3.11 Cortical Plasticity in Associative Learning and Memory

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3.11.1 Introduction

Cortical plasticity concerns the totality of nontransient changes in the structure and function of the cerebral cortex at the levels of hemispheres, lobes, systems, circuits, cells, and molecules. Restricted to the domain of learning and memory, its scope remains colossal. This chapter focuses on a central aspect of learning and memory – associative learning and memory and neurophysiological plasticity at the

levels of systems and cells in the primary sensory cortical fields: auditory (A1), somatosensory (SI), and visual (V1). For an earlier related account with a somewhat difference emphasis, see Edeline (1999). Space limitations preclude broad coverage of priming and related phenomena in humans (Schacter et al., 2004; Grill-Spector et al., 2006) and of cellular and molecular mechanisms of associative plasticity (Buonomano and Merzenich, 1998; Palmer et al., 1998; Rauschecker, 1999; Barth, 2002; Diamond et al., 2003; Edeline, 2003; Metherate and Hsieh, 2004; Weinberger, 2004b).

3.11.1.1 Rationale

Why focus on primary sensory cortices (PSCs)? There are several reasons. First, the primary sensory cortices are the last regions of the cerebral cortex to be included into the field of the neurobiology of learning and memory. Of course, there can be found no formal, and indeed only rarely a semiexplicit, denial of their importance in learning and memory. But PSCs have been largely ignored, particularly in the case of associative learning.

Second, general conceptions about cortical organization for learning and memory should be informed by the established, but still underappreciated, realization that primary sensory fields are not merely sensory analyzers. Rather, their functions, as related to intrinsic operations and integration of influences from the thalamus, other cortical areas, and neuromodulatory systems, render them as important nodes in the acquisition, representation, storage, and ultimate use of information in thought and action.

Third, beyond associative and mnemonic processes, PSCs are involved in a wide variety of functions that are not strictly sensory, including attention, motivation, the encoding of behavioral significance, motor acts, and higher cognitive functions such as learning strategy, expectancy and preparatory set, cross-modal integration, category learning, and concept formation. The emerging, broadened view of PSCs challenges normative conceptions of the structural/functional organization of the cerebral cortex as largely hierarchically sensory, associational, and motor and calls for a new cortical schema.

Fourth, but perhaps of paramount importance, is the issue of the specificity of plasticity. The substrates of memory must contain information that is sufficiently detailed to subserve cognitive processes and behaviors that are dependent on that memory. It is insufficient to merely identify structures that are involved in memory because involvement is only the first step. Without knowing the type of information that such involved structures acquire and hold, one cannot conclude that they actually do hold the type and level of detail (i.e., the contents) of memory that comprise the storage of experience.

Primary sensory cortices provide a convenient entry point into the search for specificity, largely because they contain systematic representations of their respective sensory epithelia. Of course, primary sensory cortices are not the sole sites of memories but, rather, are parts of probably widely distributed networks consisting of complex feedforward and feedback connections. But the study of PSCs contributes a powerful set of experimental tools from the field of sensory neurophysiology. Their application provides a level of specificity of plasticity beyond what can be obtained with standard approaches to the neurophysiology of learning. Furthermore, they permit the assessment of specificity for any learning task. Moreover, when appropriately employed, the use of sensory neurophysiological approaches yields posttraining determination of the specificity of plasticity that is exempt from the usually unavoidable influences of experimental extinction. In so doing, consolidation and the course of long-term retention can be studied without fear of contamination from repeated measures.

3.11.1.2 Neurophysiological Plasticity in Associative Learning and Memory

As used here, neurophysiological plasticity refers simply to any learning-related changes in the activity of neurons, regardless of the method of recording: electroencephalogram (EEG), evoked potentials, unit discharges, metabolic activity, and so forth. As generally understood, the minimum duration of change that is considered plasticity is on the order of minutes, to distinguish it from purely sensory responses that may last many seconds. This article concentrates on behaviorally validated cases of learning and memory rather than demonstrations of plasticity that are alleged to constitute learning. Conflating neural plasticity with memory is experimentally confusing and conceptually fallacious. Although learning and memory, which are behavioral-level constructs, undoubtedly are caused by neural plasticity, equating the two constitutes a category error (Ryle, 1963).

The recording of neural activity in learning and memory provides correlates of these processes and the behaviors that experimenters use to infer learning and

memory. Such correlates can gain importance for inferences about causality if they are predictive of later behavioral assessments of learning and memory. For example, the amount of conditioned stimulus (CS)-elicited gamma band activity in the EEG of A1 during training predicts the amount of specificity of behavioral memory tested 24 h later (Weinberger et al., 2006). Nonetheless, such predictive correlates cannot establish that the neural plasticity so identified is either necessary or sufficient for the learning or memory in question. Their major advantage is in identifying brain structures and systems that develop learning-based neural plasticity. In so doing, the use of neural correlates is perhaps the only way to find out what the brain is doing while it is doing it. Indeed, the discipline of sensory physiology is based essentially on neural correlates, specifically, correlations between a given stimulus and sensory system responses (Kiang, 1955). Such sensory physiology correlations have been used to understand processes such as developmental plasticity in PSCs (Weisel and Hubel, 1963).

The study of PSCs in learning and memory is more reliant on neurophysiological approaches than investigation of other structures, such as the amygdala and hippocampus, because lesions entail unique difficulties of interpretation. Because, as will be documented in the section titled 'Specificity of associative plasticity in primary sensory cortices,' PSCs develop associative plasticity during learning, their responses to sensory stimuli are governed not only by the physical parameters (e.g., sound frequency, locus of touch on the body surface) but also by the acquired behavioral relevance of those stimuli. Therefore, if lesions of a PSC disrupt learning, then resultant deficits could have been caused either by impairment of sensory/perceptual processing or by destruction of information stored in the removed tissue or both. One approach to circumvent this problem is to apply a treatment to a primary sensory cortex (e.g., stimulate, inactivate) after the sensory stimulus has ended but before a behavior dependent on the storage of that information is required (Harris et al., 2002).Investigations of plasticity in learning and memory in the primary sensory cortices vary greatly with the type of learning studied. Thus, associative learning, including classical and instrumental conditioning, has been investigated most extensively in the primary auditory cortex. Priming and perceptual learning have been most intensively examined in the visual cortex. The somatosensory cortex is becoming increasingly studied, particularly using the vibrissal system of animals, which has the advantage of a one-to-one correspondence between each whisker and its anatomically distinct recipient primary somatosensory cortex. This chapter reflects these characteristics of the literature.

3.11.2 What about Perceptual Learning?

As stated in the introduction, this chapter concerns associative learning. Where does that leave perceptual learning? Perceptual learning refers to an increase in sensory acuity within a stimulus dimension, usually as a result of increasingly difficult discrimination training (Kellman, 2002). Experiments of perceptual learning in humans typically involve thousands of trials over many days. For example, a recent study of human frequency discrimination learning involved 4000–5000 trials (Irvine et al., 2000), whereas a pitch discrimination experiment used more than 10 000 trials (Demany and Semal, 2002). Even when a single training session is employed, the number of stimulus trials is typically large. A study of learning of melodic patterns used 1200 different stimuli (Tervaniemi et al., 2001). Animal neurophysiological studies of perceptual learning typically employ very extensive discrimination training for each subject. For example, an investigation of primary visual cortex used ~130 000–325 000 trials (Schoups et al., 2001), and an experiment on inferotemporal cortical visual processing employed ~750 000–1 150 000 trials (Logothetis et al., 1995). There are reports of perceptual learning in considerably fewer trials under specific circumstances (Hawkey et al., 2004), but even so, specific plasticity in associative learning can develop in only five trials (Edeline et al., 1993).

Aside from the rate of learning, why make a distinction between perceptual learning and associative learning? One might expect that if any type of learning is characteristic of primary sensory cortices, then it must be perceptual learning. In fact, the existence of perceptual learning is often thought to subsume the category of associative learning, so that all learning-induced plasticity in PSCs is regarded as perceptual learning.

The distinction is actually critical. One might simply ask, "After a bout of perceptual learning, what is changed in a primary sensory cortex?" The answer would seem to be, "After perceptual learning, the machinery of the cortex has been altered to enable greater acuity. The sensory cortical machine now analyzes the same physical stimuli differently

(e.g., at a finer grain)." This effect certainly constitutes a type of learning by any definition. But interestingly, the study of perceptual learning does not include perceptual memory. This situation probably reflects the fact that investigators of perceptual learning are more concerned with sensory/perceptual processes than with learning and memory, and in any event, subjects 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, although perceptual learning alters the gateway to memory, increased acuity by itself is not necessary for memory, as the term is normally understood (i.e., as the contents of experience). However, the extant level of acuity can determine the precision with which the information is analyzed and may then be encoded and stored.

Consideration of the stages of training in perceptual learning indicates that, actually, it may be considered a subclass of associative learning. Subjects must first learn an association between a sensory stimulus and a reinforcer (simple classical conditioning) and, second, must learn an association between a specified response and a reinforcer contingent on whether a sensory stimulus is a CS+ (rewarded) or CS− (nonrewarded) (i.e., discriminative instrumental conditioning). After that, the discriminations simply become increasingly difficult. Because basic associative learning and its correlated cortical plasticity develop first (often in a few trials), understanding their substrates may help elucidate mechanisms of perceptual learning. Given this consideration and space limitations, perceptual learning is not reviewed. However, some brief comments will help to place it in perspective.

A general summary, necessarily imperfect, is that PSC plasticity is often (but not always) found after perceptual learning and in many instances correlates well with the type and amount of behavioral perceptual improvement, thus providing a potential explanation of the behavioral effects. For example, monkeys trained to discriminate between frequencies of vibration on a digit develop increased temporal precision of evoked discharges in S1 (i.e., decreased variance in the representation of each stimulus cycle) that could account for behaviorally measured frequency discrimination performance (correlation = 0.98) (Recanzone et al., 1992).

In addition, studies of perceptual learning can illuminate properties of PSC neurons because the extensive training allows for training the same subjects on multiple tasks. In a particularly noteworthy case, Gilbert and colleagues trained monkeys to perform two tasks using a single visual array consisting of five line segments: a central line flanked by two parallel lines at either end and either side. Subjects were trained to switch between a line bisection and a vernier task. The tuning properties of neurons in primary visual cortex (V1) changed depending on the task. Most importantly, an information theoretic analysis revealed that neurons "carried more information about a stimulus attribute when the animals were performing a task related to that attribute" (Li et al., 2004: 651). The authors suggested that V1 as a whole is an adaptive processing unit that performs different computations depending on the current problem to be solved (i.e., the behavioral context) (Li et al., 2004). These neuronal characteristics are certainly in line with the associative specificity obtained even in simple classical conditioning studies, as reviewed later.

A major issue concerns whether or not PSCs or higher cortical areas are responsible for perceptual improvement (Fahle, 2004). For example, in the case of successful frequency discrimination, the primary auditory cortex exhibits either extensive plasticity (Recanzone et al., 1993), a lack of plasticity (Brown et al., 2004), or partial plasticity (Witte and Kipke, 2005). There is no *a priori* reason why substrates of all perceptual learning should involve PSCs. It is sufficient for our present purposes to note that there is compelling evidence that some perceptual learning is tightly linked to the development of neuronal plasticity in primary sensory cortices. It seems likely that an adequate understanding of the neural bases of perceptual learning will require determination of precisely what has been learned in each study (e.g., absolute vs. relative discriminations). Interested readers should consult available reviews (Goldstone et al., 1997; Gilbert et al., 2001; Calford, 2002; Pleger et al., 2003; Ghose, 2004; Fahle, 2005; Skrandies, 2006). However, there remains a pressing need for an integration of conceptions and findings in the still separate disciplines of associative learning/memory and perceptual learning.

3.11.3 The Enduring Influence of Sensorimotor Conceptions of Cortical Organization, or Campbell's Ghost

Neurophysiological plasticity in PSCs is interesting both in its own right and as a case study in the intersection of sensory neurophysiology and the neurobiology of learning and memory, two fields that had developed

separately and with little crossover until the latter part of the last century. This is particularly remarkable because these are the two disciplines in neuroscience whose subject matter deeply involves the 'fate' of environmental stimuli in the brain. The former has traditionally been concerned with the coding and representation of the physical parameters of sensory stimuli. The latter has focused on how a previously neutral stimulus comes to influence cognition and behavior through learning. Furthermore, this topic provides a clear example of how assumptions constrained thought and experiment for most of the twentieth century. This is not merely of historical interest because the problem is still present.

