding on several octaves (see Fig. 7 in Diamond and Weinberger, 1989). Second, when the RF was tested after pseudo-conditioning, there was either a general increase or a general decrease compared with the control RF (for cases of general increase see Figs 9 and 13 in Diamond and Weinberger, 1989; for a case of general decrease see Fig. 11 in the same reference). Third, after associative conditioning, the RF were selectively modified in 12/20 cells, but, again, the effects were either increases (see for example Figs 13 and 16 in Diamond and Weinberger, 1989) or decreases (see Fig. 9 in Diamond and Weinberger, 1989).

Although some preliminary data were collected in the cat primary cortex (see Figs 12-8 and 12-9 in Weinberger *et al.*, 1984b), the bulk of the data obtained in the primary auditory cortex (AI) was obtained in awake guinea-pigs. When a simple conditioning protocol was used, CS– frequency specific increases were reported in 70% of the cases (7/10 recordings), while general increases were reported in 3/10 recordings (Bakin and Weinberger, 1990). Since the pre-training best frequency (BF) often showed decreased responses, in many cases the CS frequency became the new BF after conditioning. Thus, differential effects often led to "re-tune" the neurons to the CS frequency. These effects were not transient: both in the AII/VE areas and in AI, the effects were as selective when tested 1 hr after completion of training (Bakin and Weinberger, 1990; Diamond and Weinberger, 1986, 1989), and in few recordings obtained up to 24 hr post-training (Bakin and Weinberger, 1990) selective effects were still observed (4/6 cases). These effects were clearly distinct from those observed after pseudo-conditioning (random presentation of tones and footshocks) which produced general increased responses in the cells' RF (Bakin *et al.*, 1992).

Subsequent studies described other characteristics of selective RF changes. First, the rapidity of occurrence of the changes was determined by testing the neurons' RF after 5, 15, 30 training trials. It was found that specific effects could be detected after five training trials; the percentage of selective effects slightly increased after 15 trials, but was not larger after 30 trials (Edeline *et al.*, 1993). Second, the selectivity of the effects occurring during discrimination, when more than two stimuli are presented during training, was determined (see Figs 3 and 4). After discrimination training, there were selective increases in favour of the CS+ in 49% of the cases (20/41 recordings) and no selective increase for the CS− frequency (Edeline and Weinberger, 1993). Similar effects were also reported after instrumental training involving a two tone discrimination (Bakin *et al.*, 1996). This last result is of importance since during instrumental conditioning, once the subject has learned the appropriate response, the level of fear at the CS is probably reduced compared with the fear occurring at the CS presentation during classical conditioning. Therefore, the expression of selective RF changes does not seem to depend upon the level of fear present during the training situation.

As stated in Section 3.2, combining a sensory physiology experiment and a learning experiment within the same protocol forces to test the RF after the training session. To avoid this situation, Ohl and colleagues (Ohl *et al.*, 1992; Ohl and Scheich, 1996) designed a protocol where the RFs were tested at the same time as the training session took place. In this protocol, pure tones were delivered in a pseudo-random order with an intertone interval ranging from 250 msec to 3 sec (the interval was kept constant for a given experiment). After checking the stability of the neurons RF, the rate of acoustic stimulations was kept the same but one of the tones was followed by a mild electrotactile stimulation on the animal's tail. Because no change in the presen-

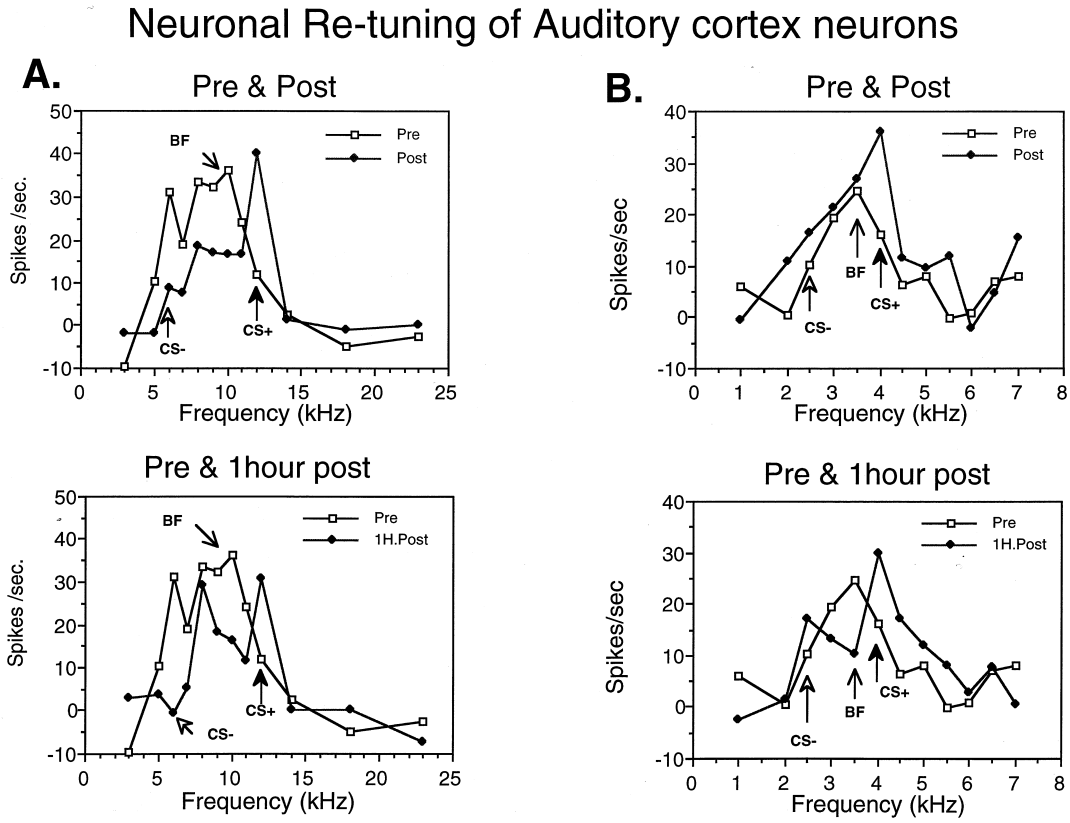

Fig. 3. Neuronal retuning of auditory cortex neurons. Two individual examples of selective RF changes obtained after discrimination training are presented in (A) and (B). (A) For this cell, testing the pre-training RF at 50 dB revealed evoked responses from 5 to 12 kHz, the BF (eliciting the largest responses) was at 10 kHz. During training, the frequency paired with the unconditioned stimulus (US) was 12 kHz, while the frequency never paired with the US was 6 kHz. When the RF was tested post-training, large increased responses were observed at the CS+ frequency, while decreased responses were observed at many other frequencies, including the pre-training BF and the CS− frequency. These differential effects allowed the CS+ to become the new best frequency after training. This effect was observed both immediately post-training and 1 hr post-training. (B) For this cell, the RF tested at 80 dB revealed responses from 2 to 5.5 kHz with a pre-training BF at 3.5 kHz. The CS+ was selected to be 4 kHz and the CS− was selected to be 2.5 kHz. Both immediately and 1 hr post-training, the responses at the CS+ frequency were increased in such a way that the CS+ became the new BF of the cell. Note that, in this case, this neuronal re-tuning occurred with general increased responses, increases at the CS− and BF responses were also obtained (modified from Edeline and Weinberger, 1993).

tation of the acoustic stimuli occurred, the introduction of the US was the only cue that indicated to the animal the onset of the training session. It is worth pointing out that in this situation, the animal was engaged in a discrimination task between a single CS+ and 11 CS−. Using this protocol, selective effects were reported in the primary cortex of awake mongolian gerbils. However, these selective effects consisted of decreased responses or no changes at the CS+ frequency, while responses at frequencies adjacent to the CS+ were increased. According to the authors, such effects contribute to building a local gradient (or to enhance a pre-existing local gradient), which allows the read-out of the CS+ frequency without interfering with the read-out of the neurons' BF. Although very attractive, these findings have to be attenuated by the fact that there is no proof that the animals actually learned about the CS+: the animals exhibited continuous bradycardia during the RF tests where the US was present, and therefore there is no guarantee that the animal has identified one given frequency as predictive of the US. However, the merit of this study is to emphasize that increased responses might not be the only way to code a newly learned aspect of an acoustic stimulus. In fact, these ideas were implicitly present in some initial studies: first, because during training trials there were as many decreases as increases in AI (Weinberger *et al*., 1984a) and AII (Diamond and Weinberger, 1984); and second, because in the post-training RF, several cells behaved like "notch filters"* (see for explanation the appendix in Diamond and Weinberger, 1989), a finding which is close to the formation of a local gradient in Ohl and Scheich (1996) experiment.

Lastly, recent findings point out that, after behavioural training, the temporal characteristics of the neuronal responses can be differentially affected at the CS frequency vs at neighbourhood of the CS frequency (Ohl and Scheich, 1997). This means that the spectro-temporal characteristics of auditory neurons can be modified by learning (the usefulness of the spectro-temporal characterization can be found in Eggermont *et al*., 1981). Such results might have important implications, since it is usually assumed that learning can affect both the strength of the responses and the time-course of the responses, and therefore integrated rate measures of neuronal responses and RFs may reveal only one aspect of the effects of learning on sensory processing.

3.3.2. *Description of the RF Plasticity in the Auditory Thalamus*

As pointed in Section 2, the anatomy forces one to consider the thalamus and cortex as two levels of processing that can hardly be dissociated. Therefore, one can wonder whether or not the effects described at the cortical level were already present in the auditory thalamus. Because studies have pointed that, within the same animal, learning can produce different effects in anatomical divisions of the MGB (Ryugo and Weinberger, 1978), it was logical to analyze separately the RF changes in these different divisions. Experimental evidences demonstrated unambiguously selective RF plasticity in favour of the CS frequency in all MGB divisions. As summarized in Table 2, using very stringent criteria, selective RF changes represented between 29% and 55% of the observed results. However, several important differences exist between thalamic divisions in terms of (i) time course of the effects, (ii) constraints for the occurrence of the effects.

A first study described the effects occurring in the dorsal division. From 38 recordings obtained in this division, 55% (21/38) showed selective effects after conditioning; 16/21 were selective increases and 5/21 were selective decreases. In all cases, when a selective effect was observed immediately after training, it maintained and was sometimes more selective 1 hr after training (Edeline and Weinberger, 1991a). In the ventral division, MGv, selective effects were observed for 29% of the recordings (5/17 cases). Two major constraints were detected in this division. First, these effects were short-lasting: they dissipated or totally disappeared 1 hr after training. Second, the selective effects only occurred if the CS frequency was selected within 1/8 of an octave from the pre-training BF; otherwise general increase in the neurons' RF was observed after training (Edeline and Weinberger, 1991b). Thus in the MGv, it is possible to predict the occurrence of selective RF plasticity. Also, this points out a potential bias in selecting the CS frequency based on the pre-training RF: in the particular case of the MGv data, the results of the experiment could have been 0% of selective effects if the CS was always selected far away from the BF, but it could have been 100% of selective effects if the CS was always selected close to the BF. Nonetheless, as this type of experiment was done "blind", i.e. without knowing in which MGB division a given neuron was recorded, the logical conclusion of these studies should be that the probability of observing selective RF plasticity in the ventral division is lower than the probability of observing such effects in the dorsal division (Figs 5–9).

The results obtained in the medial, magnocellular part of the MGB (MGm) corroborated the findings presented above (Edeline and Weinberger, 1992). Selective effects were obtained for 48% of the recordings (14/29) and as in the MGd, these effects were still present when tested 1 hr after training. Given that the MGm is probably the most heterogeneous part of the MGB, with both narrowly tuned and broadly tuned cells, with long and short latency responses (Calford, 1983), detailed analyses were carried out to look for predictors of the neuronal re-tuning. Selective RF plasticity was observed for both narrowly tuned cells and broadly tuned cells, but a differential evolution of the effects was noted. For the narrowly tuned cells, the effects tended to dissipate as in the MGv: the increase at the CS was smaller and the selectivity was impaired 1 hr after training. In contrast, for the broadly tuned cells, the effects tended to develop with time: the increase at the CS frequency was larger and the selectivity was improved 1 hr after training. Again,

*A notch-filter has a broad bandpass with a cut-off around a given frequency.

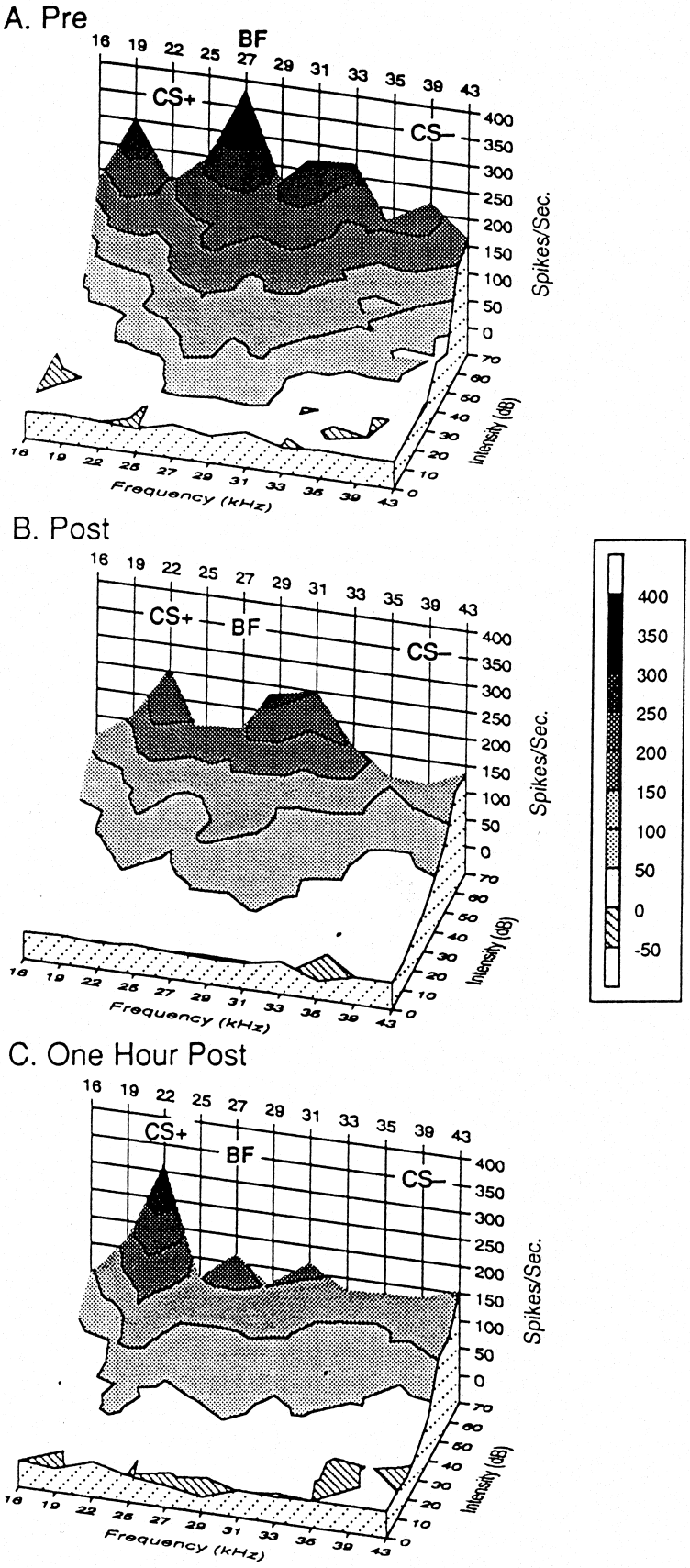

Fig. 4 *caption opposite*

Table 2. Percentage of CS-specific effects in the different divisions of the medial geniculate body. A change in the RF has to meet three stringent criteria to be classified as CS-specific effects: (i) the maximum change in the RF has to be at the CS frequency, (ii) the bandwidth of the changes has to be ±0.25 octave around the CS and (iii) the change at the CS frequency has to be at least 50% greater than the change at the pre-training best frequency (for details see Edeline and Weinberger, 1991a, Edeline and Weinberger, 1991b, Edeline and Weinberger, 1992)

		Associative training		Non-associative training	
		CS-specific	General[a]	CS-specific[b]	General[c]
Anatomical	MGd	55% (21/38)[d]	45% (17/38)	0% (0/6)	100% (6/6)
Thalamic	MGv	29% (5/17)	71% (12/17)	0% (0/6)	100% (6/6)
Divisions	MGm	48% (14/29)	52% (15/29)	0% (0/13)	100% (13/13)

[a]In all thalamic divisions, there were both general decreases and general increases after associative training. For example, there were 8/17 general increases in the MGd, 11/12 general increases in the MGv and 7/15 general increases in the MGm.[b]The recordings obtained during pseudo-conditioning never met the three criteria defined above and therefore none of them was classified as CS-specific.[c]There was both general increases and decreases after pseudo-conditioning training. For example, there were 6/6 general increases in the MGd, 4/6 general increases in the MGv and 8/13 general increases in the MGm.[d]In the MGd, 16/21 CS-specific effects were specific increases and 5/21 were specific decreases.

needless to say that this type of relations are precious because they can give clues concerning the conditions of occurrence (and of maintenance) of selective plasticity. These relationships suggest that the narrower the initial tuning of the cell, the shorter the duration of the selective changes observed after training. As it is often assumed that narrow RFs, characteristic of MGv neurons, are maintained by lateral inhibitions (Allon *et al.*, 1981; Pelleg-Toiba and Wollberg, 1989; Phillips *et al.*, 1985; Shamma and Symmes, 1985), it is conceivable that strong lateral inhibition networks play a role either in the probability of occurrence of the selective changes, or in the duration of these effects.

3.3.3. *Relationship Between RF Modifications and Behavioural Responses*

In the first cortical studies, it was mentioned that, although the animals expressed clear behavioural CR during the conditioning trials, they did not express any behavioural response during the post-conditioning RF determination, even during the presentation of the CS (e.g., Fig. 4 in Diamond and Weinberger, 1989). Also, in a discrimination task, the same percentage of selective RF changes was observed when a difficult discrimination prevented the animals from expressing behavioural discrimination and when an easy discrimination allowed the animals to express behavioural discrimination (Edeline and Weinberger, 1993). This could be due to the fact that the easier the task at the behavioural level (i.e. when the CS+ and the CS− are far apart), the more difficult it should be to induce a neuronal re-tuning since in this case the CS+ frequency is taken far away from the pre-training BF (see for discussion Edeline and Weinberger, 1993).

This absence of relationship could also be the consequence of the fact that the auditory cortex is necessary neither for discrimination between pure tones, nor for the expression of the behavioural response used in these studies (pupillary dilatation in the cat and bradycardia in the guinea-pig). As the MGB and its connections with the amygdala are necessary for the acquisition of fear conditioning (see for review, LeDoux, 1990), a relationship could have been expected at the thalamic level, especially in the MGm which sends direct input to the amygdala (Bordi and LeDoux, 1994; Clugnet *et al.*, 1990; LeDoux *et al.*, 1985). But, whatever (i) the indices used to quantify the behavioural responses, (ii) the indices used to quantify the selective RF changes and (iii) the division of the MGB, there was also no relationship between the RF changes and the behavioural performance (Fig. 10). Of course, one could simply consider that it is not relevant to look for relationships between the neuronal plasticity observed at the SU or MU level and a behavioural performance in vertebrate preparations. Nonetheless, such relationships were obtained in other situations (see Section 5.3.1).

3.3.4. *Relationship Between RF Modifications and Training Trials Data*

As the changes of SU responses during the training trials were increases or decreases (Weinberger *et al.*, 1984a; Diamond and Weinberger, 1984), and as the RF changes obtained in AII/VE were increases or decreases (Diamond and Weinberger, 1986, 1989), it was logical to look for relationships

Fig. 4. Neuronal re-tuning of auditory cortex neurons across intensity. The data collected at all the intensities tested are shown on a 3-dimensional graph where the *x*-axis is frequency, the *y*-axis the response magnitude and the *z*-axis is the intensity (10 dB step). (A) The pre-training RF determination revealed that at all the intensities the BF was at 27 kHz. The CS+ was selected in a "valley" at 22 kHz, and the CS− was a secondary peak at 39 kHz. (B) Immediately post-training there were pronounced decreased responses at the pre-training BF across intensity. Increased responses were observed at the CS+ frequency and decreased responses at the CS− frequency. (C) One hour post-training, the only peak of excitation was around the CS+ frequency. Note that the selective increase at the CS+ frequency can be observed across intensity for both the immediately post and the 1 hr post RF (modified from Edeline and Weinberger, 1993).

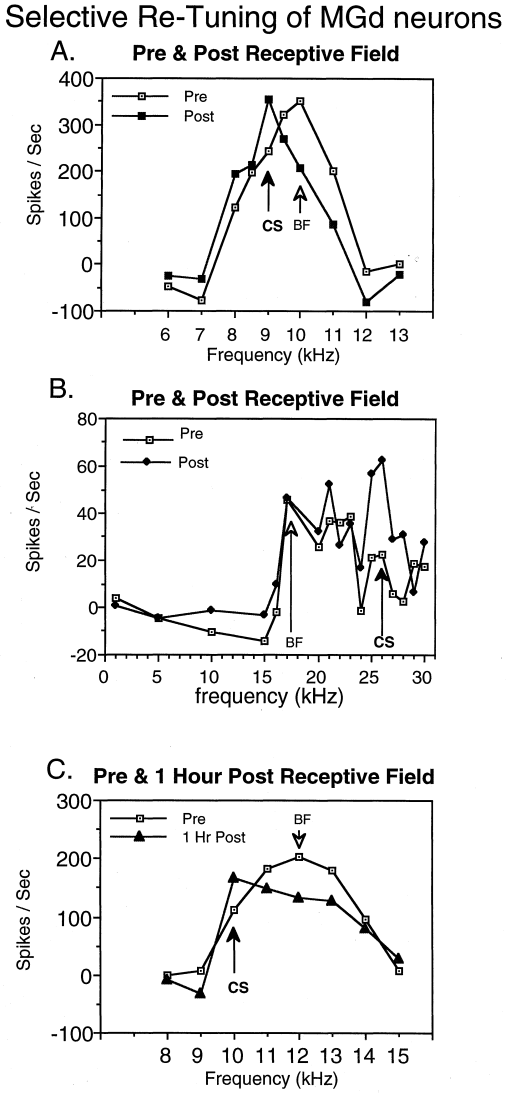

Fig. 5. Neuronal retuning of neurons in the dorsal division of the Medial Geniculate Body (MGd). Three examples of neuronal re-tuning at the CS+ frequency are presented (modified from Edeline and Weinberger, 1991a). (A) For this recording obtained in the deep dorsal nucleus at 70 dB, determination of the pre-training RF revealed responses from 8 to 11 kHz and a best frequency at 10 kHz. The CS frequency was selected at 9 kHz. The post-training RF showed that the responses at the CS were increased, but more importantly the responses were modified across the frequency dimension in such a way that the whole RF seems to shift toward the CS frequency. (B) This neuron recorded in the supragenicular showed at 60 dB a broad pre-training RF extending from 17 to 30 kHz, with a BF at 17 kHz. The CS frequency used during training was at 26 kHz. The post-training RF showed increased responses at and around the CS frequency and no increased responses at the pre-training BF. This differential effect led to re-tune the neuron at the CS frequency despite the initial important distance between CS and pre-training BF. (C) Selective re-tuning observed 1 hr post-training for a recording obtained in the depth dorsal nucleus. Pre-training a symmetrical RF centred around the BF at 12 kHz. The CS frequency used during training was 10 kHz. One hour post-training, the responses were decreased at almost all the frequencies tested, except at the CS frequency which exhibited increased responses, and was the new BF.

between the effects induced during the conditioning trials and the effects expressed after training in the post-training RF. The study by Diamond and Weinberger (1989) precisely described the lack of relationship between the effects observed during and after training. The authors have proposed that the RF plasticity observed in these cortical areas are "context dependent". This explanation is based on the fact that the animal is able to perceive that the situation differs during training and post-training. As the animal did not express CRs at CS presentation during the post-training RF while it expressed CRs during training, it can be assumed that the animal recognized the context in which the CS was presented: When the CS is presented within a rapid sequence of tones in ascending order (with a inter-

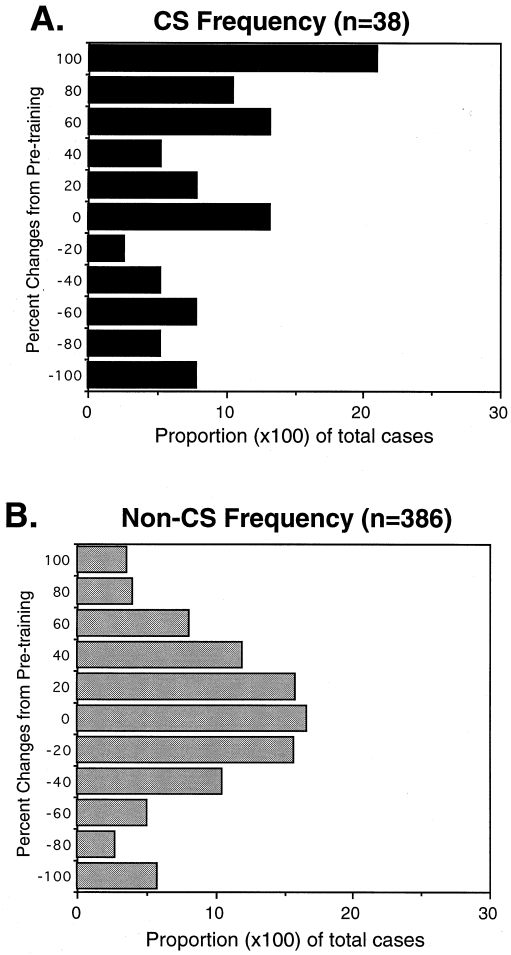

Fig. 6. Distribution of the percentage of changes obtained across all the recordings in the MGd at the CS frequency (A) vs at other frequency (B). Distribution of normalized difference scores obtained for the CS frequency (paired with the US) and for the non-CS frequencies (non-paired with the US). For each recording, the response to the frequency which displayed the maximum change in the post-training RF from the pre-training RF had a normalized score of $\pm 100\%$ (for a maximum change being an increase or a decrease, respectively). Lesser changes to other frequencies were scaled to this value. (A) For the CS frequency, the distribution differs significantly from a normal distribution centred around 0% change, due to the large number of recordings exhibiting $+100\%$ changes. (B) For the non-CS frequencies, the distribution was not significantly different from a normal distribution centred around 0%. The two distributions were significantly different ($\chi^2 = 40.13$, df = 10, $p < 0.0001$). From Edeline and Weinberger (1991a), unpublished observations.

tone interval 1–2 sec) repeated 10–20 times, the context can be considered as "safe". When the CS is presented alone with a large intertone interval (1–2 min) followed by the US, the context can be considered as "unsafe". According to the authors, the expression of neuronal plasticity in the auditory cortex is context-dependent, that is the physiological events triggered by the contextual cues are powerful enough to change the plasticity in one direction or in the other. It could be argued that this lack of relationship between training results and RF results is the consequence of the complexity of the tuning curves in the area AII and VE. However, this lack of relationship was also noted in data coming from the different thalamic divisions (Edeline and Weinberger, unpublished observations).

3.4. Map Changes After Behavioural Training

3.4.1. *Preliminary Remarks*

The rationale to look for map changes after behavioural training should have come as the logical consequence of the description of selective RF changes after learning experiments. However, the chronological order was not the rational one: map changes were described before (or at the same time) as the selective RF changes. The main reason was probably that in other sensory modalities, map changes were already reported in the adult cortex after peripheral injuries (Merzenich *et al.*, 1983a,b), and temptations were strong to look for changes after behavioural training.

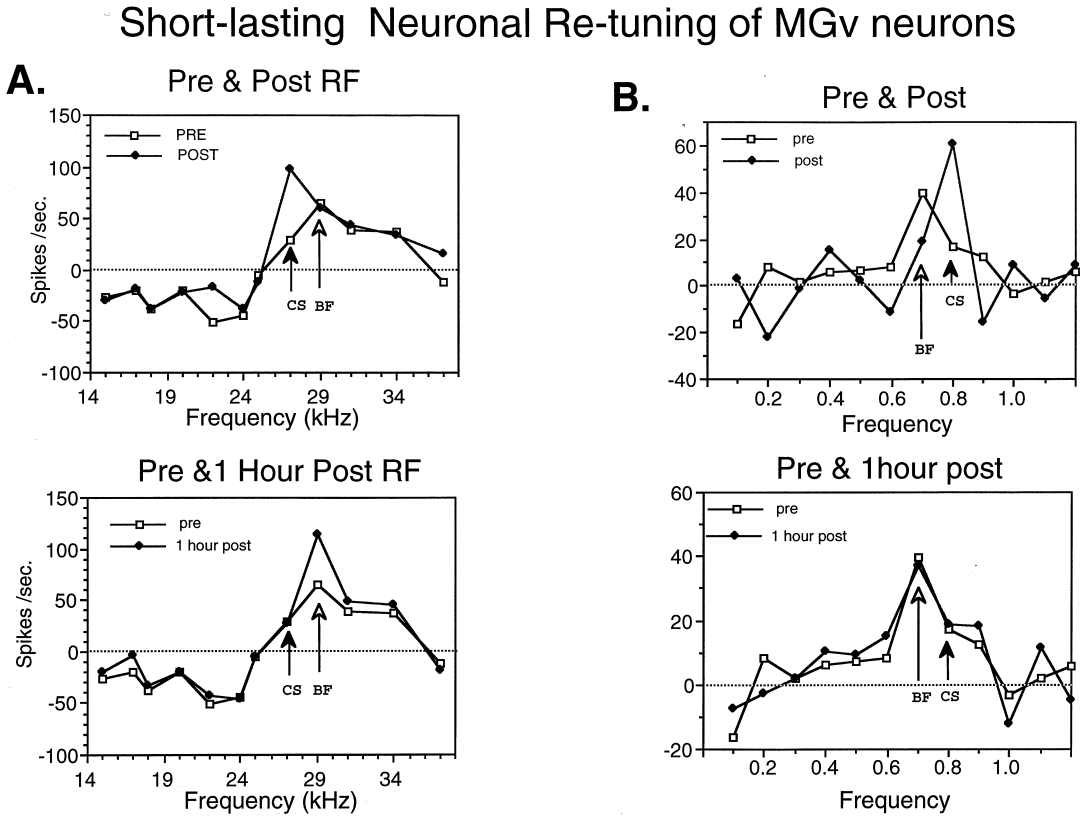

Fig. 7. Transient neuronal retuning of neurons in the ventral division of the Medial Geniculate Body (MGv). Two examples of neuronal re-tuning at the CS+ frequency are presented (modified from Edeline and Weinberger, 1991b). (A) At 40 dB this recording exhibited responses from 27 to 37 kHz with a best frequency at 29 kHz. The CS frequency was selected at 27 kHz. Immediately post-training (top), there were large increased responses at the CS, and no changes at many other frequencies. However, when the R was tested 1 hr post training (bottom), the responses evoked at the CS frequency were identical to those obtained before training, while the responses at the pre-training BF were increased. (B) For this neuron testing, the RF at 50 dB revealed a BF at 0.7 kHz and weak responses from 0.5 to 0.9 kHz. Immediately after training (top) the responses at the CS frequency (0.8 kHz) were largely increased, while the responses at the pre-training BF (0.7 kHz) and many other frequencies were decreased. One hour after training (bottom) the responses at the CS and pre-training BF were similar to those observed pre-training and the RF was virtually identical to the pre-training RF.

As explained briefly in the introduction, it is usually assumed that close relationships exist between RF and maps, because the selectivity of neurons for a particular dimension, revealed by its RF, is interpreted as a local sign of topography. Therefore, when the neurons' RF exhibit selective re-tuning after training, it is assumed that the map for this stimulus dimension is changed accordingly (see Fig. 11). However, there are several limitations to this assumption. First, this relationship between RF and maps is only true for first-order topographic maps (see Frégnac and Bienenstock, 1998). Second, it is totally unknown what is the percentage of neurons that had to exhibit selective changes in order for a map reorganization to be detected.* Third, the 2DG map changes discussed in Section 3.4.2 were inferred from the comparison between patterns of 2DG labelling obtained in animals submitted to associative training and those submitted to different control situations. As the injection of the radioactive tracer is made before training, the results obtained during this situation should be compared with the results obtained in electrophysiological experiments during the training trials, and not with the results obtained in the post-training RF determination. Fourth, the electrophysiological maps discussed in Section 3.4.3 were obtained after extensive training and were tested under general anaesthesia, not in the waking state as is the case for the post-training RF determination.

Up to now, there is no direct demonstration that the map changes inferred from the 2DG labelling are equivalent to the SU changes obtained during training trials. Also, there is no direct demonstration that the map changes inferred from sampling SU activity under general anaesthesia after weeks of training are equivalent to testing the RFs immediately

*Note that most mapping studies use multiunit recordings to determine the selectivity for a particular dimension at a given location, and that in many cases the authors aim at layer IV.

