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Experience-Dependent Response Plasticity in the Auditory Cortex: Issues, Characteristics, Mechanisms, and Functions

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1. Introduction

The goal of this chapter is to provide a guide for understanding experience-dependent neuronal plasticity in the auditory cortex and its relation to behavior. (Unless otherwise noted, "auditory cortex" refers to the tonotopic primary auditory field, AI). It focuses on research that began in the mid-1980s concerning the question of how *learning may alter the processing and representation of acoustic information in the primary auditory cortex.* As used here, the term "plasticity" refers to systematic long-term (minutes to months) changes in the responses of neurons to sound as a result of experience. Plasticity at the level of altered neural responses is the result of various subcellular and molecular processes. Selected aspects of these substrates are included, particularly those relating to the cholinergic modulation of auditory cortical plasticity. Owing to lack of space, the subcortical auditory system cannot be reviewed, except as it directly pertains to mechanisms of cortical plasticity (see Birt et al. 1979; Cruickshank et al. 1992; Edeline and Weinberger 1992; Gonzalez-Lima and Scheich 1992; Hennevin et al. 1993; McKernan and Shinnick-Gallagher 1997).

This chapter is not a comprehensive review of the literature but rather a distillation of those topics that seem to be both important and misunderstood. The latter probably reflects the diverse backgrounds of investigators interested in experiential effects, some approaching from the field of auditory neurophysiology, others from behavioral neuroscience. The decision to be selective in choice of literature while being more comprehensive in the coverage of issues and approaches is based on two factors. First, most aspects of plasticity in the auditory system have been reviewed recently (Scheich 1991; Weinberger 1995, 1998; Irvine and Rajan 1996; Scheich et al. 1997; Kraus et al. 1998; Palmer et al. 1998; Cohen and Knudsen 1999; Edeline 1999; Rauschecker 1999; Moore et al. 2001). Moreover, research on the roles of experience in auditory processing will continue to expand. Therefore, a large-scale review focused on pro-

viding a comprehensive account of findings may become rapidly dated. Continual updates on recent findings are therefore better dealt with, for example, in periodic "Trends" type reviews. Second, there is a need to address major issues in a manner that will assist readers both in the evaluation of published findings and in contemplating their own research. The material presented here is intended to be helpful over a period of some years, by providing a framework within which past and future reports of auditory system plasticity can be evaluated. In particular, the presentation and analysis of experimental designs, which has not appeared in the literature, is equally applicable to studies of all parameters of acoustic stimulation, to all structures within the auditory system, and to all investigations of the sensory bases of learning and memory.

In concluding this Introduction, it is important to be mindful that various authors inevitably cover the same subject matter differently. Views and assumptions, whether explicit or implicit, are affected by background knowledge, scientific interests, values, and personal experiences. This tendency is intensified when the author has been deeply engaged in research on the topic under review, as is the present case. As a statement relating to "truth in writing," I believe that it is both timely (actually long overdue) and essential to achieve a high level of synthesis between the sensory neurosciences and the behavioral neurosciences, particularly for cortical function and for the neurobiology of learning and memory. Such a synthesis honors the evolutionary outcome of brain–behavior relationships, in contrast to traditional disciplinary boundaries that are rooted in the "accidental" history of the 19th century and earlier. Of note, auditory research leads all other sensory systems in this regard, having initiated sensory/learning investigation in the 1950s and sustained it, with minor interruptions, to the present (reviewed in Weinberger and Diamond 1987; Weinberger 1995).

It is difficult, if not impossible, to represent the views, rationales, and experimental approaches of all other workers in this field at a level and depth equal to that of one's own predilections. Thus, there are bound to be many disagreements. The remedies are to attempt to be explicit and even-handed, goals that I have sought but cannot claim to have achieved. The larger solution is for all concerned to put forth their views on the same issues and to encourage readers to make their own comparative conclusions. In that spirit, we can move forward.

2. "Experience-Dependence" and Learning/Memory

2.1 Background

Consideration of experience-dependent effects on the auditory system (or any system for that matter) necessarily entails the field of the neurobiology of learning and memory. The rationale for an essential role for learning and memory begins with an explication of the normal meaning of "experience." "Experience" refers to the interaction of a waking, unanesthetized organism with its environment. The interactions may be very limited, such as the receipt of a

single brief acoustic stimulus, or practically unlimited, such as behaviorally dependent alterations in the reception of spectrally and temporally complex patterns of sound. An example of the former would be a sudden noise received by a stationary, awake (or even sleeping) animal. An example of the latter would be the fluctuations of simultaneously received species-specific and environmental sounds as an animal moves through space encountering various auditory scenes.