Attempts to understand sensory cortex (as well as other brain systems and structures) began in the nineteenth century within the framework of a sensorimotor conception of the nervous system. Some of the first structural–functional relationships discovered concerned the spinal cord: The dorsal roots are sensory, and the ventral roots are motor. These seminal findings are attributed jointly to the separate but largely simultaneous studies of Charles Bell in England and Francois Magendie in France, roughly in the period 1812–1840 (Fearing, 1970). Although Bell can be given primacy for establishing the major function of the ventral roots, historical analysis has revealed that Magendie discovered the sensory function of the dorsal roots (as well as independently showing ventral root function), notwithstanding Bell's subsequent falsification of the record (Cranefield, 1974). After the discoveries of Magendie and Bell, much of the research program for the rest of the century concerned the extent to which the entire neuraxis was organized on sensorimotor principles (Young, 1970). The last 30 years of the nineteenth century witnessed the discovery of the motor cortex by Fritsch and Hitzig and the approximate delineation of sensory cortices based on modality specific sensory deficits following cortical ablations (Ferrier, 1886).

Still, sensory and motor areas did not comprise the entire neocortex. Could an overarching principle of cortical organization be discovered? In 1901 Flechsig, a neuroembryologist, reported that axons in different parts of the human cortex became myelinated at different times (Flechsig, 1901). Sensory and motor cortices exhibited myelination at birth, whereas other areas could require as long as 1 postnatal month to myelinate. Flechsig's observations of fibers in the internal capsule led him to the erroneous conclusion that only the sensory and motor cortices had subcortical connections, the association areas were thought to receive inputs only from other cortical regions. In short, Flechsig's schema was that the cortex consisted of sensorimotor zones that were connected to the thalamus and brainstem and were functional at birth, and association cortices that were connected only to other cortical regions and was not functional until well after birth. The late Irving Diamond pointed out that as association cortical areas myelinate later, this sequence of myelination "is just what would be expected if an infant sees sensory qualities such as color and brightness before these impressions are associated with another to form the perception of objects." (Diamond, 1979: 5). Thus, Flechsig had provided an anatomical basis for the distinction between lower (i.e., sensorimotor) and higher psychological functions.

It remained only to specify in greater detail, and perhaps with a more authoritative voice, the nature of these lower and higher functions. This was supplied by impressive cytoarchitectonic studies. In 1905 AW Campbell (Campbell, 1905) published a landmark monograph entitled *Histological Studies on the Localization of Cerebral Function.* Campbell asserted structural–functional relationships on the grounds of cytoarchitecture. While perhaps not the first worker to use the terms sensory and psychic cortex, his influence has been profound. For example, Campbell labeled the region now identified as V1 'visual sensory,' and called regions nearby (e.g., areas 17 and 18) 'visual psychic.' Similarly, the region now known as A1 was termed 'auditory sensory,' whereas adjacent areas, in modern parlance, auditory belt areas (Kaas and Hackett, 2000), were auditory psychic. In this, Campbell intended to make a clear distinction between cortical regions he considered to be purely sensory from those he believed concerned the understanding of the meaning of stimuli. His implicit assumption was one of strictly hierarchical cortical functional architecture, with what are now referred to as cognitive functions dependent on input from sensory structures (i.e., PSCs). Association cortex has come to denote both some modality-specific regions (e.g., auditory association) and cortical territory that lies between modality-dominated cortex, generally posterior to the central sulcus.

This conceptual schema of sensory-association-motor cortex as the basis for understanding cortical function has strong resonance today. Irving Diamond held that Campbell's monograph was instrumental in removing learning and memory from primary sensory cortices (Diamond, 1985). Although a less-sequential,

more parallel thalamocortical structural organization, championed by Diamond, is generally acknowledged, its influence on beliefs about cortical functional organization seems minimal.

Within the field of learning and memory, Pavlov's theory of conditioned reflexes provided authoritative support for the distinction between sensory fields that analyze stimuli and association fields, in which learning allegedly occurs. Pavlov's proposed physiological mechanism, that learning was due to spreading ripples of excitation from the cortical sensory fields of the CS and the unconditioned stimulus (US) that met in intervening association cortex (Pavlov, 1927), has long been superseded by action potentials. But the fundamental assumed functional architecture has not changed. The standard schema based on sensory-to-association-to-motor cortex fails to the extent that primary sensory cortices are involved in associative learning and memory. We now turn to a consideration of the relevant literature.

3.11.4 Overview of Cortical Plasticity in Associative Learning: 1935–1984

This section provides a brief summary of the 50-year period (1935–1984) during which PSC plasticity in associative learning was discovered and well characterized for training trials. The unspoken assumption was that recording during training trials would be sufficient to reveal the neural bases of learning. The following section provides a more detailed account of contemporary approaches that reveal the degree of specificity of associative PSC plasticity.

Near the dawn of electroencephalography, a serendipitous discovery launched neurophysiological studies of cortical plasticity in learning/memory. The alpha rhythm, an oscillation of 8–12 Hz in the human EEG prominent from occipital (i.e., visual cortical) leads, was known to be consistently blocked by visual stimulation. (The actual effect was a shift to higher-frequency, lower-amplitude waves (i.e., EEG desynchronization or activation). Durup and Fessard were investigating alpha blocking when they found that it occurred shortly before they turned on the flashing light intended to disrupt alpha waves (Durup and Fessard, 1935). Upon further consideration of this paradoxical result, they realized that the blocking was caused by the click sound made by the shutter of their camera, which they activated immediately preceding the repeated presentation of flashes, so that they could photograph alpha blocking displayed on the screen of their oscilloscope. Durup and Fessard had inadvertently been conducting a classical conditioning experiment, with the CS being the click and the US being the flashing light. This stimulus–stimulus (S–S) pairing produced conditioned blocking of the alpha, the first demonstration of learning-induced cortical plasticity. The signal importance of this finding was immediately recognized, and other laboratories quickly replicated and expanded the finding of conditioned alpha blocking (Morrell, 1961). Thus, perhaps ironically, primary visual cortex was the first discovered site of learning-induced cortical plasticity.

Studies of cortical plasticity, much of them involving further EEG studies, expanded greatly after the end of World War II and were extended to nonhuman animals (hereafter animals). Emphasis was directed to understand classical conditioning and the major focus was to find the locus of closure, that is, the place(s) in the cortex of convergence of input from the CS and US. The dominant finding, across species and modalities and types of sensory stimuli, was that EEG changes followed a particular trajectory according to the stage of learning. First, relaxed subjects exhibited widespread cortical activation to the US. Second, continued pairing of the CS and US rapidly produced the first signs of associative learning, consisting of widespread activation that was now elicited by the previously ineffective CS. Third, as learning progressed, the cortical domain of conditioned EEG desynchronization shrank, becoming confined largely to the PSCs of the CS and US. Various controls were used to establish that conditioned EEG activation was genuine, including the use of unpaired or randomly presented CSs and USs in control groups or the use of discrimination paradigms in which a CS+ was paired with the US, whereas a CS− was not paired (Gluck and Rowland, 1959; Rowland and Gluck, 1960). The CS+ developed the ability to produce EEG activation while the CS− failed to do so (reviewed in John, 1961; Morrell, 1961; Thomas, 1962; Galeano, 1963).

That the CS developed the ability to elicit EEG plasticity in its own primary sensory cortex was a critical demonstration that PSCs were involved in learning and memory. However, this fact received little recognition. To the best of my knowledge, there has been no historical analysis of these studies in the context of the extant *Zeitgeist*. My guess is that this finding was overshadowed by the disappointment at the apparent failure to find the locus of closure. According to Pavlov and the dominant thinking at

that time, the CS and US should have converged in association areas. But conditioned EEG effects were not uniquely found in association cortex and in fact soon disappeared from there during learning.

Experiments on sensory-evoked potentials overlapped with studies of the EEG and learning and ultimately gained dominance. In an influential early study, Robert Galambos and his colleagues performed a seminal experiment in which cats were classically conditioned by pairing an auditory (click) conditioned stimulus with a puff of air (US) to the face (Galambos et al., 1956). Learning was validated by the development of behavioral conditioned responses. Evoked potentials in the primary auditory cortex elicited by the CS became larger during conditioning. This study also addressed the critical issue of stimulus control. To show that inadvertent changes in CS intensity (level) were not responsible, the authors also tested subjects under neuromuscular blockade, maintaining stimulus constancy at the periphery while eliminating putative contractions of the middle ear muscles. Interestingly, the authors failed to include a nonassociative control, such as a group that received the CS and US randomly. However, subsequent investigations confirmed and extended this basic finding, showing that facilitation of response to the CS in A1 was associative (Marsh et al., 1961; Majkowski and Sobieszek, 1975).

During the period from the late 1950s until the 1980s, an extensive literature also documented associative learning effects in V1 both in classical and instrumental conditioning in a variety of species. The dominant finding was facilitation of responses to visual conditioned stimuli (John and Killam, 1959, 1960; Saunders, 1971; Peck and Lindsley, 1972; Buresova and Bures, 1973; Suzuki et al., 1974; Sasaki and Yoshii, 1984a,b). During this period of active research, even evidence of evoked potential correlates of memory retrieval in V1 was reported (John et al., 1973; Bartlett et al., 1975; John et al., 1975). Additionally, the associative plasticity of V1 was emphasized by demonstrations that an experimenter-selected component of evoked responses could be operantly conditioned to change amplitude, contingent on the receipt of rewarding intracranial stimulation in the rat (Hetzler et al., 1977) and reward of liver and milk in the cat (Rudell, 1977). In contrast, the use of somatosensory conditioned stimuli was rarely, if ever, employed during this period.

Not surprisingly, as techniques were further developed for recording from behaving animals, research was extended to multiple-unit and even single-unit studies of plasticity. Much of the evoked potential and unit research used sounds as CSs because of convenience. Numerous laboratories demonstrated that learning-related increases in the amplitude of CS-elicited evoked potentials and unit discharges in the primary auditory cortex were indeed associative. For example, multiple unit discharges in A1 increase to a sound (CS+) paired with shock, decrease in response to a nonreinforced sound (CS−), and exhibit reversal when the CS+ and CS− are reversed. Moreover, the CSs come to elicit responses in the PSC of the unconditioned stimulus (i.e., S1), although with less specificity with respect to reinforcement contingency than in A1 (Oleson et al., 1975). For a general review, see Weinberger and Diamond (1987).

However, PSC plasticity in learning was generally ignored both within the neurobiology of learning and memory and also in the discipline of sensory neurophysiology. Several factors may have contributed to this state of affairs. For example, within learning and memory, the discovery of patient HM understandably focused attention on structures that appeared to be essential for memory, such as the hippocampus. In animal conditioning, attention was drawn to model systems, such as conditioned eyeblink and fear conditioning. Second, there was no conceptual framework within which to incorporate the findings of associative plasticity in sensory cortices, particularly as dominant assumptions of brain function restricted sensory cortices to the status of stimulus analyzers. Third, workers in learning and memory had no vested interest in sensory systems and therefore were not concerned that the research initiated by Galambos and colleagues disproved the view that sensory systems encoded only sensory parameters, not psychological parameters, such as the acquired behavioral significance of a stimulus. The ghost of A.W. Campbell might have smiled.

Neglect from sensory neurophysiologists might seen particularly unexpected because PSC plasticity has major implications. Thus, that learning modifies sensory cortical responses to physically constant stimuli implies that such neural responses are inherently ambiguous. For example, an increase in stimulus-elicited response magnitude might be due to an increase in stimulus intensity, an increase in its behavioral significance, or both. But it seems likely that sensory neurophysiology paid little heed to the learning findings both because of the dominance of the Campbellian formulation and the impoverished stimulus set used by behavioral neurophysiologists (myself included). Studies of associative learning typically

employ a small number of different stimuli. For example, standard conditioning studies use a single acoustic CS and discrimination studies use only two, a CS+ and a CS−. However, the concept of the receptive field is fundamental to sensory physiology. No sensory physiologist would attempt to describe the response properties of a cell with such a limited stimulus set.

But even within the neurophysiology of learning, a certain disquiet was growing. The EEG and evoked potential findings seemed fairly easy to interpret as either increased excitability or increased response to a behaviorally important CS. But single-unit studies invariability reported not simply increased discharges to the CS but also many instances of decreased discharges, even within the same study (Gasanov and Galashina, 1976; Woody et al., 1976; Weinberger et al., 1984b; Dumenko and Sachenko, 1979a,b). Although such cortical plasticity was shown to be associative, the findings of opposite sign made little functional sense. Thus, although recording in PSCs during training had provided foundational information, this approach appeared to be yielding diminishing returns after 50 years of use.