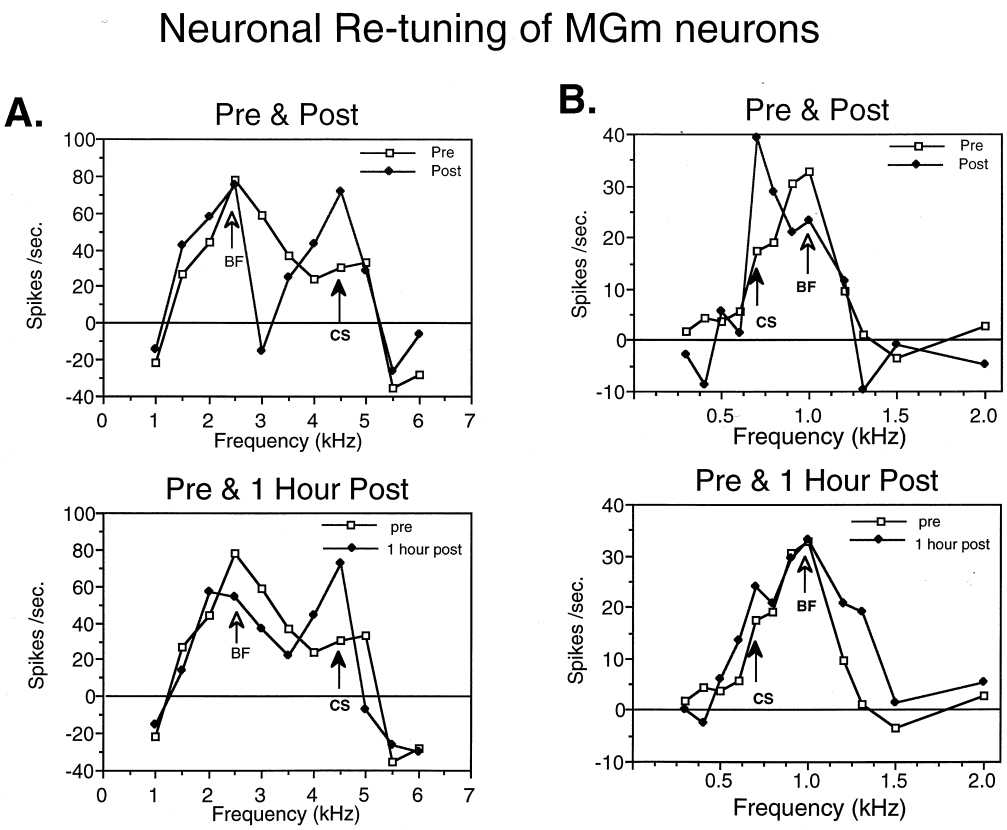

Fig. 8. Neuronal retuning of neurons in the medial division of the Medial Geniculate Body (MGm). Two examples of neuronal re-tuning at the CS frequency are presented (modified from Edeline and Weinberger, 1992). (A) At 70 dB determination of the pre-training RF indicated responses from 1.5 to 5 kHz with a BF at 2.5 kHz. The CS frequency was selected to be at 4.5 kHz. Both immediately and 1 hr after training, the responses were increased at the CS frequency. The responses at the pre-training BF were not changed immediately post-training, but were decreased 1 hr post-training. The CS was the BF 1 hr after training. (B) At 70 dB these recordings showed narrowly tuned RF centred around the BF at 1.0 kHz. The CS frequency used during training was 0.7 kHz. There were large increased responses at the CS frequency immediatly post-training, with decreased responses at the initial BF. However, 1 hr post training, the responses at the CS were only slightly increased and the initial BF showed responses identical to the pre-training RF. Thus this recording exhibited a transient shift to the CS frequency. Note that the RF were larger in (A) (f2–f1 = 1.01) than in (B) (f2–f1 = 0.28), which illustrates the fact that, in the MGm, the broader the initial tuning the better the retention and the selectivity of the neuronal re-tuning at the CS frequency.

after training. Finally, there is no direct demonstration that the map changes inferred from the 2DG labelling obtained during training are equivalent to the map changes inferred from sampling the SU under general anaesthesia after weeks of training. For these reasons, I consider that these different characterizations of learning-induced sensory plasticity have to be examined keeping in mind the conditions in which the results were obtained. They can, or cannot, reflect the same general processes; they can, or cannot, be governed by the same general mechanisms.

3.4.2. *Map Changes Revealed by 2DG Labelling After Short-Training*

From 1984, Scheich and Gonzalez-Lima started a line of research that can be viewed as the precursor of what will be cerebral imaging in the future.

These authors have used 2DG labelling to map the cellular activity of a large number of brain structures during the acquisition of classical conditioning in rats. In their protocol, a FM tone (1.5 sec, used as CS) is paired with an electrical stimulation of the mesencephalic reticular formation (0.5 sec, 300–600 μA, used as US). After injection of the radioactive element, the animals underwent 90 min of classical conditioning with a trial every 8.5 sec (i.e. about 600 pairing trials), and the bradycardia occurring during tone presentation was taken as CR. The labelling obtained on these animals were compared with those obtained in six control groups of animals submitted during 90 min to (i) CS alone, (ii) US alone, (iii) CS in extinction, (iv) 45 min of US then 45 min of CS, (v) CS/US pseudorandom presentations, (vi) CS alone after pseudoconditioning.

This protocol was used to describe the effects obtained in the subcortical auditory structures

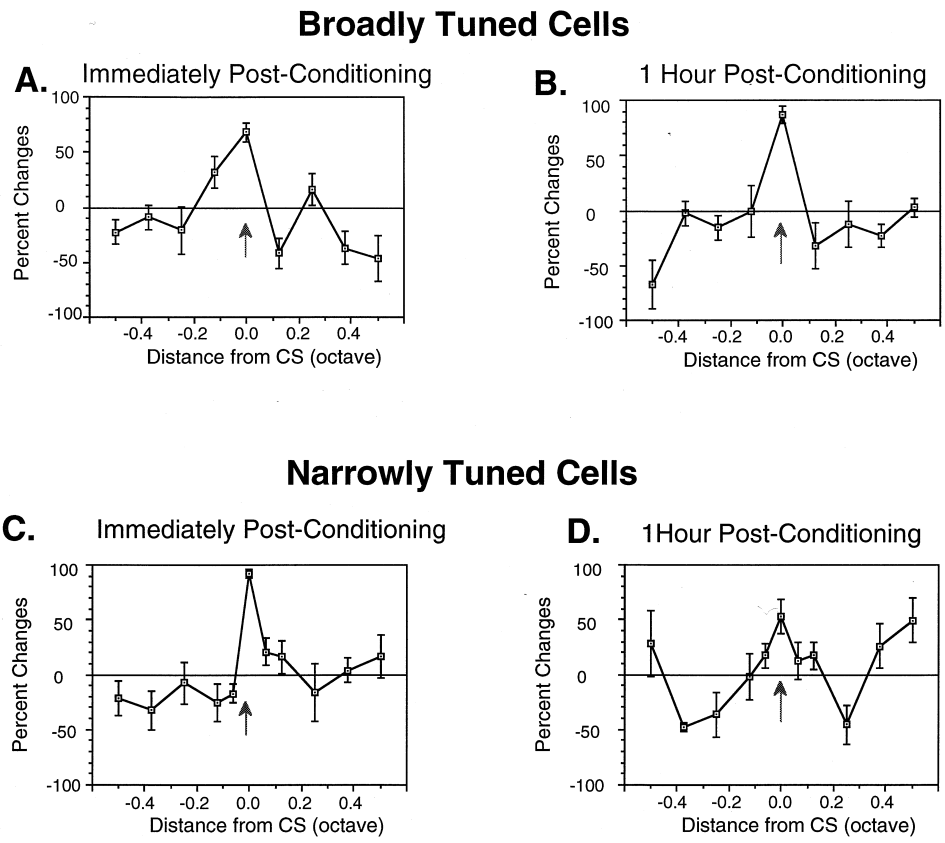

Fig. 9. Group data from the re-tuning of neurons in the medial division of the Medial Geniculate Body (MGm). The evolution of the neuronal re-tuning at the CS frequency is represented separately for the cells that were initially broadly tuned (with large RF) and for cells that were initially narrowly tuned (with small RF). The broadly tuned recordings which exhibited selective increased responses at the CS frequency immediately post-conditioning displayed a larger and more selective increase at the CS frequency when tested 1 hr after conditioning [compare (A) and (B)]. The narrowly tuned recording which exhibited selective increased responses at the CS frequency immediately post-conditioning displayed a smaller and less selective increase at the CS frequency when tested 1 hr after conditioning [compare (C) and (D)]. This exemplifies the fact that cells with different initial breadth display different evolution of the learning-induced RF changes (from Edeline and Weinberger, 1992).

(Gonzalez-Lima and Scheich, 1984) and in the auditory cortex (Gonzalez-Lima and Scheich, 1986a). At the subcortical level, increases in metabolic labelling were detected in all the structures when the tone was paired with the US. At each level, the area corresponding to the overlap between the activation induced by the CS alone and the activation induced by the US alone, showed increased 2DG labelling after associative training. In the cochlear nucleus, superior olivary complex and lateral lemniscus, the labelling measured in animals submitted to pairing was larger than those measured in animals submitted to extinction after pairing. In both conditions (pairing and extinction), the largest changes were obtained in the inferior colliculus. At the thalamic level, the results were different in the MGB divisions: in the MGd increases were observed only in conditioned animals, while in the MGm and MGv increases were also observed in animals submitted to US presentations alone; increases were also observed in the MGm after pseudo-conditioning. At the cortical level, important increased labelling was noted after conditioning, extinction and pseudo-conditioning, but the increases were always larger during conditioning than in the other conditions (Gonzalez-Lima and Scheich, 1986a).

Before considering these results further, several points have to be mentioned. First, the stimulation of the mesencephalic reticular formation (MRF) used as US seems to produce labelling in the auditory structures which, although exhibiting a different spatial distribution, are more or less as large as those produced by tone presentations. This suggests that an arousing stimulus can activate the auditory structures as strongly as an acoustic stimulus.* Second, at all levels, the zones of overlap between the CS activation and the US activation are those exhibiting the strongest conditioned changes. Therefore, one can consider that the convergence

*As the MRF stimulation produces non-habituating unconditioned responses, it is unclear whether the MRF stimulation is only an arousing stimulus, or if it has some nociceptive properties.

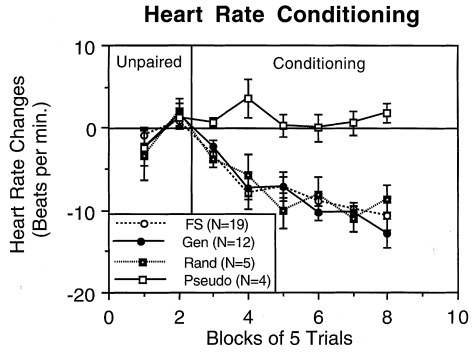

Fig. 10. Absence of relationship between behavioural responses and neuronal re-tuning. The changes in heart-rate observed at the CS presentation are presented for the animals on which different neuronal changes were observed in the dorsal division of the medial geniculate body (MGd): CS frequency specific re-tuning (FS), general changes (Gen), random changes (Rand) and for a group of animals submitted to pseudo-conditioning. The first two blocks of five trials were pseudo-random presentations of the CS and US. Subsequent trials were conditioning trials for the FS, Gen, Rand groups, but were pseudo-conditioning trials for the Pseudo group. Small decreases of heart rate were observed in all groups during the first five trial block (orienting response). Conditioned bradycardia in the first block of conditioning (block 3) increased, and was maintained in conditioned animals. In contrast, no bradycardia was detected for the pseudo group. Note the similar acquisition curves for the conditoned animals (FS, Gen, Rand) regardless the neuronal results.

between the non-specific afferences arising from the MRF and the acoustic afferences is either a permissive factor, or is sufficient to produce an increased metabolic activity in auditory structures.

Two different strategies were used after these initial findings.

On the one hand, Scheich and colleagues focused on the effects induced at the cortical level by different training protocols such as (i) simple classical conditioning, (ii) active avoidance in a shuttle box (with a single tone used as CS) and (iii) a discriminative training between CS+ and CS− (a response at the CS+ allowing US avoidance; Scheich and Simonis, 1991). Simple classical conditioning increased the cortical distance (by 100–200 μm) between the two labelled bands obtained in the tonotopic fields AI and AAF. Rather than an increase in the amount of cortical tissue devoted to the CS (a 1 kHz tone), this seems to indicate a shift of the normal CS labelling band toward low frequencies. In contrast, during active avoidance, the distance between the labelled bands in AI and AAF was smaller compared to control animals, and the width of the band was increased in both AI and AAF. This increase in width was also observed after discriminative avoidance at the CS+ frequency, and a marked decrease in labelling was noted at the CS− frequency.

In addition, this team has looked for the potential consequences of a sensory–sensory conditioning in the auditory cortex (Cahill *et al.*, 1996). During 40 trials, a flashing light was followed by a tone (in fact a mild shock was given in 1/3 of the trials to "maintain the state of vigilance of the animal"). Control animals were submitted to light alone presentations, or to unpaired presentations of light and tone. On the following day, after the injection of the radioactive element, the light alone was presented to all groups of animals. Analysis of the autoradiograms revealed no difference in overall metabolic activity of the auditory cortex between groups. However, in animals for which the light predicted the tone during training, there was a clear redistribution of the 2DG labelling between cortical fields. There was a greater activity in the anterior auditory field (AAF) and the posterior fields (DPVP) relative to the activity in the primary field (AI). This shift in relative labelling between fields reflects both an increase in activity in fields AAF and DPVP, and a concomitant decrease in AI activity in response to light stimulus. According to the authors, these results suggest that the activity of the auditory cortex cannot be concerned solely with processing various parameters of the acoustic stimuli. Related to these findings, it is interesting to note that neuromagnetic responses recorded in the human auditory cortex during syllable presentations were modified by visual information (Sams *et al.*, 1991). Obviously, this raises questions concerning the mechanisms by which a visual stimulus can drive neurons in the auditory cortex. Even if anatomical studies revealed connections of auditory cortical fields with visual or limbic cortices (Rouiller *et al.*, 1990, 1991; Vaudano *et al.*, 1991), these results remained puzzling. These findings stress the fact that the way by which sensory systems process information is far more complex than we usually imagine.

On the other hand, Gonzalez-Lima and colleagues focused on descriptions of the patterns of 2DG labelling occurring in the subcortical structures using a structural modelling approach. The structural modelling analysis was first conducted with the data obtained during a short-term and long-term habituation of the startle reflex. The pattern of labelling obtained after short-term habituation (a single session of tone presentation) and after long-term habituation (five sessions of tone presentation), revealed no difference in labelling in the thalamocortical system. In contrast, all the subthalamic structures displayed higher metabolic activity after long-term habituation, while the red nucleus and the entire reticular formation exhibited a lower metabolic activity (Gonzalez-Lima *et al.*, 1989). Structural equation modelling is a tool traditionally used in genetics and social sciences for testing hypothesis about causal influences (Bollen, 1989; Jöreskog and Sörbom, 1989). Its application to neural data requires to construct an anatomical model of the system and to use the correlation coefficients of activity between brain regions to identify the functional relationships between structures in a given experiment. The correlations between areas are used to assign path coefficients to the anatomical connections. The strengths and the signs of these path coefficients are compared across experimental conditions, and are used to determine task-specific interactions within the same anatomical network. When a functional model of the auditory system was built using the values obtained from control

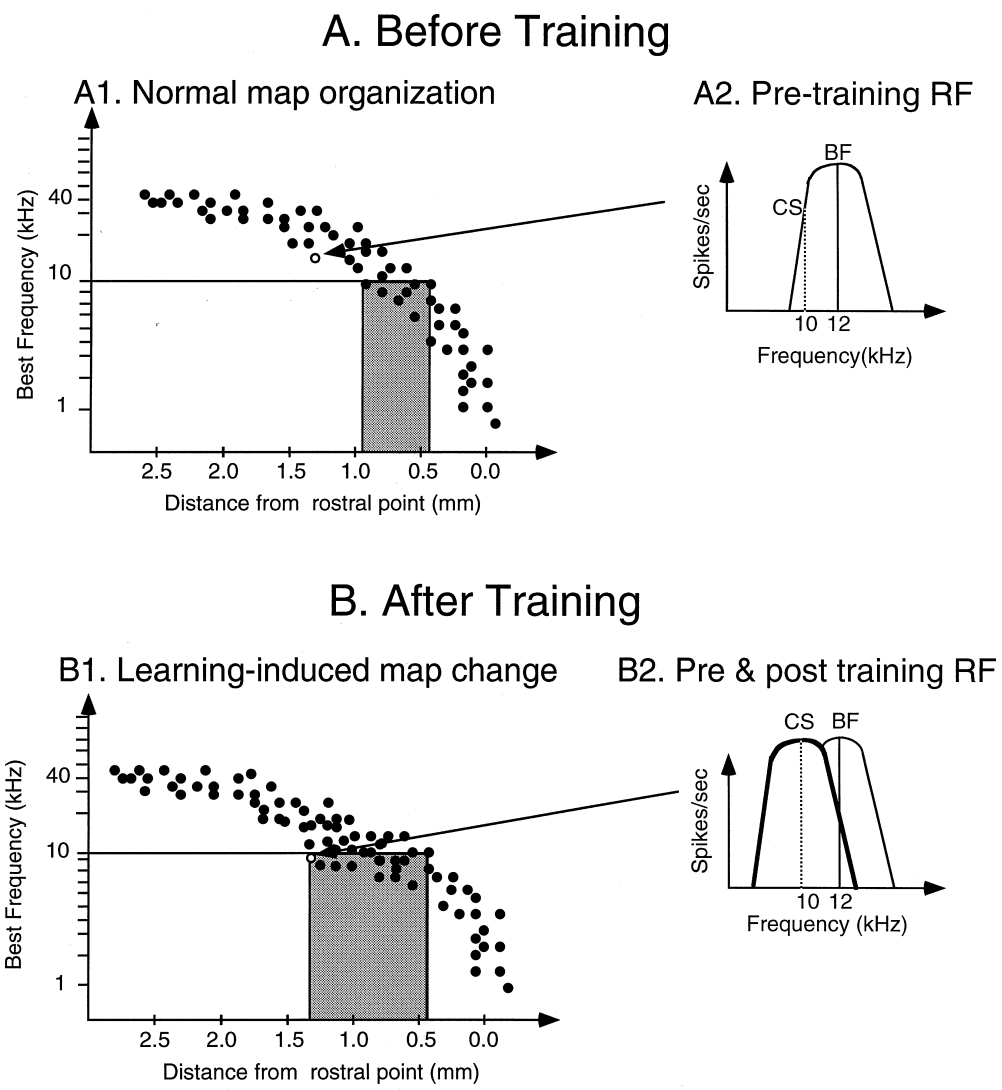

Fig. 11. Hypothetical relationships between receptive field plasticity and map reorganization. (A1) In the case of a normal map in the primary auditory cortex the low frequencies are represented in the rostral pole and the high frequencies are represented in the caudal pole (see for example, Robertson and Irvine, 1989). When neurons are sampled and their best frequency (BF) determined there is a regular progression of the neurons' BF from high to low when the electrode is moved from caudal to rostral. Based on this graph it is possible to interpolate the size of the cortical representation of a frequency: for example, the grey area delineates the area where neurons have a BF of 10 kHz, which extends from 0.45 to 0.95 mm (500 μm). (A2) At a particular location (white dot), the RF of a neuron with a BF of 12 kHz is presented. The frequency of 10 kHz is selected during conditioning. (B2) After training, a selective increase of the responses to 10 kHz allow the same neuron to have a new BF at 10 kHz. As in other locations the same shift of tuning of individual neurons is observed the size of the 10 kHz representation is enlarged: neurons with BF of 10 kHz are found from 1.35 to 0.35 mm from the rostral pole (1000 μm).

animals, the covariance relationships between auditory structures showed little influence of the lemniscal pathway. When the data from the animals submitted to short-term habituation were used, the influence of the lemniscal pathway was dominant. In contrast, the data from the animals submitted to long-term habituation revealed a decreased influence of the lemniscal pathway and an increased influence of the non-lemniscal pathway (McIntosh and Gonzalez-Lima, 1991). This type of structural analysis was then carried out in a protocol where the same tone was a Pavlovian-conditioned excitator (which systematically predicts the US) or a conditioned inhibitor (that systematically predicts the absence of the US). Surprisingly, the comparisons between path coefficients revealed little changes in the thalamo-cortical auditory system, but the outputs of the cochlear nuclei seem to be fundamentally different. During presentation of the conditioned excitator, the ventral cochlear nucleus seems to influence the lower auditory centres as predicted from the neuroanatomy. In contrast, during presentation of a conditioned inhibitor, the influence of the ventral cochlear nucleus on other structures markedly

decreased, while extra-auditory influences on the dorsal cochlear nucleus were largely increased reflecting possible interactions of this nucleus with extra-auditory regions (McIntosh and Gonzalez-Lima, 1993).

Although surprising, these results raise problems that cannot easily be addressed by electrophysiological techniques. Given the large number of feedback loops that exist in any sensory system (Section 2), it is impossible to interpret the changes in neural activity occurring in a given brain locus without knowing what is occurring upstream and downstream. Thus, this type of work points out a trivial notion: interactions between structures can be centripetal and/or centrifugal. A weakness of this work is that non-auditory structures, non-incorporated in the model (e.g. the neuromodulatory systems), can influence the activity of the auditory structures. The authors were aware of this problem, since they included in the path equations a residual error factor which is supposed to account for the influence of structures non-incorporated in the models. However, it is very difficult to estimate how a given neuromodulator will affect the reactivity of neurons at different levels of a sensory system, and how the combinations of different neuromodulators will affect the neurons at a given level in the system.

Compared with electrophysiological data, the 2DG technique has the enormous advantage to give, within the same animal, information about the reactivity of a large number of structures. The data obtained with this technique stress the fact that learning affects the way by which information is processed in the entire auditory network, and therefore they plead for applying the same electrophysiological analyses to lower levels of the auditory system.

One of the obvious pitfalls of the 2DG technique is its lack of temporal resolution, as it is necessary to average tens of trials in a short amount of time to obtain an adequate labelling. The consequence is that, as with any ex-vivo imaging technique, it is impossible to access the flow of activity occurring during a training trial, i.e. to determine the sequential order of neuronal reactivity at the presentation of a significant stimulus. Also, a disadvantage of the 2DG is that only one single set of data can be obtained with a given animal, no multiple acquisition or retention data can be obtained with this technique as with any ex-vivo technique. A last problem is, of course, to know what type of activity is exactly revealed by the 2DG technique: the neuronal activity (in terms of action potentials or in terms of membrane potential) or the activity of astrocytes (the glycogene reservoir of the brain); the somatic activity or the activity of afferent terminals? This cannot be neglected if one wants to compare these data with electrophysiological results. It is impossible to detail here the intensive field of research that, starting from the original study by Sokoloff and colleagues (Sokoloff *et al*., 1977), has investigated the relationships between neuronal activity and oxidative energy metabolism (see for reviews Gonzalez-Lima, 1992; Sokoloff and Takahashi, 1996), but for the purpose of the present review, few findings obtained in auditory structures have to be mentioned. First, in the auditory cortex analogue of chick, field L, a combined 2DG and electrophysiological study has showed the congruence between metabolic activity and extracellular (action potentials) activity. The stripes of 2DG labelling observed using presentations of a pure tone frequency matched the electrode tracks yielding neurons with the same best frequency (Theurich *et al*., 1984). However, if some studies have found a good match between units discharges and 2DG labelling (Servière and Webster, 1981; Webster *et al*., 1978), other studies have pointed that the 2DG stripes correspond better with the presynaptic afferent volley than with the somatic discharges (Auker *et al*., 1983). More generally, a dominant contribution of the afferent terminals in the 2DG labelling seems to exist in structures where there is an important spatial segregation between the afferent terminals and the zone generating action potentials, as is the case in the fascia dentata in the hippocampus (Gonzalez-Lima and Scheich, 1986b) or in some bird auditory nuclei (Lippe *et al*., 1980).

3.4.3. *Map Reorganizations Revealed by Units Sampling After Extensive Training*

Up to now, the most classical technique to map a sensory area is to sample units (or clusters of units) at regularly spaced locations, and to determine the units RF and the preferred stimulus for a particular dimension at each location. This technique was extensively used to describe the reorganizations taking place after peripheral injuries, especially by Merzenich and colleagues. This laboratory has designed several experiments to test the effects of training in the somatosensory cortex (see Section 4.3) and in the auditory cortex. The common features of these experiments were the followings: in both cases, adult monkeys were trained during several months to perform a behavioural task that forces the animal to focus its attention on a given stimulus to obtain an appetitive reward. In both cases, the task involved detecting small differences in a particular dimension of the stimulus. In both cases, the rationale was that after extensive training, testing the selectivity of cluster recordings under general anaesthesia will reveal selective changes in the maps in favour of the stimulus used during training. In both cases, the behavioural performances were analyzed using the Signal Detection Theory (Green and Swets, 1966), which allows to characterize the psychometric function of each animal and thus to quantify potential changes in the subject's strategy (quantification of false-alarm and miss).

In the acoustic version of this task, the animals were trained to detect a change in tonal frequency during presentation of pairs of tones. The first tone (S1) was 2.5 kHz, 3.0 kHz, 5 kHz or 8 kHz, depending on the animal. The second tone (S2) was at a fraction of octave from S1 and the difference in frequency between S1 and S2 (ΔF) was decreased across training sessions. In a given trial, 2–11 S1 stimuli were delivered before the S2 stimulus, and only a response to S2 was rewarded. There were 400–750 trials in a daily session and from examin-

ation of the figures it seems that there were 61–120 training sessions. Considerable improvement in behavioural performance were observed: For each animal, the mean value of the differential threshold ($\Delta F/F$) strongly decreased with training, and the psychometric functions were shifted toward the left. Because (i) the slope of the psychometric function increased, (ii) the percentage of false-alarms remained below 15% and (iii) the d′ factor (based on a roc analysis) tended to increase, it was concluded that the animals' internal criteria by which they made a response was unchanged.

The electrophysiological data were from three trained animals, two passively stimulated animals and three naive animals. The authors reported that the number of cortical sites and the total cortical area responding to the frequency used during behavioural training were increased compared to those responding to frequencies not used during training. Several indices used to quantify the map reorganizations support this claim (see Figs 12 and 13 in Recanzone *et al*., 1993), even if the selectivity of the reorganization is difficult to estimate (see Figs 10 and 11 in Recanzone *et al*., 1993). Two properties of the neuronal responses were apparently affected by training. First, the bandwidth of the tuning curves (quantified by the Q_{10dB} and the Q_{40dB}) was narrower in the experimental animals compared with the naive animals (but passively stimulated animals also showed some increases). Second, there was an increase in the minimum latency of the responses for the three trained animals, and to a lesser extent in passively stimulated animals.

Obviously, the technical difficulties of these experiments prevent to have the appropriate number of subjects to deepen some aspects of these results. As recognized by the authors, there is a large inter-animal variability of the frequency representation in naive animals. The idiosyncrasies of primates AI organization plead for the use of each animal as its own control, which is very difficult to do with electrophysiological mapping. Providing that a correct spatial resolution can be achieved, future studies using cerebral imaging techniques should be able to confirm and extend these promising data. They might also allow to test for potential contributions of subcortical structures in these cortical reorganizations.

3.4.4. *Resume*

At the RF level, associative training produces selective changes for at least 50% of the cortical cells. In the non-primary cortical areas (AII/VE), the changes were increases or decreases, while only selective increases were reported after different types of associative training in the primary cortex. These selective increases promote a neuronal re-tuning at the frequency that was significant during training. After pseudoconditioning, such selective effects were never observed, but general increases in the neurons RF were often reported. Selective re-tuning was also observed after conditioning in all the anatomical divisions of the auditory thalamus. At the thalamic level, long-lasting effects were obtained in the non-lemniscal divisions and short-lasting effects were obtained in the lemniscal division. Because of its fast decay, one cannot consider that the plasticity of the lemniscal division is directly responsible of the cortical plasticity. Nor it is possible to say that cortical plasticity contributes to the thalamic plasticity. However, it remains possible (i) that the long-lasting effects observed in non-lemniscal divisions contribute to the expression of long-lasting cortical plasticity; or (ii) that the corticofugal pathways promote long-lasting thalamic plasticity. We have previously discussed this point (Edeline and Weinberger, 1992) and proposed that the different components of the thalamo-cortical systems operate in an integrated manner rather that in a "serial chain" manner. Each component might provide its own contribution: plasticity in the thalamus, although not simply projected to a passive cortex, can play a key role in cortical plasticity. Also, as the MGm projects to layer I of all auditory cortical fields, it could activate different cortical areas and thus "binds" different dimensions of the acoustic stimuli. Lastly, both at the thalamic and cortical level no relationship was found with the behavioural expression of learning. There was also no relationship between the effects induced during the conditioning trials and the effects observed in the post-training RF.

The results from the map changes revealed by electrophysiological recordings can be viewed as a clear confirmation of the selective RF plasticity. That the total cortical area responding to the frequency used during training (the CS) was found to be larger than that representing other frequencies, can be viewed as the logical consequence of the fact that neurons shift their tuning at the CS frequency (Fig. 11). However, the 2DG mapping studies seem to point to potential limits of such view: depending on the training procedure the effects on the frequency cortical representation are different. But also, the 2DG studies revealed that during simple learning situations, the lower levels of the auditory system changed their activity as much as the thalamo-cortical system.

4. EFFECTS OF LEARNING IN THE SOMATOSENSORY SYSTEM

4.1. The Effects of Sensory–Sensory Association on RF

In the first set of experiments described below, no overt behavioural response was recorded while an association between two events was carried out. Although the status of sensory–sensory association has long been debated (Brogden, 1939), theoreticians of classical conditioning clearly consider now that associations between "neutral" stimuli belong to the field of associative learning (see Rescorla, 1980, pp. 25–40). Higher-order conditioning (or second-order conditioning) and sensory pre-conditioning are the two protocols used to reveal these associations (see Mackintosh, 1974, p. 19). Even more important, these associations are now considered as crucial tools to investigate the richness of the associations that can be formed during learning (Rescorla, 1980; Gallistel, 1990). Therefore, the data

presented (Delacour *et al.*, 1987) obtained in undrugged, fully awake animals can be considered as an associative training where the animal has to detect the relationship between the two stimuli that were explicitly paired. In this protocol, the stimulation of a single vibrissea (used as CS) preceded the stimulation of a bundle of vibrissea (used as US). During at least 50 trials, the stimulation of the single vibrissea was followed 500 msec later by the stimulation of the bundle of vibrissea with an inter-trial interval of 8 sec. Two types of effects were observed. First, in 5/13 cases the responses to the CS were increased. This increase mainly stems from the disappearance of the inhibition that normally follows the short-latency "on" excitatory response. Second, in 7/36 cases for which there was no pre-existing response before pairing, responses to the CS emerged after pairing (Delacour *et al.*, 1987). The authors reported that in addition to the changes at the CS presentation, there were similar increased responses at the US presentation: the afferent inhibition disappeared and was replaced by a sustained response. In some cases, the effects persisted up to 20 min after the end of pairing. Quantification of the electroencephalogram (EEG) suggests that during the pairing trials there was no sign of increased vigilance; there was even a slight increase in the relative power of the 5–11 Hz band and a decrease of the 26–50 Hz band across trials.

In a subset of cells which did not initially show responses to the CS, but which did after pairing, the contribution of a cholinergic mechanism in the pairing-induced effect was tested (Delacour *et al.*, 1990). Iontophoretic applications of atropine were performed at the vicinity of the recorded neurons once the pairing procedure had induced responses at the CS. In 10/11 cases, atropine abolished the responses to CS presentation, and restored the initial responses to US presentation.* In addition, it was observed that iontophoretic application of ACh mimicked the effects induced by the CS–US pairing: ACh application abolished the afferent inhibition and promoted sustained response to US presentation.

A variance of the protocol used by Delacour and colleagues was designed by Diamond and colleagues (Diamond *et al.*, 1993, 1994). In their protocol, all but two afferences of the barrel cortex were removed, and, after 65 hr of experience with the two intact vibrissea (either D2 and D1, or D2 and D3), units were sampled under general anaesthesia in the somatosensory cortex corresponding to the D2 whisker representation. The responses to the D2 whisker and to the other intact whisker (D1 or D3) were increased compared with the responses collected from normal animals (Diamond *et al.*, 1993). In addition, after only 24 hr of this "whisker-pairing" protocol, neurons from the supragranular and infragranular layers exhibited plasticity, while neurons from the granular layers (400–800 μm below pia) did not show biased responses in favour of the D-paired whiskers (Diamond *et al.*, 1994). It is difficult to compare these results with those obtained in a learning situation for several reasons. First, in the "whisker-pairing" protocol, it is unknown how many pairing trials actually took place during the 65 (or the 24 hr) of the protocol. Second, as the animal was free to use the two whiskers to explore its environment, the exact pattern of whisker activation was totally undetermined: which whisker was activated before the other and what was the interval between the two whiskers activation? These parameters which seem crucial for artificial forms of Hebbian plasticity (see Section 6.1.1) were uncontrolled here. Third, it is unknown if these pairing trials indeed involved the animals' attention as it is the case in an acute pairing protocol. Therefore, although extremely interesting, the whisker-pairing protocol should be considered as the equivalent of the digit syndactyly procedure described in Section 4.3 (Allard *et al.*, 1991; Clark *et al.*, 1988): it is a case of experience-induced plasticity, which may or may not involve learning processes.

4.2. Associative Training and Map Changes Revealed by 2DG Labelling

As in the auditory system (Section 3.4), the use of the 2DG technique was useful to extend the findings obtained with SU recordings, and to study how an entire map reorganizes after a training procedure. However, as for the above mentioned studies using SU analysis (Section 4.1), most of the work using the 2DG labelling did not really involve behavioural training, but simply imposed the use of a single vibrissea in a freely moving animal by cutting all but one vibrissea (in this case, the C3 vibrissea was usually left intact). Using such protocols, several laboratories have described that a few weeks after, the C3 vibrissea column activated by the spared vibrissea is larger (especially in layer V and II) than the column activated in control animals (Hand, 1982; Kossut *et al.*, 1988; Levin and Dunn-Meynell, 1991).

Up to now, the protocol used by Siucinska and Kossut (1996) is the only one where changes of 2DG map were described after behavioural training. In many aspects, this protocol is close to those used by several laboratories to describe RF and map changes in the auditory system. Mice were submitted to classical conditioning during which stroking the whiskers of row B on one side of the snout (used as CS) was followed by a mild tail shock (used as US). Changes in heart rate attested that the animals learned about the predictive value of the CS (Siucinska and Kossut, 1996). After 3 days of training (with 40 trials per day and a 6 sec intertrial interval), a mapping session was performed either 1, 3, or 5 days after training. Compared with results presented below, it is important to mention that the mapping session was carried out while the animals were awake. This study revealed several interesting effects. (i) Compared with the contralateral, control, row B representation (not used during training), the labelled representation of row B in the experimental side was enlarged by 45%. (ii) This increase in size

* Pharmacologists will argue that atropine control is not convincing in proving the cholinergic nature of the effects because of the non-specific "anaesthetic" properties of atropine (see for example, Krnjevic and Phillis, 1963a).

was significant only in layer IV; non-significant increases were found in supragranular and infragranular layer. (iii) This increased width of the row B was present 1 and 3 days after training but disappeared when the mapping session took place 5 days after training. There was no increase in size in animals submitted to 2 days of extinction, and no increase after pseudo-conditioning. The enlarged representation of row B vibrissea did not lead to an under-representation of the untrained vibrissea: the size of the representations of row A and row C vibrissea was unchanged after training (Kossut and Siucinska, 1994)

This experiment raises important questions regarding the results presented above. First, the layer specificity is the opposite of what was described by Diamond *et al.* (1994) after 24 hr of "whisker-pairing", which could simply reflect the fact that learning (classical conditioning) involved neuronal mechanisms that are different from experience-induced plasticity ("whisker-pairing" protocol). Second, the effects obtained here are short-lasting, which is clearly in variance with the long-lasting effects described, by some authors, after conditioning in the auditory cortex (Weinberger *et al.*, 1993).