The fields of sensory neurophysiology and learning/memory have a unique relationship. They are both concerned with the processing of sensory stimuli in the brain, but from complementary points of view. Sensory neurophysiology has traditionally been interested in how the brain responds to variations in stimulus parameters, but not in how the brain changes when the behavioral significance of a stimulus changes. Conversely, learning/memory focuses on the latter, but not the former (Table 5.1). The two fields together provide for a compre-

TABLE 5.1. Complementary nature of the basic experimental paradigms of two disciplines within Neuroscience, Auditory Physiology *versus* Learning/Memory.

	Stimulus parameters	
Neuroscience disciplines	Physical	Psychological
Auditory physiology	Vary	Constant
Learning and memory	Constant	Vary

"Auditory Physiology" applies equally to other sensory systems. Both disciplines study information processing in the brain. Sensory stimuli have two basic parameters, physical and psychological. "Physical" refers to the parameters that are manipulated by changing the physical source of stimulation, for example, frequency (kHz), level (db SPL), and so forth. "Psychological" parameters refer to the acquired behavioral significance of stimuli, such as sounds. These parameters are not specified in physical units but rather by behavioral analysis, for example, the strength of a conditioned response to a given acoustic frequency. All sounds can be described by physical parameters and may also change (increase or decrease) in behavioral importance as a result of learning. Auditory Physiology varies physical parameters and determines the characteristics of neural response. To avoid incidental learning (e.g., habituation, etc.), the psychological parameters are kept constant, for example, by studying animals that are under general anesthesia. In a complementary manner, Learning/Memory experiments vary the psychological parameters by changing the relationships between stimuli (e.g., tone and food). These studies keep the physical parameters of stimuli constant, to permit interpretation of changed neural response as due to learning rather than to change in the stimuli themselves.

hensive analysis of the processing of sensory stimuli. However, they have developed separately, with little intersection until approximately the last 15 years (see Section 4). "Learning and memory" refer in the broadest sense to the acquisition and storage of information, respectively. "Acquisition" is the initial process of intake which has no fixed duration but is reasonably treated as the period of actual experience. Depending on the duration of an acoustic experience, the period of acquisition is generally seconds to minutes. "Storage" refers to the maintenance of information, from minutes to potentially a lifetime.

But why should experience-dependent auditory cortical plasticity entail learning and memory? The reason is that awake (even sleeping) organisms can acquire and store their experiences. Having received an acoustic stimulus, the resultant neuronal responses may result in nontransient changes in the brain; they may leave their mark. It matters not whether an investigator is overtly studying the acquisition and storage of information or is interested only in the immediate responses of neurons to a given set of acoustic stimuli. If the subject is not in a state of general anesthesia, it can potentially acquire and store everything about an experience. "Everything" includes at least (1) the detailed characteristics (parameters) of the sounds (e.g., spectrotemporal pattern, stimuli levels, locus in space), (2) the detailed nature of other more or less contemporary sensory (nonauditory) events (e.g, visual, somatosensory, olfactory, vestibular), (3) the organism's current physiological state (e.g., hungry, satiated, stressed); (4) the behavioral meaning, significance, or importance of the experience; and (5) integration of the new experience with prior, stored experience.

In other words, during the course of an experiment, when presumably the investigator seeks to acquire and store information about the subject's brain, the unanesthetized subject is likely to be learning and remembering as well. The critical question is how can investigators determine what the subject has acquired and stored (e.g., see Section 6.3.2). Before turning to this issue, we need to consider experimental approaches that are often thought to avoid the effects of learning and memory.

2.2 Possible Avoidance of Experience-Dependent Effects by General Anesthesia

For the neuroscientist interested in studying function without involving learning and memory processes, the occurrence of experience-dependent effects may constitute an unwelcome, and possibly unavoidable, variable. The use of general anesthesia may avoid experience-dependent effects. In particular, deep general anesthesia appears to be a state devoid of the chance for new learning and memory, unless particular hormonal events occur, such as a marked increase in levels of epinephrine (e.g., Weinberger et al. 1984a).

