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AUDITORY ASSOCIATIVE MEMORY AND REPRESENTATIONAL PLASTICITY IN THE PRIMARY AUDITORY CORTEX

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Abstract

Historically, the primary auditory cortex has been largely ignored as a substrate of auditory memory, perhaps because studies of associative learning could not reveal the plasticity of receptive fields (RFs). The use of a unified experimental design, in which RFs are obtained before and after standard training (e.g., classical and instrumental conditioning) revealed associative representational plasticity, characterized by facilitation of responses to tonal conditioned stimuli (CSs) at the expense of other frequencies, producing CS-specific tuning shifts. Associative representational plasticity (ARP) possesses the major attributes of associative memory: it is highly specific, discriminative, rapidly acquired, consolidates over hours and days and can be retained indefinitely. The nucleus basalis cholinergic system is sufficient both for the induction of ARP and for the induction of specific auditory memory, including control of the amount of remembered acoustic details. Extant controversies regarding the form, function and neural substrates of ARP appear largely to reflect different assumptions, which are explicitly discussed. The view that the forms of plasticity are task-dependent is supported by ongoing studies in which auditory learning involves CS-specific decreases in threshold or bandwidth without affecting frequency tuning. Future research needs to focus on the factors that determine ARP and their functions in hearing and in auditory memory.

Keywords

acetylcholine; conditioning; receptive field

INTRODUCTION

This article provides a summary of our research on learning-related neurophysiological plasticity in the adult primary auditory cortex (A1). We refer to the systematic effects of associative learning on a dimension of neuronal processing, such as acoustic frequency, as “associative representational plasticity” (ARP) (Weinberger, 2007). This report begins with studies of the basic process of classical (Pavlovian) conditioning and then considers experiments on instrumental conditioning. However, the major goal of this paper is to highlight the importance of appropriate experimental designs and the objective measurement of behavior. Although central to the study of auditory memory and cortical plasticity, they have engendered controversy and confusion due to reliance on some questionable assumptions. Thus, the research reviewed here is intended to serve dual functions: (a) as findings in the

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search for a comprehensive understanding of the auditory cortex, and (b) as vehicles for the discussion of conceptual and methodological problems. We will attempt to make explicit the assumptions of our approach as well as those of other laboratories.

Before proceeding, it will be helpful to distinguish between *associative learning* and *perceptual learning* because they are often conflated. *Associative learning* simply refers to acquiring the knowledge that two events occur non-randomly, usually with one preceding the other. *Classical conditioning* is the most basic form of associative learning, in which a conditioned stimulus (CS, e.g., tone) is followed by an unconditioned stimulus (US, e.g. shock or food) without requiring any particular behavioral response. The *learned association* is that the CS predicts the US. *Instrumental conditioning*, which is based on prior classical conditioning, consists of learning to perform a particular behavioral response (e.g. key press) when presented with a CS, in order to obtain a reward or avoid a noxious stimulus. The *learned association* is that the instrumental response in the presence of the CS will produce a reinforcement (e.g., food). Such associations enable animals and humans to learn the “causal fabric” of their environments (Rescorla, 1988).

Perceptual learning is a particular form of instrumental conditioning. It consists of first learning to discriminate between two different signal stimuli (e.g., tones), one of which is designated as “correct” by the experimenter. After an easy discrimination has been achieved, increasingly difficult discrimination problems are used, until no further improvement. The result of perceptual learning is to improve perceptual abilities, such as the ability to better distinguish between two frequencies. Training often involves thousands of trials over many days. But while it can be rapid (Hawkey et al., 2004), nonetheless subjects must first learn basic associations, e.g., between an acoustic stimulus and a reinforcer (i.e., simple classical conditioning) and between a response contingent on an acoustic stimulus and a reinforcer (i.e., simple instrumental conditioning). Because basic associative learning and its correlated cortical plasticity develop very rapidly, understanding their substrates may help elucidate mechanisms of perceptual learning, further consideration of which is beyond the scope of this paper.

WHY STUDY THE AUDITORY CORTEX AND CONDITIONING?

As ablation of primary auditory cortex does not prevent classical conditioning to acoustic conditioned stimuli (CS) (e.g., Romanski and LeDoux, 1992), its study during conditioning has been questioned (Ohl and Scheich, 2004). However, even “simple” conditioning involves a widely distributed network of neural changes (Weinberger, 2004b). Even if sub-cortical circuitry can support simple associations in the absence of cortex, the auditory cortex stores information *in parallel* with the sub-cortex. Moreover, the auditory cortex appears to be the principle site of involvement (Boatman and Kim, 2006). Further, the auditory cortex has access to a much greater range of information than sub-cortical auditory structures, and A1 could store information for the *long-term*, where it can be used in a *highly flexible* manner to subserve adaptive behaviors in an unknown future. For example, after a subject forms a simple CS–US association, further challenges, such as two-tone discrimination (Teich et al., 1988) and experimental extinction (Teich et al., 1989), require primary auditory cortex.

Multiple behavioral conditioned responses develop even during learning of the same CS–US association, such as a tone–shock linkage. These include changes in heart rate, respiration, blood pressure, pupillary diameter, skin resistance, behavioral freezing, etc., any one of which can be used to verify that a CS–US (e.g., tone–shock) association has developed. We are not concerned with the particular circuitry underlying any behavioral conditioned response. Rather, we have used several of these measures to index that learning has developed. The issue

addressed is how the processing and representation of information in A1 change when associations are formed.

