Available online at www.sciencedirect.com
SCIENCE DIRECT®
Neurobiology of Learning and Memory 80 (2003) 268–284
Neurobiology of Learning and Memory
www.elsevier.com/locate/ynlme

The nucleus basalis and memory codes: Auditory cortical plasticity and the induction of specific, associative behavioral memory

Norman M. Weinberger*

Center for the Neurobiology of Learning and Memory, University of California Irvine, Irvine, CA 92797-3800, USA
Department of Neurobiology and Behavior, University of California Irvine, Irvine, CA 92797-3800, USA

Received 29 May 2003; revised 23 June 2003; accepted 2 July 2003

Abstract

Receptive field (RF) plasticity develops in the primary auditory cortex (ACx) when a tone conditioned stimulus (CS) becomes associated with an appetitive or aversive unconditioned stimulus (US). This prototypical stimulus–stimulus (S–S) association is accompanied by shifts of frequency tuning of neurons toward or to the frequency of the CS such that the area of best tuning of the CS frequency is increased in the tonotopic representation of the ACx. RF plasticity has all of the major characteristics of behavioral associative memory: it is highly specific, discriminative, rapidly induced, consolidates (becomes stronger and more specific over hours to days) and can be retained indefinitely (tested to two months). Substitution of nucleus basalis (NB) stimulation for a US induces the same associative RF plasticity, and this requires the engagement of muscarinic receptors in the ACx. Pairing a tone with NB stimulation actually induces specific, associative behavioral memory, as indexed by post-training frequency generalization gradients. The degree of acquired behavioral significance of sounds appears to be encoded by the number of neurons that become retuned in the ACx to that acoustic stimulus, the greater the importance, the greater the number of re-tuned cells. This memory code has recently been supported by direct neurobehavioral tests. In toto, these findings support the view that specific, learned auditory memory content is stored in the ACx, and further that this storage of information during learning and the instantiation of the memory code involves the engagement of the nucleus basalis and its release of acetylcholine into target structures, particularly the cerebral cortex.

Keywords: Conditioning; S–S learning; Stimulus generalization; Acetylcholine; Receptive fields; Tuning; Representation; Cortical map

1. Introduction

The conception that adult primary sensory cortex is highly plastic is now generally accepted. However, this was far from the case until relatively recently. As with most ideas, it is not possible to set a firm date of "acceptance," but the mid-1990s is the time of noticeable penetration of this idea into neuroscience, as indicated by substantial reviews followed by admittance into textbooks. It seems that from a traditional, but implicit, position of either denying or simply ignoring evidence of such plasticity, adult sensory cortical plasticity has very rapidly become thoroughly embraced. Unfortunately, the Zeitgeist now uncritically treats all instances of adult sensory cortical plasticity as cases of "perceptual plasticity." While this may prove to be technically correct, this hasty and somewhat shallow characterization lumps together a wide variety of phenomena, including the effects of: (a) controlled learning studies, (b) sensory injury and peripheral denervation, (c) priming, (d) exposure to complex environments, and (e) improvements in acuity due to extensive discrimination training. The problem with assigning purely "perceptual" functions to learning-induced sensory cortical plasticity is that this treatment implicitly tends to exclude memory and its "contents" from primary sensory cortex. The following sections will summarize evidence that, regardless of the "perceptual" aspects of such plasticity, the primary auditory cortex actually stores, at a minimum, a cardinal feature of auditory memory content, specifically, its *learned behavioral significance*.

* Fax: 1-949-824-4576.
E-mail address: nmweinbe@uci.edu.

1074-7427/$ - see front matter © 2003 Elsevier Inc. All rights reserved.
doi:10.1016/S1074-7427(03)00072-8

The goals of this paper are to: (a) explain a new general experimental paradigm that has proven very helpful in the search for substrates of memory in primary sensory cortical fields, (b) determine the role of the NB cholinergic system (NB/ACh) in the induction of auditory cortical plasticity, (c) extend the role of the NB system to the direct induction of genuine specific, associative behavioral memory, and (d) explain and test the hypothesis that there is a neural *memory code* for the learned behavioral significance of experience.

2. Background

The role of sensory cortex in learning and memory traditionally has been enigmatic. The dominant conception of the functional organization of the cerebral cortex has been one of division into sensory, motor, and association regions. This schema, which continues to influence thinking, is directly traceable to the successes of the 19th century in first delineating a matching anatomical and functional sensory and motor organization of the spinal cord, and subsequently extending this relationship throughout the neuraxis to the cerebral cortex (Young, 1970). However, regions of the cerebral cortex that seemed to be neither sensory nor motor were left without a function. These were soon labeled as "association" areas on anatomical grounds (e.g., Campbell, 1905), in part under the influence of philosophical and psychological conceptions of sensory–motor association (Bain, 1855; Ferrier, 1876; Hume, 1777/1894). Under this schema, areas of sensory cortex are responsible for the analysis of sensory stimuli, but have little if any role in the actual storage of sensory information.

Nonetheless electrophysiological studies beginning in the 1950s (e.g., Galambos, Sheatz, & Vernier, 1955) consistently reported learning-related changes in the responses of sensory cortex, particularly the auditory and visual cortices, to signal stimuli, e.g., conditioned stimuli (CS) in classical and instrumental conditioning. Associative effects were observed for all electrophysiological measures employed, viz. the electroencephalogram (EEG), steady-state (DC) potentials, evoked (field) potentials, multiple and single unit discharges (reviewed in Weinberger & Diamond, 1987).

Despite the extensive and consistent nature of this literature, sensory cortical fields continued to play, at most, a minor role in conceptions about the neural bases of learning and memory. This probably reflected two factors. First, the dominant approach was to make lesions, to determine if a candidate brain structure was essential for acquisition or retention, But this popular technique could not be applied to sensory systems, because lesions would also impair the normal processing of environmental stimuli, hence confounding sensory deficits with learning/memory deficits. Second, there remained the firm conviction that truly interesting learning processes involved other brain regions. In short, sensory cortex could not "compete" with the association cortex, hippocampus, amygdala, striatum and cerebellum.

Moreover, learning-induced sensory cortical plasticity produced negligible notice within the field of sensory neurophysiology. This neglect may have been strongly promoted by the restricted set of stimuli employed in studies of learning. Whereas progress in sensory physiology depends upon the use of an extensive array of stimulus values in order to obtain sensory receptive fields (RFs) ("tuning curves"), neurophysiological studies of learning employed only one or two values of sensory stimuli (e.g., reinforced CS+ and non-reinforced CS− during discrimination training). Therefore, the issue of specificity, which is central to the study of sensory system coding, could not be addressed by findings such as those of learning-induced facilitation of sensory cortical responses to a reinforced auditory, visual or somatosensory signal.

3. Receptive field plasticity: A new paradigm for learning and memory

3.1. Synthesis of methods in sensory physiology and learning/memory

The situation changed following the introduction of a new experimental design that combines standard learning protocols with standard sensory neurophysiology protocols (Weinberger, Diamond, & McKenna, 1984). Specifically, it consists of obtaining neuronal RFs before and after training. The training may consist of any learning paradigm, e.g., classical conditioning, discrimination training, instrumental avoidance, habituation, etc. The effects are assessed by comparing post-training RFs with pre-training RFs. This approach yields the effects of any type of training on the tuning properties of sensory cells and the functional organization of sensory cortical and subcortical structures. Another important advantage of this new paradigm is that retention of RF plasticity can be tested repeatedly over minutes to weeks in the absence of additional reinforcement, yet without involving experimental extinction. This lack of extinction is accomplished because subjects do not regard RF testing stimuli as either conditioned or differential (discriminative) stimuli. Test stimuli are processed as behaviorally neutral because the many stimuli used to obtain RFs present a sensory context that is markedly different from the training context. That is, in contrast to a period of training (e.g., tone–shock pairing), the stimuli used to obtain RFs are much briefer (e.g., 100 ms vs. 2–5 s for conditioned stimuli), presented at a much higher rate (e.g., 2/s vs. 1/90 s during pairing), of widely variable frequencies and can be delivered in a completely

different environmental context (e.g., different chamber in a different experimental room with a different level of general illumination and different incidental visual and olfactory stimuli). Under such distinctively different contexts, animals do not exhibit any behavioral response (e.g., pupillary dilation, change in heart rate) to any stimuli, including testing stimuli that are identical in acoustic frequency to the CS (Diamond & Weinberger, 1989). The difference in environmental and state context for obtaining RFs before and at various times after training can be as great as placing the animal under deep general anesthesia, during which the effects of learning remain clearly detectable (Lennartz & Weinberger, 1992a; Weinberger, Javid, & Lepan, 1993) (A detailed analysis of various related experimental designs is provided elsewhere; Weinberger, in press).

The new paradigm makes it possible to address two fundamental questions about the role of sensory systems in learning and memory. First, from the field of the neurobiology of learning and memory: "Is learning-induced RF plasticity *associative*?" Second, from the field of sensory neurophysiology: "Is this tuning plasticity *specific* to the training stimulus?"

3.2. Learning-induced receptive field plasticity in the adult primary auditory cortex

The first study performed in primary auditory cortex revealed that associative processes in classical conditioning shift neuronal tuning toward or even *to* the CS frequency (Bakin & Weinberger, 1990; Fig. 1). If the CS frequency selected is distant from the peak (or best frequency, BF) of the pre-training tuning curve (e.g., 3 octaves), and thus has a relatively weak initial response, then tuning shifts are less pronounced. However, a consistent pattern of opposite change develops regardless of the pre-training relative strength of response to the CS frequency: responses to the frequency of the CS increase while responses to the pre-training BF and most other frequencies decrease. Tuning shifts occur when the coordinated opposing change are sufficiently large (reviewed in Weinberger, 1998). Learning-induced RF shifts to the CS frequency imply that the representational map of frequency in primary auditory cortex should change as well, yielding an increased representation of signal frequencies, because such maps are the distribution of the peaks of tuning curves, more specifically, the threshold frequency, the stimulus level used to map the ACx. This predicted outcome (Weinberger et al., 1990) was obtained in the monkey (Recanzone, Schreiner, & Merzenich, 1993).