4.3. Map Reorganizations After Extensive Training

For almost two decades, Merzenich and colleagues have tested the potentials of cortical maps to reorganize in a great variety of situations ranging from denervation, deafferentation, intracortical microstimulations, nursing behaviour and behavioural training. As this review focused on the effects induced by behavioural training, most of the initial work coming from this laboratory will not be discussed here (see for reviews Kaas, 1991; Merzenich *et al.*, 1990; Recanzone and Merzenich, 1993; Weinberger, 1995a). Briefly, this laboratory has previously described cortical reorganizations in area 3b (areas 1 and 3a were also mapped on some occasions) in adult animals after different peripheral manipulations such as nerve section, digit amputation or digit syndactyly (surgical fusion of two digits). The major results were: (1) the cortical territory normally occupied by the missing or deinervated part of the epithelium was responsive to other inputs (digits adjacent to the missing one); and (2) after syndactyly, a considerable number of neurons had double digit receptive fields (i.e. respond to the inputs coming from the two adjacent digits), which is very rare in normal animals (Allard *et al.*, 1991; Clark *et al.*, 1988). The surgical syndactyly can be considered as the equivalent of the "whisker-pairing" protocol (Section 4.1) except that, in the syndactyly, the animal has the possibility to use other inputs (fingers) in its behaviour, which is not the case in the "whisker-pairing" protocol.

Because the results obtained after syndactyly suggest that map changes can occur not only after peripheral injuries, but also after continuous synchronization of peripheral inputs, the question as to whether or not a behavioural training will have the same consequences on the adult cortical map was addressed. To test this hypothesis the authors (Jenkins *et al.*, 1990) trained owl monkeys in a behavioural controlled tactile task during which the animal used a limited sector of the skin on the distal phalanges of one (or of two) finger(s) to obtain an appetitive reward. The task required that the animal maintained contact with a metal rotating disk for 10–15 sec. Wedge-shaped groves 350 μm deep were machined into the disk, in such a way that when the disk was rotating at 1 revolution/sec, the digital skin was stimulated at 20 Hz. After several months of training, neurons were recorded in middle layers of cortical area 3b under general anaesthesia and tested for their RFs. The data were from five experimental animals and, for each of them, two or three successive maps were derived (either before and after training, or after training and after extinction) in a courageous attempt to have an internal control of map changes (Jenkins *et al.*, 1990). Several important results were obtained. The most striking of them concerns RF size. Compared with the pre-training size, RF sizes obtained after training were unusually small. The RFs size returned to normal standard values when tested 2 months after the end of training. Also, the cortical magnification index (the cortical area of representation divided by the skin surface area) was selectively increased after training. The most popular results were that the skin surface used during training had an enlarged representation after training, and this enlargement disappeared when the animals were rested 2 months after the end of training. However, such enlarged representations were also observed for digits that were not used during training, and they also regressed 2 months after the end of training (see Table 1 in Jenkins *et al.*, 1990). Nonetheless, it seems that the largest absolute changes after training occurred for the most heavily stimulated phalanx. Surprisingly (as stated by Jenkins *et al.*, 1990, p. 100), the enlargements of the cortical representation of the behavioural engaged hand surface did not result in a substantial under-representation of the surrounding skin surfaces, which suggests that area 3b expanded into other cortical areas.

Several limitations in this study have led the authors to design a more elaborated protocol. First, there was no possibility to relate the behavioural performance of the animals with the neuronal changes. Second, there was no strict control of the way the animals were stimulated: each animal probably had its own unique pattern of activation of the skin surface (in addition to the fact that the animal used either one or two digits to perform the task). These two limitations were ruled out in the following studies (Recanzone *et al.*, 1992a,b,c,d). Monkeys were trained to discriminate differences in the frequency of a flutter-frequency stimulus when compared with a 20 Hz standard stimulus. For all monkeys, once the animal had placed its hand in a special groove, the tactile stimuli were applied at a constant, restricted, location on the glabrous skin of a single finger. Over the training sessions, the task difficulty was progressively increased by decreasing the frequency difference between the two tactile stimuli. Using this procedure, all but one animal progressively improved their threshold from 6–8 Hz to 2–3 Hz. As for the auditory task (Section 3.4.3),

there was an increase of the slope of the psychometric functions and an increase of the d′ factor of the SDT.

In this experiment, the somatosensory cortex was mapped only once, after the animal had reached an asymptotic level of discrimination threshold, and the specificity of the effects were assessed by comparing (i) the cortical representation of the trained finger with those of the adjacent fingers and (ii) the cortical representation of the trained hand with that of the untrained hand. In all well-trained monkeys, the size of the cortical zone of area 3b responding to the stimulated skin location was 1.5–3 times larger than the size of unstimulated skin location on adjacent digits. However, the total extent of the representation of the trained digit was not larger than that of untrained digits, or that from the same digit in the opposite hemisphere. The RFs of neurons responding to the trained digit were significantly larger than the RFs of neurons responding to the untrained digits. But the enlarged RFs were not only found in the restricted trained skin: large RFs were found in a 1–2 mm-wide zone of area 3b maps for the trained hands; and RFs were also significantly larger on at least one adjacent finger when compared with the RF sizes recorded on the homologous digit of the opposite hand. At first glance, this result can be regarded at variance with the previous experiment in which extensive training results in smaller RFs (Jenkins *et al.*, 1990). The authors explained this apparent discrepancy by the fact that a precise constant stationary skin spot was used, while Jenkins *et al.* (1990) used a stimulus moved across a small fingertip skin surface (see for discussion Recanzone *et al.*, 1992b, p. 1053, and Recanzone and Merzenich, 1993). In addition to the reorganizations observed in area 3b, there was an emergence of cutaneous responses in many area 3a locations, and the normal responses to deep receptor inputs (muscles and joint stimulations) were no longer evident at most of these locations (Recanzone *et al.*, 1992c). In the area 3a, the trained skin in the hemisphere representing the hand used in the task was over-represented compared with the skin of adjacent digits. In fact, observations by Jenkins *et al.* (1990) already suggested these effects: they proposed that the emergence of cutaneous representation of area 3a can be explained either by an expansion of the area 3b cutaneous representation, or by a transition of neurons 3a area from being responsive to deep modality inputs to being responsive only to cutaneous inputs.

Surprisingly, none of the signs of behavioural-induced map or RF changes was related with the animal behavioural performance: there was no correlation between the indices used to quantify the neural changes and the final behavioural threshold of the animal. For example, one monkey (E4) had a very high threshold but clearly showed RF size enlargements, whereas another animal (E5) showed a very low behavioural threshold but no RF changes. The only evidence in favour of a relationship between neuronal changes and behavioural performance came from an analysis which quantifies the way by which neurons responded to sinusoidal stimulations of the skin at frequencies close to those used during the training session (20–26Hz). These tests were carried out at two different locations: the restricted skin surface used during the task and a similar skin surface on the adjacent digit (Recanzone *et al.*, 1992d). The number of cortical locations where neurons showed frequency-following responses was significantly greater when stimulation was applied to the trained skin as compared with adjacent digits. At cortical locations with entrained responses neither the absolute firing rates of neurons nor the degree of the entrainment of the response were correlated with behavioural discrimination performance. But when the data collected at the different locations were pooled together, it appeared that stimulation of the trained skin produced (i) larger amplitude responses, (ii) earlier peak of responses in the stimulus cycle and (iii) temporally sharper responses than did stimulation applied to control skin sites. More importantly, the analysis of cycle histogram revealed that there was a decreased variance in the response obtained at each stimulus cycle, which can account for the improved behavioural performance. Indeed, when the rising phases of the responses in the cycle histograms were analyzed, a very strong correlation ($r = 0.98$) was found with the final behavioural threshold of the animals (such effects were only found in area 3b, not in area 3a).

Therefore, although there was a large panoply of neuronal changes described after extensive, controlled, behavioural training, the only neuronal changes that were clearly related with the behavioural performance of the animal were the temporal aspects of the neuronal discharges when the skin was stimulated with tactile stimuli of the same frequency ranges as those used during behavioural training.

4.4. Resume

Although the effects of behavioural training in the somatosensory system were not studied as extensively as in the auditory system, the findings obtained in this modality help to introduce questions that are relevant across modalities.

First, at the RF level, plasticity of barrel field neurons was observed within a few tens of pairing trials during the limited time of a single unit recording in awake animals (Delacour *et al.*, 1987). The occurrence of these changes depended, at least partly, on cholinergic inputs. One can regret that no overt behavioural response was recorded either during or after this protocol. For example, it would be interesting to run a complete sensory-preconditioning protocol after this sensory–sensory pairing to test the capacity of the sensory association to be integrated at the behavioural level. Also, it would have been nice to have quantifications about the way by which the animal used the activated vibrissea in instrumental tasks after the protocol. Such information could bring more support to the idea that cortical plasticity subserves behavioural functions.

Second, at the map level, metabolic activity revealed plastic changes after a relatively limited amount of trials (120) delivered within 3 days. These effects were short-lasting (not present when tested 5 days after training) and they dissipated even faster if an extinction procedure was conducted (Siucinska and Kossut, 1996). In addition, the layer-specificity was the opposite to what was reported with chronic whisker-pairing procedure. The cortical changes observed by electrophysiological mapping performed after an extensive training revealed the extraordinary complexity of sensory reorganizations. If enlarged cortical areas were systematically observed after training, these enlargements did not always have the expected selectivity (Jenkins *et al.*, 1990). Map reorganizations also occurred simultaneously on adjacent cortical areas (3b and 3a in Jenkins *et al.*, 1990 and in Recanzone *et al.*, 1992c), which complicated the interpretations because it was not always possible to determine if one map invades the other or if both exhibit independent reorganizations. Finally, when one tried to relate the neuronal changes with the behavioural performance, neither the strength of the responses nor the extent of the cortical representation were relevant in predicting the animal's behaviour. Only the temporal aspects of the neuronal discharges were found to correlate with the discrimination performance of the animals.

5. EFFECTS OF LEARNING IN THE VISUAL SYSTEM

The number of studies where discharges of visual neurons were studied during a learning experiment is limited. Besides the fact that the developmental plasticity of the visual system has proved its richness in exploring the mechanisms of sensory plasticity during epigenesis, methodological problems are responsible for this paucity. It is impossible to assure stimulus constancy if a visual stimulus is delivered in a freely moving animal. This is even very difficult in a restrained animal since when gaze orientation changes, the visual stimulus might fall on totally different parts of the retina. Therefore, learning experiment can be carried out either under neuromuscular blockage (see Section 5.1), or during tasks where the subject is forced to maintain the gaze in a given position, as is the case during the control conditions of studies using visual stimuli in human and non-human primates (Section 5.3).

5.1. Effects of Conditioning in Parallel Visual Pathways

Many laboratories have tried to describe the neuronal changes occurring at different levels of the neural circuit involved between a given CS and the expression of a particular CR (Cohen, 1980; Thompson, 1988; Tsukahara *et al.*, 1981; Woody, 1982). The work undertaken by Cohen and colleagues belongs to this tradition with the originality that it ultimately stresses the fact that the visual pathway exhibits rapid increased responses at multiple loci during the acquisition of classical conditioning. This laboratory has shown that curarized pigeons submitted to a light-footshock pairing protocol exhibit robust and rapid cardiac conditioned tachycardia (Cohen, 1980). Initial studies have demonstrated that, during acquisition of this training, vagal preganglionic and sympathetic postganglionic cardiac neurons exhibit increased responses to the visual CS stimulus (both the probability of a response and the magnitude of the CS-evoked responses were found to be increased). Subsequent studies looked for the visual structures where neuronal changes can be detected. At least three visual pathways can be distinguished from the bird retina: the thalamofugal pathway (ending in the visual Wulst nucleus of the telencephalon), a tectofugal pathway (ending in the ectostriatum) and a pretectofugal pathway (also ending in the ectostriatum). By recording individual optic tract fibres during the acquisition of the conditioned response, it was shown that the retinal output is unchanged during visual learning (Wild and Cohen, 1985). None of the parameters (rate of phasic or sustained discharge, latency) of optic fibre discharges showed fluctuation during learning. Subsequent studies performed in the tectofugal visual pathway demonstrated that both the telencephalic (the ectostriatum) and the thalamic components (the nucleus rotundus) showed rapid conditioned changes (Wall *et al.*, 1985). However, in both structures the changes were expressed differentially depending on the initial responses of the cells. Neurons that displayed excitatory evoked responses at the light presentation (9/47 and 9/27 in these two structures) showed clear increased evoked discharges over the 40 pairing trials (the asymptotic level was reached after 20 trials). In contrast, neurons that displayed decreased discharges at light onset (38/47 and 18/27) did not change their responses over the course of training. Because in control animals, submitted to light and footshock unpaired presentations, the responses of these cells strongly adapted within 10 trials, this absence of changes in conditioned animals was interpreted as a conditioning effect. In some thalamic cells, the responsiveness to US presentation was tested: all the cells tested were found responsive to the US either by an increase in firing rate (8/21) or by a decrease in firing rate (13/21), even if the latency of these responses were longer that those observed at the light presentation (around 60 msec for the US vs 40 msec for the light).

The data coming from the dorsal LGN (Gibbs *et al.*, 1986) gave a similar picture. The neurons presenting light-evoked excitatory responses showed increased discharges during training, and the neurons presenting light-evoked decreased discharges showed no changes during training, which was interpreted as a sign of conditioning for the same reasons as above. Again, 91% of the thalamic neurons were found to be responsive to US presentation. Because of this high proportion, the authors have made special efforts to determine the critical factors that determine whether or not the cells will exhibit discharge plasticity. They came to the conclusion that to obtain learning-induced plasticity (i) neurons need to be responsive to both the CS and the US

and (ii) the highest probability is obtained when the CS produces an increased firing rate and the US a decreased firing rate (the authors concluded that cells responding to US presentations by increased discharges showed little or no plasticity).

That different parallel pathways exhibit simultaneous neuronal changes is compatible with the results coming from lesions studies. Indeed, when separate lesions of the different parallel pathways were performed, there was no behavioural deficit. In contrast, combined lesions of both the visual Wults and ectostriatum prevent the emergence of the conditioned response (see for review Cohen, 1980). This suggests that the neuronal plasticity occurring within each ascending visual pathway provides enough information to underlie behavioural conditioned changes.

5.2. Relationships Between Thalamic and Reticular Plasticity

The procedure used by Albrecht, Davidowa and colleagues was developed to overcome the difficulties of presenting visual stimuli in freely moving animals. In all their experiments the visual stimulus (whole-field illumination) was delivered by a light-emitting diode mounted on the head of the animal, and adjusted at a distance of 5 mm in front of the eye contralateral to the recording site. Several behavioural protocols were used with this technique. Initially, cells were recorded on thirsty rats that had previously learned that presentation of visual stimuli give them access to water if they approached a water spout shortly after the signal. Comparisons were performed between the responses of dorsal LGN (dLGN) cells obtained when the animal was using the visual stimulus to obtain the reward vs the responses obtained when the same satiated animal was no longer using the signal for its behaviour (Albrecht *et al*., 1986; Davidowa *et al*., 1982). The flash-evoked responses were modified in several aspects in thirsty rats vs in satiated rats: (i) the "On" excitatory responses were often decreased in thirsty rats, (ii) the inhibitory phases following the "On" responses disappeared, (iii) the number of excitatory rebounds was lower in thirsty rat compared with satiated animals. Such changes were also observed in subsequent studies using aversive classical conditioning. When the flashing light was paired with a tail shock in waking animals, there was a reduction (or a disappearance) of the inhibitory phases following the "On" response, which produced prolonged excitatory responses (Albrecht *et al*., 1990). Again, in this study, the "On" evoked response itself was either unaffected (see Fig. 3 in Albrecht *et al*., 1990) or attenuated (see Fig. 4 in Albrecht *et al*., 1990). For few cells, the conditioning protocol was performed in waking state, then under urethane anaesthesia. Surprisingly, if conditioned changes were detected in both states, the direction of the changes could be reversed: decreased "On" responses could be observed in waking state while increased "On" responses could be observed under urethane anaesthesia.* The authors did not observe responses of dLGN cells to US presentations.

From their earliest work, the authors hypothesized that the changes observed in the dLGN result from a modulatory effect mediated by the activity of RE neurons. Several strategies were used to test this hypothesis. First, the effects of aversive conditioning on the activity of RE neurons were directly tested. The visual evoked responses of RE neurons was often reduced during the pairing trials: this was sometimes the case for the "On" evoked response, but was often the case for the "sustained activity" detected in the 900 msec interval between CS and US (Albrecht *et al*., 1992). Second, the authors tried to prevent the cholinergic modulation of RE cells (by injections of atropine in the RE) while recording dLGN neurons in behaving animals. For some dLGN cells, the injection of atropine in the RE attenuated the differences between the pattern of response observed when the animals was using the visual stimulus in its behaviour vs when the animals was not using it (Albrecht *et al*., 1986). The implication of a cholinergic mechanism was also tested in the ventral LGN (vLGN), which is part of the ventral thalamus (see Jones, 1985). In this structure, facilitation of visual responses were often observed during backward pairing (the light followed the US presentation), while forward pairing (the light preceded the US presentation) tended to produce decreased responses (Albrecht and Davidowa, 1992). No effect was observed when atropine was iontophoretically applied in the vLGN during forward pairing.

5.3. Effects of Extensive Training in Humans and Non-Human Primates

At the present time, there is no data available testing the effects of behavioural training on the organization of visual maps. However, the two following sets of data might be viewed as the functional consequences of learning-induced plasticity.

A first set of data that will be discussed concerns the relations between neuronal discharges and psychological judgement. They will be discussed to point out that even in well-trained animals, learning-induced changes can be observed. In relation to this, a long tradition of work in cognitive psychology points out that extensive training can improve the perceptive abilities of human subjects (Gibson, 1953). In the visual modality, this was recently substantiated by the work of several groups who provided evidence that long-term learning can selectively modify the way the human visual system processes information (for review see Karni and Bertini, 1997).

5.3.1. *Relationships Between Neuronal and Psychophysical Performance*

In one of the first explorations of the relations between central neuronal activity and psychophysical judgement, Werner and Mountcastle (1963)

* Descriptions of the effects induced by urethane itself on the sensory responses can be found in Albrecht and Davidowa (1989), Capsius and Leppelsack (1996) and Simons *et al*. (1992).

enunciated some fundamental principles for the analysis of neuronal discharges in a psychophysical context. Later studies (Barlow *et al*., 1987; Bradley *et al*., 1987; Tolhurst *et al*., 1983; Vogels and Orban, 1990) have compared the neuronal and psychophysical performances for several parameters of the sensory stimuli (orientation, spatial frequency, contrast) and have suggested that the sensitivity of most cortical neurons is far from the psychophysical sensitivity: only the "best" neurons exhibited performances that approached psychophysical levels. However, the conclusions of these studies were limited, since the comparisons between psychophysical and neuronal performance were often based on data obtained at different times and under different conditions.

In contrast, in the experiments performed by Newsome and collaborators, the neuronal and the psychophysical performances were measured at the same trials, on the same animals, and the psychophysical task was tailored in each experiment to match the RF characteristics of the neuron under study. Thus, these data are certainly one of the more direct approaches to relate information processing performed at the single cell level and psychophysical performance. Only the most relevant results of these studies regarding the goal of the present review are presented below.

In the middle temporal visual area (MT) and in the medial superior temporal area (MST), physiological recordings have long described that most of the cells are sensitive to moving stimuli and exhibit direction selectivity (Dubner and Zeki, 1971; Tanaka *et al*., 1986; Zeki, 1974). These direction-sensitive cells are arranged into a system of columns. In the task used by Newsome and colleagues, behaving monkeys have to discriminate the direction of motion in a stochastic visual display. The visual stimulus is composed of a stream of randomly positioned dots; the strength of the motion signal is determined by the amount of correlation introduced as the dots are plotted on the screen of the display (see Britten *et al*., 1992). At each trial, the animal has to judge the direction of motion of the random dot pattern presented in the RF of the neuron under study, while its gaze is maintained on a fixation point. The animal indicated if it has perceived a motion in the display by a saccadic eye movement in the direction of the judged motion. In this task, the sensitivities of single MT neurons to near-threshold motion signals were found to be very similar to the psychophysical sensitivity of the animal (Britten *et al*., 1992). That is, the response of a typical MT neuron can provide an accurate account of the monkey psychophysical performance. The same results were found in the MST area, an area lying downstream to MT in the hierarchy of cortical visual areas (Felleman and Van Essen, 1991; Maunsell and Van Essen, 1983). More precisely, neurons in MST exhibit thresholds for discriminating the direction of coherent motion that were on average equal to the psychophysical threshold of the animal (Celebrini and Newsome, 1994). In many cases, for repeated presentations of a given near threshold stimulus, the intensity of the neuronal responses was correlated with the monkey's psychophysical judgement. In addition, when pronounced alterations of the visual stimulus were performed (for example, severe reductions in stimulus size and speed), the neuronal and psychophysical sensitivities were affected by similar amounts, in such a way that the relation between neuronal and psychophysical threshold remained the same (Celebrini and Newsome, 1994). One can argue that these relations are only the consequences of the fact that the information carried out by the MT and MST neurons contributes to the decision process. However, these relationships are not static. Within a daily session, the animals often exhibited a steady gain in discriminative ability over the first trials. When the data of the first and second block of 200 trials of each session were compared, both the neurometric and the psychometric function indicated an improvement in the discrimination of weak motion signals: on average neuronal sensitivity increased by 13.6% and psychophysical sensitivity by 19.4% (Zohary *et al*., 1994). This demonstrates that even in well-trained animals, learning-induced plasticity can be observed within a given recording session. In addition, to determine if the neuronal plasticity observed at the level of MT and MST already occurs upstream, in structures having smaller RF (like V1 and V3), the authors tested whether or not conditioning at one location of the RF leads to increased sensitivity at another location. The results clearly indicated that conditioning of one subregion of the RF enhanced the sensitivity equally in conditioned and unconditioned location of the RF. These data suggest that in the task used by the authors, neuronal plasticity resides, at least in part, within the superior temporal sulcus.

5.3.2. *The Effects of Extensive Training in the Human Visual System*

Although there is no physiological data discussed in the results presented below, they likely to reinforce the links between experimental psychology and physiological plasticity of sensory systems.

In the task used by Karni and Sagi (Karni and Sagi, 1991, 1993) the subject had to decide whether a small target texture (an array of three diagonal line elements differing only in their orientation from a background of identical elements) was horizontal or vertical. The subject performance, measured as the mean percent correct response for increasingly shorter time intervals between the briefly presented (10 msec) stimulus and a patterned mask, showed a dramatic improvement over time. These changes in performance involved both a fast rapidly saturating improvement (within the first session) and a later progressive improvement (that is REM sleep-dependent, see Karni *et al*., 1994). According to the authors, several characteristics of the results point out that the improved performance is underlaid by neuronal plasticity occurring within the visual system. First, learning was local in the retinotopic sense, that is, it only occurred at visual field localities where targets were repeatedly presented. Second, learning was orientation specific, this speci-

ficity being for the background orientation not for the target elements orientation. New independent learning was required when the background elements' orientation was flipped. Third, learning was found to be monocular: the effects of practice showed little transfer from the trained to the untrained eye (but for discussion of this point see Schoups and Orban, 1996). Therefore, the neuronal plasticity underlying these performance improvements has to be located in brain areas where (i) retinotopic maps exist, (ii) orientation gradients are available, and (iii) neurons are committed to processing information from a specific eye. The most parsimonious interpretation of these results is that texture discrimination learning involves local neuronal plasticity within primary visual cortex or before.

Recent physiological data bring support to this hypothesis. Two studies in human subjects using either evoked potentials (Lamme *et al.*, 1993) or functional magnetic resonance imaging study (Karni *et al.*, 1993, 1995) suggest that practice leads to expansion of orientation-gradient based segmentation processing in the human primary visual cortex. Also, neuronal recordings obtained on monkeys performing a texture discrimination learning protocol suggest that the ability of primary visual cortex neurons to detect orientation-gradient based contours is improved after long-term training (Bertini *et al.*, 1995).

5.4. Resume

In the visual system, there is a clear dichotomy between the studies using a classical conditioning protocol and the studies using psychophysical tasks.

On the one hand, the studies using simple conditioning procedures have delivered a whole-field illumination as CS which prevents determination of the receptive fields properties of the recorded neurons. Thus, it is impossible to know whether or not the functional properties of visual neurons were changed during behavioural training. Gibbs and colleagues even stated that "it is unlikely that pattern recognition properties of the LGN were modified" (Gibbs *et al.*, 1986, p. 635) and they suggested that the plasticity observed in the LGN was the consequence of a "gating" action promoted by the noradrenergic system (Cohen *et al.*, 1982; Gibbs *et al.*, 1983). A contradiction between the two sets of studies involving neuronal recordings comes from the different responsiveness to US presentations. Most of the cells tested in pigeon visual pathways were found to be responsive to the US, and the type of response to the US predicted the occurrence of discharge plasticity for a given neuron. In contrast, the cells recorded in rat LGN did not respond to US presentation, although this stimulus produced short desynchronization of the EEG in the visual cortex (see for discussion Albrecht and Davidowa, 1993). A common mechanism was proposed, since in these two sets of studies it was assumed that neuromodulatory effects play an important role. In pigeon visual pathways, the noradrenergic inputs were hypothesized to be responsible for the responses to US presentation. In rat dLGN, the modulatory effects of the cholinergic system acting on RE neurons were hypothesized to be responsible for the changes in pattern of discharges during conditioning. Lastly, the work by Albrecht, Davidowa and colleagues points out the fact that the time window during which neuronal activity is considered can be crucial for the reported changes. Because evoked responses can exhibit complex sequences of excitations and inhibitions that are differentially affected by learning, decreased or increased evoked responses can be reported depending on which component of the response is considered. Obviously, it is important to analyze separately these components of the evoked responses and to report all the observed modifications (as Albrecht, Davidowa and colleagues did). In fact such analyses are in principle close to the temporal analysis recommended by Ohl and Scheich (1997) in the way that, more than the spikes rates, it is the temporal organization of the neuronal discharges that are important when one looks for the neuronal substrate of information processing during learning.

On the other hand, the results obtained using long-term practice in humans and non-human primates reveal other aspects of sensory processing that were not yet discussed in the auditory and somatosensory modality. Unit recordings in areas MT and MST of well-trained behaving monkeys demonstrated that both the neuronal threshold and the slope of the neurometric function matched the psychophysical performance of the animal. This strongly suggests that the neuronal signals carried by the neurons in certain sensory territories are used by the animal to make a decision about a stimulus. Surprisingly, even in well-trained animals, both the neuronal and the psychophysical performance can improve in a way suggesting direct relationships between these two levels of improvements. Nonetheless, caution is necessary before drawing definitive generalizations. Not all training tasks lead to changes in neuronal properties of visual cortex neurons, and the effects could be different from one animal to another (see, for example, Vogels and Orban, 1994)

Finally, long-term practice of the same discrimination task in humans induces changes of perceptual abilities that can only be explained by changes in the earlier stages of processing in the visual system (in primary visual cortex or before). This leads to the conclusion that depending on the task used during the experiment, sensory processing can exhibit both fast modifications and long-lasting, almost permanent, changes.*

* It is worth mentioning that results obtained with PET imagery suggest that the processing in the human visual system of the attribute orientation is task-dependent in the sense that different visual cortical areas are activated by the same stimulus depending on the nature of the task (for a review see Orban *et al.*, 1996).

6. PUTATIVE MECHANISMS OF SENSORY PLASTICITY

As for any physiological changes obtained during a learning situation, the mechanisms responsible for RF and map changes are still largely conjectural. First, because there is a large diversity of experimental situations during which sensory systems expressed selective changes, ranging from pairing two afferences (Section 4.1) to changes in psychophysical threshold in primates (see Section 5.3). Second, one has to clarify what is expected from a mechanism accounting for a learning-induced effect: Does it have to explain the induction and/or the expression of learning-induced plasticity? This is particularly important given that the induction and the expression of learning-induced sensory plasticity were sometimes tested in very different conditions; for example, map changes, induced by extensive training performed in the waking state, were tested in anaesthetized animals (Section 4.3). In contrast, short-lasting maps changes, induced by brief training, were tested in awake animals (Section 4.2). Therefore, a large number of mechanisms can potentially be involved and it seems legitimate to look for the more appropriate mechanism in each of these situations.

6.1. Involvement of Hebbian Synaptic Plasticity

Hebbian synaptic plasticity has shown its capabilities in explaining developmental plasticity in the visual system (see for review Frégnac and Shulz, 1994) and, to a lesser extent, the map reorganizations observed after peripheral manipulations (Allard *et al.*, 1991; Clark *et al.*, 1988). More recently, it was also proposed as the mechanism involved in learning-induced RF and map changes (Merzenich *et al.*, 1988, 1990; Weinberger *et al.*, 1990a,b). Only a small proportion of the evidence in favour of the involvement of Hebbian processes in learning-induced adult plasticity will be discussed here (an overview of the studies concerning more generally the involvement of Hebbian processes in adult cortical plasticity is provided in Cruikshank and Weinberger, 1996b).

First, recall that Hebb's original postulate was proposed to explain the "growth of the assembly as a first stage of perception" in the visual cortex. It was only postulated that when an afference A repeatedly takes part to fire a postsynaptic cell B, the connection between the afference and the cell is reinforced (see Hebb, 1949, p. 62). Generally, what is now called "Hebbian mechanisms" are a set of statements which defined the way by which changes in synaptic efficacy are expected to occur, and effectively occur in some, but not all, circumstances: (i) synaptic efficacy is increased when the pre and postsynaptic element are simultaneously active; (ii) synaptic efficacy is decreased when the presynaptic afference is active while the postsynaptic cell is inactive; (iii) synaptic efficacy is also decreased when the presynaptic afference is inactive while the postsynaptic cell is active. The modern manifestation of Hebb's principle, the covariance hypothesis, avoids the potential saturation in synaptic efficacy by considering that the pre and postsynaptic activities should be replaced by the deviation from their respective mean values averaged over a certain time window. Operationally, this means that there is a non-zero threshold of covariance above which increases in synaptic efficacy would occur, and below which decreases in synaptic efficacy would occur.

6.1.1. *Evidence that Hebbian Processes Act in Adult Sensory Cortices*

Obviously one of the prerequisites for proposing that Hebbian processes are responsible for learning-induced sensory plasticity is that Hebbian rules operate in the adult sensory neocortex. Among many experiments performed in this domain, a few of those which bring decisive elements are presented below. One of the most straightforward ways to test the sufficiency of covariance changes to selectively modify functional properties of cortical cells is to control the magnitude of the postsynaptic response while presenting constant presynaptic inputs. In a group of experiments, Frégnac and colleagues controlled the activity of postsynaptic cells with juxtacellular current stimulations through the recording electrode (Frégnac *et al.*, 1988). Two visual stimuli were presented during the recordings: one of them (the so-called S+) was paired with an excitation (ejection of positive current) of the postsynaptic cell, while the other stimulus (the so-called S–) was paired with an inhibition (ejection of negative current) of the postsynaptic cell. Thus, this protocol generated both an increased covariance at the S+ presentation and a decreased covariance at the S– presentation. The experiment was carried out using as S+ and S– either stimulations of the left and right eye, or stimulation of the same eye with stimuli of different orientations. After a variable number of pairing trials (based upon the figures, between 40 and 224 trials were delivered), the response to the S+ and S– were tested without juxtacellular currents. For 8/24 cells (33%) in the case of the ocular dominance and for 35/87 cells (40%) in the case of the orientation selectivity, significant changes were obtained, all but one in the direction predicted by the covariance hypothesis. The probability of obtaining the effects was similar in adults and in kittens (about 30%), but the total number of modified adult cells was small: five in the case of ocular dominance (Shulz and Frégnac, 1992) and one in the case of orientation selectivity (Frégnac *et al.*, 1992). Tests of orientation tuning (or of interocular orientation disparity) revealed selective changes in the neurons orientation tuning, which suggests that the effects induced by the protocol involved selective reorganizations of the neurons' RF. Three recent findings extended this initial set of data.

First, the same pairing procedure was applied to modify the spatial On/Off organization of cortical RF (Debanne *et al.*, 1998). Long-lasting predictable modifications of the ratio of On/Off responses were found in 44% of the conditioned neurons (17/39) and a similar proportion of modified cells was obtained in kittens (12/28) and in adult cats (4/11). More importantly, for 13 cells a fixed delay pairing

procedure was used: the onset of the current pulse used to force the firing rate of the cell was shifted by a few hundred milliseconds from the onset, or from the offset, of the visual stimulus. The post-pairing effects observed in 4/13 cells show a clear retention of the temporal pattern of activity imposed during the pairing procedure (see Figs 10 and 11 in Debanne *et al*., 1998). Such a recall of the pattern of activity which had been imposed during pairing was only present during stimulation of regions of the RF which were activated during pairing. Even if these effects might reflect potentiation of subthreshold inputs allowing the expression of lagged responses after pairing, they clearly show that an appropriate pairing procedure can modify the temporal characteristics of the evoked responses.

Second, using ionophoretic application of either GABA or glutamate to control postsynaptic firing rates, predictable modifications in orientation tuning were obtained in adult cat striate cortex (McLean and Palmer, 1998). This is of importance because it shows that the release of natural neurotransmitters is sufficient to reproduce effects previously described using current applications.

Lastly, using the same technique (control of the postsynaptic cell by juxtacellular current stimulation), this Hebbian protocol was transferred in the adult auditory cortex by Cruikshank and Weinberger (1996a). These authors paired the presentation of pure tone frequency with the imposed discharge of the postsynaptic cell and the presentation of another pure tone frequency with the imposed blockage of the postsynaptic cell activity. After 120 trials of pairing, 7/22 cells (32%) exhibited significant increases in responses to the S+ relative to the S−, while none had significant decreases. Significant effects were maintained in 6/7 neurons at 15 min and in 2/4 neurons at 30 min. This shows that a pairing procedure which had proved its efficiency in a given sensory cortex can be transferred to another sensory modality and can be applied to another dimension of the sensory stimuli (Fig. 12).

All these experiments show that a local control of the covariance between the pre and postsynaptic activity is sufficient to produce long-lasting and selective modifications of the neurons' RF. Nonetheless, one can argue that such a local powerful control is unlikely to occur in a physiological situation, since the probability that one neuron controls the firing rate of another is very low (see Abeles, 1982; Braitenberg and Schuz, 1991). To test the involvement of Hebbian mechanisms at the network level in a more realistic situation, Ahissar and colleagues have designed an original protocol. These authors recorded simultaneously the activity of 2–10 neurons and examined the functional connectivity between these neurons (Ahissar *et al*., 1992a). To quantify this functional connectivity, they determined the cross-correlogram between the firing time of pairs of neurons (the cross-correlogram manifests the net effect of the whole synaptic network through which the two neurons interact including both direct and indirect connections; see for details Section 7.3). The authors selected for analysis pairs of neurons that exhibited functional coupling before any manipulation. During the pairing trials, each spike of one neuron (the so-called presynaptic neuron) triggered the presentation of a pure tone frequency which either excited or inhibited the other neuron of the pair (the so-called postsynaptic neuron). By doing this, the covariance was artificially increased or decreased during the pairing via the presentation of the sensory stimulus. The cross-correlogram, retested after completion of the pairing, indicated that (i) the peak of the cross-correlation was increased when the covariance was increased during the pairing, and that (ii) the peak of the correlation was decreased when the covariance was decreased during pairing. The effects typically lasted 1–13 min (see also Ahissar and Ahissar, 1994).