To avoid misunderstanding, it is important to undercut a false dichotomy, which is that data from anesthetized subjects are either superior or inferior to those obtained from waking animals. Some investigators consider that general anesthesia provides the only stable state in which acoustic processing can be

precisely studied; for many workers, the nonanesthetized state simply adds noise, increasing the difficulty of understanding the process in question. A related point in favor of general anesthesia is that it affords better stimulus control. Complete stimulus control in awake animals is more difficult to achieve than in anesthetized animals because a closed stimulating system, permitting calibration at the tympanic membrane, would produce undue discomfort or pain. In addition, anesthesia permits multiple invasive procedures not possible in waking animals. However, an alternative viewpoint is that although "anesthetized studies" form the bedrock of auditory neurophysiology, it is inescapable that the anesthetized brain is not in a normal state. After all, anesthetics are drugs. Thus, it has been argued that only the study of animals in a normal behavioral state can lead to a full understanding of auditory processing.

The stance taken here is that both approaches have their advantages and limitations, and that it is important to maintain a balanced view. The extent to which auditory processing is the same under anesthesia and the unanesthetized state can be determined only empirically. Given the subject matter of this chapter—experience-dependent plasticity—it is hardly surprising that most of the findings reviewed here arise from studies of unanesthetized subjects. Anesthesia should be appreciated as the important tool that it is. But while it can tell us much, perhaps most, about the processing of acoustic stimuli, it cannot tell us everything, particularly about the auditory cortex which is more severely affected by anesthesia than, for example, the eighth nerve. As reviewed in the following section, the fact of marked learning effects on the auditory cortex is itself adequate indication that a full understanding of the auditory cortex (and many subcortical components of the auditory system) cannot be achieved only from the study of anesthetized animals.

However, it would be wrong to assume that the anesthetized state is irrelevant to the study of experience-dependent plasticity. General anesthesia does not necessarily eliminate the effects of prior experience, but only the effects of experience during the state of anesthesia. Rather, as will be seen, the effects of learning that are established in the waking state can be expressed in the state of general anesthesia (e.g., Lennartz and Weinberger, 1992a; Recanzone et al. 1993). Moreover, the anesthetized state provides an excellent control for unwanted potential effects of changes in the level of arousal or excitability during the determination of the properties of neurons whose tuning and other response parameters have been altered by learning in the waking state. Thus, it may be particularly advantageous for the study of the effects of prior experience.

3. Detecting Learning and Memory

3.1 The Importance of Behavioral Assessment of Learning

Learning and memory ultimately must be validated behaviorally because of the essential distinction between neural plasticity and learning/memory. Although

it has become common for many neuroscientists to regard physiological plasticity as memory [e.g., long-term potentiation (LTP)], mechanisms of memory may involve one, or more likely, many types of neural plasticity. More importantly, learning and memory are behavioral constructs, valid at the level of the organism, not at the level of a brain structure or circuit. Learning and memory cannot be observed directly, but rather can be inferred only from the behavior of organisms under whatever experimental circumstances are set up to "interrogate" the subject. Learning and memory may be behaviorally silent unless the appropriate question is posed by the investigator, in the form of sensitive behavioral measures within the context of a relevant experimental design. Conflating neural plasticity with memory is conceptually fuzzy and experimentally confusing. One solution to this problem is to refer to brain processes that are candidates for the storage of some information as indexing "physiological memory," whereas genuine memory can be called "behavioral memory" (e.g., Weinberger 1998). Alternatively, appropriate neurophysiological changes may be referred to as "learning-induced plasticity." The important point is to avoid confusing neural plasticity with genuine memory.

The detection of learning and memory require the use of appropriately sensitive behavioral measures. We will focus on examples of classical (Pavlovian) conditioning and habituation, for two reasons. First, most studies on experience-dependent plasticity in the auditory cortex employ them. Second, experimental designs to study habituation and conditioning can be accomplished rapidly and in a wide variety of preparations, from humans to analogs of conditioning for in vitro preparations.