3.2.1. Characteristics of learning-induced receptive field plasticity

RF plasticity is *associative*, as it requires stimulus pairing. Sensitization training (no pairing) produces

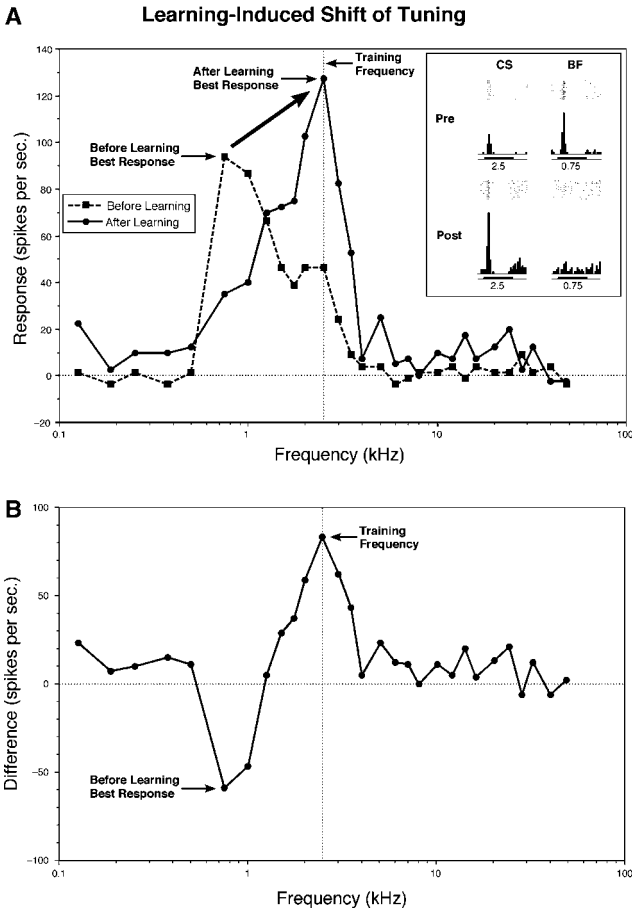

Fig. 1. An example of conditioned stimulus (CS) specific receptive field plasticity for a single cell in the primary auditory cortex following classical conditioning. Its tuning shifted to favor processing of the CS. (A) Pre-training, the best response (peak of tuning, best frequency (BF)) was 0.75 kHz. The CS was selected to be a much less effective frequency, 2.5 kHz. After 30 trials of tone–shock pairing, during which cardiac conditioned responses rapidly developed (indicating association between stimuli, i.e., tone and shock), the tuning had shifted to the CS frequency. Insets show post-stimulus histograms and rasters (20 presentations of frequency series to determine receptive field) for the CS and BF frequencies both before (pre) and after (post) training. Note in both histogram/rasters and tuning curves the increased response to the CS frequency and the decrease response to the pre-training BF, resulting in shift of tuning. (B) The difference function (post-training minus pre-training tuning curves) shows the effects of learning. Note that the largest increase is at the frequency of the CS and that responses to the pre-training BF are greatly reduced.

only a general increase in response to all frequencies across the RF (Bakin, Lepan, & Weinberger, 1992). The specificity of conditioning effects and lack of specificity of sensitization effects are illustrated in Figs. 2A and B, which provides difference RFs, i.e., post-training minus pre-training RFs. Several other characteristics of RF plasticity make it an attractive candidate for a process that operates in normal concert with sensory coding processes to subserve the storage of behaviorally relevant auditory information.

First, RF plasticity is *highly specific* to the CS frequency; responses to frequencies a small fraction of an

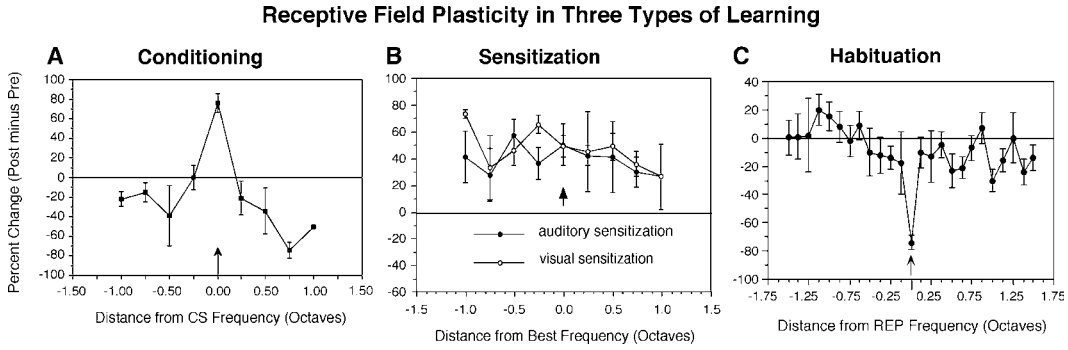

Fig. 2. Specificity of receptive field plasticity for (A) conditioning, (B) sensitization, and (C) habituation, expressed as mean($\pm SD$) group normalized difference functions (post-training minus pre-training RFs). Functions were normalized (octave distance from CS or habituated frequency). as cells across subjects have different pre-training BFs and CSs. (A) Conditioning (30 trials tone–shock pairing) produces increased response only at the CS frequency. (B) Sensitization (stimuli unpaired) increases responses at the CS but also at all other frequencies, showing conditioning effect is associative. Increased responses to the CS frequency during both conditioning and sensitization in studies employing only standard conditioning paradigms, and thus measuring responses only to the CS during training trials, (or CS+ and CS− during discrimination training) could wrongly conclude that CS increases are non-associative. Sensitization-induced non-associative general increase to all frequencies is not even auditory in nature because the same effect occurs when sensitization training consists of light and shock. (C) Habituation training (tone alone presented 1.25/s for 5–6 min) produces a highly specific decrease at the frequency of the habituated stimulus, showing that stimulus-specific receptive field plasticity develops during different types of learning.

octave away may be attenuated. Second, it exhibits *generality* across different types of training, as it develops in instrumental avoidance conditioning (Bakin, South, & Weinberger, 1996) as well as classical conditioning and for appetitive (Kisley & Gerstein, 2001) as well as aversive reinforcement. RF plasticity also develops during habituation to a single tone, showing a frequency specific decrease (Condon & Weinberger, 1991; Fig. 2C). Third, RF plasticity develops during two-tone classical discrimination training, i.e., increased responses to the CS+ frequency but decreased responses to the CS−, BF and other frequencies (Edeline, Neuenschwander-El Massioui, & Dutrieux, 1990a; Edeline & Weinberger, 1993). It also develops in discriminative instrumental avoidance conditioning (Bakin et al., 1996). Fourth, RF plasticity *develops very rapidly*, after only 5 training trials, as rapidly as the first behavioral (e.g., cardiac) signs of association (Edeline, Pham, & Weinberger, 1993). Fifth, RF plasticity *consolidates*, i.e., continues to develop increased responses to the frequency of the CS vs. decreased responses to other frequencies in the absence of further training over hours (Fig. 3) (Edeline & Weinberger, 1993; Weinberger et al., 1993) and days (Galván & Weinberger, 2002). Sixth, RF plasticity exhibits *long term retention*, enduring for the longest periods tested, up to 8 weeks after a single 30 trial conditioning session (Weinberger et al., 1993).

RF plasticity is not an artefact of arousal to the CS frequency during post-training RF determination, because, as explained above, subjects are behaviorally unresponsive to this or other frequencies. Also as noted, RF plasticity is expressed under general anesthesia. Further, learning-induced shifts of tuning are not due to random drifts because shifts are toward the CS frequency whereas they should be equally toward and away from the CS if random. Finally, direct measures of tuning stability over periods of 2–3 weeks reveal no directional drifts of tuning (Galván, Chen, & Weinberger, 2001).

Learning induced tuning plasticity is not limited to animals. The same paradigm of classical conditioning (tone paired with a mildly noxious stimulus) produces concordant specific associative changes in the primary auditory cortex of humans (Molchan, Sunderland, McIntosh, Herscovitch, & Schreurs, 1994; Morris, Friston, & Dolan, 1998; Schreurs et al., 1997), within the limits of spatial resolution of imaging methodology.

In summary, RF plasticity has major characteristics of associative memory. It is not only *associative*, but also is *highly specific*, *discriminative*, *rapidly acquired*, *retained at least for many weeks*, *develops consolidation* over hours and days, and exhibits *generality* across a variety of training tasks.

3.2.2. Regarding a cortical locus of receptive field plasticity

The CS-specific plasticity of cells in the ACx might be a reflection of plasticity projected to it from the auditory thalamus, the medial geniculate. The ventral and magnocellular subdivisions project to the ACx. However, enduring learning-induced RF plasticity in the primary auditory cortex cannot simply be "projected" from the ventral medial geniculate nucleus because this lemniscal source of frequency-specific input to the cortex is relatively stable in response to the CS during training trials (Gabriel, Saltwick, & Miller, 1975) and exhibits RF plasticity for less than 1 h after conditioning (Edeline & Weinberger, 1991). Cortical plasticity is also not simply

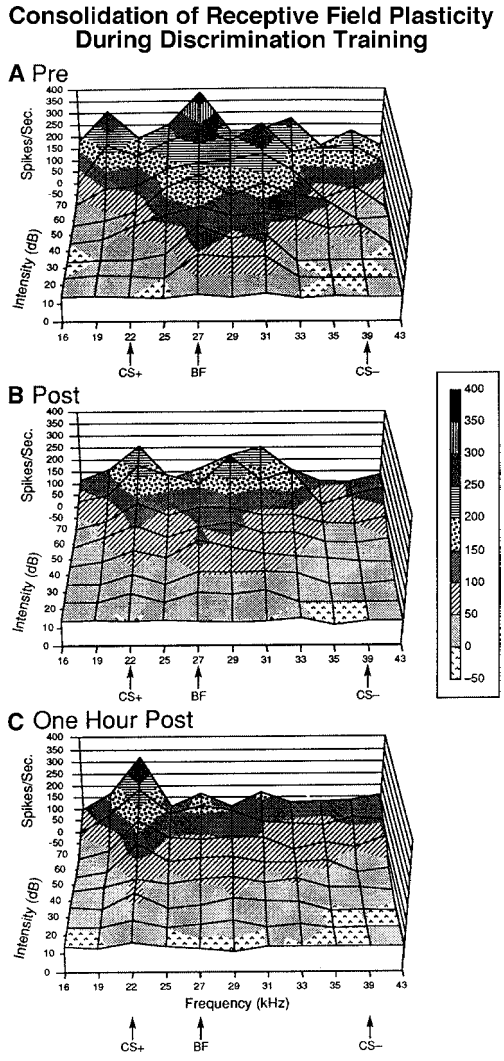

Fig. 3. Consolidation of RF plasticity during discrimination training, across acoustic frequency and stimulus level (intensity). Frequency tuning is illustrated as a 3-D graph: x-axis = frequency, y-axis = response magnitude, and the z-axis = stimulus level (10 dB steps). (A) Pre-training, the BF was 27 kHz across intensities; the CS+ was selected to be at 22 kHz (in a "valley") while the CS− frequency was chosen to be a 39 kHz (a secondary "peak"). Discrimination training was then conducted (30 trials intermixed each of CS+ followed by shock and CS− without shock (70 dB), during which discriminative behavioral (cardiac) conditioned responses developed, indicating stimulus–stimulus (CS–US) association. (B) Immediately post-training, tuning was changed to favor representation of the CS frequency. Increased excitatory responses developed at the CS+ frequency (22 kHz) while marked decreased responses were seen at the pre-training BF (27 kHz) and also at the frequency of the CS−. This CS-specific plasticity developed across stimulus levels although training was only at 70 dB. (C) Neural consolidation developed in the absence of any additional training. At the 1 h retention test, the shift in tuning favoring the CS+ frequency was even more pronounced and specific than immediately after training; the only peak of strong excitation was at the CS+ frequency and this was present across stimulus levels. (Adapted from Edeline & Weinberger, 1993.)

a reflection of projections from the magnocellular medial geniculate body (MGm), which provides non-lemniscal input to the ACx. Although MGm cells do develop increased responses to the CS and RF shifts during training (Edeline, Neuenschwander-El Massioui, & Dutrieux, 1990b; Edeline & Weinberger, 1992; Lennartz & Weinberger, 1992a), their RFs are much more complex, multi-peaked and broadly tuned than those of auditory cortical cells. Therefore, the evidence indicates that the maintenance of RF plasticity in the ACx is not simply projected from the auditory thalamus. Because no other systems analyze acoustic stimuli with sufficient precision, and as the auditory thalamus provides acoustic input to the ACx, it seems likely that the ACx is a locus of long-term RF plasticity.