DETERMINING THE SPECIFICITY OF AUDITORY CORTICAL PLASTICITY

The “Traditional Approach”

Beginning in the mid 1950s, recordings were obtained during training trials. This very logical approach was applied to all sensory systems, in fact, to all brain structures. When acoustic training stimuli were used and recordings were obtained from A1, the findings consistently showed that associative plasticity develops in the primary auditory cortex (Weinberger and Diamond, 1987). These studies are foundational to contemporary research, so their value is not in question. However, restricting recording to training trials has at least two major limitations. First, non-learning factors are invariably present during training, due in part to the presence of positive or negative reinforcement. They include changes in attention, arousal level and motor performance. Rescorla has emphasized the dangers of relying on data obtained *during training* to infer the strength of learning and those aspects of an experience that enter into memory. Rather, these attributes are best determined by appropriate post-training assessments of behavior (Rescorla, 1988). This counsel is equally applicable to plasticity that develops during training. While such plasticity may constitute adequate evidence that associative learning has a neural correlate (given controls for sensitization), the form and magnitude of that correlate is not necessarily a reflection of associative processes alone. Second, the *specificity* of plasticity cannot be ascertained because conditioning involves only one or two acoustic stimuli. Thus, it was not possible to determine the extent, if any, to which learning was accompanied by systematic changes in frequency tuning or any other stimulus parameter.

A Unified Experimental Design

Both difficulties can be overcome by expanding the learning protocols to include assessment of plasticity by sensory neurophysiological approaches. The first step is to perform a sensory neurophysiology experiment by, e.g., determining the receptive field (i.e., acoustic frequency tuning function of A1) before the learning experience. Second, any learning protocol can be run. The training part of the design need only involve an additional decision; selection of the CS frequency must be based on knowledge of the “place” of the tonal CS in the receptive field. For example, if the CS is at the peak of the tuning curve (“best frequency”, BF), then potential tuning shifts toward the CS could not be tested. Thus, the preferred strategy is to select a non-BF frequency. Third, and finally, step one is repeated, i.e., post-training determination of the frequency tuning function. Short and long-term retention can be studied by obtaining further RFs at desired intervals following training, without extinction, as explained below.

The Importance of Context

We now come to the important topic of “context”, i.e., the general sensory environment of the subject. If training and receptive field assessment occur in the *same* context (e.g., the same enclosure, lab room, ambient illumination and acoustic stimulation) then the *post-training period* will constitute experimental extinction because of the removal of reinforcement. Furthermore, we should bear in mind that subjects, whether animal or human, learn many things in any given situation. For example, a rat learns not only that a tone precedes shock but also the place that shock occurs. Thus, a state of fear could influence post-training receptive fields if training and testing have the same context. Therefore, the training context should *differ* from the RF testing context.

What about the contexts in which pre- and post-training RFs (or other measures of acoustic processing) are obtained? These must be the *same*, so that they can be directly compared; the

difference between them can thus be attributed to the intervening training. If the pre- and post-training context differ in other ways, such as in the level of fear, arousal or expectancy, then an experimental confound would be introduced. In such circumstances, any RF differences from the pre- to the post-training recording period could not be attributed only to the particular training experience.

Contexts can differ in many ways: acoustically (e.g., different durations of tone pulses, rates of tone presentation and frequencies presented), visually (e.g., ambient illumination, light vs. dark) and spatially (e.g., different experimental rooms and chambers). We routinely change auditory, visual and spatial contexts between training and recording sessions, while keeping context the same during pre- and post-training determination of receptive fields.

ASSOCIATIVE REPRESENTATIONAL PLASTICITY

Non-Primary Auditory Cortex

The unified design was first used in the mid-1980s, but not in A1. The *zeitgeist* in sensory physiology at that time was that the primary auditory, somatosensory and visual cortices were not very plastic beyond a “critical period” of development. Rather, we decided to study two non-primary areas, secondary auditory cortex (A2) and the ventral ectosylvian (VE) field. They were selected because we wrongly assumed that A1 would be less plastic. Cats were trained in fear conditioning and developed associative pupillary dilation conditioned responses. We observed that frequency RFs displayed CS-specific plasticity; the maximum changes in response were at the CS frequency (Diamond and Weinberger, 1986; Weinberger et al., 1984b). Importantly, the sign of plasticity that developed during training trials (i.e., whether the change was a facilitation or suppression of response) was not necessarily the same as that which was evident in post-training RFs. This finding indicates that acoustic and other sensory aspects of context can affect the expression of associative plasticity. Factors present during training, such as arousal and motivational factors caused by the presence of the unconditioned stimulus, may mask the underlying reorganization of the cortex, which is revealed in post-training interrogation of complete receptive fields (Diamond and Weinberger, 1989).

Although such state effects cannot be eliminated during training, they can be eliminated when pre- and post-training RFs are obtained because they can be obtained with subjects in a markedly different context that ameliorates or eliminates generalization of, e.g., fear effects. Generalization also can be prevented altogether by training subjects in the waking state but obtaining pre- and post-training RFs (or frequency maps) with subjects under deep general anesthesia (Weinberger, 2004c).

