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ACOUSTICALLY EVOKED POTENTIALS IN THE RAT DURING CONDITIONING

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Robert D. Hall and Roger Greenwood Mark

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Abstract

Acoustically evoked potentials were recorded from unanesthetized rats in a series of experiments designed to study changes in sensory evoked potentials during conditioning. It is shown that when clicks are established as conditional stimuli (CS) in conditioned emotional response (CER) situations, click-evoked potentials recorded from central auditory structures and from mesencephalic reticular formation exhibit appreciable amplitude increases. Similar increases were found with Sidman avoidance conditioning. These changes in evoked potentials during aversive conditioning were not related to acquired discriminative or conditional properties of the acoustic stimulus, since similar changes in click-evoked potentials were found when a CER was brought under control of a photic CS. These alterations in click-evoked potentials were shown to be independent of movement or movement-related variables. Potentials evoked in central auditory structures by electrical stimuli applied to the cochlear nucleus or within the cochlea also revealed increases in amplitude during acquisition of a CER. In one experiment nearly all movement was eliminated in both CS and control conditions through methods of behavioral control. Data-sampling techniques provided a further control for residual differences in amount of movement in the two periods. These procedures did not eliminate increases in amplitudes of click-evoked potentials during aversive conditioning.

In general, whenever behavioral measures indicated that rats were frightened, acoustically evoked potentials evidenced increased amplitudes, whether or not a CS was present. In all experiments only changes in late components of acoustically evoked potentials were consistently related to observed behavioral changes. It is concluded that changes in sensory evoked potentials observed during conditioning are not related to what may be considered the neural substrate of conditioning, but, in aversive conditioning situations at least, they are associated with fear elicited initially as an unconditioned response to noxious stimulation and later as a conditioned response.

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I. INTRODUCTION

The search for neuroelectric correlates of conditioning may be traced to the first report of a conditioned alpha block by Durup and Fessard,²⁰ in 1935, but with a few notable exceptions this endeavour belongs to the last decade. Experimental work with animals had to wait upon adequate techniques for the permanent implantation of electrodes. General improvements in electrophysiological methods and instrumentation have also helped to make this work feasible. At last, though hardly least, the computer, within very recent years, has added new dimensions to brain research with the behaving organism.

A review of the entire literature concerned with neuroelectric correlates of conditioning is clearly beyond the scope of this experimental report. For a most comprehensive and relatively recent review the reader may wish to consult Morrell.⁶² The published proceedings of several international symposia also provide interesting and representative cross sections of research on the electrical activity of the brain during conditioning.^{18, 24, 37, 50} Our attention here will be confined to changes in sensory evoked potentials observed during conditioning.

1.1 CHANGES IN SENSORY EVOKED POTENTIALS OBSERVED IN CLASSICAL AVERSIVE CONDITIONING STUDIES

Galambos and Morgan³² describe an experiment by two Russian workers, Artemyev and Bezladnova,³ which to the best of our knowledge is the first report of alterations in evoked potentials related to conditioning. (We make a distinction between sensory activity evoked by "flickering" stimuli that may "drive" neural potentials, and evoked responses to stimuli presented at sufficiently low repetition rates to preclude appreciable interactions between successive evoked responses.) Artemyev and Bezladnova employed tone bursts of 1.3-sec duration as conditional stimuli (CS) for a leg flexion response in cats. The unconditional stimulus (UCS) was an electric shock to the paw. The potentials evoked by the tone bursts were monitored on an oscilloscope, and electromyograms from the leg muscles provided a measure of the conditioned response (CR). As the CR developed, it was accompanied by an increase in the percentage of evoked responses that were detectable in single oscilloscope traces, and thus signified an increase in amplitude of these potentials. With extinction the potentials reverted to preconditioning levels.

The first report of similar findings from American laboratories was that of Galambos, Sheatz, and Vernier.³⁰ In this study, electrodes were permanently implanted in cochlear nucleus, auditory and visual cortex, septal area, hippocampus, amygdala, and caudate nucleus of cats. During a preconditioning period the subjects were habituated to click stimuli presented day and night at a rate of 1/3 sec for "many days or weeks." In the conditioning phase of the experiments that followed, approximately 10-20 electric shocks were presented to the chest contiguously with random clicks.

Evoked potentials recorded during this procedure were compared with potentials recorded before conditioning and with those recorded during an extinction period that followed. No systematic behavioral measures were reported, but crouching, snarling, twitching or similar responses to the click CS were regarded as evidence of conditioning. It was found that amplitudes of click-evoked potentials decreased during the long habituation period, increased when the clicks were "paired" with shock, and fell to preconditioning levels during extinction. Additional experiments were performed with cats paralyzed with Flaxedil in order to determine if the changes in evoked potentials were related to movement. Similar changes were found in the paralyzed cats.

Following this initial report, Galambos and various co-workers have published a series of papers confirming the original findings.^{27, 28, 34, 41, 59, 63} Both cats and monkeys were employed as subjects in this series of experiments. In all of these studies trains of clicks or tone bursts were used as conditional stimuli. The CS was followed by shock or, in the more recent experiments, by puffs of air to the subject's face. The subjects were always exposed to the auditory stimuli for long periods preceding the conditioning phase of an experiment; and in general, evoked potentials were found to undergo appreciable reductions in amplitude during these habituation periods. Pairing of the acoustic stimulus with a noxious one consistently led to increases in the amplitudes of acoustically evoked potentials. This was true for potentials recorded from several locations in the classical auditory projection and for potentials recorded from other CNS locations. The latter included hippocampus, caudate nucleus, reticular formation, dorsal midbrain tegmentum, habenula, cingulate cortex, and field of Forel. Auditory structures that yielded larger evoked responses with conditioning included cochlear nucleus, trapezoid body, superior olivary complex, inferior colliculus, medial geniculate body, and auditory cortex.

In the study by Moushegian, Rupert, Marsh, and Galambos,⁶³ changes in amplitudes of click-evoked cortical potentials during habituation and conditioning were found in four cats with severed middle-ear muscles. A report by Hugelin, Dumont and Paillas⁴⁷ had suggested that middle-ear muscles might play a role in the modification of acoustically evoked potentials during attentive behavior. In *encéphale isolé* cats it had been found that electrical stimulation of the reticular formation led to reductions in amplitudes of auditory cortical potentials. This effect could not be reproduced in animals with severed middle-ear muscles. The report by Moushegian et al. and the earlier one by Galambos, Sheatz, and Vernier seem to rule out middle-ear muscle activity as the explanation for changes in acoustically evoked potentials during conditioning, since the alterations were found in animals with severed middle-ear muscles and in animals paralyzed with Flaxedil.

Galambos and Sheatz³⁴ have noted that acoustically evoked potentials recorded from many sites in the central nervous system, auditory and "nonauditory" alike, assume essentially the same waveform when the acoustic stimulus has been established as a conditioned one. They have described it as a triphasic response: a positive potential

followed by a negative wave and a second positive wave. Increased similarity in wave-forms effected through conditioning has also been reported by John, Ruchkin, and Villegas.⁵¹

Among the earliest reports of alterations in sensory evoked potentials related to conditioning was a paper by Jouvét and Hernández-Peón,⁵³ first presented in 1955 at the Fifth Marseille Colloquium of the International Federation of Electroencephalography and Clinical Neurophysiology. The conditioning phase of this study was a logical extension of the authors' work on changes in sensory evoked potentials during habituation and attention, also treated in the same paper, and described in other publications of the same period.^{44, 45} We shall defer discussion of the work on habituation and attention and consider only that part of the study concerned with conditioning.

Jouvét and Hernández-Peón employed a tone burst of 2500 cps and 2.0-sec duration as a CS. This was followed by the UCS, a shock to the paw. The subjects were cats with permanently implanted electrodes in cortical and subcortical structures. These included primary auditory cortex, reticular formation, and that part of somatic, sensorimotor cortex serving the limb involved in the conditioned response. Electromyograms from the subject's leg provided a measure of the CR. With acquisition of the CR, amplitudes of evoked potentials recorded from auditory cortex increased. Moreover, potentials evoked by the auditory CS were also recorded from somatic cortex. With extinction, evoked potentials from auditory cortex diminished, while those recorded from somatic cortex could no longer be discerned in the EEG. Reconditioning returned the potentials to amplitudes seen during the initial conditioning.