New questions were being asked. Whereas most prior studies had documented cortical plasticity during various phases of learning and in different structures and diverse tasks, a critical aspect of the functional significance of plasticity had not been adequately addressed. Missing was information concerning the specificity of cortical plasticity. As noted in the introduction, knowledge of the specificity of plasticity transcends the detection of a structure or group of neurons as being involved in learning and memory. Rather, knowledge of the specific changes in neural activity (i.e., not merely the fact of plasticity but also the substance of plasticity) provides insights into the type of information being processed and its role in learning and memory.

3.11.5 Specificity of Associative Plasticity in Primary Sensory Cortices: The Overarching Importance of Experimental Design

3.11.5.1 Introduction

What may reasonably be termed the contemporary era began in the 1980s with the use of a new experimental paradigm. It involved two major departures from prior research, in which neurophysiological recordings had been obtained principally during training trials. First, the new approach obtained neuronal data either after training in between-groups designs (Gonzalez-Lima and Scheich, 1984, 1986) or before and after training for within-subjects designs (Diamond and Weinberger, 1986; Weinberger et al., 1984a). Assessing learning after training was not unprecedented, as it had been standard in purely behavioral studies of learning and memory. It just hadn't been much applied to the neurophysiology of learning and memory.

Second, the new paradigm combined basic methods from sensory neurophysiology to determine the effects of learning on neuronal tuning. This latter method required the presentation of many different stimuli (e.g., acoustic frequencies) to obtain receptive fields and assess potential receptive field plasticity. Obviously, there was nothing new about this approach in neurophysiology. Neither was this method novel in learning and memory. In fact, training with one (or a few) stimuli but later assessing learning with many stimulus values had been done starting with Pavlov; it is the method of obtaining stimulus generalization gradients in learning. Apparently, it had not been applied to neurophysiological studies of learning and memory.

Before proceeding directly to a review of major findings in the study of specificity in PSCs, it will prove helpful to take a short detour to consider why recording during training is insufficient to determine the specificity of plasticity and some other critical factors about the new experimental approaches.

3.11.5.2 Cortical Plasticity during Training and Its Limitations

The standard approach to neural correlates of learning consists of obtaining neurophysiological recordings during training trials (the DUR design; see the section titled 'Primary auditory cortex (A1) habituation'). This very logical approach, almost universally used since the inception of research in the 1930s, is not restricted to the study of cortical plasticity but is applied to all brain structures (John, 1961; Thompson et al., 1972). However, obtaining recordings during training trials has at least two major limitations: (1) they can be influenced by state factors, and (2) they do not permit assessment of the degree of specificity of plasticity.

3.11.5.3 State Factors

First, nonlearning factors are invariably present during training, due in part to the presence of positive or negative reinforcement. These factors include, but are not limited to, changes in attention, arousal state, motivational level, and motor performance. For example, arousal level and motivational state alter evoked potentials and unit discharges in the auditory cortex (Murata and Kameda, 1963; Teas and Kiang, 1964; Wickelgren, 1968; Molnar et al., 1988). Moreover, the degree of influence of performance factors can vary during training trials. It may be high early in training, when subjects have not yet solved whatever problem confronts them, and then later decrease as solutions are found and as performance improves.

It must be emphasized that cortical plasticity obtained during training trials is usually associative. That factors such as motivational state are operative in no way weakens the case for associativity, given that the plasticity in question does not develop under nonassociative circumstances, such as random CS–US presentation. However, the associative plasticity may be influenced by state and similar factors, so that it is difficult to obtain pure associative effects.

Rescorla has emphasized the dangers of relying on behavioral 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 posttraining assessments of behavior (Rescorla, 1985, 1988). This counsel is equally applicable to neurophysiological plasticity that develops during training trials. Although such plasticity may constitute adequate evidence that associative learning has a neural correlate (given controls for sensitization and pseudoconditioning), the form and magnitude of that correlate are not necessarily a reflection of associative processes alone.

3.11.5.4 Specificity of Plasticity

Second, and probably of even greater importance, recordings during training do not permit determination of the overall specificity of plasticity, because training protocols necessarily employ a limited number of stimuli along a dimension. For example, subjects may be trained with a visual stimulus, such as a vertical line followed by food reinforcement. If neurons in the primary visual cortex develop increased responses to that stimulus during training, then one can conclude that V1 cells develop associative plasticity during the task. (Of course, this assumes a control group that did not develop the plasticity when the vertical line and food were presented randomly, or equivalent control.) However, one cannot determine from such data alone if this cortical plasticity reflects changes in the processing and representation of line orientation *per se*. To resolve this issue, it would be necessary to interrogate the visual cortex with lines of many orientations after training. This could be done in a posttraining extinction session, as is routinely done when investigators obtain behavioral stimulus generalization gradients. As seen later, it is quite easy to obtain such information about the overall specificity of cortical plasticity in the absence of complications endemic to the use of extinction training (i.e., new learning that inhibits the prior learning).

3.11.5.5 Unified Experimental Designs

Both the potential problems of performance factors and the determination of specificity of cortical plasticity can be overcome by expanding the experimental designs to include assessment of plasticity by sensory neurophysiological approaches (unified designs). We describe the basic Pre-Post design and the Post design approaches (**Figure 1**).

3.11.5.5.1 The Pre-Post training trials design

The Pre-Post design allows the experimenter to determine how PSC information processing changes as a result of learning. This design involves a minimum of three stages: (1) pretraining recording, (2) actual training or other designated controlled experience, and (3) posttraining recording. The Pre and Post periods should present many sensory stimuli of interest (e.g., different frequencies of tone bursts, deflection of different whiskers, locations of targets in different visual quadrants). This contrasts with the standard presentation of a stimulus during a discrete training trial. The effects of the experiential treatment, whether habituation, classical conditioning, instrumental discrimination learning, or any other task, are determined by comparing the Post data with the Pre data. If the Pre and Post data are not statistically different, then one can conclude that the experience has had no effect on the processing or representation of the particular information under study. Conversely, significant differences between

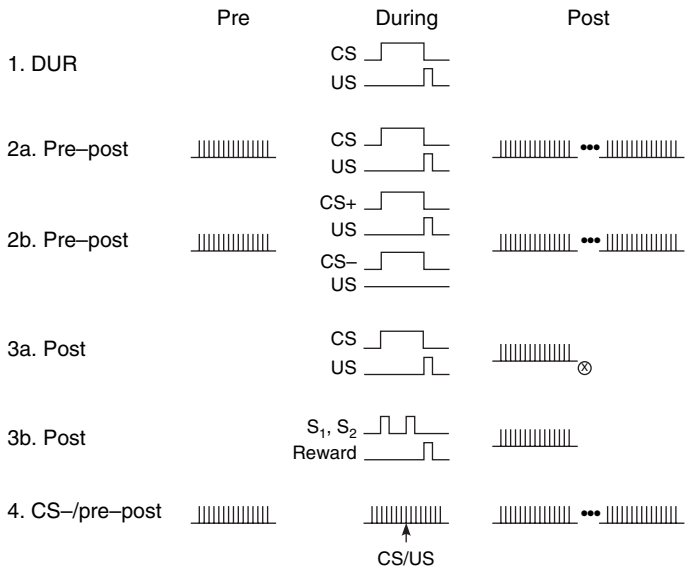

Figure 1 Schematic summary of experimental designs employed in the neurophysiological study of learning and the auditory cortex. Depicted are four basic designs (1–4) and their treatments during three experimental periods, Pre (before training), During (during training), and Post (after training). The DUR design is traditional, involving recording during training trials. Pre-Post designs 2a and 2b illustrate the fact that any training paradigm can be used. 2a shows single-tone conditioning, and 2b illustrates two-tone discrimination conditioning. Designs 3a and 3b also illustrate the fact that any training paradigms can be used with a Post design. 3a illustrates the case of single-tone conditioning, whereas 3b shows an example of two-tone instrumental training, in which reward is contingent on the correct response (i.e., one response if the two tones – S1 and S2 – are the same and another response if they are different) (responses not shown). The repeated vertical lines represent presentation of tone bursts. The dotted lines in the Post period for designs 2 and 4 indicate that additional Post periods can be used to determine long-term retention. In 3a, the x in the Post period signifies sacrifice of the animal for 2-deoxyglucose analysis following repeated presentation of a conditioned stimulus stone. In design 4, the conditioned stimulus (CS)/unconditioned stimulus (US) denotes that one of the frequencies in a series of tone bursts is designated as the CS and is paired with shock; the serial order of tones is random from one sequence to another. The problems with this design are that the behavioral state is likely to be different between the Post and Pre periods, and extinction is likely to occur in the Post periods (see text). Illustrations are not to scale.

the two periods can be attributed to the intervening experience (**Figure 1(2a), (2b)**).

It is essential that the test stimulus presentations be identical during the Pre and Post periods. Moreover, these data should be obtained in identical experimental settings to eliminate any confounds due to changes in the local environment context. No reinforcement is present during these Pre and Post tests, as that would defeat the goal of avoiding performance factors. However, despite the absence of a reinforcer, extinction learning does not develop during Post training assessment (see the section titled 'The importance of context').

It is also important to perform the training in a separate experimental setting, such as a different room with salient differences in visual and other nonauditory cues (see next section). Of course, it is important that the subjects be in the same state during the Pre and Post tests. This can be accomplished by amply habituating them to the testing (Pre and Post) situation, and this can be objectively assessed by recording heart rate or other physiological measures. Typically, heart rate is high when an animal is placed in a novel situation, but such tachycardia habituates fairly rapidly.

The Pre-Post design permits assessment of specificity while avoiding confounding performance factors that are present during training trials. Another advantage is that posttraining tests can be presented at desired intervals of hours to months, permitting detection of neural consolidation (i.e., increase in effect over time without additional training) and long-term retention or forgetting. This design also is very flexible because any desired training task can be used, yet the assessment of receptive field plasticity can be identical. This permits a direct comparison of the effects of learning on sensory representation for as many types of learning as may be of interest.

3.11.5.5.2 The importance of context: Elimination of performance factors and extinction

At least two issues are raised by this design. First, how does it eliminate or control for performance factors? Second, how does it avoid experimental extinction? (See also Diamond and Weinberger, 1989; Weinberger, 1998.)

Performance factors are reduced, if not eliminated, by minimizing similarities between the training context and the testing circumstances. The purpose of this maneuver is to reduce or eliminate any generalization from the training environment to the testing environment. For example, if an animal receives food or shock during training, it will also associate the location (context) of the training with these reinforcers. If tested in the same place, its arousal level and expectations could be affected.

Perhaps the most salient difference is the absence of a reinforcer in the Post period, which also reduces and can even eliminate changes in state (see the section titled 'The Post training trials design (POST)'). The Pre-Post design also permits sensory stimuli to be presented with several parameters that differ from the training session. Thus, training can consist of standard, discrete conditioning trials with standard parameters (e.g., an individual CS tone with a duration of 5s, a long intertrial interval of 1–2 min, and a stimulus level that is well above threshold (80 db SPL)). In contrast, determination of receptive fields can be accomplished with completely different parameters randomly presenting many tones to cover the frequency spectrum (e.g., 24 tones at quarter-octave intervals, 100 ms duration, intertone intervals of 400 ms, at stimulus levels of 0–80 dB SPL to cover the audible range). In short, the acoustic context of RF determination can be, and indeed must be, different from that during conditioning trials.

This difference in context has proven to be sufficient to eliminate any behavioral or arousal response to the CS frequency when it is embedded as a brief tone in a series of test tones. Objective measures indicate that subjects do not regard the CS frequency as a conditioned stimulus during determination of receptive fields (Diamond and Weinberger, 1989). In addition to the lack of performance confounds, elimination of potential effects of arousal to the CS frequency or any other tone can be accomplished by training subjects while they are awake (of course) but obtaining receptive fields while they are under general anesthesia (Weinberger et al., 1993).

Responses to the training stimulus during discrete trial presentation can, of course, be recorded, as long as the likely confound of performance factors is kept in mind. In such cases, it is beneficial to compare plasticity to a CS tone during training trials with plasticity in receptive fields as seen after training. Such a study revealed that there was little correspondence between changes to the CS during training with responses to that same frequency when it was presented as one of a series of rapidly presented frequencies in the Post period. In many cases, the sign of change was opposite (e.g., a decrement in response to the CS tone but a specific increase in response to that frequency during RF determination) when tuning might shift toward or to the frequency of the conditioned stimulus (Diamond and Weinberger, 1989).

The problem of experimental extinction is also eliminated by the Pre-Post design. As subjects do not regard the presentation of the frequency used as a CS as an actual CS, they neither respond to it nor extinguish during posttraining determination of receptive fields (Diamond and Weinberger, 1989).