However, it is possible that plasticity which develops in the auditory thalamus is involved in the induction of cortical RF plasticity. It might develop plasticity before the cortex. However, simultaneous recording and tracking of RF plasticity in both the thalamus and the cortex have not been accomplished. Recordings in separate comparable studies have not resolved this issue because cortical post-training RFs have been obtained after as few as five trials (Edeline et al., 1993) whereas thalamic RFs have not been obtained after fewer than 30 trials (Edeline & Weinberger, 1991). If neurons in the medial geniculate develop RF plasticity before the ACx, they would have to do so in fewer than five trials. Alternative possibilities are that the thalamic plasticity is unrelated to ACx plasticity or that ACx plasticity is involved in the development of thalamic plasticity. The first possibility has not been evaluated. However, there is evidence to support the second alternative because ACx plasticity is reported to develop before plasticity in the subcortical auditory system, and then be capable of inducing RF plasticity in the inferior colliculus (Gao & Suga, 2000). In any event, the role of the medial geniculate in the development of auditory cortical RF plasticity currently remains unresolved.

3.2.3. S–S association and RF plasticity are flexible and distinguished from S–R association and its substrates

Although decades have passed since the achievement of a clear distinction between stimulus–stimulus (S–S) and stimulus–response (S–R) associations during classical (Pavlovian) conditioning (Konorski, 1967; Lennartz & Weinberger, 1992b; Mowrer, 1947; Powell & Levine-Bryce, 1988; Schlosberg, 1937; Schneiderman, Fuentes, & Gormezano, 1962), misunderstandings and oversimplifications continue to abound, particularly in neuroscience. Thus, "conditioning" too often is equated with S–R conditioning, which has been characterized as an automatic-like process in which a stereotyped unconditioned response (UR) comes to be evoked by a previously neutral CS. For example, "conditioning" has been treated as an inflexible process whereby the same conditioned response is produced when occasion arises, i.e., whenever the CS is presented. This lack of flexibility has been contrasted with the high degree of behavioral

adaptability attributed to hippocampally dependent behaviors. Memory taxonomies often include "simple conditioning" as "procedural" learning (Eichenbaum & Cohen, 2001), but this categorization can correctly be applicable only to S–R conditioning. The treatment of conditioning as a single S–R process is incorrect and highly misleading. It is reminiscent of Hull's attempt to account for learning on the sole basis of S–R associations, while neglecting the role of S–S associations. This same neglect of S–S associations remains all too prevalent, clouding thought and experiment. It is beyond the scope of this paper to deal with the matter in detail. However, in order to understand the relevance of RF plasticity for learning and memory, a brief discussion will be helpful.

There exists a justified, standard and unequivocal distinction between stimulus–stimulus associations and stimulus–response associations. The latter involves learning to make a specific somatic motor response that is directed to a specific unconditioned stimulus (US). If the US is a shock to a limb, the specific somatic conditioned response will be a flexion response. If a shock is applied to the region of the eye, the CR will be an eyeblink (or retraction of the bulb), not a flexion. In short, such CRs index an association between a CS and a conditioned response (S–R association). In a standard aversive situation, this CS–CR learning may be directed to ameliorating the effects of the US. For example, conditioned limb flexion, but not passive flexion, is accompanied by anticipatory decreases of afferent shock volleys at the dorsal column nuclei, due to corticofugal mechanisms (Chapman, Jiang, & Lamarre, 1988; Coulter, 1974; Ghez & Lenzi, 1971; Ghez & Pisa, 1972). Such CRs must not only be specific to the locus of the nociceptive US, but they also need to be well-timed, to occur preceding and during delivery of the US. This requirement limits the ability of subjects to produce exceedingly well-timed CRs over moderate to long periods of time, as exemplified by the narrow inverted U shape of CS–US interval functions. For example, the optimum CS–US interval for the nictitating membrane CR is ~500 ms, with poor learning of CRs at CS–US intervals of a few seconds. The performance of this CR appears to reduce the neural effects of the US. Thus, neural activity within the interpositus nucleus that initiates conditioned responses apparently also reduces the transmission of the US to the cerebellum, by inhibiting sensory input from shock or air puff within the inferior olivary nucleus (Thompson & Tracy, 1995). The very effective and specific character of S–R learning limits its flexibility, as it should. Stimulus–response learning is ordinarily easily detectable, because the CR consists of overt and discrete muscle movements.

However, other CRs had developed prior to the occurrence of the first specific somatic CR. For example, within the same subject, heart rate CRs develop well before eyeblink CRs (Powell & Levine-Bryce, 1988; Schneiderman et al., 1962). In addition to heart rate, these rapidly-developing CRs include changes in respiration, blood pressure, pupillary size and skin conductance (GSR). As these CRs all develop regardless of the locus or type of US, they have been termed "non-specific" (Lennartz & Weinberger, 1992b). Such non-specific CRs have an important role in behavioral adaptation during conditioning (Winters, McCabe, & Schneiderman, 2001) and reflect the learning of the CS–US association (i.e., "S–S" learning). However, they will not be detected unless they are measured. Because these CRs in general are "internal," they are too often ignored.

In short, and as seen particularly clearly for defensive classical conditioning, Pavlovian association minimally involves two stages: rapid S–S learning followed by slower S–R learning. The first shows that the subject has learned the apparent cause–effect relationship of the stimuli, i.e., is able to predict the course of events. The second shows that the subject is attempting to alter its physical relationship to the outside world, by reducing the impact of the US if it is noxious.

The acquisition of an association between two or more stimuli is a ubiquitous form of learning. Any regularly occurring sequences of two or more events allows for the learning of their relationship. Stimulus–stimulus associations of many types are known to occur and to be pervasive. These include relationships between a CS and US, a CS and a context (which is an amalgam of sensory inputs), elements within a complex sensory stimulus, sensory pre-conditioning and second-order conditioning. Stimulus–stimulus associations are a basis for learning the "causal fabric" of the world (Rescorla, 1988).

What is the relevance of the distinction between S–S and S–R conditioning for auditory cortical receptive field plasticity? As reviewed previously, RF plasticity develops very rapidly, as quickly as behavioral verification of associative learning appears, e.g., the development of pupillary or cardiac conditioned responses. Therefore, it is a correlate of S–S association, not of S–R learning. Accordingly, one would not expect RF plasticity to be directly tied to any specific somatic conditioned response, in contrast to the development of subsequent associative plasticity in the cerebellum, which is tightly linked to nictitating membrane CRs (Thompson & Kim, 1996). Indeed, RF plasticity is not even tightly linked to non-specific CRs. For example, while its development is highly correlated with the development of cardiac conditioned responses, this relationship holds only for single tone conditioning and for easy two-tone discriminations. However, the cortical and behavioral plasticity are dissociated when the discrimination is difficult. Under such circumstances, differential cardiac CRs can fail to develop, but discriminative RF plasticity develops normally (Edeline & Weinberger, 1993).

These findings have at least three important implications ranging from highly specific to general significance.

The most specific implication is that failure to detect a behavioral index of learning, even in a highly sensitive response system, does not imply the failure of RF plasticity to develop. This suggests that RF plasticity is rather easily established when organisms can predict that a stimulus will be followed by an event of interest, such as shock or food.

At a somewhat broader level is the relationship between RF plasticity and behavior. Because RF plasticity is decoupled from particular behavioral responses, it can serve a flexible function, reflecting acquired behavioral significance for whatever unforeseen situations may demand. This is analogous to the fact that, having learned one's own name (which is probably among the most important sound patterns even learned), the underlying neuronal representation can subserve an unlimited number of responses to that name, whether heard in a noisy cocktail party or whispered by a lover. Thus, S–S associations, and their accompanying retuning of the auditory cortex to acquired important sounds, are easily and rapidly learned, can represent highly specific information, are ubiquitous and most likely highly flexible.

More generally, these findings have direct implications for conceptions of classical conditioning in the neurobiology of learning and memory. The prevalent assumptions are that classical conditioning is rather "basic" or "simple," that it is limited to "procedural," "implicit" or "non-declarative" memory, and that its substrates are subcortically confined. However, these views are no longer tenable, if ever they were, because classical conditioning is tightly linked to the development of cortical RF plasticity, whose many characteristics map onto those of associative memory probably more closely than those of any other neurophysiological correlate of memory. The major difference between the current line of inquiry and previous approaches using classical conditioning is that the study of RF plasticity focuses on the *representation and transformation of sensory information*, rather than on behavioral responses. By so doing, it reveals not only the involvement of the cerebral cortex in conditioning, but additionally supports a broader neurobiological conceptualization of S–S classical conditioning as exemplifying learned associations in general. As few neuroscientists would doubt the involvement of the cerebral cortex in paired-associate learning in humans, why should other S–S associations be denied a substrate in the cerebral cortex simply because they have been formed within a classical conditioning protocol? There was never adequate justification for a priori differential treatment of S–S conditioning and certainly there is no a posteriori justification given the characteristics of RF plasticity. The time for mental caricature and conceptual naiveté of classical conditioning in neuroscience has long since passed.

4. The nucleus basalis cholinergic system in receptive field and map plasticity

4.1. Introduction

The NB is the major source of cortical acetylcholine (Johnston, McKinney, & Coyle, 1979; Lehmann, Nagy, Atmadia, & Fibiger, 1980; Mesulam, Mufson, Wainer, & Levey, 1983). The auditory cortex in rodents is innervated by cholinergic cells within the ventral caudal globus pallidus and the caudal substantia innominata (Bigl, Woolf, & Butcher, 1982; Moriizumi & Hattori, 1992; Saper, 1984).

