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Jean-Marc Edeline

The thalamo-cortical auditory receptive fields: regulation by the states of vigilance, learning and the neuromodulatory systems

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Abstract The goal of this review is twofold. First, it aims to describe the dynamic regulation that constantly shapes the receptive fields (RFs) and maps in the thalamo-cortical sensory systems of undrugged animals. Second, it aims to discuss several important issues that remain unresolved at the intersection between behavioral neurosciences and sensory physiology. A first section presents the RF modulations observed when an undrugged animal spontaneously shifts from waking to slow-wave sleep or to paradoxical sleep (also called REM sleep). A second section shows that, in contrast with the general changes described in the first section, behavioral training can induce selective effects which favor the stimulus that has acquired significance during learning. A third section reviews the effects triggered by two major neuromodulators of the thalamo-cortical system—acetylcholine and noradrenaline—which are traditionally involved both in the switch of vigilance states and in learning experiences. The conclusion argues that because the receptive fields and maps of an awake animal are continuously modulated from minute to minute, learning-induced sensory plasticity can be viewed as a “crystallization” of the receptive fields and maps in one of the multiple possible states. Studying the interplays between neuromodulators can help understanding the neurobiological foundations of this dynamic regulation.

Keywords Thalamo-cortical auditory receptive fields · Vigilance · Learning · Neuromodulatory systems · Receptive fields · Learning-induced sensory plasticity

Introduction and aims

From the middle of the past century, the foundations of sensory physiology have been established in anesthetized preparations that have been judged more stable than the awake ones; and, thus, only a few studies have been performed in non-anesthetized animals (see, for example, Hubel et al. 1959; Evans and Whitfield 1964). The developmental plasticity occurring in the sensory neocortex as a result of an early experience imposed on waking animals was also assessed under general anesthesia (see for a review, Wiesel 1982). Obviously, the work that has been carried out in sensory physiology under general anesthesia is invaluable. It is a necessary and essential step to unraveling the fundamental principles that allow sensory neurons to extract information from the incoming messages and to code this information for the subsequent stages of processing. However, it is also necessary to examine to what extent these fundamental principles indeed operate in the waking brain.

The studies concerning the functional operations performed by thalamo-cortical neurons belong to two different domains. On the one hand, in sensory physiology, it is traditionally considered that the thalamo-cortical system is governed by the balance between excitatory and inhibitory inputs: GABA and glutamate are viewed as the two actors sculpting the receptive fields. According to this view, it is essential to dissect the effects produced on the receptive field (RF) properties by manipulations of the glutamatergic or the GABAergic inputs (Wang et al. 2000, 2002). On the other hand, researchers working (in vivo or in vitro) on the neuromodulator action on thalamic or cortical neurons described how a particular neuromodulator modifies the neuronal excitability, the neuronal accommodation, the cell firing mode and/or the synaptic transmission (review in McCormick 1992). These two domains do not interact much. However, when one describes the effects produced by attenuating the GABAergic transmission on the frequency tuning curve of auditory cortex neurons (Wang et al. 2000), one should logically wonder if this attenuation indeed occurs under

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natural circumstances. Is it possible that neuromodulators such as noradrenaline (NA), serotonin (5HT) or acetylcholine (ACh), whose concentrations fluctuate across the states of vigilance, act on the GABAergic transmission to change the RF properties? Similarly, when one describes the effects produced by NMDA receptor activation on the properties of lateral geniculate cells (Kwon et al. 1992), one should consider the natural circumstances during which changes in this activation might occur. Investigations combining the results obtained in these two fields should greatly benefit our understanding of the dynamic regulation of sensory processing.

This review will first present effects observed under natural circumstances and will summarize how the processing of auditory information is modified at shifts from one state of vigilance to another. A second part will review the results obtained when a particular sound frequency becomes significant. Then, the possibility that artificial changes in neuromodulators concentration mimic these natural effects will be discussed. In each section, several unresolved questions will be raised in an attempt to point to future investigations to clarify some key points.

Effects produced by shifts in state of vigilance

Most of the initial contributions concerning the effects produced by shifts in vigilance states come from anecdotal observations. For example, Brugge and Merzenich (1973) reported that in the auditory cortex of undrugged macaque monkeys “the most dramatic shifts in excitability occur when the animal drifts through periods of wakefulness and sleep”. In their study, spontaneous and evoked activity could be four times smaller during slow-wave sleep (SWS) than during waking (Brugge and Merzenich 1973, pp. 1146–1147, see their Fig. 12). In the visual and

somatosensory systems, several studies confirmed that, during SWS, evoked activity is largely attenuated at the thalamic (Coenen and Vendrik 1972; Livingstone and Hubel 1981; Maffei et al. 1965; Mariotti et al. 1989; Mukhametov and Rizzolatti 1970) and at the cortical level (Livingstone and Hubel 1981). During paradoxical sleep (PS; also called REM sleep), the results were more variable: whereas some studies reported that evoked responses were unchanged or increased in PS compared to waking (W; Mariotti and Formenti 1990; Mukhametov and Rizzolatti 1970), others described very weak responses in PS (Gücer 1979).

Surprisingly, until recently very few studies have looked at the selectivity of sensory coding or the RF size across natural behavioral states. Anecdotal observations mentioned that the RF stayed approximately the same when the animal switched from W to SWS and to PS (Baker 1971; Hayward 1975), and, on the basis of a few individual examples, Livingstone and Hubel (1981) stated that orientation selectivity was enhanced when passing from drowsiness to W. Recently, two studies performed in the thalamo-cortical auditory system have systematically quantified the RF size during W, SWS and PS. At the thalamic level, most of the cells (70%) exhibited smaller RF and a higher frequency selectivity during SWS than during W (Edeline et al. 2000). At the cortical level, heterogeneous effects were observed: depending on the direction of the changes in evoked responses (increases or decreases), enlargement or shrinkage of the frequency RF were obtained (Edeline et al. 2001). During PS, heterogeneous effects were described both at the thalamic and cortical levels, and, again, these effects were a function of the facilitation or depression in evoked activity: When the evoked responses were decreased, the cells usually showed smaller RFs and a higher frequency selectivity; when the evoked responses were increased, the cells

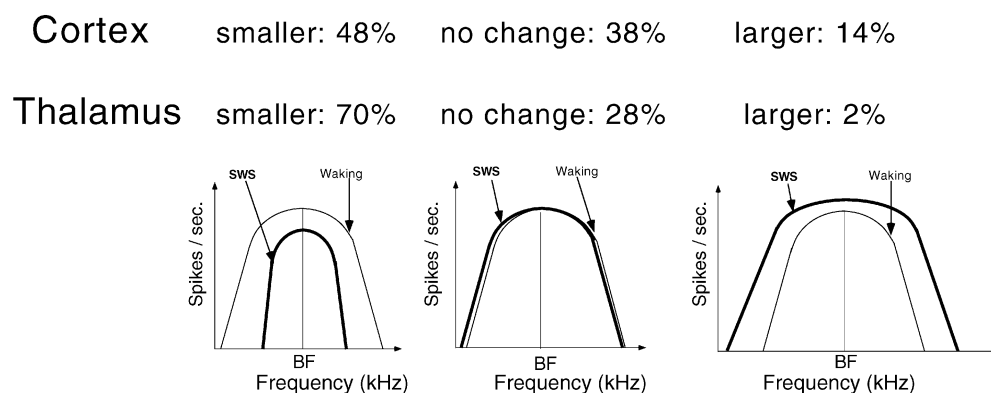


Fig. 1 Schematic diagram summarizing the effects obtained at the shift from waking to slow-wave sleep in the thalamo-cortical auditory system. At the thalamic level, most of the cells (70%) exhibited decreased evoked responses which led to a shrinking of the frequency range that activated these cells. Only few cells exhibited increased evoked responses which led to an increase in the frequency range activating these cells (Edeline et al. 2000). At the cortical level, the proportion of cells exhibiting decreased evoked responses and RF shrinkage fell to 48% and the proportion of cells exhibiting increased evoked responses and RF enlargement

extended to 14% (Edeline et al. 2001). Note that, at the cortical level, this picture is an oversimplification: decreased evoked responses did not necessarily lead to RF shrinkage as at the thalamic level. Note also that more complex effects were obtained during paradoxical sleep (REM sleep): at the thalamic level 60% of the cells had their responses attenuated and 40% had their responses increased. At the cortical level, there was no dominant change: the neurons evoked responses and their RF size was increased, decreased or unchanged in almost the same proportions

usually showed larger RFs and a lower frequency selectivity (Edeline et al. 2000, 2001).

