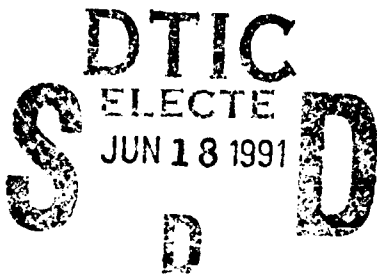

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"ADAPTIVE INFORMATION PROCESSING IN AUDITORY CORTEX"

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INTRODUCTION

Biological intelligence is the means by which the brains of animals acquire, store and use information to solve problems, to determine the causal fabric of the environment and to free organisms from being reflex machines, under the control of ambient environmental stimuli. Although it was long assumed that sensory systems were largely passive and not fundamental to biological intelligence, the discovery of adaptive information processing (AIP) in the auditory cortex rendered this view untenable (Diamond and Weinberger, 1986; 1989).

This report summarizes our further contributions to understanding adaptive information processing in the brain. Our approach has concerned four potentially important features of adaptive information processing in the auditory system: (1) Parallel Processing; (2) Regional Specificity; (3) Acquisition as distinct from Information Storage; (4) Local Circuit Functioning. The ultimate goal of this project is to achieve an understanding of adaptive information processing sufficient to serve as a foundation for the implementation of the biological principles and mechanisms so discovered, so that novel and powerful AIP machines can be built and effectively used. Although this project was of relatively brief duration, we have made considerable progress, as summarized in the following sections. However, first some background will be helpful.

BACKGROUND

Although previous workers had found that responses in sensory systems increase when animals learn that a stimulus signals reinforcement, it had long been thought that such facilitation indexed general increased arousal or vigilance during learning. For example, increased responses in the auditory cortex to sound were observed both when a conditioned stimulus (CS) was acoustic and when it was visual (Hall and Mark, 1967; Mark and Hall, 1967). The conclusion was that such facilitation was unrelated to the informational aspects of acoustic stimuli but rather indexed a general change of state.

However, a subtle but crucial assumption was that all facilitated responses represent the same underlying processes. How is it possible to determine if increased responses to an acoustic CS represent the same or different processes for different training circumstances? The combination of experimental techniques from the fields of sensory physiology and of learning and memory provided a solution. Two steps are necessary: conceptual and empirical.

The conceptual step is to think of the problem in terms of sensory system function as well as in terms of learning. When behavioral manipulations that modify sensory system activity are viewed from a sensory as well as a learning perspective, it becomes easier to see that understanding the effects of such manipulations requires the use of *many stimuli along a dimension* rather than a single stimulus value. A fundamental construct in sensory physiology is the receptive (RF) of a cell, i.e., that part of the relevant sensory epithelium which, when stimulated, affects the activity of a given sensory system neuron.

Seen from this perspective, it is evident that increased response to a sound could reflect either of two processes: (1) a general increase in neuronal excitability or (2) a highly-specific change in the coding and representation of stimuli.

The empirical step is then quite simple: determine the receptive fields of neurons before and after the behavioral manipulation(s). If the increased response to the CS is actually due to non-associative, general increases in some state of the organism, then responses to non-CS frequencies should also be increased. In contrast, if the increased response to the CS actually reflects the associative value of the CS, then responses to other frequencies will not be increased to the same extent. In short, a critical test is possible by the use of receptive field analysis when used in a hybrid learning-sensory physiology experimental design.

This type of experiment was first performed in this laboratory (Diamond and Weinberger, 1986; 1989). The receptive fields of cells in the secondary and ventral ectosylvian auditory fields were determined before and after classical conditioning, in this case, the rapid acquisition of the pupillary dilation response. The "adaptive information processing" hypothesis was supported: responses to the CS increased while responses to other frequencies often decreased. The CS frequency often became the new best frequency (BF). Moreover, this specific change in receptive fields (RFs) was retained unless behavioral extinction was accomplished.

EXPERIMENTS ELUCIDATING ADAPTIVE INFORMATION PROCESSING

Auditory Cortical Fields of Guinea Pig

As reported in ***Annual Report 1, covering the period 6/1/87-5/31/88*** (hereafter referred to as "**AR-1**"), we extended studies to the guinea pig *Cavia Porcellus* as a model system for combined behavioral and neurophysiological experiments. Previous studies had indicated that the guinea pig has two primary-like auditory fields. These are each organized tonotopically, on a rostral to caudal axis, but they are mirror images. The anterior field has low frequencies anterior, high frequencies posterior; the adjacent posterior field has the reverse frequency arrangement.