These experiments demonstrated that when produced either by a local control of the postsynaptic cell activity, or by a control via a whole neural network, imposed Hebbian treatments seem sufficient to change the neuronal responses (for a limited period of time) in the direction predicted by Hebb's original proposal.*

6.1.2. *Is There Evidence for the Involvement of Hebbian Processes in Learning-Induced RF and Map Changes?*

The rationale for involving the Hebbian schema in learning-induced sensory plasticity rises from its activity-dependent afferent plasticity. For example, in the RF plasticity observed after behavioural training, increased responses were observed at the CS frequency while decreased responses were observed at non-CS frequency including the pretraining Best Frequency. This result can be viewed as a competition among afferences to drive the recorded neuron (for review see Weinberger *et al*., 1990a). A competition between converging inputs was first suggested by (Wiesel and Hubel, 1963, 1965) to explain the developmental plasticity in the visual system. Their findings showed that, although monocular deprivation was able to eliminate the cortical responses to the deprived eye, binocular deprivation did not eliminate the response to either eye. Thus, a competition between inputs converging on a given recorded cell was the most logical hypothesis to explain modifications in ocular dominance preference when the visual environment is manipulated during critical periods (for a review see Wiesel, 1982). Because of this apparent similarity, the neuronal changes observed in learning situations were interpreted as resulting from competition between afferences to drive a postsynaptic cell, as if "extended Hebbian rules" were operating to induce the learning-induced changes.

If direct evidence for particular cellular mechanisms can be found in invertebrate preparations

*There are other indirect arguments in favour of the hypothesis that Hebbian mechanisms operate and are responsible for some forms of plasticity in sensory systems. For example, in the MGm, neuronal plasticity was induced by tetanic stimulations of afferent bundles (Gerren and Weinberger, 1983) in a similar protocol to those used to induce hippocampal long-term potentiation, an artificial form of plasticity where co-variance rules are necessary and sufficient to account for the neural changes.

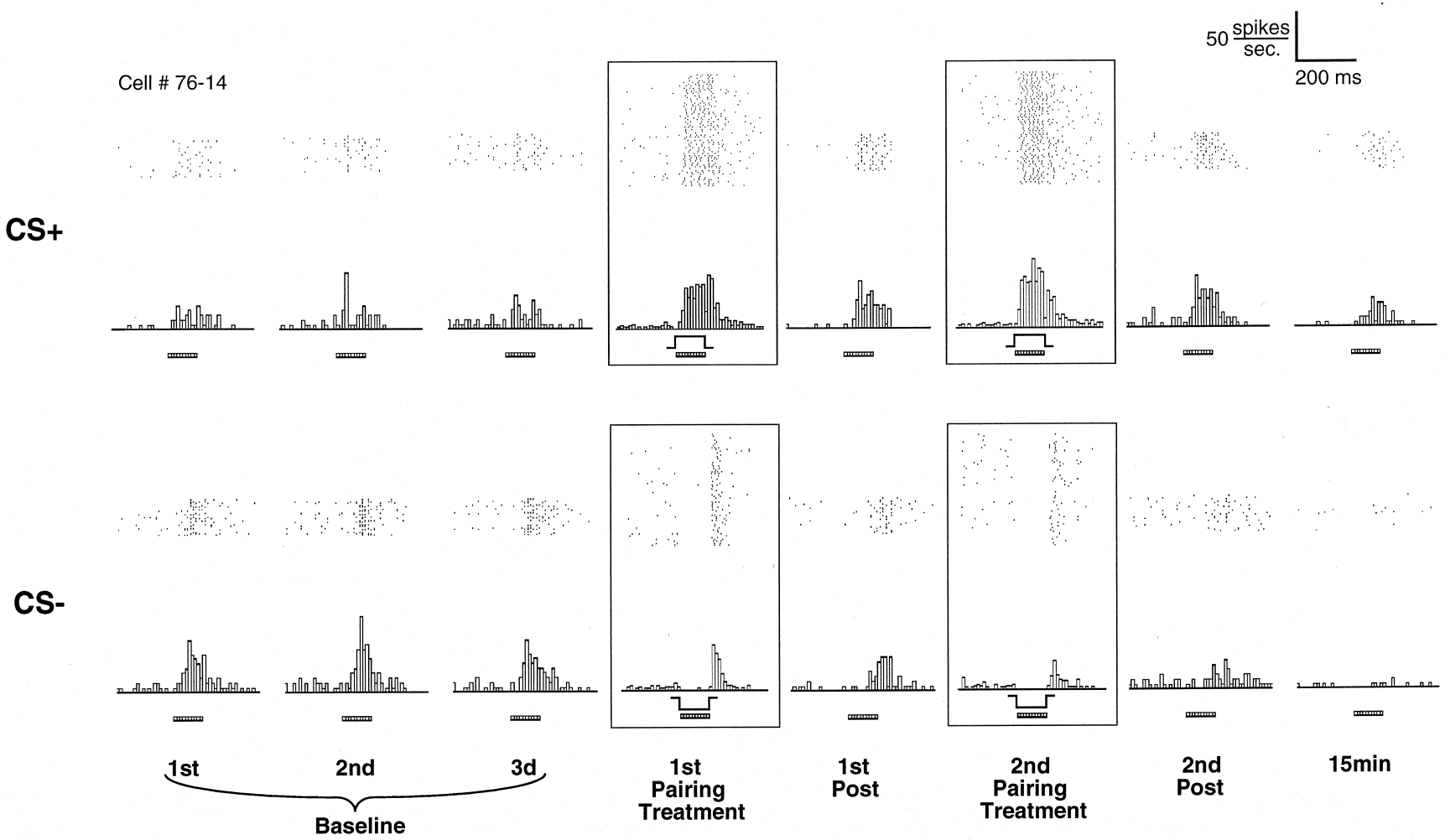

Fig. 12. Effects of Hebbian treatment in the auditory cortex. The responses of an auditory cortex neuron to two pure tone frequencies are presented. For each tone, a baseline period of three blocks of 20 presentations was performed before the treatment. Then, the presentation of one tone (the CS+) was paired with an imposed increase in discharge of the neurons via ejection of positive current (juxtacellular electrode configuration), while the presentation of the other tone (the CS–) was paired with an imposed blockade of the neuron discharges. After 60 pairing trials for CS+ and CS−, the responses to both tones were tested without current ejection. An increased response was observed at the CS+ and a decreased response at the CS−. A second pairing treatment was performed. After its completion, there was again an increased response at the CS+, and only weak responses were obtained at the CS−. Fifteen minutes after, response at the CS– were completely absent, while the responses at the CS+ were still consistent (from Cruikshank and Weinberger, 1996a with permission).

(Alkon, 1988; Hawkins and Kandel, 1984), it is very difficult to obtain direct experimental evidence in favour of any specific mechanism in mammalian preparations engaged in a learning task (but see, for example, Meftah and Rispal-Padel, 1994, 1997). The evidence in the sensory systems is as indirect as in other parts of the brain. For example, in the auditory system, the results obtained by McEchron *et al.* (1996) have been interpreted as strong arguments in favour of the view that changes in synaptic efficacy explain neuronal conditioning in the MGm. These authors have tested, before and after conditioning, the responses of MGm neurons to stimulations of the brachium of the inferior colliculus (BIC) and to stimulations of the superior colliculus (SC). They reported that after behavioural training, the stimulation of the BIC evoked responses that (i) had shorter latencies, (ii) were more reliable, and (iii) were larger compared to those evoked before training. Such changes were not observed for the responses evoked by SC stimulation. The authors' conclusion was that these changes resulted from an increase in synaptic efficacy between the BIC inputs and MGm neurons. Besides the fact that it is almost impossible to determine synaptic efficacy based upon extracellular single unit recordings, few points have to be mentioned. First, because of the non-balanced design of the experiment, one can wonder if any other results could have been expected. In short, there is no guarantee that the MGm input from the SC can be facilitated in any circumstances by experimental manipulations. Second, the observation that extracellular discharges are larger and have shorter latencies does not mean that during training changes did not occur downstream, for example, in the IC itself or before. Although the conclusions of the authors might be absolutely correct, many studies are still required to bring definitive arguments in favour of changes in synaptic efficacy. One of the merits of this study is in pointing out potential relevant experiments: for example, sampling intracellular recordings in MGm before and after behavioural training and testing their responses to BIC stimulation could reveal whether or not synaptic efficacy is increased by learning.

6.1.3. *Are Learning Experiments Appropriate Conditions for Hebbian Rules to be Involved?*

On the one hand, Hebb's original neurophysiological postulate was not initially proposed to explain learning. On the other hand, this postulate seems largely capable of explaining developmental plasticity in sensory systems. Thus, the willingness to apply the Hebbian postulate to the mechanisms of learning implies that one accepts the idea that learning and development are underlaid by exactly the same mechanisms.

Besides the fact that the pre and postsynaptic cells have to be active, one of the requirements for the induction of Hebbian plasticity is that a temporal relationship exists between pre and postsynaptic activity. For example, if kittens are raised with an artificially induced squint, most of the visual cortex cells (80%) become monocular, since in these conditions cortical neurons receive asynchronous inputs from the two eyes (Wiesel and Hubel, 1965). Very few in vivo experiments have tried to determine to what extent temporal relationships have to be present to induce Hebbian plasticity in sensory neocortex. In the auditory cortex, when the maximally enhanced portions of the postsynaptic responses occurred simultaneously with, or slightly after (< 100 msec), the estimated arrival of the presynaptic input, 91% of the cells (10/11) had subsequent relative increase at the S+ vs at the S– (i.e. 91% of the changes in the direction predicted by the Hebbian rules). In contrast, when the enhanced portion of the postsynaptic response occurred before the estimated arrival time of the presynaptic input, there was as many increases as decreases (Cruikshank and Weinberger, 1996b). Thus, the timing of the presynaptic volley in regard to the activity of the postsynaptic cell seems crucial for inducing Hebbian plasticity.

During learning protocols, such narrow constraints are difficult to find. For example, in the protocol used by Delacour and colleagues (see Section 4.1) facilitation of evoked responses in the somatosensory cortex were obtained with an inter-stimulus interval of 500 msec. Any facilitation of the postsynaptic response to the first stimulus resulting from presentation of the second was necessarily delayed by at least 500 msec, which is outside the range discussed above. This situation is even worse for the classical conditioning studies that are presented in Section 3 (auditory system), Section 4 (somatosensory system) and Section 5 (visual system). In all these studies, the authors have used a CS duration of a few seconds. Because neurons of the thalamocortical sensory system respond phasically to presentation of a sensory stimulus,* there is an interval of several seconds between the discharges evoked by the CS and those potentially evoked by the US. Therefore, direct co-activation of thalamo-cortical cells by the CS and the US is unlikely to occur during the training trials. There are several alternatives to circumvent this problem. One can first consider that co-activation of sensory neurons is realized by indirect ways. For example, Weinberger and colleagues have proposed that the plasticity occurring in the auditory cortex is the result of the convergence of two thalamic inputs on the cortical cells: a non-modified input from the MGv and a increased input from the MGm (Weinberger *et al.*, 1990a,b). Although attractive, this hypothesis only displaces the problem at the thalamic level. How can thalamic cells integrate the afferent volley from the CS with that of the US coming 6–10 sec later? As developed in the next section, the temporal integration performed by sensory neurons can be drastically modified by an increased release of neuromodulators which occur during the training trials.

In fact, this lack of temporal co-activation is a general problem when one wants to explain the

* When neuronal activity was tested during the training trials, only one of the 173 cells I have recorded in the auditory cortex and thalamus showed sustained firing at the CS presentation. Nonetheless, many of these cells exhibit selective RF changes after training.

learning-induced neuronal plasticity in any brain structure; the problem is just more acute in sensory structures because of the phasic nature of the discharges evoked by sensory stimuli.

A second major problem comes from the discrepancy between the effects obtained during training trials and the effects obtained in the RF tested after training. One of the most obvious requirements for arguing that Hebbian synaptic plasticity explains learning-induced plasticity is that the effects observed after training reflect the effects occurring during the training session. As explained in Section 3.3.4, both at the cortical and at the thalamic level, there was often no relationship between the direction of the changes observed during the training trials and the response changes observed after training in the neurons' RF. Even if explanations can be proposed (see Diamond and Weinberger, 1989), this problem should force one to admit that it is difficult to reconcile the requirements imposed by Hebbian rules and the plasticity observed during learning. Lastly, one has also to consider the diversity of

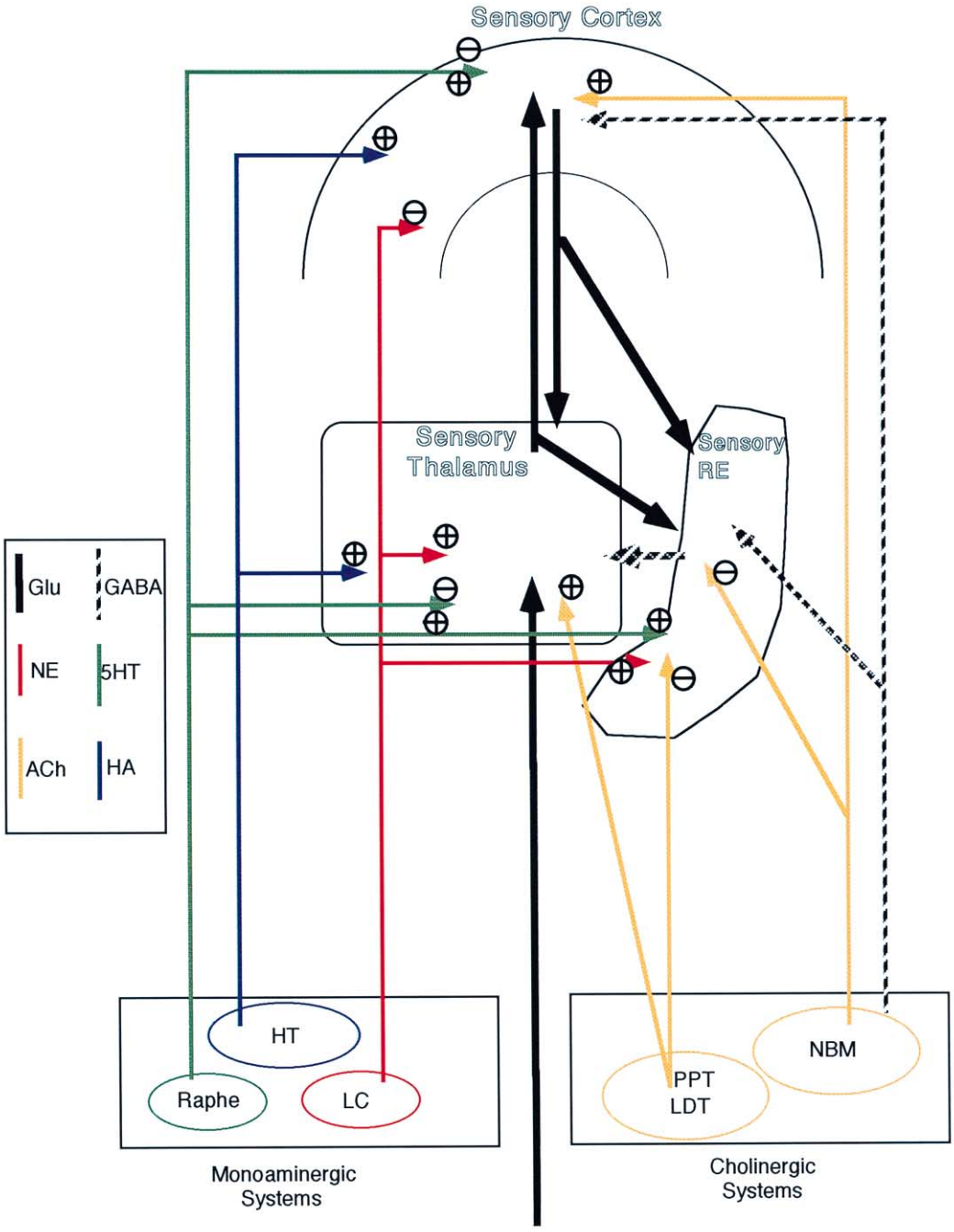

Fig. 13 *caption opposite*

effects obtained in the same structure depending on the protocol used for training. For example, it is difficult to propose the same mechanism for the increased responses at the CS frequency obtained after simple classical conditioning (Bakin and Weinberger, 1990; Edeline and Weinberger, 1993) and the increased responses observed in both sides of the CS frequency after a more complex conditioning protocol (Ohl and Scheich, 1996; see for details Section 3.3.1).

6.2. The Actions of Neuromodulators: Gating Systems?

In many studies presented in Sections 3–5, the authors have involved a neuromodulator to explain, at least partly, the neuronal plasticity observed during training. In the auditory system, the cholinergic input from the nucleus basalis magnocellularis (NBM) was proposed as a factor allowing the cortical cells to integrate the CS and the US inputs (Weinberger *et al*., 1990a). In the somatosensory system, the effects induced by a sensory–sensory association were blocked by local iontophoretic applications of a cholinergic antagonist (atropine; see Delacour *et al*., 1990). Application of atropine in the RE modified the differential responsiveness of dLGN cells that was observed when an animal was using a visual cue for its behaviour (Albrecht *et al*., 1986).

The idea behind many experimental studies, which is also developed in several review articles (Frégnac and Shulz, 1994; Cruikshank and Weinberger, 1996b), is that neuromodulators act as "gating" factors. A straightforward definition of a "gating" factor is not easy because of the different levels of interpretation of the word "gating". First, it is necessary to consider that neuromodulators can affect sensory processing independently of the occurrence of any plasticity. Second, it is necessary to consider how the release of neuromodulators (or the absence of release) modifies the results when the protocol is able by itself to induce sensory plasticity. For a long time the noradrenergic and cholinergic systems were proposed as "gating factors". For the sake of clarity, I will focus on the effects of the noradrenergic and cholinergic system, but, of course, we should consider that other pharmacological agents such as dopamine, serotonin, histamine and all the peptidergic systems can also promote similar effects (for a review see McCormick, 1992). An attempt to summarize the effects of neuromodulators on the thalamo-cortical sensory system is presented in Fig. 13.

Fig. 13. Effects of neuromodulators in the thalamo-cortical system. For the sake of clarity, many simplifications were introduced in this figure, since within the same brain area the same neuromodulator can have different effects depending on the type of receptors it reaches. In addition, conflicting results were found depending (i) on the species and (ii) on the fact that the results came from in vivo or in vitro experiments. The details listed below give a more acurate, but more complex, picture for the action of each neuromodulator (for review see McCormick, 1992). Noradrenaline: Both at the cortical and thalamic level, in vitro experiments reveal excitatory effects mediated via b-receptors which lead to a decrease in IAHP. In vivo recordings reveal both inhibitory and excitatory effects (see text). As pointed by some in vitro studies, the inhibitory effects could result from a decreased synaptic transmission (Law-Tho *et al*., 1993) or from an action on GABAergic interneurons (Mouradian *et al*., 1991; Sessler *et al*., 1995). At the thalamic level, the effects obtained in vivo seem to be a function of the species: in the lateral geniculate excitatory effects were obtained in rats (Rogawski and Aghajanian, 1980a,b), while inhibitory effects were obtained in cats (Sillito, 1987). In the reticular nucleus, only excitatory effects were described both in vivo and in vitro (McCormick and Wang, 1991; Pinault and Deschenes, 1992). Serotonine: At the thalamic level, in vivo studies have described prolonged inhibitions produced by iontophoretic application of 5-HT or raphe stimulations (Kayama *et al*., 1989; Marks *et al*., 1987; Phillis, 1971; Rogawski and Aghajanian, 1980c). As such inhibitory effects were not observed very often in vitro (McCormick and Pape, 1990), they might be the consequence of an indirect excitation of neighbouring interneurons (McCormick and Wang, 1991). At the cortical level, in vivo iontophoretic application of 5HT produces both excitatory and inhibitory effects (Bassant *et al*., 1990; Waterhouse *et al*., 1990). In vitro studies showed that inhibitory effects result from activation of a potassium conductance I_{KG}, whereas excitatory effects result from a reduction of I_{AHP} and I_M (McCormick and Williamson, 1989). In the RE in vivo (Funke and Eysel, 1993) and in vitro (McCormick and Wang, 1991) studies showed clear excitatory effects through reduction of I_{Kleak}. Acetylcholine: At both the cortical and thalamic level, ACh produces depolarizations, in vivo and in vitro. In the RE, in vivo studies using application of ACh or stimulation of cholinergic nuclei reported strong inhibitory effects (Ben Ari *et al*., 1976; Hu *et al*., 1989; but see Kayama *et al*., 1986). In vitro studies have confirmed a dominant inhibitory effect resulting from activation of a potassium conductance (McCormick and Prince, 1986). However, recent findings revealed that the hyperpolarization mediated by muscarinic receptors is preceded by a fast depolarization mediated by nicotinic receptors (Lee and McCormick, 1995). Also, it is interesting to note that the action of ACh on thalamic cells involve a transient hyperpolarization in the cat and guinea-pig medial geniculate, but not in the rat lateral geniculate (McCormick and Prince, 1987). Histamine: Both at the cortical and at the thalamic level, histamine mainly produces excitatory effects (even if inhibitory effects were sometime observed at the cortical level). These excitatory effects are supposed to be the consequence of an activation of H1 receptors (leading to strong depolarization) and an activation of H2 receptors which reduces I_{AHP}. Abbreviations: HT: tuberomammillary area of the posterior hypothalamus, LC: Locus coeruleus, LDT: Laterodorsal tegmental nucleus, NBM: nucleus basalis magnocellularis, PPT: pedonculopontine tegmental nucleus, RE thalamic reticular nucleus. $\oplus$ Depolarization, $\ominus$ hyperpolarization.

6.2.1. *Do Neuromodulators Act as Gating Factors on Sensory Processing?*

A first basic step is to determine what are the effects of neuromodulators on sensory processing, and to reach this goal determination of the effects of neuromodulators on the neurons' RF is a straightforward procedure. Ionophoretic application of ACh was shown to increase the neurons excitability in the early 1960s (Krnjevic and Phillis, 1963b,c), but its effects on the neurons' RF were tested more recently. In the visual cortex, facilitation of visual responses often occur with an enhancement of orientation or direction selectivity (Murphy and Sillito, 1991; Sillito and Kemp, 1983). A modulation of RF properties by ionophoretic applications of ACh was also reported in the lateral geniculate (Sillito *et al*., 1983). In the somatosensory cortex, the main effects of ACh application on RFs from the forelimbs or hindlimbs were (i) the appearance of RF on unresponsive neurons or the enhancement of preexisting RF characteristics, (ii) lowering of response threshold in the RF area, and (iii) the increase of RF size (Lamour *et al*., 1988). Even if these RF changes seem in good agreement with the known excitatory effect of ACh, it is important to mention that the effects of ACh on afferent response properties could not be predicted from its ability to excite a cell (Lamour *et al*., 1988) This suggests that the mechanisms by which ACh modifies the effectiveness of somatic inputs is different from the mechanisms leading to excitation. The same picture was also reported in the auditory cortex (Fig. 14). The most common effect of ACh application was a facilitation of the tone "On" evoked response (but decreased responses were also observed, see Figs 3, 6 and 9 in McKenna *et al*., 1988). However, when the effects of ACh on the RF of auditory cortex neurons were tested, general facilitation in the neurons' RF were not observed very often (19%, 10/51 cells). In most cases (77%, 39/51 cells), responses to some frequencies were decreased, and responses to others were increased (McKenna *et al*., 1989). The same type of differential effects were also observed when anticholinesterases were applied (Ashe *et al*., 1989), suggesting that endogenous release of ACh affects the frequency processing of auditory cortex cells in a complex fashion.

The effects induced by NE applications in the thalamo-cortical system are as complex. At the cortical level, some earlier studies have mainly observed decreased evoked responses (Foote *et al*., 1975), but others have stressed differential facilitation, i.e. the fact that evoked responses are less affected than the spontaneous activity (Waterhouse *et al*., 1981; Waterhouse and Woodward, 1980). This promotes the popular view that NE application increases the signal-to-noise (S/N) ratio, defined as the evoked response divided by the spontaneous activity. If the dominant inhibitory effect of NE at the cortical level was confirmed, the increase in S/N ratio was not found systematically in other studies using iontophoretic application of NE (Kasamatsu and Heggelund, 1982; Manunta and Edeline, 1996, 1997; Videen *et al*., 1984) or LC stimulation (Sato *et al*., 1989). Tests of the action of NE on the neurons' RF were only carried out recently, and conflicting results were found. In the visual cortex, McLean and Waterhouse (1994) have reported a narrowing of velocity tuning curves in 16 of 28 neurons. But in their data, and in that of others (Shulz and Bringuier, 1993), orientation selectivity was unaffected by NE. In the auditory cortex (see Fig. 15), increases in frequency tuning were reported using either iontophoretic application of NE (Manunta and Edeline, 1997, 1996) or pharmacological release of NE (Edeline, 1995).

The effects obtained in some occasions led some authors to suggest that NE acts as a "gating" factor. In this particular context, this term refers to the occurrence of a response when a subthreshold stimulus is delivered in the presence of NE. According to Waterhouse *et al*. (1988), this should be distinguished from the classical facilitatory effect on pre-existing responses. However, systematic tests of a "gating" effect in the auditory cortex (by testing the neurons' acoustic threshold) revealed that decreased threshold (i.e. a gating effect) was obtained for only a few cells (12%, 10/84 cells), while the opposite effect (increased threshold, i.e. the reverse of a gating effect) was obtained for a large number of cells (57%, 48/84 cells; see Fig. 16; Manunta and Edeline, 1998). In contrast, at the thalamic level, both application of NE (Rogawski and Aghajanian, 1980a,b) and LC stimulation (Kayama *et al*., 1982) decreased the threshold response to single shock stimulation of the optic nerve. From these data one can conclude (i) either that the gating effects observed at the thalamic level is not transferred at the cortical level; or (ii) that a gating effect can be obtained using electrical stimulation of afferent bundles but not with presentation of sensory stimuli. The effects of ACh were not tested as often as those of NE, but since it decreased the responses threshold in many cells (Metherate *et al*., 1990), ACh seems more suitable to act as a gating factor. Given that ACh depolarizes the cortical cells, one can wonder if any pharmacological agent that will depolarize the neurons will not act as gating factor. With this notion in mind, it seems paradoxical to consider a "gating" function for neuromodulators (for example for NE) which have inhibitory or excitatory properties depending on the type of receptors that they bind with.

6.2.2. *Do Neuromodulators Act as Gating Factors on Sensory Plasticity?*

The involvement of neuromodulators in sensory plasticity was first proposed for developmental plasticity. Even if controverted (see Adrien *et al*., 1985; Frégnac, 1987), a long series of experiments has tried to demonstrate that the noradrenergic system is crucial for ocular dominance plasticity (Kasamatsu and Pettigrew, 1976; Kasamatsu *et al*., 1979, 1981). The major problem is that one of the methods used to produce NE depletion (local infusion of 6-OHDA) blocked ocular dominance plasticity in kittens, while other methods of depletion did not (for review about this controversy see Frégnac, 1987). This problem was potentially solved

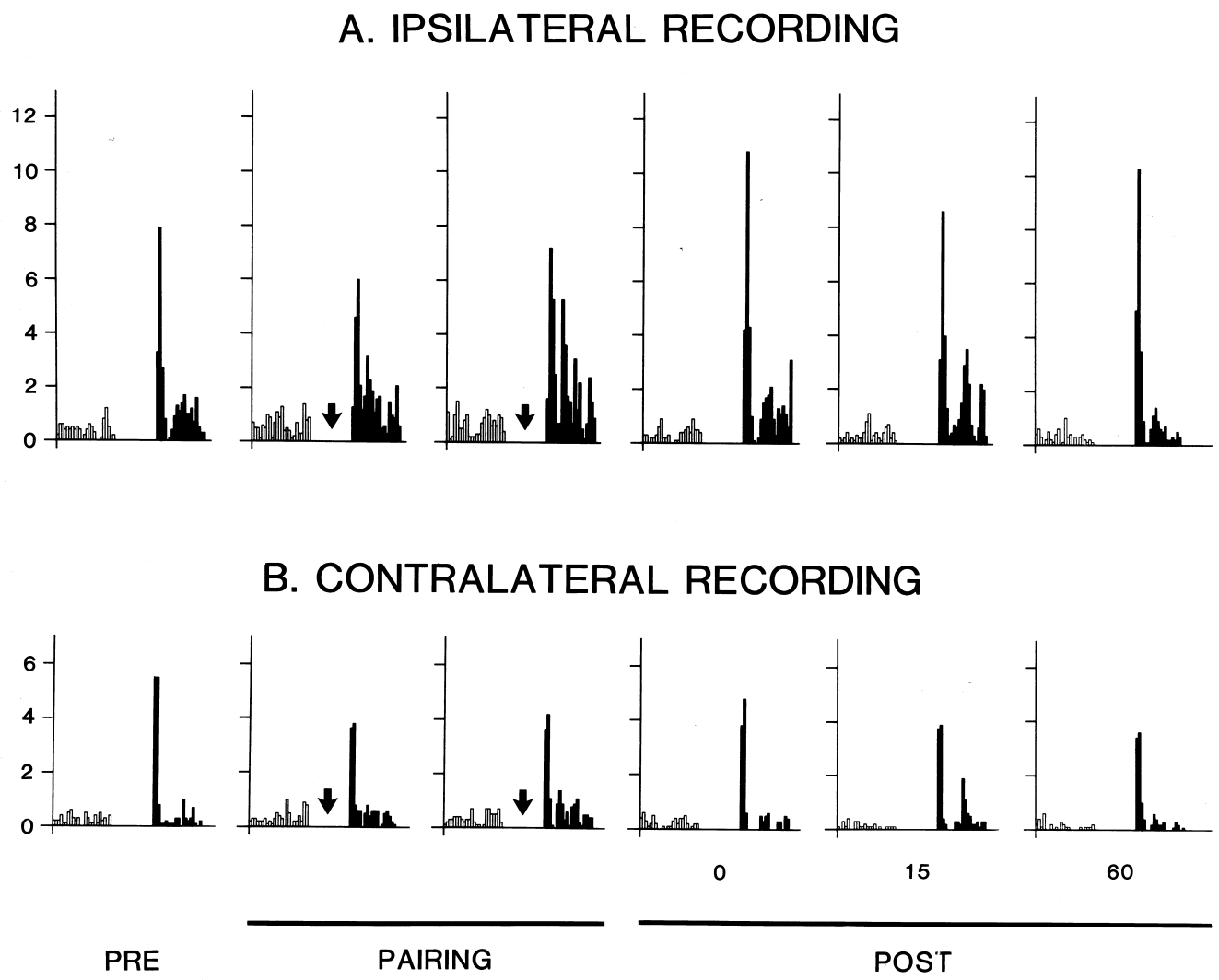

Fig. 14. Effects of NBM stimulation on evoked responses in the ipsilateral (A) and contralateral (B) auditory cortex during wakefulness. Histograms (bin width 20 msec) of neuronal discharge obtained simultaneously before, during, and after pairing between tone presentation and NBM stimulation (delivered at 300 μA, an intensity which desynchronized the EEG). The stimulations lasted 300 msec (ending 30 msec before tone onset) and the preamplifier was ground from 1 msec before to 1 msec after the stimulation to avoid its saturation. The horizontal bar below the *x*-axis denotes the tone (4 kHz) duration (200 msec). Note that the ipsilateral responses were largely increased during pairing, and that they remained increased after pairing. In contrast the contralateral responses were unaffected (from Edeline *et al.*, 1994a). On each histogram, the open bars represent the spontaneous activity collected during 500 msec preceding the stimulation, and the dark bars represent the activity during the first 400 msec of tone presentation. During pairing, the arrow denotes the stimulation which lasted 300 msec (the preamplifier was ground during stimulation to avoid its saturation). For both recordings the short-latency "on" evoked responses were slightly decreased during the two blocks of pairing trials, while the long latency activity was increased. After pairing there was a facilitation of the ipsilateral "on" responses immediately post-pairing and 1 hr post-pairing. Note in contrast the absence of increase for the contralateral responses (from Hars *et al.*, 1993).

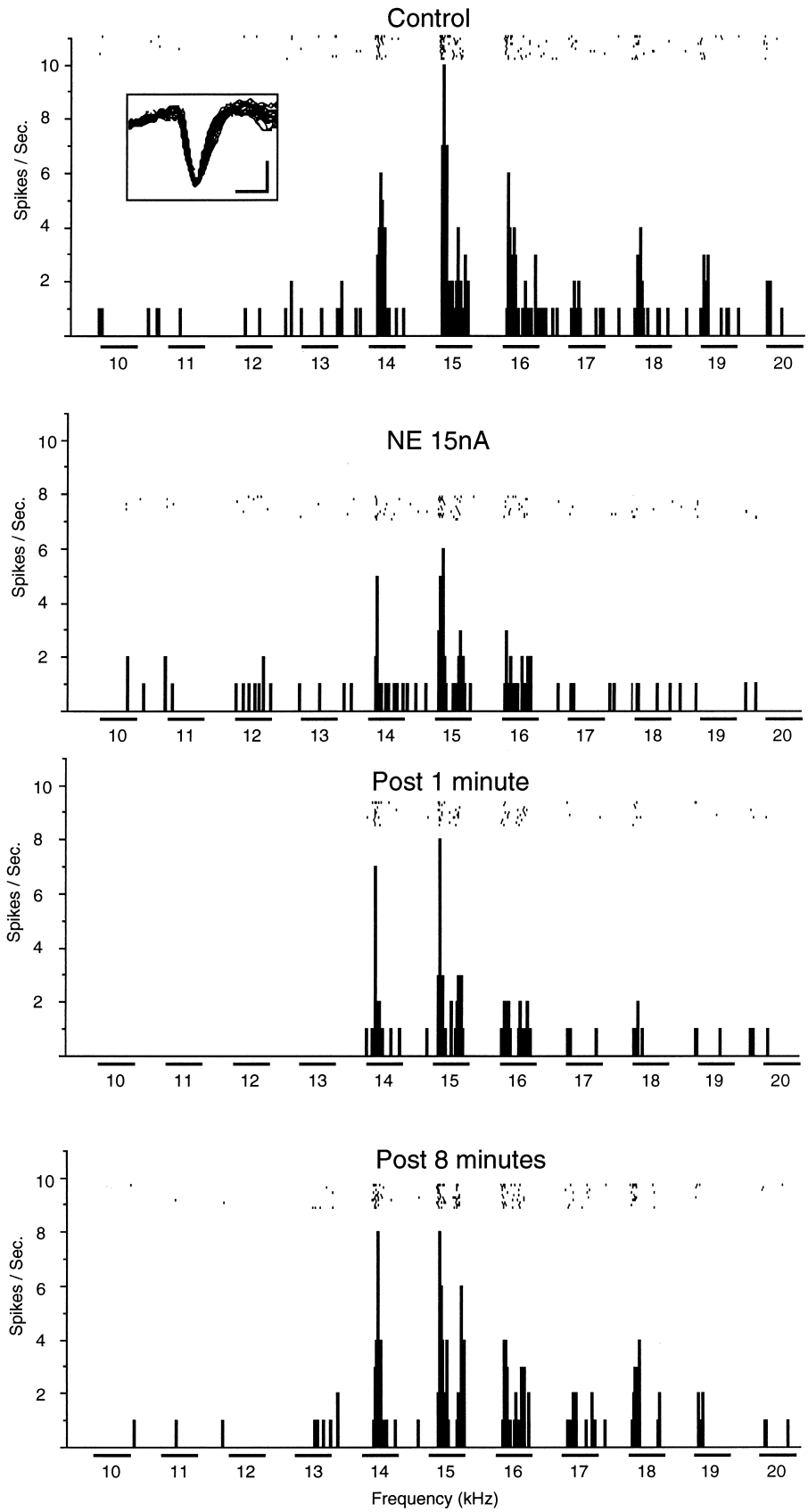

Fig. 15 *caption opposite*

by Bear and Singer (1986) when they showed that the 6-OHDA lesion (which was supposed to selectively impair the noradrenergic system) actually interferes with the cholinergic system. Thus, the use of local application of 6-OHDA results in dysfunction of both the noradrenergic and cholinergic system. According to Bear and Singer (1986), ocular dominance could only be blocked by lesion of both the noradrenergic and cholinergic systems; a lesion of either system alone was ineffective in their hands. More recently, other forms of plasticity were shown to depend upon the integrity of the cholinergic system. For example, lesions of the cholinergic system, or ACh depletion, were able to prevent the plasticity of the somatosensory cortex observed following peripheral manipulations (Juliano *et al*., 1991; Webster *et al*., 1991).