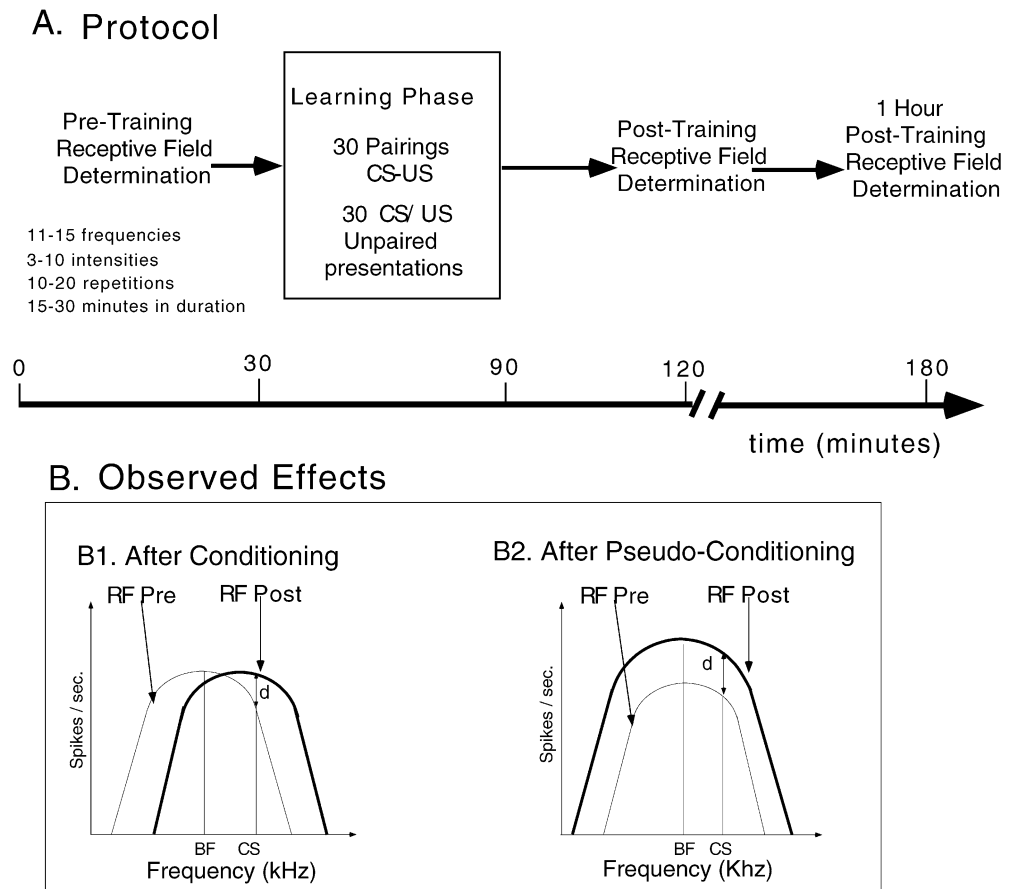
Figure 1 summarizes the effects observed on the frequency RF from W to SWS at the thalamic and cortical levels. Clearly, these effects are at variance with those described during EEG fluctuations in anesthetized animals (Wörgötter et al. 1998). In the visual cortex of halothane anesthetized animals, the neurons RF were found to be larger during periods of synchronized EEG than during desynchronized EEG. As previously stated (Edeline et al. 2001), these discordances point out that apparent resemblance in the EEG does not permit the conclusion that EEG states under sleep-waking vs under anesthesia reflect the same underlying physiological states, functions and modes of information processing. Caution has to be exerted in considering that RF changes observed in anesthetized preparations mimic those occurring across the natural states of vigilance. This is also true in undrugged animals: waking and PS are characterized by a desynchronized EEG, but they constitute different behavioral states and, in many brain areas, neuronal activity fundamentally differs during these two states.

Limitations and unresolved issues

The first question concerning these findings is whether similar modulations of the RF already exist in the

subthalamic stations of the auditory system. Unfortunately, no systematic RF analysis has been carried out so far at these levels; the studies performed by Velluti and colleagues did not answer the question as only one sound frequency was tested at these lower levels. In the cochlear nucleus, increased evoked responses were mainly observed as shifts from waking to SWS (Pena et al. 1992), and equivalent proportions of increases and decreases were found in the lateral superior olive and the inferior colliculus (Morales-Cobas et al. 1995; Pedemonte et al. 1994). In fact, the situation is more complex because the effects observed at a given level such as the inferior colliculus might result from the modifications occurring downstream but also from those occurring upstream. A second puzzling question is whether a progression of the changes also exists within each state of vigilance. Does the deepness of SWS influence the size of the RF and the acoustic threshold, and does the quality of wakefulness influence these parameters? If true, one can envision that there is a continuum across the different states of vigilance and that any functional property of the thalamo-cortical neurons constantly moves along this continuum. Lastly, one can suspect that, in addition to modulating RF properties, the states of vigilance influence the timing of neuronal discharges and of neuronal interactions which can be essential for coding sound parameters. These aspects have not been investigated so far.

Fig. 2A, B Schematic diagram showing the protocol used and the main results obtained in several experiments after behavioral training. **A** The protocol used in many studies is a Pre-Post comparison of the RF obtained before and after a behavioral conditioning. After determination of the neuron frequency tuning at various intensities, one frequency was selected as the conditioned stimulus (CS) predicting the occurrence of the unconditioned stimulus (US). After a few tens of training trials the RF was re-determined and when the re-cording was stable enough the RF was determined 1 h or 24 h later. **B** In most of the cases, this protocol led to selective retuning of the frequency RF at the cortical and at the thalamic level (B1), whereas general effects across the RF were obtained after pseudoconditioning during which the US occurrence could not be predicted by the CS occurrence (B2). Note that the increase in evoked responses at the CS frequency (*d*) could be exactly the same magnitude in the two situations



Effects observed after behavioral training

As several reviews have been published recently on this topic (Weinberger 1995, 1998; Edeline 1999), only the key findings will be presented here. Although it has long been known that the sensory evoked responses exhibited plasticity when an animal is engaged in a learning task (review in Diamond and Weinberger 1987), unambiguous demonstrations that this plasticity reflects a modification in the sensory code have progressively emerged since the end of the '80s. The two initial studies performed by Diamond and Weinberger (1986, 1989) in the cat secondary auditory areas (AII/VE) clearly showed that effects, specific to the conditioned stimulus (CS), occurred after a brief training period (40–70 trials, about 60 min of training) during which a particular sound frequency predicted the occurrence of an unconditioned stimulus (US). In these initial studies, both increases and decreases in evoked responses were observed at the CS frequency, leading either to frequency-specific increases (neuronal re-tuning) or to frequency-specific decreases (notch filters) in the neurons' receptive field. Subsequent studies performed in the primary auditory cortex of guinea pigs confirmed that neurons can be retuned at the CS frequency. Selective facilitations were observed in the neurons' RF after (i) a classical conditioning protocol (Bakin and Weinberger 1990), (ii) a two-tone discrimination training (Edeline and

Weinberger 1993) and (iii) an instrumental conditioning (Bakin et al. 1996). In all these studies, the effects were very selective for the CS frequency, which contrasts with the unspecific increases that were detected after a pseudo-conditioning protocol (see Fig. 2) during which the tone and the unconditioned stimulus were not temporally associated (Bakin et al. 1992). Two time points relative to this selective plasticity have to be kept in mind. First, its induction was rapid and required only a few training trials (5–15 trials, i.e., 10–30 min; see Edeline et al. 1993). Second, this plasticity was almost systematically expressed 1 h after the end of the training (Bakin and Weinberger 1990; Edeline and Weinberger 1993), and in some cases up to 24 h after the training (Bakin and Weinberger 1990; Bakin et al. 1996). Table 1 summarizes the results observed at the cortical level.

If auditory cortex neurons had their best-frequency (BF) re-tuned to the CS frequency, and if this re-tuning lasts long enough after the training period, then the topographic organization should be dramatically modified after a daily training. This rationale has guided the research that has been carried out by Merzenich and colleagues from almost two decades. In a set of outstanding experiments, adult monkeys were submitted to an extensive training period (2–3 months, with several hundreds of trials/day), and the cortical map of primary sensory cortices was tested under general anesthesia. Both in the auditory and in the

Table 1 Percentage of selective and non-selective effects observed at the cortical level after behavioral training

	Cortical area	Protocol	Type of CS and US	Behavioral response (CR)	No. of recordings	% of selective effects	% of non-selective effects
Diamond and Weinberger 1986, 1989	AII/VE	Classical conditioning	Pure tone, footshock	Pupillary dilatation	19	68%	32%
Bakin and Weinberger 1990	AI	Classical conditioning	Pure tone, footshock	None	10 ^a	70%	30%
Bakin et al. 1992	AI	Sensitization ^b	Pure tone, footshock	None	12 ^a	0%	100%
Edeline and Weinberger 1993	AI	Two tone discrimination	Pure tone, footshock	Bradycardia	41 ^a	48%	52%
Edeline et al. 1993	AI	Classical conditioning	Pure tone, footshock	Bradycardia	33 ^a	33%	67%
Bakin et al. 1996	AI	Instrumental training	Pure tone, footshock	Avoidance response	25 ^a	52%	48%
Ohl and Scheich 1996	AI	Classical conditioning ^c	Pure tone, tail shock	Non-specific bradycardia	35	63%	37%
Ohl and Scheich 1997	AI	Classical conditioning ^c	Pure tone, tail shock	Non-specific bradycardia	69	(x) ^e	(x) ^e
Kisley and Gerstein 2001	AI	Classical conditioning ^d	Pure tone, brain stimulation	None	33	18%	82%