A negative case illustrates the importance of appreciating the unified design (Ohl and Scheich, 1996, 1997, 2005). The authors failed to appreciate the difference between plasticity observed during training trials from plasticity observed in Post-training assessments. They used a tone-shock discrimination protocol in which a single CS+ tone 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 the presence of an occasional shock during training provided the only information that training was underway (**Figure 1(4)**). Relative to pretraining, the posttraining period exhibited a specific decrease in response to the CS frequency in A1. Unfortunately, no behavioral data were obtained, so there was no substantiation for the assumption that the animals had learned this unique, difficult discrimination. However, if learning had occurred, then the posttraining period would have constituted a period of extinction, due to the elimination of shock. Thus, the posttraining period undoubtedly differed from the pretraining period in the subjects' state of arousal and fear due to the anticipation of shock, and in the new extinction learning that shock was no longer forthcoming. Therefore, the findings might document a decrease in response to a CS frequency due to experimental extinction. The authors' claim that the behavioral importance of the CS is represented by a specific decrease in response seems unsupported.

3.11.5.5.3 The Post training trials design (POST)

The POST design has been used extensively in sensory neuroscience to determine the effects of peripheral sensory denervation or central insult (stroke) on the organization of primary auditory (Robertson and Irvine, 1989; Mount et al., 1991; Kaltenbach et al., 1992; Harrison et al., 1993), somatosensory (Kelahan et al., 1981; Rasmusson, 1982; Wall et al., 1986; Calford and Tweedale, 1988), and visual (Weisel and Hubel, 1963; Rauschecker et al., 1987; Heinen and Skavenski, 1991; Pettet et al., 1992) cortices.

Review of resultant plasticity is beyond the scope of this chapter, but a general conclusion is that peripheral denervation produces an expanded cortical representation of intact neighbors on the receptor epithelia: in the cochlea, on the body surface, and in the retina. However, these conclusions are necessarily oversimplifications, and the original sources should be consulted. What these sorts of studies do demonstrate is that adult PSCs are capable of considerable reorganization as a function of experience. Whether such experiences constitute genuine learning is unknown. Learning may well develop in animals and humans who find themselves with deficits in peripheral sensory capabilities. Of interest, prior learning can be necessary for adjustment or recalibration of a sensory system following peripheral impairment. Ferrets can relearn to localize sounds after reversible blocking of one ear, but only if they had been trained previously to use the relevant spatial cues (Kacelnik et al., 2006).

The considerations necessitating the Pre-Post design, and the advantages thereof, also apply to the POST design. Simply put, this design consists of recording only after the designated learning experience. Because of the absence of pretraining data, at least two groups are needed, one that receives the learning experience and a control group that either is not trained or preferably undergoes a different learning protocol (e.g., sensitization). The POST design has often been used when data can be obtained only once from a subject (e.g., in detailed terminal studies of cortical organization) (**Figure 1(3a), (3b)**).

3.11.6 Specificity of Associative Plasticity: Contemporary Approaches

The following sections review associative plasticity in the primary auditory, somatosensory, and visual cortices since 1985. The coverage is extensive but not exhaustive, as the goal is merely to establish PSC plasticity in learning and memory.

3.11.6.1 Primary Auditory Cortex (A1)

3.11.6.1.1 Habituation

Studies of habituation that used the DUR design had documented that repeated presentation of sounds results in a progressive response decrement in A1 (Marsh and Worden, 1964; Wickelgren, 1968). Specificity of habituation with control for state of arousal was first studied (before 1985) using a preliminary version of the Pre-Post design (Westenberg and Weinberger, 1976; Westenberg et al., 1976). Evoked potential was recorded in A1 of the waking cat. Two frequencies (A and B) were presented as alternating brief tone bursts (prehabituation). In the next stage, one tone (A) was presented repeatedly. Finally, the posttest was performed; the tones were again presented in an alternating pattern identical to the prehabituation phase. Average evoked potentials for each tone were determined separately for the pre- and posthabituation periods and compared. Because the Pre and Post tones alternated, the average responses were obtained for both A and B when the subjects were in the same state; hence, any differences between responses to the tones could be attributed to the effects of the intervening repeated stimulation with one frequency. The Post responses to the repeated tone (A) were significantly smaller than the Pre responses to this tone, but there was no difference for the nonrepeated (B) tone. Counterbalancing using repetitive presentation of B also yielded frequency specific decrements. These findings demonstrate that repeated acoustic stimulation produces frequency specific habituation.

The Pre-Post design has been expanded to determine the entire frequency receptive field (RF, tuning curves) of auditory cortical neurons in waking guinea pigs (Condon and Weinberger, 1991). After researchers determined the tuning of unit clusters and ensured their stability, subjects received single tone pips at the rate of 1.25 Hz for 5–7 min. Habituation produced a decreased response that was specific to the frequency that had been repeatedly presented; frequencies 0.125 octaves from the habituated frequency exhibited little or no response decrement. Consolidation, in the form of continued increased development of specific decrements, was often observed for periods as long as an hour. This attribute links frequency-specific habituation to other forms of memory.

3.11.6.1.2 Conditioning

In this section we consider studies of the specificity of plasticity in A1 induced by associative learning. Research to date has focused on classical and instrumental conditioning, with the implication that investigation of these heavily studied forms of learning is an appropriate entry point into the issue of specificity.

Gonzalez-Lima and Scheich (1984, 1986) investigated the specificity of plasticity by determining the effects of conditioning on the uptake of 2-deoxyglucose (2-DG) after training. As this necessitated a terminal treatment of the subjects, the authors used a between-groups POST design. (The use of metabolic measures permits investigation of specificity without using many different stimuli when the locus of stimulus representation in a PSC map is known.) Gerbils received tone paired with strong aversive electrical stimulation of the mesencephalic reticular formation or a control treatment (e.g., CS–US unpaired, CS alone, US alone). The paired group alone developed the behavioral index of learning, conditioned bradycardia. All groups received continual presentation of the CS alone during an injection of 2-DG in a posttraining session. As this treatment may involve some experimental extinction, the associative findings might be considered somewhat weakened. Nonetheless, analysis of patterns of 2-DG uptake in A1 revealed a CS-specific increase in metabolic activity for the cortical area that represented the CS frequency. The absence of similar effects in the other groups showed that the CS-specific plasticity was associative.

The first use of the Pre-Post design with receptive field (RF) analysis involved single units in two nonprimary auditory fields, secondary (AII) and ventral ectosylvian (VE) cortices (Diamond and Weinberger, 1986, 1989; Weinberger et al., 1984a). Cats were trained in a single, brief (20–45 trials) session of tone-shock pairing. Behavioral learning was validated by the formation of the pupillary dilation conditioned response. CS-specific plasticity was found in the paired group, but not when tone and shock were unpaired. Some cells developed a CS-specific increase, whereas others developed a CS-specific decrease. Extinction produced loss of the RF plasticity. The findings received little notice, probably because these auditory fields were not well understood.

Similar studies were then undertaken in A1 of the guinea pig with behavioral validation of associative learning (e.g., conditioned bradycardia). Following determination of frequency receptive fields, the frequency to be used as the CS was then selected to not be the best frequency (BF, peak of the tuning curve) to determine whether conditioning caused shifts of tuning toward the CS frequency. Animals then received a single session (30–45 trials) of tone paired with shock. A comparison of posttraining with pretraining RFs revealed a dominance of CS-specific increased responses. Moreover, responses to the pretraining BF and other frequencies tended to decrease. These opposing changes were often sufficiently large to produce frank shifts of tuning toward, and even to, the frequency of the CS, which could become the new BF (Bakin and Weinberger, 1990) (**Figure 2(a)**). RF plasticity was found to be associative, as it required stimulus pairing; sensitization training produced only a general increase in response to all frequencies across the RF (Bakin and Weinberger, 1990; Bakin et al., 1992).

CS-specific increased responses in RFs also can develop when tuning curves are complex and even nonexistent. **Figure 2(b)** shows an example of a pretraining double-peaked frequency RF. The CS frequency was selected to be in the valley between the peaks. Posttraining, the maximum change was an increase in response at the CS frequency. **Figure 2(c)** illustrates a case in which there was no response to any frequency before conditioning. Nonetheless, postconditioning observations revealed a clear excitatory response to the previously ineffective CS frequency, alone.

Several other attributes of RF plasticity make it an attractive candidate for a process that operates in normal concert with sensory coding processes to subserve the storage of behaviorally relevant auditory information. First, RF plasticity is highly specific to the CS frequency; responses to frequencies a small fraction of an octave away are attenuated. Second, it exhibits generality across different types of training (e.g., instrumental avoidance conditioning) (Bakin et al., 1996), two-tone classical discrimination training (i.e., increased responses to the CS+ frequency but decreased responses to the CS−, BF, and other frequencies) (Edeline and Weinberger, 1993; Edeline et al., 1990), and discriminative instrumental avoidance conditioning (Bakin et al., 1996). Third, RF plasticity develops very rapidly, after only five training trials, as rapidly as the first behavioral (e.g., cardiac) signs of association (Edeline et al., 1993). Fourth, RF plasticity exhibits long-term retention, enduring for the longest periods tested, up to 8 weeks after a single 30-trial conditioning session

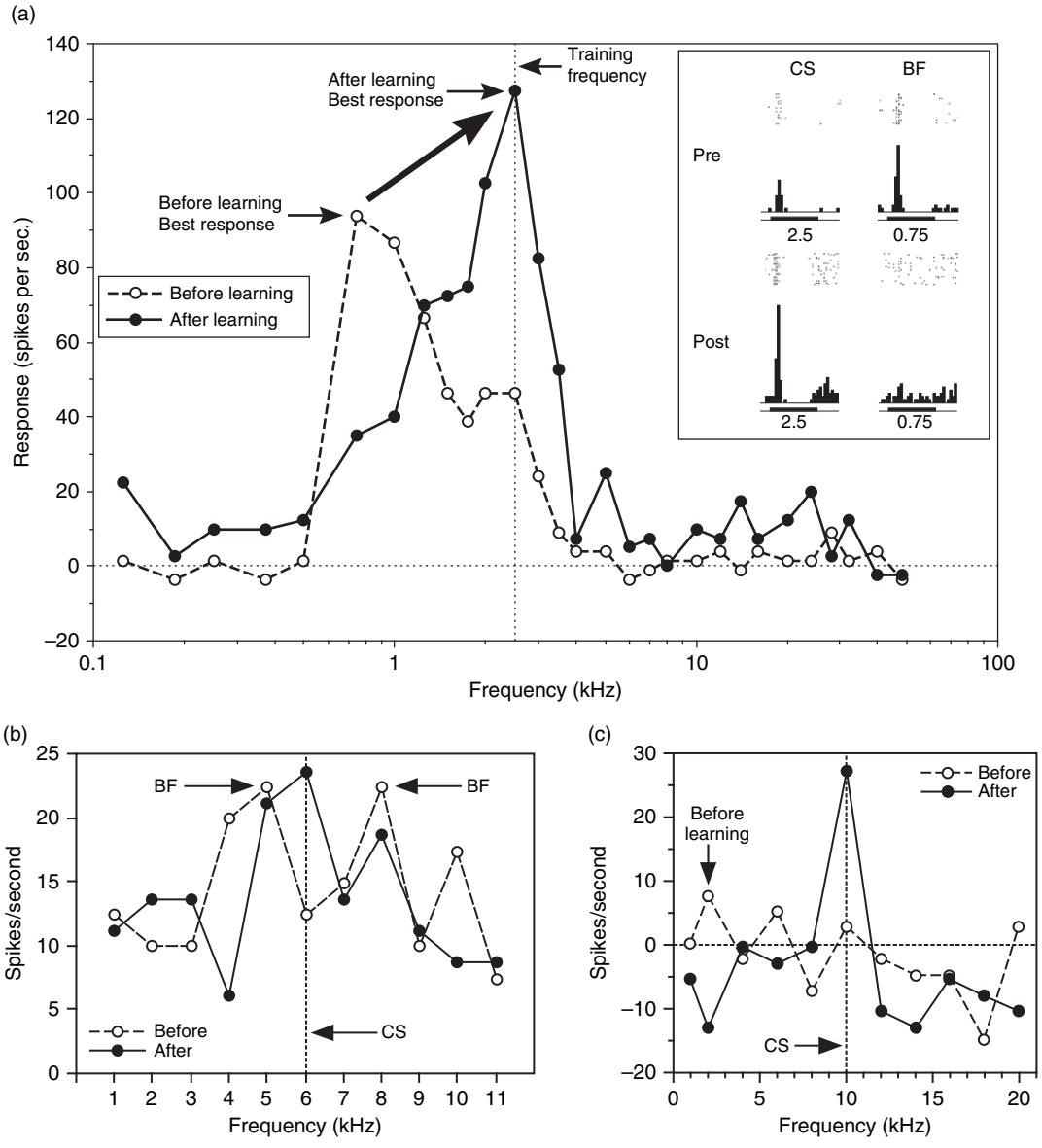

Figure 2 Classical conditioning produces conditioned stimulus (CS)-specific facilitation and tuning shifts. (a) An example of a complete shift of frequency tuning of a single cell in A1 of the guinea pig, from a pretraining best frequency (BF) of 0.75 kHz to the CS frequency of 2.5 kHz after 30 trials of conditioning. Inset shows pre- and posttraining poststimulus time histograms (PSTHs) for the pretraining BF and the CS frequencies. (b) Double-peaked tuning, with pretraining 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).