The discovery of ARPs in A2 and VE was largely ignored. This may have reflected the fact that little was known about these auditory fields, which do not contain the fine-grain tonotopic organization found in A1. Thus, an “anything is possible” belief about A2 and VE would tend to reduce attention to any findings, no matter how distinctive.

Primary Auditory Cortex

Attributes of ARP in A1—Inquiry was thereafter directed to unit discharges in A1. The first such study involved tone–shock pairing (Bakin and Weinberger, 1990). Guinea pigs received a single brief (30–45 trial) training session. Cardiac conditioned responses typically develop in a few trials; such behaviors are used only to validate learning, i.e., CS–US association, *not* for the purpose of CR circuit-tracing, which is not at issue. Immediately after training, the peak of the tuning function had shifted from the pre-training BF toward or all the way to the CS frequency so that it could become the new best frequency (Figure 1A). Shifts were caused by a simultaneous increase in response to the CS frequency while responses to the pre-training BF and many other frequencies decreased. We also observed CS-specific increased responses

in RFs when tuning curves were complex and even non-existent. Figure 1B shows an example of a pre-training double-peaked frequency RF. The CS frequency was selected to be in the “valley” between the peaks. At post-training, the maximum change was an increase in response at the CS frequency. Figure 1C illustrates a case in which there was no response to any frequency before conditioning. Nonetheless, post-conditioning observations revealed a clear excitatory response to the previously ineffective CS frequency, alone.

CS-specific RF plasticity has the major features of associative memory and therefore is a good model for the study of learning-induced information storage in the cerebral cortex. It is associative, as it requires stimulus pairing; sensitization training produces only a general increase in response to all frequencies across the RF. Also, it is highly specific to the CS frequency, develops very rapidly (detectable after 5 training trials, as rapidly as behavioral, e.g., cardiac conditioned responses), consolidates (i.e., continues to develop in the absence of further training) and is enduring (tracked so far to eight weeks) (reviewed in Weinberger, 2004a, 2004c) (Figure 2). RF plasticity induced by training at one level of CS loudness (e.g., 70 dB) is expressed at all stimulus levels, indicative of a marked modification of underlying circuitry (Galván and Weinberger, 2002). Figure 3 summarizes changes in tuning for conditioning, sensitization and habituation; the latter produces frequency-specific response decrements.

RF plasticity is not an artifact of arousal state. Whereas animals exhibit arousal and related responses to sustained (e.g., 2 s) CS frequencies during training trials, they do not exhibit any behavioral (e.g., cardiac) responses to the frequency of the CS when it is presented as one of a number of rapidly presented, brief (e.g., 200 ms) sequential tone bursts during RF determination (Diamond and Weinberger, 1989). Moreover, animals trained in the waking state exhibit RF plasticity when tested under deep general anesthesia (Weinberger et al., 1993). Shifts of tuning are also not due to random drifts of tuning as they are toward the CS frequency. Finally, direct measures of tuning stability over periods of 2–3 weeks revealed no drifts of tuning (Galván et al., 2001). Learning induced tuning plasticity is not limited to animals. The same paradigm of classical conditioning (tone paired with a mildly noxious stimulus) produces concordant specific associative changes in the primary auditory cortex of humans (Molchan et al., 1994; Morris et al., 1998).

The CS-specific plasticity of cells in A1 might be a reflection of plasticity projected to it from the auditory thalamus. However, the ventral medial geniculate nucleus changes little during training trials (Gabriel et al., 1975) and exhibits RF plasticity for less than 1 hr after conditioning (Edeline and Weinberger, 1991). The magnocellular medial geniculate (MGm), does develop RF plasticity but its RFs are much more complex, multi-peaked and broader than auditory cortical cells (Edeline and Weinberger, 1992). Therefore, it seems likely that RF plasticity in the auditory cortex is, at least in part, local in origin. This conclusion is also supported by cholinergic studies.

Acetylcholine, the Nucleus Basalis and ARP in A1—Acetylcholine (ACh) and the nucleus basalis (NB), the major source of ACh to the cortex, have been strongly implicated in auditory cortical plasticity and learning. Iontophoretic application of muscarinic agonists (McKenna et al., 1989) or anti-cholinesterases (Ashe et al., 1989) to the ACx produces lasting modification of frequency tuning. Further, pairing a tone with iontophoretic application of muscarinic agonists produces pairing-specific, atropine-sensitive, modification of RFs (Metherate and Weinberger, 1990). Stimulation of the nucleus basalis can produce long-lasting atropine-sensitive, facilitation of local field potentials, cellular discharges and EPSPs elicited by medial geniculate stimulation (Metherate and Ashe, 1991, 1993), and facilitation of neuronal discharges to tones (Hars et al., 1993; Edeline et al., 1994a, 1994b). Furthermore, NB neurons projecting to the ACx selectively increase transcription of the gene for ACh’s synthetic

enzyme, choline acetyltransferase, following tone–shock conditioning (Oh et al., 1996). Also, pairing a tone with NB stimulation induces associative RF plasticity (Bakin and Weinberger, 1996; Kilgard and Merzenich, 1998). Two-tone discriminative RF plasticity develops when one tone is paired with NB stimulation while another is presented alone. Moreover, NB-induced RF plasticity shows consolidation (increased post-training effect over 24 h) and requires the engagement of muscarinic receptors in the ACx (reviewed in Weinberger, 2004a, 2004c).