^aEach recording was tested at 3–10 intensities, leading to many sets of data for the same cell

^bThe protocol involved unpaired presentations of the unconditioned stimulus (US) with an acoustic stimulus in seven cases and with a visual stimulus in five cases

^cIn these experiments, the RF were continuously tested, and during some tests a particular frequency was associated with the US presentation. Thus, the period of conditioning was not dissociated from the period of RF determination

^dThe conditioning protocol involved pairing between a particular tone frequency and a stimulation of the medial forebrain bundle

^e(x) The data were analyzed as a group and it was not specified what proportion of cells showed a selective effect

somatosensory cortex, enlarged map representations were reported after behavioral training. In a first experiment, the training required that the animal touched a rotating disk for a brief period of time (45 s) with a limited sector of the distal phalange of one (or of two) finger(s) to obtain an appetitive reward (Jenkins et al. 1990). In a second experiment, the training required that the animal discriminated differences in the frequency of tactile stimulation delivered on a particular point of the hand (Recanzone et al. 1992). In both experiments, enlarged cortical representations were observed in favor of the trained skin surface. In auditory cortex, an enlargement of the tonotopic map organization was found after a 3-month training in a perceptive discrimination task involving auditory stimuli (Recanzone et al. 1993). In this task, adult monkeys had to distinguish between pairs of stimuli made of two identical tone frequencies (the S1 stimulus) and pairs made of two slightly different frequencies (the S2 stimulus). Correct detection of the S2 stimulus allowed the animal to obtain a food reward, but this S2 stimulus was modified from session to session, being harder to detect each time the animal reached a level of 70% of detection. The number of cortical sites responding to the frequency of the S1 stimulus was greater in the trained animals, leading to an increase of the cortical area corresponding to the trained frequency. Also, it was noted that the Q10dB (an index of the sharpness of tuning) was greater in trained than in control animals. Finally, the minimum latency of the evoked responses was increased in the trained animals, which might indicate that a recruitment of connections underlies the effects observed on the cortical map organization.

It might be wrong to assimilate learning-induced RF plasticity detected after a short training session and cortical map reorganizations revealed after extensive perceptual training. Although rapid RF plasticity and map reorganizations after extensive training both involve facilitated processing of behaviorally important frequencies, distinctions should be made because these situations involve different operations and the cortical machinery might process acoustic information quite differently (for review on this point see Weinberger, in press). However, this distinction should not prevent the main conclusion from being reached: sensory cortex exhibits a highly selective plasticity in learning situations ranging from a few trials in a classical conditioning paradigm up to thousands of trials delivered in perceptual learning tasks. Thus, it is unwise to state that rapidly acquired memory exclusively concerns non-sensory structures such as the amygdala (Fanselow and Ledoux 1999), as it is to envision that performance improvement in perceptual tasks mainly results from top-down processes (see discussions in Gilbert et al. 2001).

Intrinsic cortical plasticity or thalamo-cortical plasticity?

Because (i) map reorganizations were only described at the cortical level, (ii) because the cortex is viewed as the last

and most complex stage of sensory processing, and (iii) because its laminar structure seems more sophisticated than the anatomical organization of the subcortical relays, the temptation is great to envision that learning-induced cortical plasticity results from intrinsic cortical reorganizations. However, this view is challenged by the fact that there are as many experiments showing learning-induced plasticity at the thalamic and at the cortical level (for a review see Edeline 1999). More importantly, RF plasticity was observed at the thalamic level and was as selective as the one observed at the cortical level (see Table 2, Fig. 3). It was present in the three main anatomical divisions of the auditory thalamus (Edeline and Weinberger 1991a, 1991b, 1992); the only difference between these three divisions was that the selective effects were long lasting in the two non-lemniscal divisions (MGd and MGm), whereas they were short lasting in the lemniscal division (the MGv). Several explanations can be proposed to account for this different temporal decay. First, the two non-lemniscal divisions receive more non-auditory inputs (Ledoux et al. 1987; Bordi and Ledoux 1994) which might contribute to the duration of the learning-induced plasticity. However, that the MGm receives non-auditory inputs is usually considered as an explanation for the induction of the plasticity (Weinberger et al. 1990), not as an explanation for its duration. A second possibility is that the strength of GABAergic inhibitions differs between the lemniscal and the non-lemniscal divisions¹ and controls the decay of the plasticity. This possibility is supported by two different sets of data. First, in anesthetized (Calford 1983; Bordi and Ledoux 1994; Morel et al. 1987) and unanesthetized animals (Edeline et al. 1999), MGv neurons exhibited sharper frequency RF than MGd and MGm neurons, which can result from stronger GABAergic inputs onto these cells.² Second, it was shown that recruitment of layer IV GABAergic neurons prevents the induction of long-term plasticity in the visual cortex, whereas by-passing these inputs allows long-lasting plasticity to develop in the visual cortex (Kirkwood and Bear 1994).

It is important to point here that, because learning-induced plasticity dissipated over time in the lemniscal division (MGv), whereas it lasted up to 24 h in the primary auditory cortex, it is unlikely that thalamic plasticity passively reflects cortical plasticity. If the cortex was imposing its plasticity on the thalamus via the cortico-thalamic afferences, the temporal decays should be the same in the cortex and in the thalamus. This independence was confirmed by the effects obtained in the bat inferior colliculus. When unit recordings were performed in the auditory cortex and inferior colliculus of awake bats after a conditioning protocol, shifts in best frequency were

¹The fact that parvalbumin immunoreactivity, almost exclusively limited to the neuropil, is much stronger in MGv than in any other divisions pleads in favor of this possibility (Cruikshank et al. 2001).

²Note that this GABAergic input can come from the inferior colliculus, from the thalamic reticular nucleus, or from the intrinsic MGB interneurons whose proportion varies from 33% of the cells in the cat to less than 1% in the rat (Huang et al. 1999; Winer and Larue 1988).

Table 2 Percentage of selective and non-selective effects observed at the thalamic level after behavioral training

	Area	Protocol	Type of CS and US	Behavioral response (CR)	No. of recordings ^a	% of selective effects	% of non-selective effects
Edeline and Weinberger 1991a	MGd	Classical conditioning	Pure tone: footshock	Bradycardia	38	55%	32% ^b
Edeline and Weinberger 1991b	MGv	Classical conditioning	Pure tone: footshock	Bradycardia	17	29%	71%
Edeline and Weinberger 1992	MGm	Classical conditioning	Pure tone: footshock	Bradycardia	29	48%	52%
Lennartz and Weinberger 1992	MGB ^c	Classical conditioning ^c	Pure tone: footshock	None	28	18% ^d	11%

^aEach recording was tested at 3–10 intensities, leading to many sets of data for the same cell

^bIn this experiment, five recordings were classified as “random” changes which corresponded to cases of “stability” (absence of obvious changes in the neuron RF)

^cData were from all the anatomical subdivisions of the MGB and the neuron RFs were tested before and after training under ketamine anesthesia

^dThe quantification of the data set indicated 5 complete shifts of the CS frequency which corresponded to selective effects and 18 partial shifts which were not equivalent to CS-specific effects but were also not non-specific (general) changes. One can even envision that these partial shifts observed under ketamine anesthesia might be CS-specific effects whose specificity was altered by the anesthesia

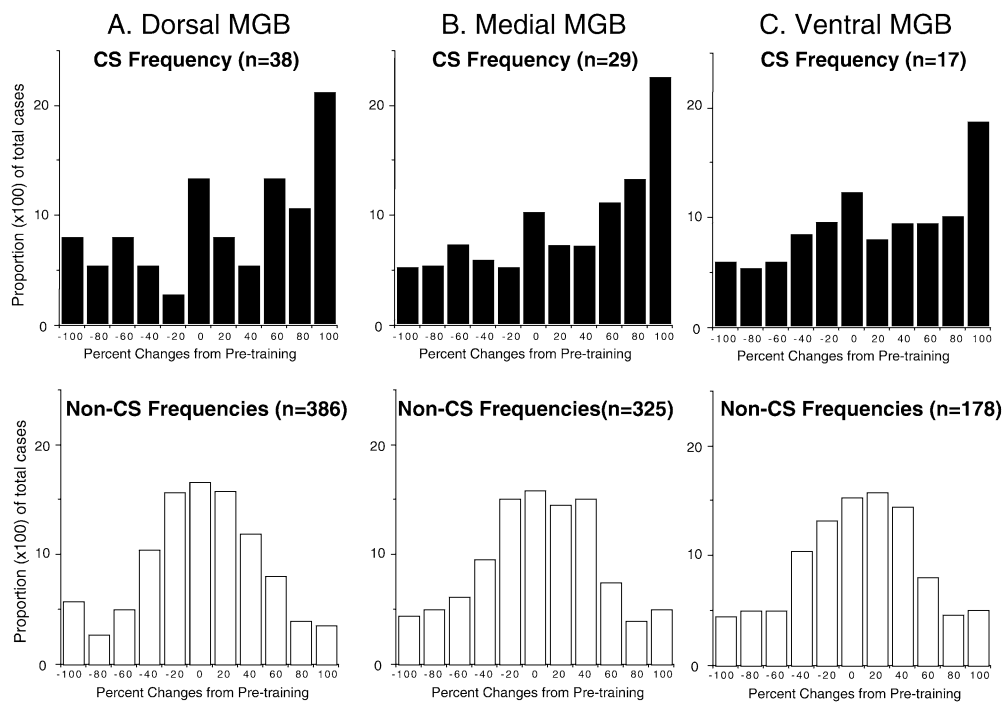


Fig. 3A–C Group data obtained in the three main divisions of the auditory thalamus after behavioral training. Distributions of normalized difference scores obtained for the CS frequency (paired with the US) and for the non-CS frequencies (non-paired with the US). For each recording, the response to the frequency which displayed in the post-training RF the maximum change 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. In the three divisions, similar effects were observed immediately post-training. For the CS frequency, the distributions differed significantly from a normal