As proposed by Cruikshank and Weinberger (1996b), there are two modes of action to take into account when one wants to explain how neuromodulators act to "gate" neuronal plasticity (see Fig. 17). The first mode supposes that the presence of gating factors during the induction protocol allows significantly larger increased covariance compared with the control situation. The second mode supposes that gating factors enhance synaptic changes without directly affecting the covariance levels during the pairing situation (Cruikshank and Weinberger, 1996b). Even if there is very little direct evidence in favour of one or the other of these modes, recent findings enlighten this question. For example, in the experiments carried out by Ahissar and colleagues (see Section 6.1.1) comparisons were made between the effects obtained when the animal was not using the stimuli in its behaviour vs when it was. Recall that in these experiments the covariance between two cortical cells is artificially increased during Hebbian treatment, and that the apparent synaptic effectiveness remained increased for few minutes after the treatment. The authors observed that for a given level of imposed covariance, the effects were larger if the animals have to use the stimulus for obtaining a reward, which suggests that the strength of the changes was "gated" by the behavioural performance. Another type of evidence come from the data obtained by Cruikshank and Weinberger (1996a). As presented above (Section 6.1.1) the Hebbian treatment used by these authors consisted of pairing a pure tone with an increased firing rate, while another pure tone was paired with blockage of neuronal discharge. As in most of the experiments performed under urethane anaesthesia, the authors observed considerable spontaneous EEG changes, in such a way that for some cells the Hebbian treatment was conducted during periods of synchronized EEG (high voltage, 1–5 Hz), while for other cells the Hebbian treatment was conducted during periods of desynchronized EEG (low voltage, 1–20 Hz). Post-hoc analysis of their data revealed that the probability of obtaining plasticity was significantly greater if the cortical EEG was desynchronized during the pairing treatment (5/9 cells vs 2/13 cells). More important is the fact that the imposed covariance during the Hebbian treatment was similar, which indicates that covariance levels that were not sufficient to induce plasticity in EEG synchronized state, were sufficient in EEG desynchronized state.

In both types of experiments, the factors that were actually responsible for the largest degree of plasticity (in Ahissar *et al*., 1992a), or for the higher probability of occurrence of the plasticity (in Cruikshank and Weinberger, 1996a) are unknown. Nonetheless, it seems logical to propose that in both cases neuromodulators are involved. This is logical for the results of Ahissar *et al*. (1992a) since the neurons of the source nuclei providing ACh and NE at the cortical level, the nucleus basalis magnocellularis (NBM) and the locus coerulus (LC) show marked increases in firing rate in situations involving presentation of a reward and/or association of a sensory stimulus with a reward [for the NBM see Maho *et al*. (1995); Richardson and DeLong (1986); for the LC see Rasmussen and Jacobs (1986); Sara *et al*. (1988)]. This is also logical for the results of Cruikshank and Weinberger (1996a) since the involvement of ACh and NE in controlling the state of the EEG is well-known: stimulations of either the NBM (Belardetti *et al*., 1977; Casamenti *et al*., 1986; Metherate *et al*., 1992 Edeline *et al*., 1994a) or of the LC (Berridge and Foote, 1991) produce shifts from synchronized EEG to desynchronized EEG. Lastly, more direct arguments recently came from a collaborative study by Ahissar *et al*. (1996). To test the possible involvement of neuromodulators in the plasticity induced by their Hebbian treatment in waking monkeys, the authors have compared the results obtained when this treatment was applied to anaesthetized animals with and without local iontophoretic application of neuromodulators. As in the case of non-behaving monkeys, the effects obtained in anaesthetized animals without neuromodulators were weak; significant lasting modifications were only observed occasionally. In contrast, when the Hebbian treatment was conducted with concurrent application of cholinergic and noradrenergic agents, lasting modifications of functional coupling were found (Ahissar *et al*., 1996).

Fig. 15. Transient inhibitory effects of ionotophoretic application of norepinephrine in the RF of an auditory cortex neuron during wakefulness. For this cell recorded in an awake guinea pig, evoked responses were observed between 14 and 20 kHz in the control RF. The cell's BF was 15 kHz. During NE application (15 nA), the tone-evoked responses were attenuated; the cell was only responding to 14–16 kHz. This effect persisted when the tuning was tested 1 min after the end of NE ejection. The responses almost fully recovered 8 min after the end of NE ejection. Note that during and after NE ejection the cell's selectivity was enhanced. The insert in the top of the figure displays the waveform of the action potential (30 sweeps, 50 kHz sampling rate. Scales bars: 0.5 mV, 0.5 ms) (from Manunta and Edeline, 1996).

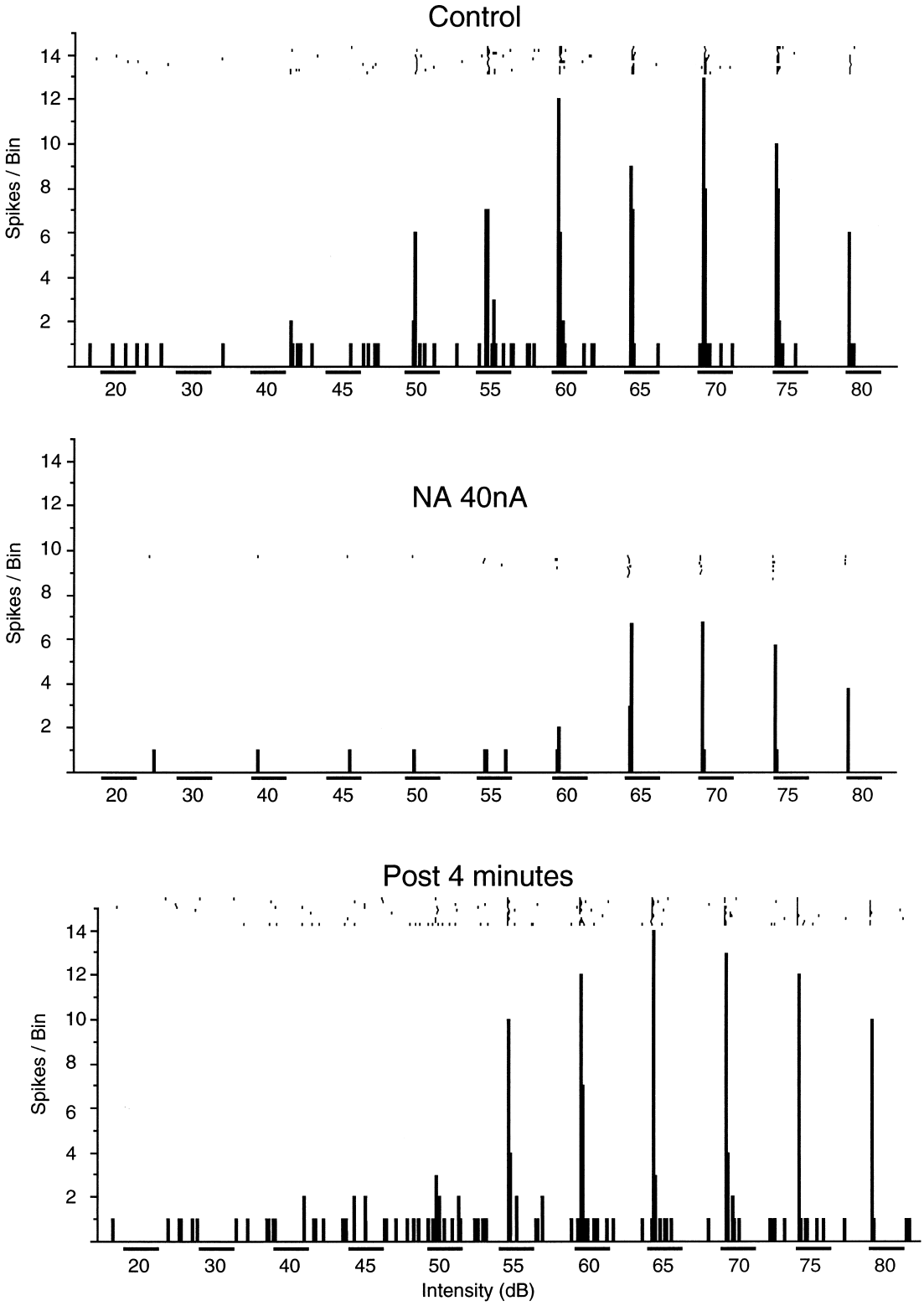

Fig. 16. Increased acoustic threshold of an auditory cortex neuron during ionotophoretic application of norepinephrine. The test of the rate level function of a given neuron is a way to determine the acoustic threshold for neurons in the auditory system. These tests are performed by increasing the absolute intensity of the tones at a given frequency. In control conditions, testing the rate-level function of this cell revealed a monotonic function with a threshold at 50 dB. During NE application there was a clear decrease of the evoked response at all intensities, which led to increase the neuron threshold at 65 dB. Four minutes after the end of the ejection, the responses recovered and the threshold was back at 50 dB (from Manunta and Edeline, 1998).

Another procedure for studying the involvement of neuromodulators in sensory plasticity is to pair the presentation of a given sensory stimulus with the delivery of a given neuromodulator. The rationale for this relies on the fact that in a learning task there is an increased release of different modulators while a stimulus acquired significance. For example, iontophoretic ACh application was paired with presentation of a given pure tone frequency, and the frequency RF of the neurons was tested before and after this pairing (Metherate and Weinberger, 1990).* It was observed that during pairing ACh produced mostly facilitatory effects on spontaneous activity and on tone-evoked responses. However, even if highly specific RF changes were obtained, they were not related to the effects observed during pairing: in the majority of the cases (22/28 cases), the specific effects were decreases at the frequency paired with ACh application.* In the same vein, several studies have stimulated the NBM, the source nucleus providing ACh at the cortical level. In most of these experiments, the effects were similar to those obtained with iontophoretic application. When stimulation of the NBM was associated with presentation of a somatosensory or an acoustic stimulus, increased responses were obtained in many cases (Edeline *et al.*, 1994a; Metherate and Ashe, 1991; Rasmusson and Dykes, 1988; Webster *et al.*, 1991) even if decreased responses were obtained in some occasions (Edeline *et al.*, 1994b; Webster *et al.*, 1991). Testing the evoked responses after the pairing protocol revealed prolonged facilitations (Rasmusson and Dykes, 1988; Tremblay *et al.*, 1990; Webster *et al.*, 1991). Again, the effects obtained during the pairing trials did not necessarily predict the effects obtained after pairing (see Fig. 14). For example, in the auditory and somatosensory cortices, no changes or decreased responses were observed during the pairing trials, while increases were obtained after pairing both in anaesthetized (Fig. 8 in Edeline *et al.*, 1994a; Fig. 4 in Tremblay *et al.*, 1990) and in unanesthetized animals (Hars *et al.*, 1993).

Stimulation of source nuclei presents theoretically several advantages compared with the ionophoretic technique: (i) the release of the drugs is closer to physiological conditions since it is from afferent terminals; and (ii) a more precise control of the timing of the release can potentially be achieved. Regarding this timing, the different protocols used raise an important question. In most of the cases, the stimulation of the source nuclei was delivered just before (usually less than 100 msec) the presentation of the sensory stimuli (Rasmusson and Dykes, 1988; Tremblay *et al.*, 1990; Metherate and Ashe, 1991; Metherate *et al.*, 1992; Webster *et al.*, 1991; Hars *et al.*, 1993; Howard and Simons, 1994; Edeline *et al.*, 1994a,b). The logic of these protocols was that the neuromodulator has to be present at the vicinity of the cells when the afferent volley produced by the sensory stimulus reaches the recorded neurons. In a parametric study, Rasmusson and Dykes (1988) have estimated that facilitations of sensory-evoked responses are obtained when the interval between the NBM stimulation and the stimulus is up to 200 msec, i.e. when the stimulation precedes the sensory stimulus by 200 msec or less. For longer intervals (200–320 msec), no effects or opposite effects (decreased evoked responses in their case) were observed. In contrast, in two studies NBM stimulations were delivered at the end of a 1 sec duration sensory stimulus, to mimic a classical conditioning protocol where the US is replaced by the NBM stimulation (Bakin, 1995; Bakin and Weinberger, 1996). In these studies, evoked responses were also facilitated, and the selective facilitations observed for the frequency paired with the NB stimulation was not observed when pseudo-pairing protocol was performed. Therefore, it seems that

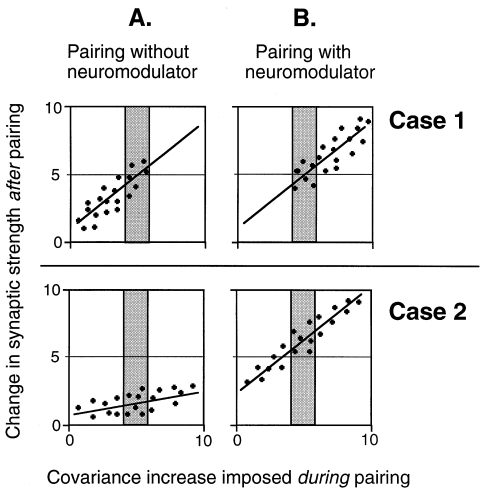

Fig. 17. Two hypothetical effects of neuromodulators on covariance plasticity: direct effect on covariance (case 1) vs gating (case 2). On each graph, the hypothetical changes in synaptic strength (y-axis) are presented as functions of the increases in pre/postsynaptic covariance imposed during the Hebbian treatment (x-axis). On each graph, the points represent individual recordings, and the line shows the relationship between the effects observed after pairing and the effects observed during pairing. It is supposed that the changes in synaptic strength are greater when the neuromodulators are present (part B, right) than without the neuromodulators (part A, left). In case 1, the neuromodulators increases the covariance levels during the Hebbian pairing treatment: this is visualized by a shift toward the right of the cluster of dots in case 1B compared with 1A. This leads to an increase in synaptic strength after pairing (higher y-axis values in 1B compared with 1A). In case 2, there is no increase in covariance levels during the pairing treatment (the cluster of points have the same x-axis values in 2B compared with 2A. However, the increase in synaptic strength is larger (higher y-axis values in 2B compared with 2A), which is shown by the fact there is a change in the slope of the line. The experimental results of Ahissar *et al.* (1992a, 1996) and of Cruikshank and Weinberger (1996a) favour case 2 (from Cruikshank and Weinberger (1996b, with permission).

*The pairing protocol involved either continuous release of the drug or, in some cases ($n = 22$), delivery of short (200 msec) pulses of ACh during or just before tone presentation.

*To account for these discrepancies, an explanation relying on the non-monotonicity of the rate-level functions in the auditory cortex was proprosed by Ashe and Weinberger (1991).

these results are, in several aspects, quite similar to the effects described after associative learning.* However, the protocol designed by the authors reflects strong assumptions about the factors that naturally increase the firing rate of NBM neurons. In the scheme envisioned by the authors, the activation of cholinergic neurons is supposed to be triggered by the US presentation, via activation of the amygdala which projects on the NBM (Weinberger *et al*., 1990a,b). Although it is clear that rewarding stimuli activates NBM neurons (as well as other neumodulatory neurons), it is clear also that other stimuli activate these neurons. Studies in primates and rats indicate that any significant stimulus that is relevant for the animal behaviour is able to change the firing rate of NBM neurons. The conditioned stimulus (CS) is of course one of these stimuli, but often neglected, the contextual cues that are present in any learning situation can also modulate the firing rate of NBM neurons (Richardson and DeLong, 1990). Therefore, the exact role of the US in the physiological mechanism of sensory plasticity remains an open question. For example, one can propose that the US presentation triggers increased release of neuromodulators which are able to produce long lasting EPSP as it was shown in vitro (Benardo, 1993). However, it is clear that if the US presentation generates physiological events that last tens of seconds or minutes, the effects produced by US presentations during conditioning and pseudoconditioning will be the same. As previously stated (Edeline, 1996), the major problem is clearly to find physiological mechanisms that will favour highly selective plasticity during conditioning and not during pseudoconditioning. In addition, given that the CS–US interval is different from one protocol to another (from 250–500 msec in the nictitating membrane conditioning but up to hours in conditioned taste aversion), it is clear that the physiological events triggered by the US (i) either have to be totally different depending on the protocol, (ii) or have nothing to do with the integration of the CS–US information that is performed at the behavioural level.

6.3. When and How Neuromodulatory Systems Act During Learning Experiments?

It is trivial to say that to clarify how neuromodulatory systems influence learning-induced plasticity it is crucial to determine when and how these neurons react during learning protocols.

For a long time, studies have tried to determine how neurons of the NBM and LC react during behavioural training. For example, unit recordings in primate NBM demonstrated that some neurons respond (by increased or decreased discharges) to the delivery (DeLong, 1971; Richardson and DeLong, 1986) or to the sight (Mora *et al*., 1976; Rolls *et al*., 1979) of a rewarding stimulus. They also respond to events preceding the occurrence of reward (Richardson and DeLong, 1986; Travis and Sparks, 1968; Wilson and Rolls, 1990a,b). Similarly, neurons of the LC were shown to respond to nociceptive stimuli (Hirata and Aston-Jones, 1994), or to stimuli associated with presentation of nociceptive (Sara and Segal, 1991) or of appetitive (Rasmussen and Jacobs, 1986) stimuli. To be able to influence cortical (and thalamic) neurons during a learning experiment, the neuromodulatory neurons have to react quickly after the beginning of training. This is indeed the case: neurons of the NBM (Maho *et al*., 1995) or of the LC (Rasmussen and Jacobs, 1986; Sara and Segal, 1991) increase their discharges after few (less than 10) conditioning trials (see Fig. 18). Also, to be able to influence cortical (and thalamic) responsiveness at a given trial, neuromodulatory neurons have to react at short latency after presentation of a significant stimulus. This is indeed the case: both NBM neurons and LC neurons exhibit increased discharges at short latency at presentation of an acoustic CS (Maho *et al*., 1995; Sara and Segal, 1991), even if the neuroanatomical substrate for these short latencies remain unclear [see Maho *et al*. (1995) for a discussion of this point concerning NBM neurons]. In particular, useful information is provided when cortical neurons are recorded at the same time as neuromodulatory neurons during the same learning experiment. For example, when conditioned tone-evoked discharges were recorded simultaneously in the auditory cortex and in the NBM, a temporal 30–40 msec overlap was found between the conditioned evoked responses obtained from the two structures (Maho *et al*., 1995). That is, at a given trial, there were about 30 msec during which ACh was present while the cortical cells were still depolarized by the afferent sensory volley produces by the CS (see Fig. 19). This means that a temporal correlation might exist between the CS driven activity and the ACh release in the cortex. In these conditions, the release of ACh can be viewed as a US signal moved up in time in such a way that its occurrence coincides with the CS occurrence (Figs 18 and 19).

At this point, it is clear that speculations have to be replaced by experimental findings. Inactivation of the source nuclei providing ACh and NE in the thalamo-cortical system, or specific immunolesioning studies have to be performed to clarify the role of neuromodulators as permissive agents of learning-induced sensory plasticity.

To summarize the effect of neuromodulators, it is clear that caution is necessary before accepting the idea that neuromodulators act as gating factors. First, the fact that they actively gate sensory processing is at least questionable. Second, their role in gating sensory plasticity seems based on more convincing data, but so far direct evidence is rare. Also, it is unclear whether or not the effects of neuromodulators per se have to be considered independently of their potential effects on covariance. Lastly, data from learning experiments suggest that cholinergic and noradrenergic neurons can potentially influence the conditions where sensory plasticity occurs. However, more explicit predictions

*It will be important that future studies test, on the same recordings, the effects of forward and backward pairing between a sensory stimulus and NBM stimulation. This can help to specify the conditions that are the more appropriate to produce facilitation of evoked responses.

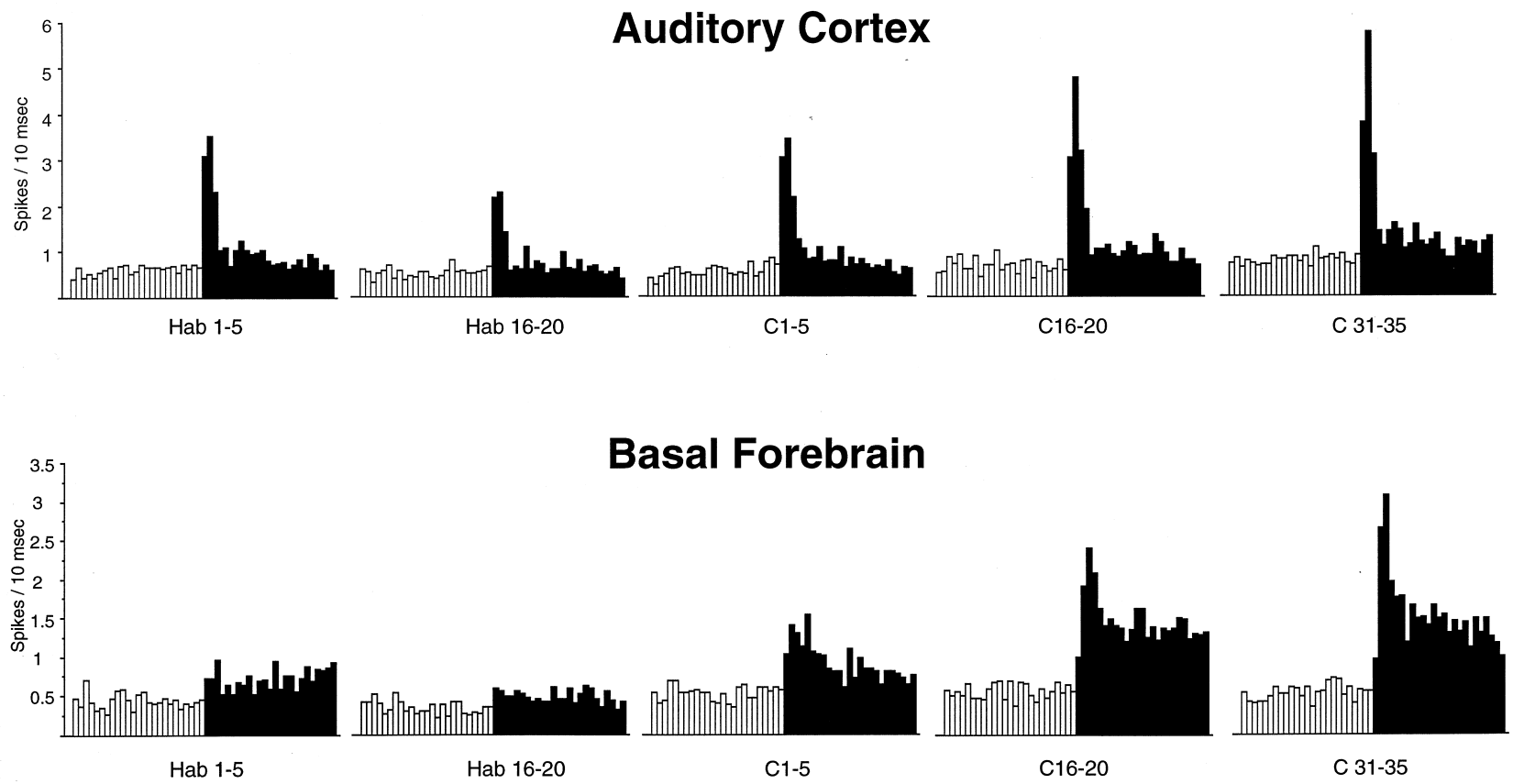

Fig. 18. Simultaneous habituation and conditioning of tone-evoked responses in auditory cortex and basal forebrain. Each histogram represents the mean number of spikes per bin of 20 msec during the 500 msec preceding (open bars) and the 500 msec following (dark bars) tone onset. The histograms are from the first five and the last five trials of habituation (respectively, Hab 1–5 and Hab 16–20), and from the trials 1–5, 16–20 and 31–35 of conditioning (respectively, C1–5; C16–20; and C31–35). Note the decrement of the evoked responses in both structures between Hab 1–5 and Hab 16–20. Note also that as early as the first block of five conditioning trials (C1–5), the response evoked in the basal forebrain was above the level of the first trials of habituation, while the cortical response only recovered the same level as at the beginning of habituation (from Maho *et al.* (1995), with permission).

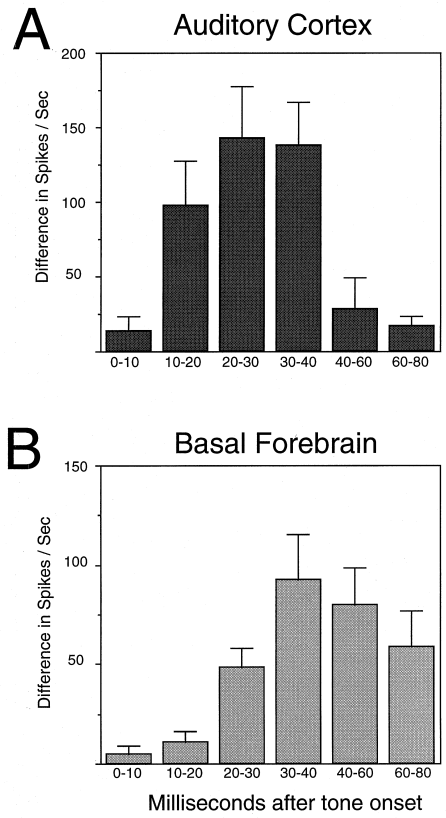

Fig. 19. Time course of the conditioned changes after tone onset. For each recording and each period of analysis, the mean tone-evoked response obtained during the 20 trials of habituation was subtracted from the response obtained at the last 20 trials of conditioning. The resulting values were averaged across recordings and represented ±sem. Increased reactivity was analyzed using 10 msec resolution for the first 40 msec of tone, then using 20 msec resolution for the following 40 msec. Note that the conditioned increased response was prominent from 10 to 40 msec after tone onset in the auditory cortex, while it was from 20 to 80 msec in the basal forebrain (from Maho *et al.*, 1995, with permission).

have to be stated and specifically designed learning experiments have to be carried out to delineate precisely the functional roles of neuromodulators in learning-induced sensory plasticity.

7. TENTATIVE CONCLUSIONS

7.1. Summary of the Findings

The present review focused on experiments where sensory plasticity was expressed after the acquisition of behavioural associative training. Because the learning situations were very different, ranging from sensory–sensory associations (e.g. Delacour *et al.*, 1987) to classical conditioning (e.g. Diamond and Weinberger, 1989; Bakin and Weinberger, 1990) and up to long-lasting psychophysic training (e.g. Karni and Sagi, 1991), the only synthetic picture that can emerge is the following: despite the large diversity of learning situations, sensory plasticity was detected and was specific for the relevant stimulus used during training. Besides its occurrence and its specificity, it is almost impossible to state other general rules about this plasticity. The number of trials used for its induction was from very few training trials (Edeline *et al.*, 1993) to 2–3 months of extensive training (Jenkins *et al.*, 1990; Recanzone *et al.*, 1992b,c,d, 1993). The duration of the changes was from a few minutes in the auditory cortex (Ahissar *et al.*, 1992a) to 2–3 days in the somatosensory cortex (Siucinska and Kossut, 1996), and up to months in some cases (Weinberger *et al.*, 1993). The RF or map changes were tested either in the waking state shortly after completion of training* (Bakin and Weinberger, 1990; Diamond and Weinberger, 1986, 1989; Edeline and Weinberger, 1991a,b, 1992, 1993; Edeline *et al.*, 1993; Siucinska and Kossut, 1996; Delacour *et al.*, 1987) or under general anaesthesia after training (Lennartz and Weinberger, 1992; Weinberger *et al.*, 1993; Jenkins *et al.*, 1990; Recanzone *et al.*, 1992a,b, 1993).

That learning-induced changes preferentially occur in the non-lemniscal pathway does not seem to be correct. Receptive field and map changes were reported from the primary cortical areas, and selective RF changes were also found in the lemniscal division of the auditory thalamus (note also that increased responses were described at subthalamic levels). We can suspect that the effects in the lemniscal pathway might be of shorter duration than those in the non-lemniscal pathway. For example, after 30 trials of conditioning, the selective RF plasticity observed immediately after training disappeared 1 hr after training in the MGv, whereas it was maintained in the MGd and MGm.

Across sensory modalities, it is very difficult to propose general rules between the expression of sensory plasticity and behavioural response. No relationships were found in the auditory system between the RF plasticity and the expression of a conditioned response. The extent of the map reorganization was found to be correlated with the behavioural performance in the auditory cortex; but this relationship was not found in the somatosensory cortex. In contrast, in that cortex, the temporal aspects of the neuronal discharges were correlated with the behaviour. In extrastriate cortical areas, when neurons and behavioural performance were tested in the same psychophysical task, strong relationships were found. Thus, the relationship between the plasticity of sensory systems and the behavioural performance seems to be (i) task dependent and (ii) modality dependent. It is only by exploring the parameters across a large number of experiments that more general rules could emerge in the future.

Lastly, it is very difficult to bring direct arguments in favour of the involvement of a particular physiological mechanism, whether in favour of an "Hebbian plasticity scheme", or in favour of the action of neuromodulators acting as gating factors

* Learning-induced plasticity in the MGm was also expressed during phases of REM sleep following behavioural training (Hennevin *et al.*, in press; Hennevin *et al.*, 1993).

for this plasticity. However, this problem is not specific to sensory systems: it is generally difficult to propose mechanisms for learning if one really wants to account (i) for the large diversity of the behavioural situations where learning is expressed and (ii) for neuronal constraints of the central nervous system. What needs to be done is to directly test, in learning experiments, whether or not some potential mechanisms are necessary and sufficient to explain learning-induced sensory plasticity. Also, there is a need to focus on mechanisms compatible with the conditions during which learning is taking place, instead of focusing on mechanisms that apply to other forms of sensory plasticity like developmental plasticity. Lastly, needless to say that the word "learning" needs to be re-defined (see for details Dudai, 1992): by talking of learning to describe neuronal changes which occur during development, artificial forms of plasticity, or in response to stress or to injury, we end up using a word which has no meaning.

In the following sections, rather than presenting a theory about the functional role of sensory plasticity, I will raise questions and point directions, which at short-term, or at long-term, might be helpful to understand this role.

7.2. Are RF and Map Changes Necessary for Learning?

This question raises the problems of the relationships between the neuronal plasticity occurring in the thalamo-cortical system and any conditioned behavioural responses quantified during a learning experiment. There are several ways to answer these questions. First, one can consider whether or not correlations are found between selective neuronal reorganizations and behavioural performances. Second, one can consider whether or not the animal performance is impaired when the sensory structures exhibiting plasticity are inactivated or removed from the circuit. Third, one can wonder if the conditions where learning-induced sensory plasticity was revealed, are the more appropriate to test whether sensory plasticity is involved in learning.

7.2.1. *Correlations Between Sensory Reorganizations and Behavioural Performance*

At the cell level, the descriptions of the findings in the three sensory modalities suggest that simple relationships are difficult to detect. For example, no relationships could be revealed in the auditory system between the RF changes and the behavioural responses of the animals. This is not very surprising for the RF changes obtained at the cortical levels since the integrity of the cortex is not required for the expression of the selected behavioural responses (pupillary dilatation or conditioned bradycardia). This is more surprising for the thalamic level, especially in the medial division of the MGB (the MGm) since this part of the auditory thalamus was shown to be necessary for the acquisition of classical conditioning to a tone (Iwata *et al*., 1986; LeDoux *et al*., 1984, 1986). Recent results obtained during trace conditioning suggest that in some conditions relationships might be detectable. Changes in activity during the tone and the trace interval were largest in the auditory thalamus (MGd and MGm) on trials in which behavioural CR was made. Also, the neural activity on fast CR trials was generally greater and tended to occur earlier (O'Connors *et al*., 1997). This suggests that thalamic neurons can potentially contribute to CR generation and timing. Lastly, the data of Newsome and colleagues (Section 5.3.1) demonstrate that, when the task is tailored to the neurons characteristics, strong relationships can be found between neuronal and behavioural performance (for discussion see Shadlen *et al*., 1996). Therefore, on a cell-to-animal basis, it seems difficult, but not impossible, to relate RF plasticity with the occurrence of a behavioural response.

At the map level, the same conclusion can be stated: when maps of the somatosensory cortex were tested after extensive behavioural training neither the strength of the neuronal responses nor the extent of the cortical representation were found to correlate with the discrimination performance of the animals (Recanzone *et al*., 1992a,b,c,d). Only the temporal aspects of the neuronal discharges collected over the entire map were clearly related with the behavioural performance of the animal, and only when the skin was stimulated with tactile stimuli of the same frequency ranges as those used during behavioural training.

7.2.2. *Findings from Lesions Studies*

One of the questions that is rarely raised in articles describing or reviewing sensory plasticity is whether or not this literature is in agreement with the findings coming from lesions studies. Even if the goals in these two fields are quite different, it is relevant to meditate about the findings obtained in lesion studies to weigh the judgements that are made based on physiological findings concerning the functional role of sensory plasticity.