Generality of Associative Representational Plasticity

ARP exhibits generality across the types of tasks and motivational situations under which it develops. In addition to simple classical aversive (shock) conditioning, ARP develops during aversive discriminative (Edeline and Weinberger, 1993) and instrumental avoidance conditioning (Bakin et al., 1996), and with reward motivation in classical (Kisley and Gerstein, 2001) and instrumental (Blake et al., 2002) conditioning. In addition to RF plasticity, ARP is revealed in CS-specific increases in area in the tonotopic map; these findings provide evidence that the increased area of representation could serve as a “memory code” for the level of acquired importance of a sound (Rutkowski and Weinberger, 2005). Recently, instrumental avoidance conditioning has been used in studies that employ a clever “on-line” method of determining changes in spectro-temporal receptive fields (STRF) in A1. Ferrets trained to detect a target tone exhibited tone-specific facilitative changes in STRF shape, which were rapid in development. Some ARPs were retained for hours after task completion and the authors suggest may contribute to long-term auditory memory (Fritz et al., 2003, 2005). In all of these studies, which included behavioral validation of learning, the dominant result was a CS-specific *enhancement* of response.

Auditory Memory, the Nucleus Basalis and Associative Representational Plasticity

The development of ARPs and their long-term retention during associative behavioral learning indicate that at least some components of auditory memory are likely to be stored in the primary auditory cortex. Research on the cholinergic system supports the possibility that this neuromodulator, acting at muscarinic receptors, promotes the storage of information in the primary auditory cortex.

Recent studies have provided a more direct link between the NB, ARP and behavioral auditory memory. Pairing a tone with NB stimulation induces CS-specific behavioral memory. Rats received trials in which a 2-s CS tone was paired with a co-terminating 0.2-s train of stimulation to the nucleus basalis; controls received the stimuli unpaired. The NB stimulation itself produced EEG activation (shift from higher voltage slow waves to lower voltage fast waves) but no behavioral responses. On the day after training, they were presented with the CS and many other tones randomly, to determine the effects of tone presentation on their respiration and heart rate. As we hypothesized that the NB is “downstream” of motivational brain systems, i.e., as a “final common neuromodulatory path to A1”, associative learning could develop although NB stimulation lacks motivational significance. Any tone that had acquired behavioral importance would interrupt respiration and change heart rate. The method of training with one tone but testing with many tones generates a behavioral gradient of frequency generalization. A flat gradient would indicate that acoustic frequency per se had not become important whereas a gradient with a peak at the CS frequency would indicate that the animals had learned that the CS frequency had become more important than any other tones.

The findings are summarized in Figure 4A–B. CS-specific behavioral auditory memory was found, but only in the paired group showing the effect is associative (McLin et al., 2002). The frequency generalization gradients are indistinguishable from those that develop in standard learning protocols using standard motivational reinforcers (Mackintosh, 1974). Thus, the behavior meets the same criteria used to assess specific frequency learning under normal

circumstances. In addition, specific auditory memory develops simultaneously with cortical plasticity (Miasnikov et al., 2006).

NB stimulation can actually control the *amount of detail* in that auditory memory. Rats received tone and NB stimulation either paired or randomly with either low ($\sim 45 \mu\text{A}$) or moderate ($\sim 65 \mu\text{A}$) levels of NB stimulation. Previous induction of CS-specific memory had used the moderate level. As in the past, the moderate paired group developed associative CS-specific memory; the only significant increased response was at the spectral range containing the CS frequency (6.0 kHz). In contrast, the weak stimulation group developed only associative memory without any frequency specificity (Figure 4D–G). These findings indicate that the weak paired group learned that tone (or sound per se) had become important but did not form an auditory memory of the actual frequency of the CS. In contrast, the moderate paired group remembered the actual CS frequency (Weinberger et al., 2006a).

A comparison of associative memory, learning-induced ARP, NB-induced ARP and NB-induced behavioral auditory memory indicates that they have the same attributes (Table 1). In toto, these findings suggest that A1 stores specific information and that the NB normally is engaged during auditory learning such that its release of ACh promotes the storage of information in the primary auditory cortex, which contributes to specific auditory memory. It remains to be determined if neuronal plasticity in A1 represents information that is indeed the neuronal substrate of identifiable memories.

CONTROVERSIES AND ASSUMPTIONS

Currently, there are substantial controversies about associative representational plasticity. These include opposing claims regarding the form of receptive field plasticity, the interpretation of its functional significance and its underlying neural mechanisms. We will consider form and function first, and mechanisms next.

The Form and Function of Associative Receptive Field Plasticity

Ohl and Scheich (1996, 1997, 2005) found in the gerbil that tone–shock pairing induces *decreased* responses at the CS frequency, i.e., the opposite direction of change found in other laboratories. They proposed that this plasticity provides for “contrast enhancement”, rather than reflecting learning-induced increases in CS behavioral importance. Further, they maintain that we ignored our previous findings of decreased responses to the CS (Weinberger et al., 1984a) to bolster our proposal that RF plasticity reflects the increased behavioral importance of the CS (Weinberger et al., 1990a). But their allegation is based on the assumption that plasticity which develops *during training trials* is the *same* as plasticity that is observed in *post-training receptive field determination*. The 1984 study to which they referred was performed using the “traditional approach”, i.e., recording only during training trials. We had indeed observed both increased and decreased responses of units to the conditioned stimulus. Ironically, that study convinced us to abandon the traditional approach in favor of RF analyses using the unified experimental design. As discussed above, the sign of plasticity *during* training trials is often different than the sign of changes in response to the CS *after* training (Diamond and Weinberger, 1989). This may well reflect the different states of subjects between such periods, e.g., the training period includes fear of shock. Regardless, studies of ARP from different laboratories, all of which include behavioral validation of learning, have found *increased* responses to the CS frequency and *tuning shifts*.