The report by Hernández-Peón, Jouvét and Scherrer,⁴⁵ concerned mainly with habituation of evoked potentials, also described a conditioning experiment with cats in which amplitudes of acoustically evoked potentials increased when a tone-burst CS was paired with shock to the paw. Other reports by Hernández-Peón and his co-workers have described similar changes in evoked potentials recorded from the visual pathway and reticular formation when photic stimuli were employed as conditional stimuli in classical aversive conditioning situations.^{43, 66}

An early report by Buser, Jouvét, and Hernández-Peón¹¹ described a variation on the modification of sensory evoked potentials during conditioning. In this experiment with three unanesthetized cats, the "excitability cycle" of mesencephalic reticular formation was altered by conditioning procedures. Potentials evoked by pairs of clicks were recorded before, during, and after a conditioning procedure in which click pairs were regularly followed by shock to the paw. The second click of each pair typically followed the first by 300-400 msec. Before the introduction of shock, the response evoked by the second click was appreciably smaller than the response evoked by the first. The difference in amplitudes was reduced when shocks to the paw were presented after each pair of clicks. Responses to both clicks were enhanced, but the enhancement was greater for potentials evoked by the second click. The change was interpreted as a decrease in the subnormal excitability of the reticular formation that ordinarily

followed a response to the first click of each pair. Omission of the shock provided little evidence of an expected extinction effect. Interestingly, a pseudoconditioning control procedure had ambiguous effects. This control consisted of shock presentations that were "random" with respect to the acoustic stimuli. One subject evidenced changes in evoked potentials similar to those observed during conditioning; another subject did not. This is one of very few experiments that have employed any controls of this kind.

In one of the few experiments to employ rats as subjects, Macadar, Ginés, Bove, and García-Austt⁵⁷ have described changes in photically evoked potentials recorded from visual cortex during conditioning. The conditioning procedure was one in which shocks were presented at either the beginning or the end of 40-sec periods in which light flashes were presented at 1/sec. Photic stimulation periods alternated with 40-sec periods of no stimulation. Flash-evoked cortical potentials evidenced increased amplitudes when shocks were presented during a train of flashes. It apparently made no difference whether the shocks were delivered at the beginning or the end of the flash series.

From the same Montevideo laboratory, Buño, Velluti, Handler, and García-Austt¹⁰ have described changes in round-window potentials recorded from guinea pigs during conditioning. Acoustic stimuli, clicks or tone pips were in some cases presented directly to the middle ear through a tube fixed in place at the time round-window electrodes were implanted. Parts of the ossicular chain in the middle ear were also removed at the same time. Electric shocks delivered to the contralateral pinna were paired with acoustic stimuli in the following way: Clicks or tone pips presented at 1/sec were each followed by a shock for a period of three minutes. No evoked potentials were recorded during these shock periods. The shock periods alternated with three-minute periods in which no shocks were presented. During the latter, round-window potentials were recorded. Cochlear microphonics evoked by tone pips were found to increase in amplitude with the commencement of shocking, but with continued shocking underwent reductions which the authors regarded as evidence of "rehabilitation." When shocks were discontinued this reduction was accelerated. Similar changes were found in the N1 response to click stimulation. Buño et al. believe that the way in which stimuli were presented, i.e., directly into the middle ear through a tube, rules out an explanation of the changes in terms of uncontrolled stimulus parameters. Removal of the ossicles eliminated the possibility that changes in round-window potentials were due to contractions of middle-ear muscles. In view of the potential significance of the findings, the appreciable variability in the data presented is disturbing. We can only wish that additional systematic data from a number of subjects had been presented.

To the best of our knowledge, Beck, Doty, and Kooi⁶ have been the only workers to report that sensory evoked potentials did not change when acoustic stimuli were made conditional stimuli in a classical aversive conditioning situation. Their experiments were concerned primarily with conditioned cortical arousal responses. Cats immobilized with bulbocapnine were employed as subjects. Cortical arousal was elicited by 2-sec tone bursts after the acoustic stimulus had been paired with shock to the paw, but

evoked cortical responses to tone onset showed no systematic changes during conditioning. For one subject, a series of four clicks was employed as the CS, and the click-evoked potentials did not appear to change either. Whether or not these findings can be attributed to the use of bulbo-capnine is difficult to say.

Behavioral measures of a conditioned response have been conspicuously absent in most of the published reports reviewed above. In many instances there has been neither definition nor measurement of the response that presumably has been conditioned. Justification for use of the term "conditioning" has been that the relevant sensory stimulus was "paired" in some more or less systematic way with another stimulus, usually electric shock. The so-called "pairing of stimuli" is not, however, a sufficient operation to define a conditioning situation, including that of "sensory-sensory conditioning." The conditioning process is influenced by a number of important variables, and there are conditions under which the pairing of stimuli does not lead to the occurrence of conditioned responses. To assume that the temporal contiguity of two stimuli has led to some sort of conditioning would seem to be poor practice in a scientific endeavour struggling with such complex problems. We believe, and will attempt to show, that repeated failures to obtain careful systematic measures of behavior have from the outset led to a misunderstanding about the nature of changes in evoked potentials during conditioning. To assume that alterations in sensory evoked potentials are a sign that conditioning has occurred would seem to beg the question, at least if we are talking about conditioned changes in behavior. The phrase 'neural correlates of conditioning' will be meaningful only when systematic alterations in neuroelectric activity are related to orderly changes in measures of a conditioned response.

It may not be unreasonable to regard a change in evoked potentials as a conditioned response, quite independently of any measurable changes in behavior, be it muscular or glandular. If, however, such changes are to be viewed within a Pavlovian conditioning paradigm (and this seems to have been the model that has dictated the "pairing" of stimuli in studies employing such procedures), then the UCS, shock in most cases, must be regarded as a stimulus that itself is capable of eliciting the changes in evoked potentials. The essential role of the unconditional stimulus in classical conditioning paradigms revolves around its capacity to elicit the response that is to be conditioned. Briefly, this implies that in classical aversive conditioning situations, a shock UCS should elicit changes in evoked potentials similar to those that have been reported as a function of conditioning, independently of any associative processes. No one seems to have considered this possibility, but in fact it turns out to be so. The changes are not, however, independent of measurable and correlated changes in behavior.

In summary, it would seem unwise to consider changes in sensory evoked potentials as neuroelectric correlates of conditioned changes in behavior when it is not shown that orderly changes in behavior accompany the recorded alterations in evoked potentials. On the other hand, if changes in evoked potentials are themselves to be regarded as conditioned responses, then some substitute must be found for the Pavlovian conditioning

paradigm (certainly the operant one is not appropriate) or we must recognize the capacity of the UCS to elicit similar changes in evoked potentials.

Although many of the experiments reviewed above have serious methodological shortcomings, the cumulated data strongly suggest that when impulsive physiological stimuli are employed as conditional stimuli in classical aversive conditioning paradigms, there are appreciable changes in the potentials evoked by these stimuli during the course of conditioning. Although this finding, on the face of it at least, seems clear enough, the interpretations afforded it have been rather less than clear. There is in all of these studies, however, the implication that the alterations in sensory evoked potentials are somehow intimately related to the neural substrate of conditioning. This notion we shall have ample reason to question.

1.2 CHANGES IN SENSORY EVOKED POTENTIALS OBSERVED DURING AVOIDANCE CONDITIONING

Changes in sensory evoked potentials during avoidance conditioning have proved to be more complex than those seen in situations employing unavoidable noxious stimuli. Pickenhain and Klingberg,⁶⁷ for example, have described a complex series of changes in visual cortical potentials during several phases of avoidance conditioning. Electrodes were implanted in rats over olfactory bulbs, visual cortex, and other cortical areas. Following a short habituation period, subjects were trained to avoid shocks to the feet by climbing upon a vertical rod. The discriminative stimulus signaling shock consisted of a train of 5 or 10 brief light flashes presented at a rate of 1.5/sec. In the analysis of the neuroelectric and behavioral data, conditioning and extinction periods were subdivided according to several criteria. The conditioning period was first divided into two major subperiods. The first, called the period of reinforcement, included all trials before the occurrence of the first CR. The second, the conditioning period, included all trials from the first trial on which a CR occurred to the trial preceding the first unreinforced failure to respond during extinction. The extinction period consisted of the trial marked by the first unreinforced failure to respond and the trials that followed. The two conditioning periods and extinction period were further subdivided when the data appeared to delineate three phases common to each of them. In this regard there has been a modification of the analysis offered in the 1965 publication, and we shall consider only the later findings. These were described by Dr. Pickenhain in a talk before the Communications Biophysics Group, Research Laboratory of Electronics, M.I.T., on March 10, 1966. The first phase in each of the three major periods was called the "phase of disturbance." It was characterized by general excitability, increases in respiratory rate (measured from recordings of olfactory bulb activity), strong desynchronization of the electrocorticogram, and decreases in the amplitudes of flash-evoked potentials. The second phase, called the "phase of adaptation," was marked by arrest reactions, less general excitability, and goal-directed behavior. During this period, photically evoked potentials evidenced increases in amplitude and

prominent afterdischarges. The last phase, the phase of well-adapted behavior, was characterized by quiet, orderly behavior, and the "automatic" occurrence of conditioned responses during the conditioning period. Flash-evoked potentials were relatively small in this period, and afterdischarges were not conspicuous.