Several lines of evidence implicate the NB, and its cholinergic projections to the cortex, in plasticity in the ACx, as summarized below. (For original studies of the somatosensory cortex, see Dykes, 1997.) However, ACh is not the only neuromodulator that can affect processing in the auditory cortex. For example, tuning can be altered by norepinephrine (Manunta & Edeline, 1997). Pairing a tone with activation of the dopaminergic ventral tegmental reward area can increase the representation of that frequency (Bao, Chan, & Merzenich, 2001). Serotonin can regulate level-dependent response functions (Juckel, Hegerl, Molna, Csepe, & Karmos, 1999) and exhibits increased levels in the ACx during initial stages of avoidance training (Stark & Scheich, 1997). Therefore, ACh is not viewed as an exclusive modulator of the auditory cortex. It is unlikely that the various neuromodulators perform the same functions in the promotion of memory. However, too little is known at present about non-cholinergic modulators and speculation would take us too far afield. An understanding of the role of any single neuromodulator in learning-induced plasticity and memory will markedly promote inquiry of other modulators. At this point, most is known about the role of acetylcholine.

4.2. ACh and behavioral memory

The established links between the cholinergic system and memory provide a behavioral framework for investigating its role in auditory cortical plasticity. For example, pharmacological blockade of the cholinergic system impairs many forms of memory (e.g., Blozovski & Hennocq, 1982; Deutsch, 1971; Potter, Pickles, Roberts, & Rugg, 2000; Rudy, 1996). Cholinergic agonists and cholinesterase antagonists can facilitate memory (e.g., Flood, Landry, & Jarvik, 1981; Gower, 1987; Introini-Collison & McGaugh, 1988; Stratton & Pertinovich, 1963), promote recovery of memory from brain damage (Russell, Escobar, Booth, & Bermudez-

Rattoni, 1994) and achieve rescue from memory deficits in transgenic mice (Fisher, Brandeis, Chapman, Pittel, & Michaelson, 1998). Also, several non-cholinergic treatments that facilitate memory, such as adrenergic agents and stress hormones, affect memory via actions on the cholinergic system (Salinas, Introini-Collison, Dalmaz, & McGaugh, 1997).

However, there is not yet general agreement regarding the role of the cholinergic system in learning and memory. Several laboratories have reported the failure of substantial cholinergic depletion to impair learning. These include studies of delayed alternation and passive avoidance (Wenk, Stoehr, Quintana, Mobley, & Wiley, 1994), place learning in the Morris water maze (6, Baxter et al., 1996) and olfactory learning sets (Bailey, Rudidill, Hoof, & Long, 2003). Such findings are often prematurely generalized to suggest that the cholinergic system is not actually involved in learning and memory per se. However, as cholinergic depletion studies have not yet been performed for auditory cortical plasticity, prior negative findings neither directly contradict nor necessarily mitigate the putative role of the cholinergic system in associative processes within the primary auditory cortex. Until the field attains a comprehensive understanding of the processes involved in learning and memory within each of the many tasks and situations employed, it will be difficult, if not impossible, to adequately understand the role of any particular brain system, including the cholinergic system, in the broad discipline of learning and memory.

4.3. The NB and cortical state

Stimulation of the NB releases ACh in the cortex (Casamenti, Deffenu, Abbamondi, & Pepeu, 1986; Kurosawa, Sato, & Sato, 1989; Rasmusson, Clow, & Szerb, 1992) and produces widespread EEG activation (''desynchonization''), which is the waking cortical state optimal for learning. Conversely, lesions of the NB reduce cortical levels of ACh and impair cortical activation (Celesia & Jasper, 1966; Jimenez-Capdeville & Dykes, 1996; LoConte, Bartolini, Casamenti, Marconcini-Pepeu, & Pepeu, 1982; Riekkinen, Riekkinen, Sirvio, Miettinen, & Riekkinen, 1992). The discharge rate of identified cholinergic projection cells increases during cortical activation and decreases during cortical slow waves (reviewed in Duque, Balatoni, Detari, & Zaborszky, 2000).

4.4. NB-induced modification of auditory cortical responses to sound

ACh produces long-lasting modification of RFs in primary sensory cortices (e.g., Metherate, Tremblay, & Dykes, 1988; Sillito & Kemp, 1983). Iontophoretic application of cholinergic agents to the ACx produces long-lasting modification of frequency tuning via muscarinic receptors (Ashe, McKenna, & Weinberger, 1989; McKenna, Ashe, & Weinberger, 1989). Stimulation of the NB produces atropine-sensitive, persistent modification of evoked responses in the auditory cortex, including facilitation of field potentials, cellular discharges and EPSPs elicited by medial geniculate stimulation (Metherate & Ashe, 1991, 1993). NB stimulation also facilitates neuronal discharges to tones in the ACx (Edeline, Hars, Maho, & Hennevin, 1994a, 1994b; Hars, Maho, Edeline, & Hennevin, 1993). Pairing a tone with iontophoretic application of muscarinic agonists to the ACx produces pairing-specific, atropine sensitive, modification of RFs that include shifts of tuning toward the frequency of the paired tone; however, this protocol is more likely to produce frequency-specific decreases (Metherate & Weinberger, 1990). This outcome indicates that NB stimulation and iontophoretic administration of muscarinic agonists cannot be assumed to directly substitute for each other. As emphasized by Rasmusson (2000), while electrical stimulation of the NB may be viewed as relatively crude, it has the advantage that spatial and temporal characteristics of ACh release are more consistent with the normal anatomy and physiology of this system.

4.5. ACh and the NB in neurophysiological studies of learning

ACh is preferentially released into relevant sensory cortical areas at the time of learning (Butt, Testylier, & Dykes, 1997; Orsetti, Casamenti, & Pepeu, 1996). ACh applied to the ACx augments RF shifts during tone–shock pairing while cortical atropine prevents such RF shifts (Ji, Gao, & Suga, 2001). Studies of neuronal responses in the NB are consistent with an important role for the NB/ACh in cortical plasticity. NB cells exhibit frequency tuning for pure tones, indicating that specific acoustic information can reach this structure (Chernychev & Weinberger, 1998). Stimuli that signal appetitive or aversive reinforcement elicit increased responses of NB cells during learning (Richardson & DeLong, 1986; Travis & Sparks, 1968; Whalen, Kapp, & Pascoe, 1994; Wilson & Rolls, 1990). Of particular relevance, cells in the NB develop increased discharges to the CS+ during tone–shock conditioning *before* the development of neuronal plasticity in the ACx and thus could be causal to the cortical RF plasticity (Maho, Hars, Edeline, & Hennevin, 1995). Furthermore, NB neurons projecting to the ACx selectively increase transcription of the gene for ACh's synthetic enzyme, choline acetyltransferase, during tone–shock conditioning, indicating that acoustic learning engages specific cholinergic sub-cellular mechanisms (Oh, Edwards, & Woolf, 1996).

4.6. NB induction of receptive field and map plasticity

If learning-induced plasticity in the ACx develops via engagement of the NB, then NB stimulation should be able to substitute for a standard reinforcer, such as food or shock, although no motivational reinforcement would be involved. The NB cholinergic system is capable of inducing RF plasticity that has the same characteristics as learning-induced RF plasticity. Pairing a tone with NB stimulation for only 30 trials induces RF plasticity. This plasticity is associative, as is the case for standard behavioral learning, because it requires stimulus pairing (Bakin & Weinberger, 1996). Moreover, as in the case of learning, two-tone discriminative RF plasticity develops when one tone is paired with NB stimulation while another is presented alone (30 trials each of the CS+ and CS−; Dimyan & Weinberger, 1999). Additionally, like behavioral learning, a single session of pairing that produces NB-induced RF plasticity also produces *consolidation* i.e., increased strength of effect without additional training, when tested over 24 h (the longest period tested) (Bjordahl, Dimyan, & Weinberger, 1998; Fig. 4). NB-induced RF plasticity is blocked by atropine directly applied to the ACx showing that the engagement of muscarinic receptors in the ACx is necessary for this specific change in frequency tuning (Miasnikov, McLin, & Weinberger, 2001).

As in the case of learning-induced plasticity, RF plasticity would be expected to produce an increased representation of the paired tone frequency because the tonotopic map is the distribution (at threshold) of BFs, including those that have shifted toward or to the CS frequency. As predicted, this outcome has been observed, using a long-term paradigm of hundreds of trials per day for weeks (Kilgard & Merzenich, 1998; Kilgard et al., 2001). In view of the induction of RF plasticity with a single session of training, it is probably not necessary to use thousands of trials over many days.

5. Induction of specific, associative behavioral memory by stimulation of the NB

The previous findings reveal that the NB is capable of inducing associative, specific RF plasticity. Because this RF plasticity has the same characteristics as those that are induced during behavioral learning, it is possible that the NB is normally engaged during behavioral learning to induce behavioral memory. We investigated this possibility by substituting NB stimulation for a standard reinforcer such as food or shock. Rats were conditioned for several days with a 6.0 kHz tone (2 s) paired with weak stimulation of the NB (200 ms, CS–US interval = 1.8 s). The EEG and two behaviors (heart rate and respiration) were recorded before and 24 h after training, in the absence of NB stimulation. We selected changes in heart rate and respiration as behavioral indices of newly formed memory because they are highly sensitive, reliable and robust indicators of behavioral conditioning, specifically rapidly developing S–S (CS–US) associations.

We assessed the induction of specific behavioral memory using accepted criteria and proven techniques that pertain to standard behavioral training. That is, the development of specific, associative memory due to a treatment may be inferred from behavioral change if behavior meets the dual criteria of associativity and specificity. The first criterion requires that that pairing of the CS and US be necessary. An unpaired group (random tone and NB stimulation) controlled for possible non-associative effects. For the second criterion of specificity, we used the well-established metric of the stimulus generalization gradient, obtained when a subject is trained with one stimulus (CS) and later tested with many stimuli. We reasoned that if NB stimulation paired with a tone induces specific memory about that tone, then this CS frequency should later elicit the largest behavioral responses to all tones tested, i.e., occupy the peak of the frequency generalization gradient.

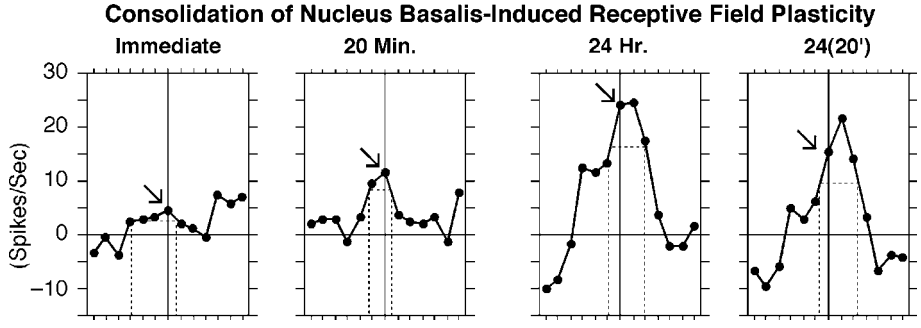

Fig. 4. Induction and consolidation of receptive field plasticity induced by pairing a tone with stimulation of the nucleus basalis (NB). Shown are normalized group receptive field difference functions (post-training RFs minus pre-training RFs, centered on the CS frequency (arrow). Note the absence of a strong effect immediately post-training, the development of a CS-specific increase at 20 min, and the much stronger effect 24 h later, i.e., neural consolidation. The dotted lines are the 75% bandwidth (BW) markers. C. (Adapted from Bjordahl et al., 1998.)