distribution centered around 0% change, due to recordings exhibiting $+100\%$ changes. For the non-CS frequencies, the distribution was not significantly different from a normal distribution centered around 0%. The two distributions were significantly different ($\chi^2=40.13$, df 10 $p<0.0001$; $\chi^2=25.85$, df 10, $p<0.001$ and $\chi^2=20.56$, df 10, $p<0.003$ for the dorsal, medial and ventral divisions, respectively). Note that the effect dissipated over time in the ventral division whereas it was long-lasting in the dorsal and medial divisions. (From Edeline and Weinberger 1991a, b; 1992, unpublished observations)

observed both at the cortical and at the collicular level. Here too, different temporal decays were observed: the cortical changes lasted more than 7 h but the collicular changes lasted only 2–3 h (Gao and Suga 2000). However, because an inactivation of the auditory cortex during conditioning abolished the collicular shift, it was proposed that the collicular plasticity is produced by the corticofugal system (Gao and Suga 1998). Note that subsequent experiments showed that, in fact, inactivation by muscimol of the somatosensory cortex prevents plasticity in both auditory cortex and inferior colliculus (Gao and Suga 2000). Although these findings have to be viewed against the fact that muscimol (as any other compound injected in the brain at high concentration) can travel a considerable distance from its injection site (Edeline et al. 2002), such studies led to important working hypotheses concerning the role of the corticofugal system (Suga et al. 2000; Sakai and Suga 2002) and should promote future research on the relationship between cortical and subcortical plasticity.

A context-dependent plasticity?

A point that needs to be discussed with regard to the previous and following sections is whether or not this learning-induced sensory plasticity observed at the RF and at the map level can be expressed outside the training situation. Two situations have to be distinguished here. On the one hand, some studies have mentioned that learning-induced RF plasticity can be differentially expressed depending on the behavioral context where the plasticity is tested. On the other hand, other studies have tested RF or map plasticity in another brain state than the one presenting during the induction of the plastic changes. Although the term “context” has such a versatile use that its meaning has become difficult to define, these two types of experiments are discussed here within the same section mainly because changing the “behavioral context” affects the brain state during which the plasticity is tested.

In their seminal paper, Diamond and Weinberger (1989) pointed out that the selective RF alterations observed after classical conditioning were “context-dependent”. In that case, it indicates that the changes observed in post-training RF determination were not a function of the changes detected during the training trials. In other words, decreased responses could be observed during the training trials, whereas selective increased responses could be observed after training (see, for example, Diamond and Weinberger 1989, Figs. 12, 13).³ Note that these “context-dependent effects” led Ohl and Scheich (1996, 1997) to develop a protocol where one particular frequency was associated with the presentation of the US during tests of the RFs. Elimination of contextual effects was the positive aspect of this design; the negative one was that the selectivity of the behavioral acquisition is uncertain. Using

³Selective re-tunings in favor of the CS without increases (or even with decreases) in evoked responses during the training trials were also observed in the auditory thalamus, particularly in the dorsal division (Edeline and Weinberger, unpublished observations).

this protocol, a different type of selective effects was described: Instead of being the largest changes in the FRF, the CS was in a valley surrounded by two selective increases, thus allowing formation of a local gradient centered on the CS frequency.

In contrast, the map reorganizations described after extensive training were clearly not “state-dependent”: they were detected in anesthetized animals whereas the training was performed in fully awake animals (Recanzone et al. 1993). One can suspect that the difference with the “contextual effect” described above simply results from the large difference in amount of training that was imposed on the animals. After a brief training period, the effects could be “context-dependent” (Diamond and Weinberger 1989), whereas after extensive training they could be “context-independent” (Recanzone et al. 1993). This explanation might be correct but is contradicted by several findings. First, after a brief classical conditioning protocol performed in the waking state, selective RF reorganizations were observed under ketamine anesthesia using either an aversive (Lennartz and Weinberger 1992) or an attractive reward (stimulation of the medial forebrain bundle; Kisley and Gerstein 2001). Second, a set of experiments carried by Hennevin and colleagues has demonstrated that learning-induced plasticity obtained in the auditory thalamus can be expressed during the subsequent paradoxical sleep (PS) episodes, i.e., during a state that differs from waking both from the behavioral and neurochemical point of view. In these experiments, an increased responsiveness of MGB neurons was observed during an aversive classical conditioning experiment performed in waking animals. When the conditioned stimulus was presented alone during the PS episodes following training, MGB cells exhibited larger responses compared with those obtained during PS before the tone became significant (Hennevin et al. 1993, 1998). Similar findings were recently replicated after appetitive conditioning (Maho and Hennevin 2002). These results strongly suggested that the expression of neuronal plasticity occurring in the waking state can transcend its conditions of induction and can be expressed later in another brain state (see Fig. 5).

Relations with behavioral performances?

A second important question concerns the relationships between the neural changes and the animal behavioral responses and/or performance. At the single unit level, some observations argue against a direct relationship (Fig. 4). First, selective or non-selective effects developed at the thalamic level independently of the behavioral responses (Edeline and Weinberger 1991a). Second, during a discrimination task that was either easy or difficult for the animal, no relationship could be found between the neuronal re-tuning of auditory cortex neurons and the behavioral response (Edeline and Weinberger 1993). Also, in the situation designed by Ohl and Scheich (1996, 1997), the animals did not express selective

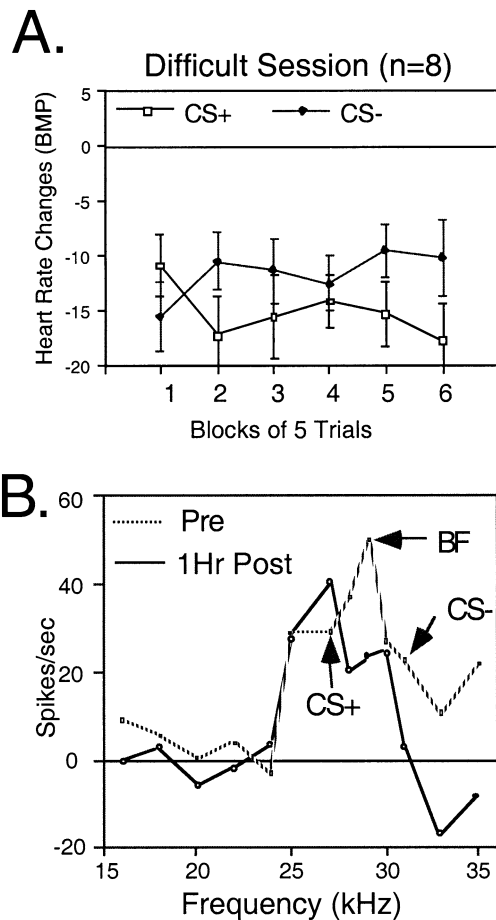
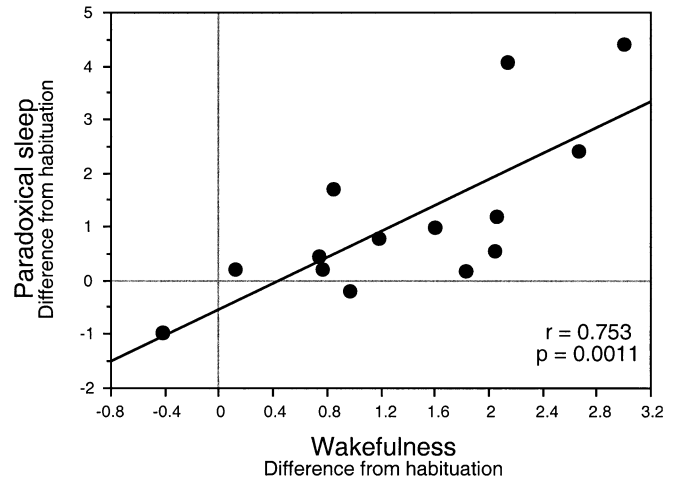


Fig. 4A, B Dissociation between the behavioral performance and RF plasticity obtained in the auditory cortex after a single training session of discrimination. The animals were first trained in an easy discrimination task during which all subjects expressed different behavioral responses to the CS+ and the CS-. They were subsequently trained in a difficult discrimination task where they did not express different behavioral responses to the CS+ and the CS- (**A**). However, the percentage of recordings exhibiting a selective re-tuning in favor of the CS+ frequency was similar during the first and the second recording sessions. A selective re-tuning in favor of the CS+ frequency is shown in **B**. This indicates that the RF plasticity of auditory cortex neurons transcended the behavioral expression of the conditioned responses. (Modified from Edeline and Weinberger 1993)

behavioral responses to the CS frequency, but selective effects were detected in the auditory cortex.