Pickenhain and Klingberg have interpreted their findings in terms of changes in the level of vigilance, or level of arousal. They do not view the alterations in evoked potentials as evidence of neural mechanisms underlying the conditioned avoidance behavior. Jasper⁴⁹ has reached a similar conclusion in a brief report presented during a discussion at the Pavlovian Conference on Higher Nervous Activity held at the New York Academy of Sciences. Jasper described an experiment in which a conditioned leg withdrawal was established in cats. The CS consisted of a train of clicks presented at a rate of 5/sec. Measures of evoked potentials were reported only for electrodes on primary auditory cortex. During the first 10 days of the experiment, the clicks were not followed by shock, and the cortical potentials decreased in this period to approximately 50% of their original amplitudes. During the first few days of conditioning, the potentials continued to show reductions in amplitude. But around the third day, still before the occurrence of many avoidance responses, amplitudes increased and continued to do so until the percentage of avoidance responses became appreciable. At this point, evoked potentials again diminished. Jasper noted the poor correlation between measures of avoidance behavior and amplitudes of evoked potentials. He suggested that the changes in auditory potentials seemed more related to alerting reactions.

A similar suggestion has been made by Gerken and Neff,³⁸ following the analysis of data from a study in which several conditioning procedures were employed. Evoked potentials were recorded from auditory cortex of cats under four conditions: (i) preconditioning, essentially a habituation procedure, (ii) pseudoconditioning, in which acoustic stimuli and shocks were presented in a "random" manner, (iii) classical conditioning, and (iv) avoidance conditioning. Two kinds of acoustic stimuli were employed: the CS consisted of a 4-sec burst of clicks presented at 4000/sec, and a test stimulus consisted of a single click. The potentials evoked by these two stimuli were found to be similar. Four separate amplitude measurements were made on evoked responses recorded under each experimental condition. All subjects were not exposed to all of these procedures. Some, for example, did not receive the pseudoconditioning treatment before one kind of conditioning or the other. During preconditioning, evoked potentials, especially the later components, tended to increase, while the early components showed some evidence of reduced amplitudes. The patterns of change shown in the published records are marred, however, by considerable variability from subject to subject. Evidence of increases in the amplitudes of cortical potentials was also found during pseudoconditioning, again primarily in the later components. Curiously, the changes were sometimes seen in potentials recorded from one electrode in a given subject, but not from other cortical electrodes in the same subject. The potentials also showed increased amplitudes during both classical and avoidance conditioning – but not when

conditioning had been preceded by the pseudoconditioning procedure. On the basis of these and other findings, Gerken and Neff concluded that the alterations in evoked potentials did not appear to be related to the learning process, but rather to the emotional state or alertness of the subjects.

Hearst, Beer, Sheatz, and Galambos⁴¹ have also studied acoustically evoked potentials during avoidance conditioning. Only one subject was employed, a monkey with electrodes implanted in cochlear nucleus, medial geniculate body, caudate nucleus, and hippocampus. Bar-pressing behavior was maintained on a multiple schedule of reinforcement in which clicks, presented at approximately 1/sec, were correlated with a Sidman avoidance component. The results are rather perplexing. During periods when the monkey was clearly responding discriminatively to the clicks, no appreciable click-evoked activity could be seen in any of the brain sites monitored. With removal of the lever, the animal continued to slap his hand at the place where the lever had been. When this behavior finally weakened (after 18 consecutive hours during which no shocks were presented) potentials recorded from medial geniculate, caudate nucleus, and hippocampus were larger than they had been during any previous phase of the experiment. When the avoidance procedure was resumed, click-evoked potentials were once more difficult to detect in the EEG.

John, Ruchkin, and Villegas^{51, 52} have described an avoidance conditioning study with cats in which 4/sec flashes were established as discriminative stimuli. Many electrodes, 14-30, were implanted in each subject, in both specific sensory pathways and nonspecific structures. Average evoked responses were computed for potentials recorded from all electrodes in each subject. Correlation coefficients, Pearson's r , were also computed for all possible pairs of average responses. This was the first step in the factor analysis of the evoked potentials. The correlation coefficients (not reported) and the subsequent factor analysis suggested that waveforms of the average responses tended to become more similar with the establishment of the conditioned avoidance response. Functional groupings of some neural loci were also indicated by similar changes in factor loadings for potentials recorded from these structures at different stages of the experiment. We must confess we find the data that have been presented unconvincing on both counts. The finding of increased similarity in waveforms of evoked potentials during conditioning has also been described by Galambos and Sheatz,³⁴ as noted above.

In summary, the data from avoidance conditioning experiments reveal some inconsistencies, and, at the very least, some rather complex changes in sensory evoked potentials. Some of these inconsistencies and complexities are more apparent than real. This should become apparent in the work to be reported here. One idea of consequence does emerge from the three studies of Jasper, Pickenhain, and Klingberg, and Gerken and Neff: Changes in evoked potentials seen during avoidance conditioning are not related to the conditioning process. They appear, rather, to be associated with some more general change, specifically with a change in arousal level or emotional "state."

1.3 CHANGES IN EVOKED POTENTIALS OBSERVED UNDER APPETITIVE CONDITIONING PROCEDURES

Most of the reported studies of sensory evoked potentials during conditioning have employed aversive conditioning techniques. Of the few that have employed positive reinforcement, only one, to the best of our knowledge, has made use of a Pavlovian paradigm, though even in this one no measures of a behavioral respondent were obtained. This was described by Hearst, Beer, Sheatz, and Galambos⁴¹ in their study of evoked potentials in four different conditioning situations. The one subject, a monkey, had permanently implanted electrodes in hippocampus, caudate nucleus, cerebellar white matter, and medial geniculate body. The CS consisted of 400-cps tone pips, 0.5 sec in duration, presented every 1.5 sec for 15 seconds. This was followed by the delivery of a sugar pellet that the subject, reportedly, ate each time. A conditioned respondent was not defined. A habituation period was followed by conditioning, extinction, and reconditioning periods. Evoked potentials recorded from hippocampus increased during conditioning, diminished during extinction, and grew again with reconditioning. Evoked potentials from other electrodes evidenced no changes during the experiment.

Hearst et al. also measured click-evoked potentials during an operant discrimination procedure employing the same sugar reinforcement. Potentials were recorded from the hippocampus, caudate nucleus, medial geniculate body, and cochlear nucleus. The monkey, again the only subject, was trained to press a lever only during presentations of a click stimulus. Reinforcement in the S_D periods was presented on a 1-minute Fixed Interval schedule. With the establishment of the discriminative behavior, amplitudes of evoked potentials from all electrodes were smaller than those recorded in preconditioning sessions. Removal of both the lever and food cup from the situation led to an increase in the amplitudes of evoked responses, while a return to the normal discrimination procedure again resulted in diminished evoked potentials. It will be recalled that the avoidance conditioning experiment described in the same report also indicated that evoked potentials decreased in amplitude with the acquisition of a discriminative operant.

Somewhat different findings have been reported by Worden⁷⁵ in a study of acoustically evoked potentials during operant discrimination training with a single cat. The animal had electrodes implanted in nearly all projection sites of the classical auditory system, but emphasis has been placed on potentials recorded from the trapezoid body or inferior olivary complex. (Histological verification of electrode placements had not been accomplished at the time of the report.) Short tone bursts, presented at a rate of 2/sec, were established as discriminative stimuli for lever-pressing. Before the acquisition of the discrimination, only small evoked responses, if any, were recorded. By the third day of training, when the cat appeared to be "waiting" for the acoustic signal, large potentials appeared in the trapezoid body. On the sixth day, potentials from all recording sites were large. More complex changes were seen in later stages of the

experiment; this suggested that evoked potentials do not remain large as long as discriminative behavior is maintained, but revert to smaller amplitudes when discriminations are well established.

Brazier, Killam, and Hance⁸ have found changes of still another kind in flash-evoked potentials recorded from lateral geniculate body during acquisition of an operant discrimination. Again only one subject was used, a cat. The animal was trained to press a lever in the presence of light flashes presented at 10/sec. No changes in the lateral geniculate potentials were seen until the animal was required to respond within 15 sec following the onset of the flashes. Under these conditions, an increase in the amplitudes of both primary and secondary responses was seen. The discriminative behavior was further differentiated by establishing 6/sec flashes as an S_{Δ} signalling no food reinforcement for lever-pressing. The acquisition of this discrimination led to further increases in amplitude of the lateral geniculate responses, as well as to changes in waveform of the later components.