(Weinberger et al., 1993). Fifth, RF plasticity exhibits consolidation (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 (Weinberger et al., 1993; Galvan and Weinberger, 2002).

CS-specific associative tuning shifts develop in the primary auditory cortex of diverse taxa. Thus, studies of fear conditioning (tone, shock) in the big brown bat demonstrate not only that learning induces tuning shifts but that these can develop with small absolute differences in frequency in these echolocating animals (Gao and Suga, 1998, 2000; Ji et al., 2001; Ji and Suga,

2003; Suga and Ma, 2003). Nonassociative controls did not develop tuning shifts. In these studies, leg flexion was used to validate associative learning, but the use of a fixed (30-s) intertrial interval does not rule out possible effects of temporal conditioning.

Kisley and Gerstein questioned whether tuning shifts are caused by learning because they observed tuning changes over days in the absence of training (Kisley and Gerstein, 1999). This concern was rather curious because spontaneous shifts had previously been eliminated as tuning shifts are directional (toward the CS), associative, and discriminative, that is, toward the CS+, not the CS– (Bakin and Weinberger, 1990; Bakin et al., 1992; Edeline and Weinberger, 1993).

The authors next studied classical conditioning, pairing a tone with intracranial self-stimulation (Olds, 1962). In so doing, they extended inquiry to another species, the rat, and another type of motivation, reward (Kisley and Gerstein, 2001). Animals underwent a single 30-trial session of classical conditioning. Subjects were studied under light ketamine anesthesia throughout, rather than in an undrugged waking state (see also Edeline, 1990). Behavioral evidence of conditioning to the tone was nonetheless obtained. The authors did find that conditioning produced CS-specific plasticity, including shifts of tuning toward or to the frequency of the CS. Also in agreement with prior studies, this RF plasticity was associative because it required CS–US pairing. The learning effects were above and beyond any spontaneous changes, which were indexed by reduced day-to-day correlation coefficients actually between entire tuning curves. However, the authors did not actually measure tuning by tracking the best frequency over days. The reduced correlations reflect the fact that responses to all frequencies within a tuning curve received equal weighting in the statistical analysis. Thus, decreased correlations might well be caused by loss of weak responses to frequencies distant from the BF (i.e., at the lower and upper limits of the tuning curves). The stability of tuning has been established over periods of 2–4 weeks, during which time there were no drifts of the best frequency (Galvan et al., 2001).

As RF plasticity is not an artifact of spontaneous changes in tuning, neither is it an artifact of state. As noted earlier, whereas animals exhibit arousal and related responses to sustained (e.g., 2–5 s) CS frequencies during training trials, they do not exhibit any behavioral 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 pips during RF determination (Diamond and Weinberger, 1989). Moreover, animals trained in the waking state exhibit RF plasticity when tested under deep general anesthesia (Lennartz and Weinberger, 1992b; Weinberger et al., 1993).

Learning induced tuning plasticity is not limited to animals. The same paradigm of classical conditioning (tone paired with a mildly noxious stimulus) produces concordant CS-specific associative changes in the primary auditory cortex of humans (Molchan et al., 1994; Schreurs et al., 1997; Morris et al., 1998).

In summary, RF plasticity has major characteristics of associative memory. It is not only associative but is also highly specific, discriminative, rapidly acquired, retained at least for many weeks, develops consolidation over hours and days, and exhibits generality across training tasks, types of motivation, and species. Thus, RF plasticity in the auditory cortex reflects the learned importance of experiences. **Figure 3** summarizes changes in tuning for conditioning, sensitization, and habituation.

The associative specificity of tuning for acoustic frequency raises the issue of whether the observed effects indicate a special type of adaptation for frequency or are exemplars of a general neural strategy for the processing, representation, and storage of experience. Recent studies have addressed this issue by determining the effects of associative processes on parameters other than acoustic frequency.

Bao and colleagues (2004) trained rats in a sound maze in which food reward was contingent on successful navigation using only auditory cues. In this task, the repetition rate of noise pulses increased as the distance between the rat and target location decreased. After subjects had learned this maze, the responses of neurons in A1 were investigated in a terminal posttraining session. A1 cells exhibited enhanced responses to high-rate noise pulses and stronger phase-locking of responses to the stimuli. The effects were due to learning because controls that had received identical sound stimulation, but were given free access to food, failed to exhibit such plasticity of temporal processing and, in fact, were not different from naive subjects. Thus, learning produced a shift in tuning to high repetition rates (i.e., the stimulus feature that was most closely associated with procurement of food).

The plasticity of sound intensity (level) processing has been investigated in A1 (Polley et al., 2004b). Rats were trained to move to a place in a small arena at which sound levels to ongoing sound bursts

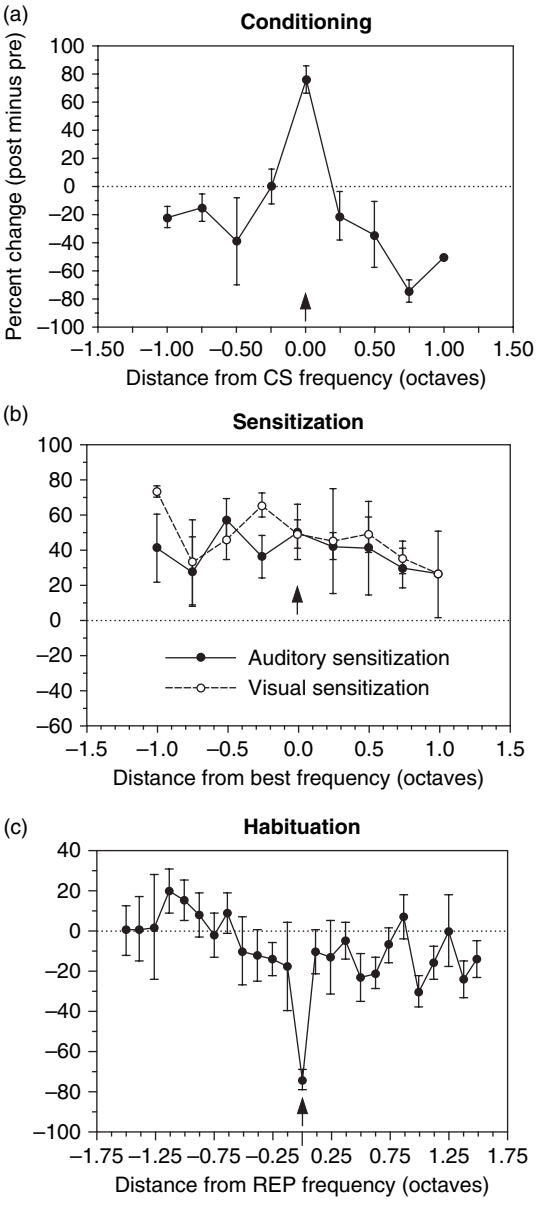

Figure 3 Summary of the effects of conditioning, sensitization, and habituation on frequency receptive fields in the primary auditory cortex of the guinea pig. Data are normalized to octave distance from (a) the conditioned stimulus (CS) frequency, (b) the presensitization best frequency, or (c) the 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.

became maximal. They were guided by having stimulus levels increase as the subject moved closer to the otherwise unidentified locus, and contrary, levels were reduced as the rats moved farther away. Yoked controls received the same acoustic experience, which was not linked to their behavior. In trained animals only, A1 responses became selective to more restricted ranges of sound intensities. The findings indicated that associative processes can selectively modify the representation of stimulus magnitude.

3.11.6.2 Primary Somatosensory Cortex (S1)

Stimulation (deflection) of the mystacial vibrissae of the rat has often been the conditioned stimulus of choice in the study of associative plasticity in S1, specifically in the posteromedial barrel subfield (PMBSF, hereafter whisker barrel field) (Welker, 1976; Simons, 1978). Early studies simply paired the deflection of a vibrissa that elicited little response at a particular barrel recording site with that of a subsequent deflection of a whisker that did elicit an excitatory response; a typical CS–US interval was 500 ms. In many cases, pairing produced an increased response to the CS (Delacour et al., 1987, 1990a,b). When a whisker is stimulated alone continuously, the response in S1 declines, probably due to habituation, whereas subsequent pairing with shock enhances response amplitude (Kublik, 2004). Such studies were not concerned with the specificity of plasticity and included neither nonassociative controls nor behavioral evidence of learning. However, the findings attested to the malleability of the vibrissal system in the adult, waking animal.

The specificity of plasticity, with nonassociative controls, has been studied in this system. The findings appear to be generally concordant with studies of auditory cortex. That is, tactile stimuli that gain behavioral significance as signals for reinforcement appear to gain cortical territory. For example, pairing the deflection of a row of mystacial vibrissae (CS) with a tail shock (US) in mice produces behavioral evidence of conditioning (e.g., postural changes and/or CS-elicited bradycardia). The following day, S1 was analyzed using with 2-DG mapping of functional activity. Conditioning sessions produced an increase of the functional representation in somatosensory cortex of the specific CS row of the whiskers stimulated during the training. The effect is associative, as it did not develop in pseudoconditioned mice or in animals that received only the CS. When training was discontinued, the enlargement of vibrissal representation returned to baseline. This loss of

specific associative plasticity could be accelerated by extinction training (CS alone) (Siucinska and Kossut, 1996).

As in the case of the auditory cortex, CS-specific increased representation is not limited to aversive reinforcement. Mice received pairing of whisker stimulation with a drop of sweet water. Cortical representations of rows of whiskers were mapped by 2-DG autoradiography after 3 days or 2 months of training. No quantified behavior was obtained, although the authors noted increased activity to the CS. In any event, conditioning resulted in enlargement of the cortical representation of vibrissae comprising the CS, compared with the contralateral representation of a row of whiskers that were not stimulated. Interestingly, the duration of training affects laminar plasticity. Three sessions increased the width of the 2-DG activity in supra (II/III) and infragranular (V/VI) layers, whereas the effects of 2 months of training were confined to layer IV. The changes were not observed in animals that received whisker stimulation alone or unpaired stimuli (Siucinska and Kossut, 2004).

Recently, Disterhoft and colleagues have used the well-studied conditioned eyeblink response to study associative changes in the representation of vibrissae in S1 (Galvez et al., 2006). Rabbits received deflection of a single row of whiskers (CS), followed by corneal air puff after a 500-ms trace period. Trace conditioning is known to require an intact hippocampus in contrast to delay conditioning (i.e., no intervening trace period) (Solomon et al., 1986; see also Beylin et al., 2001; Bangasser et al., 2006). The subjects developed conditioned responses over a period of 7–9 days, in contrast to pseudoconditioned rabbits. Barrels were identified by cytochrome oxidase staining and confirmed by single-unit electrophysiology. The authors found a specific expansion in the representation of the CS row of whiskers, compared both to the control animals and to the nontrained hemisphere, showing specific associative plasticity.

Matthew Diamond and coworkers have argued that, "if memories are stored within topographically organized sensory cortical areas, then access to those memories should be topographically distributed" (Harris et al., 2001b: 316). In one study, rats were trained on a gap-crossing task using the only whisker that had not be trimmed. After successful learning, the trained whisker was clipped and a prosthetic whisker attached to a different whisker stub. Transfer was tested by the rate of new learning, which was inversely related to the distance between the original and new whisker. Electrophysiological recordings revealed that the degree of overlap between cortical response patterns of two whiskers could account for the degree of transfer ($r = 0.98$) (Harris et al., 1999).

They also trained humans to use one fingertip to discriminate between two stimuli in the submodalities of vibration, punctate pressure, and roughness. Tests of posttraining generalization (transfer) to digits on the trained and untrained hands revealed no transfer for vibration but positive transfer for pressure and roughness discrimination as a function of topographic distance from the trained fingertip. The authors concluded that "tactile learning is organized within a somatotopic framework" (Harris et al., 2001a: 1056). Interestingly, Pavlov had predicted the existence of somatotopic cortical organization on the basis of similar training and generalization tests in dogs (Pavlov, 1927).