We undertook systematic mapping of the guinea pig cortical auditory fields using quantitative analysis of neuronal responses in the anesthetized (sodium pentobarbital and innovar) guinea pig. A major goal was to determine if there are systematic differences in parameters of frequency organization, e.g., threshold, bandwidth, etc., particularly for the anterior field. A tonotopic organization was validated for this field by multiple penetrations , with low frequencies anterior and high frequencies, posterior. Complete response areas (frequency vs intensity) were obtained for each site.

Frequency Specific Receptive Field Plasticity during Habituation

Associative learning produces conditioned stimulus (CS)-specific plasticity of frequency receptive fields (RFs) in non-primary auditory cortex of the cat; responses to the CS frequency are increased, whereas responses to other frequencies are decreased. This study determined the effects of habituation on the RF of neurons in the auditory cortex of the guinea pig, (**AR-1**). One frequency was presented repeatedly (REP) followed by redetermination of the RF. After REP, 26/36 (72%) RFs exhibited a substantial reduction (70-75%) of response to the repeated frequency, and this was highly specific (bandwidth less than 0.125 octaves). This RF plasticity involves an initial decrease in response during REP but does not require attenuated responses at the end of REP. Incubation (i.e., development over

time after cessation of REP) and long-term frequency-specific effects are evident (Condon and Weinberger, 1990; in press). Thus, habituation induces a specific change in the processing of frequency information rather than a general reduction in responsivity. In short, AIP applies to habituation as well as associative learning.

The Expression of Frequency Specific Receptive Field Plasticity Under Anesthesia

Does adaptive information processing store information in a way that permits retrieval under a variety of conditions, rather than only the circumstances in which it was acquired? This is very important because biological AIP might be very tightly linked to the circumstances of acquisition, and therefore more difficult to instantiate in a machine. Therefore, as reported in **AR-1**,we trained animals in the waking state (tone-shock pairing) and obtained RFs before, 1 hr. and 24 hrs. after training, while subjects were under deep barbiturate anesthesia. RFs were obtained from the medial geniculate body (MGB), the thalamic gateway to the auditory cortex. RFs were altered by conditioning, particularly with respect to the CS frequency. Increased responses were found at or near the CS frequency whereas responses to the pre-training BF were reduced. The pre-training BFs changed, mainly shifting toward the CS frequency. Moreover, the CS specific RF plasticity was present 24 hrs. later. (Lennartz et al, 1987; Lennartz and Weinberger, in preparation). In summary, these findings produce the first evidence that learning produces physiological plasticity that can be expressed in the anesthetized state. In short, AIP that operates during the waking state can have its effects "read-out" in another, very different state. These findings also attest to the robustness of AIP.

Classical Conditioning Induces CS-Specific RF Plasticity in Primary Auditory Cortex

If parallel processing is a fundamental characteristic of AIP, then it ought to develop not only in secondary auditory cortex (Diamond and Weinberger, 1986; 1989) but also in primary auditory cortex. Moreover, the discovery of AIP in primary auditory cortex would indicate that AIP is a very fundamental biological process, that is not restricted to "higher" cortical fields. To determine if classical conditioning produces general or specific modification of responses to acoustic conditioned stimuli in primary auditory cortex, frequency receptive fields of neurons in guinea pig auditory cortex were determined before and up to 24 hr after fear conditioning. As reported in **AR-1**, highly specific RF, plasticity characterized by maximal increased responses to the CS frequency and decreased responses to the pretraining BF and other frequencies, was observed in 70% of conditioning cases. These opposing changes were often sufficient to produce a shift in tuning such that the frequency of the CS became the new BF. CS frequency specific plasticity was maintained as long as 24 h. Sensitization training produced general increased responses across the RF without CS specificity (Bakin et al, 1988; Bakin and Weinberger, 1990). The findings indicate that associative processes produce systematic modification of the auditory system's processing of frequency information in primary auditory cortex, thus supporting the view that AIP involves parallel processing at the cortical level and extending AIP to the first level of cortical processing.