In several reports, Freeman^{25, 26} has also described increases in amplitudes of evoked potentials recorded from prepyriform cortex when cats were trained to discriminate electrical stimuli applied to lateral olfactory tracts or prepyriform cortex. In one experiment, animals were trained to traverse a runway on the presentation of electrical stimuli to prepyriform cortex. In the other, stimulation of the lateral olfactory tracts was employed as a discriminative stimulus for bar-pressing. Food and milk reinforcers were employed in these experiments. Amplitude-frequency functions for evoked potentials were obtained by systematic manipulation of stimulus repetition rates at various stages of the experiments. In general, it was found that these functions had sharper peaks when the stimuli had become discriminative. The functions were flatter during extinction of the discriminative response and in preconditioning, habituation sessions. Increases in amplitudes of some components of evoked prepyriform potentials during acquisition of the discrimination were also reported.

Data from the few conditioning studies that have employed positive reinforcing stimuli are, at best, fragmentary. With the exception of the studies of Freeman, none employed more than a single subject, and it is not surprising that the results have been rather inconsistent. Changes in amplitudes of evoked potentials as a function of conditioning procedures have been described in each report, but increases were found in some experiments, decreases in others, and nonmonotonic alterations in the rest. This was how things stood when our own investigations began. It seemed clear at that time that much work had yet to be done in the study of sensory evoked potentials during conditioning, especially in operant situations in which discriminations were established with positive reinforcement.

1.4 EXPERIMENTAL BACKGROUND OF THE PRESENT INVESTIGATION

Findings from the classical aversive conditioning studies reviewed above certainly suggest that changes in evoked potentials occur when a stimulus is established as a

conditioned one in a Pavlovian paradigm. At the outset of the present investigation, in 1961, we had hoped to extend this finding to the case of operant discriminations established with positive reinforcers. At that time, none of the studies employing operant conditioning techniques, aversive or appetitive, had provided convincing evidence of changes in sensory evoked potentials correlated with the acquisition of a discriminative operant. In our opinion, this statement is still correct. But we had hoped to find such changes and set about in earnest to do so. For it seemed to us, as certainly it has to others, that an unequivocal demonstration of changes in sensory activity during the establishment of some discriminative behavior would provide a convenient starting point for the analysis of neural mechanisms underlying conditioning.

Our first attempts were rather clumsy, both in design and execution. It was not especially alarming, therefore, to find no changes in potentials evoked by either visual or auditory stimuli as the stimuli were made discriminative. But repeated attempts did not alter the picture. None revealed any systematic and reproducible changes in evoked responses. The last two experiments of that series deserve some brief mention, for they appeared optimal in their design and were reasonably executed.

Rats were employed as subjects, and for the most part our concern was with cortical evoked potentials. In two essentially parallel experiments, click stimuli were employed with one group of animals and photic stimuli with another group. Evoked potentials were recorded from the primary cortical projection areas. The experimental situations were quite analogous to a simple reaction time situation employed with human subjects. Animals were trained to respond rapidly, by releasing a lever, to a single click or photic stimulus presented on each trial. Rats were first trained to hold the lever depressed until a reinforcement was presented. Activation of the feeder and other stimulus changes served as stimuli for release of the lever in this initial stage of the experiment. The discrimination was then transferred to either the click or photic stimulus, the latter consisting of a two-second illumination of a circular target immediately in front of the subject's face. Food reinforcement was contingent upon release of the lever within 2 seconds of stimulus onset, and in final stages of training within 1 second. The discriminative stimulus was presented at some variable interval, 3-8 sec, following initiation of the bar-holding response. Evoked potentials were averaged across trials to obtain an average response for each daily session. It was also possible to obtain separate averages for trials on which animals responded correctly and for trials on which responses were incorrect. When the discrimination had become well established, the situation was reversed to the original conditions in which activation of the feeder served as signal for the bar-release, and then reversed again.

Throughout the course of these experiments, there was no evidence of any change in cortical evoked potentials that could be related to the conditioned changes in behavior. With sufficient training the rats responded correctly on 90-95% of the approximately 250 daily trials. Response latencies had modal values of approximately 0.5 sec. There was no doubt that the bar-release was under control of the auditory or visual stimulus,

but there was no indication of any change in evoked potentials as this behavior was established. Nor did the average evoked potentials associated with correct or incorrect behavioral responses show any differences. We could only conclude that the establishment of a stimulus as a discriminative one with positive reinforcement procedures does not alter evoked potentials recorded from primary sensory cortex. It also seemed unlikely that changes would occur at lower stations in the classical sensory pathways and not be reflected in the cortical responses.

It was at this point that we began to question seriously the fact that consistent and convincing changes in evoked potentials had been reported only for the classical aversive conditioning paradigm. Our question had a two-fold nature: (i) Could we reproduce those changes in rats in our laboratory? (ii) What could be unique about classical aversive conditioning with respect to alterations in sensory evoked potentials? Was it the use of noxious stimulation? No one had demonstrated that changes in evoked potentials were dependent upon the acquisition of a conditioned response. Few had even measured a conditioned response. Nor had anyone determined whether the changes might be a sensitization or pseudoconditioning effect. To answer these and other questions, the experiments described below were undertaken. It was a relatively simple matter to show that alterations in evoked potentials found during classical aversive conditioning were not directly related to the conditioning process. It was somewhat more difficult to show that they were related to an emotional response dependent upon the use of noxious stimulation.

II. GENERAL EXPERIMENTAL METHODS AND PROCEDURES

Many of the experimental methods and procedures employed in the experiments described below were common to most, if not all, of the individual experiments. It will be economical, therefore, to describe them once here, and consider only critical differences in later descriptions of particular experiments.

2.1 SUBJECTS

Thirty-four albino rats, descendants of the Sprague-Dawley strain, were employed in this series of experiments. Rats were purchased from the Charles River Breeding Laboratories. In most cases only three or four subjects were used in each experiment. Although this number may seem small, it will become apparent that many of the experiments served to a considerable degree as replications of earlier experiments. Weights of the animals ranged from approximately 300 gm to 450 gm.

2.2 ELECTRODES

All electrodes were made of stainless steel. Cortical electrodes, unless noted otherwise, had ball tips approximately 0.5 mm in diameter and were placed on the dural surface. Deep electrodes were in most cases made from Teflon-insulated wire, 125 μ in diameter. In a few instances we used 250- μ wire insulated with a 4-ply enamel coating. In the earlier experiments the recording tip of a deep electrode was simply the transverse section of the wire. In later experiments exposed tips were electrolytically etched to points, 0.5 mm long. In all but a few cases monopolar derivations were employed. Reference electrodes consisted of stainless-steel screws. These were placed in one of several locations: over olfactory bulbs, frontal cortex or cerebellum. We have not been able to detect any differences in click-evoked potentials associated with these different placements of reference electrodes. Each subject was adequately grounded by means of a large neck electrode which consisted of a loop of 250- μ wire, approximately 1 cm long, laid next to the occipital bone. Neck muscles on the posterior aspect of the skull were retracted, the neck electrode was fixed in place, and the muscles were then laid over it. Smaller electrodes for recording neck-muscle activity were employed in some instances.

2.3 PROCEDURES FOR IMPLANTING ELECTRODES

The rats were anesthetized with Nembutal during the implanting operations. Initial doses of 50 mg/kg of body weight were used, and supplementary doses were administered as needed. Three or four screws were threaded into the skull to serve as anchoring screws for the electrode assembly or as reference electrodes. Recording electrodes were inserted through trephine holes, 1.5 mm in diameter.

Deep electrodes were placed stereotaxically with the aid of coordinates calculated from DeGroot's atlas of the rat brain.¹⁷ Click-evoked potentials were monitored during

the placement of each electrode as an additional aid in placing the electrode correctly. When the position was considered satisfactory, the hole in the skull was filled with bone wax and the electrode was cemented in place. Electrode wires were then soldered to either 9- or 15-pole connectors of the Cannon Electric Company's Micro-D series.

2.4 HISTOLOGICAL VERIFICATION OF ELECTRODE PLACEMENTS

At the end of each experiment the animals were anesthetized and perfused first with normal saline and then with 10% formalin. The head was cut off, all extracranial tissue was removed, and the head was placed in 10% formalin over night. In order to remove the electrodes carefully, without having to grind away the dental cement, the head was mounted in a jig that held the skull and electrode connector rigidly with respect to each other. The jig and head were then placed in Carnoy's fixative which is 30% chloroform. After two or three days in this solution, the dental cement was completely dissolved by the chloroform. The electrodes could then be easily removed while the entire assembly and skull were still held rigidly.

