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Chapter 7

New perspectives on the auditory cortex: learning and memory

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INTRODUCTION

This chapter concerns a paradigm shift in conceptions of the primary auditory cortex (A1). Alone among the multitudinous cortical fields, the primary sensory cortices have had the dubious honor of having their functions "known" before any physiologic data had been obtained. This function has been assumed to be "pure sensory analysis," specifically excluding any psychologic or cognitive functions. Campbell crystallized this view in his highly influential 1905 monograph, *Histological Studies on the Localisation of Cerebral Function*. An insightful perspective on the matter has been provided by Irving Diamond, late professor of neuroscience at Duke University: "Campbell's influential monograph was largely responsible for cleaving learning and memory from sensory processes" (Diamond, 1979). It might seem odd that Campbell's aged work should be cited here, but the conception that he championed has become so woven into the fabric of neuroscience as to constitute an invisible core assumption that still guides much research and thought.

Nonetheless, the position that the primary sensory cortices are exclusively "sensory analytic," and proscribed from learning, memory, and a variety of other cognitive processes has been eroded to the point of collapse by two lines of research. First, Galambos and colleagues (1956) discovered that training a cat with a click followed by an air puff to its eye both produced learning to predict this annoyance and also greatly increased the amplitude of the click-evoked potential in A1. Thus, the responses of the auditory cortex to sound were shown to be altered when it became behaviorally important. This finding, using classic (pavlovian) associative conditioning, was soon pursued in many laboratories internationally to include controls for general arousal and sensitization, and extend the phenomenon to various species, including humans, different types of auditory cues, multisound discrimination training, and more complex tasks such as instrumental/operant conditioning (reviewed in Weinberger and Diamond, 1987).

Second, studies that combined auditory neurophysiology with associative conditioning discovered representational plasticity (RP) in the primary auditory cortex. Beyond "physiological plasticity" (hereafter "plasticity"), which refers to most types of non-transient changes in the nervous system, RP refers to a systematic change in the encoding of sensory stimuli along a dimension, e.g., acoustic frequency, level, duration tuning, frequency-modulated (FM) envelope, repetition rate, and localization in space. In the best-studied example, the coding of acoustic frequency is modified so that neuronal receptive fields ("tuning functions") are systematically altered in learning and memory. More specifically, the frequency tuning of neurons in A1 shifts toward and to the frequency of the signal tone ("receptive field shift") (Diamond and Weinberger, 1986; Bakin and Weinberger, 1990; Edeline and Weinberger, 1993).

The implications of RP are great. Thus, simple "plasticity" in the form of an increased cortical response to an important sound may be limited to that sound. In stark contrast, RP is not limited to a particular experienced stimulus, but rather biases an entire sensory dimension to emphasize behaviorally important sensory stimuli. Therefore, the processing of future and hitherto non-experienced stimuli in that dimension will be altered. Such learning-based predispositions to classes of sounds or types of acoustic parameters are likely to have major consequences for each individual, including modifying the effects of remedial auditory training in ways not yet appreciated.

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These types of finding have at least three major implications. First, they provide a foundation for understanding how the contents of auditory experience are acquired, represented, stored, and ultimately employed in the service of adaptive behavior. Second, they force a reconceptualization of the auditory cortex (and other "early" sensory cortices). Third, they demonstrate the need for a new way of thinking about overall cortical organization. Insofar as the primary auditory cortex is clearly deeply involved in learning, memory, and other cognitive processes (as documented below), it seems likely that all of the cerebral cortex is "cognitive," but various regions conduct different and somewhat specialized computations. Much less research on this new approach has been conducted in the primary somatosensory (S1) and visual (V1) cortices. But the findings to date appear to be fundamentally the same as for A1 (e.g., S1: Wiest et al., 2010; V1: Miller et al., 2008). In short, "pure sensory cortex" now appears to be a misconception. This no longer tenable belief about primary sensory cortices remains largely unexamined and dominant in neuroscience, perhaps because it seems to be supported by personal experience. Thus, "introspection" may suggest that sensation and perception precede and are separate from all cognition. But how the brain creates experience is not bound by folk psychology. It is past time to drop this long-outdated concept, which is not only demonstrably false but also shackles thought and impedes progress both in the laboratory and in the clinic (see also Masterton, 1993).

What follows is an account of the current state of the involvement of the primary auditory cortex in auditory associative learning and memory, as these are dominant processes in knowledge acquisition and behavioral adaptation. Implications for the treatment of certain human disorders are included. Emphasis is placed on animal studies because they have been most revealing, including permitting manipulations unavailable in humans. However, the recording and imaging studies reported to date for the human brain appear to be consistent with the findings from animal studies. Rather than provide an exhaustive review of the literature, the choice of examples is based on explaining types of findings and illustrating specific issues. Readers who wish to pursue various other aspects of this topic may consult prior reviews (e.g., Palmer et al., 1998; Rauschecker, 1999; Kilgard et al., 2002; Edeline, 2003; Suga and Ma, 2003; Weinberger, 2004 (analysis of experimental designs), 2007 (intersections of learning/memory and sensory physiology), 2008 (cognitive functions of auditory cortex); Ohl and Scheich, 2005; Scheich et al., 2011). This article draws from Weinberger (2011b) for early neurobehavioral research.

BASIC CONSIDERATIONS AND EARLY FINDINGS

Introduction

For present purposes, we use broad definitions of learning and memory to give them widespread applicability. "Learning" is the acquisition of information and "memory" is the storage of information for periods as short as many seconds (e.g., memorizing a telephone number to order a pizza) to lifetime (one's own name). Two important points should be kept in mind. First, neither learning nor memory is directly observable. They must always be inferred from behavior. Therefore, simply placing a subject in a learning situation, such as repeated presentation of a sound that is followed by a reward, cannot justify the conclusion that learning has taken place. Rather, learning must be inferred from changes in behavior. The necessity of behavioral validation means that neural plasticity cannot be used to verify that learning has occurred; rather, it is a presumptive substrate of learning and memory. Second, because learning and memory are inferred from behavior, all causes of a behavioral change, other than the acquisition and storage of information, must be ruled out. These include general changes in a subject's state of arousal or excitability, drug condition, sensory abilities, and capability for motor action.

Much learning-brain research concerns the relationship between two or more stimuli, experiences, or events, i.e., the learning of associations. For example, whenever there are regularities in experience, such that one sound predicts another event, an association can form so that the sound predicts (and may bring to mind or elicit an image of) the second event. A common example is the expectation of seeing a car after hearing a car horn. Such predictive associations occur continually and in myriad ways, thus enabling people and other animals to predict the consequences of events or of their own behavior, rather than simply be passive recipients of stimuli. In the laboratory, daily associations are modeled generally by classic (pavlovian) conditioning, in which one stimulus regularly precedes another experience, and instrumental/operant conditioning, in which one's own behavior is regularly followed by an event, e.g., a reward.

Background findings

This section provides a summary of the approximately 30-year period (1956–1984) that formed the foundations for contemporary research. During this era, learning-induced plasticity in A1 was discovered, validated, and extended to many learning tasks. The issues focused on the fate of sensory signals when they predicted an

important event, such as reward or negative reinforcement. The main question, often implicit, was: "When a stimulus gains behavioral relevance through experience, do the neural bases of learning (i.e., plasticity) begin during or after analysis of that signal?" This issue was part of the larger program of seeking the neural circuitry underlying learning and memory. Naturally, researchers simply recorded the responses of the auditory cortex to signal sounds during training trials.

Galambos and his colleagues (1956) published the first western study on learning and plasticity in primary sensory cortex. Cats received an auditory (click) conditioned stimulus (CS) paired with an immediately following puff of air to the face (unconditioned stimulus, US). As a result of this classic conditioning procedure, CS-elicited local field potentials (LFPs) in A1 increased in magnitude. The authors validated learning by noting the development of eyeblink conditioned responses. Furthermore, they also controlled for CS constancy at the ear by obtaining the same findings with subjects under neuromuscular blockade, thus preventing head and pinna movements and possible contractions of the middle-ear muscles. Interestingly, the authors failed to include a non-associative control for sensitization or general excitability, such as a group that received the CS and US unpaired. However, subsequent investigators did include proper controls, confirming the associative nature of increased response magnitude of LFPs in A1 (Marsh et al., 1961; Majkowski and Sobieszek, 1975; Molnár et al., 1988).

LFP research was extended to different conditioning tasks and pavlovian processes, with essentially the same findings of enhanced responses to sounds that became behaviorally important (reviewed in Weinberger and Diamond, 1987). Similar results were obtained for instrumental avoidance learning. In fact, systematic increases in CS-evoked LFPs could be obtained in the same dogs that were successively switched between classic conditioning and instrumental avoidance conditioning with the same CS and US, despite the learning of different responses for the two types of conditioning (Cassady et al., 1973).

In addition to the use of LFPs, workers began recording cellular discharges in A1. Most studies recorded from clusters of cells ("multiple-unit" activity). The results generally were the same, i.e., increased discharges to an acoustic CS that predicted reward or punishment, as animals formed behavioral conditioned responses indicating successful associations. This increase in response was fairly consistent, both in simple (one-tone) conditioning and in two-tone discrimination training (reinforced CS+, non-reinforced CS–) (Buchwald et al., 1966; Saunders and Chabora, 1969). Reversal was also obtained when the CS+and CS– acoustic stimuli were interchanged after initial learning. Moreover, acoustic CS+stimuli acquired the ability to elicit responses in the sensory cortex of the shock US, i.e., in primary somatosensory cortex (Oleson et al., 1975).

Such "cluster" recordings have the advantage over single-unit recordings of yielding consistent data over days. They have the disadvantage of being unable to determine if single cells develop different directions of plasticity, i.e., either increased or decreased responses. That is, if associative processes produce both increased and decreased responses to the CS, but increased responses dominate, then the decreased responses would not be detected.

Studies of single units in auditory cortex during learning also found plasticity. However, as suspected, despite the detection of many cells that developed increased responses to the CS, a substantial number of cells developed decreased responses, and yet others exhibited no change (Gasanov and Galashina, 1976; Woody et al., 1976; Dumenko and Sachenko, 1978, 1979; Weinberger et al., 1984). Similar heterogeneity of unit discharge plasticity was also found in auditory field A2 (Diamond and Weinberger, 1984). Such divergent results were not attributable to inadvertent changes in effective acoustic stimulus level at the auditory periphery, undetected movements, muscle contractions, or feedback from muscle spindles, because the same results were obtained when animals were trained while under neuromuscular blockade (Weinberger et al., 1984).

Although studies of associative learning had firmly established that the neural bases of learning start with sensory analysis of acoustic signals, and that single-unit plasticity in A1 was associative, the findings of opposite sign made no functional sense. Thus, while recording in A1 during training trials had provided foundational information, this approach appeared to have reached an impasse. A new direction was needed.

CONTEMPORARY APPROACHES: REPRESENTATIONAL PLASTICITY

A synthesis of two disciplines

Paradigm shifts in both concept and method developed once the issue changed from whether the auditory cortex was involved in learning and memory to that of how A1 was involved. Thus, while one could easily determine that plasticity had developed during training trials, it was impossible to know whether changes were restricted to, e.g., the signal tone, or were perhaps even greater to other frequencies that had not been tested. The situation was similar for behavior; detection that learning had

happened merely required observing behavioral changes during trials, but it was impossible thereby to know what had been learned. Thus, while the subject might have learned that a particular acoustic frequency predicted or provided the opportunity to press a button to get reward, she might have merely learned that sound predicted reward, or simply that a sudden stimulus predicted reward. In fact, subjects can learn about any single stimulus parameter or any combination of parameters of a given sound (e.g., frequency, level, duration, location, pattern) because they coexist and therefore are all predictive of reinforcement. In short, research began to address the specificity of both cortical plasticity and memory.

The solution to solving the specificity problem for both plasticity and memory was to invent a hybrid approach that was based on a synthesis of two previously non-intersecting disciplines: auditory neurophysiology and the neurobiology of learning and memory. Thus, to determine if learning alters neuronal coding of sound in the auditory cortex, researchers began to obtain auditory cortical receptive fields before and after training subjects in any desired learning task that used sounds. For example, receptive fields for acoustic frequency were obtained by giving many tones to obtain tuning functions before training, then training with one of the tones, and again obtaining tuning functions after training. To determine if learning specifically alters tuning, one merely subtracts the pretraining from the posttraining receptive fields.

The same logic and general procedure apply to behavior. Subjects are trained with one tone but tested after learning with many tones. The resultant behavioral data generate a "behavioral stimulus generalization gradient," the peak of which reflects the stimulus value that had gained the greatest memory value due to training. In most tasks, pretraining gradients cannot be obtained because no behavioral response is available. In these cases, a control group can be trained with a signal and reinforcement not paired, and the posttraining gradient from this group is subtracted from that of the paired (associative) group. However, investigators have also made use of recording autonomic behavioral responses that respond to sound before training (changes in heart rate or respiration) (McLin et al., 2002), and so have been able to obtain behavioral frequency gradients before and after training in the same subjects (Miasnikov et al., 2006).

Representational plasticity reveals specificity of auditory cortical dynamics

The "contemporary era" may be considered to have been initiated in the 1980s when a new question was posed that focused on specificity: "Does learning cause a 'retuning' of the primary auditory cortex?" Initially, studies concentrated on neural recording of the frequency-receptive fields of neurons in A1 before and after training. Later, behavioral frequency generalization gradients were also obtained. In so doing, new dimensions of learning and plasticity were uncovered, including unsuspected mnemonic functions and the role of the cholinergic system.

Gonzalez-Lima and Scheich (1984, 1986) found specificity of A1 plasticity by determining the spatially restricted increase in metabolic activity (2-deoxyglucose uptake) in the gerbil after classic conditioning with tone and aversive brain stimulation. Posttraining analysis of patterns of 2-deoxyglucose uptake in A1 revealed a CS-specific increase in metabolic activity for the cortical area that represented the CS frequency. However, most other research has employed neurophysiologic recording, primarily because of its greater spatial and temporal specificity and ability to repeatedly obtain data from the same subjects.