Facilitated Discriminative Avoidance Behavior

In order to explore the domain of tuning curve changes, as reported in **AR-1**, we trained guinea pigs in an instrumental avoidance situation to complement work

in classical conditioning. Guinea pigs were trained in a Brogden wheel using two tones and CS durations of 10 sec. We were able to facilitate two-tone discrimination by reducing responding to the CS- using a response-contingent paradigm. Responses during the CS+ produced termination of the stimulus and avoidance of shock. Responses to the CS- produced *another CS* (10 sec.) until animals no longer responded during this stimulus. In contrast to a control group (non-contingent), the experimental group exhibited superior discriminative performance.

Adaptive Information Processing in Auditory Cortex During Instrumental Learning

Also as reported in **AR-1**, we used the facilitated avoidance paradigm described above to determine whether AIP in auditory cortex develops for instrumental conditioning as well as for habituation and classical conditioning. Frequency receptive fields were obtained before and after successful avoidance training. The CS+ was selected as a frequency, often the best frequency, within the response area of the neuron. The CS- was selected in the initial study as a frequency to which neurons were minimally responsive. As for habituation and classical conditioning, avoidance conditioning resulted in *frequency-specific* modification of tuning curves. In particular, if the CS+ was also the best frequency then the major effect was a facilitation of response to the CS frequency (Bakin et al, 1988).

Neural Adaptive Information Processing: A Preliminary Model of Receptive Field Plasticity in Auditory Cortex

Based on our findings of adaptive information in the auditory cortex, plus relevant previous findings from our laboratory and those of other workers, we were able to formulate a comprehensive, testable model of AIP (Weinberger et al, 1990a, 1990b; Ashe and Weinberger, in press). We present here the basic model, which has been presented in less detail in **AR-2 (1988-89)**. A mathematical model based on this model is under development in collaboration with Dr. J. Sklansky, Dept. of Electrical & Computer Engineering, UCI (supported by DARPA).

COMPONENTS OF THE MODEL

The core of the model is that AIP in auditory cortex results from the coordinated action of three systems, each unique but complementary. These systems are characterized with respect to two dimensions: (1) degree of specificity of auditory information conveyed and (2) extent of physiological plasticity during learning. Each system has a root nucleus that is the basis of its projection to auditory cortex.

Ventral Medial Geniculate Nucleus: Auditory-lemniscal, Precise Projection to Auditory Cortex, Non-Plastic. This system projects precise information about the physical parameters of sound to auditory cortex in a point-to-point, tonotopic manner. Several laboratories have consistently failed to obtain discharge plasticity in the MGv (Weinberger and Diamond, 1987).

Magnocellular Medial Geniculate Nucleus: Auditory-nonlemniscal, Diffuse Projections to Auditory Cortex, Plastic. This system is concerned with information about the acquired significance of acoustic stimuli, but not about the precise physical parameters of sound. Its neurons are broadly tuned to frequency, and are bimodal, i.e., respond to somatosensory or noxious input as well as auditory input

(Erickson, Jane, Waite and Diamond, 1964; Lund and Webster, 1967; Poggio and Mountcastle, 1960; Wepsic, 1966). This is likely to be the basis for CS-UCS convergence and associative plasticity in the MGm. The MGm projects diffusely to all auditory cortical fields (Winer, Diamond and Raczwokswi, 1977). Replicable findings from several laboratories demonstrate that the MGm does develop discharge plasticity during classical conditioning (Weinberger and Diamond, 1987).

Nucleus Basalis of Meynert: Non-auditory, Cholinergic Projections to the Cerebral Cortex. Neurons in the NBM respond to sensory stimulation in behaving animals but they are poly-modal and definitely are not restricted to acoustic stimuli (Richardson, Mitchell, Baker and DeLong, 1988). Its cortical projections are global and extend across most of the cortical mantle; they are not confined to auditory cortex. NBM neurons appear to develop discharge plasticity during learning (Burton, Rolls and Mora, 1976; Mora, Rolls and Burton, 1976; Rolls, Sanghera and Roper-Hall, 1979). It appears that the majority of cholinergic synapses are located on the dendritic shafts of pyramidal (P) cells (Houser, et al., 1985) such that an ACh-induced increase in input resistance would be to increase the time and space constants of P cells (Shepherd, 1988). Thus, other synaptic inputs would be integrated over a longer time, providing additional opportunity for temporal summation. Also, a given synaptic input would produce a larger voltage change in the post-synaptic target following ACh-induced increased input resistance. Therefore, ACh could "amplify" the effects of MGm input on distal dendrites, increasing its influence on the probability of discharge of a P cell.