Brains were imbedded by using the hot celloidon technique of E. C. Clayden.¹⁵ When electrodes had been implanted in the cochlear nuclei, the tympanic bullae were left in place when the brain was removed from the skull. The bone was then decalcified before the celloidon imbedding. The brains were cut, typically in 50- μ sections, and stained with either Weil or cresyl violet stains. The identification of neural structures in which electrode tips were located was accomplished with the aid of König and Klippel's atlas of the rat brain.⁵⁶ The revised edition of Craigie's atlas by Zeman and Innes⁷⁷ was also employed in the identification of brain-stem auditory structures.

2.5 RECORDING AND PROCESSING NEURAL POTENTIALS

Electric potentials were amplified by Grass P-5 or P-5 11 AC amplifiers. The amplified signals were then recorded on FM, 7-channel magnetic tape. Ampex FR 1100 or Sanborn Ampex 2000 tape recorders were employed for this purpose. The variation of the frequency response of the entire recording system depended upon the source of the potentials. Channels used in recording potentials from eighth nerve and cochlear nucleus had a frequency response that was flat between 1.5 cps and 2500 cps. High-frequency limits (half-amplitude) were 2000 cps for medial geniculate and inferior colliculus channels, and 500 cps for cortical recordings.

Evoked potentials were averaged with the aid of the Average Response Computer, ARC,^{14,16} or a PDP-4 computer (Digital Equipment Corporation). An X-Y plotter was used to obtain permanent records of the average responses, and amplitude measurements were made from these plots.

Records of brain potentials, muscle activity and other signals were sometimes obtained on a Grass Model 3 EEG. All electric signals were routinely monitored on oscilloscopes. Special details of recording procedures will be considered in descriptions of the appropriate experiments.

2.6 CONDITIONED EMOTIONAL RESPONSE SITUATION

We have employed the conditioned emotional response (CER) situation of Estes and Skinner²² and Brady and Hunt⁷ in many of the experiments that will be described. In this situation a bar-pressing response is first established and maintained at relatively constant rates on an intermittent schedule of reinforcement. A reinforcement in the present experiments consisted of a single 0.045-gm food pellet. In place of the Variable Interval (VI) schedule of reinforcement usually employed in CER experiments, we have used a tandem Variable Interval Fixed Ratio schedule, typically a tand. VI 30 sec FR 4. This kind of schedule tends to generate higher rates of responding than the simple VI schedule, but has some of the conveniences associated with the latter, e.g., long programmed intervals of no reinforcement. Conditioning of an emotional response is initiated when bar-pressing has become stable. This is accomplished by presenting a conditional stimulus (CS), for 1-minute periods in our experiments, which is followed on each occasion by an unavoidable noxious electric shock. Acquisition of the conditioned anxiety or fear can readily be traced in the increasing suppression of bar-pressing during CS presentations. The ease with which this conditioning can be followed in measures of bar-pressing, and the ease with which the behavior is established make the CER situation a particularly convenient aversive conditioning paradigm. An example of the behavior generated in such situations can be seen in Fig. 1. The cumulative response record shows a relatively high rate of bar-pressing in the absence of the CS, but virtually no responding at all during CS presentations.

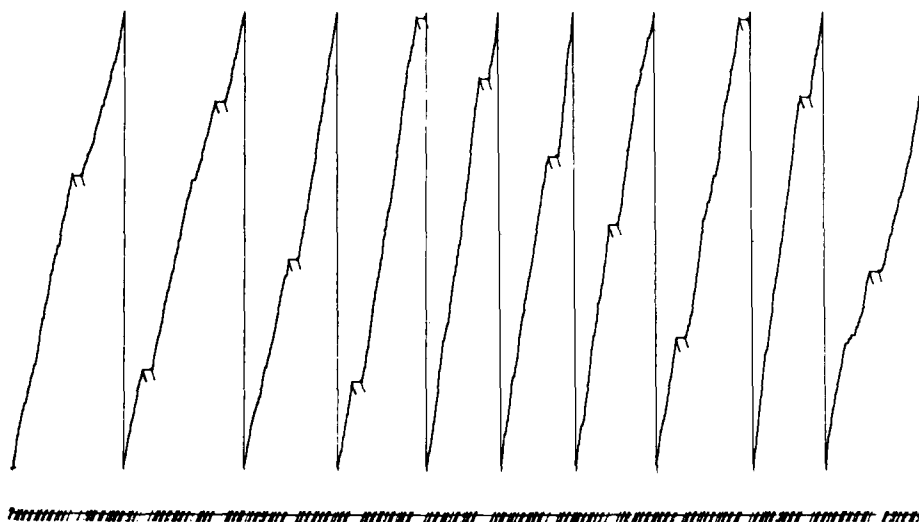


Fig. 1. Cumulative response record of bar-pressing in conditioned emotional response (CER) situation. First pip of each pair on the response curves indicates onset of CS. Second pip indicates termination of CS and presentation of shock UCS. Food reinforcements are indicated by pips on the bottom line.

2.7 BEHAVIORAL APPARATUS

In all but two experiments, the subjects were not restrained. They worked in long narrow boxes made of black Bakelite, 12 in. long, 3 in. wide, and 15 in. high. The food cup was located 3 in. above the lever at one end of the box. Dimensions of the box and location of the food cup minimized the amount of circling behavior and, therefore, the troublesome twisting of electrode leads. The food cup was also made of Bakelite, and the lever which the animals pressed was covered with a gravel and epoxy mixture. The use of nonconducting materials for food cup and lever eliminated noise arising from contact potentials. The gravel-epoxy compound on the lever was the only nonmetallic material we could find that was hard enough to discourage or withstand chewing. Photoelectric switches were used on levers to avoid the noise associated with mechanical switches, and the limiting stops were cotton-cushioned for the same reason.

The box contained a grid floor consisting of only 4 bars. Shock stimuli were delivered to the subjects' feet through this grid. Two methods were employed (in different experiments) to eliminate the possibility that subjects might escape shock by standing on isopotential bars. In one, adjacent bars were connected through 10-k Ω resistors so that the grid was a simple voltage divider. The second method employed a special scrambling circuit designed by Richard J. Clayton. A variac provided a variable shock source of 60 cps AC. This current was usually chopped by means of an oscillating relay and then led through an isolation transformer to the grid or scrambling circuit. Shock duration in each instance was 0.5 sec.

The rat boxes were housed in sound-attenuating, electrically shielded chambers, 22 in. wide, 21 in. deep, and 45 in. high. The chambers were located in a separate room to insure acoustic isolation from the control and recording equipment. The experiments, except for the changing of subjects, were completely automated. This was accomplished with the aid of conventional relay circuitry plus some solid-state devices. The latter were also designed by Richard J. Clayton.

In several cases, subjects were placed on food-deprivation schedules and were handled daily for a week or more before electrodes were implanted, but in most experiments these procedures were not initiated until 5-7 days following surgery. Body weights were maintained at 75-80% of the animals' ad libitum feeding weights. It has been our experience that bar-pressing behavior in CER situations is best when animals are required to work for their entire daily food ration in the experimental situation, and when this allotment is ample. Experimental sessions, therefore, usually lasted 2.5-3.0 hours, and the animals received approximately 300-350 reinforcements, i. e., 13.5-15.75 gm of food. Water, with an added vitamin supplement, was always available to subjects in their home cages.

Bar-pressing was established under continuous reinforcement. Intermittent reinforcement was introduced with schedules of low values. These were gradually increased until the final values were reached in order to maintain relatively high rates of

responding. No acoustic stimuli were ever introduced until rats had achieved high stable response rates. For at least 2-3 days before the first recording session, animals were run with electrode leads attached so that adaptation to the leads would not confound any effects related to the introduction of auditory stimuli.

2.8 ACOUSTIC STIMULI

Evoked potentials of concern in these experiments were all evoked by clicks. The clicks were generated by applying 0.15-msec square pulses across a loudspeaker. The loudspeaker was located 37 in. above the floor of the experimental chamber. Walls of the chamber were lined with acoustic tile to reduce the amount of reflected sound. Click intensities were generally moderate, approximately 30-35 db above the rat's threshold. One of us determined the approximate threshold for click stimuli under the conditions of our experiments from both behavioral and evoked-potential measurements.⁵⁸ Click stimuli were always presented against a low-level background masking noise that was present throughout experimental sessions. In all experiments clicks were presented at a rate of 1/sec.

It was often the case that a food reinforcement was presented during a train of clicks, simply because such presentations were determined by the behavior and reinforcement schedule. On these occasions, there was no interruption of the click train. The stimuli presented during the 5-6 sec immediately following a reinforcement were not marked, however, on the magnetic tape. Consequently, click-evoked potentials recorded in post-reinforcement periods were not included in the average responses. This was done to eliminate the masking effects of chewing. It was clear from the muscle activity seen on cortical electrodes that ingestion of a food pellet was nearly always accomplished within 6 seconds.