Ohl and Scheich found CS-specific decreased responses using a novel design in which a single CS+ tone (paired with shock) was randomly intermixed with 11–30 different CS– (no shock) frequencies in a single training session. The same frequencies were presented before, during and after training without break, so that the only information that training was underway was

the presence of an occasional shock. Two assumptions seem to underlie the claimed validity of CS-specific decreased responses. First, that animals learned the CS–shock association. Unfortunately, there were no behavioral measures of learning. Second, that differences between RFs from pre- and post-training periods are attributable only to CS–US learning during training. However, the post-training period constituted a period of conditioned extinction due to the elimination of shock, because the same CS+ tone was being presented with the other CS – tones. Thus, the post-training period almost certainly differed from the pre-training period in both the subjects' state of arousal and fear due to the anticipation of shock, and then in the new extinction learning that shock was no longer forthcoming. If the animals had not learned the discrimination, then CS decreases might be attributable to uncontrolled state effects. If the animals had learned the discrimination, then the results might be attributable to conditioned extinction, which is known to produce decreased responses to the previously reinforced CS.

Of course, it is quite possible that there are circumstances under which such decreases do develop. At this time, CS-specific increases, CS-directed tuning shifts and CS-expansions of area in the tonotopic map remain the dominant behaviorally validated ARPs in the primary auditory cortex. However, Ohl and Scheich also drew a conclusion that is more important than their particular findings. It is that the *forms* of ARPs in A1 are *task dependent*. This is implied in the cell assembly formulation of Hebb (1949) and part of the common belief that a neuron participates in numerous networks and memories (Sakurai, 1994). Their raising awareness on this basic point is proving beneficial. We defer consideration of “task-dependency” until the final section.

Mechanisms and Models of ARP and Associative Memory

There are currently two models of ARP in the primary auditory cortex, that of Weinberger and associates (Weinberger and Bakin, 1998; Weinberger et al., 1990a, 1990b) and that of Suga and associates (Suga and Ma, 2003). Analyses with greater detail are available (Suga and Ma, 2003; Weinberger, 2004a, 2007).

CS–US Convergence in the Magnocellular Medial Geniculate—The goal of the first model was to suggest the minimum circuitry sufficient to account both for ARP in A1 and behavioral (autonomic) signs of fear conditioning (Figure 5) (Weinberger et al., 1990a, 1990b). The key ideas are (a) CS–US convergence occurs first in the (non-lemniscal) magnocellular medial geniculate nucleus (MGm), where the resultant plasticity results in shifts of tuning that favors the CS frequency; (b) projection of this MGm plasticity to the amygdala; (c) projection of the effects of the plasticity (i.e., increased response to the CS) from the amygdala to both the cholinergic nucleus basalis and to brain stem nuclei controlling autonomic behavioral responses (e.g., heart rate); (d) convergence of MGm and auditory lemniscal tonal information in the primary auditory cortex to promote short-term plasticity; and (e) convergence of NB/ACh and auditory information in A1 to promote long-term plasticity. This model incorporated many established findings (e.g., convergence of auditory and nociceptive somatosensory information in the MGm (Love and Scott, 1969; Wepsic, 1966), the necessity for an intact MGm region for auditory fear conditioning (LeDoux et al., 1984) and the ability of NB/cholinergic influences to facilitate cortical responses in sensory cortex (Ashe et al., 1989).

This model was soon shown to be incorrect with respect to the ventral medial geniculate nucleus. Although it hypothesizes that the MGv sent only the “physical parameters” of sound to A1, i.e., that the MGv did not develop RF plasticity, in fact it does develop CS-specific tuning plasticity. Unlike A1 and the MGm, tuning shifts in the MGv are short-lived, disappearing by one hour post-training (Edeline and Weinberger, 1991). However, the model was successful in several other respects. It correctly predicted RF plasticity in the MGm

(Edeline and Weinberger, 1992) and that electrical stimulation of the MGm could be substituted for the shock-US in fear (cardiac) conditioning (Cruikshank et al., 1992). It also explains the CS/tone associative plasticity in the NB that develops before associative tuning shifts in A1 (Maho et al., 1995). The model correctly held that electrical stimulation of the NB should be able to substitute for the US to induce CS-specific tuning plasticity in A1 (Bakin and Weinberger, 1996; Kilgard and Merzenich, 1998), and that this plasticity is dependent on muscarinic receptors in A1 (Miasnikov et al., 2001). It also explains why lesions of the MGm both blocks associative plasticity that develops in the amygdala and elsewhere in the brain, and also impairs conditioning (Poremba and Gabriel, 1997). Additionally, imaging studies in humans have obtained results predicted by the model. For example, aversive two-tone discriminative conditioning produces CS-specific plasticity in the primary auditory cortex and associative changes *only* in the medial geniculate, amygdala, basal forebrain and orbitofrontal cortex (Morris et al., 1998). These structures, except the orbitofrontal cortex, are the core of the model.