Receptive field analysis was first applied to classic auditory (tone) fear conditioning in the cat. Single-unit discharges were recorded in two non-primary auditory fields, "secondary" (A2) and ventral ectosylvian (VE) cortices (Diamond and Weinberger, 1986, 1989). Neural tuning became biased toward the tonal CS in a paired group but not in unpaired controls, demonstrating specific associative plasticity. Extinction (additional CS presentation without the shock US) produced loss of the receptive field plasticity. The findings received little notice, perhaps because these "higher" auditory fields were both expected to have plasticity and also were not well understood compared to A1.

Similar studies were then undertaken in A1 of the guinea pig with behavioral validation of associative learning, viz., conditioned bradycardia. Auditory fear conditioning produced increased discharges to the CS frequency with simultaneous decreased responses to many other frequencies. These opposing changes produced CS-directed shifts of tuning, so that the signal frequency could become the new "best frequency (BF)," i.e., peak of the tuning function (Bakin and Weinberger, 1990) (Fig. 7.1). Thus, associative learning can retune cells in the primary auditory cortex to increase the representation of sounds that become behaviorally important.

Representational plasticity across species

CS-specific associative tuning shifts develop in the primary auditory cortex of all species studied to date: guinea pig (Bakin and Weinberger, 1990), big brown bat (Gao and Suga, 2000), cat (Diamond and Weinberger, 1986), and rat (Kisley and Gerstein, 2001).

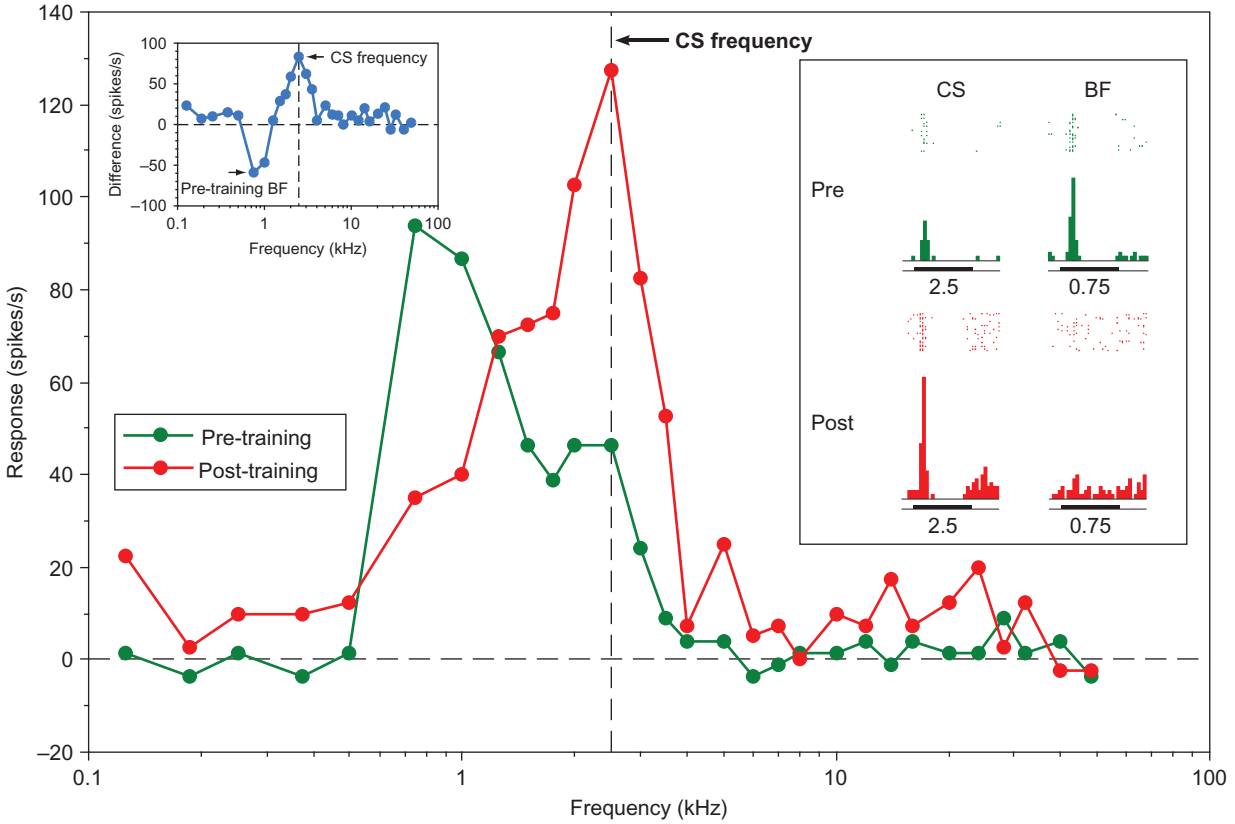

Fig. 7.1. Basic associative learning (classical conditioning) produces conditioned stimulus (CS)-specific facilitation and tuning shifts. An example of a complete shift of frequency tuning of a single cell in A1 of the guinea pig, from a pretraining best frequency (BF) of 0.75 kHz to the CS frequency of 2.5 kHz after 30 trials of auditory fear conditioning (tone–shock pairing). Right inset shows pre- and posttraining poststimulus time histograms (PSTHs) for the pretraining BF and the CS frequencies. Note the marked increase in response to the tone signal (2.5 kHz) and the concomitant decrease in response to the pretraining peak of the tuning function (0.75 kHz). The overall changes (post- minus pretuning) are shown in the upper left inset, revealing the high level of specificity of retuning to emphasize the signal frequency, caused by associative learning.

Furthermore, CS-specific expanded representations in the tonotopic map of A1, which are predicted from CS-directed frequency tuning shifts, develop in the owl monkey (Recanzone et al., 1993) and the rat (Rutkowski and Weinberger, 2005).

Associative plasticity also develops in the auditory cortex of humans during auditory learning. For example, Molchan and coworkers (1994) paired tone with air puffs to the right eye, causing the development of a conditioned eyeblink; this was reversed when the air puff was eliminated (i.e., "experimental extinction"). Compared to control conditions (tone and air puff not paired), they found an increase in regional cerebral blood flow (rCBF) in the left primary auditory cortex. These authors replicated and extended this finding, applying air puff to the left eye; they found associative increased rCBF in the right A1 (Schreurs et al., 1997). Thus, the auditory cortex contralateral to the locus of the noxious air puff developed associative plasticity.

Specificity within the tonotopic map also has been reported. Morris and associates (1998) conducted a two-tone discrimination study in which one tone (CS+) predicted a noxious sound (100 dB white noise) while the other (CS–) was presented without noise; the two types of trial were randomly intermixed. All subjects developed discriminative conditioned associations, detected as a change in skin conductance (galvanic skin response) only to the CS+tone. Positron emission tomography imaging revealed changes in rCBF within the tonotopic representation that were specific to the tones: responses to the CS+changed, whereas responses to the CS– did not change.

Thus, RP appears to be a ubiquitous aspect of auditory cortical functioning, in which associative learning specifically modifies the coding of acoustic stimuli, favoring the processing of behaviorally important stimuli at the expense of less relevant sounds. It is expected that the context of learning is part of a broad network that includes the representation of sounds, so that

auditory cortical processing is sufficiently flexible to enable stimuli that are not important in one situation to become behaviorally relevant in another situation. However, research on contextual aspects of RP has not yet been actively pursued.

ISN'T ALL AUDITORY LEARNING ACTUALLY "PERCEPTUAL LEARNING"?

The early studies of RP in the auditory cortex had established that learning alters the coding of sounds. While this constituted a "sea change" in conceptions of auditory cortical function, it did not have much influence on assumptions about cortical organization in general. Rather, Campbell's (1905) exclusion of learning, memory, and cognition from the primary auditory cortex underwent a slight modification. Instead of having the function of pure sensory analysis, A1 is often now viewed as an "adaptive auditory analyzer." It simply adjusts its analysis of the physical parameters of sound to emphasize those that become better perceived. That is, a widespread assumption is now that all auditory learning is simply "perceptual learning" and unrelated to associative learning and genuine behavioral memory.

Perceptual learning refers to an increase in sensory acuity within a stimulus dimension, due usually to extensive practice. Everyone is familiar with the highly tuned sensitivities of "noses" (perfumers), oenophiles, and musicians. Perceptual learning typically is the result of extensive and increasingly difficult discrimination training (Kellman, 2002). Such learning may require thousands of trials, over many days or weeks: e.g., frequency discrimination learning of 4000–5000 trials (Irvine et al., 2000); pitch discrimination of more than 10 000 trials (Demany and Semal, 2002); melodic patterns trained extensively with 1200 different stimuli (Tervaniemi et al., 2001). There are reports of perceptual learning in considerably fewer trials (Hawkey et al., 2004), but even so, associative learning can develop in five or fewer trials (Lennartz and Weinberger, 1992; Edeline et al., 1993). Associative learning can include discrimination learning but, unlike much perceptual learning, associations can be formed in the absence of discrimination training. However, that is not the most distinctive difference.

We can best appreciate the distinction by asking, "After an episode of perceptual learning, what is changed in the auditory cortex?" The answer would seem to be that the "machinery" of the cortex has been altered to enable greater acuity. This is certainly an interesting aspect of learning. However, in contrast to associative learning, perceptual learning does not seem to include "perceptual memory." This absence might reflect the fact that most investigators of perceptual learning are more concerned with sensory/perceptual processes than with mnemonic processes. But of greater import, subjects apparently do not actually remember the specific "contents" of their experience, that is, the particular stimuli or stimulus values given during certain of their multitude of trials. Thus, while increased acuity is an important aspect of auditory perception, it appears to be a process that is distinct from the storage of sounds. Therefore, perceptual learning might be thought of as controlling the gateway to memory; sounds that can be remembered first have to be distinguished and increased acuity provides increased acoustic detail of sounds that may enter memory, i.e., become the contents of experience.

An argument can be made that perceptual learning is a subclass of associative learning because subjects generally first have to learn an association between a sound and whatever comes next, usually a reward. Next, the discriminations become increasingly difficult. Because basic associative learning and its correlated cortical plasticity develop rapidly, they may help elucidate mechanisms of subsequent perceptual learning. In short, associative learning and perceptual learning are not the same, although both can affect primary sensory cortices in general, and the auditory cortex in particular (Weinberger, 2008).

DOES THE PRIMARY AUDITORY CORTEX HOLD SPECIFIC MEMORY TRACES?

The preceding review indicates that the coding of acoustic frequency in the primary auditory cortex is systematically modified by associative learning, to remodel this dimension to those spectra that become behaviorally important are emphasized at the expense of unimportant sounds. Moreover, the findings cannot be explained simply as only subserving perceptual learning. These considerations suggest that RP may be a basis for specific auditory memory. We evaluate this possibility in the following sections.

Forms of representational plasticity

To this point, we have focused on shifts in frequency tuning toward or to the training frequency. This has been justified by the fact that this was the first form of RP discovered (Diamond and Weinberger, 1986; Bakin and Weinberger, 1990). However, the possible domain of forms of plasticity is very large. It encompasses all parameters of acoustic response. There are many ways to organize and quantify neuronal responses to sound. Each of them might develop RP, i.e., exhibit bias toward sounds that gain behavioral significance, generally accompanied by relative loss of emphasis on some

other stimulus values within the domain of the modified acoustic dimension (but see the section on three classes of auditory tasks and representational plasticity, below).

One of the most extensively used methods of characterizing response to the acoustic spectrum is to randomly and repeatedly present brief pure tone pips across acoustic frequency and stimulus level ("intensity"), yielding a frequency response area while recording unit or multiunit discharges from microelectrodes in the animal brain. This approach delimits the spectro-level space within which neurons respond. The "characteristic frequency" (CF) is a cardinal parameter of response: the frequency to which the cells are most sensitive; the level at which the CF occurs is the threshold. Response selectivity can be determined by measuring the bandwidth (BW) of response, usually from 10–30 dB above threshold. The BW is simply the frequency range over which the neurons respond at each of the levels specified; it is usually given in octaves. In addition, researchers often designate the BF, which is the frequency–level combination that elicits the greatest magnitude of neuronal response (usually given in spikes/second above pretone background activity rate). Figure 7.2A presents a typical frequency response area.

In addition, the primary auditory cortex contains a "tonotopic map," in which the CFs of neighboring cells are likely to be similar, but not identical, and the organization of CFs across A1 is across the spectrum (low–high), very roughly like the layout of a piano keyboard, although far less precise (Fig. 7.2B). The amount of area representing different frequencies (or fairly narrow frequency bands) is determined by interpolation from the "maps" of CFs, which usually contain 60–80 spaced recording sites, and require many hours to obtain by moving microelectrodes across the cortex in anesthetized subjects.

In summary, three major forms of RP for acoustic frequency are available: (1) specific decrease in threshold and BW near threshold; (2) tuning shift toward or to a signal frequency above threshold; and (3) specific increase of signal area in the tonotopic map of A1. These forms may be linked along the dimension of magnitude of effect. Thus, decreased threshold and BW may be the minimal expression of RP. Greater effects may be manifest as actual changes in frequency tuning above threshold, and the largest expression of plasticity seems to be a frank increase in representational area. The relationship between tuning shifts and map expansions is most clearly understood, because the area of representation is simply the distribution of frequency tuning across the entire primary auditory cortex. Therefore, if many loci shift their tuning to favor the signal frequency, then an increase in representational area for that frequency should result. However, research on the relationships of different forms of RP is still in its earliest stages and so no definitive conclusions can be drawn at this time.