2.9 PRESENTATION OF DATA

Our primary concern in this investigation has been with correlated changes in sensory evoked potentials and behavior in the individual organism. At this time there would appear to be no good justification for combining data from individual subjects, for at this stage of our inquiry into neuroelectric correlates of conditioning a model that might justify the use of group measures is clearly lacking. Moreover, group means or other measures of central tendency often obscure important features of the data, and only rarely do they present a more convincing summary of experimental findings than do data from individual subjects. The presentation of data from individual subjects is not without its own problems. If all data are to be presented there are clearly problems of economy. If the "typical case" is the adopted solution to these problems, one runs the risk of serious sampling errors. Throughout this report we have tried to find some compromise, but in all cases each subject is represented in data presented for the several experiments.

Habituation of evoked potentials in unanesthetized subjects has been described in

many reports (see, for example, Hernández-Peón⁴³; García-Austt³⁶). This habituation refers to a more or less systematic reduction in the amplitudes of sensory evoked potentials associated with repeated presentations of the stimulus. The nature of these changes is still a matter of dispute. The conditions under which it occurs, and where in the nervous system evoked potentials show such changes are problems that have not been resolved.

In order to obtain stable baseline measures of evoked potentials, we have routinely employed habituation procedures before any conditioning operations. These procedures were often in effect for 10 days or more. Although we have found evidence of habituation in click-evoked potentials, these data will not be considered here. A discussion of this problem would only lengthen this very long report and detract from its principal thesis. Habituation data from these and other experiments will be described elsewhere.

III. CLICK-EVOKED POTENTIALS RECORDED FROM CENTRAL AUDITORY STRUCTURES

Electric potentials evoked by impulsive sensory stimuli and recorded with macro-electrodes are summations of the electric responses in relatively large populations of cells. Different cell populations and several kinds of neural potentials, e. g., unit "spikes" and postsynaptic potentials, may contribute to these summated responses. In this report we shall employ the term 'sensory evoked potential' in its narrower sense to mean the summated responses recorded by means of macroelectrodes. Such potentials often assume complex waveforms that are difficult to describe and difficult to quantify in some physiologically meaningful way. These difficulties are due in large measure to our inadequate understanding of the nature of these potentials. Three decades or more of experimental work have yet to provide a generally accepted and reasonably precise account of evoked responses from primary projection areas of the cortex, perhaps the most extensively studied evoked potentials in the central nervous system. The analysis of evoked potentials from most subcortical stations of specific sensory systems has been only rudimentary. Moreover, the analysis has barely dealt with the potentials recorded from unanesthetized organisms, potentials that are admittedly more complex than those recorded from anesthetized preparations. But in spite of these difficulties, we pursue the study of evoked potentials, for it is clear that much has been learned about functions of the C. N. S. through these efforts.

In the work reported here it was often necessary to proceed in considerable ignorance regarding evoked potentials to be found in subcortical structures of unanesthetized rats. Moreover, the present report will not permit a detailed analysis of such activity. In some instances we cannot be sure that all components of evoked responses recorded from electrodes within a given structure have their origins in the activity of that structure. Current spread from nearby structures is an ever present hazard when recording evoked potentials in the C. N. S. by means of so-called monopolar derivations. The problem of interpretation is somewhat ameliorated by the use of "bipolar" electrodes, but this technique introduces its own problems. We have found monopolar recording desirable for two reasons: (i) Electrodes are smaller than bipolar types and inflict less damage on neural tissue. (ii) In our experience, the reproducibility of evoked potentials from one subject to the next, and the correlation of these potentials with electrode locations have proved much easier with monopolar derivations. In the rest of this section, evoked potentials recorded in these experiments from cortical and subcortical auditory structures are described. It can be understood that these potentials were recorded from electrodes within or on the surface of the several structures. It cannot be assumed that these potentials necessarily have their origins in the same structures. An experimental analysis of some of these potentials is in progress, but until it is complete no definite statements can be made regarding the sources of at least some components of the evoked responses. We emphasize this problem for it will become clear that changes

in acoustically evoked potentials during conditioning are complex changes that may or may not involve particular response components. A component analysis of the waveforms is therefore critical for any fundamental understanding of the changes.

Figure 2 shows average click-evoked responses that are representative of evoked potentials recorded in this study from the several auditory structures. Evoked responses that deviated markedly from these potentials were generally excluded from the analysis.

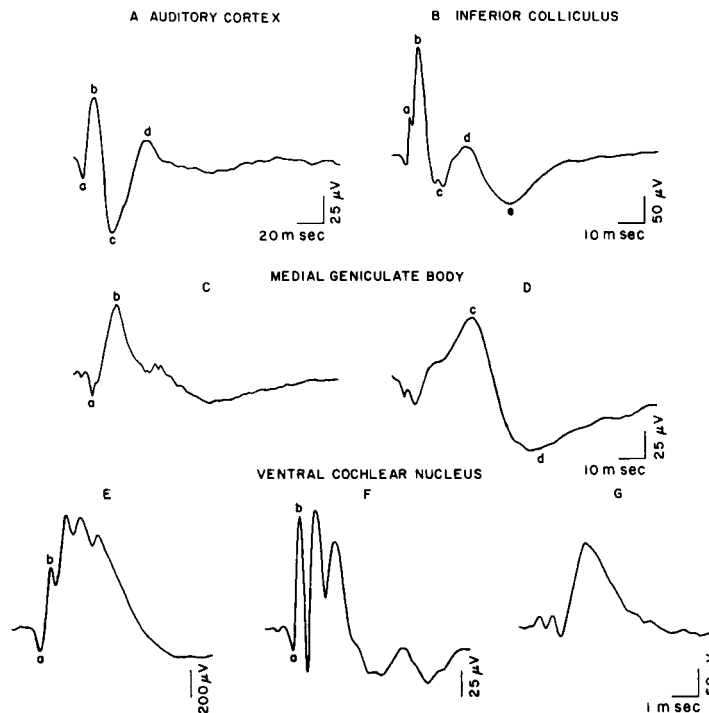


Fig. 2. Average click-evoked potentials from auditory cortex, inferior colliculus, medial geniculate body, and ventral cochlear nucleus. Response of medial geniculate on the left is from anterior portions of the nucleus; on the right, from more posterior portions. See text for description of electrode placements for responses from cochlear nucleus. Averages were computed from 500-600 evoked potentials. Note different time and voltage calibrations. In this and succeeding figures, positive changes of potential are indicated by downward deflections.

The cortical response in Fig. 2A is similar to click-evoked cortical potentials in unanesthetized cats described by other workers.^{33, 38, 74} An initial positive deflection (labeled a) is followed by three other peaks of alternate polarities (peaks b, c, and d). Respective latencies of the four peaks are 7-12, 12-17, 25-29, and 40-45 msec. (All latencies reported here have been corrected for the approximately 3 msec required for the sound-pressure wave to reach the subject.) The late negative wave, d, may occasionally peak as late as 65-70 msec, although it is by no means clear that such late

potentials are completely comparable to those with shorter latencies. Cortical potentials presented in this report are like the average response of Fig. 2A or differ mainly in the relative amplitudes of the various components. Other waveforms, have been encountered, however, which suggest that a complete description of the cortical surface potentials must be more complex than the one presented here.

It will be convenient to make a distinction between early and late components of click-evoked potentials recorded from auditory cortex, medial geniculate body and inferior colliculus. This distinction will provide a convenient brief means of describing the potentials, but it appears also to have physiological significance in the present analysis.

The primary components a and b of the cortical response will be called the early components, and their amplitudes will be taken as the voltage difference between them. Similarly, peaks c and d will be called the late components, and their amplitudes will be expressed as the voltage difference between the two peaks.

All evoked potentials recorded from inferior colliculus were from electrodes in anterior portions of the nucleus. Several lines of evidence suggest that the first sharp negative deflection (a) with a peak at 3 msec represents activity of the lateral lemniscus. Peaks b and c will be considered the early components of the collicular response, and their amplitudes will be measured peak to peak. Peak latencies of these components are 5-8 and 12-17 msec, respectively. The late components are peaks d (24-31 msec) and e (42-49 msec). Except for the late components, the response depicted here is similar to click-evoked potentials recorded from curarized cats by Jungert.⁵⁴

Click-evoked potentials recorded from the medial geniculate body were of two more or less distinct types. From anterior portions of the geniculate the responses looked like those on the left in Fig. 2C. An initial positive wave with its peak at 5-6 msec was followed by a much larger negative deflection that peaked at 14-17 msec. For somewhat similar potentials recorded from parts of the medial geniculate in anesthetized cats, Rose and Galambos⁶⁸ have presented evidence that the first positive deflection may be due to presynaptic activity. To facilitate measurements, however, we have taken the voltage difference between the first positive (a) and the first negative (b) peaks as the amplitude of the early components of the geniculate response. From electrodes in more posterior parts of the medial geniculate, evoked potentials acquired a second large negative peak (22-29 msec) that was followed by a slow positive wave with a peak at 42-57 msec, peaks c and d in the average response of Fig. 2D. The origin of these late components is a matter of concern, for their time course and polarities are much like those of late components of the collicular response. We cannot ignore the possibility that potentials from one site represent current spread from the other, or that these components in responses from both locations are due to activity in a third neighboring structure. We have not yet resolved this problem. Gershuni et al.³⁹ have recorded click-evoked potentials from the medial geniculate body of unanesthetized cats, and some of the potentials they present appear to be like those we have recorded from posterior portions of the nucleus. We have not determined whether these workers are

satisfied that the late components of the response are due to activity in the medial geniculate body.