In contrast, in a frequency discrimination task, the effects observed at the cortical map level show a clear relationship: the better the performance at the last training session the larger the frequency map enlargement (Recanzone et al. 1993). Obviously, these two sets of results differ by the way the behavioral responses were quantified: after several tens of training trials, learning was indexed by conditioned responses (vegetative indices in all but one case), whereas after extensive training the performances were quantified in terms of numbers of hits and false alarms, using the tools of the signal detection theory (Green and Swet 1966). These measures might

A. Fear conditioning



B. Appetitive conditioning

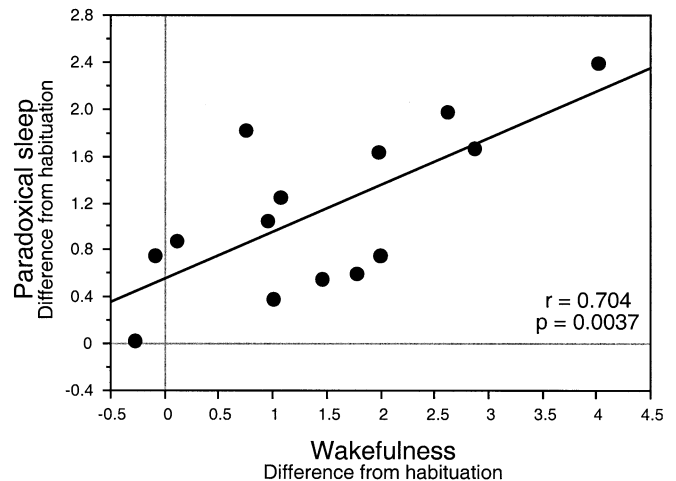


Fig. 5A, B Relationship between the expression of auditory thalamus plasticity in wakefulness and in paradoxical sleep (PS). Learning-induced changes were computed relative to the responses obtained before training during an habituation session (during which the tone was neutral) performed both during wakefulness and during PS. The changes obtained during waking were plotted against the changes obtained during PS. Both during fear conditioning (**A**) and during appetitive conditioning (**B**) there was a clear relationship between the changes obtained during training in wakefulness and the changes obtained during PS post-training. Data are modified from Hennevin et al. (1998) and from Maho and Hennevin (2002)

index very different levels of processing of a significant stimulus.

However, these results can be reconciled if we consider that, in an initial stage of learning, after a few tens of training trials, thalamic and cortical RF are re-tuned selectively to the frequency of the significant stimulus even if the animal does not express signs of behavioral discrimination. In a second stage, after 2–3 months of training, map reorganization can be detected, and at this time neural changes in auditory cortex correlate with behavioral performance. This view is derived from the one

that has been proposed to account for the effects observed after motor skill learning and perceptual learning (see for discussion Karni et al. 1998; Hauptmann and Karni 2002). Such a conception is reinforced by the results obtained using local EEG patterns derived from 18 positions in the auditory cortex during a categorization task. The animals could discriminate the sounds within a training session, but categorization required much longer training and occurred simultaneously with the stabilization of dynamic patterns in the auditory cortex (Ohl et al. 2001).

Finally, recent findings revealing the lack of relationship between sensory plasticity and behavioral performance require comment. It was shown that with appropriate parameters, intracortical microstimulations can produce map and RF changes (Dinse et al. 1993; Maldonado and Gerstein 1996). However, when the animals' performance was tested in a frequency discrimination task before and after this treatment, the discrimination performance was found unaffected (Talwar and Gerstein 2001). Although such results could be interpreted as the evidence that auditory cortex plasticity is unrelated to behavioral performance, it should be considered as a warning against the "Cartesian" conception of the brain. As with many areas of the brain, sensory cortices have a very high potential of plasticity and, therefore, many protocols can trigger plasticity. But, when this plasticity is induced in a context which has no behavioral significance, it can neither be used by the animal nor influence its performance. In fact, rather than demonstrating the lack of relationship between sensory cortex plasticity and behavior, these findings suggest that lumping together learning-induced plasticity and artificial forms of plasticity can only lead to confusion in an already complex area of research.

Relationship between RF and map?

One question remains open, not only in the field of learning-induced sensory plasticity but, more generally in the field of sensory physiology: to what extent are the RF properties determined at suprathreshold intensities related to the cortical map organization? This point needs discussion because selective learning-induced RF changes were mostly reported at suprathreshold intensities, whereas map reorganizations were always determined at threshold. It is commonly assumed that a relationship exists between RF selectivity and map organization, but some findings obtained in the auditory cortex contradicted this assumption. The cortical area responsive to a given suprathreshold stimulus (e.g. a 70-dB tone) could not be predicted from the threshold map (Phillips et al. 1994; see for discussion Calford 2002). Thus, it seems speculative to conclude about map organization and, *a fortiori*, about map reorganizations on the only basis of RF modifications occurring at suprathreshold intensities. This is particularly important given that future research will probably use less invasive techniques (such as the intrinsic signal, or the fMRI) to study map reorganizations after

behavioral training. Even if efforts were made to conciliate the results obtained with these techniques and the electrophysiological results (Bakin et al. 1996; Das and Gilbert 1995) strong discrepancies still exist (Spitzer et al. 2001).

To conclude, it appears that the links between RF plasticity, map re-organization and behavioral performance still need clarification. Clarifying (i) the relationship between changes occurring at the neuronal scale and those occurring at the map scale and (ii) the relationships between these changes and behavior still remains an important challenge for future investigations.

Effects of neuromodulators: toward cellular mechanisms?

In this section, it is essential to consider that two very different strategies have been employed to study the effects produced by neuromodulators on sensory coding. In both strategies, most of the data came from anesthetized animals, and most of the studies have recorded neurons in sensory cortices rather than in subcortical sensory relays.

The first strategy aims at describing the effects obtained on sensory processing during local application of a neuromodulator without specific temporal association between the sensory stimuli and the neuromodulator application. The results obtained with this paradigm were usually compared with those obtained when an animal is suddenly aroused, or when shifts in state of vigilance occur.

The second strategy aims at describing the effects induced when presentation of a particular stimulus is temporally correlated with either the application of a neuromodulator or the activation of a neuromodulatory system. In this case, the goal is to examine to what extent the temporal association between the stimulus and the neuromodulator induces an effect, "a plasticity", that is specific for that particular stimulus. Explicitly or implicitly, these studies want to mimic learning situations (more precisely a classical conditioning situation) during which a particular stimulus becomes significant. These two strategies lead to different expectations, not only in terms of selectivity of the effects but also in terms of duration of the effects. When using the first strategy, a progressive recovery from the effect obtained during drug application is supposed to occur during the post-drug application period. In contrast, using the second strategy, a lack of recovery after completion of the pairing protocol is usually interpreted as a long-lasting plasticity triggered by the pairing between the neuromodulator and the sensory stimulus.

The following sections will focus on the effects produced by applications of acetylcholine and of noradrenaline. This bias mainly reflects the large number of published works using these two neuromodulators; other fundamental neuromodulators, such as dopamine and serotonin, have not been extensively studied in sensory systems (but for examples using the first strategy see

Waterhouse et al. 1986; and for examples using the second strategy see Bao et al. 2001).

Effects obtained without explicit pairing protocol

When one looks at the experiments using the first strategy, it quickly appears that, paradoxically, the cholinergic and the aminergic systems—two major neuromodulatory systems involved in awaking—act in opposite directions. This dichotomy was already noted in initial iontophoretic studies: whereas application of acetylcholine (ACh) was found to increase the spontaneous firing rate (Krnjevic and Phillis 1963a, 1963b), application of monoamines such as noradrenaline (NA) decreased it (Krnjevic and Phillis 1963c). Studying the evoked responses in the somatosensory, visual and auditory cortices, subsequent studies have extensively confirmed this dichotomy (Fig. 6). Application of ACh increased the evoked responses (Sato et al. 1987; Lamour et al. 1988; Metherate et al. 1988), whereas NA application depressed them (Foote et al. 1975; Videen et al. 1984; Kolta et al. 1987; Manunta and Edeline 1997). Note that a few studies replicated these findings in undrugged animals (Foote et al. 1975; Bassant et al. 1990a, 1990b; Manunta and Edeline 1999), which argues against the possibility that the anesthetics change the balance between depolarizing and hyperpolarizing effects produced by ACh and NA.