3.11.6.3 Primary Visual Cortex (V1)

In contrast to the primary auditory and somatosensory cortices, there appear to be no studies of the specificity of associative processes in the primary visual cortex. This is curious in light of the previous extensive investigation of V1 in classical and instrumental conditioning in animals during the period of 1935–1984. As noted earlier, most subsequent studies of V1 have focused on perceptual learning. Recent reports of classical conditioning in humans may indicate a resurrection of interest in associative learning. Functional magnetic resonance imaging (fMRI) has been used to investigate Pavlovian delay fear conditioning, using a blinking red light as the CS and shock as the US (Knight et al., 1999). Paired subjects exhibited a larger amount of active tissue in V1 compared to controls that received light and shock unpaired. However, the individual group effects were a decrease in response in the controls and no change in the paired group, suggesting that associative processes prevented habituation in this case. The absence of a behavioral measure of learning limits interpretations as well.

A further study of both delay and trace (10 s) conditioning has been more revealing. Using a discrimination protocol in which the three conditioned stimuli (CS+, CS+ trace, and CS−) were different colored shapes, the authors found significant behavioral learning and discrimination (development of conditioned galvanic skin responses, GSR) for both delay and trace protocols. Functional MRI responses

were larger to the CS+ versus CS− in delay conditioning and also larger to the CS+ trace versus the CS− in trace conditioning.

Perhaps similar studies will be conducted in animals using a stimulus dimension (e.g., line tilt) that could determine receptive field plasticity and thus reveal the extent of specificity of associative processes in V1. Given the earlier EEG and evoked potential studies, as well as the recent fMRI experiments, there is reason to expect that, like A1 and S1, V1 is specifically involved in associative learning and memory.

3.11.7 Do Lesions of PSCs Impair or Prevent Learning and Memory?

A frequently asked question (which I paraphrase) is, "As associative plasticity develops in PSCs, shouldn't lesions of PSCs impair or prevent conditioning? If not, why be interested in plasticity that would appear to be epiphenomenal?" The answer to the first question is based on studies of A1, for which the relevant findings are known. The simple answer is "No." It has long been known that simple (i.e., single-tone, nondiscriminative) classical conditioned responses can develop after ablation of A1 alone or as part of extensive cortical destruction (DiCara et al., 1970; Berntson et al., 1983; Romanski and LeDoux, 1992).

However, these questions are based on certain assumptions, which include (1) neurophysiological studies of conditioning seek stimulus–response (S-R) circuitry, (2) the memory trace formed is localized, (3) neurophysiological plasticity that develops is the substrate of the CR, and (4) destruction of the site of such plasticity should disrupt the CR (see Ohl and Scheich, 2004, vs. Weinberger, 2004a).

These assumptions may be relevant to learning a single, specific S-R relationship, such as learning to produce a conditioned eyeblink to a tone paired with air puff (Christian and Thompson, 2005). However, they do not apply to the vast majority of associative learning, which involves stimulus–stimulus (CS–US) links. First, classical conditioning transcends stimulus–response associations. Even S-R conditioning involves prior stimulus–stimulus (CS–US) associations. Moreover, other associations are invariably formed, such as between a stimulus and the location or general context within which learning occurs. Second, CS–US associations are known to develop rapidly, in a few trials, preceding CS–CR associations (Lavond et al., 1984), and therefore are likely be involved in the development of S–R links (Schlosberg, 1937; Mowrer, 1947; Konorski, 1967; Lennartz and Weinberger, 1992a). Third, multiple behavioral CRs develop during rapid CS–US learning (e.g., changes in heart rate, respiration, blood pressure, pupillary diameter, skin resistance, behavioral freezing), any one of which can be used to verify that a CS–US association has developed (of course, given appropriate nonassociative controls). Fourth, although its components may be localized, the total memory for a given event is almost certainly distributed across the cortex and other brain regions, including relevant sensory systems. Fifth, although circuitry for an association can be completely subcortical, the cerebral cortex also can store information in parallel with subcortical systems. Sixth, the cerebral cortex has access to a much greater range of information than the subcortex. It undoubtedly stores information that can be used in a highly flexible manner to subserve adaptive behaviors in an unknown future. For example, although simple auditory conditioning is not destroyed by lesions of A1, as soon as two-tone discrimination is demanded, A1 is required (Teich et al., 1988). A1 is also obligatory to achieve experimental extinction (Teich et al., 1989).

Thus, in response to the question posed at the outset of this section, PSCs can be profitably studied to determine the cortical fate of stimuli that enter into associations. In short, such studies of neurophysiological plasticity can be directed to issues of the representation of stimuli and the transformations, which they may develop during learning, without any reference to particular behaviors that index the establishment of stimulus–stimulus associations.

3.11.8 Memory and Retrieval in Primary Sensory Cortices

As primary sensory cortices develop highly specific representational plasticity in learning, they may be expected to exhibit memory. One such case has already been mentioned, that of a 2-month retention of CS-specific tuning shifts in A1 (Weinberger et al., 1993). Further, memory codes in PSCs have been proposed. Memory codes specify the relationship between an experience and the nature of its neural storage (e.g., the memory code for the acquired behavioral importance of a stimulus might be the number of cells that become tuned to that stimulus)

(Weinberger, 2001). We now summarize additional evidence of mnemonic processes in A1, S1, and V1.

3.11.8.1 Working and Reference Memory

If PSCs store at least some contents of memory, then they should hold that information for a period of time following presentation of a stimulus. There is evidence that the primary somatosensory cortex is involved in working memory. Monkeys trained in a haptic delayed matching to sample (DMTS) task (two different objects), with an 18-s delay period, exhibit sustained changes in activity of neurons in S1 (Koch and Fuster, 1989). Similar effects were also found in a haptic DMTS study in which objects were identical in shape but differed in surface features (Zhou and Fuster, 1996). Patterns of spike trains, not merely changes in unit firing, also are correlates of working memory in S1 (Bodner et al., 1998; Bodner et al., 2005).

Disruption of working memory in S1 also has been found. Humans were trained to discriminate the frequencies of two vibrations presented at an interval of 1500 ms. A pulse of transcranial magnetic stimulation (TMS) applied to the contralateral S1 early in the retention period of the first vibratory stimulus (600 ms or less) impaired discrimination performance. There was no effect when TMS was applied to the ipsilateral S1. The authors concluded that S1 serves as a temporary site of information storage (Harris et al., 2002).

Sakurai's laboratory has documented neural correlates of working memory and also long-term storage (reference memory) in A1. Rats were trained in a continuous nonmatching-to-sample working memory task to remember whether or not the current tone frequency was the same or different from the preceding tone. About 20% of single units in A1 (and the medial geniculate as well) developed sustained differential activity during the delay period after exposure to the sample tone, leading the authors to conclude that the thalamocortical auditory system retains auditory information in working memory (Sakurai, 1990). The task was then modified so that either working memory (WM) or reference memory (RM) could be tested in alternating fashion within a single session (Sakurai, 1992). Unit recordings were obtained from hippocampus CA1, CA3, dentate gyrus, and A1. Only the auditory cortex showed differential responses to the physical characteristics of the stimuli, low and high tones, respectively, in both WM and RM tasks. This itself is not surprising. Cells in the hippocampal formation exhibited changes in firing related to either WM or RM but not both. In contrast, neurons in A1 could exhibit increased activity for both the WM and RM tasks, indicating the flexible involvement of A1 in both working and reference memory (Sakurai, 1994). Further research using cross-correlations between pairs of neurons to detect cell assemblies revealed that most correlated pairs in the hippocampal formation occurred during WM, whereas correlated cells in A1 could participate equally in WM and RM (Sakurai, 1998). The results highlight the flexibility of the same cells in PSCs to participate in multiple functional networks.

3.11.8.2 Procedural Memory

There is at least one report that links PSC neural plasticity to procedural memory. Rabbits trained in eyeblink conditioning (tone/corneal air puff) developed tone-elicited neural responses in primary somatosensory cortex together with conditioned eyeblink responses. However on trials of CR failure, there was also an absence of S1 responses to the acoustic CS. It might be thought that both omissions were due to a failure to process the CS, perhaps in the lower auditory system. However, on such failure trials, the unconditioned response was still modulated by the CS, as indexed by more vigorous unconditioned responses, compared to unconditioned response–alone trials. Another explanation might be that the response in S1 represented sensory feedback from CRs, but its latency preceded CRs. The authors concluded that the response of S1 to the acoustic CS reflects the efferent copy of the memory of the response that was elicited by the CS from the cerebellum, which they view as a procedural memory trace (Wikgren et al., 2003).

3.11.8.3 Imagery

If cortical networks involved in memory storage and retrieval include PSCs, then they should reveal themselves in the absence of relevant sensory stimulation. That is, neural activation should occur when the prior sensory experiences are recalled. Although probably less widely accepted than some other approaches, studies of imagery in humans support such involvement. Imagery often is considered to be a higher cognitive function, but it seems most relevant to retrieval in the present context. Bearing in

mind caveats concerning precise localization and the need to validate the presumptive imagery behaviorally, there is evidence for the involvement of PSCs. For example, imaging studies have detected activation of V1 after subjects studied novel visual stimuli while they had to make decisions about visual details with their eyes closed. Further, the extent of activation of V1 was proportional to the size of the stimulus feature being remembered, supporting the view that imagery was taking place within the retinotopic map (Kosslyn et al., 1995, 1999).

Somatosensory imagery effects also have been reported. S1 was imaged in humans during the tapping of a finger. When subjects later imagined tapping the finger, the same region of S1 was activated (Porro et al., 1996). One cannot rule out undetected kinesthetic stimuli or subthreshold motor contributions to these findings, however. Studies of musical imagery are less subject to such problems. For example, imagery for musical timbre activates the primary auditory cortex with some right-side asymmetry, also present for timbre perception (Halpern et al., 2004; see also Halpern and Zatorre, 1999; Halpern, 2001; Zatorre and Halpern, 2005).

3.11.9 Nonsensory and Higher Cognitive Functions

In addition to associative processes, PSCs are also involved in nonsensory and higher cognitive processes. These are summarized alphabetically.

3.11.9.1 Attention

Attention has long been known to modulate sensory cortices. Although many effects are seen in higher areas, PSCs are also subject to selective attention, such as auditory (Alho, 1992), somatosensory (Johansen-Berg and Lloyd, 2000), and visual (Sengpiel and Hubener, 1999). However until recently, studies of attention had not been able to demonstrate the extreme specificity of rapid attentive modulation in PSCs. Fritz, Shamma, and colleagues devised a clever and sensitive method of obtaining spectrotemporal receptive fields (STRFs) while ferrets waited to detect a previously learned tone to avoid shock. They found that attention modulates primary auditory cortex by facilitating responses to the target frequency while suppressing responses to other frequencies (Fritz et al., 2003). When trained in both frequency detection and frequency discrimination tasks, the reinforced and target frequencies were enhanced, as might be expected, but because the target during tone detection (CS+) could be the nonreinforced (CS−) frequency during discrimination, the authors were able to show that responses to the same physical stimulus could be facilitated or suppressed depending on the task (Fritz et al., 2005b). In a third study, ferrets learned both tone detection and gap detection tasks. As expected, tone detection had the same target-specific enhancement. Additionally, during gap detection, the STRF was changed along the temporal dimension, specifically, the temporal dynamics of discharge were sharpened (Fritz et al., 2005a). In all the studies, the effects could last for hours in some cases, suggesting an involvement in memory as well as in selective attention. Overall, the findings demonstrate that attention has a strong influence on A1. At least some of this plasticity is due to top-down processes because switching tasks, and therefore the significance of a particular frequency, differentially affects responses to the same physical stimulus. The findings also highlight the ability of the same cells to participate in multiple adaptive networks. Of course, RF shifts in learning could be the result of top-down, bottom-up, or a combination of these influences.

3.11.9.2 Category Learning and Concept Formation

Perceptual category formation involves grouping sensory stimuli by abstract relationships based on some aspect of similar physical attributes. Ohl et al. (2001) trained rats to form the categories of rising and falling frequency modulation of tones (i.e., independent of their absolute frequencies). They detected category learning by a sudden change in learning strategy. Recordings from A1 revealed that the transition to category formation was correlated with the emergence of patterns of stimulus representation in the EEG in which frequency-modulated tones are distinguished into the categories of rising and falling modulation. The authors believe that the electrographic plasticity reflects the abstraction that defines these categories (Ohl et al., 2001). Categorical effects have also been observed in monkeys trained for more than 2 years to classify steps in acoustic frequency (Selezneva et al., 2006). The authors found that phasic activity of cells in A1 indicates the direction of frequency steps, whereas slow changes in activity are tied to procedures involved in solving the task.