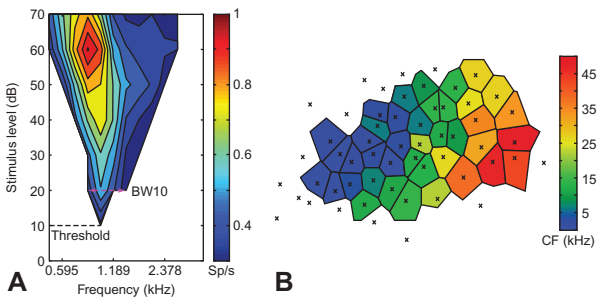

Fig. 7.2. (**A**) Example of a frequency response area (FRA), which provides the response of neurons in the auditory cortex to tonal frequencies (kHz) over a wide range of stimulus levels (intensity, dB). The frequency tuning of cells at threshold (characteristic frequency, CF) and the selectivity of tuning (measured at 10 dB above threshold) are indicated. The CF in this case is ~1.0 kHz. The colors indicate the magnitude of response, which in this case is at 60 dB. (**B**) Example of a tonotopic map in the primary auditory cortex of the rats. The CFs of all recordings are represented in the standard measure as interpolated polygons based on Voronoi tessellation methods. This enables determination of the area of the cortex that represents each acoustic frequency band. In this case, frequencies below ~5.0 kHz are overrepresented because the animal was trained with a low-frequency tone. The increase in representational area is attributable to tuning many shifts toward and to the signal tone frequency in the auditory cortex.

Basic considerations of specific memory traces

If RP is part of the substrate of specific auditory memory, then it might be expected to possess the major characteristics of behavioral associative memory itself. This would impose a set of criteria that have not previously been demanded of any other neurophysiologic correlates of learning and memory. The apparent "double standard" does not reflect a prejudice against sensory cortical bases of memory, but rather that studies of non-sensory regions of the brain (perhaps 99% of literature) are generally not concerned with memory content, i.e., the neural bases of specific representations of stimuli, but rather focus on the processes that enable memory, such as the time-limited role of the medial temporal lobe in long-term memories stored in the cerebral cortex (Squire et al., 2004).

What are these major characteristics of associative memory? In addition to being associative, specific memory traces (SMTs) should also exhibit specificity, develop fairly rapidly, exhibit long-term retention, and even show consolidation, i.e., continued strengthening over time after training in the absence of additional reinforcement.

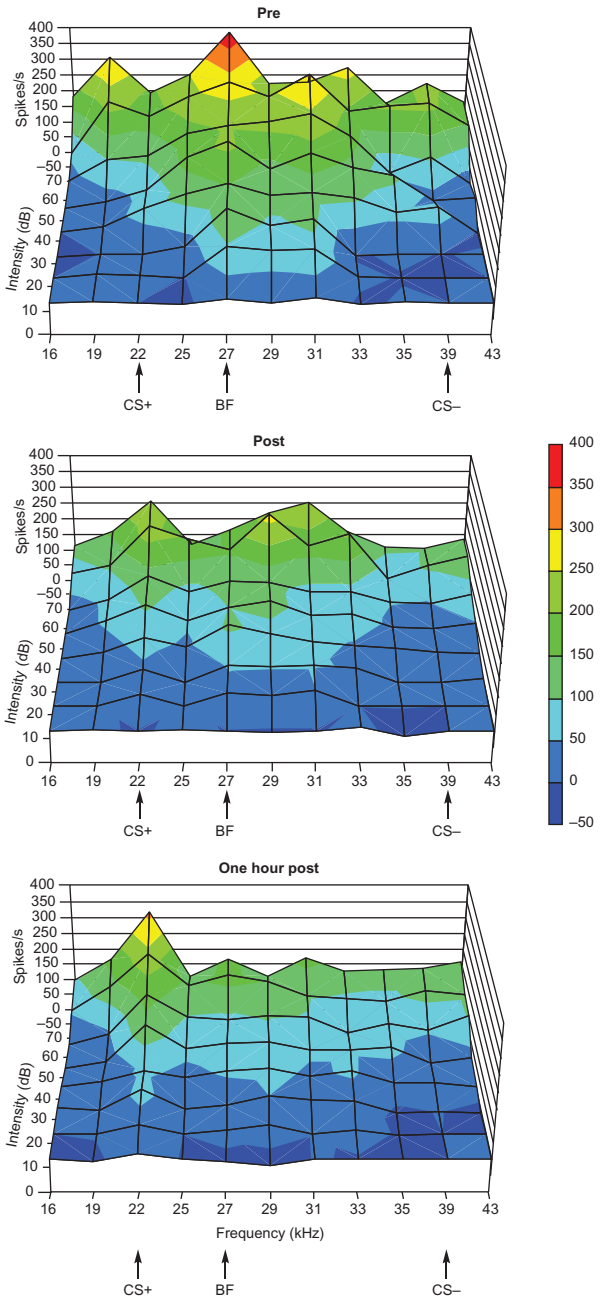

Fig. 7.3. Retuning and neural consolidation of the auditory cortex in a two-tone discrimination task. Representation of neuronal responses in A1 before (Pre), immediately after (Post), and 1 hour after two-tone discrimination training (30 × each: conditioned stimulus (CS) + (22.0 kHz) and CS– (39.0 kHz), intermixed trials). Displayed are rates of discharge (*x*-axis) as a function of tonal frequency (*y*-axis) and level of testing stimuli (*z*-axis) (10–70 dB). Note that associative learning produced a massive remodeling of the auditory cortex, i.e., the "topography" of neuronal response across frequency and stimulus level. The pretraining best frequency (BF) of 27.0 kHz suffered a reduction in response, as did the CS– frequency. In contrast, responses to the CS + frequency increased. Note consolidation, in the form of a continued development of these changes; after 1 hour of silence, the only excitatory response is at the CS + frequency. (Based on Edeline and Weinberger, 1993.)

In addition to having the major features of memory itself, SMTs should be found for whatever the types of CS or signal stimuli are used in training, i.e., should not be limited to plasticity of frequency representation. Another feature of memory is that it can be formed in a wide variety of tasks, rather than being confined to, e.g., classic conditioning. A further key feature of memory is that it transcends a particular type of motivation, but develops in both appetitive and aversive situations. Finally, as in the case of memory, SMTs should be biologically conserved, that is, developing across diverse taxa. This last criterion has been met, as reviewed above (see the section on representational plasticity across species, above). As described below, the findings from various laboratories support the conclusion that SMTs develop in the primary auditory cortex.

Cardinal characteristics of representational plasticity

How well do the major characteristics of RP match those of behavioral associative memory? The most direct test of associativity is to train separate groups, one receiving a tone paired with reinforcement (reward or punishment), the other with the same sound and reinforcement but not paired. In such cases, only the paired group develops tuning shifts (e.g., Diamond and Weinberger, 1986; Bakin and Weinberger, 1990; Bakin et al., 1992). Another test is discrimination training, in which one tone is followed by reinforcement (CS+) while another tone is not (CS–). The development of behavioral responses only to the CS+demonstrates associativity rather than enhanced excitability to all (or both) sounds. A selective enhancement of responses to the CS+in A1 does develop in discrimination learning (Edeline and Weinberger, 1993) (Fig. 7.3). This finding demonstrates not only associativity but also the highly selective nature of RP. Like memory, RP can be established rapidly, within five training trials (Edeline et al., 1993) (Fig. 7.4), and 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; see also Edeline et al., 1990) (Fig. 7.5). Finally, RP 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 (Edeline and Weinberger, 1993) and days after a single training session (Galván and Weinberger, 2002) (Fig. 7.6). In summary, RP satisfies the criterion of having the same cardinal characteristics as behavioral associative memory.

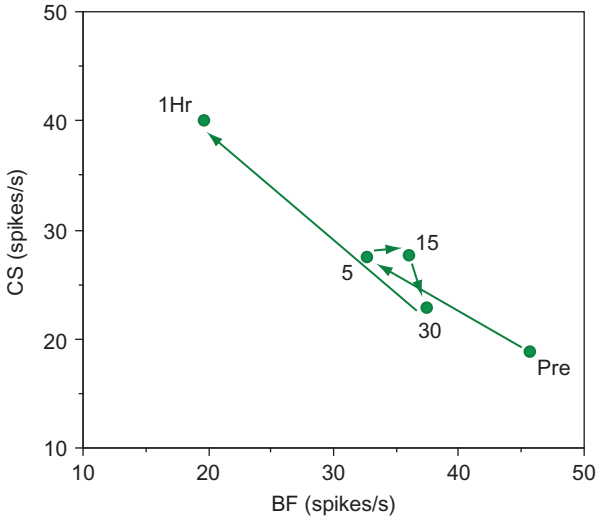

Fig. 7.4. Rapid induction of receptive field (RF) plasticity shown as vector diagrams of changes in response to the pretraining best frequency (BF) and the conditioned stimulus (CS) frequency during auditory fear learning. After five trials, responses to the BF had decreased, while those to the CS increased, changes that were maintained after 15 and 30 trials. However neural consolidation (continued development of neural substrates of memory) was detected 1 hour after training, at which time the CS frequency became the new BF. These findings illustrate that retuning of the primary auditory cortex can develop very rapidly (e.g., after only 5 minutes of training) and that the full extent of this plasticity cannot be known immediately after training but must be evaluated after the potential for neural consolidation has been tested. (Reproduced from Edeline et al., 1993.)

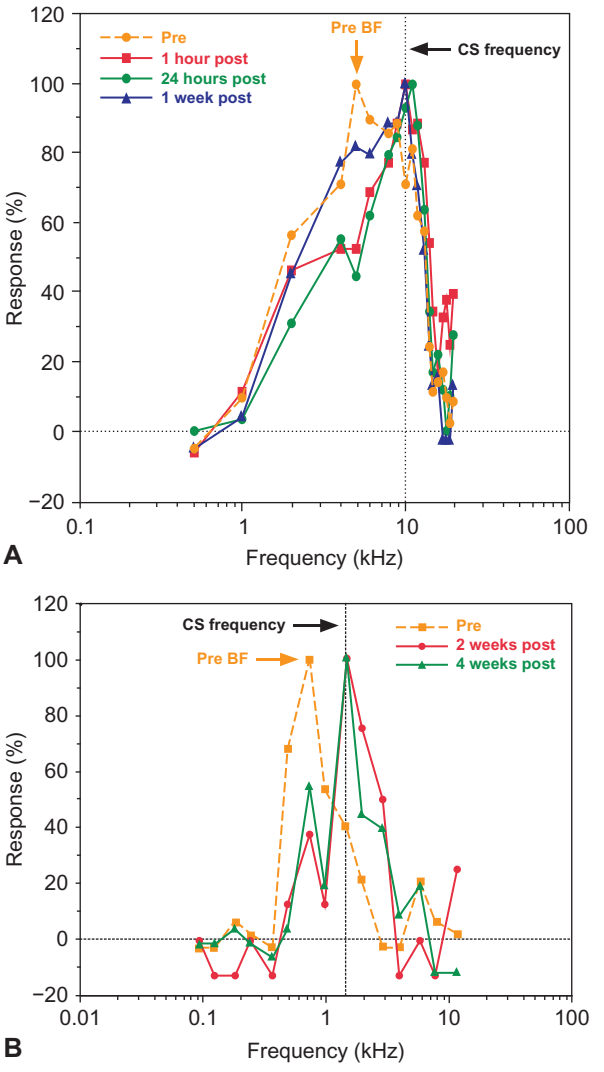

Fig. 7.5. Long-term retention of associative, specific receptive field plasticity in the primary auditory cortex. In both examples, conditioning induced a tuning shift to the frequency of the conditioned stimulus (CS). (**A**) An example of a CS-specific tuning shift over a period of 1 week. The best frequency (BF) shifted from 4.9 kHz to the CS frequency of 10.0 kHz, detected 1 hour after completion of training (tone–shock pairing: 30 trials). This shift was maintained at 24 hours and 1 week posttraining. (**B**) An example of a CS-specific tuning shift over a period of 4 weeks. The peak of tuning shifted from the pretraining BF of 0.69 kHz to the CS frequency of 1.45 kHz. Data depict tuning at 2 and 4 weeks posttraining (tone–shock pairing: 30 trials). (Based on Weinberger et al., 1993.)

Generality across types of acoustic stimulus parameters

Although most research has concerned acoustic frequency, RP has been found for all other stimulus parameters examined. For example, when sound level ("loudness") is the relevant cue, cells in A1 become selectively responsive to those intensities (Polley et al., 2004, 2006). Comparable findings apply to the repetition rate of noise pulses (Bao et al., 2004), the envelope frequency of a sinusoidally modulated tone (Beitel et al., 2003), sequences of particular sounds (Zhou et al., 2010), the size of step change in frequency (Selezneva et al., 2006), and the direction of frequency modulation (ascending vs descending) (Ohl et al., 2001). Moreover, RP linked to hemispheric specialization has been found in humans. Using functional magnetic resonance imaging (fMRI), Brechmann and Scheich (2005) engaged subjects in different tasks to identical stimuli, which were FM glides of various frequencies and durations. When their task was to categorize these sounds according to their direction of change (ascending or descending), the blood oxygen level-dependent (BOLD) signal increased in the right auditory cortex. In contrast, during judging of the duration of the tones, activation was found only in the left auditory cortex. Thus, the responses of auditory cortex can depend not merely on the involvement in a task, but rather on the nature of the task itself. Overall, the generality of RP includes

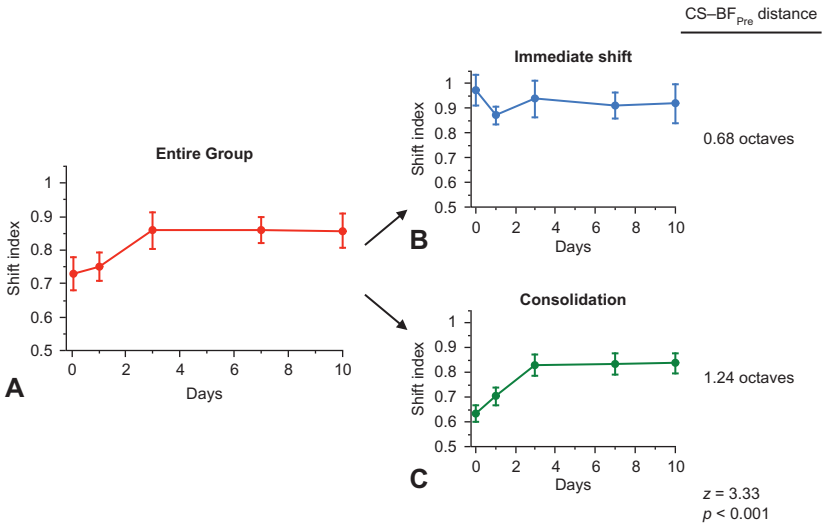

Fig. 7.6. Neural consolidation of representational plasticity over a period of 10 days posttraining. The magnitudes of tuning shifts (*y*-axes) are shown as a function of the time (1 hour to 10 days) after a single training session (auditory fear conditioning). An index of 1.0 would indicate a complete shift to the training frequency. (**A**) Group data show tuning shifts had developed by 1 hour posttraining, increasing over 3 days to asymptote. A breakdown according to the frequency distance of the training tone from the pretraining best frequency (BF) (cells' baseline tuning preference) further reveals the temporal dynamics of neural consolidation. (**B**) Cells tuned near the frequency of the signal tone (±0.68 octaves) shifted greatly (~90% of the distance to the training tone) immediately and maintained their new tuning for at least 10 days. (**C**) Cells tuned farther away (±1.24 octaves) required 3 days to complete their tuning shift (viz., 72 hours of neural consolidation). Overall, the findings reveal the dynamics by which neurons are "recruited" to increase the representation of behaviorally important sounds, with completion of retuning (neural consolidation) requiring 3 days for neurons originally tuned distantly from the training tone. Thus, the full effects of learning on cortical representations of behaviorally important stimuli cannot be determined until days after a learning experience. CS, conditioned stimulus. (Reproduced from Galván and Weinberger, 2002.)

both the physical parameters of sound and types of tasks. No limit on either one has yet been reached.