More important are the effects on functional properties such as the neuronal threshold and the selectivity for a particular dimension of a sensory stimulus, two parameters

traditionally determined to assess sensory processing. As for the effects on the evoked response, the cholinergic and noradrenergic modulation apparently induced opposite effects on the neurons' threshold. Iontophoretic application of ACh unmasked receptive fields in the somatosensory cortex (Lamour et al. 1988), and decreased the neurons' threshold in the auditory cortex (Metherate et al. 1990). Conversely, increases in neuronal threshold were usually obtained using NA application. The "gating" effect—a facilitation of subthreshold responses leading to decreased threshold—proposed by Waterhouse et al. (1988) was confirmed neither by subsequent extracellular recording studies (Edeline 1995; Manunta and Edeline 1998), nor by a recent intracellular study (Ego-Stengel et al. 2002). Also, an extension of a decreased threshold should be that sensory neurons extract more easily sensory signals from the continuous background activity that exists in the central nervous system. Although Waterhouse and colleagues stressed the fact that NA enhanced the so-called "signal-to-noise ratio" (Waterhouse and Woodward 1980; Waterhouse et al. 1981, 1988), other studies showed that in most of the cases iontophoretic NA applications did not change this ratio (Videen et al. 1984; Sato et al. 1989; Warren and Dykes 1996; Manunta and Edeline 1997, 1999; Ego-Stengel et al. 2002).

Contrasting with their opposite effects on the response strength and on neuronal threshold, ACh and NA seem both capable of improving the neuronal selectivity for a particular dimension of the stimulus. For example, ACh application in visual cortex enhanced the orientation and direction selectivity (Sillito and Kemp 1983; Murphy and

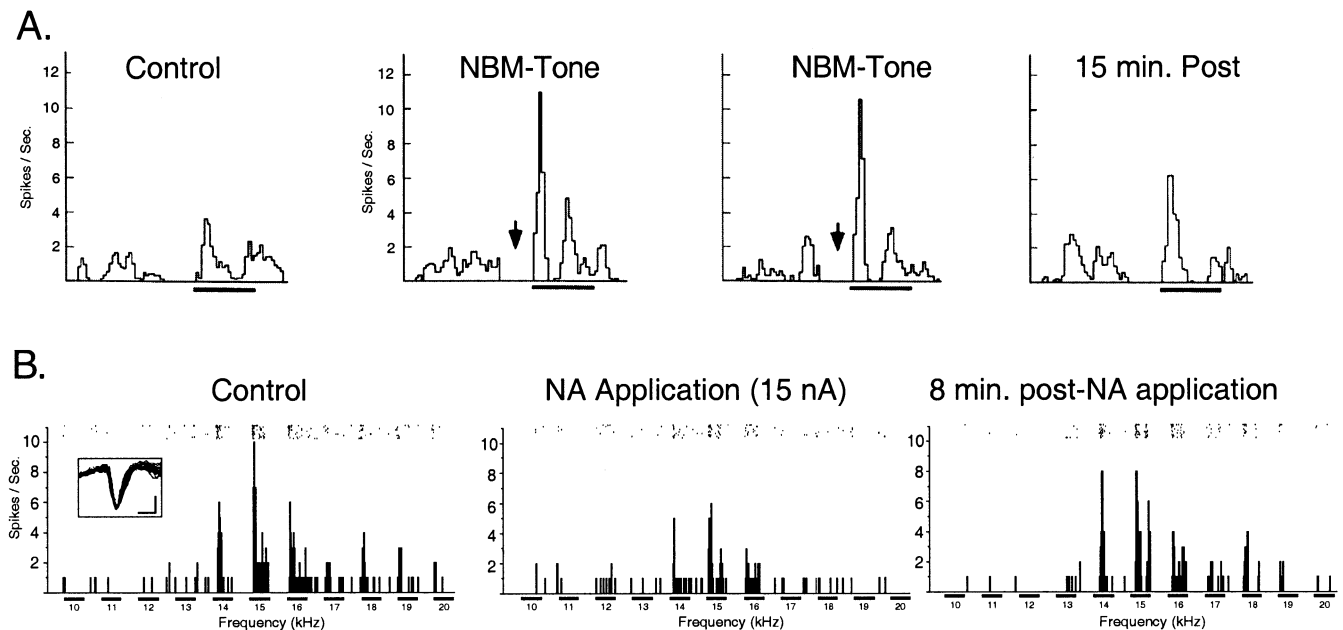


Fig. 6A, B Opposite effects of acetylcholine and of noradrenaline in the auditory cortex. **A** When nucleus basalis (NB) neurons were activated (*arrow*) just before (30–50 ms) the presentation of an acoustic stimulus, the evoked responses were facilitated relative to the control situation without NB activation. As few as 20 pairing trials were able to facilitate the evoked responses for a period of 15 min after the last pairing trial (modified from Edeline et al.

1994a). **B** When NA was iontophoretically applied at the vicinity of a cortical cell, the evoked responses were depressed and the frequency range to which the cell responded was smaller. The effects lasted for a few minutes and a recovery was usually observed in less than 15 min (in the present case, the responses recovered in 8–10 min). (Modified from Manunta and Edeline 1999)

Sillito 1991). In the auditory cortex ACh (or anticholinesterase) application facilitated the responses for the neurons' best frequency and for the adjacent frequencies, without generating general changes across the frequency RF (Ashe et al. 1989; McKenna et al. 1989). An increase in selectivity was also observed in the visual thalamus: ACh can enhance the contrast between the responses obtained when a stimulus fell in excitatory zones and inhibitory zones of the receptive field (Sillito et al. 1983). Iontophoretic application of NA also improved the functional selectivity in several cortical areas. In the auditory cortex, the suppressive effect of NA promoted an increase in frequency selectivity in anesthetized and unanesthetized animals (Edeline 1995; Manunta and Edeline 1997, 1999). In the visual cortex, NA application was found to improve the velocity and direction selectivity without modification of the orientation selectivity (McLean and Waterhouse 1994). Recently, this lack of effect on orientation selectivity was confirmed despite strong attenuation of the evoked responses (Ego-Stengel et al. 2002). These authors proposed that, contrary to a subtractive effect which would lead to an increased selectivity, the action of NA is rather a divisive effect (i.e. a gain control), which affects the level of cortical responsiveness without affecting the functional selectivity. These results point out that potentially the effects of NA (and may be of any other neurotransmitter) can differ depending on the stimulus dimension. For example, a dimension that critically depends on the thalamo-cortical afferences (such as the frequency tuning in the auditory cortex, or the size of the RF in the visual cortex) could be more affected than a dimension which relies more on the cortico-cortical afferences (such as frequency modulation tuning in the auditory cortex, or the velocity tuning in the visual cortex). This possibility is supported by the fact that, in several areas, testing different inputs converging at the same cortical location revealed that both NA and ACh can strongly attenuate the synaptic responses of one input while exerting less suppression on, or even enhancing, the responses of the other input (Hasselmo et al. 1997; Hsieh et al. 2000).

Other factors, which are crucial for sensory coding, such as the temporal aspects of neuronal discharges, have been often ignored by the studies looking at the effects of neuromodulators. For example, in the lower levels of the auditory system, it was reported that NA decreased the latency variability of evoked responses (Kössl and Vater 1989), a factor that is fundamental for sound localization and for the detection of frequency modulated sounds. That the noradrenergic modulation influences the timing of cortical processing was recently confirmed by simultaneous analysis of current source density and single unit responses (Lecas 2001, 2002). Phasic activation of LC neurons produced (i) a compression of the supragranular sink responses which appeared sooner and had a shorter duration than in the control situation, and (ii) a reduction of both the single unit response latency and its variability. Lastly, it is important to determine how the neuromodulatory systems influence the between-cell function inter-

actions, another aspect of neuronal processing by which neurons can code for additional dimensions of a stimulus (see, for example, Ahissar et al. 1992b; DeCharm and Merzenich 1996). In this line, it is worth mentioning that ACh application can produce significant changes in cross-correlations without concomitant changes in average firing rate, or changes in autocorrelations, suggesting that the cholinergic modulation can affect cortico-cortical or thalamo-cortical connections without affecting neuronal excitability (Shulz et al. 1997).

In conclusion, these studies point out that whatever their effects on the spontaneous and evoked activity and on the signal/noise ratio, neuromodulators usually enhance the neurons' functional selectivity for a particular dimension of the stimulus. These studies are extremely useful because they described the potential contribution of a given neuromodulator to the changes observed at arousal, or when the animal state of vigilance shifts from SWS to W. The characterization of the pharmacological profile of the effects performed in several studies indicates which types of receptors (and sometimes which subtypes) are responsible for the modulation observed in a given structure (see Metherate et al. 1990; Warren and Dykes 1996; Manunta and Edeline 1997).