Auditory system. In the auditory system, the role of auditory cortex in learning was questioned by lesions studies in the late 1950s. Earliest studies have stressed the fact that frequency discrimination was intact after auditory cortex lesions (Butler *et al*., 1957). In particular, ablations restricted to AI did not produce impairments, while more extensive lesions involving the secondary fields AII and Ep temporarily affected discrimination performance (Diamond and Neff, 1957). However, even in the early studies, it was indicated that the same lesions produced either important deficits or no deficits depending on the training procedure (Thompson, 1960). In some studies, the contribution of subcortical structures to the observed deficits was discussed (Goldberg and Neff, 1961). In their stimulating review, Ravizza and Belmore (1978) argued that the available evidence indicates that the auditory forebrain is not involved in the analysis of the physical parameters of sounds, such as frequency and intensity. Instead, they considered that there is much evidence that the auditory cortex is involved in natural process of localizing sounds in space and the temporal aspects of hearing [see also Whitfield (1979)

for a review of the "object of the sensory neocortex"]. The involvement of the auditory cortex in processing these two dimensions of the acoustic stimuli was confirmed by subsequent studies. For example, impairments in sound location were found after auditory cortex lesions (Jenkins and Merzenich, 1984; but see Kelly, 1980). More recently, Phillips and Farmer (1990) concluded, based on electrophysiological and clinical data, that temporal processing (especially temporal processing involved in speech discrimination) is indeed one of the key functions of the auditory cortex (see also Kelly *et al*., 1996). Related to the temporal processing, several studies have indicated that in humans, lesion of auditory cortex leads to deficit in understanding language and music (Tramo *et al*., 1990; Zatorre *et al*., 1996).

Somatosensory system. The necessity of the somatosensory cortex to perform a behavioural task was demonstrated in two studies. In a first study, Hutson and Masterton (1986) have shown that deficits in behavioural performance are not general after lesions of the barrel cortex. In several tasks, the lesions of barrel cortex did not impair the spatial and temporal acuity of vibrissae discrimination. However, the barrel cortex was critical for a task which tested the animal's ability to make a jump–no jump decision on the basis of vibrissae-transduced information. In this task, the loss of the barrel cortex is tantamount to loss of the vibrissae itself. These results were confirmed by an elegant investigation which studied the consequence of a thrombotic infarction of the vibrissal barrel-field cortex on sensory-motor tasks (Hurwitz *et al*., 1990). When the animals had to use the information collected via their vibrissae to obtain an appetitive reward, a reliable decrement in task performance was observed after infarction irrespective of whether the task required active or passive vibrissal sensory discrimination.

Visual system. In a series of studies, the threshold in orientation discrimination of cats was tested before and after lesions of different areas of the visual cortex. Lesions restricted to area 17 or to area 18 had little effect, but lesions involving area 17 and a substantial part of area 18 increased discrimination thresholds (Orban *et al*., 1990). In addition, although extensive lesions of both areas 17 and 18 (without subcortical damage) resulted in marked deficits in orientation discrimination of simple bars, the basic capacity to perceive and discriminate oriented contours was not abolished (Vandenbussche *et al*., 1991). Recent data suggest that several extrastriate areas contribute to such discrimination tasks (Sprague *et al*., 1996). Lastly, in the task used by Newsome and collaborators (Section 5.3.1), lesions of the area MT was found to severely impair motion perception (Newsome and Paré, 1988).

To conclude this brief survey of lesion studies, it seems clear that learning deficits can be found after lesions in the thalamo-cortical sensory system. However, these deficits depend (i) on the sensory modality and (ii) on the types of task and the types of training that were used. This is particularly striking in the auditory system: depending on the dimension of the sensory stimulus that was relevant during the training task, impairments were observed or not. Surprisingly, for the frequency dimension, for which no deficit was ever described after cortical lesions, tests of RF and maps have systematically revealed plasticity in the auditory cortex. This suggests that RF and map plasticity can be expressed for a particular dimension of the stimulus independently of whether or not a sensory structure is critical for processing that particular dimension.* Even if this could be interpreted as a clue that there is no direct link between sensory plasticity and the expression of a particular behavioural response, other hypotheses can be proposed to explain this lack of relationship.

First, one can consider that learning-induced plasticity might develop in lower stages of sensory processing. For example, learning-induced changes were reported at lower levels of the auditory system [inferior colliculus: Disterhoft and Stuart (1977); Nienhuis and Olds (1978); Olds *et al*. (1978); cochlear nucleus: Edeline *et al*. (1990b); Oleson *et al*. (1975)], and it is unknown if these changes contribute, at least partially, to the RF and map changes in the thalamo-cortical system. However, we cannot reject the opposite hypothesis, that is, the thalamo-cortical plasticity may be able to influence the neural activity in the lower sensory relays via corticofugal pathways (see Fig. 1).

Second, one can also consider that the absence of causal relationships between the thalamo-cortical plasticity and behaviour is the consequence of the fact that the dimensions tested in the RF and map changes did not critically involve the thalamo-cortical system (for example, discrimination of tonal frequency does not critically involve the auditory cortex). In contrast, clear relationships were found in the visual system when the dimension of the stimulus used in the behavioural task critically involved the recorded neurons (see Section 5.3.1).

Third, it can be proposed that revealing or not relationships between sensory plasticity and behaviour critically depends on the conditions during which sensory plasticity is tested. Two questions can be raised regarding this problem.

7.2.3. *Is It Appropriate to Test Sensory Plasticity in Anaesthetized Animals?*

In all the experiments where electrophysiological mapping was performed after training, the plasticity induced by the training protocol was tested under general anaesthesia. It is trivial to say that anaesthetics change in many aspects the properties of neuronal processing both at the single cell level and at the network level. At the cellular level, in most of the brain areas the hyperpolarization produced by

*The same problem exists in the field of learning and memory concerning the role of the hippocampal formation. Lesions of the hippocampus do not produce any deficits in the acquisition or in the retention of various types of classical conditioning. However, an impressive amount of electrophysiological studies have described learning-induced changes in firing rate of hippocampal neurons during acquisition or retention of classical conditioning.

several types of anaesthetics (especially barbiturates) tends to decrease both the spontaneous firing rate and the strength of the evoked responses, and to promote a bursting mode which is not often present in waking state. In sensory structures this can have drastic effects on several parameters that are used to quantify sensory plasticity. For example, in the somatosensory cortex, comparisons between responses obtained from the same recordings in waking state and under urethane anaesthesia showed enlargements of RF and changes in latency under anaesthesia (Simons *et al*., 1992). In the visual system, the light-evoked rhythmic discharges observed in undrugged animals were absent under urethane anaesthesia both on the cortical local field potential and on the single unit thalamic activity (Albrecht and Davidowa, 1989). In the auditory cortex and thalamus, the bandwidth of tuning was considerably changed under both barbiturates and ketamine anaesthesia (Zurita *et al*., 1994). At the network level, barbiturate anaesthesia was shown to produce changes in 2DG labelling in the auditory system, in such a way that it favours labelling in some lower brain stem structures and depresses the labelling of the thalamo-cortical system (Wang *et al*., 1987). As stated by Weinberger (1995a) "we should bear in mind that the use of anaesthesia without comparing findings to the waking brain constitutes a sort of drug experiment without a control". We can hope that the development of non-invasive imagery techniques [intrinsic signals: Grinvald *et al*. (1991); Masino and Frostig (1996); thermal image: Brugge *et al*. (1995); PET and MRI: Fiez *et al*. (1996); Paulesu *et al*. (1993); Zatorre *et al*. (1996)] will allow the determination of sensory maps in waking animals. This will be a great benefit in the field of learning-induced plasticity, but also in the field of sensory physiology.

7.2.4. *How is Sensory Plasticity Used to Guide the Animal's Behaviour?*

For most of the selective RF changes collected in the auditory system, sensory plasticity was tested "off-line", immediately after completion of training, while the animal was not using the acoustic stimuli for its behaviour. Without question, these data were of enormous importance, and this line of research needs to be continued. However, one can wonder if the changes observed in the post-training RF reflected changes in sensory processing that actually occurred during the training situation, as well as during other situations where the animal might have to face a discrimination involving a dimension on which it was trained. The fact that the direction of the changes was not always the same during training trials and in the post-training RFs suggests that modifications of sensory processing could be different in the two circumstances.

More generally, we have to consider that neurons in sensory systems are not "built" to have their receptive field tested. Neuronal selectivities exist, and we can reveal them by presenting sets of stimuli among a given dimension. But in normal physiological conditions, the animals use the neuronal selectivities present in their sensory systems to analyze the external world and to guide their behaviour. It will be very important to determine how sensory processing is modified while the animal uses sensory plasticity for a behavioural performance. Therefore, important efforts have to be made to design protocols allowing the testing of RF and of maps while the animals are engaged in a behavioural performance (as is the case in Section 5.3.1). In their principles, such protocols could be close to those already used to test the neuronal selectivity in attentional tasks (Motter, 1993; Spitzer *et al*., 1988).

Finally, another major problem relies on what is considered as the relevant code in the central nervous system (see for reviews Barlow, 1995; Skarda and Freeman, 1987). Indeed, the way to quantify RF and maps in sensory systems, and therefore to quantify RF and map changes (i.e. the increased responses or the enlarged representation at the CS frequency), is only based upon the firing rates of single cells or of groups of cells. Alternatives exist; some of them are presented below.

7.3. Future Directions: the Concept of Functional Connectivity

Ideas based on firing rate are easy to understand: the responses to a given stimulus increase while the responses to other stimuli decrease, and/or the cortical map enlarges for a given stimulus. However, the way by which the brain is processing information is probably not as simple as it is assumed by such a conception. Conceptions of neuronal information processing in terms of firing rate allow the dissection of neuronal plasticity in terms of receptors, molecules, channels and genes, i.e. in terms of building blocks used to subserve any other physiological function (see Dudai, 1992). If indeed neurons are using (almost) the same cellular machinery as other cells, the algorithms used by groups of neurons to code information are still a matter of speculation. In contrast, conceptions of neuronal information processing based on temporal processing allows the dissection of neuronal plasticity in terms of neuronal interactions, synchronizations, dynamics of non-linear systems, i.e. in terms of building blocks used in engineering sciences (see Skarda and Freeman, 1987). The problem is probably that neither of these two approaches is entirely correct when it comes to understanding what types of computations are performed by the central nervous system.

First, because an approach based on the building blocks used in molecular biology denies the fact the brain uses other codes than firing rate to code information. This is very surprising given that many studies in sensory physiology, especially in the auditory system, have stressed the fact that the timing of neuronal discharges is more reliable than firing rate to code both the frequency and the intensity of acoustic stimuli [Hind *et al*., 1963; Kitzes *et al*., 1978; see also Ehret and Merzenich (1988) for the inability of the firing rate to code for the sound intensity]. Even in the visual system, where the responses latencies are much larger than in the auditory and somatosensory systems, the temporal precision of the discharges is high while the firing

rate shows considerable variability (Reich *et al.*, 1997).

Second, because an approach based on the building blocks used in engineering sciences denies the fact the brain is first a biological machine where (i) non-neural (glial) elements can participate in computations performed by neurons (see for review Muller, 1992), (ii) where each molecular component of the neuronal and non-neuronal elements undergoes a continuous turn-over and (iii) where the continuous turn-over of each of these components is submitted to independent genetic regulations.

Besides the statement that neither molecular biology nor engineering science can be a stand-alone approach in explaining the way by which sensory systems process information, neuronal plasticity and especially sensory plasticity can benefit from new conceptions which do not rely on firing rates.

For more than a decade, the work performed by several teams points out the necessity of looking at the relationships between the precise timing of discharges of neighbouring neurons. Initial studies by Gerstein and colleagues (Dickson and Gerstein, 1974) and by Abeles and colleagues (Frostig *et al.*, 1983) have provided the technical and theoretical background to investigate neuronal interactions in sensory systems. The simplest way to look at neuronal interactions is to use cross-correlogram histograms which allow the examination of the interactions between two cells (Perkel *et al.*, 1967). Few examples taken from the recent literature will illustrate this point. Studying the encoding of sound-source location and movement in the auditory cortex, it was found that pairs of neurons can have similar firing rates for two different localizations, while their cross-correlogram show striking differences (see Fig. 8 in Ahissar *et al.*, 1992b). When moving stimuli were used, identical responses can be obtained for opposite movements while the cross correlogram is inverted (Fig. 7 in Ahissar *et al.*, 1992b). In fact, recent findings revealed that neuronal coordination to stimulus presentation can exist independently of the fact that there is an increased firing rate for one, or both, neuron(s) in a pair (deCharms and Merzenich, 1996).

But more important is the fact that neuronal interactions are not static. This notion was already present in the initial work by Dickson and Gerstein (1974), which showed that neuronal interactions which do not exist in spontaneous activity can emerge during acoustic stimulation. Another step further was made with the work by Aersten and colleagues, who conceptualized quantification procedures to follow the neuronal coupling during stimulus presentation on a millisecond basis (Aertsen *et al.*, 1989). Their techniques allow the unravelling, and quantitative description of, direct and indirect stimulus effects on correlated firing of two neurons. Thus, fast-stimulus-locked modulation of "effective connectivity" can be revealed even if it is masked by strong direct modulation of individual firing rates. According to the authors, in no case "effective connectivity" should be understood as reflecting an actual anatomic connectivity, since more than one anatomical arrangement can provide the same overall network behaviour. Also, the authors note that various physiological mechanisms can achieve such rapid modulation of effective connectivity. Of course, one possible type of mechanism could involve rapidly modulated synaptic strengths (Von Der Malsburg, 1981), but there are many alternative possibilities that can work with constant synaptic strengths. This point was clearly illustrated when simulations showed that the observed connectivity between a pair of neurons can be strongly modulated by the firing rate of a pool of neurons connected to one neuron of the pair (Boven and Aertsen, 1990).

This breakthrough has strong implications in the field of learning in general since this suggests that the concept of neurons with static interconnections of fixed or slowly changing efficacy (during learning) is no longer appropriate. The structural or anatomical connectivity should be distinguished from the functional or effective connectivity. The former can presumably be described as quasi-stationary, but the latter is highly dynamic with time constants of modulation in the range of tens to hundreds of milliseconds. In the field of learning-induced sensory plasticity, this means that in no case is it possible to interpret changes in cross-correlograms during presentation of a stimulus as the results of changes in synaptic efficacy occurring at a given locus (Quirk *et al.*, 1995; Skaggs and McNaughton, 1996; Wilson and McNaughton, 1994). By extension, one can wonder if it is possible to interpret an increased evoked response at presentation of a stimulus as the result of an increased synaptic efficacy.

Not only have the approaches based on the dynamic of neuronal interactions shown their validity for revealing parts of the neural code, but they also have proved their relevance to provide information directly related with animal behaviour. In the frontal cortex of monkeys performing a Go–NoGo task, effective connectivity between neurons evolved, within a trial, in tens of milliseconds with totally different patterns during the Go and NoGo trials (Vaadia *et al.*, 1995). Again, in these cases, no change in firing rate was present between these two types of trials. These findings support the notion that, in behaving animals, single neurons can intermittently participate in different computations by rapidly changing their coupling without associated changes in firing rate.

Lastly, the dynamic of functional coupling between pairs of neurons is only one of the aspects (the easiest to study) of neuronal coordinations. Theoretical considerations have led Abeles and colleagues to postulate that cortical activity is processed and transmitted by "syn-fire chains" which represent groups of cells with diverging–converging connections organized in a multilayered feed-forward network (see for review Abeles, 1982, 1991). Recording the activity of groups of 6–16 single cells, these authors found that spatio-temporal patterns of firing between neurons repeat with a much higher probability than expected by chance (Abeles and Gerstein, 1988). These patterns are tight time-locked (1–3 msec) neuronal coordinations between 6 and 10 cells that can persist over hundreds of milliseconds in the cortex of behaving monkeys (Abeles *et al.*, 1993). At this point, it is useful to mention that

it would be misleading to promote the idea that the anatomical particularities of cortical networks generate these patterns. Complex patterns of firing were also found in the auditory thalamus, between neurons located in different parts of MGB; some patterns even included neurons located in the auditory sector of the RE. More importantly, these patterns were still present during cortical cooling (Villa and Abeles, 1990). Thus, these long time scale neuronal coordinations might represent another aspect of neuronal coding that should be considered, even if its behavioural significance remains to be investigated.

The general purpose of this section was to point out that other codes than the firing rate of single neurons exist, especially in sensory systems [see also Skarda and Freeman (1987); Skarda and Freeman, 1990) for alternative views concerning the way by which the central nervous system codes information]. In the long-term, these future directions will probably promote a better description of sensory processing, and therefore they will allow a better description of the learning-induced sensory plasticity. Because we know so little about the neural code that actually underlies a psychological function such as learning, we should concentrate our efforts on characterizing the dynamic of sensory processing, rather than speculating on the fact that mechanisms proposed as cellular basis of developmental sensory plasticity can also apply as cellular basis of learning-induced sensory plasticity. This can be illustrated by a concluding metaphor. By analyzing sensory RFs in waking animals engaged in learning tasks, or by analyzing sensory maps before and after training, we might have discovered the tip of an iceberg. At this point, it looks like we spend most of our efforts trying to prove that this tip is made of the same type of rock as the Egyptian pyramids. It would be more useful to try to characterize more precisely what type of iceberg it is. The actual shape of the whole iceberg might have nothing to do with a pyramid, and it might be composed on several types of rocks, which can or cannot be similar to those of the pyramids. In any case, discovering more and more the whole iceberg of learning-induced sensory plasticity will obviously benefit both the field of sensory physiology and the field of learning.

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REFERENCES

Abeles, M. (1982) *Local Cortical Circuits. An Electrophysiological Study*. Springer: New York.

Abeles, M. (1991) *Corticonics*. Cambridge University Press: Cambridge.

Abeles, M. and Gerstein, G. L. (1988) Detecting spatio-temporal firing patterns among simultaneously recorded single neurons. *J. Neurophysiol.* **60,** 909–924.

Abeles, M., Bergman, H., Margalit, E. and Vaadia, E. (1993) Spatiotemporal firing patterns in the frontal cortex of behaving monkeys. *J. Neurophysiol.* **70,** 1629–1643.

Adrien, J. G. B., Buisseret, P., Frégnac, Y., Gary-Bobo, E., Imbert, M., Tassin, J.-P. and Trotter, Y. (1985) Noradrenaline and functionnal plasticity in kitten visual cortex: a re-examination. *J. Physiol. Lond.* **367,** 73–98.

Aertsen, A. M. J. H., Gerstein, G. L., Habib, M. K. and Palm, G. (1989) Dynamics of neuronal firing correlation: modulation of "effective connectivity". *J. Neurophysiol.* **61**, 900–917.

Ahissar, E. and Ahissar, M. (1994) Plasticity in auditory cortical circuitry. *Curr. Opin. Neurobiol.* **4,** 580–587.

Ahissar, E., Haidarliu, S. and Shulz, D. E. (1996) Possible involvement of neuromodulatory systems in cortical Hebbian-like plasticity. *J. Physiol. (Paris)* **90,** 353–360.

Ahissar, E., Vaadia, E., Ahissar, M., Bergman, H., Arieli, A. and Abeles, M. (1992a) Dependence of cortical plasticity on correlated activity of single neurons and on behavioral context. *Science* **257,** 1412–1415.

Ahissar, M., Ahissar, E., Bergman, H. and Vaadia, E. (1992b) Encoding of sound-source location and movement: activity of single neurons and interactions between adjacent neurons in the monkey auditory cortex. *J. Neurophysiol.* **67,** 203–215.

Aitkin, L. M. (1973) Medial geniculate body of the cat: response to tonal stimuli of neurons in medial division. *J. Neurophysiol.* **36,** 275–283.

Aitkin, L. M. and Webster, W. R. (1972) Medial geniculate body of the cat: organization and responses to tonal stimuli of neurons in ventral division. *J. Neurophysiol.* **35,** 365–380.

Albrecht, D. and Davidowa, H. (1989) Action of urethane on dorsal lateral geniculate neurons. *Brain Res. Bull.* **22,** 923–927.

Albrecht, D. and Davidowa, H. (1992) Modulation of visually evoked responses in units of the ventral lateral geniculate nucleus of the rat by somatic stimuli. *Behav. Brain Res.* **50,** 127–133.

Albrecht, D. and Davidowa, H. (1993) Extraretinal modulation of geniculate neuronal activity by conditioning. In: *The Visually Responsive Neuron: From Basic Neurophysiology to Behavior, Progress in Brain Research*, Vol. 95, pp. 271–286. Eds. T. P. Hicks and S. Molotchnikoff. Elsevier Science: Amsterdam.

Albrecht, D., Davidowa, H. and Gabriel, H.-J. (1986) Influence of atropine microinjection into nucleus reticularis thalami on activity of lateral geniculate neurones in freely moving rat. *Behav. Brain Res.* **19,** 49–57.

Albrecht, D., Davidowa, H. and Gabriel, H.-J. (1990) Conditioning-related changes of unit activity in the dorsal lateral geniculate nucleus of urethane-anaesthetized rats. *Brain Res. Bull.* **25,** 55–63.

Albrecht, D., Uhlmann, A. and Davidowa, H. (1992) Inhibitory action of a conditioning procedure on visual responsive neurons of the nucleus reticularis thalami in rats. *Exp. Brain Res.* **88,** 199–203.

Alkon, D. L. (1988) *Memory Trace in the Brain*. Cambridge University Press: Cambridge.

Allard, T., Clark, S. A., Jenkins, W. M. and Merzenich, M. M. (1991) Reorganization of somatosensory area 3b representation in adult owl monkeys after digital syndactyly. *J. Neurophysiol.* **66,** 1048–1058.

Allon, N., Yeshurun, Y. and Wollberg, Z. (1981) Responses of single cells in the medial geniculate body of awake squirrel monkey. *Exp. Brain Res.* **41,** 222–232.

Andersen, R. A., Knight, P. L. and Merzenich, M. M. (1980) The thalamocortical and corticothalamic connections of AI, AII, and the anterior auditory field (AAF) in the cat: evidence for two largely segregated systems of connections. *J. Comp. Physiol. Psychol.* **194,** 663–701.

Ashe, J. H. and Weinberger, N. M. (1991) Acetylcholine modulation of cellular excitability via muscarinic receptors: functional plasticity in auditory cortex. In: *Activation to Acquisition: Functional Aspects of the Basal Forebrain Cholinergic System*, pp. 189–246. Ed. R. T. Richardson. Birkhauser: Boston.

Ashe, J. H., McKenna, T. M. and Weinberger, N. M. (1989) Cholinergic modulation of frequency receptive fields in auditory cortex: II. Frequency-specific effects of anticholinesterases provide evidence for a modulatory action of endogenous ACh. *Synapse* **4,** 44–54.

Auker, C. R., Meszler, B. M. and Carpenter, D. O. (1983) Apparent discrepancy between single unit activity and [14C]

deoxyglucose labeling in optic tectum of the rattle snake. *J. Neurophysiol.* **49,** 1504–1516.
Bakin, J. S. (1995) Learning induced CS specific receptive field plasticity in the auditory cortex of adult guinea pigs and rats: from behavior to mechanism. Unpublished doctoral dissertation, University of California at Irvine, USA.
Bakin, J. S. and Weinberger, N. M. (1990) Classical conditioning induces CS-specific receptive field plasticity in the auditory cortex of the guinea pig. *Brain Res.* **536,** 271–286.
Bakin, J. S. and Weinberger, N. M. (1996) Induction of a physiological memory in the cerebral cortex by stimulation of the nucleus basalis. *Proc. Natl Acad. Sci. USA* **93,** 11219–11224.
Bakin, J. S., Lepan, B. and Weinberger, N. M. (1992) Sensitization induced receptive field plasticity in the auditory cortex is independent of CS-modality. *Brain Res.* **577,** 226–235.
Bakin, J. S., South, D. A. and Weinberger, N. M. (1996) Induction of receptive field plasticity in the auditory cortex of the guinea pig during instrumental avoidance training. *Behav. Neurosci.* **110,** 905–913.
Bal, T. and McCormick, D. A. (1993) Mechanisms of oscillatory activity in guinea-pig nucleus-reticularis thalami in vitro—a mammalian pacemaker. *J. Physiol. Lond.* **468,** 669–691.
Bal, T. and McCormick, D. A. (1996) What stops synchronized thalamocortical oscillation. *Neuron* **17,** 297–308.
Bal, T., von Krosigk, M. and McCormick, D. A. (1995a) Role of the ferret perigeniculate nucleus in the generation of synchronized oscillations in vitro. *J. Physiol. Lond.* **483,** 665–685.
Bal, T., von Krosigk, M. and McCormick, D. A. (1995b) Synaptic and membrane mechanisms underlying synchronized oscillations in the ferret lateral geniculate nucleus in vitro. *J. Physiol. Lond.* **483,** 641–663.
Barlow, H. (1995) The neuron doctrine in perception. In: *The Cognitive Neurosciences*, pp. 415–435. Ed. M. S. Gazzaniga. MIT Press: Cambridge, MA.
Barlow, H. B., Kaushal, T. P., Hawken, M. and Parker, A. J. (1987) Human contrast discrimination and the threshold of cortical neurons. *J. Opt. Soc. Am. A.* **4,** 2366–2371.
Bassant, M. H., Ennouri, K. and Lamour, Y. (1990) Effects of iontophoretically applied monoamines on somatosensory cortical neurons of unanesthetized rats. *Neuroscience* **39,** 431–439.
Baust, W. and Berlucchi, G. (1964) Reflex responses to click of cat's tensor tympani during sleep and wakefulness and the influence on the auditory cortex. *Arch. Ital. Biol.* **102,** 686–712.
Baust, W., Berlucchi, G. and Moruzzi, G. (1964) Changes in the auditory input during arousal in cat with tenotomized middle ear muscles. *Arch. Ital. Biol.* **102,** 675–685.
Bear, M. F. and Singer, W. (1986) Modulation of visual cortical plasticity by acetylcholine and noradrenaline. *Nature* **320,** 172–176.
Beck, B. C., Doty, R. W. and Kooi, K. D. (1958) Electrocortical reactions associated with conditioned flexion reflexes. *Electroenceph. Clin. Neurophysiol.* **10,** 279–289.
Belardetti, F., Borgia, R. and Mancia, M. (1977) Prosencephalic mechanisms of EEG desynchronization in cerveau isolé cats. *Electroenceph. Clin. Neurophysiol.* **42,** 213–225.
Ben Ari, Y., Dingledine, R., Kanazawa, R. and Kelly, J. S. (1976) Inhibitory effects of acetylcholine on neurones in the feline nucleus reticularis thalami. *J. Physiol. Lond.* **261,** 647–671.
Benardo, L. S. (1993) Characterization of cholinergic and noradrenergic slow excitatory postsynaptic potentials from rat cerebral cortical neurons. *Neuroscience* **53,** 11–22.
Berridge, C. W. and Foote, S. L. (1991) Effects of locus coeruleus activation on electroencephalographic activity in neocortex and hippocampus. *J. Neurosci.* **11,** 3135–3145.
Bertini, G., Karni, A., DeWeerd, P., Desimone, R. and Ungerleider, L. G. (1995) A behavioral and electrophysiological study of monkey visual cortex plasticity. *Soc. Neurosci. Abstr.* **21,** 276.
Birt, D. and Olds, M. (1981) Associative response changes in lateral midbrain tegmentum and medial geniculate during differential appetitive conditioning. *J. Neurophysiol.* **46,** 1039–1055.
Birt, D., Nienhuis, R. and Olds, M. (1979) Separation of associative from non-associative short latency changes in medial geniculate and inferior colliculus during differential conditioning and reversal in rats. *Brain Res.* **167,** 129–138.
Bollen, K. A. (1989) *Structural Equations with Latent Variables*. Wiley: New York.
Bordi, F. and LeDoux, J. E. (1994) Response properties of single units in areas of rat auditory thalamus that project to the amygdala. II. Cells receiving convergent auditory and somatosensory inputs and cells antidromically activated by amygdala stimulation. *Exp. Brain Res.* **98,** 275–286.
Boven, K.-H. and Aertsen, A. (1990) Dynamics of activity in neuronal networks give rise to fast modulations of functional connectivity. In: *Parallel Processing in Neural Systems and Computers*, pp. 53–56. Eds. Eckmiller, G. Hartman and G. Hauske. Elsevier Science: Amsterdam.
Bradley, A., Skottun, B. C., Ohzawa, I., Sclar, G. and Freeman, R. D. (1987) Visual orientation and spatial frequency discrimination: a comparison of single cells and behavior. *J. Neurophysiol.* **57,** 755–772.
Braitenberg, V. and Schuz, A. (1991) *Anatomy of the Cortex: Statistic and Geometry*. Springer: Berlin.
Britten, K. H., Shadlen, M. N., Newsome, W. T. and Movshon, J. A. (1992) The analysis of visual motion: a comparison of neuronal and psychophysical performance. *J. Neurosci.* **12,** 4745–4765.
Brogden, W. J. (1939) Sensory pre-conditioning. *J. Exp. Psychol.* **25,** 323–332.
Brugge, J. F., Poon, P. W. F., So, A. T. P., Wu, B.-M., Chan, H. Y. and Lam, F. K. (1995) Thermal images of somatic sensory cortex obtained through the skull of rat and gerbil. *Exp. Brain Res.* **106,** 7–18.
Buchwald, J. S., Halas, E. S. and Schramm, S. (1966) Changes in cortical and subcortical unit activity during behavioral conditioning. *Physiol. Behav.* **1,** 11–22.
Butler, R. A., Diamond, I. T. and Neff, W. D. (1957) Role of auditory cortex in discrimination of changes in frequency. *J. Neurophysiol.* **20,** 108–120.
Cahill, L., Ohl, F. and Scheich, H. (1996) Alteration of auditory cortex activity with a visual stimulus through conditioning: a 2-deoxyglucose analysis. *Neurobiol. Lear. Mem.* **65,** 213–222.
Calford, M. B. (1983) The parcellation of the medial geniculate body of the cat defined by the auditory response properties of single units. *J. Neurosci.* **3,** 2350–2365.
Calford, M. B. and Aitkin, L. M. (1983) Ascending projections to the medial geniculate body of the cat: evidence for multiple parallel auditory pathways through thalamus. *J. Neurosci.* **11,** 2365–2380.
Capsius, B. and Leppelsack, H.-J. (1996) Influence of urethane anesthesia on neural processing in the auditory cortex analogue of a songbird. *Hearing Res.* **96,** 59–70.
Carmel, P. W. and Starr, A. (1963) Acoustical and nonacoustical factors modifying middle ear muscle activity in waking cats. *J. Neurophysiol.* **26,** 598–616.
Casamenti, F., Deffenu, G., Abbamondi, A. L. and Pepeu, G. (1986) Changes in cortical acetylcholine output induced by modulation of the nucleus basalis. *Brain Res. Bull.* **16,** 689–695.
Celebrini, S. and Newsome, W. T. (1994) Neuronal and psychophysical sensitivity to motion signals in extrastriate area MST of the macaque monkey. *J. Neurosci.* **14,** 4109–4124.
Chmielowska, J., Carvell, G. E. and Simons, D. (1989) Spatial organizations of thalamocortical and corticothalamic projection system in the rat SmI barrel cortex. *J. Comp. Neurol.* **285,** 325–338.
Clark, S. A., Allard, T., Jenkins, W. M. and Merzenich, M. M. (1988) Receptive fields in the body-surface map in adult cortex defined by temporally correlated inputs. *Nature* **332,** 444–445.
Clerici, W. J. and Coleman, J. R. (1990) Anatomy of the rat medial geniculate body: I cytoarchitecture, myeloarchitecture, and neocortical connectivity. *J. Comp. Neurol.* **297,** 14–31.
Clerici, W. J., McDonald, A. J., Thompson, R. and Coleman, J. R. (1990) Anatomy of the rat medial geniculate body: II Dentritic morphology. *J. Comp. Neurol.* **297,** 32–54.
Clugnet, C., LeDoux, J. E. and Morrison, S. F. (1990) Unit responses evoked in the amygdala and striatum by electrical stimulation of the medial geniculate body. *J. Neurosci.* **10,** 1055–1061.
Cohen, D. H. (1980) The functional neuroanatomy of a conditioned response. In: *Neural Mechanisms of Goal-directed Behavior and Learning*, pp. 283–302. Eds. R. F. Thompson, L. H. Hick and V. B. Shvyrkov. Academic Press: New York.
Cohen, D. H., Gibbs, C. M., Seigelman, J., Gamlin, P. and Broyles, J. L. (1982) Is locus coeruleus involved in plasticity of the lateral geniculate neurons during learning? *Soc. Neurosci. Abstr.* **8,** 666.
Conley, M. and Diamond, I. T. (1990) Organization of the visual sector of the thalamic reticular nucleus in Galago. *Eur. J. Neurosci.* **2,** 211–226.
Conley, M., Kupersmith, A. C. and Diamond, I. T. (1991) The organization of projections from subdivisions of the auditory cortex and thalamus to the auditory sector of the thalamic reticular nucleus in Galago. *Eur. J. Neurosci.* **3,** 1089–1103.

Cox, C. L., Huguenard, J. R. and Prince, D. A. (1996) Heterogeneous axonal arborizations of rat thalamic reticular neurons in the ventrobasal nucleus. *J. Comp. Neurol.* **366,** 416–430.

Crabtree, J. W. (1992a) The somatotopic organization within the cat's thalamic reticular nucleus. *Eur. J. Neurosci.* **4,** 1352–1361.

Crabtree, J. W. (1992b) The somatotopic organization within the rabbit's thalamic reticular nucleus. *Eur. J. Neurosci.* **4,** 1343–1351.

Crabtree, J. W. (1996) Organization of the somatosensory sector of the cat's thalamic reticular nucleus. *J. Comp. Neurol.* **366,** 207–222.

Crabtree, J. W. and Killackey, H. P. (1989) The topographic organization and axis of projection within the visual sector of the rabbit's thalamic reticular nucleus. *Eur. J. Neurosci.* **1,** 94–109.

Crick, F. (1984) Function of the thalamic reticular complex: the searchlight hypothesis. *Proc. Natl Acad. Sci. USA* **81,** 4586–4590.

Crick, F. and Koch, C. (1998) Constraints on cortical and thalamic projections: the no-strong-loops hypothesis. *Nature* **391,** 245–250.

Cruikshank, S. J. and Weinberger, N. M. (1996a) Receptive-field plasticity in the adult auditory cortex induced by Hebbian covariance. *J. Neurosci.* **16,** 861–875.

Cruikshank, S. J. and Weinberger, N. M. (1996b) Evidence for the Hebbian hypothesis in experience-dependent physiological plasticity of neocortex: a critical review. *Brain Res. Rev.* **22,** 191–228.

Das, A. and Gilbert, C. D. (1995) Long-range horizontal connections and their role in cortical reorganization revealed by optical recording of cat primary visual cortex. *Nature* **375,** 780–784.

Davidowa, H., Nicolai, A., Gabriel, H.-J. and Albrecht, D. (1982) Lateral geniculate unit activity in freely moving rats. I relation to behavior and stimulus relevance. *Acta Neurobiol. Exp.* **42,** 483–494.