Auditory Cortex: Pyramidal cells are likely to be some if not all of the population modified by learning because the laminar distribution of plasticity is consistent with pyramidal cell involvement (Diamond and Weinberger, 1984) and microelectrode recordings are heavily biased toward

Amygdala: A link between conditioning-dependent plasticity in the magnocellular medial geniculate body and the nucleus basalis may be provided via the central nucleus of the amygdala (ACE). First, the MGm projects to the lateral amygdala that in turn projects to the ACE (Kapp, Gallagher, Applegate and Frysinger, 1984; LeDoux, Ruggiero and Reis, 1985) . Second, amygdala-dependent behavioral conditioned responses to acoustic (but not visual) stimuli are abolished by lesions of the MGm (Jarrell, Gentile, McCabe and Schneiderman, 1986a; Jarrell, Romanski, Gentile, McCabe and Schneiderman, 1986b; LeDoux, Sakaguchi and Reis, 1984). Third, lesions of auditory cortex do not alter such conditioned responses (LeDoux, et al., 1984). Fourth, the ACE projects to the NBM (Krettek and Price, 1978; Price and Amaral, 1981; Russchen, Amaral and Price, 1985). Fifth, neurons in the NBM respond selectively to stimuli (conditioned stimuli or unconditioned stimuli) that activate ACE cells (Burton, et al., 1976; DeLong, 1971; Mora, et al., 1976; Richardson, et al., 1988). Therefore, learning-induced changes in response to acoustic stimuli in the MGm may produce changes in NBM discharge via the amygdala.

MODIFICATION OF SYNAPTIC STRENGTHS

We propose that the frequency-specific information provided by the MGv to P cells is modulated by the auditory-significant information provided by the MGm. From this point of view, the pyramidal cells of auditory cortex are the first neurons in which information about both the frequency and the acquired signal value or significance of the same stimulus come together. During classical conditioning, the MGv output to the cortex does not change, but the synaptic strengths of MGv effects

on pyramidal neurons are modified during learning; inputs that carry CS frequency information are strengthened while non-active inputs (those for other frequencies not presented as the CS) are weakened. The MGm excitatory effects on pyramidal cells should increase across trials, since neurons in this nucleus do develop physiological plasticity during conditioning. The NBM, is hypothesized to play a critical role in amplifying the MGm effects to induce long-term changes in synaptic strengths. That is, by releasing ACh in the auditory cortex, the NBM serves as the "record now"mechanism for long term memory. This increased release of ACh is presumably due to the conditioned increase in MGm discharge via the MGm ->amygdala -> NBM circuit.

Changes in synaptic strengths are hypothesized to depend upon two modified Hebbian rules (Baranyi and Szente, 1988; Fregnac, Shultz, Thorpe and Bienenstock, 1988; Gustafsson and Wigstrom, 1988; Reiter and Stryker, 1988).

(I) If the post-synaptic cell is active when pre-synaptic input is present then synaptic strength is increased.

(II) If the post-synaptic cell is active when pre-synaptic input is absent then synaptic strength is weakened . The term "active" refers to a state of increased excitability, not restricted to cellular discharge.

We add one corollary: The amount of change in synaptic strength is directly proportional to the degree of post-synaptic excitability.