Effects obtained with pairing protocols

The second, and most popular, strategy used extensively over the last decade involved a temporal association, "a pairing", between presentation of sensory stimuli and the application of a given neuromodulator. Initial studies have associated iontophoretic application of ACh and presentation of somatosensory stimuli (Metherate et al. 1987, 1988). In many cases (42/52 cells in Metherate et al. 1988), evoked responses were facilitated for periods of time ranging from a few minutes up to 1 h. When performed in the auditory cortex, the same protocol generated slightly different results: if pairing between ACh and a particular tone frequency did produce effects selective for that frequency, selective decreases were more frequent than selective increases (Metherate and Weinberger 1989, 1990). Immediately after these pioneering investigations, an impressive number of studies have described the facilitatory effects produced by associations between a sensory stimulus and the activation of the main source of cortical ACh, the nucleus basalis magnocellularis (NBM). Both in the somatosensory (Rasmusson and Dykes 1988; Tremblay et al. 1990; Webster et al. 1991) and in the auditory cortex (Metherate and Ashe 1991; Hars et al. 1993; Edeline et al. 1994a, 1994b; Bakin and Weinberger 1996; Bjordahl et al. 1998; Dimyan and Weinberger 1999), such a pairing facilitated the sensory evoked responses. This effect was obtained using evoked potentials (Rasmusson and Dykes 1988; Metherate and Ashe 1991), multi-unit (Hars et al. 1993; Edeline et al. 1994a, 1994b) or single unit recordings (Tremblay et al. 1990).

The most remarkable feature of the plasticity induced by the pairing between NBM activation and sensory stimuli is its important selectivity. In auditory cortex, several studies have shown that the tone-NBM pairing produced very specific modifications in the neurons' RF (Bakin and Weinberger 1996; Bjordahl et al. 1998; Dimyan and Weinberger 1999). Also, after 2 or 3 weeks (with several hundreds of pairings per day), the cortical map was selectively enlarged for the representation of the frequency associated with the NBM stimulation (Kilgard and Merzenich 1998a). These selective effects can also affect the temporal properties of neuronal responses. When a particular rhythm of presentation of the acoustic stimuli (15 Hz for example) was associated with the NBM activation, the best repetition rate of auditory cortex neurons was shifted from its normal range (1 and 7 Hz) to higher rates (above 10 Hz) of stimulus presentation (Kilgard and Merzenich 1998b). A similar effect was subsequently described in the somatosensory cortex after iontophoretic applications of ACh: the tuning of barrel cortex neurons to the temporal frequency of whiskers' deflections was selectively modified after a short period of association between ACh application and a fixed temporal frequency (Shulz et al. 2000; Ego-Stengel et al. 2001). In these experiments, the normal low-pass band characteristic of cortical neurons was transformed in a band-pass filter centered on the frequency associated with ACh application.

At first glance, these characteristics resemble those obtained after behavioral training. Thus, the temptation is great to compare these effects with those triggered by a behavioral training protocol, and, implicitly, to propose that learning-induced plasticity is the direct consequence of the activation of NBM neurons. This temptation is accentuated by the finding that NBM stimulation could, by itself, be used as an unconditioned stimulus and produce behavioral conditioning as attested by several central and peripheral indices (McLin et al. 2002). However, as we will see in the following paragraphs, these questions remain open and require more investigations.

Efficacy, duration and "context dependency" of these effects

It is first interesting to compare the efficacy and duration of the effects triggered by the pairing protocols involving neuromodulators with those produced by behavioral training. In both cases, the efficacy seems high. As few as 15 training trials were enough to produce selective RF plasticity after behavioral training (Edeline et al. 1993). Similarly, 20 associations between NBM stimulation and acoustic stimuli were found to be efficient to facilitate the evoked responses for a short period of time (Edeline et al. 1994a). Also, if one compares the extent of cortical map expansion after behavioral training (Recanzone et al. 1993) and after NBM-induced plasticity (Kilgard and Merzenich 1998a), it seems that the cholinergic mechanisms can, by themselves, produce a plasticity as large (or

even larger) as that triggered by behavioral training. After learning protocols, long-lasting effects (1–24 h) were almost systematically observed.⁴ After pairings between NBM and sensory stimulation, facilitations could be observed up to a few hours (Rasmusson and Dykes 1988; Tremblay et al. 1990; Bakin et al. 1996; Bjordahl et al. 1998; Dimyan and Weinberger 1999). However, it is worth mentioning that in some cases, the effects dissipated after a few minutes (Hars et al. 1993; Edeline et al. 1994a, 1994b).⁵

In the previous section, we saw that learning-induced plasticity was found to be "state dependent" in some studies. Similarly, the plasticity triggered by pairings between neuromodulators and sensory stimuli was found to be "state-dependent" or not. On the one hand, the clearest evidence in favor of a state dependency came from the studies performed by Shulz and colleagues. Pairing whisker deflection at a particular rate with iontophoretic application of ACh led to selective modifications of the tuning to the rate of whisker deflection, which were expressed only when this tuning was tested in the presence of ACh (Shulz et al. 2000; Ego-Stengel et al. 2001). This indicates that the expression of this plasticity required conditions that are similar to those present during its induction. However, using a similar protocol, selective plasticity of auditory cortex neurons was observed without ACh being present (Metherate and Weinberger 1989, 1990). On the other hand, the clearest evidence against a state-dependency plasticity came from the selective map reorganizations obtained after several weeks of pairings. Although the pairing was daily performed on undrugged rats (in a behavioral state that was not specified), selective effects were obtained under depth pentobarbital anesthesia (Kilgard and Merzenich 1998a, 1998b; Kilgard et al. 2001) when the cholinergic system is largely depressed.

Unresolved issues: temporal constraints and pharmacological profile

Two important issues remained unresolved. First, one should consider that very few studies tried to investigate how precise should be the temporal relationship between presentation of the sensory stimulus and the cholinergic activation. Many studies have used a pairing protocol during which the NBM activation preceded the presentation of the sensory stimulus (Tremblay et al. 1990a, 1990b; Metherate et al. 1991; Webster et al. 1991; Hars et al. 1993; Edeline et al. 1994a, 1994b), whereas others used a pairing protocol during which the sensory stimulus preceded the NBM stimulation (Bakin and Weinberger 1996; Bjordahl et al. 1998; Dimyan and Weinberger 1999). Only two studies have compared the magnitude of the effects obtained using various intervals between NBM

⁴The only exception was from the ventral division of the auditory thalamus where the selective effects tended to dissipate over time.

⁵Initial works have already pointed out that the different duration of the effects can be observed from one cell to another (Metherate et al. 1988a).

stimulation and the sensory stimulus (Rasmusson and Dykes 1988; Metherate and Ashe 1991). Facilitation of evoked potentials was optimum when NBM stimulation preceded the somatosensory stimulus by a few tens or a few hundreds of milliseconds, but no comparison was made with a situation where the NBM stimulation is delivered after the sensory stimulus.

Second, contrasting with the detailed pharmacological analyses usually performed when neuromodulators were applied without pairing protocols, the "pairing" studies did not always characterize precisely their effects, leading to uncertainties about the pharmacological nature of the plasticity. In most of the studies, the only control involved repeating the same protocol after either systemic (Rasmusson and Dykes 1988; Hars et al. 1993; Edeline et al. 1994a, 1994b; Bakin and Weinberger 1996) or local (Metherate et al. 1989, 1990; Shulz et al. 2000; Miasnikov et al. 2001) injections of atropine.⁶ Pharmacologists will argue that atropine is not convincing in proving the cholinergic nature of an effect, because it can induce direct, depressive ("anesthetic") effects (Krnjevic and Phillis 1963a, McLennan and Hick 1978; see also for discussion Tremblay et al. 1990a). Under high doses of atropine, one wonders if the neurons still have a normal spontaneous firing rate, and/or if any effect produced by non-cholinergic mechanisms is not also blocked. This is particularly important given that the NBM is not an homogeneous nucleus. It contains non-cholinergic cells (including GABAergic cells) that also project to the cortex (see for review Sarter and Bruno 2002). Thus, it is essential to know to what extent the RF and map modifications indeed result from a cholinergic effect and not from combined effects of various neurotransmitters. One possibility of assessing the cholinergic nature of the plasticity is to compare, within the same experiment, the effects produced by iontophoretic application of ACh and those produced by NBM stimulation. Although technically feasible (see Sato et al. 1987), this comparison has never been performed in any studies using pairing between a neuromodulator and a sensory stimulus.

Effects of neuromodulators on Hebbian plasticity

This overview would be incomplete without considering the data from the cellular analogues of epigenesis and of learning that have been developed in several laboratories. At the end of the '80s a line of research was initiated by Frégnac and collaborators to test the involvement of the covariance hypothesis (Sejnowski 1977) in the mechanisms allowing changes in functional properties during development (Frégnac et al. 1988; Shulz and Frégnac 1992). In this model of visual cortex plasticity, extraretinal signals are viewed as factors amplifying the covariance changes during critical periods of the development, and it

was proposed that the neuromodulatory systems conveyed, at least partly, these extraretinal "gating" signals (Frégnac 1987; Frégnac and Shulz 1989). This appealing possibility has not been extensively tested, and only indirect arguments can be presented. In fact, the strongest evidence came from a modified, and more "natural", version of the "cellular analogues of learning" developed by Ahissar and colleagues. In these experiments, the covariance between two cortical cells was enhanced by presenting the preferred tone frequency of cell "B" just after the emission of an action potential by cell "A" (Ahissar et al. 1992a). After a brief period of this imposed covariance, the functional coupling between cells was enhanced for a few minutes, but this enhancement was much more pronounced when the animal was attending the stimuli to perform a behavioral task than when it was passively listening to the sounds. Subsequently, this protocol was applied in anesthetized animals with the idea of replacing the animal's attention by direct application of neuromodulators. In this case, the "Hebbian treatment" did not produce any effect without neuromodulators, whereas an effect, similar to those observed in awake, attentive animals, was observed when ACh and NA were co-applied in the vicinity of the cells (Ahissar et al. 1996). However, not all Hebbian treatments can be boosted by neuromodulators: NBM activation delivered during a pairing protocol that was efficient, by itself, in producing selective plasticity in evoked responses, almost totally prevented the occurrence of the Hebbian plasticity (Cruikshank and Weinberger 2000).