Rats were overtrained, receiving 200 trials per day for 14 days. NB stimulus levels were kept low (~100 μA), near threshold for eliciting 3–4 s of EEG activation but below threshold for the elicitation of any overt movements. Extensive training was used because we had set the NB stimulus to be weak and because we assumed its apparent lack of motivational significance would further contribute to weak learning. We hoped to compensate for this by increasing the number of trials. (Overtraining proved to be unnecessary, as described below.)

Post-training generalization gradients revealed that the sensitization control group exhibited generally flat functions, i.e., tones elicited the same degree of change in heart rate and respiration across the broad range of test frequencies (1–15 kHz). In contrast, the paired group exhibited sharp generalization gradients. Most importantly, the greatest magnitude of response, that is, the peak of the generalization gradients was at the CS frequency (Fig. 5; McLin et al., 2002a, 2002b). From a behavioral standpoint, the gradients for changes in heart rate and in respiration could not be distinguished from those that develop in standard learning protocols using standard motivational reinforcers (e.g., Mackintosh, 1974). These findings indicate that behavioral memory can be induced by pairing a tone with NB stimulation and support the view that the NB is normally engaged during associative S–S conditioning, promoting the establishment of specific cortical plasticity that itself may be a substrate for specific behavioral memory.

To determine if NB stimulation is actually a very weak means of inducing memory, necessitating very extensive pairing, we determined the effects of a single 200 trial session. Paired and random stimulation groups were used, with even weaker NB stimulation (~60 μA). The same induction of specific associative behavioral memory was evident during the 24 h. generalization test. Groups then received one session of "reversed" training (paired to random, random to paired). Extinction was found in the previously paired group while the previously random group developed specific memory (Miasnikov & Weinberger, 2003). Taken in toto, the findings indicate that NB-induced behavioral memory has additional characteristics of "normal" memory that develops during standard associative learning situations. That is, paired NB stimulation can serve as a highly effective means of rapidly inducing behavioral memory, even after unpaired ("negative") training, and behavioral extinction develops when the CS–US relationship is eliminated.

However, these studies did not directly address the possibility that NB stimulation is effective because it acts as a positive or aversive reinforcer. For example, stimulation of the ventral tegmental area (VTA) is positively reinforcing and produces auditory cortical plasticity when paired with a preceding tone (Bao et al., 2001; Kisley & Gerstein, 2001). Furthermore, motivational

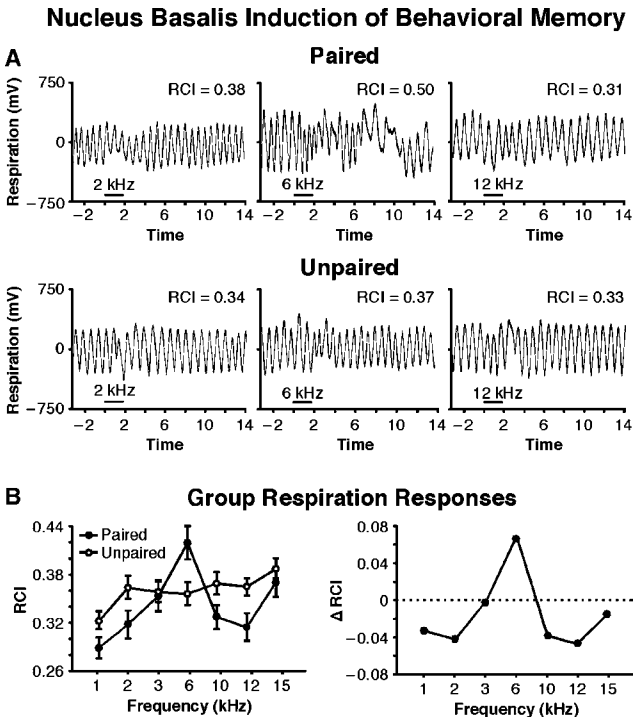

Fig. 5. Induction of behavioral memory by pairing a tone with stimulation of the nucleus basalis. The assessment of memory was based on training with one stimulus value (6.0 kHz) and testing with many frequencies (1.0–15.0 kHz), i.e., obtaining behavioral generalization gradients. Shown are post-treatment data for respiration behavior. (A) Examples of individual respiration records (with value of respiration change index, RCI) to three test frequencies (2, 6, and 12 kHz) for one animal each from the paired and unpaired groups. The largest response (change in respiration) was at 6.0 kHz for the paired animal. Horizontal bar indicates tone duration. (B) Left panel provides group mean(±*SE*) response for both groups. The maximal response was at 6.0 kHz for the paired group, but not for the unpaired group. The generalization gradient for only the paired group was significantly quadratic, with responses to 6 kHz being of greatest magnitude. The group difference function (right panel) shows a high degree of specificity of respiratory responses to the frequency paired with NB stimulation. Thus, the criteria for specific, associative memory have been satisfied. (From McLin, Miasnikov, & Weinberger, 2002a.)

reinforcers elicit unconditioned responses and stimulation of the NB itself elicits unconditioned EEG activation and can produce signs of behavioral arousal, i.e., cardiac and respiratory responses (McLin et al., 2002a, 2002b). Nonetheless, it appears unlikely that NB stimulation induces memory via motivational effects. Unlike the VTA, the NB is not part of any known hedonic or motivational system (reviewed in Pennartz, 1995). Furthermore, it has long been known that motivationally neutral sites can elicit URs that produce EEG activation and behavioral arousal (Olds & Peretz, 1960). Moreover, Wester (1971, 1972) found that stimulation of motivationally neutral sites within the midline and intralaminar nuclei of the thalamus elicited EEG activation and behavioral arousal. Notably, the midbrain sites were later identified as including ascending projections

of the midbrain cholinergic system, some of which innervate the medial and intralaminar thalamus while others innervate the NB (Steriade & Buzsaki, 1990).

Stimulation of the NB also increases cerebral blood flow (CBF) (e.g., Biesold, Inanami, Sato, & Sato, 1989; Lacombe et al., 1989), so perhaps increases in CBF might be detected in some way. However, we used a 200 ms train of stimulation, which is 1/50th the duration of the briefest stimulation (10 s) employed in NB/CBF studies (Sato, Sato, & Uchida, 2001). Therefore, this brief stimulus probably did not produce notable CBF effects.

It should be remembered that an US need not have motivational impact in order to establish associations. Sensory pre-conditioning is an example. The NB may act in yet a different manner. Ordinarily, the NB may operate "downstream" of systems that evaluate and determine the hedonic value of stimuli. As these systems have efferents to other brain systems, it is possible that the NB is ordinarily engaged to modulate the cerebral cortex, and perhaps other structures, by the release of acetylcholine, having received excitatory input from evaluative systems. In such a location in the processing stream, the NB could exert widespread cortical effects in response to a multitude of inputs without itself constituting part of any motivational system.

The resultant memory would be one in which the animals learned that the 6.0 kHz tone was behaviorally important, but the basis for its importance (e.g., as a signal for food or shock) would be missing. Therefore, the use of NB stimulation to induce memory may not only elucidate the mechanisms of memory induction but also allow "dissection" of memory into its components of *sensory content* and *level of behavioral importance*. During normal motivated learning both aspects of memory are produced but the NB may be a substrate of the latter learning, but not of the full sensory content of memory.

6. A neural memory code for the behavioral importance of experience

The previous sections have been concerned with learning-induced RF plasticity and the findings that activation of the NB is sufficient to induce both RF plasticity and specific, associative behavioral memory. This final major section places these findings in an orthogonal (i.e., non-reductionistic) context, that of *memory codes*. The issue is whether there exist neuronal memory codes for cardinal features of stored experience, and if so, what might they be (Weinberger, 2001). We now summarize the concept of memory codes, outline an experimental test of a memory code for the learned importance of experience, and present recent supporting findings.

6.1. What is a neural memory code?

By a "neural memory code" I mean—"*a relationship that describes the transformation of an experience into an enduring neural form.*" Because this concept has not been expounded in the literature, it may seem vague at this point. However, it should clarify soon, given a specific example and experimental findings. We suggest that there is at least one memory code for the acquired behavioral importance of a stimulus and that it is the *amount of learning-induced RF re-tuning toward or to that stimulus*. In short, more cells would become tuned to important stimuli and fewer cells would become tuned to less important stimuli.

How are such codes related to engrams? Engrams and memory codes are related but they are not at all the same sort of things. "Engrams" are considered to be the totality of neural changes that comprise a memory. One seeks engrams, or at least places where particular engrams exist. When found in whole, or more likely in part, engrams can be subjected to reductionistic analyses at circuit, cellular and molecular levels. For example, there is substantial evidence for an engram in the cerebellum of a learned S–R association between a tone and the conditioned nictitating membrane response (Thompson & Kim, 1996). Similarly, we have summarized evidence above of engrammatic substrates in the auditory cortex of a learned S–S association between a tone and a shock.

Memory codes are not the neural substrates of memories themselves. It is thought that each separate memory for the unique experiences of individual organisms involves an individual engram. In contrast, memory codes would comprise a finite class of relationships that denote an attribute of memories. More specifically, a memory code denotes a particular type of "input–output" function. A memory code describes the transform function from, e.g., patterns of sensory-derived neuronal discharges [Input] into long-lasting changes in nervous tissue [Output]. The long lasting changes in neural organization constitute an engram.

Memory codes need be no more conceptually mysterious than are sensory codes. A sensory code describes the input–output relationship between a pattern of energy on a receptor epithelium ["input"] and the discharges of sensory neurons ["output"]. A well-known sensory code is the increase in rate of discharge ["output"] as stimulus intensity increases ["input"]. The code is described by the "input–output" function, i.e., stimulus intensity vs. rate of discharge.

6.2. Testing the hypothesis of a neural memory code for stimulus importance

We tested the hypothesis that a neural memory code for acquired stimulus importance is the number of cells

that become preferentially tuned to that stimulus. This hypothesis predicts that the area of representation for a tone frequency will increase directly as a function of the increasing level of acquired importance of that tone.