Generality across motivational states and tasks

RP develops in all tasks reported to date, and for both positive (reward) and negative (fear) motivations: e.g., simple classic conditioning of fear (Diamond and Weinberger, 1986; Bakin and Weinberger, 1990; Gao and Suga, 2000) and reward (Kisley and Gerstein, 2001; Blake et al., 2006), discriminative classic conditioning of fear (Edeline et al., 1990; Edeline and Weinberger, 1993; Ohl and Scheich, 1996, 1997) and reward (Blake et al., 2002; Polley et al., 2004, 2006), simple and two-tone discriminative instrumental avoidance (fear) association (Bakin et al., 1996), operant reward training (Hui et al., 2009), and categoric discrimination for reward (Wetzel et al., 1998; Ohl et al., 2001; Selezneva et al., 2006).

Therefore, RP is not confined to particular tasks or types of motivation, but appears to develop regardless of task or motivation. It thus satisfies additional criteria for matching major features of associative learning.

Multiple rule tasks and the role of learning strategy

Most of the findings reviewed above have concerned learning situations in which subjects confront a relatively well-defined task like learning that a sound predicts a reward or the threat of nociception, or learning to produce a particular behavioral response to achieve reward or to avoid discomfort. To what extent does RP develop when subjects are in a more complex situation, such as having to solve a problem that has several rules? One particular type of such problem has been well studied.

Rats were trained to bar-press for water reward during occasional 10-s tone presentations. However, bar-presses made after the tone ended, during silent intertrial periods, were subjected to two rules: if made within 2 seconds of tone offset, they were neither rewarded nor punished ("grace period"); if made later, they were punished by presentation of a flashing-light error signal and a time-out penalty that lengthened the current intertrial interval. This task can be solved in two ways. First, animals could use the strategy of starting to respond at tone onset and stopping at tone offset ("tone duration" strategy: T-Dur). Second, they could start at onset and continue to respond after offset until receiving an error

signal ("tone onset to error" strategy: TOTE). A second group was trained the same way except that they had no grace period and tended to use the T-Dur strategy. In contrast, rats trained with the grace period were inclined to use the TOTE strategy; that is, they paid attention to tone onset but not to tone offset. While both groups achieved the same level of correct performance, only the animals that used the TOTE strategy developed RP. In this case, the signal tone's threshold and BW decreased, increasing its sensitivity and selectivity (Fig. 7.7) (Berlau and Weinberger, 2008). The plasticity based on tone onset may reflect a proclivity of A1 to process onset transients (Phillips and Hall, 1990; Phillips et al., 2002), while other auditory fields may be more computationally adept for acoustic steady state (plateaus) and offsets. But whatever the explanation, these findings demonstrate that learning strategy, i.e., how an auditory problem is solved, can determine the development of RP.

The form of RP depends on the amount of use of the TOTE strategy: more extensive use (viz., on a greater proportion of training trials) produced a frank increase in the area of the cortex representing the training frequency band. Moreover, the amount of area gain is proportional to the amount of TOTE strategy use (Bieszczad and Weinberger, 2010b) (Fig. 7.8). Surprisingly, learning strategy is more critical in determining whether or not RP would develop in A1 than the level of motivation. In animal studies, motivational level can be determined by the hedonic value of a reward and validated by increased behavioral responses as a function of increasing value. Thus, animals will make more responses (e.g., lever presses) to attain a more desirable reward provided by the experimenter. Highly motivated subjects that do not use the TOTE strategy do not develop RP, despite making more responses, whereas moderately motivated animals that do use TOTE also develop RP (Bieszczad and Weinberger, 2010a).

Reversal and loss of representational gain in A1

Representational plasticity is subject to reversal when a tone no longer signals reward, as revealed in experimental extinction. Importantly, the amount of area loss is correlated with the amount of behavioral extinction (Bieszczad and Weinberger, 2012). These findings indicate that A1 "tracks" the current level of behavioral importance of sound and also that a loss of representational area is an active rather than a passive process.

Dissipation of area gain has also been reported in a very different circumstance, with undoubtedly different mechanisms. Rats were trained in a discrimination task to a high level of performance, and then overtrained for several thousand trials. At the end of overtraining, the previous gain in area was no longer evident; this has been referred to as "renormalization" (Reed et al., 2011). It has long been known that overtraining promotes a shift from cognitive memory, which is thought to be cortically dependent, to more habit-like response strategies, considered to be more dependent on subcortical striatal and cerebellar circuits (Mishkin and Petrie, 1984; Yin and Knowlton, 2006). In fact, since the dawn of experimental psychology, a distinction has been made between "memory" and "habit," to the extent that they were considered as separate chapters in *The Principles of Psychology* (James, 1893). So it is possible that the loss of area gain is due to overtraining.

To test this possibility, two groups of rats were trained in an appetitive tonal discrimination task; one was then mapped, while the other was overtrained for 2 weeks before being mapped. Both groups learned the task, but only the first group developed tone-specific area expansions; cortical representations in the second overtrained group did not did not differ from naïve subjects. During overtraining, the second group had shifted its learning strategy away from use of the TOTE strategy. Thus, "renormalization" appears to be attributable to a shift in how the task was solved, caused by overtraining (Elias, 2014). Two important questions remain to be answered: (1) Is the behavioral change a shift from cognitive memory to habit-like behavior? (2) Is there a neural shift of the critical locus from the primary auditory cortex to subcortical structures, such as the striatum?

Individual vs group analysis

The vast majority of findings in neuroscience are based on group analyses. In the case of the relationships between RP and learning, they have yielded many important results. However, individualistic analyses can be even more revealing. This advantage is evident in a study of gamma activity and auditory learning. It is well known that the magnitude of gamma-band oscillations (~40–120 Hz) in the electroencephalogram (EEG) is related to cognitive processes in humans and animals (see section on mechanisms of representational plasticity and specific auditory memory, below). For example, an increase in tone-induced gamma-band activity in A1 of the rat is correlated with the magnitude of subsequent behavioral conditioned responses to the signal tone. However, an analysis of posttraining responses across the tonal spectrum revealed that many animals did not exhibit maximum behavioral responses to the training frequency. This is not unusual (although often overlooked), because subjects are not *tabula rasa* but have different prior auditory experiences that can interact with new learning. A reanalysis of the data based on

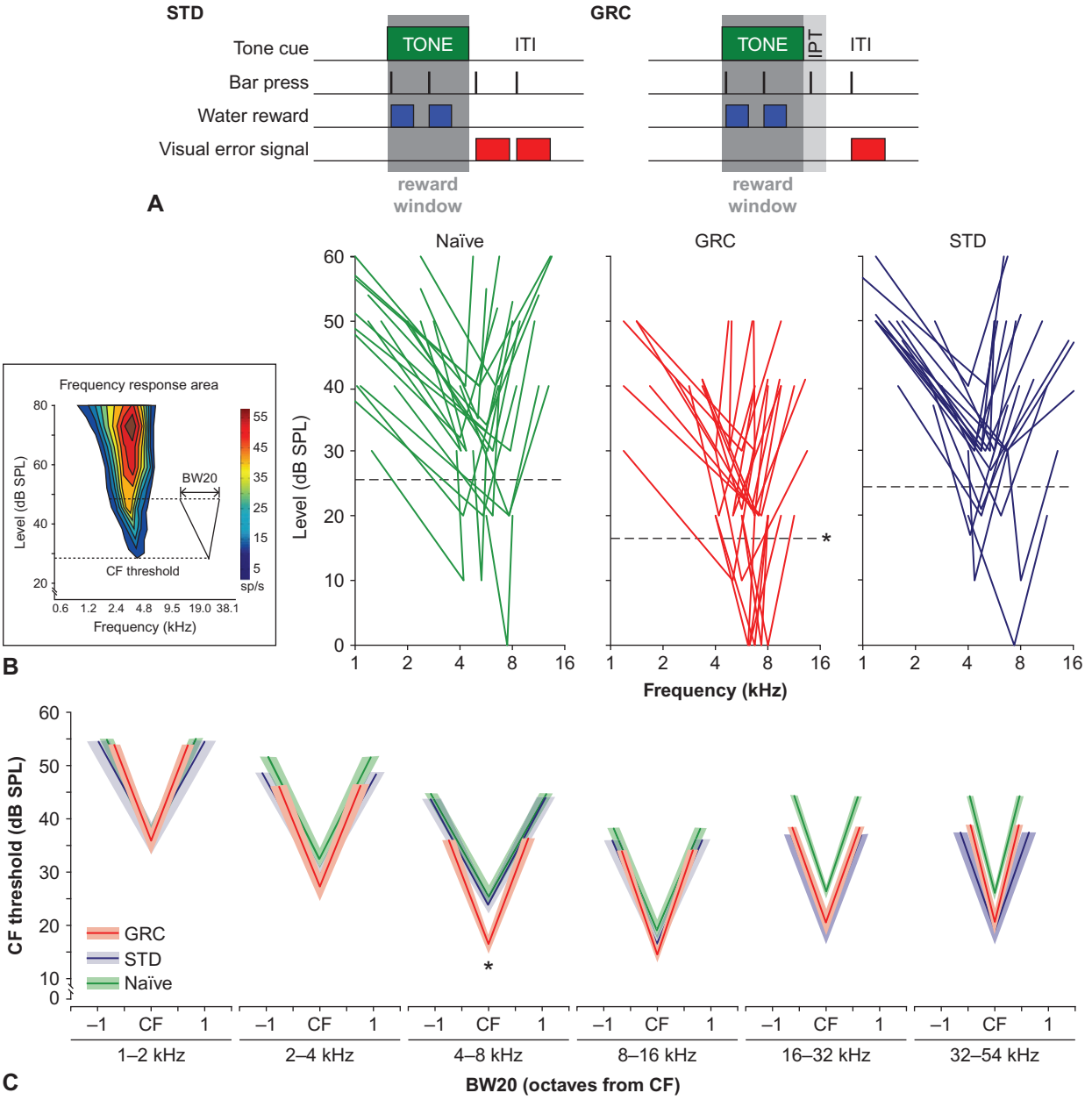

Fig. 7.7. Learning strategy determines auditory cortical plasticity. Rats learned to bar-press (BP) during a 5.0-kHz (10 seconds, 70 dB) tone for water reward. BPs made during intertrial interval silences resulted in a flashing-light error signal and a time-out penalty. (**A**) For the standard (STD) group all BPs during silence were signaled as errors. For the grace period (GRC) group, BPs made within 2 seconds of tone offset were neither rewarded nor signaled as an error, thus directing attention away from tone offset. Both groups learned the task to the same high level of performance, but used different strategies. STD behavior was based on attention to both tone onset and tone offset (tone duration (T-DUR) strategy). In contrast, GRC behavior was based on attention to tone onset and responding until receiving an error signal for BPs made after the grace period (tone onset to error (TOTE) strategy). (**B**) Posttraining frequency response areas revealed that only the GRC group developed specific representational plasticity (RP). Inset shows typical frequency response area (FRA) with characteristic frequency (CF) tuning and bandwidth (BW) indicated. Use of the TOTE strategy produced reduced threshold (increased sensitivity) and bandwidth (increased selectivity) in the signal-band tone. Shown are FRA "tuning tips" in groups STD, GRC, and a naïve group. Each V shape delineates the CF threshold, and BW20 of a recorded FRA (inset) that had a CF within the signal-tone frequency band (4–8 kHz) in each respective group. For sake of clarity, subsets of the total population of FRAs are depicted. Dashed lines represent the mean CF threshold for the entire population of each group. The asterisk shows that the GRC group had significantly lower CF thresholds than either naïve or STD groups, which are not different from each other. SPL, sound pressure level. (**C**) Plasticity in threshold and bandwidth in the

(Continued)

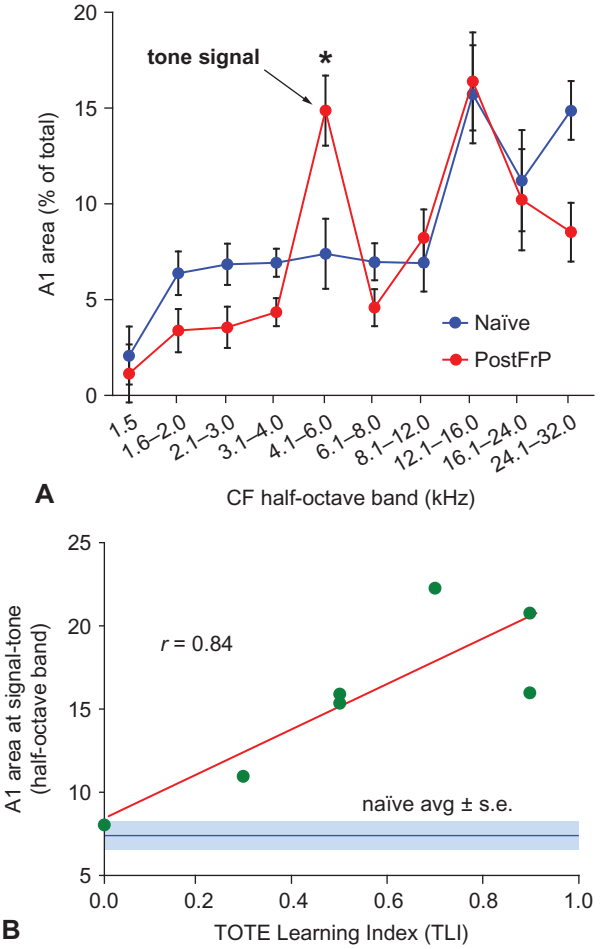

Fig. 7.8. The degree to which animals use the tone-onset-to-error (TOTE) strategy determines the magnitude of gain in representational area of the signal tone. (**A**) The magnitude of representational area for a group that was trained with a strategy ("PostFrP") that promoted use of the TOTE strategy, compared to an untrained control group. Note the significant increase in area of the trained group for the frequency band (4.0–6.0 kHz) centered on the signal tone (5.0 kHz). There were no other differences from the controls, showing specificity of representational plasticity. (**B**) The relationship between the degree of use of the TOTE strategy and the area representing the signal frequency band. Within the trained group, individual variability revealed a significant positive relationship: the greater the use of TOTE (i.e., the more trials on which it was used), the greater the gain in representational area. Thus, learning strategy, i.e., how a problem is solved, dictates the nature and amount of plasticity in the primary auditory cortex. CF, characteristic frequency. (Reproduced from Bieszczad and Weinberger, 2010b.)

the maximum response (peak of the behavioral frequency gradient) for each animal yielded a significantly stronger relationship between gamma activity and behavior. Thus, gamma-band plasticity was revealed as a signature of the frequency memory that gained the most strength due to training, not the memory of the training stimulus (Weinberger et al., 2013) (Fig. 7.9).