The context for this discussion is a "model" experiment, in which the investigator asks whether the development of plasticity in the auditory cortex accompanies learning. The critical issue for understanding experience-dependent effects on stimulus processing in the auditory cortex is not merely whether changes occur, but rather the extent to which learning has *specific vs. general effects.*

3.2 Habituation

Habituation, that is, learning that a repeated (usually unexpected or novel) stimulus is behaviorally unimportant, is perhaps the simplest example of the acquisition of information. Visual observation of an animal may reveal little or no change in overt behavior. However, the recording of autonomic responses, such as heart rate or blood pressure, would reveal a systematic change in response with stimulus repetition. Decrement of behavioral and neural responses does not distinguish habituation from fatigue or refractory-like processes, but demonstration of specificity of decrement to the repeated stimulus solves this problem. However, determination of specificity cannot be accomplished during stimulus repetition itself, but rather must be assayed after training. This is a crucial point that is elaborated in later discussion of experimental designs.

3.3 Classical Conditioning

Acquiring an association between two or more stimuli is a ubiquitous form of learning. Any regularly occurring sequences of two or more events allows for the learning of their relationship. Such associations are a basis for the common inference of cause–effect relationships (Rescorla 1988).

An accepted distinction is made between stimulus–stimulus associations and stimulus–response associations. The latter involve learning to make a particular behavioral response to a specified sensory stimulus. Obviously, stimulus–response learning should be easily detectable, because the second component is ordinarily an overt behavior. For example, pairing a tone with shock to the eyelid will come to produce an eyeblink to the tone itself. The detection of stimulus–stimulus (S–S) relationships may be more difficult but is of equal or greater importance because stimulus–stimulus associations appear to be involved in stimulus–response (S–R) associations. In the preceding example, animals learn that the tone signals the shock. Again, sensitive behavioral measures, such as heart rate, respiration, blood pressure, and pupillary dilation clearly validate the learning of an association between stimuli (e.g., the tone and shock). Moreover, this S–S learning develops more rapidly, in a few trials, whereas the eyeblink conditioned response may not be evident for 50 or more trials (reviewed in Lennartz and Weinberger 1992b). If one measured only eyeblink, one would conclude that learning had not taken place until the eyeblink conditioned response appeared. The initial S–S learning would go undetected. Moreover, as we will see later (Section 5.3.2.2), plasticity in the auditory cortex during conditioning develops in 5–30 trials, well in advance of S–R learning, such as the conditioned eyeblink response.

Given these basic aspects of learning and memory, it will be helpful to obtain a brief historical perspective on studies of learning in the auditory system. This will provide a context within which contemporary approaches and findings may best be considered, and perhaps appreciated.

4. A Brief History of Neural Plasticity in the Auditory Cortex

Neural plasticity in the auditory cortex is interesting not only in itself but also as a case study in the intersection of two scientific fields that had developed quite separately, those of sensory physiology and the neurobiology of learning and memory. Furthermore, this topic provides a clear example of how assumptions constrained thought and experiment for most of the 20th century. This is not merely of historical interest because differential approaches of auditory neurophysiology vs. learning/memory continue to influence, and in many instances plague, contemporary research. Finally, because the majority of studies on learning and sensory systems have been carried out in the auditory cortex, the

development of new ideas and findings in the auditory cortex has direct implications for studies of neural plasticity in other sensory systems.

The evolution of research on neuronal plasticity in the auditory cortex involves four stages: (1) sensory–motor framework excluding auditory cortex from learning and memory; (2) delineation of cortical responses to sounds in anesthetized animals; (3) documentation of plasticity during learning; and (4) discovery that learning systematically changes the basic acoustic parameters, such as frequency tuning, of neurons in the auditory cortex.

Attempts to understand the auditory cortex (as well as many other brain systems and structures) have their origin in the 19th century, within the framework of a sensory–motor conception of the nervous system. Following the early discoveries of Magendie and Bell of sensory and motor roots of the spinal cord (Cranefield 1974), much of the research program for the rest of the century concerned the extent to which the entire neuraxis was organized on sensory–motor principles (Young 1970). By the beginning of the 20th century, the sensory–motor principle had been extended from the spinal cord to the cerebral cortex. However, many regions of the cortex appeared to be neither sensory nor motor. Several of these were labeled "association cortex." The implication of this formulation was that the substrates of learning were to be found in the association cortex. Implicit in this schema was the assumption that sensory (and motor) regions of the cortex were not sites of information storage in learning and memory.