We approached this problem by training rats to bar press in the presence of a 6 kHz tone for water reward. We defined "acquired stimulus importance" as stimulus control of behavior, operationally as the percent of bar presses during the tone to bar presses in the absence of the tone, which produced a time out. We manipulated the amount of stimulus control by giving different rats different amounts of supplemental water in their home cages. After achieving differential asymptotic levels of stimulus control, as quantified by different levels of correct performance, the auditory cortex of the rats was mapped. The memory code hypothesis predicts that the greater the stimulus control, the greater the area of representation of 6 kHz. There were also two control groups. One was naïve, the other was rewarded for bar pressing during presentation of a light stimulus. To equate for mere exposure to the 6 kHz tone, these subjects also received the same density of tone presentation as the main acoustic training group but the tones were presently randomly and therefore were unrelated to either bar pressing or water reward.

Fig. 6 presents a summary of the findings. The area of the primary auditory cortex that was best tuned to the frequency band containing the 6 kHz signal (the 4–8 kHz octave band) increased significantly, compared to both the naives and the trained controls. Most importantly, there is a significant linear relationship between performance level and the area of representation (Fig. 7) (Rutkowski, Than, & Weinberger, 2002). The findings support the hypothesis that the learned behavioral importance of a stimulus is represented in the cortex by the number of cells (i.e., area) that become best tuned to that stimulus.

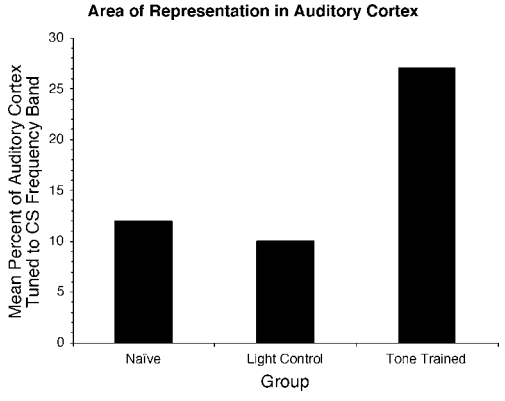

Fig. 6. The area of primary auditory cortex (ACx) that represents the octave frequency band centered on the training frequency of 6 kHz. There was no difference in the area of representation between the naïve group and the control group that received 6 kHz tones while learning to bar press in response to presentation of a light. The tone-trained group exhibited a significantly larger area of representation.

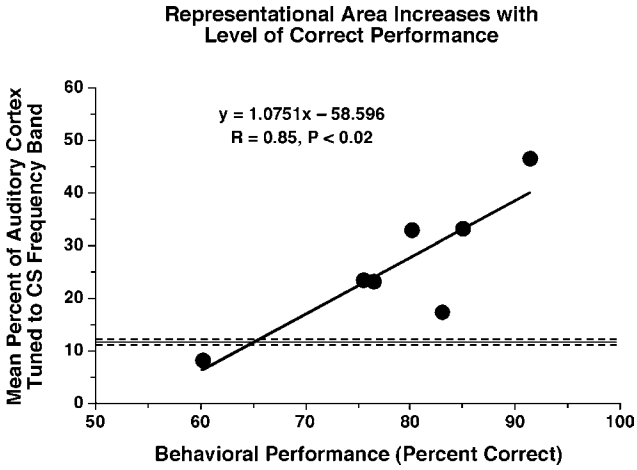

Fig. 7. The relationship between asymptotic performance level and the area of representation for the band centered on the training frequency. Data points are for individual subjects. The horizontal line indicates the amount of cortical area for the naïve group (and 95% confidence limits). Note the significant, positive linear correlation between performance and cortical area. These findings support the hypothesis of a neural code for the learned importance of a stimulus: the overall amount of tuning shift to a stimulus encodes the level of its acquired behavioral significance, the greater the significance, the greater the tuning shift.

6.3. Future directions in the investigation of neural memory codes

The general formulation of neural memory codes need not be restricted to the type of code described above. Thus, two major dimensions of these codes are immediately apparent: (a) the type of coded memory content, (b) the type of code itself. We have described and successfully tested a code for the contents of memory concerned with the *learned behavioral importance* of a stimulus (tone). The type of this code that we identified is a *spatial* code. That is, this particular neural code consists of the *number* of neurons whose tuning becomes shifted to/toward that of the acoustic CS. In addition to spatial neural memory codes, there are probably many other types whose nature might encompass any neurobiological process involved in the storage of experience, for example *temporal* codes. These would be manifested as the *pattern* of neuronal discharges or other cellular processes, that might represent a cardinal feature of memory. For example, the discharge patterns of involved cells might also encode learned stimulus importance. These might not be as easily detectable as spatially based codes but they should be sought.

The *type of content*, the other memory code dimension considered here, is more difficult to deal with in brief because of its very high dimensionality. This con-

sists of all possible aspects of the subject matter of memories, that is *what memories are about*, which is the entire domain of experience (including but not limited to all sensory events) and even individual reactions to an experience, such as its emotional overtones (see Weinberger, 2001 for a more detailed consideration). This complexity is precisely why we chose to first study *acquired importance*, because some level of behavioral significance would seem common to all experiences and their memories. A somewhat more limited domain for present purposes is to consider "levels of encoding." A prime example of levels is the learning of words, which may be achieved on the basis of their physical appearance (orthographic), sound (phonemic), or behavioral meaning (semantic). Even for stimuli not involving language, any sensory stimulus may be encoded at different levels. Thus an arbitrary visual pattern might be encoded only at the level of its modality (something seen), at the level of its particular detailed physical features (size, color, orientation, location, etc.), or at the level of its acquired behavioral relevance (as when associated with another event, e.g. the site of a baby bottle followed by the taste of milk). There may well be neural memory codes that are specific for different levels of encoding, which constitute and delimit cardinal features of types of memory content. Such codes might be spatial, temporal or both. These possibilities are open to experimental inquiry.

7. Summary and future inquiry

Inquiry into the role of acetylcholine, or any neuromodulator, can proceed along a large number of paths. The road that my laboratory has taken begins with an attempt to detect and characterize changes in the neuronal representation of a stimulus as it gains psychological meaning, and therefore behavioral importance, through learning. This required the development of a new type of paradigm, one in which the components previously had been used routinely in two fields, the experimental psychology of learning/memory and sensory neurophysiology. This led to the discovery that neurons in the primary auditory cortex are retuned during learning, shifting their preferred tuning frequency toward and to that of a signal stimulus. This RF plasticity, which is the basis for the increased representation of these stimuli when plasticity is viewed from the perspective of tonotopic maps, added a critical dimension to prior approaches to the neural substrates of learning and memory. Specifically, it revealed that sensory cortex, long ignored in formulations about brain and learning, exhibits the characteristics of associative memory, including specificity, rapid development, consolidation and long term retention. It is not clear whether any other neural correlates of normal learning (as contrasted with plasticity induced by analogues of learning, e.g., LTP, LTD) match the features of behavioral memory to the same high degree.

A reductionistic analysis rapidly implicated the NB and its cholinergic projections to the auditory cortex. The same RF plasticity could be induced by substituting NB stimulation for a standard US, such as shock. Muscarinic receptors in the auditory cortex were implicated by the finding that NB induced tuning plasticity could be blocked by application of atropine to the auditory cortex. A considerable amount of research is still required to fully understand how the NB gains such great modulatory control over the functional organization of the cortex. Analytic studies focusing on the cortex, at the circuit, cellular and subcellular levels, are still needed.

Perhaps most striking of all, extension of this approach revealed that NB stimulation can induce specific, associative behavioral memory. Once again, no completely new techniques were needed. It was adequate to employ the method of obtaining behavioral generalization gradients to assess the degree of specificity of the induced behavioral index of memory. The possibility now exists to dissect components of the contents of memory by neural means. That is, the use of NB induction suggests that acquired stimulus importance can be cleaved to some extent from normal sensory content. While this idea is intriguing, there are also pressing needs to fully understand how NB stimulation induces actual memory, that is produces in animals the information that a particular stimulus (tone frequency) is behaviorally important, although it seems to signal nothing else in the environment.

Within this problem area, it is essential to point out that two major issues have not yet been addressed. The first concerns the relationship of the effects of NB stimulation to acetylcholine. As discussed in detail elsewhere (McLin, Miasnikov, & Weinberger, 2003), while the same type of stimulation produces RF plasticity and specific, associative memory, these two effects might be induced by engaging different brain systems. The induction of plasticity has been linked to muscarinic receptors in the auditory cortex but the induction of memory by NB stimulation has not yet been linked to ACh. Second, RF plasticity and behavioral memory, whether induced during normal learning or by NB stimulation, have not yet been tightly linked. While the major pieces of the puzzle, i.e., the NB, ACh, RF plasticity and specific, associative behavioral memory, seem to fit together, much needs to be done.

Finally, the formulation of memory codes seems to hold considerable promise, particularly given experimental findings that support a code for acquired stimulus importance. The serious consideration of memory codes has the capacity to open a new phase of conceptualization and experiment, one that may promote uni-

fication across different forms of memory within the neurobiology of learning and memory. The nucleus basalis appears to play a key, perhaps critical role in all of the processes under consideration. Thus, during learning, the NB is likely to be engaged in the storage of the auditory contents of memory in the primary auditory cortex (and probably other auditory regions), in the instantiation of the memory code for acquired behavioral significance of sound and in other acquisition processes that ultimately lead to the expression of memories in behavior. The influence of the NB, while currently best understood and documented for auditory cortical plasticity and the induction of specific auditory memory, is likely to operate in a similar manner for the acquisition and storage of environmental events that impinge on other sensory systems.

Acknowledgments

This research was supported by Grants MH-57235, DC-02346, DC-02398 and DC-05592. I wish to thank Gabriel Hui and Jacquie Weinberger for assistance with the preparation of the figures and text.

References

Ashe, J. H., McKenna, T. M., & 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*, 45–54.

Bailey, A. M., Rudidill, M. L., Hoof, E. J., & Long, M. I. (2003). 192 IgG-saporin lesions to the nucleus basalis magnocellularis (nBM) disrupt acquisition of learning set formation. *Brain Research, 969*, 147–159.

Bain, A. (1855). *The senses and the intellect*. London: Parker.

Bakin, J. S., Lepan, B., & Weinberger, N. M. (1992). Sensitization induced receptive field plasticity in the auditory cortex is independent of CS-modality. *Brain Research, 577*, 226–235.

Bakin, J. S., South, D. A., & Weinberger, N. M. (1996). Induction of receptive field plasticity in the auditory cortex of the guinea pig during instrumental avoidance conditioning. *Behavioral Neuroscience, 110*, 905–913.

Bakin, J. S., & Weinberger, N. M. (1990). Classical conditioning induces CS-specific receptive field plasticity in the auditory cortex of the guinea pig. *Brain Research, 536*, 271–286.

Bakin, J. S., & Weinberger, N. M. (1996). Induction of a physiological memory in the cerebral cortex by stimulation of the nucleus basalis. *Proceedings of the National Academy of Sciences of the United States of America, 93*, 11219–11224.