Therefore, studies of learning, whether pertaining to the auditory cortex or to other brain sites, can benefit from determining what each subject has actually learned or remembered. This is easily accomplished by training with one stimulus and performing posttraining assessment by testing with many stimuli (i.e., yielding "generalization gradients"). The peak of the gradient shows the stimulus that is most strongly linked to the learning. Even when group analyses yield significant effects, they may not reveal the full extent of relationships. Furthermore, lacking knowledge of the actual contents of individual learning, negative findings based on group treatments may mask significant relationships that exist at the level of the individual subjects. Insofar as individualized analyses (based on within-group variability) can be performed without compromising group-based evaluations, they ought to be encouraged.

Three classes of auditory tasks and representational plasticity

An important distinction has been made that classifies auditory associative learning tasks into three types: (1) detection; (2) discrimination; and (3) categorization (Scheich et al., 2011). The first refers to single-stimulus situations, e.g., in which a sound becomes associated with a reward or opportunity to avoid an aversive stimulus. The second refers to distinguishing between two or more sounds, only one of which is associated with reinforcement. The third refers to having two or more sounds that are discriminated from each other, not on the basis of having different physical properties (e.g., frequencies) that are differential-reinforced, but as a member of a differentially reinforced class of sounds. An example is differentiating between ascending and descending frequency sweeps (frequency modulations) irrespective of the particular acoustic frequencies they contain. Thus categorization requires abstracting a common property among sounds, although their particular physical features differ.

Fig. 7.7.—Cont'd GRC group is specific to the frequency band of the signal tone (asterisk). Both threshold and BW20 decreased only in the signal-tone frequency band. CF threshold and BW20 values are not significantly different from naïves in any frequency band in the STD group. Solid lines surrounded by shaded areas represent group means ± SE, respectively. Thus, specific RP in primary auditory cortex is determined by learning strategy, not merely whether or not learning occurred. The findings support the theory that different cortical fields are somewhat specialized to compute the relationship of different stimulus parameters to the acquired behavioral meaning of stimuli. A1 is known to be particularly sensitive to onset transients of sound and the GRC group attended only to tone onset, not to tone offset. (Reproduced from Berlau and Weinberger, 2008.)

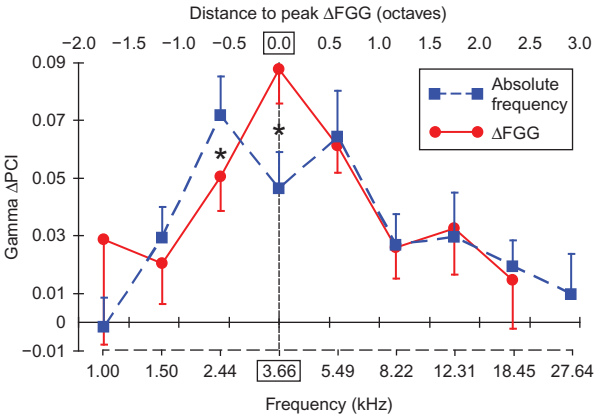

Fig. 7.9. Individual analyses based on what each rat learned (associative conditioning with signal frequency = 3.66 kHz) revealed a stronger relationship between the magnitude of tone-induced gamma activity in A1 (*y*-axis) and behavioral conditioned responses. There are two *x*-axes: bottom is standard, i.e., for absolute acoustic frequency; top is for octave distance from the peak of the individual behavioral frequency generalization gradients (FGG). Although all animals were trained at 3.66 kHz, the peaks of individual gradients varied widely (not shown), reflecting normal differential acoustic experiences outside of the lab that interact with the training frequency. The blue line shows the standard group analysis reflecting the amount of increase in gamma activity as a function of absolute acoustic frequency. Note that the peak increase in gamma is at 2.44 kHz, not at the training frequency. However, when the individual gradients are expressed as (octave) distance from their own behavioral generalization peaks (red line), then the greatest mean increase in gamma activity is precisely at the behavioral peak, i.e., the largest increase in gamma oscillations in A1 is at the frequency that was strongest in the memory of the animals. In short, increased gamma activity is a signature of the most behaviorally important memory, not the memory of the training frequency. The difference between standard group and individualized analyses is statistically significant (asterisks). PCI, power change index. (Reproduced from Weinberger et al., 2013).

According to this schema, three different forms of plasticity accompany the three types of tasks. Detection is accompanied by tuning shifts and expanded representation. This is consistent with the findings reviewed above. However, discrimination is said to be not accompanied by enhanced representation of the signal stimulus, but by increased responses to adjacent frequencies, often with a decrease of response to the CS+, producing an overall increase in local contrast (Ohl and Scheich, 1996, 1997). These findings are based on the use of one reinforced (shock) CS+tone and numerous (12–30) intermixed non-reinforced CS– tones. Insofar as two-tone discrimination studies had found increased responses to the CS+and tuning shifts rather than decreased responses to the CS+and local contrast change (Fig. 7.3), this formulation may not hold for simple discriminations. Categorization of the direction of FM sweep revealed a different form of RP; similar sounds (e.g., upward sweeps) became identified with a particular spatiotemporal activity pattern of LFPs in A1. This pattern emerged at the time that behavior switched from discrimination based on sound frequencies to categoric behavior (Ohl et al., 2001). Another form of plasticity was reported for a more complex variation of direction of FM in the monkey (Brosch et al., 2005; Selezneva et al., 2006). In all of these classes of auditory learning tasks, studies have shown that the primary auditory cortex is part of a multimodal matrix, in which its neurons are not merely modulated by other sensory stimuli but actually respond thereto (Scheich et al., 2011). No doubt future research will elaborate on the properties and mechanisms of complex discriminations and concept formation.

FUNCTIONS OF REPRESENTATIONAL PLASTICITY IN THE PRIMARY AUDITORY CORTEX

Given findings that support the establishment of SMTs in the primary auditory cortex, what can be said about their functions? While research is still in early stages, several studies have delineated various functions, all of which support auditory memory.

Encoding the behavioral importance of a sound

One possibility is that the area of representation of a tone encodes the degree of its behavioral importance. To test this hypothesis, rats were trained at different motivational levels (amounts of water restriction) to bar-press for reward contingent on the presence of a tone. They achieved corresponding levels of correct performance. Posttraining mapping of A1 revealed that subjects developed expanded representation for the tone's frequency; the higher their level of correct performance (presumably reflecting the tone's importance), the greater the area of tonal representation (Rutkowski and Weinberger, 2005) (Fig. 7.10).

Reinforcement prediction

Another potential function of RP is that of predicting reinforcement outcome, which is clearly related to the representation of stimulus importance. If expanded representation serves to predict reinforcement, then it should be reversed by extinction because reward is withdrawn. However, if it is a sign of any relevant change in auditory predictions of the state of affairs, then extinction should not eliminate cortical expansion because the

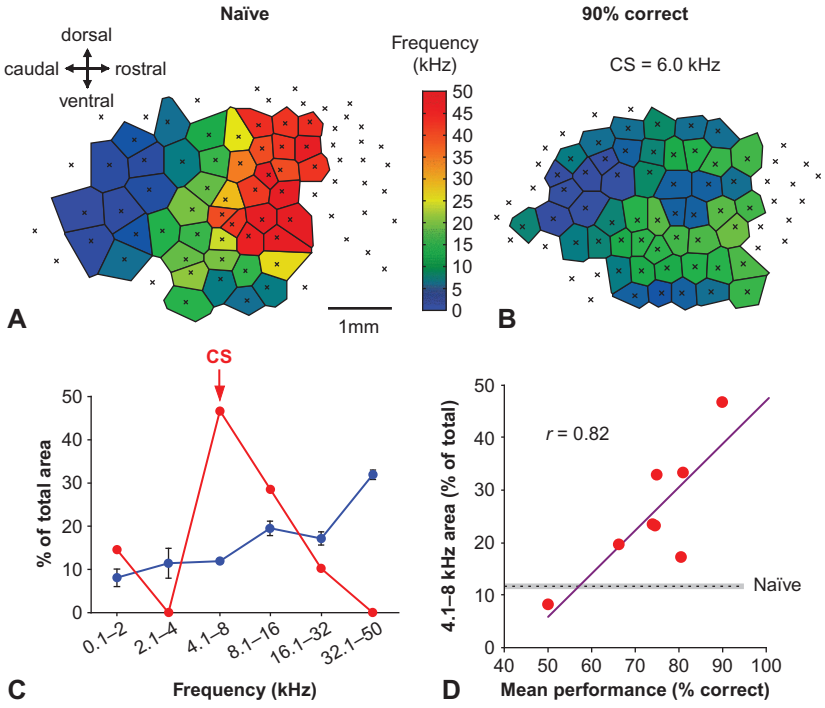

Fig. 7.10. The degree of acquired importance of a tone is correlated directly with the amount of area of frequency representation in the tonotopic map of A1. Trained rats received water reward for bar-presses in the presence of a 6.0 kHz tone. (**A, B**) Tonotopic maps for a naïve rat and a rat that attained over 90% correct performance, respectively. (**C**) Quantification of areas of representation across all frequency bands. Note that training greatly increased the area of representation for the frequency band containing the 6.0-kHz tone signal compared to the naïve animal. (**D**) Evidence of a "memory code" for the acquired behavioral importance of sound. The area of representation of the frequency band containing the 6.0-kHz tone signal increases as a function of the level of behavioral importance of the tone, as operationally indexed by the level of correct performance. CS, conditioned stimulus. (Reproduced from Rutkowski and Weinberger, 2005; Weinberger, 2007.)

absence of expected reward following response to an acoustic signal is itself a behaviorally significant event. Animals were trained in the same bar-pressing task described previously (see section on multiple rule tasks and the role of learning strategy, above). Following extinction, signal-specific area gains were reversed, supporting the "reinforcement prediction" hypothesis (Bieszczad and Weinberger, 2012). This is consistent with evidence of reward feedback in primary auditory cortex of primates (Brosch et al., 2011).

Substrate of memory strength

A third potential function of RP is as a neural substrate for the strength of memory, for which mechanisms are currently unknown. Rats trained in the same task later underwent experimental extinction. Memory strength is considered inversely proportional to the rate of extinction: the longer animals persist in bar-pressing, the slower the extinction and the stronger the memory. Terminal mapping revealed a significant positive relationship between the amount of area representing the signal tone and the strength of memory. Thus, the number of neurons that become tuned to a sound, the stronger the memory for that sound (Bieszczad and Weinberger, 2010c, 2012) (Fig. 7.11).

ARGUMENTS TO THE CONTRARY

Representational plasticity in A1 has the major characteristics of associative memory, as indexed in the forms of specific decreases in threshold and BW, tuning shifts and expansion of cortical area. Further, it exhibits generality across tasks, motivational valences, types of acoustic stimuli and species. While evidence continues to accumulate in this very active area of research, the overall picture emerging from research over approximately the past 25 years is one of consistency and replicability. On the other hand, there have been challenges to the conception of A1 as being deeply involved in learning and memory, particularly in storing SMTs.

It is entirely appropriate and necessary for new ideas and findings to be scrutinized deeply. In particular, the idea that the primary auditory cortex is a site of specific auditory memory storage is at variance with traditional views of A1 as exclusively an acoustic analyzer.

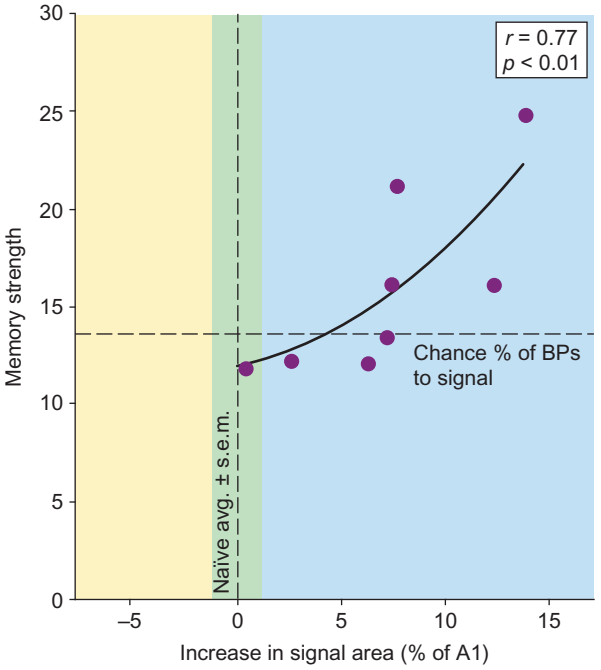

Fig. 7.11. Memory strength correlates with the amount of signal-specific area gains in the primary auditory cortex (A1). The *x*-axis shows the amount of relative area in A1 for the signal frequency (half-octave band). The *y*-axis shows the strength of memory for the signal tone (5.0 kHz) determined by its resistance to extinction relative to non-signal test frequencies. Trained animals showed increases in area relative to the naïve group (vertical dashed line, SE marked by shaded area). Increased memory strength for the signal tone is significantly positively correlated with the amount of area gain in A1 (best-fit regression, curvilinear: $r = 0.77$, $p < 0.01$). BP, barpress. (Reproduced from Bieszczad and Weinberger, 2010c.)