SEQUENCE OF EVENTS

The acquisition of information about the physical parameters and the behavioral significance of an acoustic stimulus, including CS-specific changes in frequency receptive fields, could come about as follows.

a. The MGv specifies the physical (e.g., frequency) parameters, providing such information to pyramidal cells (and others not considered here) whose current receptive field includes the frequency of the conditioned stimulus. Output of the MGv to the auditory cortex is not changed during learning but its effect on pyramidal cells is changed.

b. The MGm specifies the importance of the stimulus. The first neural change during conditioning is hypothesized to be the induction of plasticity due to convergence of CS and UCS inputs in this nucleus. Effectively, its output message to the auditory cortex is the equivalent of the presence of the unconditioned stimulus (UCS), moved up in time so that it coincides with the presence of the CS rather than with the presence of the UCS. In short, the MGm mechanism converts a non-auditory UCS which occurs following the CS into an auditory-coded representation of the anticipated UCS. The auditory modality-specific nature of the MGm means that there is a general increase in pyramidal cell excitability within and between all auditory cortical fields; our concern at this point is with primary tonotopic auditory cortex.

There is convergence of the MGv input (from neurons responding to the frequency of the conditioned stimulus) with the MGm increase in excitability. Convergence occurs only for a subset of auditory cortical pyramidal cells, that is, for those neurons that receive input from the CS frequency. Pre-synaptic inputs initiated either indirectly via a stellate cells or directly from the MGv will be strengthened, according to by Rule (I). In contrast, by Rule (II) all other pre-synaptic inputs, for frequencies not present as the conditioned stimulus, will be weakened.

However, by themselves, MGm inputs are likely to produce only a small increase in pyramidal cell excitability because of their distal location on dendrites, as explained above. Corollary (A) suggests that an amplification of the MGm effect would produce larger changes in the synapses that are concerned with frequency information. We suggest that the role of ACh is to amplify the MGm effects.

c. The nucleus basalis of Meynert facilitates synaptic transmission in auditory cortex. That is, the NBM increases release of ACh in response to the plasticity that is rapidly expressed in the MGm during conditioning. This occurs via the amygdala which is "driven" by the MGm. This release of ACh in the auditory cortex would produce increased input resistance, including effects on the dendrites of pyramidal cells. As pointed out above, increased input resistance would produce an increase in the time constant and effectively increase the length constant of the target neurons. Consequently, weak excitatory MGm inputs would be amplified. Thus, the MGm input to pyramidal cell dendrites would increase post-synaptic excitability and thus provide the basis for changing the strength of inputs concerned with frequency information.

CONCLUSIONS

This model accounts for all relevant findings and shows how the distribution of various properties to different components of the auditory system and related forebrain structures are integrated to produce AIP. Preliminary machine designs, based on this model, are encouraged.

Adaptive Information Processing in the Auditory Thalamus

In order to fully understand AIP in the auditory cortex, it is necessary to determine the processing at its inputs, the medial geniculate body. We therefore undertook and completed studies of RF plasticity during conditioning or sensitization training in the three subdivisions of the MGB, the dorsal, ventral and medial divisions.

Subcortical Adaptive Filtering in the Auditory System: Associative Receptive Field Plasticity in the Dorsal Medial Geniculate

As reported in preliminary form in **AR-2**, highly specific subcortical receptive field (RF) plasticity was found in the dorsal division of the guinea pig medial geniculate body during cardiac conditioning to a tonal frequency. There was increased response to the conditioned-stimulus (CS) frequency, and there were decreased responses to adjacent frequencies, especially at the pretraining best frequency (BF), which often resulted in a shift of tuning such that the CS became the new BF. Moreover, 1 hr later the effects were stronger, more sharply tuned, and centered on the CS frequency. A sensitization paradigm produced only broad, general increases of response across the RF (Edeline and Weinberger, 1989; 1991)

Thalamic Short Term Plasticity in the Auditory System: Associative Retuning of Receptive Fields in the Ventral Medial Geniculate Body

Classical conditioning induces highly specific plasticity in the receptive fields (RF) of neurons in the auditory cortex (Diamond and Weinberger, 1986; Bakin and Weinberger, 1990) and in the dorsal division of the medial geniculate body (Edeline and Weinberger, 1990). We report here the effects of classical conditioning on frequency RFs in the ventral, tonotopic part of the guinea pig medial geniculate

body (MGB). Frequency RF were determined before, immediately post, and 1 hour post-conditioning (tone-footshock training that produced the cardiac deceleration conditioned response). Associative frequency-specific plasticity, in which the receptive field was retuned to the frequency of the conditioned stimulus, developed if the CS frequency was within 1/8 octave of the pre-training best frequency. Otherwise, a general increase across the RF developed. Sensitization training also produced general increased responses. The frequency-specific plasticity was short-term, being observed only immediately after training whereas the general effects were maintained. These results suggest that frequency-specific RF plasticity in the MGv may be a substrate of short-term mnemonic processes that could participate in long-term storage of information and modification of the representation of the CS at the auditory cortex. General increases may reflect overall facilitation of sensory responsivity, engendered by the relationship between background contextual cues of the training environment and the negative reinforcement (Edeline and Weinberger, 1991, in press).