The availability of sensitive electronic amplifiers in the 1930s enabled scientists to record brain potentials that were elicited by controlled sensory stimuli, thereby initiating the modern field of sensory neurophysiology. In the auditory system, recordings in the 1940s by Woolsey and Walzl (1942) in the cat and by Tunturi (1944) in the dog delineated auditory cortical fields, in particular "tonotopic maps." Subsequent studies showed that single eighth nerve fibers exhibited specific tuning functions, responding best to one frequency [the "characteristic frequency" (CF) at threshold]. In the period immediately following World War II, auditory neurophysiology began a period of increasingly precise and sophisticated analysis of relationships between the full range of acoustic stimulus parameters and the responses of the auditory neuraxis, from the cochlea to the several fields of the auditory cortex.

The third stage, that learning induced auditory plasticity, may be dated from 1955. Robert Galambos and his colleagues performed a seminal experiment in which cats were classically conditioned by pairing an auditory conditioned stimulus (CS) with a puff of air [unconditioned stimulus (US)] to the face. Learning was validated by behavioral measurements. Evoked potentials 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 (Galambos et al. 1955).

However, these findings did not unequivocally demonstrate that the plasticity

was due to associative learning, because it could have reflected a general increase in excitability due to the presentation of the air puff ("sensitization"). Gluck and Rowland (1959) used a control that showed that plasticity developed only when a sound (CS) and a mild shock (US) were paired, not when the shock was present but not predicted by the sound. Another type of control to show associativity is the use of a two-tone discrimination protocol, in which one tone is followed by the US ("CS+") another tone ("CS−") is not followed by the US or any other stimulus (and the tone trials are presented in random order). Typically, both auditory plasticity and behavioral conditioned responses develop to the CS+ but not to the CS−.

Over the next decades, numerous additional studies in various animals and training situations demonstrated that the responses of the auditory cortex to sounds were affected not only by the physical sounds themselves, but also by the learned psychological or behavioral importance of acoustic stimuli (see Weinberger and Diamond 1987 for review). These findings clearly showed the error of the traditional belief that sensory cortices had purely sensory functions and were not regions directly involved in learning and memory.

However, the documentation of neural plasticity had little effect on the field of sensory neurophysiology, probably for several reasons. First, learning studies used only one or two tones, which were not interesting to sensory workers who used many stimuli. Second, there appears to have been conceptual confusion in which sensation was equated with perception so that the constructive aspect of the latter was not appreciated; hence plasticity of sensory responses was mistakenly seen as incompatible with perceptual accuracy. Neither was sensory cortical plasticity initially influential within the field of learning and memory itself. This relative neglect appeared to reflect the traditional belief in association cortex as sites of learning and memory on the one hand and emphasis on the hippocampus and other nonsensory structures on the other hand.

The fourth stage began in the mid-1980s, when studies of learning began to focus on obtained neurophysiological data that were commonly obtained in auditory neurophysiology. As this brings us to what may be described as the "Contemporary Era," we now proceed to a more detailed account of conceptual issues and empirical inquiries.

5. Experimental Designs and Findings

5.1 Introduction

An accepted canon of science is that experimental designs constrain possible results. Designs that do not include observations of certain variables cannot produce direct findings about these variables. Designs that do not adequately control for confounding variables are limited in their ability to determine the factors that produce the results. Within the present context, neural changes in the auditory system may be closely related to *what* the subjects learn, rather

than to the *mere fact* of learning itself. For example, if experimenters pair a tone with reinforcement and find increased responses to that tone in the auditory cortex, they may conclude that this plasticity reflects learning about the frequency of that tone. However, the subject may have learned only that a sound is followed by reinforcement. At the very least, one would have to employ tests with many frequency values across the spectrum to determine if the cortical plasticity is specific to the training frequency.

Several experimental designs have been developed to address the issue of learning-induced specificity of plasticity in the auditory system, primarily in the auditory cortex. These are illustrated in Figure 5.1 and are discussed in turn. But first, it is necessary to consider the standard design that accounts for perhaps more than 95% of all research on the auditory system and learning over the past 50 years, the "During Trial" design.

5.2 The "During" Training Trials Design (DUR)

This design consists of recording from the auditory system during the training trials employed in habituation, conditioning, or other types of training. It has provided the vast bulk of findings and firmly established that processing in the auditory system is subject to experience.