Debanne, D., Shulz, D. E. and Frégnac, Y. (1998) Activity dependent regulation of On- and Off-responses in cat visual cortex receptive fields. *J. Physiol. Lond.* **508,** 523–548.

deCharms, R. C. and Merzenich, M. M. (1996) Primary cortical representation of sounds by the coordination of action-potential timing. *Nature* **381,** 610–613.

Delacour, J., Houcine, O. and Talbi, B. (1987) "Learned" changes in the responses of the rat barrel field neurons. *Neuroscience* **23,** 63–71.

Delacour, J., Houcine, O. and Costa, J. C. (1990) Evidence for a cholinergic mechanism of "learned" changes in the responses of barrel field neurons of the awake and undrugged rat. *Neuroscience* **34,** 1–8.

DeLong, M. R. (1971) Activity of pallidal neurons during movement. *J. Neurophysiol.* **43,** 414–427.

Diamond, I. T. and Neff, W. D. (1957) Ablation of temporal cortex and discrimination of auditory patterns. *J. Neurophysiol.* **20,** 300–315.

Diamond, M. E. and Armstrong-James, M. (1992) Role of parallel sensory pathways and cortical colums in learning. *Concepts in Neurosci.* **3,** 55–78.

Diamond, D. M. and Weinberger, N. M. (1984) Physiological plasticity of single neurons in auditory cortex of cat during acquisition of the pupillary conditioned response. II. Secondary field (AII). *Behav. Neurosci.* **98,** 189–210.

Diamond, D. M. and Weinberger, N. M. (1986) Classical conditioning rapidly induces specific changes in frequency receptive fields of single neurons in secondary and ventral ectosylvian auditory cortical fields. *Brain Res.* **372,** 357–360.

Diamond, D. M. and Weinberger, N. M. (1989) Role of context in the expression of learning-induced plasticity of single neurons in auditory cortex. *Behav. Neurosci.* **103,** 471–494.

Diamond, I. T., Jones, E. G. and Powell, T. P. S. (1969) The projection of the auditory cortex upon the diencephalon and brainstem in the cat. *Brain Res.* **15,** 205–340.

Diamond, M. E., Armstrong-James, M. and Ebner, F. F. (1993) Experience-dependent plasticity in adult rat barrel cortex. *Proc. Natl Acad. Sci. USA* **90,** 2082–2086.

Diamond, M. E., Huang, W. and Ebner, F. F. (1994) Laminar comparison of somatosensory cortical plasticity. *Science* **265,** 1885–1888.

Dickson, J. W. and Gerstein, G. L. (1974) Interactions between neurons in auditory cortex of the cat. *J. Neurophysiol.* **37,** 1239–1261.

Disterhoft, J. R. (1977) Short-latency discriminative unit response: a way to search for the engram. *Physiol. Psychol.* **5,** 275–280.

Disterhoft, J. F. and Olds, J. (1972) Differentials development of conditioned unit changes in thalamus and cortex of rat. *J. Neurophysiol.* **35,** 665–679.

Disterhoft, J. F. and Stuart, D. K. (1976) Trial sequence of changed unit activity in auditory system of alert rat during conditioned response acquisition and extinction. *J. Neurophysiol.* **39,** 266–281.

Disterhoft, J. F. and Stuart, D. K. (1977) Different short latency response increases after conditioning in inferior colliculus neurons of alert rat. *Brain Res.* **130,** 315–334.

Dubner, R. and Zeki, S. M. (1971) Response properties and receptive fields of cells in an anatomically defined region of the superior temporal sulcus. *Brain Res.* **35,** 528–532.

Dudai, Y. (1992) Why "learning" and "memory" should be redefined (or an agenda for focus reductionism). *Concepts in Neurosci.* **3,** 99–121.

Edeline, J-M. (1990) Frequency-specific plasticity of single unit discharges in the rat medial geniculate body. *Brain Res.* **529,** 109–119.

Edeline, J-M. (1995) The α2-adrenergic antagonist Idazoxan enhances the frequency selectivity and increases the threshold of auditory cortex neurons. *Exp. Brain Res.* **107,** 221–240.

Edeline, J-M. (1996) Does Hebbian synaptic plasticity explain learning-induced sensory plasticity in adult mammals? *J. Physiol. (Paris)* **90,** 271–276.

Edeline, J-M. and Weinberger, N. M. (1991a) Subcortical adaptive filtering in the auditory system: associative receptive field plasticity in the dorsal medial geniculate body. *Behav. Neurosci.* **105,** 154–175.

Edeline, J-M. and Weinberger, N. M. (1991b) Thalamic short term plasticity in the auditory system: associative retuning of receptive fields in the ventral medial geniculate body. *Behav. Neurosci.* **105,** 618–639.

Edeline, J-M. and Weinberger, N. M. (1992) Associative retuning in the thalamic source of input to the amygdala and auditory cortex: receptive field plasticity in the medial division of the medial geniculate body. *Behav. Neurosci.* **106,** 81–105.

Edeline, J-M. and Weinberger, N. M. (1993) Receptive field plasticity in the auditory cortex during frequency discrimination training: selective retuning independent of task difficulty. *Behav. Neurosci.* **107,** 82–103.

Edeline, J-M., Neuenschwander-El Massioui, N. and Dutrieux, G. (1990a) Discriminative long-term retention of rapidly induced multiunit changes in the hippocampus, medial geniculate and auditory cortex. *Behav. Brain Res.* **39,** 145–155.

Edeline, J-M., Neuenschwander-El Massioui, N. and Dutrieux, G. (1990b) Frequency-specific cellular changes in the auditory system during acquisition and reversal of discriminative conditioning. *Psychobiol.* **18,** 382–393.

Edeline, J-M., Pham, P. and Weinberger, N. M. (1993) Rapid development of learning-induced receptive field plasticity in the auditory cortex. *Behav. Neurosci.* **107,** 539–551.

Edeline, J-M., Hars, B., Maho, C. and Hennevin, E. (1994a) Transient and prolonged facilitation of tone-evoked responses induced by basal forebrain stimulation in the rat auditory cortex. *Exp. Brain Res.* **97,** 373–386.

Edeline, J-M., Maho, C., Hars, B. and Hennevin, E. (1994b) Nonawaking basal forebrain stimulation enhances auditory cortex responsiveness during slow-wave sleep. *Brain Res.* **636,** 333–337.

Edeline, J-M., Cotillon, N., Hars, B. and Hennevin, E. (1997) Tone-evoked spindles-like oscillations in the thalamocortical auditory system: dependance upon reticular nucleus activity *Neural Networks, past and future,, Arcachon, P3*..

Eggermont, J. J., Aertsen, A. M. H. J., Hermes, D. H. and Johannesma, P. I. M. (1981) Spectro-temporal characterization of auditory neurons: redundant or necessary? *Hearing Res.* **5,** 109–121.

Ehret, G. and Merzenich, M. M. (1988) Neuronal discharge rate is unsuitable for encoding sound intensity at the inferior-colliculus level. *Hearing Res.* **35,** 1–8.

Felleman, D. J. and Van Essen, D. C. (1991) Distributed hierarchical processing in the primate cerebral cortex. *Cereb. Cor.* **1,** 1–47.

Fiez, J. A., Raife, E. A., Balota, D. A., Schwarz, J. P., Raichle, M. E. and Petersen, S. E. (1996) A positron emission tomography study of the short-term maintenance of verbal information. *J. Neurosci.* **16,** 808–822.

Foote, S. L., Freedman, R. and Oliver, A. P. (1975) Effects of putative neurotransmitters on neuronal activity in monkey auditory cortex. *Brain Res.* **86,** 229–242.

Frégnac, Y. (1987) Cellular mechanisms of epigenesis in cat visual cortex. In: *Imprinting and Cortical Plasticity. Comparative*

Aspect of Sensitive Period, pp. 221–266. Eds. J. P. Rauscheker and P. Marler, Wiley and Sons: New York.

Frégnac, Y. and Bienenstock, E. (1998) Correlational models of synaptic plasticity: development, learning and cortical dynamics of mental representations. In: *In Mechanistic Relationships between Development and Learning*, pp. 113–148. Eds. T. J. Carew, R. Menzel and C. J. Shatz. Wiley: New York.

Frégnac, Y. and Shulz, D. (1994) Models of synaptic plasticity and cellular analogs of learning in the developing and adult vertebrate visual cortex. In: *Advances in Neural and Behavioral Development*, pp. 149–235. Eds. V. Casagrande and P. Shinkman. Neural Ablex: New Jersey.

Frégnac, Y., Shulz, D., Thorpe, S. and Bienenstock, E. (1988) A cellular analogue of visual cortical plasticity. *Nature* **333,** 367–370.

Frégnac, Y., Shulz, D., Thorpe, S. and Bienenstock, E. (1992) Cellular analogs of visual cortical epigenesis. I plasticity of orientation selectivity. *J. Neurosci.* **12,** 1280–1300.

Frostig, R., Gottlieb, Y., Vaadia, E. and Abeles, M. (1983) The effects of stimuli on the activity and functional connectivity of local groups in the cat auditory cortex. *Brain Res.* **272,** 211–221.

Funke, K. and Eysel, U. T. (1993) Modulatory effects of acetylcholine, serotonin and noradrenaline on the activity of cat perigeniculate neurons. *Exp. Brain Res.* **95,** 409–420.

Fuster, J. M. (1995) *Memory in the Cerebral Cortex: An Empirical Approach to Neural Networks in the Human and Non-human Primate*. MIT Press: Cambridge, MA.

Gabriel, M. (1976) Short latency discriminative unit response: Emgram or bias? *Psychol. Physiol.* **4,** 275–280.

Gabriel, M., Saltwick, S. E. and Miller, J. D. (1975) Conditioning and reversal of short-latency multiple-unit responses in the rabbit medial geniculate nucleus. *Science* **189,** 1108–1109.

Gabriel, M., Miller, J. D. and Saltwick, S. E. (1976) Multiple-unit activity of the rabbit medial geniculate nucleus in conditioning, extinction and reversal. *Physiol. Psychol.* **4,** 124–134.

Gabriel, M., Orona, E., Foster, K. and Lambert, R. W. (1982) *Mechanism and Generality of Stimulus Significance Coding in a Mammalian Model System*, pp. 535–565. Plenum: New York.

Galambos, R. and Rupert, A. (1959) Action of middle ear muscles in normal cats. *J. Acoust. Soc. Am.* **31,** 349–355.

Galambos, R., Sheatz, G. and Vernier, V. (1956) Electrophysiological correlates of a conditioned response in cats. *Science*, **123,** 376–377.

Gallistel, C. R. (1990) *The Organization of Learning*. MIT Press: Cambridge, MA.

Gerren, R. and Weinberger, N. M. (1983) Long term potentiation in the magnocellular medial geniculate nucleus of the anesthetized cat. *Brain Res.* **265,** 138–142.

Gibbs, C. M., Broyles, J. L. and Cohen, D. H. (1983) Further studies of the involvement of locus coeruleus in plasticity of avian lateral geniculate neurons during learning. *Soc. Neurosci. Abstr.* **9,** 641.

Gibbs, C. M., Cohen, D. H. and Broyles, J. L. (1986) Modification of discharge of lateral geniculate neurons during visual learning. *J. Neurosci.* **6,** 627–636.

Gibson, E. J. (1953) Improvement in perceptual judgements as a function of controlled practice or training. *Psychol. Bull.* **50,** 401–431.

Gilbert, C. D. (1983) Microcircuitry of the visual cortex. *Ann. Rev. Neurosci.* **6,** 217–247.

Gilbert, C. D. (1993) Rapid dynamic changes in adult cerebral cortex. *Curr. Opin. Neurobiol.* **3,** 100–103.

Gilbert, C. D. and Kelly, J. P. (1975) The projections of cells in different layers of the cat's visual cortex. *J. Comp. Neurol.* **163,** 81–106.

Godecke, I. and Bonhoeffer, T. (1996) Development of identical orientation maps for two eyes without common visual experience. *Nature* **379,** 251–254.

Goldberg, J. M. and Neff, W. D. (1961) Frequency discrimination after bilateral ablation of cortical auditory areas. *J. Neurophysiol.* **24,** 119–128.

Gonzalez-Lima, F. (1992) Brain imaging of auditory learning function in rats: studies with fluorodeoxyglucose autoradiography and cytochrome oxidase histochemistry. In: *Advances in Metabolic Mapping Techniques for Brain Imaging of Behavioral and Learning Function*, pp. 39–109. Eds. F. Gonzalez-Lima, T. Finkelstadt and H. Scheich. Kluwer Academic: London.

Gonzalez-Lima, F. and Scheich, H. (1984) Neural substrates for tone-conditioned bradycardia demonstrated with 2 deoxyglucose I. Activation of the auditory nuclei. *Behav. Brain Res.* **14,** 213–233.

Gonzalez-Lima, F. and Scheich, H. (1986a) Neural substrates for tone-conditioned bradycardia demonstrated with 2 deoxyglucose II. Auditory cortex plasticity. *Behav. Brain Res.* **20,** 281–293.

Gonzalez-Lima, F. and Scheich, H. (1986b) Classical conditioning of tone-signaled bradycardia modifies 2-deoxyglucose uptake patterns in cortex, thalamus, habenula caudate-putamen and hippocampal formation. *Brain Res.* **363,** 239–256.

Gonzalez-Lima, F., Finkenstadt, T. and Ewert, J.-P. (1989) Neural substrates for long-term habituation of the acoustic startle reflex in rats: a 2-deoxyglucose study. *Neurosci. Lett.* **96,** 151–156.

Graybiel, A. M. (1970) Some thalamocortical projections of the pulvinar-posterior system of the thalamus in the cat. *Brain Res.* **22,** 131–136.

Graybiel, A. M. (1972a) Some extrageniculate visual pathways in the cat. *Invest. Ophthalmol.* **11,** 322–332.

Graybiel, A. M. (1972b) Some fiber pathways related to the posterior thalamic region in the cat. *Brain Behav. Evol.* **6,** 363–393.

Graybiel, A. M. (1973) The thalamo-cortical projection of the so-called posterior nuclear group: a study with anterograde degeneration methods in the cat. *Brain Res.* **49,** 229–244.

Green, D. M. and Swets, J. A. (1966) *Signal Detection Theory*. Wiley: New York.

Grinvald, A., Frostig, R. D., Siegel, R. M. and Bartfeld, E. (1991) High-resolution optical imaging of functional brain architecture in the awake monkey. *Proc. Natl Acad. Sci. USA* **88,** 11559–11563.

Guillery, R. W., Feig, S. L. and Lozsadi, D. A. (1998) Paying attention to the thalamic reticular nucleus. *Trends Neurosci.* **21,** 28–32.

Halas, E. S., Beardsley, J. V. and Sandlie, M. E. (1970) Conditioned neuronal responses at various level in conditioning paradigms. *Electroenceph. Clin. Neurophysiol.* **28,** 468–477.

Hand, P. J. (1982) Plasticity of the rat cortical barrel system. In: *Changing Concept of the Nervous System*, pp. 49–68. Eds. P. L. Strick and A. D. Morrison. Academic Press: New York.

Hars, B., Maho, C., Edeline, J.-M. and Hennevin, E. (1993) Basal forebrain stimulation facilitates tone-evoked responses in the auditory cortex of awake rat. *Neuroscience* **56,** 61–74.

Hawkins, R. D. and Kandel, E. (1984) Is there a cell-biological alphabet for simple forms of learning. *Psychol. Rev.* **91,** 375–391.

He, J. (1997) Modulatory effects of regional cortical activation on the onset responses of the cat medial geniculate neurons. *J. Neurophysiol.* **77,** 896–908.

Hebb, D. O. (1949) *The Organization of Behavior*. Wiley: New York.

Hennevin, E., Maho, C. and Hars, B. (in press) Neuronal plasticity induced by fear conditioning is expressed during paradoxical sleep: evidence from simultaneous recordings in the lateral amygdala and the medial geniculate. *Behav. Neurosci.*

Hennevin, E., Maho, C., Hars, B. and Dutrieux, G. (1993) Learning-induced plasticity in the medial geniculate nucleus is expressed during paradoxical sleep. *Behav. Neurosci.* **107,** 1018–1030.

Hind, J. E., Goldberg, J. M., Greenwood, D. D. and Rose, J. E. (1963) Some discharge characteristics of single neurons in the inferior colliculus of the cat. II. Timing of discharges and observations on binaural stimulation. *J. Neurophysiol.* **26,** 321–341.

Hirata, H. and Aston-Jones, G. (1994) A novel long-latency response of Locus Coeruleus neurons to noxious stimuli: mediation by peripherical C-fibers. *J. Neurophysiol.* **71,** 1752–1761.

Howard, M. A. and Simons, D. J. (1994) Physiologic effects of nucleus basalis magnocellularis stimulation on rat barrel cortex neurons. *Exp. Brain Res.* **102,** 21–33.

Hu, B., Steriade, M. and Deschêne, M. (1989) The effects of brainstem peribrachial stimulation on perigeniculate neurons: the block of spindles waves. *Neuroscience* **31,** 1–12.

Huffman, R. F. and Henson, O. W. J. (1990) The descending auditory pathway and acousticomotor systems: connections with the inferior collicullus. *Brain Res. Rev.* **15,** 295–323.

Hurwitz, B. E., Dietrich, W. D., McCabe, P. M., Watson, B. D., Ginsberg, M. D. and Schneiderman, N. (1990) Sensory-motor deficit and recovery from thrombotic infarction of the vibrissal barrel-field cortex. *Brain Res.* **512,** 210–220.

Hutson, K. A. and Masterton, R. B. (1986) The sensory contribution of a single vibrissa's cortical barrel. *J. Neurophysiol.* **56,** 1196–1223.

Imig, T. J. and Morel, A. (1985) Tonotopic organization in ventral nucleus of medial geniculate body in the cat. *J. Neurophysiol.* **53,** 309–340.

Irvine, D. R. F. and Webster, W. R. (1972) Arousal effects on cochlear potentials: investigation of a two-factor hypothesis. *Brain Res*., 109–119.

Iwata, J., LeDoux, J. E. and Reis, D. J. (1986) Destruction of intrinsic neurons in the lateral hypothalamus disrupts cardiovascular but not behavioral conditioned emotional responses. *Brain Res*. **368,** 161–166.

Jenkins, W. M. and Merzenich, M. M. (1984) Role of cat primary cortex for sound-localization behavior. *J. Neurophysiol*. **52,** 819–847.

Jenkins, W. M., Merzenich, M., Ochs, M. T., Allard, T. and Guic-Robles, E. (1990) Functional reorganization of primary somatosensory cortex in adult owl monkeys after behaviorally controlled tactile stimulation. *J. Neurophysiol*. **63,** 82–104.

Jones, E. G. (1985) *The Thalamus*. Plenum: New York.

Jones, E. D. and Friedman, D. P. (1982) Projection pattern of functional components of thalamic ventrobasal complex on monkey somatosensory complex. *J. Neurophysiol*. **48,** 521–544.

Jöreskog, K. and Sörbom, D. (1989) *LISREL 7 User's Reference Guide*. Scientific Software: Mooresville, IN.

Jouvet, M. (1956) Analyse électroencéphalographique de quelques aspects du conditionnement chez le chat. *Acta Neurol. Latinoamer*. **2,** 107–115.

Juliano, S. L., Ma, W. and Eslin, D. (1991) Cholinergic depletion prevents expansion of topographic maps in somatosensory cortex. *Proc. Natl Acad. Sci. USA* **88,** 780–784.

Kaas, J. H. (1991) Plasticity of sensory and motor maps in adult mammals. *Ann. Rev. Neurosci*. **14,** 137–167.

Kaas, J. H., Krubitzer, L. A., Chino, Y. M., Langston, A. L., Polley, E. H. and Blair, N. (1990) Reorganization of retinotopic cortical maps in adult mammals after lesion of the retina. *Science* **248,** 229–231.

Kaas, J. H., Merzenich, M. M. and Killackey, H. P. (1983) The reorganization of somatosensory cortex following peripheral nerve damage in adult and developing mammals. *Ann. Rev. Neurosci*. **6,** 325–356.

Karni, A. and Bertini, G. (1997) Learning perceptual skills: behavioral probes into adult cortical plasticity. *Curr. Opin. Neurobiol*. **7,** 530–535.

Karni, A. and Sagi, D. (1991) Where practice makes perfect in texture discrimination: evidence for primary visual cortex plasticity. *Proc. Natl Acad. Sci. USA* **88,** 4966–4970.

Karni, A. and Sagi, D. (1993) The time course of learning a visual skill. *Nature* **365,** 250–252.

Karni, A., Ungerleider, L. G., Haxby, J., Jezzard, P., Pannier, L., Cuenod, C. A., Turner, R. and Lebihan, D. (1993) Stimulus dependent MRI signals evoked by oriented line-element textures in human visual cortex. *Soc. Neurosci. Abstr*. **19,** 1501.

Karni, A., Tanne, D., Rubenstein, B. S., Askenasy, J. J. M. and Sagi, D. (1994) Dependence on REM sleep of overnight improvement of a perceptual skill. *Science* **265,** 679–682.

Karni, A., Weisberg, J., Lalonde, F. and Ungerleider, L. G. (1995) An fMRI study of human visual cortex plasticity. *Soc. Neurosci. Abstr*. **21,** 276.

Kasamatsu, T. and Heggelund, P. (1982) Single cell responses in cat visual cortex to visual stimulation during iontophoresis of noradrenaline. *Exp. Brain Res*. **45,** 317–327.

Kasamatsu, T. and Pettigrew, J. D. (1976) Depletion of brain catecholamines: failure of ocular dominance shift after monocular occlusion in kittens. *Science* **194,** 206–208.

Kasamatsu, T., Pettigrew, J. D. and Ary, M. (1979) Restoration of visual cortical plasticity by local perfusion of norepinephrine. *J. Comp. Neurol*. **185,** 163–182.

Kasamatsu, T., Pettigrew, J. D. and Ary, M. (1981) Cortical recovery from effects of monocular deprivation: acceleration with norepinephrine and suppression with 6-hydroxydopamine. *J. Neurophysiol*. **45,** 254–266.

Kayama, Y., Negi, T., Sugitani, M. and Iwama, K. (1982) Effects of locus coeruleus stimulation on neuronal activities of dorsal lateral geniculate nucleus and perigeniculate reticular nucleus of the rat. *Neuroscience* **7,** 655–666.

Kayama, Y., Sumitomo, I. and Ogawa, T. (1986) Does the ascending cholinergic projection inhibit or excite neurons in the rat thalamic reticular nucleus. *J. Neurophysiol*. **56,** 1310–1320.

Kayama, Y., Shimada, S., Hishikawa, Y. and Ogawa, T. (1989) Effects of stimulating the dorsal raphe nucleus of the rat on neuronal activity in the dorsal lateral geniculate nucleus. *Brain Res*. **489,** 1–11.

Kelly, J. B. (1980) Effects of auditory cortical lesions on sound localization by the rat. *J. Neurophysiol*. **44,** 1161–1174.

Kelly, J. B., Rooney, B. J. and Phillips, D. P. (1996) Effects of bilateral auditory cortical lesions on gap-detection threshold in the ferret (*Mustela putorius*). *Behav. Neurosci*. **110,** 542–550.

Kitzes, L. M., Morton-Gibson, M., Rose, J. E. and Hind, J. E. (1978) Initial discharge latency and threshold considerations for some neurons in the cochlear nucleus complex of the cat. *J. Neurophysiol*. **41,** 1165–1182.

Koch, C. (1987) The action of the corticofugal pathway on sensory thalamic nuclei: a hypothesis. *Neuroscience* **23,** 399–406.

Koralek, K.-A., Jensen, K. F. and Killackey, H. P. (1988) Evidence for two complementary patterns of thalamic input to the rat somatosensory cortex. *Brain Res*. **463,** 346–351.

Kossut, M. (1992) Plasticity of the barrel cortex neurons. *Prog. Neurobiol*. **39,** 389–422.

Kossut, M. and Siucinska, E. (1994) Representation plasticity after sensory learning—maps of trained sensory surfaces expand but those of adjacent receptors do not shrink, *17th Annual Meeting of the European Neuroscience Association*, 114.07.

Kossut, M., Hand, P. J., Greenberg, J. and Hand, C. (1988) Single vibrissea cortical column in SI cortex of rat and its alterations in neonatal and adult vibrissea deafferented animals—a quantitative 2DG study. *J. Neurophysiol*. **60,** 829–852.

Kraus, N. and Disterhoft, J. F. (1982) Responses plasticity of single neurons in rabbit auditory association cortex during tone-signalled learning. *Brain Res*. **246,** 205–215.

Krnjevic, K. and Phillis, J. W. (1963a) Ionophoretic studies of neurones in the mammalian cerebral cortex. *J. Physiol. Lond*. **165,** 274–304.

Krnjevic, K. and Phillis, J. W. (1963b) Acetylcholine-sensitive cells in the cerebral cortex. *J. Physiol. Lond*. **166,** 296–327.

Krnjevic, K. and Phillis, J. W. (1963c) Pharmacological properties of acetylcholine sensitive cells in the cerebral cortex. *J. Physiol. Lond*. **166,** 328–350.

Lamme, A. F., van Dick, B. W. and Spekreijse, H. (1993) Organization of texture segregation processing in primate visual cortex. *Visual Neurosci*. **10,** 781–790.

Lamour, Y., Dutar, P., Jobert, A. and Dykes, R. W. (1988) An iontophoretic study of single somatosensory neurons in rat granular cortex serving the limb: a laminar analysis of glutamate and acetylcholine effects on receptive field properties. *J. Neurophysiol*. **60,** 725–750.

Law-Tho, D., Crépel, F. and Hirsch, J. C. (1993) Noradrenaline decreases transmission of NMDA and non-NMDA-receptor mediated monosynaptic EPSPs in rat prefrontal cortex in vitro. *Eur. J. Neurosci*. **5,** 1494–1500.

LeDoux, J. E. (1990) Information flow from sensation to emotion: plasticity in the neural computation of stimulus value. In: *Learning and Computational Neuroscience: Foundations of Adaptive Networks*, pp. 3–51. Eds. M. Gabriel and J. W. Moore. Bradford/MIT Press: Cambridge, Mass.

LeDoux, J. E., Sakaguchi, A. and Reis, D. J. (1984) Subcortical efferent projections of the medial geniculate emotional responses conditioned to acoustic stimuli. *J. Neurosci*. **4,** 683–698.

LeDoux, J. E., Ruggiero, D. A. and Reis, D. J. (1985) Projections to the subcortical forebrain from anatomically defined regions of the medial geniculate body in the rat. *J. Comp. Neurol*. **242,** 182–213.

LeDoux, J. E., Sakaguchi, A., Iwata, J. and Reis, D. J. (1986) Interruption of projections from the medial geniculate body to an archi-neostriatal field disrupts the classical conditioning of emotional responses to acoustic stimuli. *Neuroscience* **17,** 615–627.

Lee, K. H. and McCormick, D. A. (1995) Acetylcholine excites GABAergic neurons of the ferret perigeniculate nucleus through nicotinic receptors. *J. Neurophysiol*. **73,** 2123–2128.

Lee, S. M., Friedberg, M. H. and Ebner, F. F. (1994) The role of GABA-mediated inhibition in the rat ventral posterior medial thalamus. I. Assessment of receptive field changes following thalamic reticular nucleus lesions. *J. Neurophysiol*. **71,** 1702–1715.

Lennartz, R. C. and Weinberger, N. M. (1992) Frequency-specific receptive field plasticity in the medial geniculate body induced by pavlovian fear conditioning is expressed in the anesthetized brain. *Behav. Neurosci*. **106,** 484–497.

Levin, B. E. and Dunn-Meynell, A. (1991) Adult rat barrel cortex plasticity occurs at 1 week but not at 1 day after vibrissectomy as demonstrated by the 2-deoxyglucose methods. *Exp. Neurol*. **113,** 237–248.

Lippe, W. R., Steward, O. and Rubel, E. W. (1980) The effect of unilateral basillar papilla removal upon nuclei laminaris and magnocellularis of the chick examined with H3-2-deoxyglucose autoradiography. *Brain Res*. **196,** 43–58.

Mackintosh, N. J. (1974) *The Psychology of Animal Learning*. Academic Press: London.

Maho, C., Hars, B., Edeline, J.-M. and Hennevin, E. (1995) Conditioned changes in the basal forebrain: relations with learning-induced cortical plasticity. *Psychobiol.* **23,** 10–25.

Manunta, Y. and Edeline, J.-M. (1996). Ionophoretic application of noradrenaline on frequency receptive field (FRF) of auditory cortex neurons in awake guinea pig. *The 2nd Meeting of European Neuroscience*, Strasbourg, p. 89.

Manunta, Y. and Edeline, J.-M. (1997) Effects of noradrenaline on frequency tuning of rat auditory cortex neurons. *Eur. J. Neurosci.* **9,** 833–847.

Manunta, Y. and Edeline, J.-M. (1998) Effects of noradrenaline on rate-level function of auditory cortex neurons: is there a "gating" effect of noradrenaline? *Exp. Brain Res.* **118,** 361–372.

Marks, G. A., Speciale, S. G., Cobbey, K. and Roffwarg, H. P. (1987) Serotonergic inhibition of the dorsal lateral geniculate nucleus. *Brain Res.* **418,** 76–84.

Masino, S. A. and Frostig, R. D. (1996) Quantitative long-term imaging of functional representation of a whisker in rat barrel cortex. *Proc. Natl Acad. Sci. USA* **93,** 4942–4947.

Maunsell, J. H. R. and Van Essen, D. C. (1983) The connections of the middle temporal visual area (MT) and their relationship to a cortical hierarchy in the macaque monkey. *J. Neurosci.* **3,** 2563–2586.

McCormick, D. A. (1992) Neurotransmitter actions in the thalamus and cerebral cortex and their role in neuromodulation of thalamocortical activity. *Prog. Neurobiol.* **39,** 337–388.

McCormick, D. A. and Pape, H. C. (1990) Noradrenergic and serotonergic modulation of a hyperpolarization-activated cation current in thalamic relay neurons. *J. Physiol. Lond.* **431,** 319–342.

McCormick, D. A. and Prince, D. A. (1986) Acetylcholine induces burst firing in thalamic reticular neurones by activating a potassium conductance. *Nature* **319,** 402–406.

McCormick, D. A. and Prince, D. A. (1987) Actions of acetylcholine in the guinea-pig and cat medial lateral and cat medial and lateral geniculate nuclei, in vitro. *J. Physiol. Lond.* **392,** 147–165.

McCormick, D. and Wang, Z. (1991) Serotonin and noradrenaline excite GABAergic neurones of the guinea-pig and cat nucleus reticularis thalami. *J. Physiol. Lond.* **442,** 235–255.

McCormick, D. A. and Williamson, A. (1989) Convergence and divergence of neurotransmitter action in human cerebral cortex. *Proc. Natl Acad. Sci. USA* **86,** 8098–8102.

McEchron, M. D., Green, E. J., Winters, R. W., Nolen, T. G., Schneiderman, N. and McCabe, P. M. (1996) Changes of synaptic efficacy in the medial geniculate nucleus as a result of auditory classical conditioning. *J. Neurosci.* **16,** 1273–1283.

McIntosh, A. R. and Gonzalez-Lima, F. (1991) Structural modeling of functional neural pathways mapped with 2-deoxyglucose: effects of acoustic startle habituation on the auditory system. *Brain Res.* **547,** 295–302.

McIntosh, A. R. and Gonzalez-Lima, F. (1993) Network analysis of functional auditory pathways mapped with fluorodeoxyglucose—associative effects of a tone conditioned as a Pavlovian excitor or inhibitor. *Brain Res.* **627,** 129–140.

McKenna, T. M., Ashe, J. H. and Weinberger, N. M. (1989) Cholinergic modulation of frequency receptive fields in auditory cortex: I. Frequency-specific effects of muscarinic agonists. *Synapse* **4,** 30–43.

McKenna, T. M., Ashe, J. H., Hui, G. K. and Weinberger, N. M. (1988) Muscarinic agonists modulate spontaneous and evoked unit discharge in auditory cortex of cat. *Synapse* **2,** 54–68.

McLean, J. and Palmer, L. A. (1998) Plasticity of neuronal response properties in adult cat striate cortex. *Visual Neurosci.* **15,** 177–196.

McLean, J. and Waterhouse, B. D. (1994) Noradrenergic modulation of cat area 17 neuronal responses to moving stimuli. *Brain Res.* **667,** 83–97.

Meftah, E. M. and Rispal-Padel, L. (1994) Synaptic plasticity in the thalamo-cortical pathway as one of the neurobiological correlates of forelimb flexion conditioning: electrophysiological investigation in the cat. *J. Neurophysiol.* **72,** 2631–2647.

Meftah, E. M. and Rispal-Padel, L. (1997) Reverse effects of conditioning produced by two different unconditioned stimuli on thalamocortical transmission. *J. Neurophysiol.* **77,** 1663–1678.

Merzenich, M. M., Jenkins, W. M. and Middlebrooks, J. C. (1984) Observations and hypotheses on special organizational features of the central auditory nervous system. In: *Dynamic Aspects of Neocortical Function*, pp. 397–424. Eds. G. M. Edelman, W. E. Gall and W. M. Cowan. Wiley: New York.

Merzenich, M. M., Kaas, J. H., Wall, J., Nelson, R. J., Sur, M. and Felleman, D. (1983a) Topographic reorganization of somatosensory cortical areas 3b and 1 in adult monkey following restricted deafferentation. *Neuroscience* **8,** 33–55.

Merzenich, M. M., Kaas, J. H., Wall, J., Sur, M., Nelson, R. J. and Felleman, D. (1983b) Progression of changes following median nerve section in the cortical representation of the hand in areas 3b and 1 in adult owl and squirrel monkeys. *Neuroscience* **10,** 639–665.

Merzenich, M. M., Recanzone, G. H., Jenkins, W. M., Allard, T. T. and Nudo, R. J. (1988) Cortical representational plasticity. In: *Neurobiology of Neocortex*, pp. 41–67. Eds. P. Rakic and W. Singer. Wiley: New York.

Merzenich, M. M., Recanzone, G. H., Jenkins, W. M. and Nudo, R. J. (1990) How the brain functionally rewired itself. In: *Natural and Artifical Parallel Computations*, pp. 177–210. Eds. M. Arbib and J. A. Robinson. MIT Press: Cambridge, MA.

Metherate, R. and Ashe, J. H. (1991) Basal forebrain stimulation modifies auditory cortex responsiveness by an action at muscarinic receptors. *Brain Res.* **559,** 163–167.

Metherate, R. and Weinberger, N. M. (1990) Cholinergic modulation of responses to single tones produces tone-specific receptive field alterations in cat auditory cortex. *Synapse* **6,** 133–145.

Metherate, R., Ashe, J. H. and Weinberger, N. M. (1990) Acetylcholine modifies neuronal acoustic rate-level functions in guinea pig auditory cortex by an action at muscarinic receptors. *Synapse* **6,** 364–368.