A recent related experiment extends the involvement of auditory cortex to humans. Subjects were required to classify sound on the basis of either the direction of change (rising or falling frequency modulation) or the duration of stimulation (short or long). fMRI revealed activation in the right auditory cortex for categorization by direction of change, whereas categorization by duration of stimulation activated the left auditory cortex (Brechmann and Scheich, 2005). The hemispheric specializations for the two types of stimulus parameters are consistent with prior studies of the human auditory cortex, but the linkage of the findings to categorization, rather than to the physical parameters of the stimuli *per se,* demonstrates that the human auditory cortex is involved in higher cognitive processes.

3.11.9.3 Cross-Modality Effects

Associative involvement of PSCs is also evident in cross-modal effects, consisting of a stimulus in one sensory modality being able to elicit responses in the PSC of another sensory modality. Indeed, cross-modality effects are so numerous that their significance is generally overlooked. They began with the EEG studies of conditioning. For example, the development of the ability of the click of a camera shutter to block alpha waves in the human occipital cortex when it preceded a flashing light US is evidence for cross-modal effects, although in this serendipitous seminal study, the authors could not have detected actual auditory evoked responses in visual cortex (Durup and Fessard, 1935). In animal studies of conditioning, the ability of the CS to elicit EEG activation in the PSC of the US is similarly an example of cross-modality effects. Beyond EEG findings, direct studies of evoked sensory responses consistently documented the development of CS-elicited responses in the PSC of the US (Oleson et al., 1975).

Recent studies reinforce these earlier findings. For example, studies in which primates are cued to perform a tactile discrimination by an auditory or visual stimulus found the development of responses to the auditory (Zhou and Fuster, 2004) and visual cues (Zhou and Fuster, 1997, 2000), respectively, in the primary somatosensory cortex. The reverse relationships also exist. For example, monkeys were trained to perform a complex auditory discrimination. Following presentation of a cue light, they could initiate a sequence of tones by pressing a bar. Many neurons in A1 developed responses elicited by the bar press, of course, prior to the presentation of the sounds. And given the prevalence of cross-modality neural responses, one would predict that presentation of the cue light also would elicit responses in A1, and this also was observed (Brosch et al., 2004).

Similar effects are reported in A1 of humans. Several studies have linked the primary auditory cortex of humans to speech in the absence of sound. Thus, the presentation of visual stimuli associated with language sounds, whether the sight of a letter or of silent speech, elicits neural activity in the primary auditory cortex (Sams et al., 1991; van Atteveldt et al., 2004; Pekkola et al., 2005; Ruytjens et al., 2006). This cross-modal effect might derive from earlier associative learning, as the sight of a face, especially the lips, during speech is highly correlated with hearing the emitted speech. Some effects are not limited to putative associations. Visual stimuli can be transformed into a phonological code. Apparently, the left primary auditory cortex is activated during such recoding (Suchan et al., 2006).

A recent anatomical study in the gerbil may provide an anatomical basis for some cross-modality effects. The authors found a surprisingly large number of inputs to A1 from nonauditory regions of both the cortex and the thalamus. They argue against the view that primary sensory cortices are unimodal (Budinger et al., 2006).

3.11.9.4 Expectancy, Preparatory Set

Subjects previously trained on a task form expectancies or preparatory sets that are based on the probability that a certain stimulus or event is likely to occur. Although generally regarded as a higher cognitive function, they are manifest in PSCs. In one such case, rats were trained in a visual reaction time task with a very brief (10-ms) warning tone, 1.4 s preceding the light stimulus. A subset of single neurons in A1 developed a significant sustained increase in discharge rate during the warning period that did not occur when the same warning stimulus was given by itself. The authors suggested that this activity constitutes a substrate of preparatory set (Shinba et al., 1995). A phasic increase in arousal might have been responsible for increased cellular activity, as preparatory set and expectancy often involves increased arousal. Direct measures of arousal level and recordings taken in arousing situations outside the task would help resolve this issue.

A more detailed study by Villa and coworkers provides compelling evidence for an expectancy function in A1 (Villa et al., 1998). They obtained

simultaneous single-unit spike trains while rats performed a complex cognitive task, specifically a two-choice task (Go/NoGo) with a two-component (pitch and location) auditory stimulus lasting 500 ms. They observed that functional interactions (cross-correlations) are dynamically modified in the waiting period preceding the onset of auditory stimulation. Further, they found spatiotemporal firing patterns both within and across spike trains several seconds before the actual stimulus delivery. These patterns have a very precise repetition of spike discharges separated by long intervals (up to several hundreds of milliseconds) in the absence of a change in mean rate. The authors suggested that network activity in A1 reflects "participation of recurrent neuronal networks in processes anticipating the expected sensory input" (Villa et al., 1998: 269).

3.11.9.5 Motivation, Behavioral Importance

Several studies have found plasticity in PSCs based on motivational level or the acquired behavioral importance of sensory stimuli. In a complex appetitive instrumental task, rats were trained in three phases, and the amount of c-Fos expression was determined in different subgroups at the end of each phase: (1) tone–food association, (2) two-tone discrimination, and (3) two-tone discrimination contingent on location of the sound source. Auditory stimuli were bursts of complex sounds lasting 500 ms. Compared to various control groups, successful animals exhibited no difference in phase 1 but had significantly greater cFos activity in primary auditory cortex during the next two phases. No subcortical auditory structures (cochlea through medial geniculate) differed from controls (Carretta et al., 1999). The authors concluded that auditory cortex is involved in the coding of stimulus significance. Of note, their failure to find an effect after simple tone–food association suggests that not all associative learning involves PSC plasticity. Moreover, it is clear that more complex learning (i.e., discrimination problems) is more likely to engage a PSC.

Although the previous study neither manipulated the level of motivation nor determined specificity of plasticity, a recent experiment addressed these issues directly. Rats were trained to bar press for water contingent on the presence of a tone (6.0 kHz), each at different levels of water deprivation. Terminal mapping of A1 revealed a specific increase in area of representation of the CS frequency in the tonotopic map. More importantly, the amount of area was directly proportional to the level of correct performance, itself controlled by the level of motivation for water (**Figure 4**) (Rutkowski and Weinberger, 2005). These findings were predicted by the memory code hypothesis that the level of behavioral significance of a stimulus is encoded by the increase in the number of cells that become tuned to that stimulus (Weinberger, 2001).

The primary visual cortex has been studied during associative learning only rarely during the past 30 years. However, V1 has now been linked to reward processes. Rats wearing goggles that provided controlled stimulation to either eye were trained to associate whole-field illumination with water reward. Many neurons in V1 that originally responded only to the visual stimuli developed discharges that accurately predicted the timing of the reward (Shuler and Bear, 2006).

There is evidence of motivational effects in the barrel field of S1. Rats were studied under conditions of (1) searching for an object with their vibrissae for a food reward, (2) whisking in the air for the goal of returning to the home cage, or (3) whisking in the absence of reward (Ganguly and Kleinfeld, 2004). The amount of phase-locking of neurons in S1 was greatly increased when whisking resulted in reward compared to whisking without reward.

3.11.9.6 Learning Strategy

The strategies used to solve problems are significant factors in human cognition. However, the role of learning strategy has been neglected in studies of learning and brain plasticity. A recent study reveals that learning strategy can be decisive in the development of specific plasticity in the primary auditory cortex. Two groups of animals were trained to solve the same problem, achieve the same asymptotic level of performance, and exhibit the same degree of learning about absolute frequency, but accomplish these goals using two different learning strategies. Specifically, adult male rats were trained to bar-press for water contingent on the presence of a 5.0-kHz tone. A bar-press response made during the silent intertrial interval resulted in a time out (i.e., 3–7 s lengthening of time to the next trial) signaled by a flashing cue light. This apparently simple problem can be solved two ways: 'bar-press during tone presence' ('tone duration strategy') or 'bar-press from tone onset until receiving the error signal' ('onset-error strategy'). However, these alternatives cannot

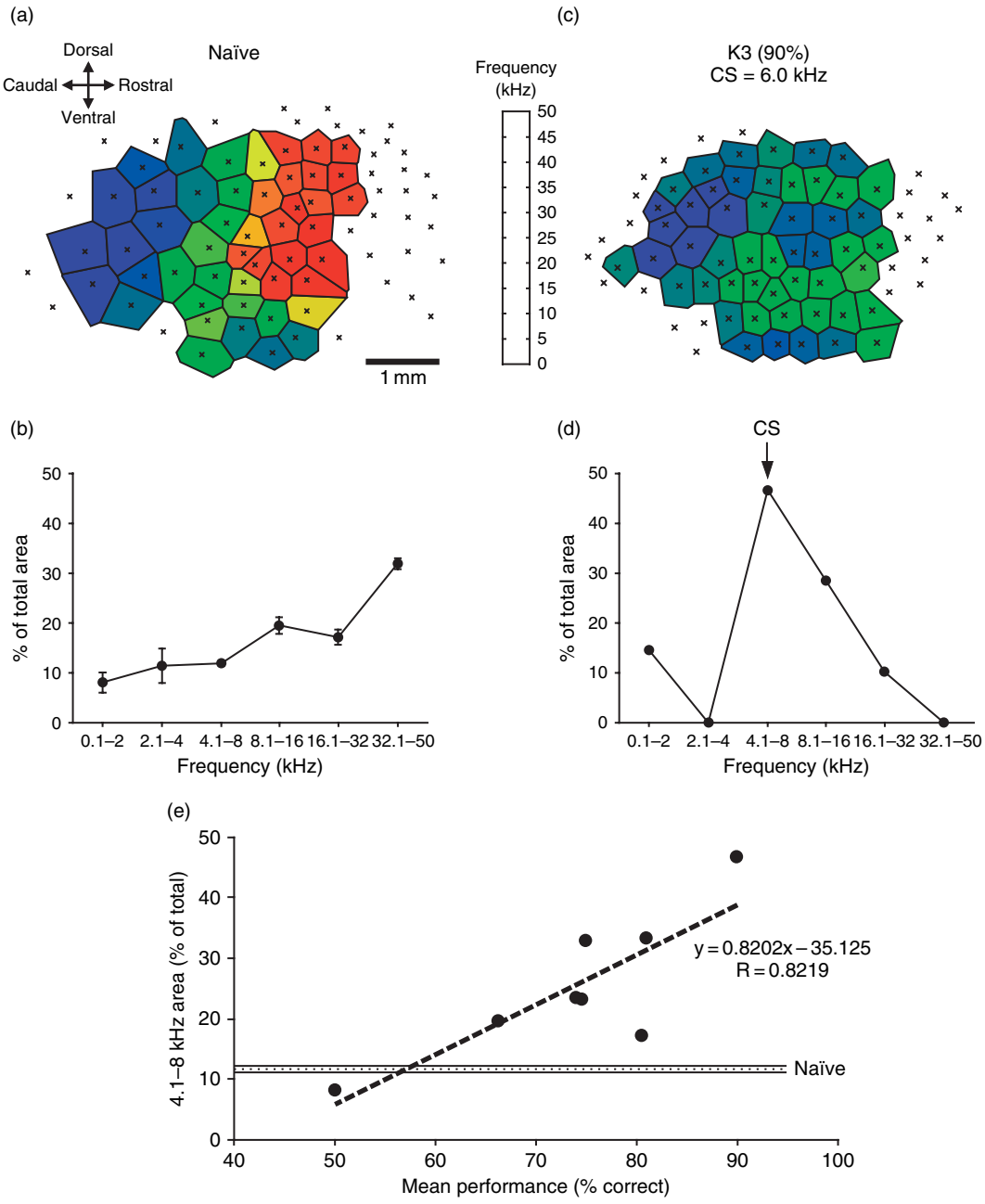

Figure 4 Motivational effects on area of frequency representation in tonotopic map of A1. Trained rats received water reward for bar-presses in the presence of a 6.0-kHz tone. (a). The tonotopic maps of a naive rat. (b). Quantification of the percent of total area for each six octave bands for the map above. (c). The tonotopic map of a subject that attained over 90% correct performance. (d). The corresponding quantification. Note that the band containing the CS frequency is much greater (~50% vs. ~10% in the naive). (e). Evidence of a memory code for the acquired behavioral importance of sound. Level of tone importance was controlled by the motivation for water (amount of water deprivation). Asymptotic performance was significantly correlated with motivation level. The area of representation of the frequency band containing the 6.0-kHz tone signal increases as a direct function of the level of behavioral importance of the tone, as operationally indexed by the level of correct performance. For details, see Rutkowski RG, and Weinberger NM (2005) Encoding of learned importance of sound by magnitude of representational area in primary auditory cortex. *Proc. Natl. Acad. Sci. USA* 102: 12664–13669.

be distinguished because error signals are always given for responses made starting immediately after tone offset. Therefore, although one group was trained in the standard manner, a second group was given a 2-s grace period starting at tone offset, during which bar-presses did not produce the error signal (or water reward). Evidence for the 'onset-error strategy' would be continued bar-pressing after tone-offset during the grace period.