5.2.1 Disadvantages of Relying on Recording During Training Trials

Although this design is supported by common sense, it is far more limited than generally appreciated. The overall degree of specificity of learning effects in the auditory (or any other) system cannot be determined *during* the experience itself. There are two reasons. The first is almost trivially technical rather than conceptual. The second is of critical importance, woefully ignored or misunderstood, yet easy to grasp given minimal knowledge of basic principles of learning and memory.

5.2.1.1 Comparison Stimuli

The technical limitation is that the number of comparison stimuli is too small, in the limit only a single repeated stimulus or conditioned stimulus, in habituation or classical conditioning, respectively. Conditioning paradigms can be extended to become discrete discrimination paradigms, that is, two tones are presented. One (CS+) is followed by reinforcement (e.g., food or an aversive stimulus) and the other (CS−) is unreinforced. Development of a behavioral response to the CS+ but not the CS− is evidence of discrimination. This level of specificity also demonstrates that a genuine association had been established between the CS+ and the reinforcement. (In single-stimulus conditioning, a demonstration of association requires use of a control group in which the CS is randomly related to the reinforcer, with a resultant failure to establish a conditioned response to the stimulus.)

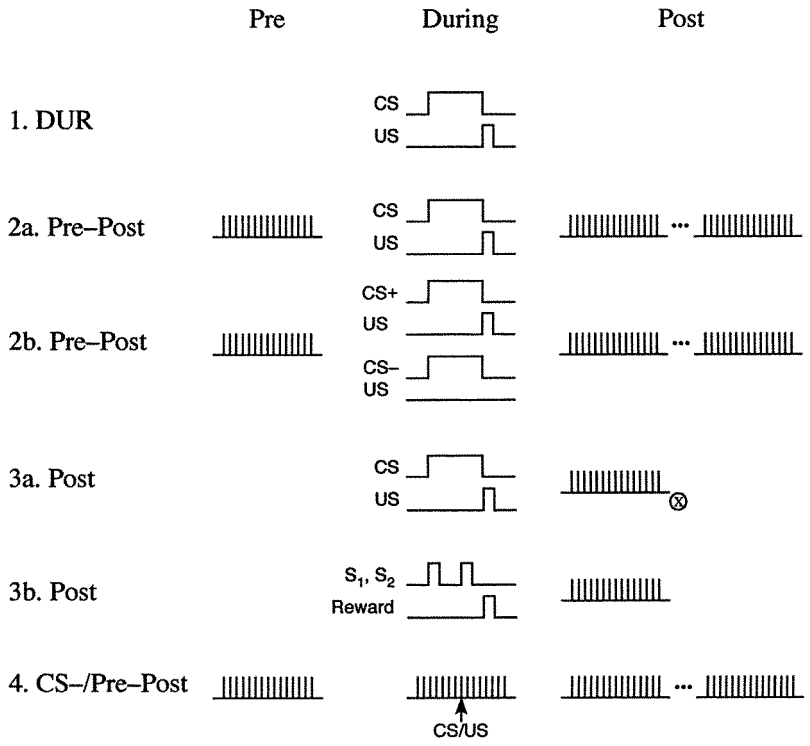

FIGURE 5.1. Schematic summary of experimental designs employed in the neurophysiological study of learning and the auditory cortex. Depicted are four basic designs (1–4) and their treatments during three experimental periods, "Pre" (before training), "During" (during training) and "Post" (after training). Pre–Post designs 2a and 2b illustrate the fact that any training paradigm can be used. Design 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. 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, that is, 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, and so forth. In 3a, the "x" in the Post period signifies sacrifice of the animal for 2-DG analysis following repeated presentation of a conditioned stimulus tone. In design 4, the "CS/US" denotes that one of the frequencies in a series of tone bursts is designated as the conditioned stimulus and is paired with shock; the serial order of tones is random from one sequence to another. Illustrations are not to scale.