Bao, S., Chan, V. T., & Merzenich, M. M. (2001). Cortical remodeling induced by activity of ventral tegmental dopamine neurons. *Nature, 412*, 79–83.

Baxter, M. G., Bucci, D. J., Sobel, T. J., Williams, M. J., Gorman, L. K., & Gallagher, M. (1996). Intact spatial learning following lesions of basal forebrain cholinergic neurons. *Neuroreport, 7*, 1417–1420.

Biesold, D., Inanami, O., Sato, A., & Sato, Y. (1989). Stimulation of the nucleus basalis of Meynert increases cerebral cortical blood flow in rats. *Neuroscience Letters, 98*, 39–44.

Bigl, V., Woolf, N. J., & Butcher, L. L. (1982). Cholinergic projections from the basal forebrain to frontal, parietal, temporal, occipital and cingulate cortices: A combined fluorescent tracer and acetylcholinesterase analysis. *Brain Research Bulletin, 8*, 727–749.

Bjordahl, T. S., Dimyan, M. A., & Weinberger, N. M. (1998). Induction of long-term receptive field plasticity in the auditory cortex of the waking guinea pig by stimulation of the nucleus basalis. *Behavioral Neuroscience, 112*, 467–479.

Blozovski, D., & Hennocq, N. (1982). Effects of antimuscarinic cholinergic drugs injected systemically or into the hippocampo-entorhinal area upon passive avoidance learning in young rats. *Psychopharmacology, 76*, 351–358.

Butt, A. E., Testylier, G., & Dykes, R. W. (1997). Acetylcholine release in rat frontal and somatosensory cortex is enhanced during tactile discrimination learning. *Psychobiology, 25*, 18–33.

Campbell, A. W. (1905). *Histological studies on the localization of cerebral function*. Cambridge: Cambridge University Press.

Casamenti, F., Deffenu, G., Abbamondi, A. L., & Pepeu, G. (1986). Changes in cortical acetylcholine output induced by modulation of the nucleus basalis. *Brain Research Bulletin, 16*, 689–695.

Celesia, G. G., & Jasper, H. H. (1966). Acetylcholine released from cerebral cortex in relation to state of activation. *Neurology, 16*, 1053–1063.

Chapman, C. E., Jiang, W., & Lamarre, Y. (1988). Modulation of lemniscal input during conditioned arm movements in the monkey. *Experimental Brain Research, 72*, 316–334.

Chernychev, B. V., & Weinberger, N. M. (1998). Acoustic frequency tuning of neurons in the basal forebrain of the waking guinea pig. *Brain Research, 793*, 79–94.

Condon, C. D., & Weinberger, N. M. (1991). Habituation produces frequency-specific plasticity of receptive fields in the auditory cortex. *Behavioral Neuroscience, 105*, 416–430.

Coulter, J. D. (1974). Sensory transmission through lemniscal pathway during voluntary movement in the cat. *Journal of Neurophysiology, 37*, 831–845.

Deutsch, J. A. (1971). The cholinergic synapse and the site of memory. *Science, 174*, 788–794.

Diamond, D. M., & Weinberger, N. M. (1989). The role of context in the expression of learning-induced plasticity of single neurons in auditory cortex. *Behavioral Neuroscience, 103*, 471–494.

Dimyan, M. A., & Weinberger, N. M. (1999). Basal forebrain stimulation induces discriminative receptive field plasticity in auditory cortex. *Behavioral Neuroscience, 113*, 691–702.

Duque, A., Balatoni, B., Detari, L., & Zaborszky, L. (2000). EEG correlation of the discharge properties of identified neurons in the basal forebrain. *Journal of Neurophysiology, 84*, 1627–1635.

Dykes, R. W. (1997). Mechanisms controlling neuronal plasticity in somatosensory cortex. *Canadian Journal of Physiological Pharmacology, 75*, 535–545.

Edeline, J.-M., Hars, B., Maho, C., & Hennevin, E. (1994a). Transient and prolonged facilitation of tone-evoked responses induced by basal forebrain stimulation in the rat auditory cortex. *Experimental Brain Research, 96*, 373–386.

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

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

Edeline, J.-M., Neuenschwander-El Massioui, N., & Dutrieux, G. (1990b). Discriminative long-term retention of rapidly induced

multiunit changes in the hippocampus, medial geniculate and auditory cortex. *Behavioral Brain Research, 39*, 145–155.

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

Edeline, J.-M., & Weinberger, N. M. (1991). Thalamic short-term plasticity in the auditory system: Associative retuning of receptive fields in the ventral medial geniculate body. *Behavioral Neuroscience, 105*, 618–639.

Edeline, J.-M., & 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. *Behavioral Neuroscience, 106*, 81–105.

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

Eichenbaum, H., & Cohen, N. J. (2001). *From conditioning to conscious recollection: Memory systems of the brain*. New York: Oxford Press.

Ferrier, D. (1876). *The functions of the brain*. London: Smith & Elder.

Fisher, A., Brandeis, R., Chapman, S., Pittel, Z., & Michaelson, D. M. (1998). M1 muscarinic agonist treatment reverses cognitive and cholinergic impairments of apolipo protein E-deficient mice. *Journal of Neurochemistry, 70*, 1197–1991.

Flood, J. F., Landry, D. W., & Jarvik, M. E. (1981). Cholinergic receptor interactions and their effects on long-term memory processing. *Brain Research, 215*, 177–185.

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

Galambos, R., Sheatz, G., & Vernier, V. G. (1955). Electrophysiological correlates of a conditioned response in cats. *Science, 123*, 376–377.

Galván, V. V., Chen, J., & Weinberger, N. M. (2001). Long term frequency tuning of local field potentials in the auditory cortex of the waking guinea pig. *Journal of the Association for Research in Otolaryngology, 2*, 199–215.

Galván, V. V., & Weinberger, N. M. (2002). Long-term consolidation and retention of learning: Induced tuning plasticity in the auditory cortex of the guinea pig. *Neurobiology of Learning and Memory, 77*, 78–108.

Gao, E., & Suga, N. (2000). Experience-dependent plasticity in the auditory cortex and the inferior colliculus of bats: Role of the corticofugal system. *Proceedings of the National Academy of Sciences of the United States of America, 97*, 8081–8086.

Ghez, C., & Lenzi, G. L. (1971). Modulation of sensory transmission to cat lemniscal system during voluntary movement. *Pflugers Archieve, 323*, 273–278.

Ghez, C., & Pisa, M. (1972). Inhibition of afferent transmission in cuncate nucleus during voluntary movement in the cat. *Brain Research, 40*, 145–151.

Gower, A. J. (1987). Enhancement by secoverine and physostigmine of retention of passive avoidance response in mice. *Psychopharmacology, 91*, 326–329.

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

Hume, D. (1777/1894). *An enquiry concerning the human understanding*. Oxford: Clarendon Press.

Introini-Collison, I. B., & McGaugh, J. L. (1988). Modulation of memory by post-training epinephrine: Involvement of cholinergic mechanisms. *Psychopharmacology, 94*, 379–385.

Ji, W., Gao, E., & Suga, N. (2001). Effects of acetylcholine and atropine on plasticity of central auditory neurons caused by conditioning in bats. *Journal of Neurophysiology, 86*, 211–225.

Jimenez-Capdeville, M. E., & Dykes, R. W. (1996). Changes in cortical acetylcholine release in the rat during day and night: Differences between motor and sensory areas. *Neuroscience, 71*, 567–579.

Johnston, M. V., McKinney, M., & Coyle, J. T. (1979). Evidence for a cholinergic projection to neocortex from neurons in the basal forebrain. *Proceedings of the National Academy of Sciences of the United States of America, 76*, 5392–5396.

Juckel, G., Hegerl, U., Molna, M., Csepe, V., & Karmos, G. (1999). Auditory evoked potentials reflect serotonergic neuronal activity—a study in behaving cats administered drugs acting on 5-HT1A autoreceptors in the dorsal raphe nucleus. *Neuropsychopharmacology, 21*, 710–716.

Kilgard, M. P., & Merzenich, M. M. (1998). Cortical map reorganization enabled by nucleus basalis activity. *Science, 279*, 1714–1718.

Kilgard, M. P., Pandya, P. K., Vazquez, J., Gehi, A., Schreiner, C. E., & Merzenich, M. M. (2001). Sensory input directs spatial and temporal plasticity in primary auditory cortex. *Journal of Neurophysiology, 86*, 326–338.

Kisley, M. A., & Gerstein, G. L. (2001). Daily variation and appetitive conditioning-induced plasticity of auditory cortex receptive fields. *European Journal of Neuroscience, 13*, 1993–2003.

Konorski, J. (1967). *Integrative activity of the brain*. Chicago: University of Chicago Press.

Kurosawa, M., Sato, A., & Sato, Y. (1989). Stimulation of the nucleus basalis of Meynert increases acetylcholine release in the cerebral cortex in rats. *Neuroscience Letters, 98*, 45–50.

Lacombe, P., Sercombe, R., Verrecchia, C., Philipson, V., MacKenzie, E. T., & Seylaz, J. (1989). Cortical blood flow increases induced by stimulation of the substantia innominata in the unanesthetized rat. *Brain Research, 491*, 1–14.

Lehmann, J., Nagy, J. I., Atmadia, S., & Fibiger, H. C. (1980). The nucleus basalis magnocellularis: The origin of a cholinergic projection to the neocortex of the rat. *Neuroscience, 5*, 1161–1174.

Lennartz, R. C., & Weinberger, N. M. (1992a). Frequency-specific receptive field plasticity in the medial geniculate body induced by Pavlovian fear conditioning is expressed in the anesthetized brain. *Behavioral Neuroscience, 106*, 484–497.

Lennartz, R. C., & Weinberger, N. M. (1992b). Analysis of response systems in Pavlovian conditioning reveal rapidly vs. slowly acquired conditioned responses: Support for two-factors and implications for neurobiology. *Psychobiology, 20*, 93–119.

LoConte, G., Bartolini, L., Casamenti, F., Marconcini-Pepeu, I., & Pepeu, G. (1982). Lesions of cholinergic forebrain nuclei: Changes in avoidance behavior and scopolamine actions. *Pharmacology, Biochemistry and Behavior, 17*, 933–937.

Mackintosh, N. J. (1974). *The psychology of animal learning*. London: Academic Press.

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

Manunta, Y., & Edeline, J.-M. (1997). Effects of noradrenaline on frequency tuning of rat auditory cortex neurons. *European Journal of Neuroscience, 9*, 833–847.

McKenna, T. M., Ashe, J. H., & Weinberger, N. M. (1989). Cholinergic modulation of frequency receptive fields in auditory cortex: I. Frequency-specific effects of muscarinic agonists. *Synapse, 4*, 30–44.