Tentative conclusions

As reviewed here, a large body of evidence indicates that the thalamo-cortical system of a behaving animal is processing sensory information from 1 min to the next with an unsuspected large degree of flexibility. This dynamic is exemplified in the most extreme situations, when an animal shifts from one state of vigilance to another. During SWS, thalamic neurons have generally smaller RFs than in W, but cortical neurons can exhibit either smaller or larger RF than in W. The consequences at the level of the map organization are still unexplored, mainly because obtaining a minute to minute map of the sensory cortex in an undrugged animal is a technical "tour de force" that only started to be possible recently (Strata et al. 2001). Although no systematic study has been performed so far, one can suspect that within the waking state large fluctuations also exist and might be related to the level of attention and of arousal of the animal (see, for example, Fig. 7). In light of this large, continuous and natural flexibility, one can consider that the plasticity described after a behavioral training results from an "oriented selection" among one of the various states that are possible for the RF and for the map organization. Thus, learning-induced sensory plasticity can be viewed as a naturally emerging phenomenon that reflects the intrinsic

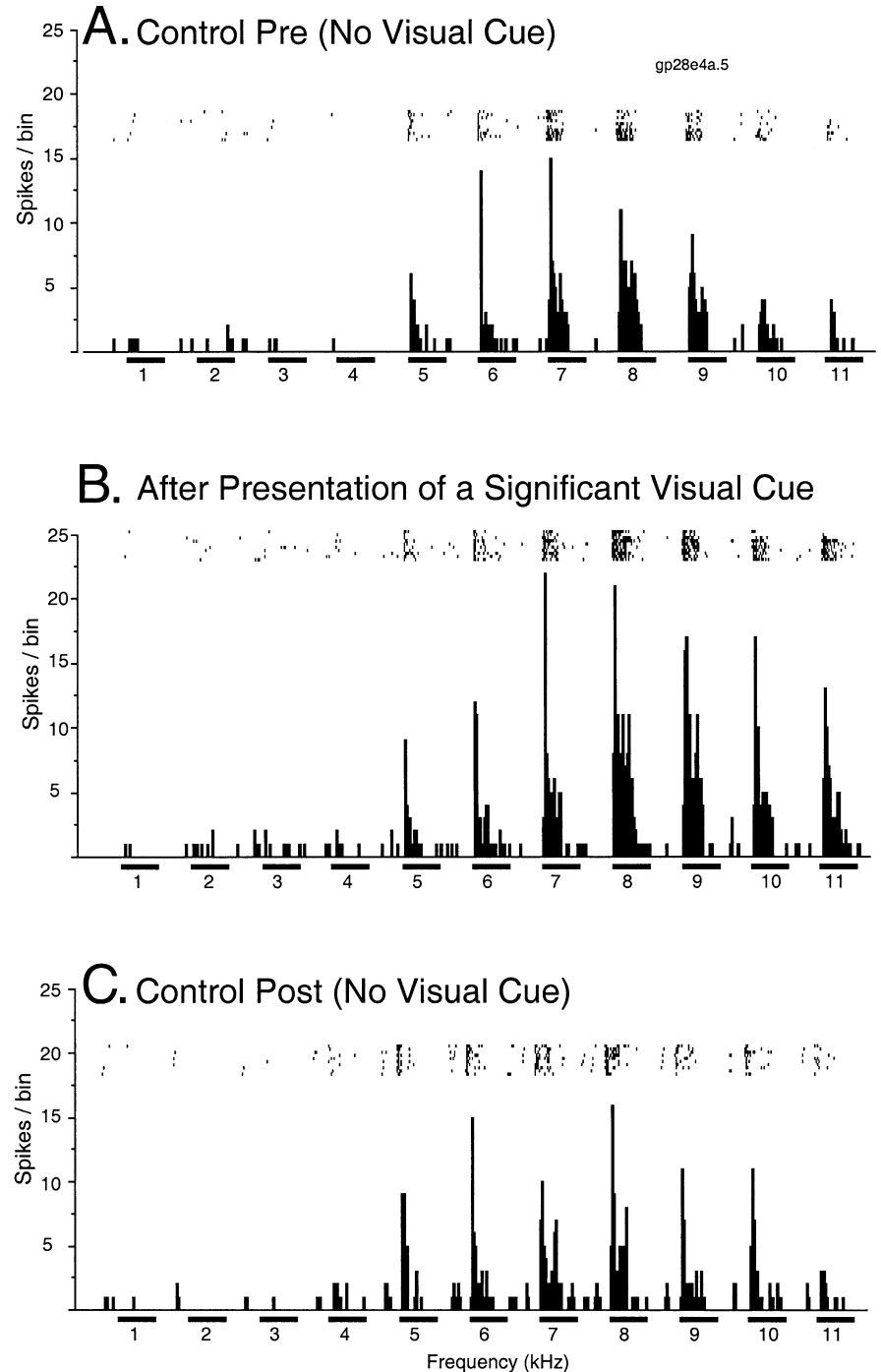
⁶In other cases, the data from cholinergic control animals were never presented (Kilgard and Merzenich 1998a, 1998b; Kilgard et al. 2001).

dynamics of RF and map organizations within the thalamo-cortical system of an undrugged animal.

Because neuromodulators are traditionally involved in the neurobiological mechanisms of attention and learning, they were logically proposed as permissive factors in the induction and/or the expression of learning-induced cortical plasticity. In line with this idea, many studies reported that a temporal pairing between NBM stimulation and a sensory stimulus produces cortical plasticity that looks like the effects described after associative learning. However, several unresolved issues still need clarification in this

domain. Surprisingly, among the neuromodulatory systems, the cholinergic projections arising from the NBM were the only ones that were considered as playing a key role in learning-induced plasticity. This is not due to the lack of studies involving other neuromodulators, but to the existence of different working frameworks. Among the few studies that have paired the activation of LC neurons with a sensory stimulation (Rogawski and Aghajanian 1980, 1982; Waterhouse et al. 1998; Holdefer and Jacobs 1994; Kayama et al. 1982; Lecas 2001, 2002), none of them has interpreted the observed effects as mimicking a

Fig. 7A–C Significant visual cues can modulate the evoked responses of auditory cortex neurons. The frequency tuning of auditory cortex neurons was tested in waking animals, which were previously conditioned in a visual task: presentation of a 10-s flashing light was followed by two slight footshocks randomly delivered during a 2-min period following the end of the flashing light presentation. After 5 days of training (30 trials/days), the frequency tuning of auditory cortex neurons was tested in awake animals with and without a presentation of a 10-s flashing light in the tone presentations. Strong modulations of the strength of the evoked responses and of the RF size were noted in many cases. For example, increased responses and enlarged frequency tuning were observed after presentation of the flashing light (**B**) compared with control situations (**A**, **C**). (From Manta and Edeline, unpublished data)



learning situation. Lastly, and more importantly, because the various neuromodulators act “in concert” at any level of the thalamo-cortical system (and probably at any level in the brain), it is essential to evaluate the effects triggered by the co-activation of several neuromodulators. Progressing in this direction is necessary because there is increasing evidence in favor of cross-interactions between neuromodulators, both at the presynaptic and at the postsynaptic level (see for review Vizi and Labos 1991). For example, the release of NA can control that of ACh, 5-HT or DA via stimulation of alpha2-adrenoceptors. One should also consider that the release of glutamate (and maybe also that of GABA) can control locally the release of neuromodulators such as ACh or NA (Marrocco et al. 1987; Metherate and Ashe 1995; Materi and Semba 2001).

Pointing out the limitations of the past studies and of our current knowledge does not aim to deny the large amount of progress that has been achieved in understanding the role of neuromodulators in sensory plasticity. But, we should always have in mind that the more sophisticated scheme envisioned to explain learning-induced plasticity in the thalamo-cortical system might still be a gross oversimplification of the actual mechanisms put into play. Finally, it is crucial to remember that sensory systems used other codes than the firing rate to analyze environmental stimuli and encode information. Most likely, both the temporal precision of single neuron firing and the temporal precision of neuronal interactions are fundamental to extracting information on stimulus parameters that is not directly provided by the afferent inputs such as the sound localization in the auditory system. The states of vigilance, behavioral training and the neuromodulatory systems can modulate these temporal aspects of the neuronal discharges as strongly as they modulate the neurons' firing rate. Providing an integrative view that will describe how these various aspects of the neural code are modulated by behavioral states is extremely challenging, but it might be the only way to understand how the activity of sensory systems contributes to our daily perception.

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