Both groups achieved the same high levels of correct performance, and both groups revealed equivalent learning of absolute frequency during training. Analysis of behavior showed that the second group did indeed use the 'onset-error strategy.' Posttraining 'mapping' of the auditory cortex revealed that this group alone developed specific plasticity. Threshold was decreased ~10 dB, and tuning bandwidth was narrowed by ~0.7 octaves. Moreover, this plasticity was restricted to the frequency band of the 5.0-kHz tone cue. The findings show both that auditory learning can develop without plasticity in threshold or bandwidth and, perhaps more important, that learning strategy – not learning performance – can determine cortical plasticity (Berlau and Weinberger, 2008).

3.11.9.7 Motor Processes

It might seem most unlikely that primary sensory cortices could be intimately linked to motor functions, but there is clear evidence of motor involvement. Within A1, patterns of neuronal activity constituted predictive neural correlates of later motor behavior. Rats were trained in a Go/NoGo task to distinguish combinations of two frequency-modulated sounds (based on low- [3.0 kHz] or high- [12.0 kHz] base frequencies) and two speaker locations (left or right). They were rewarded for correct Go and NoGo behavior (e.g., Go to low tone on left, NoGo to high tones simultaneously from left and right). Single-unit discharges were recorded simultaneously from up to 15 neurons while animals waited for the auditory cues. Using a pattern-detection algorithm, the authors detected 235 reliable spatiotemporal patterns of activity, 55% of which were significantly related to the type of response that the animal made several seconds later. Patterns predictive of Go and NoGo behaviors were about equal in number. Note that the predictive correlates were not elicited by the acoustic stimuli, which were delivered after the waiting period (by definition). Of particular interest, mean discharge rates did not vary, emphasizing the importance of the analysis of temporal parameters of cellular discharge. The patterns in A1 might be parts of motor programs that are engaged in auditory tasks (Villa et al., 1999).

3.11.10 Concerning the Direction of Plasticity

Heretofore, we have not focused on the direction or sign of changes in the magnitude of PSC plasticity. (Plasticity of temporal aspects of cellular discharge may be equally important but has not yet been studied extensively in PSCs during learning; see Edeline, 1999.) The dominant, almost exclusive, finding in conditioning has been that stimuli that gain behavioral importance become facilitated, as indexed by the fact that they come to elicit increased magnitude of response. (Of course, memory in habituation is indexed by a decrease in response magnitude.) Larger responses could be advantageous by increasing the signal-to-noise ratio when the task at hand is stimulus detection. In many cases, increased response involves CS-specific tuning shifts and increased area of representation, indicative of the recruitment of more cells to the CS or other important stimulus. As noted previously, the amount of increased area of representation is directly proportional to the level of behavioral importance of a tone (Rutkowski and Weinberger, 2005). More cells could also increase the probability of attention to stimuli whose behavioral significance has increased due to learning. The strength of memory might be an increasing function of the number of cells that preferentially involved the sensory experience. The favored processing of important stimuli by more cells could also increase the probability of complete processing in an unknown future, including one of neuropathology. In the latter case, more cells could serve the function of a safety net. Thus, increased response magnitude would seem to make good functional sense. If associative processes produced decreased responses or reduced the number of cells tuned to an important stimulus, in the limit to zero, then the stimulus in question would seem to decrease, or lose, its ability to be stored and to guide current and future behavior.

But increased magnitude of response is undoubtedly only part of the complete story of PSC plasticity. Observations from studies involving naturalistic environmental situations indicate that specific decreased responses are the likely outcome of at least some

experiences (for review, see Frostig, 2006). For example, many formulations of PSC plasticity are based on a competition model, in which stimuli that produce more afferent input win (i.e., elicit larger responses and/or gain control of more cells). This outcome is prevalent in the whisker barrel field of S1 for surviving whiskers when others are clipped (Armstrong-James et al., 1994; Diamond et al., 1993). However, when the vibrissae are not altered, the representation of a whisker is smaller during active exploratory whisking than during quiet wakefulness (Fanselow and Nicolelis, 1999). Spared whiskers exhibit reduced representation when rats are permitted to explore for brief periods outside their home cages (Polley et al., 1999), and the same occurs for the intact vibrissal system when animals live for weeks in a naturalistic habitat, including tunneling, which makes increased demands on the use of whiskers (Polley et al., 2004a). Behavioral arousal, expected during active whisking, produces reduced representation coupled with increased synchronization of firing, resulting in sharper receptive fields that could subserve increased discrimination (Castro-Alamancos, 2004).

These studies did not involve explicit associative learning. However, one cannot discount the possibility of associative learning during naturalistic whisking. That is, an episode of whisking involves numerous instances of stimulus–stimulus relationships (e.g., successive tactile stimuli constituting within-modality sensory preconditioning). However, naturalistic situations are not optimal for determining fine-grain stimulus relationships. The trade-offs between increased ecological relevance in field or fieldlike studies and decreased manipulation of stimulus relationships are well known.

Exploratory whisking may also be related to .-perceptual learning, as animals have had uncountable trials of experience, discriminating objects by use of their vibrissae. The possibility that decreased responses reflect mechanisms underlying perceptual learning is supported by a recent study of frequency discrimination in A1 of the cat. Decreased responses were found for frequencies between the CS+ and CS−, during extended tonal perceptual learning. The authors suggest that such plasticity may facilitate the classification of stimuli with different behavioral outcomes by reducing similarity between reinforced and nonreinforced stimuli (Witte and Kipke, 2005). This finding contrasts with rapid two-tone discriminative learning (i.e., a single training session), in which responses to the CS+ are increased while responses to the CS−, pretraining BF, and other frequencies are reduced, the effects becoming even more pronounced during a subsequent silent period of consolidation (Edeline and Weinberger, 1993).

In summary, rapid associative learning appears to be dominated at present by findings of increased responses to behaviorally important stimuli. In contrast, extensive discrimination learning, particularly formal learning of increasingly difficult discriminations (i.e., perceptual learning), may involve reduced response magnitude with concomitant increased precision of receptive fields. However, a comprehensive understanding of the sign of plasticity must await further research of the relationships between the direction of PSC plasticity and its functional and behavioral significance.

3.11.11 Implications

The primary auditory, somatosensory, and visual cortices develop associative plasticity during behaviorally validated learning. They exhibit evidence of the storage of memory, including procedural, working, and reference memory, the latter validated for an indefinite period of at least months after training. Recent studies have revealed a high degree of specificity of plasticity in A1 and S1 (appropriate studies of V1 have not been conducted), including a remodeling of cortical processing that emphasizes responses to signal stimuli of acquired behavioral importance and indicative of the storage of discrete details of experience. Moreover, A1, S1, and V1 are clearly involved in a number of higher processes including attention, expectancy/preparatory set, category learning/concept formation, cross-modality interactions, imagery, learning strategy, motivation, and the degree of acquired behavioral importance of stimuli and motor actions.

This range of involved functions amply documents the extensive engagement of PSCs in adaptive cognitive and behavioral processes that far transcend their presumptive normative sensory functions. Space permits brief consideration of four implications.

First, primary sensory cortex, as commonly functionally understood, does not exist. There is probably no region of the cerebral cortex that is devoted only to the analysis of sensory stimuli; certainly, A1, S1, and V1 are not so limited. It follows that the responses of all neurons in these PSCs are almost certainly affected both by nonsensory processes (such as the acquired meaning of a stimulus) and the physical parameters of modality-specific stimuli as commonly studied in sensory neurophysiology. The caveat is that the cell type

that generates each type of neural response cannot yet be known, a task that may require many years to complete. So it is possible that some types of PSC cells respond only to the physical parameters of stimuli but so far have escaped detection.

Second, the developing concept that information is stored where it is processed, which attributes mnemonic functions to PSCs (as well as myriad other cerebral structures) may be correct but highly incomplete. For example, concept and category formation deal with abstract properties of stimuli, not merely their root physical parameters. Therefore, PSCs appear to serve supra-stimulus functions.

Third, and a related point, because the degree of plasticity reflects the level of acquired behavioral importance (Rutkowski and Weinberger, 2005), motivational information that is presumably not assessed in PSCs is nonetheless represented therein (see also Shuler and Bear, 2006). Therefore, PSCs appear to serve extrastimulus functions.

Fourth, normative concepts of cortical organization need to be revised. Because of specific, associative plasticity in PSCs, they cannot be distinguished from other cortical regions on the basis of sensory versus associative functions. Campbell was wrong, and all theories based on such a distinction are obsolete. Formulation of new, testable organizational principles is perhaps the major task facing the integrative neurobiology of the cerebral cortex.

3.11.12 Toward a New Functional Architecture of the Cerebral Cortex

Kuhn's analysis of scientific revolutions holds that extant but outmoded paradigms are not discarded until a new paradigm accounts both for old facts and newer, inharmonious findings (Kuhn, 1970). The issue of new principles for the functional organization of the cerebral cortex is far beyond the capabilities of this chapter. However, as its major point has been to show that primary sensory cortices are involved much more broadly in learning, memory, cognition, and adaptive behavior than generally recognized, one approach to thinking anew about cortical organization is to consider PSCs from a different point of view. With that in mind, I suggest the following.

First, the sensory specialization of each PSC must be retained. Regardless of cross-modality influences, V1 is specialized for vision, S1 for somatic sensation, and A1 for audition. But if they are not purely sensory, then what are they?

Second, I propose that PSCs deal with their modality-specific information in the context of solving whatever problem, challenge, or opportunity faces the organism. We may regard them as continually assembling components to form situational functional systems (see also Anokhin, 1974).

Thus, PSCs are reconceptualized as having three types of function: (1) modality-specific sensory, (2) learning/memory, and (3) broadly integrative with respect to modality-dominated problem solving.

For example, if a specific motor act is required with respect to acoustic stimulation, then the auditory cortex integrates (unknown aspects of) motor function with the analysis, acquisition, and storage of information about the relevant sound. The result would not be confined to auditory information but, rather, auditory information combined with relevant motor and spatial information for the situation in question. This may explain why selective lesions of frequency bands within the tonotopic map of A1 in the cat produce selective impairment of locomotion to the source of the corresponding sound frequency (Jenkins and Merzenich, 1984).

In no case would A1, S1, or V1 execute the requisite behavioral act. Nor would they assess or determine the motivational state or determine the nature goal object, such as food, water, or opportunity for sex. Nonetheless, they would be major sites in which the relevant information is brought together. PSCs would not be the only sensory cortical sites because belt and higher sensory regions would be involved as well. In fact, the manner in which all PSCs and their related higher fields work together, with both feedforward and feedback interactions, remains a central problem for cortical function.

As animals face many problems, including gathering information without the need for immediate effector action (overt behavior), it follows that their PSCs must be able both to store a multiplicity of relevant modality-specific information while also being able to rapidly organize and mobilize the appropriate information as environmental situations, challenges, and opportunities appear – often rapidly. The available data do indicate that the same PSC cells not only participate in multiple behaviorally relevant networks but also can rapidly switch mode as the task changes (Sakurai, 1994, 1998; Fritz et al., 2005a,b; see also Gilbert et al., 2001).

We currently have little information about multifunctional aspects of PSCs because the issue has seldom been broached and so few appropriate experiments have been conducted. Fortunately, their

involvement in learning and memory is now on such solid ground that it can provide a foundation for further inquiry about other cognitive processes. Although learning-induced plasticity is now widely accepted, it is often contrasted with much greater plasticity during development, the adult animal being regarded as retaining some developmental plasticity. However, instead of regarding associative plasticity as an add-on to sensory processing, the default position probably should be that PSCs store information as a normal part of their functions.

Clearly, this liberalized view of PSCs is preliminary and really little more than an outline of an idea. However, even in its nascent state, it offers an alternative to the traditional sensory role of primary auditory, somatosensory, and visual cortices. If it does nothing more than provoke thought and reaction, it will have served a beneficial purpose. However, I believe that although further characterization of PSCs is needed, it is now time to seek the functional principles governing the involvement of A1, S1, and V1 in learning, memory, and a multiplicity of nonsensory processes.

We may currently be as explorers in a strange land, approaching a barely discernible, yet clearly existing, mountain range. At present, details cannot be seen, and perhaps different peaks can barely be distinguished, but by continuing the journey, the detailed topography will be discovered eventually, as well as the inner geology. Perhaps we truly have only a dim view of the functional principles of the cerebral cortex. The next steps should be revealing, but they require a willingness to travel from the comfort of the conceptually comfortable to the extreme discomfort of a landscape fraught with unknown and perhaps strange hazards.

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