McLin, D. E., III, Miasnikov, A. A., & Weinberger, N. M. (2002a). Induction of behavioral associative memory by stimulation of the nucleus basalis. *Proceedings of the National Academy of Sciences of the United States of America, 99*, 4002–4007.

McLin, D. E., III, Miasnikov, A. A., & Weinberger, N. M. (2002b). The effects of electrical stimulation of the nucleus basalis on the electroencephalogram, heart rate and respiration. *Behavioral Neuroscience, 116*, 795–806.

McLin, D. E., III, Miasnikov, A. A., & Weinberger, N. M. (2003). CS-specific γ, θ, and α EEG activity detected in stimulus generalization

following induction of behavioral memory by stimulation of the nucleus basalis. *Neurobiology of Learning and Memory, 79*, 152–176.

Mesulam, M. M., Mufson, E. J., Wainer, B. H., & Levey, A. I. (1983). Central cholinergic pathways in the rat: An overview based on an alternative nomenclature. *Neuroscience, 114*, 64–76.

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

Metherate, R., & Ashe, J. H. (1993). Nucleus basalis stimulation facilitates thalamocortical synaptic transmission in the rat auditory cortex. *Synapse, 14*, 132–143.

Metherate, R., Tremblay, N., & Dykes, R. W. (1988). Transient and prolonged effects of acetylcholine on responsiveness of cat somatosensory cortical neurons. *Journal of Neurophysiology, 59*, 1231–1252.

Metherate, R., & 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.

Miasnikov, A., McLin, D., III, & Weinberger, N. M. (2001). Muscarinic dependence of nucleus basalis induced conditioned receptive field plasticity. *Neuroreport, 12*, 1537–1542.

Miasnikov, A. A., & Weinberger, N. M., (2003). Rapid formation of behavioral memory to tone aired with nucleus basalis stimulation in rat. *Society for Neuroscience Abstracts* (in press).

Molchan, S. E., Sunderland, T., McIntosh, A. R., Herscovitch, P., & Schreurs, B. G. (1994). A functional anatomical study of associative learning in humans. *Proceedings of the National Academy of Sciences of the United States of America, 91*, 8122–8126.

Moriizumi, T., & Hattori, T. (1992). Separate neuronal populations of the rat globus pallidus projecting to the subthalamic nucleus, auditory cortex and pedunculopontine tegmental area. *Neuroscience, 46*, 701–710.

Morris, J. S., Friston, K. J., & Dolan, R. J. (1998). Experience-dependent modulation of tonotopic neural responses in human auditory cortex. *Proceedings of the Royal Society of London, 265*, 649–657.

Mowrer, O. H. (1947). On the dual nature of leaning: A reinterpretation of "conditioning" and problem-solving. *Harvard Educational Review, 17*, 102–148.

Oh, J. D., Edwards, R. H., & Woolf, N. J. (1996). Choline acetyltransferase mRNA plasticity with Pavlovian conditioning. *Experimental Neurology, 140*, 95–99.

Olds, J., & Peretz, B. (1960). A motivational analysis of the reticular activating system. *Electroencephalography and Clinical Neurophysiology, 12*, 445–454.

Orsetti, M., Casamenti, F., & Pepeu, G. (1996). Enhanced acetylcholine release in the hippocampus and cortex during acquisition of an operant behavior. *Brain Research, 724*, 89–96.

Pennartz, C. M. (1995). The ascending neuromodulatory systems in learning by reinforcement: Comparing computational conjectures with experimental findings. *Brain Research Review, 21*, 219–245.

Potter, D. D., Pickles, C. D., Roberts, R. C., & Rugg, M. D. (2000). Scopolamine impairs memory performance and reduces frontal but not parietal visual P3 amplitude. *Biological Psychology, 52*, 37–52.

Powell, D. A., & Levine-Bryce, D. (1988). A comparison of two model systems of associative learning: Heart rate and eyeblink conditioning in the rabbit. *Psychophysiology, 25*, 672–682.

Rasmusson, D. D. (2000). The role of acetylcholine in cortical synaptic plasticity. *Behavioral Brain Research, 115*, 205–218.

Rasmusson, D. D., Clow, K., & Szerb, J. C. (1992). Frequency-dependent increase in cortical acetylcholine release evoked by stimulation of the nucleus basalis magnocellularis in the rat. *Brain Research, 594*, 150–154.

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

Rescorla, R. A. (1988). Behavioral studies of Pavlovian conditioning. *Annual Review of Neuroscience, 11*, 329–352.

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

Riekkinen, P., Jr., Riekkinen, M., Sirvio, J., Miettinen, R., & Riekkinen, P. (1992). Loss of cholinergic neurons in the nucleus basalis induces neocortical electroencephalographic and passive avoidance deficits. *Neuroscience, 47*, 823–831.

Rudy, J. W. (1996). Scopolamine administered before and after training impairs both contextual and auditory-cue fear conditioning. *Neurobiology of Learning and Memory, 65*, 73–81.

Russell, R. W., Escobar, M. L., Booth, R. A., & Bermudez-Rattoni, F. (1994). Accelerating behavioral recovery after cortical lesions: II. In vivo evidence for cholinergic involvement. *Behavioral Neural Biology, 61*, 81–92.

Rutkowski, R., Than, K., & Weinberger, N. M. (2002). Evidence for area of frequency representation encoding acquired stimulus importance in rat primary auditory cortex. *Society for Neuroscience Abstracts, 24*.

Salinas, J. A., Introini-Collison, I. B., Dalmaz, C., & McGaugh, J. L. (1997). Posttraining intra-amygdala infusion of oxotremorine and propranolol modulate storage of memory for reductions in reward magnitude. *Neurobiology of Learning and Memory, 68*, 51–59.

Saper, C. B. (1984). Organization of cerebral cortical afferent systems in the rat: II. Magnocellular basal nucleus. *Journal of Comparative Neurology, 222*, 313–342.

Sato, A., Sato, Y., & Uchida, S. (2001). Regulation of regional cerebral blood flow by cholinergic fibers originating in the basal forebrain. *International Journal of Developmental Neuroscience, 19*, 327–337.

Schlosberg, H. (1937). The relationship between success and the laws of conditioning. *Psychological Review, 44*, 379–394.

Schneiderman, N., Fuentes, I., & Gormezano, I. (1962). Acquisition and extinction of the classically conditioned eyeblink response in the albino rabbit. *Science, 136*, 650–652.

Schreurs, B. G., McIntosh, A. R., Bahro, M., Herscovitch, P., Sunderland, T., & Molchan, S. E. (1997). Lateralization and behavioral correlation of changes in regional cerebral blood flow with classical conditioning of the human eyeblink response. *Journal of Neurophysiology, 77*, 2153–2163.

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

Stark, H., & Scheich, H. (1997). Dopaminergic and serotonergic neurotransmission systems are differentially involved in auditory cortex learning: A long-term microdialysis study of metabolites. *Journal of Neurochemistry, 68*, 691–697.

Steriade, M., & Buzsaki, G. (1990). Parallel activation of thalamic and cortical neurons by brainstem and basal forebrain cholinergic systems. In M. Steriade, & D. Biesold (Eds.), *Brain cholinergic systems* (pp. 3–64). Oxford: University of Oxford Press.

Stratton, L., & Pertinovich, L. (1963). Post-trial injections of an anticholinesterase drug and maze learning in two strains of rats. *Psychopharmacology, 5*, 47–54.

Thompson, R. R., & Kim, J. J. (1996). Memory systems in the brain and localization of a memory. *Proceedings of the National Academy of Sciences of the United States of America, 93*, 13438–13444.

Thompson, R. F., & Tracy, J. A. (1995). Cerebellar localization of a memory trace. In J. L. McGaugh, F. Bermudez-Rattoni, & R. A. Prado-Alcala (Eds.), *Plasticity in the central nervous system, learning and memory* (pp. 107–127). New Jersey: Erlbaum.

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

Weinberger, N. M. (1998). Physiological memory in primary auditory cortex: Characteristics and mechanisms. *Neurobiology of Learning and Memory, 70*, 226–251.

Weinberger, N. M. (2001). Memory codes: A new concept for an old problem. In P. Gold, & W. Greenough (Eds.), *Memory Consolidation: Essays in Honor of James L. McGaugh* (pp. 321–342). Washington, DC: American Psychological Association.

Weinberger, N. M. (in press). Experience-dependent response plasticity in the auditory cortex: Issues, characteristics, mechanism and function. In T. Parks, E. Rubel, A. Popper, & Fay (Eds.), *Springer handbook of auditory research*. New York: Springer-Verlag.

Weinberger, N. M., Ashe, J. H., Metherate, R., McKenna, T. M., Diamond, D. M., Bakin, J. S., Lennartz, R. C., & Cassady, J. M. (1990). Neural adaptive information processing: A preliminary model of receptive field plasticity in auditory cortex during Pavlovian conditioning. In M. Gabriel, & J. Moore (Eds.), *Neurocomputation and learning: Foundations of adaptive networks*. Cambridge: Bradford Books/MIT Press.

Weinberger, N. M., & Diamond, D. M. (1987). Physiological plasticity of single neurons in auditory cortex: Rapid induction by learning. *Progress in Neurobiology, 29*, 1–55.

Weinberger, N. M., Diamond, D. M., & McKenna, T. M. (1984). Initial events in conditioning: Plasticity in the pupillomotor and auditory systems. In G. Lynch, J. L. McGaugh, & N. M. Weinberger (Eds.), *Neurobiology of learning and memory*. New York: Gilford Press.

Weinberger, N. M., Javid, R., & Lepan, B. (1993). Long-term retention of learning-induced receptive field plasticity in the auditory cortex. *Proceedings of the National Academy of Sciences of the United States of America, 90*, 2394–2398.

Wenk, G. L., Stoehr, J. D., Quintana, G., Mobley, S., & Wiley, R. G. (1994). Behavioral, biochemical, histological, and electrophysiological effects of 192 IgG-saporin injections into the basal forebrain of rats. *Journal of Neuroscience, 10*, 5986–5995.

Wester, K. (1971). Habituation to electrical stimulation of the thalamus in unanaesthetized cats. *Electroencephalography and Clinical Neurophysiology, 30*, 52–61.

Wester, K. (1972). Reinforcing effects of thalamic stimulation resistant to habituation. *Brain Research, 43*, 139–145.

Whalen, P. J., Kapp, B. S., & Pascoe, J. P. (1994). Neuronal activity within the nucleus basalis and conditioned neocortical electroencephalographic activation. *Journal of Neuroscience, 14*, 1623–1633.

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

Winters, R. W., McCabe, P. M., & Schneiderman, N. (2001). Functional utility and neurobiology of conditioned autonomic responses. In J. W. Moore (Ed.), *A neuroscientist's guide to classical conditioning*. New York: Springer.

Young, R. M. (1970). *Mind, brain and adaptation in the nineteenth century*. Oxford: Clarendon Press.