Additionally, it is not yet clear how the modulation and plasticity of auditory neurons by the acquired behavioral meaning of sounds can be reconciled with the traditional and dominant concept that cellular discharges always encode the same specific physical parameters of sound. We will consider some major criticisms of the idea of, and findings supporting, SMTs in the primary auditory cortex.

Is representational plasticity caused by fear or increased arousal?

It has been argued that confounded state changes, not learning or memory, produce plasticity in A1. For example, the state of fear during the use of negative reinforcement (Hall and Mark, 1967; Mark and Hall, 1967) or increased arousal with any reinforcement (Kitzes et al., 1978) are claimed to explain facilitated responses to signal stimuli. Such state effects might either be elicited by an acoustic signal, be present as background throughout training, or both. However, these possibilities can be ruled out. First, the latency of most signal-evoked plasticity in A1 (~10–100 ms) is less than sound-induced fear or arousal, which requires at least 100 ms. Second, potential confounds by changes in background state due to the presence of shock have been ruled out by the use of sensitization control groups (i.e., tone and shock randomly presented) and the use of two-tone discrimination protocols have shown for fear conditioning that pairing of tone and shock is necessary for RP (Edeline and Weinberger, 1993). Simply creating a state of fear or heightened arousal is insufficient. Third, and perhaps most importantly, receptive field analysis has revealed that such tonic state changes do not cause specific tuning shifts but rather produce increased responses non-selectively to all acoustic frequencies (Bakin et al., 1992). In contrast, associations are far more specific, as revealed by increased responses to the CS (and closely related frequencies), while there is a simultaneous decline in responses to other frequencies (Weinberger and Diamond, 1988; Bakin and Weinberger, 1990). Contemporary research based on the determination of specificity of plasticity resolves all such state issues, but any studies that fail to control for non-associative effects and fail to demonstrate specificity run the risk of similar criticisms.

Attention is often confused with increased arousal because they sometimes occur together. However, they are fundamentally different. Attention refers to preferential processing of particular stimuli, and is usually highly selective. For example, responses in A1 to specific acoustic parameters can be facilitated by selective changes in frequency tuning involving both augmentation of processing a target tone while attenuating responses to irrelevant frequencies (e.g., Fritz et al., 2003, 2005). Selective attention can take place without any change in the overall state of arousal or behavioral excitability, and can be switched between visual targets without any change in cortical state or even any eye movements. Similarly, auditory attention can be redirected rapidly and repeatedly, as when tracking one or another voice, without any movement of the head or change in arousal level. In most cases selective attention is a product of previously learning which stimuli or items in the environment are or may become behaviorally important in a given situation. Therefore, while selective attention can modify processing in A1 and other cortical fields, it is neither independent of, nor in any way in opposition to, prior learning processes.

Are tuning shifts spontaneous, not induced by learning?

Kisley and Gerstein (1999) questioned whether tuning shifts were due to learning or spontaneous changes,

because they observed tuning changes over days in the absence of training. This concern is understandable in the abstract. However, it had already been established that tuning shifts during learning experiments are toward, not also away from, the CS frequency, are associative, as they develop only in animals receiving paired CS and US, and are discriminative, i.e., toward the CS+, not the CS– (Bakin and Weinberger, 1990; Bakin et al., 1992; Edeline and Weinberger, 1993). Spontaneous shifts of tuning could not account for any of these attributes of learning-induced RP.

Furthermore, the "spontaneous tuning shifts" that they reported are readily explained as an artifact of their data analysis. This is best understood in a subsequent experiment in which these authors studied classic conditioning, pairing a tone with reward (Kisley and Gerstein, 2001). They did find that conditioning produces shifts directed toward or even to the CS. Also in agreement with prior studies, this receptive field plasticity was associative because it required CS–US pairing. The learning effects were above and beyond any spontaneous changes in tuning. However, what was the evidence for spontaneous drifts of tuning? The authors reported that the entire tuning curves from the same recording site became less correlated over days in the absence of conditioning, but they gave equal weighting to each of the many test tones used, including those that did not excite cells. So such random activity added noise to the analysis. A more direct test of their hypothesis is to directly determine the BF tuning over days. This has been accomplished for a period of 14–21 days. BF did not drift over days, neither did thresholds nor BWs (Galván et al., 2001; Galván and Weinberger, 2002).

"But, cortical lesions don't prevent memory"

Lesions of the auditory cortex can spare the acquisition of auditory fear memory (Romanski and LeDoux, 1992a). Some authors have concluded that, as the auditory cortex is apparently not necessary for the acquisition of auditory memory, RP cannot be a substrate of SMTs (e.g., Ohl and Scheich, 2004; but see Weinberger, 2004, 2007). This conclusion seems to reflect the assumption that memory substrates are localized. In so doing, it supposes that the claim that A1 contains SMTs seems to imply that all of the relevant traces are localized there. Following this logic, then lesions of A1 should prevent all auditory learning.

However, contemporary formulations hold that memory is ordinarily multimodal and multidimensional, and so its substrates involve the distributed representation of stored experience. Therefore, lesions that fail to prevent acquisition do not necessarily imply that the destroyed tissue held no SMTs, but only that the tissue was not essential for the behavioral measure that was used to assess learning. It should be emphasized that, as associative learning can be expressed through many effector systems, impairment of one behavioral measure should be interpreted cautiously. For example, lesions of the amygdala impair freezing (inhibition of all movements except respiration) to sounds or environmental contexts that induce fear due to prior association with nociceptive stimulation. This change in behavior is assumed to demonstrate that memory traces are stored in the amygdala (LeDoux, 1995). However, basolateral amygdala lesions actually impair unconditioned freezing (Vazdarjanova et al., 2001), so the conclusion that amygdala lesions destroy learned fear is questionable. In fact, rats with amygdala lesions that are unable to freeze can still express conditioned fear by avoiding the place of shock administration if given the physical context to do, like a simple maze rather than an inescapable standard test box (Vazdarjanova and McGaugh, 1998). Therefore, it appears that the amygdala is necessary for the behavioral expression of fear as measured by freezing and changes in autonomic behavior such as heart rate and blood pressure.

Furthermore, auditory memory traces for simple tone-shock learning can be stored in parallel, at the levels of both the medial geniculate (magnocellular (MGm) and posterior intralaminar (PIN) nuclei) and the auditory cortex. Thus lesions of either level spare the acquisition of simple one-tone auditory fear conditioning as measured by freezing (Romanski and LeDoux, 1992b). In short, although A1 may not be essential for learning to fear a single, simple tone, it is nonetheless "interested"; thus it could use its memory traces for an unknown future, or for the present if the task becomes more complicated and also in the unlikely event of lesions to the MGm/PIN (Weinberger, 2011a). The transactions of A1 with other cortical and subcortical targets, even in a task as simple as tone–shock pairing, are likely to proceed regardless of the involvement of the thalamoamygdaloid circuit. However, they are likely to remain unknown to the experimenter unless the animal is appropriately interrogated. For example, while the development of simple one-tone auditory conditioning does not require an intact A1 (DiCara et al., 1970; Berntson et al., 1983; Romanski and LeDoux, 1992a, b), as soon as two-tone discrimination is demanded, A1 is required (Teich et al., 1988). An intact A1 is also obligatory to achieve experimental extinction in the future (Teich et al., 1989), so memory traces in the cortex appear necessary for behavioral inhibition to the tone when it no longer predicts shock. Of course, information stored in the auditory cortex has interactions with far more

widespread inputs and outputs than the subcortical auditory system, and can handle far more complex problems while still solving simple problems.

Finally, it is important to distinguish acquisition processes from memory storage. Thus, even if cortical lesions do not prevent acquisition of simple associations (due to subcortical capabilities), it is nonetheless the case that destruction of the primary auditory cortex after learning can abolish auditory memory (Boatman and Kim, 2006). In summary, the failure of a lesion of A1 to prevent behavioral evidence of acquisition cannot itself demonstrate that it holds no SMTs.

MECHANISMS OF REPRESENTATIONAL PLASTICITY AND SPECIFIC AUDITORY MEMORY

To date, most studies of the mechanism underlying RP have concerned neuromodulators. Recent work has begun to address the role of gamma-band oscillations and neural synchrony as well as synaptic mechanisms. Considerations of the contributions of the thalamic auditory system are beyond the scope of this article and have been reviewed elsewhere (Weinberger, 1995). However, it can be said that RP in the cortex is not simply projected from the medial geniculate nucleus. Thus, while the ventral medial geniculate possesses the requisite frequency specificity in its own tonotopic organization and does develop specific tuning shifts, they are very restricted and not maintained even for 1 hour (Edeline and Weinberger, 1991).

Neuromodulators in representational plasticity

The following neuromodulators have been studied most in RP: acetylcholine (ACh), dopamine (DA), norepinephrine, (NE) and serotonin (5HT).

Acetylcholine

ACh is the only neuromodulator that has been implicated in both RP and in the induction of specific behavioral memory by activation of the cholinergic nucleus basalis (NB), producing "implanted memory."

ACh and representational plasticity

ACh, particularly acting at muscarinic receptors, has long been implicated as important for memory (Deutsch, 1971; Vanderwolf, 1987; van der Zee and Luiten, 1999). The NB supplies ACh to the cortex (Mesulam et al., 1983) and copious evidence implicates it in auditory cortical function. For example, NB ACh cells project directly to A1 (Bigl et al., 1982), and NB stimulation releases ACh (Casamenti et al., 1986) that produces cortical EEG activation, especially increased gamma-band power (~40–120 Hz) (Cape and Jones, 1998, 2000), which depends on the engagement of muscarinic cholinergic receptors (mAChRs) in A1 (Metherate et al., 1992). Conversely, NB lesions reduce cortical ACh (Arendash et al., 1987) and gamma activity (Berntson et al., 2002). NB stimulation modifies A1 responses to sensory volleys (Metherate and Ashe, 1991; Hars et al., 1993) and facilitates field potentials, cellular discharges, and excitatory postsynaptic potentials via mAChRs in A1 (Metherate and Ashe, 1991, 1993). NB cells can differentially respond to specific acoustic frequencies (Chernyshev and Weinberger, 1998). NB responses to tones that signal appetitive or aversive reinforcement increase during learning (Richardson and DeLong, 1986) and NB cells develop increased discharges to signal tones during auditory fear conditioning (Whalen et al., 1994) preceding neuronal plasticity in A1 (Maho et al., 1995). An important, but underappreciated, finding is that NB cells projecting to A1 selectively increase transcription of the gene for ACh's synthetic enzyme, choline acetyltransferase, during auditory fear conditioning (Oh et al., 1996). Finally, but of no less importance, ACh is selectively released in A1 as animals learn that a sound signals forthcoming reward (Butt et al., 2009).

Given the implication of ACh in learning and memory, coupled with the fact that RP is formed during learning, one might expect ACh to have an important role in RP. Indeed, this is the case. Pairing a tone with NB stimulation actually induces associative RP in A1, in the form of receptive field tuning shifts (Bakin and Weinberger, 1990). Moreover, RP induced by paired NB stimulation has the same characteristics as learning-induced RP: in addition to being associative, it is specific, rapidly acquired, consolidates, and is retained (Bakin and Weinberger, 1996; Bjordahl et al., 1998; Dimyan and Weinberger, 1999). Given the fact that gains in representational area in A1 must be based on many individual shifts in tuning, it is not surprising that tone paired with NB stimulation produces RP in the form of specific area gains (Kilgard and Merzenich, 1998). Also, as with learning-induced RP, stimulation of the NB can specifically modulate the representation of parameters other than acoustic frequency (Kilgard et al., 2001a, b). RP can be induced by pairing a tone with ACh applied directly to A1 and NB-induced RP is dependent on the engagement of mAChRs in A1 (Ji et al., 2001; Miasnikov et al., 2001; Ji and Suga, 2003; Yan and Zhang, 2005).

Finally, the NB is almost certainly activated by other structures that hold information about the current need to store information. For example, the basolateral amygdala is known to modulate the strength of memory that is stored elsewhere (McGaugh, 2004). Tone paired with stimulation of the basolateral amygdala induces the same specific tuning shifts as develops in natural

learning and when tone is paired with stimulation of the NB (Chavez et al., 2009). This form of RP is highly specific, consolidates (becomes stronger over days) and lasts indefinitely, as tracked to 3 weeks (Chavez et al., 2013). These findings suggest that memory modulation by the basolateral amygdala is accomplished by activating the NB. Of course, as this nucleus receives input from numerous brain regions, the relevant area for a given learning situation may initiate release of ACh in the cortex.

ACh and the implantation of specific associative behavioral memory

Remarkably, a sound paired with NB stimulation also implants specific behavioral auditory associative memory (McLin et al., 2002). After pairing, many tones across the acoustic spectrum were presented and changes in heart rate and respiration were measured. A control group received tone and NB stimulation unpaired. The results showed that the paired tone alone elicited larger behavioral responses after pairing (Fig. 7.12). The behavioral frequency gradients are indistinguishable from those generated by natural memory. Moreover, like natural memory, implanted memory is associative and specific (McLin et al., 2002), rapidly acquired (Miasnikov et al., 2006), consolidates (Weinberger et al., 2009; Miasnikov et al., 2011), is long-lasting (Miasnikov et al., 2011) and extinguishes due to the removal of "reinforcement" (NB stimulation) (Miasnikov et al., 2009). Furthermore, implanted memory depends on intrinsic ACh (Miasnikov et al., 2008b).