Metherate, R., Cox, C. L. and Ashe, J. H. (1992) Cellular bases of neocortical activation: modulation of neural oscillation by the nucleus basalis and endogenous acetylcholine. *J. Neurosci.* **12,** 4701–4711.

Mora, F., Rolls, E. T. and Burton, M. J. (1976) Modulation during learning of the responses of neurons in the lateral hypothalamus to the sight of food. *Exp. Neurol.* **53,** 508–519.

Morest, D. K. (1964) The neuronal architecture of the medial geniculate body of the cat. *J. Anat. (London)* **98,** 611–630.

Morest, D. K. (1965) The laminea structure of the medial geniculate body of the cat. *J. Anat. (London)* **99,** 143–160.

Morest, D. K. and Winer, J. A. (1986) The comparative anatomy of neurons: homologous neurons in the medial geniculate body of the oppossum and the cat. *Adv. Anat., Embrol. Cell Biol.* **97,** 1–96.

Motter, B. C. (1993) Focal attention produces spatially selective processing in visual cortical areas V1, V2 and V4 in the presence of competing stimuli. *J. Neurophysiol.* **70,** 909–919.

Mountcastle, V. B. and Henneman, E. (1952) The representation of tactile sensibility in the thalamus of the monkey. *J. Comp. Neurol.* **12,** 85–100.

Mouradian, R. D., Sessler, F. M. and Waterhouse, B. D. (1991) Noradrenergic potentiation of excitatory transmitter action in cerebrocortical slices: evidence for mediation by an a1 receptor-linked second messenger pathway. *Brain Res.* **546,** 83–95.

Muller, C. M. (1992) A role for glial cells in activity-dependent central nervous plasticity? Review and hypothesis. *Intern. Rev. Neurobiol.* **34,** 215–281.

Murphy, P. C. and Sillito, A. M. (1987) Corticofugal feedback influences the generation of length tuning in the visual patway. *Nature* **329,** 727–729.

Murphy, P. C. and Sillito, A. M. (1991) Cholinergic enhancement of direction selectivity in the visual cortex of the cat. *Neuroscience* **40,** 13–20.

Newsome, W. T. and Paré, E. B. (1988) A selective impairment of motion perception following lesions of the middle temporal visual area (MT). *J. Neurosci.* **8,** 2201–2211.

Nienhuis, R. and Olds, J. (1978) Changes in unit response to tone after food reinforcement in the auditory pathway of the rat: intertrial arousal. *Exp. Neurol.* **59,** 229–242.

O'Connors, K. N., Allison, T. L., Rosenfield, M. E. and Moore, J. W. (1997) Neural activity in the medial geniculate nucleus during auditory trace conditioning. *Exp. Brain Res.* **113,** 534–556.

Ohl, F. and Scheich, H. (1996) Differential frequency conditioning enhances spectral contrast sensitivity of units in the auditory cortex (field AI) of the alert mongolian Gergil. *Eur. J. Neurosci.* **8,** 1001–1017.

Ohl, F. and Scheich, H. (1997) Learning-induced dynamic receptive field changes in primary auditory cortex (AI) of the unanaesthetized Mongolian gerbil. *J. Comp. Physiol. A* **181,** 685–696.

Ohl, F., Simonis, C. and Scheich, H. (1992) Coding associative auditory information by spectral gradient enhancement. *Soc. Neurosci. Abstr* **18,** 841.

Olds, J., Disterhoft, J. F., Segal, M., Kornblith, D. L. and Hirch, R. (1972) Learning center of rat brain mapped by measuring latencies of conditioned unit responses. *J. Neurophysiol.* **35,** 202–219.

Olds, J., Niennhuis, R. and Olds, M. E. (1978) Patterns of conditioned unit responses in the auditory system of the rat. *Exp. Neurol.* **59,** 209–228.

Oleson, T., Ashe, J. and Weinberger, N. M. (1975) Modification of auditory and somatosensory activity during pupillary conditioning in the paralyzed cat. *J. Neurophysiol.* **38,** 1114–1139.

Orban, G. A., Vandenbussche, E., Sprague, J. M. and De Weerd, P. (1990) Orientation discrimination in the cat: a distributed function. *Proc. Natl Acad. Sci. USA* **87,** 1134–1138.

Orban, G. A., Dupont, P., Vogels, R., De Bruyn, B., Bormans, G. and Mortelmans, L. (1996) Task dependency of visual processing in the human visual system. *Behav. Brain Res.* **76,** 215–233.

Paulesu, E., Frith, C. D. and Frackowiak, R. J. S. (1993) the neural correlates of the verbal component of working memory. *Nature* **362,** 342–345.

Pelleg-Toiba, R. and Wollberg, Z. (1989) Tuning properties of auditory cortex cells in the awake squirrel monkey. *Exp. Brain Res.* **74,** 353–364.

Penny, G. R., Fitzpatrick, D., Schmechel, D. E. and Diamond, I. T. (1983) Glutamic acid decarboxylase-immunoreactive neurons and horseradish-peroxydase-labeled projection neurons in the ventral posterior nucleus of the cat and *Galago senegalensis*. *J. Neurosci.* **3,** 1868–1887.

Perkel, D. H., Gerstein, G. L. and Moore, G. P. (1967) Neuronal spike trains and stochastic point processes. II. Simultaneous spike train. *Biophys. J.* **7,** 419–440.

Phillips, D. P. and Farmer, M. E. (1990) Acquired word deafness, and the temporal grain of sound representation in the primary auditory cortex. *Behav. Brain Res.* **40,** 85–94.

Phillips, D. P., Orman, S. S., Musicant, A. D. and Wilson, G. F. (1985) Neurons in cat's primary auditory cortex distinguished by their responses to tones and white noise. *Brain Res.* **18,** 75–86.

Phillis, J. W. (1971) The pharmacology of thalamic and geniculate neurons. *Int. Rev. Neurobiol.* **14,** 1–48.

Pinault, D. and Deschenes, M. (1992) Control of 40-Hz firing of reticular thalamic cells by neurotransmitters. *Neuroscience* **51,** 259–268.

Poggio, G. F. and Mountcastle, V. B. (1960) A study of the functional contributions of the lemniscal and spinothalamic systems to somatic sensibility. *Bull. Johns Hopkins Hospital* **106,** 266–316.

Quirk, G. J., Repa, C. and LeDoux, J. E. (1995) Fear conditioning enhances short-latency auditory responses of lateral amygdala neurons: parallel recordings in the freely behaving rat. *Neuron* **15,** 1029–1039.

Rapisarda, C., Palmeri, A. and Sapienza, S. (1992) Cortical modulation of thalamo-cortical neurons relaying exteroceptive information: a microstimulation study in guinea-pig. *Exp. Brain Res.* **88,** 140–150.

Rasmusson, D. D. (1996a) Changes in the organization of the ventroposterior lateral thalamic nucleus after digit removal in adult racoon. *J. Comp. Neurol.* **364,** 92–103.

Rasmusson, D. D. (1996b) Changes in the response properties of neurons in the ventroposterior lateral thalamic nucleus of the racoon after peripheral deafferentiation. *J. Neurophysiol.* **75,** 2441–2450.

Rasmusson, D. D. and Dykes, R. W. (1988) Long-term enhancement of evoked potentials in cat somatosensory cortex produced by co-activation of basal forebrain and cutaneous receptors. *Exp. Brain Res.* **70,** 276–286.

Rasmussen, K. and Jacobs, B. L. (1986) Single unit activity of the locus coeruleus neurons in the freely moving cat. II. Conditioning and pharmacological studies. *Brain Res.* **371,** 335–344.

Rauschecker, J. P. (1991) Mechanisms of visual plasticity: hebb synapses, NMDA receptors, and beyond. *Physiol. Rev.* **71,** 587–615.

Rausell, E. and Jones, E. G. (1991a) Histochemical and immunocytochemical compartment of the thalamic VPM nucleus in monkeys and their relationships to the representation map. *J. Neurosci.* **11,** 210–225.

Rausell, E. and Jones, E. G. (1991b) Chemically distinct compartments of the thalamic VPM nucleus in monkeys relay principal and spinal trigeminal pathways to different layers of the somatosensory cortex. *J. Neurosci.* **11,** 226–237.

Rausell, E., Bae, C. S., Vinuela, A., Huntley, G. W. and Jones, E. G. (1992) Calbindin and parvalbumin cells in monkey VPL thalamic nucleus, distribution, laminar cortical projections and relations to spinothalamic terminations. *J. Neurosci.* **12,** 4088–4111.

Ravizza, R. J. and Belmore, S. M. (1978) Auditory forebrain: evidence from anatomical and behavioral experiments involving human and animal subjects. In: *Handbook of Behavioral Neurobiology*, pp. 459–501. Ed. R. B. Masterton. Plenum: New York.

Recanzone, G. H. and Merzenich, M. M. (1993) Functional plasticity in the cerebral cortex: mechanisms of improved perceptual abilities and skill acquisition. *Concepts Neurosci.* **4,** 1–23.

Recanzone, G. H., Jenkins, W. M., Hradek, G. T. and Merzenich, M. M. (1992a) Progressive improvement in discriminative abilities in adult owl monkeys performing a tactile frequency discrimination task. *J. Neurophysiol.* **67,** 1015–1030.

Recanzone, G. H., Merzenich, M. M. and Jenkins, W. M. (1992b) Frequency discrimination training engaging a restricted skin surface results in an emergence of a cutaneous response zone in cortical area 3a. *J. Neurophysiol.* **67,** 1057–1070.

Recanzone, G. H., Merzenich, M. M., Jenkins, W. M., Grajski, K. A. and Dinse, H. A. (1992c) Topographic reorganization of the hand representation in cortical area 3b of owl monkeys trained in a frequency discrimination task. *J. Neurophysiol.* **67,** 1031–1056.

Recanzone, G. H., Merzenich, M. M. and Schreiner, C. E. (1992d) Changes in the distributed temporal response properties of SI cortical neurons reflect improvements in performance on a temporally-based tactile discrimination task. *J. Neurophysiol.* **67,** 1071–1091.

Recanzone, G. H., Schreiner, C. E. and Merzenich, M. M. (1993) Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. *J. Neurosci.* **13,** 87–103.

Reich, D. S., Victor, J. D., Knight, B. W., Ozaki, T. and Kaplan, E. (1997) Response variability and timing precision of neuronal spike trains in vivo. *J. Neurophysiol.* **77,** 2836–2841.

Rescorla, R. A. (1980) *Pavlovian Second-order Conditioning*. Erlbaum: Hillsdale, NJ.

Richardson, R. T. and DeLong, M. R. (1986) Nucleus basalis of Meynert neuronal activity during a delayed response task in monkey. *Brain Res.* **399,** 364–368.

Richardson, R. T. and DeLong, M. R. (1990) Context-dependant responses of primate nucleus basalis neurons in a Go/no-Go task. *J. Neurosci.* **10,** 2528–2540.

Robertson, D. and Irvine, D. R. F. (1989) Plasticity of frequency organization in auditory cortex of guinea pigs with partial unilateral deafness. *J. Comp. Neurol.* **282,** 456–471.

Rodriguez-Nodal, F., Manunta, Y., Edeline, J.-M. and Bajo, V. (1996) Descending projections from primary auditory cortex to the thalamus: study with biocytin in the guinea-pig. *J. Physiol. Lond.* **493P,** 15S.

Rogawski, M. A. and Aghajanian, G. K. (1980a) Activation of lateral geniculate neurons by norepinephrine: mediation by an alpha-adrenergic receptor. *Brain Res.* **182,** 345–359.

Rogawski, M. A. and Aghajanian, G. K. (1980b) Modulation of lateral geniculate neuron excitability by noradrenaline microiontophoresis or locus coeruleus stimulation. *Nature* **287,** 731–734.

Rogawski, M. A. and Aghajanian, G. K. (1980c) Norephinephrine and serotonine: opposite effects on the activity of lateral geniculate neurons evoked by optic pathway stimulation. *Exp. Neurol.* **69,** 678–694.

Rolls, E. T., Sanghera, M. K. and Roper-Hall, A. (1979) The latency of activation of neurones in the lateral hypothalamus and substantia innominata during feeding in the monkey. *Brain Res.* **164,** 121–135.

Rouiller, E., Innocenti, G. M. and DeRibaupierre, F. (1990) Interconnections of the auditory cortical fields of the cat with the cingulate and parahippocampal cortices. *Exp. Brain Res.* **80,** 510–511.

Rouiller, E. M., Rodrigues-Dagaeff, C., Simm, G., de Ribaupierre, Y., Villa, A. and de Ribaupierre, F. (1989) Functional organization of the medial division of the medial geniculate body of the cat: tonotopic organization, spatial distribution of response properties and cortical connections. *Hearing Res.* **39,** 127–142.

Rouiller, E. M., Simm, G. M., Villa, A. E. P., deRibaupierre, Y. and deRibaupierre, F. (1991) Auditory corticocortical interconnections in the cat: evidence for parallel and hierarchical arragement of the auditory cortical areas. *Exp. Brain Res.* **1991,** 483–505.

Ryugo, D. K. and Weinberger, N. M. (1976) Corticofugal modulation of the medial geniculate body. *Exp. Neurol.* **51,** 377–391.

Ryugo, D. K. and Weinberger, N. M. (1978) Differential plasticity of morphologically distinct neuron populations in the medial geniculate body of the cat during classical conditioning. *Behav. Biol.* **22,** 275–301.

Salin, P. A. and Bullier, J. (1995) Corticocortical connections in the visual system: structure and function. *Physiol. Rev.* **75,** 107–154.

Sams, M., Aulanko, R., Hämäläinen, M., Hari, R., Lounasmaa, O. V., Lu, S.-T. and Simola, J. (1991) Seeing speech: visual information from lip movements modifies activity in the human auditory cortex. *Neurosci. Lett.* **127,** 141–145.

Sara, S. J. and Segal, M. (1991) Plasticity of sensory responses of locus coeruleus neurons in the behaving rat: implication for cognition. In: *Progress in Brain Research*, pp. 571–585. Eds C. D. Barnes and O. Pompeiano. Elsevier: Amsterdam.

Sara, S. J., Devauges, V. and Segal, M. (1988) Locus coeruleus engagement in memory retrieval and attention. In: *Progress in Catecholamine Research*, pp. 151–161. Eds. A. Dahlstom, M. Sandler and H. Belmaker. A. Liss: New York.

Sato, H., Fox, K. and Daw, N. (1989) Effect of electrical stimulation of locus coeruleus on the activity of neurons in the cat visual cortex. *J. Neurophysiol.* **62,** 946–958.

Scheich, H. and Simonis, C. (1991) Conditioning changes frequency representation in gerbil auditory cortex. *Soc. Neurosci. Abstr.* **17,** 450.

Schmielau, F. and Singer, W. (1977) The role of the visual cortex for binocular interactions in the cat lateral geniculate. *Brain Res.* **120,** 354–361.

Schoups, A. A. and Orban, G. A. (1996) Interocular transfer in perceptual learning of a pop-out discrimination task. *Proc. Natl Acad. Sci. USA* **93,** 7358–7362.

Servière, J. and Webster, W. R. (1981) A combined electrophysiological and 2-DG study of the frequency organization of the inferior colliculus of the cat. *Neurosci. Lett.* **27,** 113–118.

Sessler, F. M., Lui, W., Kirifides, M. L., Mouradian, R. D., Lin, R. C. S. and Waterhouse, B. D. (1995) Noradrenergic enhancement of GABA-induced input resistance changes in layer V regular spiking pyramidal neurons of rat somatosensory cortex. *Brain Res.* **675,** 171–182.

Shadlen, M. N., Britten, K. H., Newsome, W. T. and Movshon, J. A. (1996) A computational analysis of the relationship between neuronal and behavioral responses to visual motion. *J. Neurosci.* **16,** 1486–1510.

Shamma, S. A. and Symmes, D. (1985) Patterns of inhibition in auditory cortical cells in awake squirrel monkeys. *Hearing Res.* **19,** 1–13.

Sherman, M. S. and Guillery, R. W. (1996) Functional organization of thalamocortical relays. *J. Neurophysiol.* **76,** 1367–1395.

Sherman, S. M. and Koch, C. (1986) The control of retinogeniculate transmission in the mammalian lateral geniculate nucleus. *Exp. Brain Res.* **63,** 1–20.

Shosaku, A. and Sumitomo, I. (1983) Auditory neurons in the rat thalamic reticular nucleus. *Exp. Brain Res.* **49,** 432–442.

Shulz, D. and Bringuier, V. (1993) Effects of noradrenaline on the functional selectivity of visual cortical receptive fields. *16th Meeting of the European Neuroscience Association*, p. 134.

Shulz, D. and Frégnac, Y. (1992) Cellular analogs of visual cortical epigenesis. II. Plasticity of binocular integration. *J. Neurosci.* **12,** 1301–1318.

Sillito, A. M. (1987) Synaptic processes and neurotransmitters operating in the central visual system: a systems approach. In: *Synaptic Function*, pp. 329–371. Eds. G. M. Edelman, W. E. Gall and W. M. Cowan. Wiley: New York.

Sillito, A. and Kemp, J. A. (1983) Cholinergic modulation of the functional organization of the cat visual cortex. *Brain Res.* **289,** 143–155.

Sillito, A. M., Kemp, J. A. and Berardi, N. (1983) The cholinergic influence on the function of the cat dorsal lateral geniculate nucleus (dLGN). *Brain Res.* **280,** 299–307.

Sillito, A. M., Jones, H. E., Gerstein, G. L. and West, D. C. (1994) Feature-linked synchronization of thalamic relay cell firing induced by feedback from the visual cortex. *Nature* **369,** 479–482.

Simons, D. J., Carvell, G. E., Hershey, A. E. and Bryant, D. P. (1992) Responses of barrel cortex neurons in awake rats and effects of urethane anesthesia. *Exp. Brain Res.* **91,** 259–272.

Singer, W. (1977) Control of thalamic transmission by corticofugal and ascending reticular pathways in the visual system. *Physiol. Rev.* **57,** 386–420.

Siucinska, E. and Kossut, M. (1996) Short-lasting classical conditioning induces reversible changes of representational maps of vibrissea in the mouse SI cortex—a 2DG study. *Cereb. Cor.* **6,** 506–513.

Skaggs, W. E. and McNaughton, B. L. (1996) Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience [see comments]. *Science* **271,** 1870–1873.

Skarda, C. A. and Freeman, W. J. (1987) How brains make chaos in order to make sense of the world. *Behav. Brain Sci.* **10,** 161–195.

Skarda, C. A. and Freeman, W. J. (1990) Chaos and the new science of the brain. *Concepts in Neurosci.* **1,** 275–285.

Sokoloff, L. and Takahashi, S. (1996) Functional activation of energy metabolism in nervous tissue: where and why. In: *Neurodegenerative Diseases*, pp. 147–169. Ed. G. Fiskum. Plenum: New York.

Sokoloff, L., Reivich, M., Kennedy, C., Des Rosiers, M. H., Patlak, C. S., Pettigrew, K. D., Sakurada, O. and Shinohara, M. (1977) The [14C] deoxyglucose method for the measurement of local cerebral glocose utilization: theory, procedure and normal values in conscious and anesthetized albino rats. *J. Neurochem.* **28,** 897–916.

Spitzer, H., Desimone, R. and Moran, J. (1988) Increased attention enhances both behavioral and neuronal performance. *Science* **240,** 338–340.

Sprague, J. M., De Weerd, P., Xiao, D.-K., Vandenbussche, E. and Orban, G. A. (1996) Orientation discrimination in the cat: its cortical locus. II. extrastriate cortical areas. *J. Comp. Neurol.* **364,** 32–50.

Spreafico, R., Schmechel, D. E., Ellis, L. C. J. and Rustioni, A. (1983) Cortical relay neurons and interneurons in the N. ventralis posterolateralis of cats: a horseradish peroxydase, electronmicroscopic, golgi and immunocytochemical study. *Neuroscience* **9,** 491–509.

Starr, A. (1964) Influence of motor activity on click-evoked responses in the auditory pathway of waking cats. *Exp. Neurol.* **10,** 191–204.

Steriade, M., Deschênes, M., Domich, L. and Mulle, C. (1985) Abolition of spindle oscillations in thalamic neurons disconnected from nucleus reticularis thalami. *J. Neurophysiol.* **54,** 1473–1497.

Steriade, M., Domich, L., Oakson, G. and Deschênes, M. (1987) The deafferented reticular thalamic nucleus generates spindle rythmicity. *J. Neurophysiol.* **57,** 260–273.

Suga, N., Yan, J. and Zhang, Y. (1997) Cortical maps for hearing and egocentric selection for self-organization. *Trends Cogn. Sci.* **1,** 13–20.

Sun, X., Jen, P. H.-S. and Zhang, S. (1989) Corticofugal influence on the responses of bat inferior collicular neurons to sound stimulation. *Brain Res.* **495,** 1–8.

Supple, W. F. and Kapp, B. S. (1989) Response characteristics of neurons in the medial component of the medial geniculate nucleus during pavlovian differential fear conditioning in rabbits. *Behav. Neurosci.* **103,** 1276–1286.

Tanaka, K., Hikosaka, H., Saito, H., Yukie, Y., Fukada, Y. and Iwai, E. (1986) Analysis of local and wide-field movements in the superior temporal visual areas of the macaque monkey. *J. Neurosci.* **6,** 134–144.

Theurich, M., Müller, C. M. and Scheich, H. (1984) 2-deoxyglucose accumulation parallels extracellularly recorded spike activity in the avian auditory neostriatum. *Brain Res.* **322,** 157–161.

Thompson, R. F. (1960) Function of auditory cortex of cat in frequency discrimination. *J. Neurophysiol.* **23,** 321–334.

Thompson, R. F. (1988) The neural basis of basic associative learning of discrete behavioral responses. *Trends Neurosci.* **11,** 152–155.

Tolhurst, D. J., Movshon, J. A. and Dean, A. F. (1983) The statistical reliability of signals in single neurons in cat and monkey visual cortex. *Vision Res.* **23,** 775–786.

Tramo, M. J., Bharucha, J. J. and Musiek, F. E. (1990) Music perception and cognition following bilateral lesions of auditory cortex. *J. Cogni. Neurosci.* **2,** 195–212.

Travis, R. P. and Sparks, D. L. (1968) Unitary responses and discrimination learning in the squirrel monkey: the globus pallidus. *Physiol. Behav.* **3,** 187–196.

Tremblay, N., Warren, R. A. and Dykes, R. W. (1990) Electrophysiological studies of acetylcholine and the role of the basal forebrain in the somatosensory cortex of the cat. II. Cortical neurons excited by somatic stimuli. *J. Neurophysiol.* **64,** 1212–1222.

Tsukahara, N., Oda, Y. and Notsu, T. (1981) Classical conditioning mediated by the red nucleus in the cat. *J. Neurosci.* **1,** 72–79.

Updyke, B. V. (1977) Topographic organization of the projections from cortical area 17, 18 and 19 onto the thalamus, pretectum and superior colliculus in the cat. *J. Comp. Neurol.* **173,** 81–122.

Vaadia, E., Haalman, I., Abeles, M., Bergmen, H., Prut, Y., Slovin, H. and Aertsen, A. (1995) Dynamics of neuronal interactions in monkey cortex in relation to behavioural events. *Nature* **373,** 515–518.

Van der Loos, H. (1976) Barreloids in mouse somatosensory thalamus. *Neurosci. Lett.* **2,** 1–6.

Vandenbussche, E., Sprague, J. M., De Weerd, P. and Orban, G. A. (1991) Orientation discrimination in the cat: its cortical locus. I. Areas 17 and 18. *J. Comp. Neurol.* **305,** 632–658.

Vaudano, E., Legg, C. R. and Glickstein, M. (1991) Afferent and efferent connections of temporal association cortex in the rat: a horseradish peroxidase study. *Eur. J. Neurosci.* **3,** 317–330.

Videen, T. O., Daw, N. W. and Rader, R. K. (1984) The effect of norepinephrine on visual cortical neurons in kitten and adult cats. *J. Neurosci.* **4,** 1607–1617.

Villa, A. E. P. and Abeles, M. (1990) Evidence for spatiotemporal firing patterns within the auditory thalamus of the cat. *Brain Res.* **509,** 325–327.

Villa, A. E. P., Rouiller, E. M., Simm, G. M., Zurita, P., deRibaupierre, Y. and deRibaupierre, F. (1991) Corticofugal modulation of the information processing in the auditory thalamus of the cat. *Exp. Brain Res.* **86,** 506–517.

Vogels, R. and Orban, G. A. (1990) How well do response changes of striate neurons signal differences in orientation: a study in the discriminating monkey? *J. Neurosci.* **10,** 3543–3558.

Vogels, R. and Orban, G. A. (1994) Does practice in orientation discrimination lead to changes in the response properties of macaque inferior temporal neurons? *Eur. J. Neurosci.* **6,** 1680–1690.

Von Der Malsburg, C. (1981) *The Correlation Theory of Brain Function.* Max-Planck Institute for Biophysical Chemistry: Goettingen.

Wall, J. T., Gibbs, C. M., Broyles, J. L. and Cohen, D. H. (1985) Modification of neuronal discharge along the ascending tectofugal pathway during visual conditioning. *Brain Res.* **342,** 67–76.

Wang, Z.-X., Ryan, A. F. and Woolf, N. K. (1987) Pentobarbital and Ketamine alter the pattern of 2-deoxyglucose uptake in the central auditory system of the gerbila. *Brain Res.* **27,** 145–155.

Warren, R. A. and Jones, E. G. (1994) Glutamate activation of cat thalamic reticular nucleus: effects on response properties of ventroposterior neurons. *Exp. Brain Res.* **100,** 215–226.

Waterhouse, B. D. and Woodward, D. J. (1980) Interaction of norepinephrine with cerebrocortical activity evoked by stimulation of somatosensory afferent pathways in the rat. *Exp. Neurol.* **67,** 11–34.

Waterhouse, B. D., Moises, H. C. and Woodward, D. J. (1981) Alpha-receptor-mediated facilitation of somatosensory cortical neuronal responses to excitatory synaptic inputs and iontophoretically applied acetylcholine. *Neuropharmacol.* **20,** 907–920.

Waterhouse, B. D., Azizi, S. A., Burne, R. A. and Woodward, D. J. (1990) Modulation of rat cortical area 17 neuronal responses to moving visual stimuli during norepinephrine and serotonin microintophoresis. *Brain Res.* **514,** 276–292.

Waterhouse, B. D., Sessler, F. M., Cheng, J. T., Woodward, D. J., Azizi, S. A. and Moises, H. C. (1988) New evidence for a gating action of norepinephrine in central neuronal circuits of mammalian brain. *Brain Res. Bull.* **21,** 425–432.

Webster, W. R., Servière, J., Batini, C. and Laplante, S. (1978) Autoradiographic demonstration with 2-14C deoxyglocose of frequency slectivity in the auditory system of cat under conditions of functional activity. *Neurosci. Lett.* **10,** 43–48.

Webster, H. H., Rasmusson, D. D., Dykes, R. W., Schliebs, R., Schober, W., Bruckner, G. and Bieslod, D. (1991) Long-term enhancement of evoked potentials in raccoon somatosensory cortex following co-activation of the nucleus basalis of Meynert complex and cutaneous receptors. *Brain Res.* **545,** 292–296.

Weedman, D. L. and Ryugo, D. K. (1996) Pyramidal cells in primary auditory cortex project to cochlear nucleus in rat. *Brain Res.* **706,** 97–102.

Weinberger, N. M. (1980) Neurophysiological studies of learning in association with the pupillary dilation conditoned reflex. In: *Neural Mechanisms of Goal-directed Behavior and Learning*, pp. 241–261. Eds. R. F. Thompson, L. H. Hicks and V. B. Shvyrkov. Academic Press: New York.

Weinberger, N. M. (1982a) Effects of conditioned arousal on the auditory system. In: *The Neural Basis of Behavior*, pp. 63–91. Ed. A. L. Beckman. Spectrum: New York.

Weinberger, N. M. (1982b) Sensory plasticity and learning: the magnocellular medial geniculate nucleus of the auditory system. In: *Conditioning: Representation of Involved Neural Function*, pp. 697–710. Ed. C. D. Woody. Plenum: New York.

Weinberger, N. M. (1984) The neurophysiology of learning: a view from the sensory side. In: *The Neuropsychology of Memory*, pp. 489–503. Eds. L. Squire and N. Butters. Guilford Press: New York.

Weinberger, N. M. (1995a) Dynamic regulation of receptive fields and maps in the adult sensory cortex. *Ann. Rev. Neurosci.* **18,** 129–158.

Weinberger, N. M. (1995b) Retuning the brain by fear conditioning. In: *The Cognitive Neurosciences*, pp. 1071–1089. Ed. M. S. Gazzaniga. MIT Press: Cambridge, MA.

Weinberger, N. M. and Diamond, D. M. (1987) Physiological plasticity in auditory cortex: rapid induction by learning. *Prog. Neurobiol.* **29,** 1–55.

Weinberger, N. M., Hopkins, W. and Diamond, D. M. (1984a) Physiological plasticity of single neurons in auditory cortex of cat during acquisition of the pupillary conditioned response: I. Primary Field (AI). *Behav. Neurosci.* **98,** 171–188.

Weinberger, N. M., Diamond, D. M. and McKenna, T. M. (1984b) Initial events in conditioning: plasticity in the pupillomotor and auditory systems. In: *Neurobiology of Learning and Memory*, pp. 197–227. Eds. G. Lynch, J. L. McGaugh and N. M. Weinberger. Guilford: New York.

Weinberger, N. M., Ashe, J. H., Metherate, R., McKenna, T. M., Diamond, D. M. and Bakin, J. (1990a) Retuning auditory cortex by learning: a preliminary model of receptive field plasticity. *Concepts in Neurosci.* **1,** 91–132.

Weinberger, N. M., Ashe, J. H., Metherate, R., McKenna, T. M., Diamond, D. M., Bakin, J. S., Lennartz, R. C. and Cassady, J. M. (1990b) Neural adaptive information processing: a preliminary model of receptive field plasticity in auditory cortex during Pavlovian conditioning. In: *Neurocomputation and Learning: Foundations of Adaptive Networks*, pp. 91–138. Eds. M. Gabriel and J. Moore. Bradford Books/MIT Press: Cambridge, MA.

Weinberger, N. M., Javid, R. and Lepan, B. (1993) Long-term retention of learning-induced receptive-field plasticity in the auditory cortex. *Proc. Natl Acad. Sci. USA* **90,** 2394–2398.

Welker, W. I. (1974) Principles of organization of the ventrobasal complex in mammals. *Brain Behav. Evol.* **7,** 253–336.

Werner, G. and Mountcastle, V. B. (1963) The variability of central neural activity in a sensory system, and its applications for the central reflection of sensory events. *J. Neurophysiol.* **26,** 958–977.

Whitfield, I. C. (1979) The object of the sensory cortex. *Brain Behav. Evol.*, **16**, 129–154.

Wiener, J. M., Pfeiffer, R. R. and Backus, A. S. M. (1966) On the sound pressure transformation by the head and auditory meatus of the cat. *Acta Oto-Laryngol.* **61,** 255–269.

Wiesel, T. N. (1982) Postnatal development of the visual cortex and the influence of environment. *Nature* **299,** 583–591.

Wiesel, T. N. and Hubel, D. H. (1963) Single cell responses in striate cortex of kittens deprived of vision in one eye. *J. Neurophysiol.* **26,** 1003–1017.

Wiesel, T. N. and Hubel, D. H. (1965) Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. *J. Neurophysiol.* **28,** 1029–1040.

Wild, J. M. and Cohen, D. H. (1985) Invariance of retinal output during learning. *Brain Res.* **331,** 127–135.

Wilson, M. A. and McNaughton, B. L. (1994) Reactivation of hippocampal ensemble memories during sleep. *Science* **265,** 676–679.

Wilson, F. A. and Rolls, E. T. (1990a) Neuronal responses related to reinforcement in the primate basal forebrain. *Brain Res.* **509,** 213–231.

Wilson, F. A. W. and Rolls, E. T. (1990b) Learning and memory is reflected in the responses of reinforcement-related in the primate basal forebrain. *J. Neurosci.* **10,** 1254–1267.

Winer, J. A. (1992) The functional architecture of the medial geniculate body and primary auditory cortex. In: *The Mammalian Auditory Pathway: Neuroanatomy*, pp. 222–409. Eds. D. B. Webster, A. N. Popper and R. R. Fay. Springer: New York.

Winer, J. E. and Larue, D. T. (1988) Anatomy of glutamic acid decarboxylase immunoreactive neurons and axons in the rat medial geniculate body. *J. Comp. Neurol.* **278,** 47–68.

Winer, J. A. and Larue, D. T. (1996) Evolution of GABAergic circuitry in the mammalian medial geniculate body. *Proc. Natl Acad. Sci. USA* **93,** 3083–3087.

Winer, J. A. and Morest, D. K. (1983a) The neuronal architecture of the dorsal division of the medial geniculate body of the cat. A study with the rapid golgi method. *J. Comp. Neurol.* **221,** 1–30.

Winer, J. A. and Morest, K. D. (1983b) The medial division of the medial geniculate body of the cat: implication for thalamic organization. *J. Neurosci.* **3,** 2629–2651.

Winer, J. A. and Morest, K. D. (1984) Axons of the dorsal division of the medial geniculate body of the cat: a study with the rapid golgi method. *J. Comp. Neurol.* **224,** 344–370.

Woody, C. D. (1982) *Memory, Learning, and Higher Function: A Cellular View*. Springer: New York.

Xerri, C., Stern, J. M. and Merzenich, M. M. (1994) Alterations of the cortical representation of the rat ventrum induced by nursing behavior. *J. Neurosci.* **14,** 1710–1721.

Yan, J. and Suga, N. (1996) Corticofugal modulation of time-domain processing of biosonar information in bats. *Science* **273,** 1100–1103.

Yuan, B., Morrow, T. J. and Casey, K. L. (1986) Corticofugal influence of S1 cortex on ventrobasal thalamic neurons in the awake rat. *J. Neurosci.* **6,** 3611–3617.

Zatorre, R. J., Halpern, A. R., Perry, D. W., Meyer, E. and Evans, A. C. (1996) Hearing in the mind's ear: a PET investigation of musical imagery and perception. *J. Cogni. Neurosci.* **8,** 29–46.

Zeki, S. M. (1974) Functional organization of a visual area in the posterior bank of the superior temporal sulcus of the rhesus monkey. *J. Physiol. Lond.* **236,** 549–573.

Zohary, E., Celebrini, S., Britten, K. and Newsome, W. T. (1994) Neuronal plasticity that underlies improvement in perceptual performance. *Science* **263,** 1289–1292.

Zurita, P., Villa, A. E. P., deRibaupierre, Y., deRibaupierre, F. and Rouiller, E. M. (1994) Changes of single unit activity in the cat's auditory thalamus and cortex associated to different anesthetic conditions. *Neurosci. Res.* **19,** 303–316.