Adaptive Information Processing in the Diffuse Thalamic Auditory System: Associative Retuning of Receptive Fields in the Medial Division of the Medial Geniculate Body

The medial division of the medial geniculate body (MGB) is the part of the auditory thalamus that projects both to the auditory cortex and to the amygdala. In the present experiment, we analysed the effects of classical conditioning (tone followed by a footshock) on receptive fields of neurons in the guinea pig medial MGB. After associative training, during which conditioned bradycardia indexed the acquisition of the CS-US relation, 48% (14/29) of the recordings showed a specific increased at the CS frequency. A sensitization paradigm never induced frequency-specific effects in the RFs, but generated general increased (8/13 recordings, 62%) or general decreased responses (5/13 recordings, 38%) across the RFs. Two major characteristic were observed for these CS-Frequency Specific increases. First, the probability of observing such effect was higher the in the rostral part than in the caudal part of the nucleus (66% vs. 28%). Second, there was a differential evolution of the CS-FS increases depending on the initial breadth of the tuning : the effects regressed (i.e. became smaller and less selective) for narrowly tuned cells; but developed (i.e., became greater and more selective) for broadly tuned cells. These results show that receptive field analysis provides rules to understand and predict how AIP occurs (Edeline and Weinberger, 1990; in preparation).

Response Properties of Single Neurons Within Clusters in Inferior Colliculus and Auditory Cortex

"Cluster" recordings ("multiple unit activity"), consisting of the discharges of several neurons, are widely employed. However, the extent to which individual cells within a cluster have the same response characteristics has received little, if any, study. This is critical information for understanding local circuit processing. In barbiturate-anesthetized guinea pigs, the responses of neuronal clusters to contralateral tone stimulation were obtained using tungsten microelectrodes (tips 1-3 microns, impedances 1-2 megohms). On-line separation of single unit waveforms was achieved for 2-4 neurons per cluster (central nucleus of inferior colliculus: 16 clusters, 38 cells; primary auditory cortex: 25 clusters, 60 cells) using a computer algorithm that included waveform confidence limits. Response characteristics

included best frequency (BF), bandwidth, and discharge pattern. For both the ICc and ACx, differences in one or more characteristics were found in approximately 1/3 to 3/4 of the clusters, including BF differing by at least 0.5 octaves (**AR-2**). These findings indicate that cluster recordings usually consist of the discharges of neurons that have one or more different response characteristics. This local circuit property, in which neighboring cells have similar, but not identical characteristics, is thought to be the basis for the plasticity which underlies AIP (Hui et al, 1989).

Responses of Single Auditory Cortical Neurons to Tone Sequences

The responses of single neurons in the primary and secondary auditory cortex of cat were recorded during the presentation of sequences consisting of five tones of different frequencies to determine if neurons code for temporal as well as frequency parameters of sound. Discharges to tones within these sequences usually (84%) exhibited a dependence on the 'direction' of the sequence (ascending, descending, or mixed frequencies). For sequences consisting of 5 tones of identical frequency (monotone) the response often depended on serial position, including cases in which the neuron only responded to later tones in the sequence. Comparison of responses to heterogeneous and monotone sequences showed that response dependence on serial position was a factor in response dependence on sequence direction. Auditory cortical neurons can exhibit stronger responses to a tone presented in a sequence than to the same tone presented alone. Hence, the responses to tones within sequences may not be highly predictable from the responses to isolated tones (Weinberger and McKenna, 1988; McKenna et al, 1989).

Cholinergic Modulation of Responses to Single Tones Produces Tone-Specific Receptive Field Alterations in Cat Auditory Cortex.