5.2.1.2 Confounds by Performance Factors

The second, and more critical reason, is that the *state of a subject fluctuates during training trials.* All of the nonassociative variables that occur during training trials are referred to collectively as "performance factors," because they ultimately affect the performance, that is, "read out," of associatively based behavioral and neural responses, but do not change the underlying associations (e.g., Mackintosh 1974). Performance factors during training trials include changes in general arousal level, attention, and motivational factors induced by the training milieu, such as by the expected and actual presence of an aversive or appetitive reinforcer (i.e., punishment or reward). Within a training trial, changes in arousal can greatly affect both behavior and neural processing of stimuli, both for lowered arousal (e.g., due to reduced processing, inattention, etc.) and heightened arousal (e.g., due to distraction, stress, etc.). For the auditory cortex, there are numerous reports that arousal level and motivational state alter evoked potentials and unit discharges (e.g., Murata and Kameda 1963; Teas and Kiang 1964; Wickelgren 1968a; Molnar et al. 1988; but see Oatman 1971). Some of the confounds involve changes in activity of the middle ear muscles (e.g., Baust et al. 1964; Irvine and Webster 1972). Moreover, the degree of influence of nonassociative processes can vary during a learning situation as a subject itself acquires information about the learning context, the contingencies among stimuli, and so forth. The situation is complicated by the fact that investigators may not be able to control or even detect performance factors. For example, the release of stress hormones during learning may affect processing in the auditory system, as elsewhere in the brain.

These considerations and findings indicate that neural responses to a training stimulus during training trials are likely to reflect both direct associative processes and nonassociative performance factors. Thus, the sign and magnitude of change of neural response to a training stimulus should not be interpreted to exclusively reflect learning effects on the processing and representation of acoustic information. Moreover, it is clear that the assessment of learning by measurement of behavioral change during training trials also involves the same risks. A solution to this problem is to assess the effects of a training regimen after training has been completed. Specifically, groups that have been trained differently must be assessed under identical circumstances during post-training periods (Rescorla 1988) (see also Sections 5.3 and 5.4).

The use of a nonassociative control group (e.g., CS and US presented randomly) does permit workers to determine that neural effects obtained in the standard conditioning (paired) group are attributable to the pairing process itself. However, this does not eliminate the effects of performance factors in the paired group. Similarly, the use of a discrimination paradigm within the paired group (CS+ tone paired with reinforcer, CS− tone not followed by reinforcer) does allow one to conclude that neural changes to the CS+ are associative (require pairing). However, it does not eliminate the effects of performance factors on neural response to the CS+ or the CS− for that matter. Thus, even if the

number of different CS− tone frequencies were increased during training trials, in an attempt to determine specificity of plasticity (Section 5.5), performance factors could affect responses to any or all of these tones, as they do for a single CS+ and CS− tone.

In short, while one can detect changes in the response of the auditory cortex to, for example, the CS frequency during training trials, one can neither determine the *specificity* of the changes across the for example, frequency spectrum, nor be confident that the observed changes reflect *only the associative effects* of learning.

5.2.2 What Can We Deduce from Data Obtained During Training Trials?

The foregoing indicates that neural data obtained during training trials cannot be assumed to reflect only the influences of learning per se. This conclusion does not render such data without value but it does indicate that extreme caution should be exercised in their interpretation. If neuronal plasticity develops during training trials in one group compared to a nonassociative control group, then the fact of such plasticity, but not necessarily its magnitude or form, may be attributed to associative processes. Similar considerations apply to behavioral measures of learning. One can determine whether or nor behavioral signs of learning develop during training trials, but conclusions about form and magnitude need to be qualified. [Exceptions may apply to noncortical sites if they are little influenced by performance factors, for example, dentate/interpositus nuclei in direct stimulus–response eyelid conditioning, Thompson and Tracy (1995).] On the other hand, the absence of neural plasticity or a behavioral response might be due either to masking due to interference by performance factors, or to a failure to learn. Thus, as in other areas of science, interpretation of negative data presents problems. Nonetheless, while some authors assume that pairing a tone with a reinforcer produces associative learning, the actual development of an appropriate behavioral index is a sine qua non for the inference of learning and memory. This is particularly important because the training parameters sometimes used are known to be inappropriate to induce associative, for example, presenting trials at too rapid a rate.

5.2.3 Findings

The early and later use of the DUR design was discussed in the previous section on history, so the present discussion is brief. A detailed review has been provided previously (Weinberger and Diamond 1987). After the seminal study of Galambos et al. (1955), that inaugurated Western neurophysiological studies of learning in the auditory system, additional experiments were performed both for classical conditioning and also for habituation and instrumental conditioning in animals. Habituation studies reported systematic response decrements in AI in evoked potentials (Wickelgren 1968b) and unit discharges (Weinberger et al. 1975). The large majority of conditioning studies replicated and extended the findings of Galambos and associates. Over the next 30 years or so, evoked