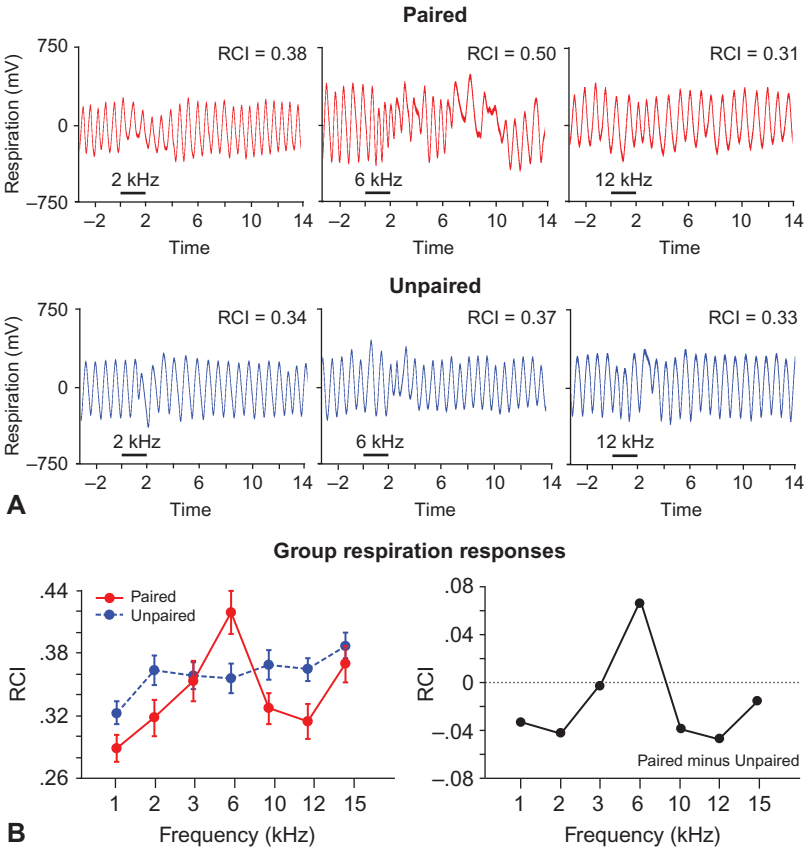

Fig. 7.12. Implantation of specific associative behavioral memory by pairing a tone with activation of the cholinergic nucleus basalis. Rats heard a 6.0-kHz tone followed by microstimulation of the nucleus basalis, which released acetylcholine into the cerebral cortex. After many pairing trials, they were tested for the implantation of specific memory of 6.0 kHz by being tested with many different frequencies, including the training signal. Interruption of ongoing respiration was used as a sensitive behavioral index of associative and specific memory. (**A**) Examples of individual respiration records to three frequencies (2.0, 6.0, and 12.0 kHz) for one animal each from the paired group and an unpaired control group. Note that the largest response was at 6.0 kHz for the paired animal. The control subject exhibited little response. Horizontal bars indicate tone duration. (**B**) Group mean change in respiration to all tones for both groups. Left shows that the maximal response was at 6.0 kHz for the paired group but not for the unpaired group. The group difference function (paired minus unpaired) (right) shows the high degree of specificity of associative respiratory responses to the 6.0-kHz training tone; it was the only stimulus to elicit a significant behavioral response. Implanted memory that the training tone was behaviorally important depends on the engagement of muscarinic cholinergic receptors in the primary auditory cortex. RCI, respiration change index. (Reproduced from McLin et al., 2002.)

In short, animals behave as though they had an experience that never happened; they have a false memory. What is likely to be the content of such implanted memory? It should not have any emotional content because the NB is "downstream" of motivational centers such as the amygdala and stimulation of this cholinergic nucleus is neither rewarding nor aversive (Miasnikov et al., 2008a). It seems that animals with implanted memory "know" that the signal tone is now important, but don't know why. This may not be as strange as it at first might seem. People often remember that an event was significant long after they have forgotten the particular details of how it became so.

The use of NB stimulation can yield information about cortical plasticity and memory that is not easily obtainable using natural memory tasks. For example, it permits control of the amount of specific detail in auditory memory, by varying the level of current; weak stimulation produces a general meaning that sound is important, but without any specificity for the training tone, whereas moderate stimulation produces highly specific meaning in memory (Weinberger et al., 2006). This finding suggests that the degree of detail in auditory memory may be determined in part or entirely by the amount of ACh released by an experience that engages mAChRs in the auditory cortex.

Overall, the attributes of natural associative learning, RP induced during natural learning, RP induced by tone paired with NB stimulation, and memory implanted by NB stimulation are the same (Table 7.1).

In toto, the ACh findings suggest that the direct induction of RP in A1 might be sufficient for the formation of specific auditory memory. However, no link had been demonstrated between artificial increase in RP for a tone and the implantation of memory.

To test this possibility, rats received a 3.66-kHz tone paired with NB stimulation and were tested for the implantation of specific behavioral memory. Next, their cortical tonotopic maps were determined. These revealed that pairing had induced gains in representational area. However, the areas of maximum increase were not exactly at the 3.66-kHz training frequency, but distributed across various frequencies. As noted previously (see section on individual vs group analysis, above), individuals are not functional or behavioral clones as each comes to a common training experience with different prior experiences; these often interact with new experiences, the result being that they often remember somewhat different things, in this case, exactly what frequency had been paired with NB stimulation. Nonetheless, there was a match on an individual basis between the frequency whose area increased the most and the behavioral frequency memory that was strongest (Bieszczad et al., 2013). This finding constitutes the first demonstration of the artificial induction of specific memory by direct remodeling of the cerebral cortex.

Naturally, such invasive research cannot be conducted with human subjects. However, other types of evidence show that the cholinergic system is involved in associative learning and auditory cortical plasticity in humans (reviewed in Thiel, 2003). For example, fMRI studies have revealed that scopolamine blocks discriminative conditioned changes in auditory cortical responses (enhanced BOLD signal) to tones that were paired with electric shock (CS+) compared to tones without shock (CS–) (Thiel et al., 2002).

Dopamine

There is increased release of homovanillic acid (a metabolite of DA) from the primary auditory cortex of gerbils during the initial stages of avoidance learning. Insofar as performance was maintained on succeeding days without the same elevation of release, DA appears to be involved in the acquisition of information rather than on retention of memory (Stark and Scheich, 1997). Increasing DA release by self-stimulation of the ventral tegmental area facilitates avoidance learning, potentially

Table 7.1

Comparison of the attributes of natural associative memory with learning-induced receptive field plasticity, nucleus basalis (NB)-induced plasticity, and specific behavioral memory implanted by NB stimulation

Characteristic	Associative memory	Receptive field plasticity	NB-induced receptive field plasticity	NB-induced memory
Associative?	Yes	Yes	Yes	Yes
Highly specific?	Yes	Yes	Yes	Yes
Rapidly acquired?	Yes	Yes	Yes	Yes
Consolidation?	Yes	Yes	Yes	Yes
Long-lasting?	Yes	Yes	Yes	Yes

acting in A1. Consistent with this, direct application of D1/D5 receptor agonists into the auditory cortex facilitates the consolidation of discrimination of auditory stimuli during avoidance learning, while D1/D5 receptor antagonists suppress this effect (Schicknick et al., 2008, 2012).

Norepinephrine

NE (noradrenaline: NA) is known to increase the frequency selectivity of neurons in the primary auditory cortex of animals (Edeline, 1995), apparently by reducing both spontaneous activity and receptive field size for frequency tuning (Manunta and Edeline, 1997, 1999). Most relevant for present purposes are the effects of pairing a tone with iontophoretic application of NE/NA to the primary auditory cortex. The increase in frequency selectivity by reduction of receptive field size was found to be specific to the paired tone, the effects extending only to 0.25 octaves. This plasticity was unaffected by propranolol but blocked by phentolamine, indicating the involvement of alpha receptors (Manunta and Edeline, 2004).

Serotonin

Very little is known about the role of 5HT in associative RP in the auditory cortex. A microdialysis study revealed no increase in release of its metabolite 5-hydroxyindoleacetic acid during avoidance learning. Levels of release appeared to be more closely related to the animals' stress levels (Stark and Scheich, 1997).

Neural synchrony and gamma-band oscillations

Cortical gamma-band oscillations (~40–120 Hz) reflect synchronous neuronal activity involving a systematic interplay between excitatory and inhibitory cells (Buzsáki and Wang, 2012). Gamma's time scale is appropriate for synaptic integration (Salinas and Sejnowski, 2001) and spike timing-dependent plasticity (Bi and Poo, 1998; Wespatat et al., 2004), which can enable synaptic strengthening both within auditory cortex and between auditory cortex and other regions. Indeed, synchronous activities do occur at different spatial scales, i.e., within a sensory field (Gray et al., 1989) and between cortical areas (Gregoriou et al., 2009). Within auditory cortex, synchronous activity representing a sound should be more effective in communicating with its targets than a less coherent representational population (Börgers et al., 2005, 2008). If synchrony increases after initial processing of sounds that become behaviorally significant, they could gain greater control both within A1 and over more distant targets. These effects could result in expanded representation locally and enhanced influence distally, promoting the formation of distributed networks for auditory memories and ultimately finding expression in behavior.

Gamma can easily be recorded in humans with scalp electrodes and increases during visual associative learning (Miltner et al., 1999). Animal studies that can reveal the relevant mechanisms have extended research in this relatively neglected area. Thus, increased gamma activity in A1 has been implicated in auditory learning and memory for both natural memory (Jeschke et al., 2008) and for memory implanted by stimulation of the NB (McLin et al., 2003). More recently, it has been found that both gamma and synchronous unit firing are enhanced in A1 during auditory fear conditioning when frequency tuning is shifted toward the signal tone and cells representing the signal tone increasingly discharge together, likely strengthening its effectiveness. Importantly, increased gamma activity predicts behavioral memory 24 hours later, greatly strengthening a causal role for increased neural synchrony in auditory learning and memory (Headley and Weinberger, 2011, 2013) (Fig. 7.13). Further, pairing a tone with stimulation of the basolateral amygdala, which can strengthen memories, also produces specific tuning shifts and increased gamma to the CS+tone (Chavez et al., 2013). *In toto*, these gamma findings bridge the gap between cholinergic mechanisms in RP and behavioral memory because gamma is itself induced by NB stimulation acting at muscarinic receptors in A1 (Metherate et al., 1992).

Circuit and synaptic processes

Research on circuit and synaptic processes in RP and learning is at a very early stage, but the findings appear promising. For example, given that associative learning produces tuning shifts and area gain for the signal frequency, one might suspect a "lateral" spread or recruitment of neighboring cells. Evidence for this mechanism has been recently reported. Rats were trained to detect a 5.0-kHz target to obtain food. After training, current-source density profiles obtained to a wide spectrum of test tones revealed that current sinks were enhanced in response to the training tone in layers 2–3 but not thalamo-recipient layer 4. Enhancement was limited to 1.0 octaves from the 5.0-kHz training frequency; sites more spectrally distant showed no change (Guo et al., 2013). The findings provide strong evidence that auditory learning increases the frequency domain of behaviorally important sounds via intracortical pathways.

Synaptic changes linked to behavior have been reported. Animals received extensive training of tone

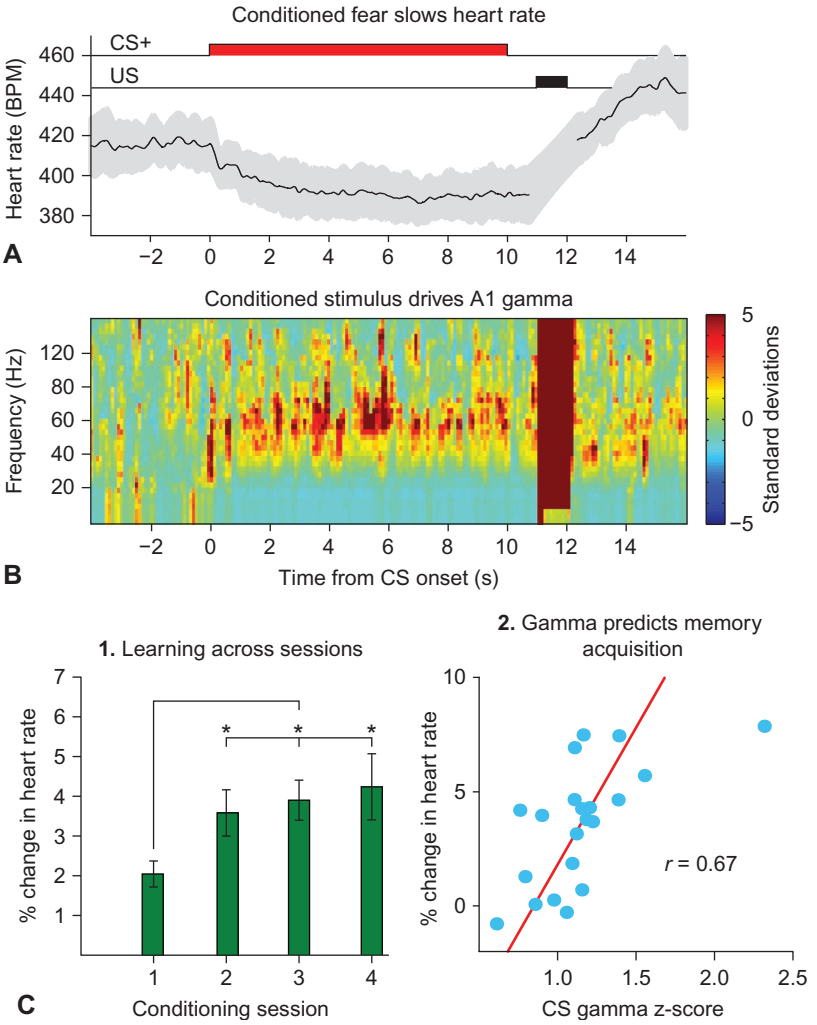

Fig. 7.13. Increased gamma-band activity in the primary auditory cortex predicts the formation of associative memory. Rats received a tone conditioned stimulus (CS) paired with shock (auditory fear conditioning). Conditioning cardiac slowing was used as the index of behavioral change. (**A**) Conditioned bradycardia (±SE) for an exemplar subject. Note the sustained reduction in heart rate during the 10-second conditioned stimulus. (**B**) The CS tone induces conditioned gamma oscillations (~40–120 Hz) in A1 after having been paired with shock; thick red line is shock artifact. (**C**) Group findings. (1) The magnitude of the conditioned response: asymptotic behavior was attained on session #2 and maintained thereafter. (2) The amount of tone-induced increased gamma activity (during tone minus pre-tone baseline) on session #1 predicts the magnitude of conditioned behavioral response on session #2. US, unconditioned stimulus. (Reproduced from Headley and Weinberger, 2011.)

paired with stimulation of the NB. This produced synaptic modifications in A1, the main effect of which was to decrease discharge variability and thereby increase neural signal-to-noise ratios. Neuronal sensitivity increased, e.g., thresholds were lowered and subjects were able to detect signals that were weak or previously undetectable (Froemke et al., 2013). Insofar as pairing a tone with NB stimulation implants a memory that the tone is behaviorally important (see section on ACh and the implantation of specific associative behavioral memory, above), it is very likely that the animals in this study also had memory implantation. Thus, the increased sensitivity to tones that had been paired with NB stimulation may have been a consequence of associative learning that was not evaluated in this study.