CS-US Convergence in Association Cortex—Suga and colleagues have proposed that the CS and US ascend to the auditory and somatosensory cortices, respectively, and are projected to association cortex, which is claimed as the locus of CS-US convergence (Suga and Ma, 2003). This model also includes the descending (corticofugal) auditory system and asserts that plasticity, which develops in the association cortex, is relayed via the amygdala to the inferior colliculus, which in turn promotes CS-specific plasticity in A1. The Suga model accepts the components of the Weinberger et al. model (a) that link the amygdala to the initiation of behavioral CRs, (b) hypothesize that the amygdala engages the nucleus basalis and (c) that the cholinergic projections of the nucleus basalis to A1 promote long term CS-specific tuning shifts therein.

Suga and colleagues ignore the MGm, but tone and shock are known to converge on its bimodal cells and at least 14 experiments have found associative plasticity during conditioning trials (reviewed in Weinberger, 2004a reviewed in Weinberger, 2007). Moreover, the MGm develops CS-specific RF plasticity (Edeline and Weinberger, 1992). The MGm projects to Layer I and the apical dendrites of pyramidal cells in A1 and in all other auditory cortical fields (Winer and Morest, 1983) and does so via giant axons that provide the fastest thalamo-cortical transmission (Huang and Winer, 2000). Additionally, LTP can be induced in the MGm (Gerren and Weinberger, 1983) and stimulation of the MGm induces heterosynaptic LTP in A1 (Weinberger et al., 1995). Suga's claim that essential CS-US convergence occurs in the cerebral cortex is refuted by prior findings that neither the auditory cortex, nor indeed the cerebral cortex as a whole, are necessary for simple classical conditioning (Norman et al., 1977; Romanski and LeDoux, 1992; Teich et al., 1988).

The Suga model is based on studies of tone-shock pairing in the big brown bat (*Eptesicus fuscus*) (Suga and Ma, 2003). The authors assumed that the bats learned the tone-shock association, based on the development of limb flexion responses (Gao and Suga, 1998). But they provided no behavioral data and they previously reported that bats cannot develop flexion CRs with tone CSs (Riquimaroux et al., 1992). Further, as the subjects are trained under whole body restraint while receiving shock, and apparently, access to the brain is obtained while they are awake, the bats are likely under high levels of stress. Body struggling produces leg movements that have been incorrectly interpreted as flexion CRs (Konorski, 1967). Further, their conditioning protocol is faulty because intertrial intervals were fixed at 30 s rather than being randomized. Thus, any putative CRs could have been caused by temporal conditioning, without any control by the tonal CS itself. The authors further assumed that extinction trials (tone without shock) "erase" the effects of prior training, returning them to a naïve state. But, as is well known, Pavlov himself emphasized that extinction is not erasure but new learning, which interacts with the prior learning. Only data from the first training sessions in different

animals would have been interpretable, but data from all sessions and subjects were combined. Finally, repeated presentation of a tone alone produced tuning shifts toward the repeated frequency (Gao and Suga, 1998). This is in direct opposition to the extensive literature on the effects of repeated auditory stimulation, which produces response decrements (habituation) in the auditory cortices in other taxa (e.g., Condon and Weinberger, 1991; Marsh and Worden, 1964; Weber, 1970; Westenberg and Weinberger, 1976; Wickelgren, 1968). This discordance suggests that the echolocating big brown bat may not be a good general model for mammalian ARP in the primary auditory cortex.

AUDITORY LEARNING WITHOUT FREQUENCY TUNING SHIFTS

We noted previously that Ohl and Scheich have proposed that the form of learning-induced plasticity is task dependent. Their formulation, as a subclass of the general expectation that cortical cells subserve whatever adaptive needs are present, is proving to be correct (see also Fritz et al., 2005). For example, while there is overwhelming evidence of tuning shifts caused by increased responses to the CS frequency and decreased responses to the pre-training BF in associative learning, this is not invariably the case if subjects are challenged in new ways.

In ongoing studies, we have simply trained rats to bar press for water in the presence of a tone (Weinberger et al., 2006b). Two groups received the same auditory exposure and contingencies but were trained with different levels of task difficulty based on the presence or absence of a signal to inhibit responses at tone offset. The Easy group was rewarded for bar presses during a 10 s, 5.0 kHz tone but punished for all responses in the absence of tone, by an error signal (flashing light) and an added delay (“time out”) until the next scheduled trial. The Difficult group was trained identically except that there was no penalty for bar pressing during the 2-s (“catch”) period following tone offset (Figure 6A). The Easy group rapidly learned to suppress responding when the tone was off, including during the catch period, while the Difficult group never learned to suppress responding during this period (Figure 6B). The Easy group exhibited more rapid learning than the Difficult group, because the latter also tended to fail to inhibit bar pressing even after the 2-s catch period, but eventually learned to inhibit when they received the error signal/time out. Thus, the Difficult group finally was able to attain the same level of asymptotic performance. Moreover, both groups learned that the actual CS frequency was relevant as generalization gradients obtained after training (i.e., in the absence of water reward) were the same, both peaking at 7.5 kHz (Figure 6C). The lack of maximal response at the CS frequency of 5.0 kHz is attributable to the absence of discrimination training; subjects subsequently trained in a two-tone discrimination exhibited peak responses at whatever frequency had been used as the CS+.