Click-evoked potentials recorded from the ventral cochlear nucleus also exhibit several more or less distinct forms that have proved to be reasonably correlated with differences in electrode placements. In general, they are similar to evoked potentials from this nucleus described by other workers for both anesthetized and unanesthetized cats.^{2, 54, 64} The largest responses were usually found in the more ventral portions of the nucleus. An example of these potentials is seen in Fig. 2E. The first positive deflection with a peak latency of 0.7-0.9 msec is almost certainly the response of eighth nerve. The latency of this potential seems too short for it to be anything else. We have also recorded this positive wave together with the cochlear microphonic from electrodes against the bony wall of the tympanic bulla. In such cases the short-latency positive wave was contiguous with the microphonic potentials. Moreover, there seems to be general agreement among all workers that eighth-nerve responses can be recorded from within the ventral cochlear nucleus. We have measured the amplitude of peak a from the baseline, and in some cases we have also measured the voltage difference between a and b. The two measures are highly correlated, and either measure will be referred to as the amplitude of the auditory nerve response.

The later and generally slower components of responses recorded from ventral cochlear nucleus can reasonably be attributed to activity in the nucleus. The amplitude of the VCN response was determined by taking a peak-to-peak measure on the "backside" of the response. This was necessary because, at present, we are not able to distinguish with certainty the later components of the eighth-nerve response from the initial activity attributable to cochlear nucleus. Since the waveforms of evoked responses recorded from the cochlear nucleus fall into several groups, the amplitude measure has not been precisely the same for all responses. In all cases, however, it represents the voltage difference between the last large negative peak and the peak of a positive potential following it.

The cochlear nucleus potential in Fig. 2F was obtained from an electrode situated more dorsally in the nucleus than the electrode from which the response in Fig. 2E was obtained. All the sharp peaks of the two responses are coincident. The major difference in waveform seems to be that peaks of the response in Fig. 2F do not appear to be riding on a slow potential as do peaks in the response in Fig. 2E. There is also an appreciable difference in amplitude between the two responses.

The evoked response from ventral cochlear nucleus in Fig. 2G is typical of those recorded from electrodes within lateral or dorsolateral portions of the nucleus. It consists primarily of a relatively slow negative wave. A similar response is recorded from the surface of the nucleus in the same regions, but in such instances the prominent wave is often of the opposite polarity.

IV. EXPERIMENTAL ANALYSIS OF CHANGES IN ACOUSTICALLY EVOKED POTENTIALS DURING CONDITIONING

4.1 EXPERIMENT I

The present series of experiments was undertaken to determine, first of all, if changes in click-evoked potentials could be found in this laboratory when clicks were made conditional stimuli in aversive conditioning situations. We had previously been unsuccessful in our attempts to demonstrate alterations in evoked potentials recorded from primary sensory cortex during the acquisition of appetitive operant discriminations. This first experiment simply demonstrates that with aversive conditioning procedures conditioned changes in behavior are accompanied by changes in acoustically evoked potentials. Click-evoked responses evidenced appreciable increases in amplitude when clicks were established as conditional stimuli for a Conditioned Emotional Response (CER). The analysis of these changes is the subject of the following experiments.

4.1.1 Methods

Three rats, S14, S15, and S16, were employed. Ball-tip electrodes were implanted bilaterally on the dura overlying the auditory cortex. An attempt was also made to implant electrodes in the medial geniculate body, but the electrodes were actually placed in the reticular formation, slightly medial and slightly posterior to the medial geniculate. Potentials recorded from these electrodes showed significant changes during conditioning and the data will be presented. In two subjects, S14 and S16, electrodes were successfully implanted in the ventral cochlear nucleus.

Unfortunately, the electrode assembly on S15 was detached from the skull on the third day of conditioning. Changes in evoked potentials were quite apparent, however, in all three subjects by the first or second day of conditioning, and the lack of complete data for S15 does not seem critical.

When bar-pressing behavior had become stable under the tandem VI 30 sec FR 4 schedule of food reinforcement, 1-minute trains of 1/sec clicks were introduced. Thirteen to fifteen such click trains were presented in each daily session. Experimental sessions were approximately 2 hours long. A background masking noise was continuously present.

During the first four sessions of auditory stimulation, click trains were not followed by electric shocks. Conditioning of the emotional response began on the fifth day when each train of clicks was followed by an unavoidable shock to the subjects' feet. Thirteen to fifteen conditioning trials were presented in each session, and conditioning continued for 7 days. The conditioned suppression of bar-pressing was then extinguished for 6 days by withholding shock in these sessions.

4.1.2 Results

Average cortical evoked responses showed appreciable increases during conditioning. This can be seen in Fig. 3 in which average evoked potentials from the

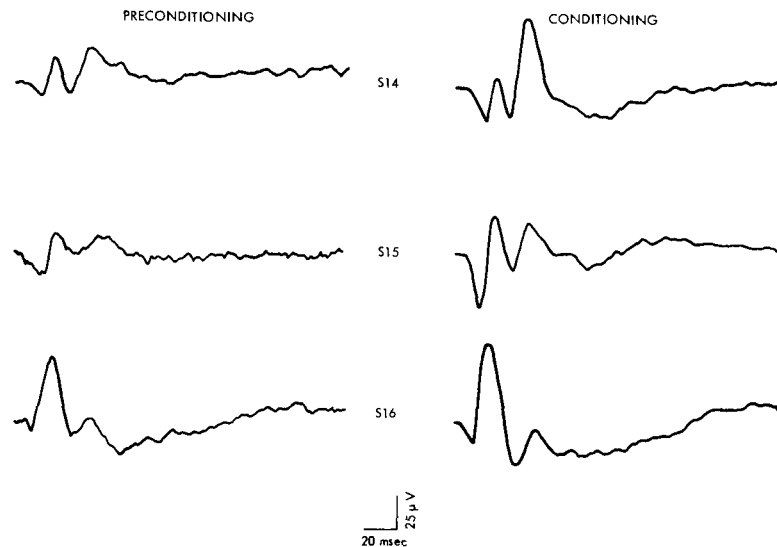


Fig. 3. Average click-evoked cortical responses from three subjects taken from last preconditioning session and second conditioning session of a CER situation. Averages computed from first 550 evoked potentials recorded in each session.

last preconditioning session and the second conditioning session are shown for each subject. Data from the second day of conditioning were chosen because this was S15's last session. It appears that all components of the cortical potentials were larger during conditioning than they were in the last preconditioning session; however, the most consistent and orderly changes were seen in the late components. A more quantitative view of the changes in late components can be seen in Figs. 4 and 5. Here amplitudes are plotted as a function of daily sessions for S14 and S16, respectively. Amplitudes are expressed as percentage differences relative to amplitudes of potentials recorded in the last preconditioning session. A behavioral index, which will be employed throughout this report, is shown in the lower graphs. This is a ratio of the number of bar-presses that occurred during CS presentations to the number of bar-presses emitted during 1-minute control periods immediately preceding each CS. This ratio goes to zero with complete suppression of bar-pressing during CS presentations. It is clear from Figs. 4 and 5 that the CER was quickly established and the changes in behavior were more or less paralleled by increases in the amplitudes of late components of cortical responses.