IMPLICATIONS FOR TREATMENT OF AUDITORY AND RELATED DISORDERS

The results of research on learning, plasticity, and the primary auditory cortex have implications for the clinic. Four of these are discussed below: (1) memory strength and posttraumatic stress disorder (PTSD); (2) gamma-band oscillations in assessment and treatment; (3) individualized analyses of neural plasticity, learning, and memory; and (4) cholinergic implantation of specific memory.

Memory strength and posttraumatic stress disorder

The area of cortical representation of a behaviorally important sound in A1 is increased; the greater the area, the stronger the memory (see section on substrate of memory strength, above). Less is known about representations for more complex important sounds (including speech) in other auditory cortical fields of both animals and humans. At this early stage of research, there is no reason to assume that RP is confined to A1; this is simply a convenient auditory field because its tonotopic organization provides for neural signatures of RP. On the contrary, although little studied, non-primary cortical fields also develop RP (Diamond and Weinberger, 1986; rat: Puckett et al., 2007). PTSD, with its intrusive "flashbacks" triggered by a stimulus related to the original traumatic experience, can be considered as an instance of abnormally strong memory. A testable hypothesis is that PTSD involves abnormally large representation in the cortex of all relevant sensory fields and modalities, as well as involved emotional neural representations. Such an extensive network of relevant neurons would likely be triggered by any stimulus whose similarity to a component of the traumatic memory is sufficient to activate part of the memory representation, and produce recall or flashback. Such flashbacks could even be triggered spontaneously, given the extremely large representational network, any of whose components might be activated in the normal course of daily events or dream sequences. Therefore, clinical studies should be directed to determining the size of involved representational networks in all cortical auditory fields, i.e., primary, belt and parabelt (Kaas and Hackett, 1998; Woods and Alain, 2009). If the hypothesis is confirmed, then treatments aimed at reducing the size of the representational area should be explored (see section on reversal and loss of representational gain in A1, above).

Gamma-band oscillations in assessment and treatment

Gamma-band oscillations index neural synchrony and such coordinated activity is likely to be more effective in communication with and influence on their targets, both locally and distally. Therefore sounds with greater gamma may have larger areas of tuning and promote associations. Indeed, tone signals do develop increased gamma and predict behavioral associations detected 24 hours later (see section on neural synchrony and gamma-band oscillations, above; Headley and Weinberger, 2011, 2013). Naturally, acoustic stimuli are used in treatments for auditory-processing disorders and other hearing problems. Such treatments constitute learning opportunities. Sounds that induce high levels of gamma prior to training may be more effective in forming new associations than sounds that induce lower levels of gamma. As gamma oscillations are routinely recorded from humans, we suggest that sounds planned for remedial training first be screened for their effectiveness in the induction of gamma oscillations, and the most effective relevant sounds be employed. Double-blind studies would reveal if this approach has hypothesized advantages.

Cholinergic implantation of specific memory

The importance of a given sound can be implanted by pairing it with stimulation of the NB, given the engagement of mAChRs in the primary auditory cortex (see section on acetylcholine, above). Similar effects may occur in other auditory fields when the sounds are complex or linguistic. It might be possible to induce or facilitate specific memory formation in humans by pairing a desired sound (simple, complex, linguistic) with the release of ACh in auditory cortical primary, "belt" and "parabelt" fields. It is already known that RP develops in non-primary fields even with tones (Diamond and Weinberger, 1986; Puckett et al., 2007). Indeed, RP probably develops in all auditory cortical fields simultaneously, if their constituent neurons respond reasonably strongly to the particular sounds that are used as a signal in associative learning.

Although direct stimulation of the NB is not possible in humans, RP can be induced by pairing a tone with stimulation of the vagus nerve, which already has been approved as therapeutic treatment for non-auditory problems (Engineer et al., 2011, 2013). Vagus stimulation is known to facilitate the memory of preceding stimuli in humans (Clark et al., 1999) as well as in the rat (Clark et al., 1998). Its effects depend upon activation of the basolateral amygdala, which has been established to modulate memory strength when activated shortly after an experience, via a cholinergic link (McGaugh, 2004). Vagus afferents appear to strengthen memory by detecting increased release of epinephrine in the periphery caused by an exciting event (Chen and Williams, 2012). The vagus then synapses in the nucleus of the solitary tract, which projects to the locus coeruleus, which releases NE that in turn activates the basolateral amygdala to facilitate the formation of memory traces in the cortex (McIntyre et al., 2012). Supporting this account, direct stimulation of the basolateral amygdala does induce long-lasting specific receptive field shifts in A1, possibly via the NB (Chavez et al., 2013).

Therefore, it should now be possible to determine if specific memory implantation or augmentation can be accomplished therapeutically for auditory-processing

disorders, and perhaps facilitation of language comprehension in cochlear implant patients. An important consideration is that cholinergic effects depend on the relevance of a sound or visual stimulus; agonists enhance neural and behavioral measures only when the current stimuli are task-relevant, but reduce or have no effect when sensory stimuli are given in passive or task-irrelevant situations (Bentley et al., 2011). As signal sounds are task-relevant in auditory associative learning, it would probably be more efficacious to use pro-cholinergic agents therapeutically, with appropriate timing, during learning tasks rather than in passive situations. We recommend that human protocols be based on the animal protocols now in use for more than a decade (McLin et al., 2002), including within-subject evaluation of the difference between pre- and posttraining behavioral gradients in heart rate, respiration, or other convenient physiologic measure (Miasnikov et al., 2006). This approach could be used as an adjunct or sole treatment for many problems, including perception, learning, memory, attention, and a variety of cognitive disorders.

Individualized analyses of neural plasticity, learning, and memory

The ability to induce specific memory by directed reorganization of auditory cortical representations has translational implications. Thus, training with a given auditory stimulus does not necessarily produce the best learning about that particular training sound. Posttraining generalization gradients can reveal which sound gained the greatest strength through training. In fact, when memory is implanted by tone paired with stimulation of the NB, the area of greatest gain in A1 matches the stimulus at the peak of the frequency gradient, rather than matching the training tone (Bieszczad et al., 2013). Therefore, it is important to actually determine what was learned by each subject or patient, rather than assume that the learning was to the training signal. As noted above, stimulation-based treatments have already shown promise for cortical remodeling to alter perceptual functions (Reed et al., 2011), including the potential to reverse maladaptive effects of tinnitus (Engineer et al., 2011, 2013). However, the findings reviewed above reveal that individual differences must be factored into both conceptions and empirical aspects of research (see Three classes of auditory tasks and representational plasticity, above). Reduction of potentially harmful, e.g., phantom-limb-like, effects of pain or aggravation that may result if map expansion develops "off target" (i.e., for an unintended stimulus) (Lozano, 2011) may be achieved by taking advantage of individualized approaches that promote intended therapeutic functional benefits.

CONCLUSIONS AND GENERAL IMPLICATIONS

Primary auditory cortex, learning, and plasticity

The primary auditory cortex can no longer be considered as only a sensory analyzer. Likewise, it can no longer be excluded from being deeply involved in associative learning and memory. Three major implications of the paradigm-changing findings reviewed above are considered: (1) the attribution of meaning to sound; (2) reconceptualization of the primary auditory cortex and, by extension, (3) the need for a new model for the entire cerebral cortex.

Beyond perception: The acquisition of meaning to sound

Auditory comprehension is essential to hearing because it gives meaning to sounds, whether of natural or human origin. Yet, remarkably, the amount of research devoted to this central problem of how sounds gain behavioral meaning has been vanishingly small compared to the wealth of effort expended to understand the detection and perception of sound. However, without foundational research on the neural bases of auditory perception, progress on auditory meaning would not have been possible.

This problem is also of fundamental importance to the field of the neurobiology of learning and memory because the meaning of sensory events is acquired through experience. This article has concerned the results of combining the two disciplines of auditory and learning/memory neuroscience to solve this common problem.

An answer has begun to emerge. First, associative learning systematically modifies the representation of acoustic stimuli in A1. For the vast majority of studies to date, the processing of meaningful sounds is augmented, including learning that a sound predicts reinforcement, discriminating a reinforced from a non-reinforced stimulus, solving instrumental problems that require behavioral acts to be performed or withheld under a wide variety of simple to complex task structures and demands. Such RP develops across species, types of motivation, and acoustic stimulus parameters. This selective facilitation can take several forms, including increased sensitivity and selectivity (decreased threshold and BW, respectively), tuning shifts directed to the signal in question, and increased area of representation in the tonotopic map.

Second, RP is formed when sounds are paired with stimulation of the cholinergic NB. It appears that activation of mAChRs in the auditory cortex is a mandatory

step in this process, although more research is needed. Third, specific behavioral memory is implanted by this same pairing of sound with NB stimulation. Fourth, directly increasing the area of representation artificially by pairing a tone with NB stimulation actually implants *de novo* specific behavioral auditory memory (Bieszczad et al., 2013).

The RP formed and the behavioral associative memory implanted by activation of the NB are indistinguishable from those that develop during natural learning. Overall, the findings satisfy cardinal criteria for a neural substrate of learning and memory (Martin et al., 2000).

The physiologic mode by which ACh acting at mAChRs may produce RP also has been identified, i.e., increasing neuronal synchrony, as detected in gamma oscillations and the covariance of discharge of separate neurons.

Future studies need not only to expand upon these findings but also to uncover the neural circuitry that normally activates the NB. One candidate is the basolateral amygdala, which projects to the NB and whose activation induces RP. However, numerous cortical structures project to the NB, including the frontal cortex, which probably is concerned with top-down control of ACh release.

Reconceptualizing the primary auditory cortex

Insofar as A1 is not simply an acoustic analyzer, what is it? We have summarized evidence for several mnemonic functions: (1) encoding the behavioral importance of sound; (2) reinforcement prediction; and (3) as a substrate of the strength of memory. Given this start, future research can be directed at the discovery of other potential functions, with the goal of achieving a comprehensive understanding of the functions of A1, and also of all other auditory cortical fields, and their modes of interaction. New conceptions of A1 have been advanced by two laboratories, which have approached the problem from different perspectives. Primary auditory cortex is viewed as a "semantic processor" (Scheich et al., 2011) or as an "acoustic problem solver" (Weinberger, 2011b). Both conceptions have converged on the similar formulation of A1 as a cortical field that is concerned with assigning meaning to sound, including all multimodal components of any auditory learning situation, be they other sensory, motivational, emotional, or the planning of behavioral acts. Regardless of the outcome, there can be no doubt it is essential to achieve a reconceptualization of the primary auditory cortex.

Toward a new model of the cerebral cortex

The cerebral cortex can no longer be considered to process information from the purely "sensory analytic" fields of A1, S1, and V1 because they are not merely sensory analyzers. It is speculative to consider that S1 and V1 have mnemonic and cognitive properties like those of A1, but not unreasonable given many similar reports for these two less-studied "early" sensory cortices (e.g., S1: Wiest et al, 2010; Kattoor et al., 2013; V1: Miller et al, 2008; Gavornik et al., 2009). Extensive research on the primary auditory cortex over the past 30 years or so, and particularly during the past decade, is incompatible with the view that its function is limited to the analysis of acoustic stimuli independent of their acquired behavioral significance or meaning. In short, responses of A1 neurons reflect both the physical and psychologic properties of sound. Therefore, primary auditory cortex should no longer be assumed to be merely an acoustic feature detector.

As A1 is influenced by and responds to multimodal inputs, and is involved in cognitive processes even beyond associative learning and memory, it would seem to perform highly complex, integrative computations. There is no reason to assume that A1 is the only cortical field so endowed. We suggest that the broad scope of A1, while specializing in auditory afferentation, is not fundamentally different from other cortical fields. Every field can be presumed to specialize in the processing of its input, the storage of somewhat specialized information, and the synthesis of both, to provide its special contribution to behavioral adaptation in concert with other fields.

While presently hypothetical, this concept suggests that the brain is more egalitarian and less authoritarian than assumed. This formulation does not eliminate hierarchic relationships but it does argue against the characterization of cortical fields as being isomorphic with common-sense or folk psychology ideas. This is the simplistic approach exemplified by Campbell's (1905) assumption that primary sensory fields are sensory analytic while "higher" adjacent cortical fields are cognitive ("psychic" in the terminology of his day). While specialized functions are maintained in this proposed model, they simply are not the functions that have been assumed. The challenge is not only to reconceptualize primary sensory cortices, but also to arrive at a far better model of a more dynamic, interactive cerebral cortex. We do not yet know how the computations of cortical fields should best be conceived. But that challenge has been with us for more than two decades. It is past time to refocus our thinking.

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