Terminal mapping of A1 revealed an absence of any differences in frequency organization, including the area of representation for the 4–8 kHz octave containing the CS frequency; there was neither difference between groups nor difference between each group and untrained (naïve) controls. However, CS-specific plasticity was found for *sensitivity* and *selectivity*; the Difficult group developed significantly lower thresholds and narrower bandwidths only for the octave containing the CS frequency (4–8 kHz) (Figure 6D–E).

These aspects of CS-specific representational plasticity can be attributed neither to the level of learned performance nor to what was learned, i.e., bar press during a tone of a certain frequency. Different levels of motor inhibition demands might be responsible for the differences in plasticity. That is, the Easy group had a clear cue of when to start suppressing responding, at *tone offset*, whereas the Difficult group was forced to learn to inhibit when the tone was off without a clear (tone offset) signal. Of importance, the Easy group learned the task yet exhibited *no cortical plasticity*, at least none for frequency, threshold and bandwidth.

CONCLUSIONS AND FUTURE DIRECTIONS

It is now well-established that learning systematically modifies the processing and representation of acoustic information in the primary auditory cortex. Tuning shifts that favor the frequency of an important, signal stimulus are a consistent and dominant finding across types of training, types of reinforcement motivation and different laboratories. Moreover, the persistence of associative representational plasticity indicates that some of the substrates of auditory memory are probably stored in A1. Studies of acetylcholine and the nucleus basalis support the hypothesis that this neuromodulator is sufficient to induce both ARP and specific behavioral auditory memory.

Extant controversies regarding the form, function and neuronal circuitry of A1 plasticity appear largely to reflect differences in implicit assumptions about experimental designs and whether or not behavioral verification of associative learning is necessary. Naturally, we believe that our assumptions are generally well-founded while some assumptions of other laboratories are not. Readers will come to their own conclusions based upon all relevant publications. But transcending the details of past and current findings are implications for conceptions of auditory cortical functions. Space permits brief mention of two.

Ohl and Scheich's view that learning-induced plasticity in A1 is "task dependent" has heuristic value. It is essential to determine exactly *what aspects of a task* are critical to cortical plasticity. We do not have a clear explanation for our recent observations that plasticity developed only in the Difficult group that did not receive a "stop pressing" cue at tone offset (Figure 6). As this group eventually reached the same level of performance and exhibited the same frequency generalization gradient as the Easy group, these factors cannot explain the difference in plasticity. Rather, the *means by which a problem is solved* may determine the involvement of the auditory cortex. Another current study in the rat has found evidence that the development and expression of ARP can be reversed and then reinstituted based on the *strategy of "win-stay, lose-drop plasticity"* (Bieszczad et al., 2006). Determining the dimensions of task-specific effects and their causes are major challenges for future research.

The *zeitgeist* seems to be increasingly shifting from the concept of the primary auditory cortex as primarily a sensory processing structure to one that is cognitive in nature, albeit specializing in acoustic processing and hearing (e.g., King, 2006; Sussman and Steinschneider, 2006). Research that expands the domain of inquiry about the auditory cortex will undoubtedly substantially increase complexity and perhaps confusion. The design of learning tasks that fully take into account the nature of the problems faced by the subjects and that can determine their strategies for solutions should be helpful. It is becoming increasingly clear that seemingly trivial changes in experimental designs, from the standpoint of investigators, may constitute major factors from the viewpoint of subjects.

A convergence of seemingly disparate findings ultimately needs to occur at the level of *function*. What "use" do animals and humans make of the various representational plasticities that develop in their auditory cortices, or for that matter elsewhere in their auditory systems? This is perhaps the most challenging issue in the study of learning and auditory memory. However, it is the same problem faced by investigations of the relationships between acoustic stimulus parameters, neuronal responses and perception. In both lines of inquiry, which are becoming increasingly intertwined, the answers probably will rely to a great extent on auditory-based behavior, including objective measures of learning and auditory memory. The auditory cortex presents a greater challenge than may have been assumed, but by the same token promises greater rewards. A more comprehensive understanding may well have important implications for a far larger domain of neuroscience because the adaptive plasticity of the auditory cortex may be a prototype for all experience-based cortical function.

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Figure 1.

Classical conditioning produces CS-specific facilitation and tuning shifts. **(A)** An example of a complete shift of frequency tuning of a single cell in A1 of the guinea pig, from a pre-training best frequency (BF) of 0.75 kHz to the CS frequency of 2.5 kHz after 30 trials of conditioning. Inset shows pre- and post-training post-stimulus time histograms (PSTHs) for the pre-training BF and the CS frequencies. **(B)** Double-peaked tuning, with pre-training BFs at 5.0 and 8.0 kHz. The CS was selected to be 6.0 kHz, a low point. After conditioning (30 trials), responses to the CS frequency increased to become the peak of tuning. **(C)** A cell that exhibited minimal or no response to tones before tuning developed tuning specifically to the CS frequency after conditioning (30 trials).