Acetylcholine (ACh), acting via muscarinic receptors, is known to modulate neuronal responsiveness in primary sensory neocortex. The administration of ACh to cortical neurons facilitates or suppresses responses to sensory stimuli, and these effects can endure well beyond the period of ACh application (McKenna et al, 1988). In the present study, we sought to determine whether ACh produces a general change in sensory information processing or whether it can *specifically* alter the processing of sensory stimuli with which it was "paired" (**AR-2**). To answer this question, we restricted acoustic stimulation in the presence of ACh to a single frequency, and determined single neuron frequency receptive fields in primary auditory cortex before and after this pairing. During its administration, ACh produced mostly facilitory effects on spontaneous activity and "on" responses to the single frequency tone. Examination of frequency receptive fields after ACh administration revealed receptive field modifications in 56% of the cells. In half of these cases, the receptive field alterations were highly specific to the frequency of the tone previously paired with ACh. Thus ACh can produce stimulus-specific modulation of auditory information processing (Metherate & Weinberger, 1990). An additional and unexpected finding was that the type of modulation during ACh administration did not predict the type of receptive field modulation observed after ACh administration; this may be related to the physiological "context" of the same stimulus in two different conditions (Diamond & Weinberger, 1989). These findings support our model of AIP in the auditory cortex.

M_1 and M_2 Muscarinic Receptors Mediate Acetylcholine (ACh) Modulation of Auditory Cortical Neurons

ACh modifies the activity of auditory cortical neurons via muscarinic receptors (McKenna et al, 1988). This experiment concerned the involvement of M_1 and M_2 muscarinic receptor subtypes in the effects of ACh. In barbitutate-anesthetized guinea pigs, iontophoretically-applied ACh modified intensity functions (IFs) at best frequency by facilitating or depressing tone-evoked activity. Facilitation of evoked responses could decrease IF thresholds by over 10dB. To examine mechanisms underlying multiple ACh effects, we applied the muscarinic receptor antagonists pirenzepine and gallamine to 14 cells whose single tone responses were modified by ACh. ACh-induced facilitation of spontaneous or evoked activity was antagonized more effectively by pirenzepine than by gallamine. However, gallamine effectively blocked ACh depression of activity. As pirenzepine and gallamine are selective antagonists at muscarinic M_1 and M_2 receptors, respectively, these initial findings suggest that the modulatory effects of ACh in auditory cortex involve both receptor subtypes (Metherate et al, 1989).

Classical Conditioning Selectively Alters Thresholds in the Auditory Cortex of the Guinea Pig

Classical conditioning produces frequency-specific plasticity in the auditory cortex. Specifically, responses to the frequency of the conditioned stimulus (CS) are increased while responses to other frequencies, including that of the pre-training best frequency (BF), are reduced (Bakin and Weinberger, 1990). The purpose of this experiment was to determine whether classical conditioning alters thresholds. Conditioning consisted of presentation of a tone (6 sec.) and footshock (0.3 sec.) unpaired (sensitization control) or paired (conditioning) during the development of the cardiac deceleration conditioned response. Thresholds were determined before and after training (immediate, 1 hour and 24 hours) at the frequency of the conditioned stimulus and the frequency of the pre-training characteristic frequency (frequency with lowest threshold, CF). Following training, thresholds were changed, with the dominant effect consisting of a relative change between the frequency of the CS and the CF such that thresholds to the former were lowered relative to the latter. These findings indicate that classical conditioning can produce a relative decrease in threshold for a stimulus that has acquired behavioral significance and a relative increase for a potent stimulus that is not involved in training. Thus, learning alters thresholds as well as response magnitudes of neurons within the auditory cortex (South et al, 1990).

Sensitization Produces Non-Specific Increased Responses of Receptive Fields in Guinea Pig Auditory Cortex