Figure 2. Additional attributes of associative representational plasticity. **(A)** Two-tone discrimination. Representation of neuronal responses in A1 before, immediately after and one hour after two-tone discrimination training (30 each CS+ [22.0 kHz] and CS- [39 kHz] intermixed trials). Displayed are rates of discharge (Y-axis) as a function of tonal frequency (X-axis) and level of testing stimuli (10–70 dB). Note that conditioning changed the “topography” of neuronal response. The pre-training best frequency 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 one hour of silence, the only excitatory response is at the CS+ frequency. **(B)** Rapid development of RF plasticity. Vector

diagram of increase in response to the CS frequency and decrease in response to the pre-training BF after 5, 15, 30 training trials and one hour later. Note specific facilitation to CS frequency after only 5 trials and the consolidation after 1 hour of silence. (C) Long term retention and stability of RF plasticity over weeks.

Figure 3.

Summary of the effects of conditioning, sensitization and habituation on frequency receptive fields in the primary auditory cortex of the guinea pig. Data are normalized to octave distance from (A) the CS frequency, (B) the pre-sensitization best frequency or (C) the repeated frequency. Note that conditioning produces a CS-specific increased response whereas sensitization (tone-shock or light-shock unpaired) produces general increases across the spectrum. Habituation produces frequency-specific decreased response.

Figure 4.

CS-specific auditory memory and control of memory detail, induced by tone paired with stimulation of the nucleus basalis (respiration responses to post-training tone and generalization gradients). (A) Individual respiration records (with value of respiration change index, RCI) to three frequencies (2, 6 and 12 kHz) for one animal each from the paired and unpaired groups. The largest response was at the CS frequency of 6 kHz for the paired animal (RCI = 0.50). Horizontal bar indicates tone duration. (B) Left panel, group mean ($\pm$ SE) change in respiration to all tones for both groups. Note that the maximal response was at 6 kHz for the paired group, but not for the unpaired group. The group difference function (paired minus unpaired) (right panel) shows a high degree of specificity of respiratory responses to 6 kHz. (C) Level of NB

stimulation controls specificity of contents of memory. Pre-training responses to test tones in the Moderate and Weak NB stimulation (NBs) groups. **(D)** Post-training responses for the Moderate NBs groups. Note the significant difference between the paired and unpaired groups, confined to the CS-band frequencies. This indicates that training with a moderate level of NBs produced memory that was both associative and CS-specific. **(E)** Comparisons of changes within the Moderate group (post- minus pre-training responses to test tones). Note that the paired group had developed a significant increase to the CS-band frequencies only, while the unpaired group had developed a significant decrease, probably indicating frequency-specific habituation due to lack of pairing with NB stimulation. **(F)** Post-training responses for the Weak NBs groups. In contrast to the Moderate NBs group, pairing produced a significant difference in response across all test frequencies compared to its unpaired controls. This indicates that training with weak NBs was sufficient to produce associative memory but insufficient to produce memory for frequency detail, i.e., memory that the frequency of the CS was paired with NBs. **(G)** Comparisons of changes within the Weak NBs groups showed that the paired group did not develop absolute increased responses but that the unpaired group did develop significant decreases in responses across the spectrum of test frequencies. Thus, pairing the CS with weak NBs apparently prevented a habituated decrement in the Weak paired group, which is evident in the Weak unpaired group.

Figure 5.

The model of ARP and autonomic conditioned responses based on convergence of the CS and US in the magnocellular medial geniculate. This model hypothesizes the minimal circuitry that would be *sufficient* to account for short and long term associative representational plasticity and rapidly-acquired conditioned autonomic responses. See text for details.

Figure 6.

Learning without plasticity of frequency processing. The development of ARP, in the form of CS-specific reduction of threshold and bandwidth, depends on “modest” change in training protocol. (A) Protocol for Easy and Difficult task groups, the latter differing only in the non-punishment/error signal during 2 s at tone offset. (B) The Difficult group never learned to inhibit responses during the 2 s catch period, in contrast to the Easy group which learned to inhibit rapidly; note the difference in Y-axis values. (C) Learning curves showing the retarded acquisition of the Difficult group until the 17th training day at which time they achieved the same asymptotic performance as the Easy group, by learning to inhibit responses during silence, when error signal was present after 2 s catch period. (Performance = bar presses during the tone divided by total bar presses during intertrial period when error signal was equally present for both groups). Inset: behavioral generalization gradients (without reward) showing same behavior. (D) Frequency response areas (FRAs) with the same CF showing a decrease in threshold and reduction in bandwidth at the CS frequency (5.0 kHz) for Difficult training. (No tuning shifts were found across A1 in this study.) (E) Thresholds and BW20 for Easy, Difficult and Naïve (untrained) groups. The only significant effects were found in the Difficult group: a decrease in threshold (increased sensitivity) and a narrowing of bandwidth (increased selectivity) for octave band containing the CS frequency.

TABLE 1

Attributes of Associative Memory, Learning-Induced Receptive Field Plasticity and NB-Induced RF Plasticity

Attribute	Associative Memory	Receptive Field Plasticity	NB-Induced RF Plasticity	NB-Induced Memory
Associative?	Yes	Yes	Yes	Yes
Highly Specific?	Yes	Yes	Yes	Yes
Discriminative?	Yes	Yes	Yes	?
Rapidly Acquired?	Yes	Yes	Yes	Yes
Consolidation?	Yes	Yes	Yes	Yes
Long Lasting?	Yes	Yes	Yes	Yes

“?” indicates experiment has not been done.