Previously we reported that classical conditioning produces frequency-specific receptive fields (RF) plasticity in the auditory cortex of the guinea pig (Bakin, and Weinberger, 1990). Following tone-shock pairing until development of behavioral conditioned responses (CR), 70% of single neurons or neuronal clusters showed maximal increased responses to the CS frequency, while responses to the pre-training best-frequency (BF) and other frequencies exhibited decreased responses. These effects were observed immediately and at the longest post-conditioning

interval tested, 24 hours. The present experiment determined the effects of sensitization training on receptive fields. Training consisted of unpaired presentation of 30 trials in which a non-best frequency tone or light (10 sec) and footshock (2 sec) were presented with the same density as during conditioning. RF were obtained prior to training and immediately, 1 hr and 24 hours following training. Sensitization training produced no behavioral CRs and a general increased response across the RF, with no specificity to the CS frequency both for auditory and visual sensitization. Such non-specific RF plasticity was present immediately and for as long as 24 hours post-training. These results indicate that sensitization can produce a long-lasting general facilitation of acoustic processing in distinction to classical conditioning which produces a highly CS-specific modification of frequency receptive fields. Moreover, this sensitization effect is not induced by acoustic stimulation during training because the same effect is produced by the use of visual stimulus unpaired with shock. The general increase in RFs is probably due to fear of the training context (Bakin and Weinberger, 1990)

Excitability and Frequency Tuning in the Guinea Pig Medial Geniculate Body.

Excitability changes following an acoustic stimulus involve periods of inhibition and facilitation in the medial geniculate body (MGB) but their relation to other major features of auditory information processing is largely unknown. To determine if frequency tuning is related to tone-evoked excitability patterns, measures of both were obtained from single neurons in the MGB of anesthetized guinea pigs. Tuning was determined by measuring bandwidth (20dB above threshold, square-root transform of range to eliminate frequency bias, (Calford et al, 1983). Excitability was determined by presenting pairs of tones at or near the characteristic frequency (20dB above threshold, 50 ms, 15-2000 ms intervals). As revealed by responses to the second tone, the first tone usually produced varying duration periods of suppression and facilitation. For each neuron, an index of excitability change was computed and correlated with tuning bandwidth. A significant negative correlation was obtained; cells with the greatest excitability (sometimes including no suppression even at the 15 ms interval) had the narrowest frequency bandwidth. These findings suggest that the most narrowly tuned neurons can process frequency information with the highest degree of reliability and that two-tone excitability functions may provide a convenient index of the degree of "lemniscal" properties (Lennartz and Weinberger, 1990). Since narrowly tuned cells do not retain CS-FS plasticity, we have a physiological predictor of AIP retention: lower excitability predicts broader tuning, and therefore better retention.

SUMMARY

Having discovered that biological intelligence involves adaptive information processing in the acquisition of information concerning acoustic stimuli, we have investigated the extent to which AIP is based on (1) parallel processing, (2) regional specificity, (3) acquisition vs. retention and (4) local circuit functioning. It is now clear that AIP, as indexed by signal-specific receptive field plasticity, is based upon each of these characteristics of real biological computing. Frequency-specific receptive field (CS-FS) plasticity develops in parallel in both primary and secondary

auditory cortical fields and in all three of the MGB subdivisions that are the major inputs to these fields. However, there is regional specificity for each locus of CS-FS plasticity. Moreover, the substrate of AIP appears to involve local circuit variability in the processing characteristics of neighboring neurons, such that informational aspects of the environment can selectively enhance or suppress various parameters of stimulus representation. That is, the inherent variance among neighboring cells is probably the basis on which selective processes can operate to produce systematic plasticity of receptive fields. The regional specificity is evident along several dimensions: tuning bandwidth, complexity of tuning functions, degree of retention and linkage to extra-auditory, modulatory systems. Moreover, the modulatory mechanisms for AIP have been identified as including at least the muscarinic cholinergic system . Our model of AIP easily incorporates new findings on CS-FS plasticity in the MGB, such that the thalamo-cortical system is an interactive substrate for AIP, rather than a "reflex chain" organization. The lemniscal MGv maintains its role as providing accurate information about the physical parameters of acoustic stimuli, acting adaptively only very briefly to facilitate probable strengthening of CS synapses in the auditory cortex. In contrast, the diffusely projecting MGm probably initiates immediate behavioral responses to signal stimuli, via its link to the amygdala, induces the release of ACh in the cortex and directly provides the post-synaptic cortical activation that alters synaptic weights across the frequency domain. The complete and detailed acquired information about both the frequency parameters and the behavioral significance of acoustic stimuli, is probably stored where it is fully processed, in the auditory cortex. The results of this project have provided adequate basis for the formulation of testable mathematical models and for the initiation of designs for AIP machines based on biological intelligence.

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