Measurements of the early components of cortical potentials have not revealed such an orderly picture. In general, a trend toward increased response amplitudes appeared during conditioning. These changes were quite variable, however, and relatively small when amplitudes of the early components were measured from the first positive to the first negative peaks. This can be seen in Fig. 6B, in which these amplitudes have been plotted, again as relative changes, for all three subjects. In Fig. 6A another measure of the primary cortical response has been plotted in a similar way. This is a measure of the amplitude of the first positive component, taken from the baseline to the peak of

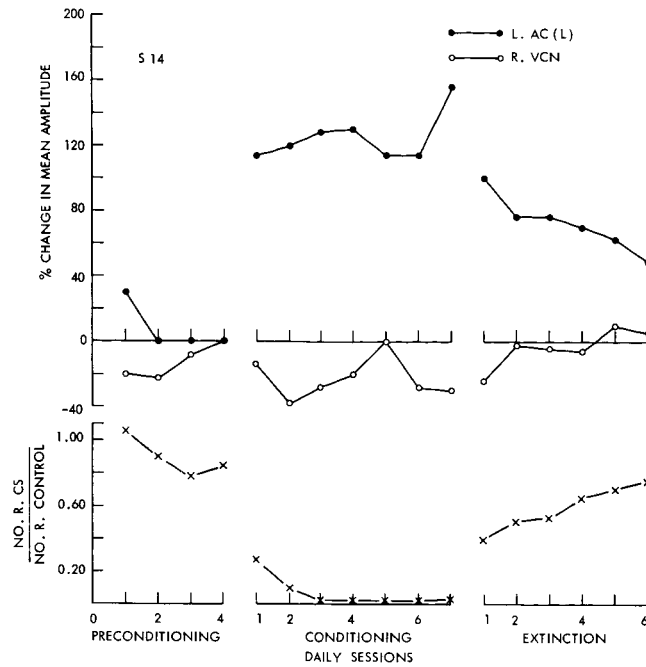


Fig. 4. Percentage change in mean amplitudes of late components of click-evoked potentials recorded from left auditory cortex, L. AC(L), and right ventral cochlear nucleus, R. VCN, of S14. Lower graph shows behavioral index employed throughout this report.

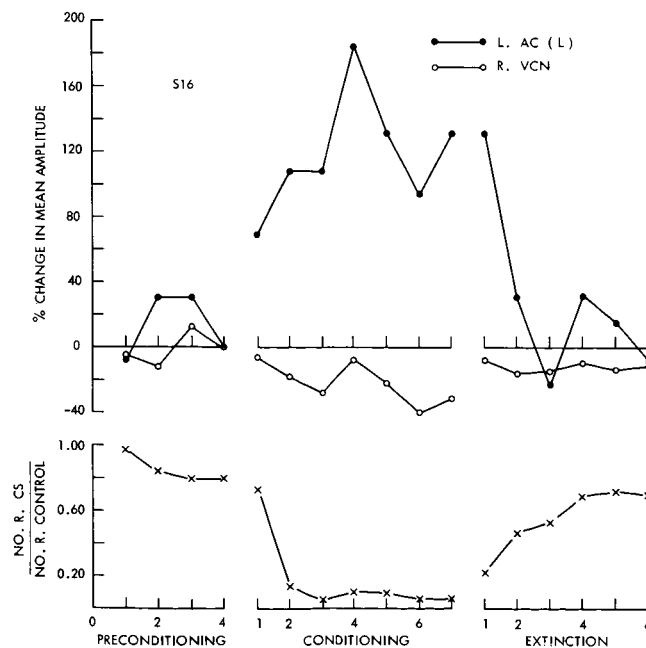


Fig. 5. Percentage change in mean amplitudes of late components of click-evoked potentials recorded from left auditory cortex, L. AC(L), and right ventral cochlear nucleus, R. VCN, of S16. Lower graph shows behavioral index as in Fig. 4.

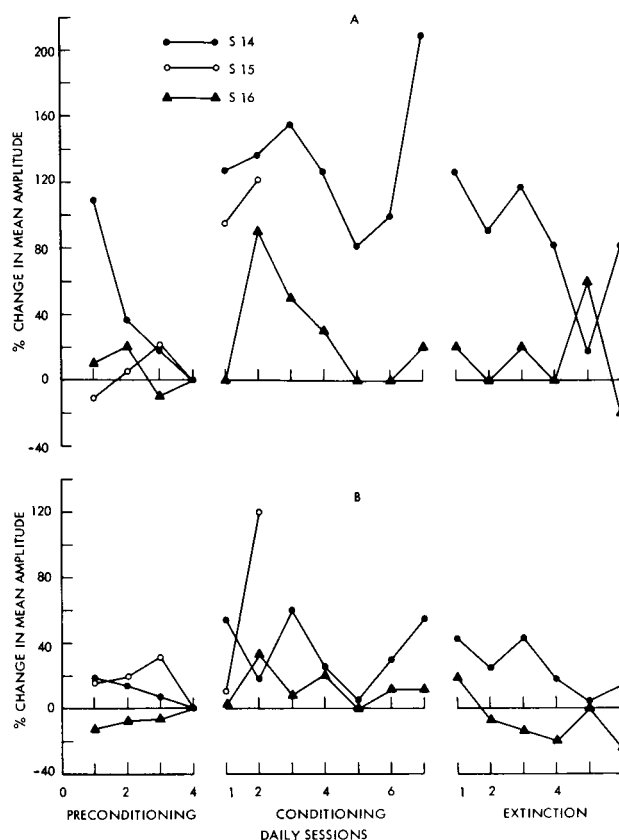


Fig. 6. A: Percentage change in mean amplitudes of first surface positive component of click-evoked cortical responses from 3 subjects plotted as a function of daily sessions. Amplitudes measured from baseline to first positive peak.
B: Plots similar to those in A for early components of cortical evoked responses. Amplitudes measured from first positive peak to first negative peak.

this potential. In this measure the amplitude changes were much more conspicuous, but no less variable. The curves for S16 show a rather interesting pattern with an initial increase during the first few conditioning sessions, but little evidence of increased response amplitudes in later sessions. These irregular patterns of change in the amplitudes of early cortical potentials have appeared throughout the course of this investigation.

Click-evoked potentials recorded from ventral cochlear nucleus showed no evidence of increased amplitudes during conditioning. Quite the contrary, there was some indication of a small decrease in the amplitudes of these potentials. This can be seen in Figs. 4 and 5, in which the relative changes in amplitude have been plotted as a function of daily experimental sessions.

Examples of the changes noted in click-evoked potentials recorded from mesencephalic reticular formation can be seen in Fig. 7. These average responses were taken from the last preconditioning session and second conditioning session, as were the

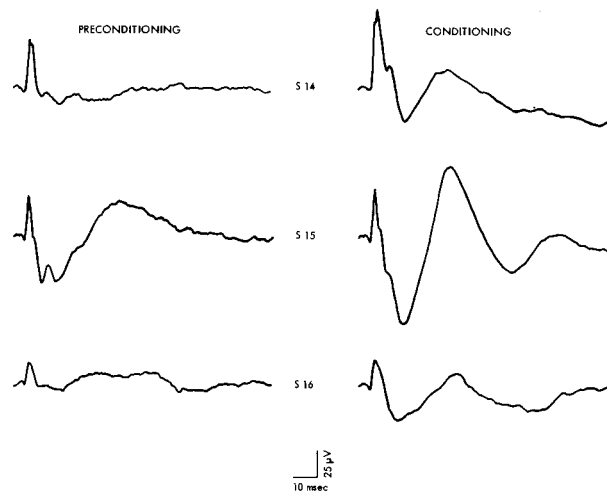


Fig. 7. Average click-evoked responses recorded from mesencephalic reticular formation in 3 subjects. Potentials on left were taken from the last preconditioning session; those on right from the second day of conditioning in CER situation. Averages were computed from first 550 evoked potentials recorded in each session.

cortical potentials shown in Fig. 3. The first sharp negative peak of the potentials recorded from the reticular formation is probably due to activity in the lateral lemniscus. Detailed arguments to support this notion will be presented elsewhere. The slower positive-negative complex with peak latencies of approximately 15 and 40 msec can be attributed with reasonable certainty to the reticular formation. This diphasic wave is often followed by a series of rhythmic waves that become more prominent during aversive conditioning. We have not been able to record this activity from more lateral electrode placements. In any case, it is clear that these click-evoked potentials recorded from mesencephalic reticular formation undergo significant changes during the establishment of a conditioned emotional response. The course of these changes was quite parallel to the alterations in late cortical responses.

4.1.3 Discussion

Data from this experiment leave no doubt that sensory evoked potentials are appreciably altered during aversive conditioning. But the patterns of change are by no means simple. Changes in late components of cortical responses and in evoked potentials recorded from the reticular formation seemed to follow rather closely the establishment of a CER. Early components of cortical responses were also affected by the conditioning procedures, but these changes seemed to bear no simple relationship to the conditioned changes in behavior. The suggestion of diminished amplitudes in responses of ventral cochlear nucleus seems paradoxical. Early cortical potentials, attributable, in part at least, to activity in the classical auditory projection, evidenced changes, however irregular, in the opposite direction. These patterns of change will be considered again

when data sufficient to justify their consideration have been presented. For the moment, the most important question is whether or not the systematic changes found in the potentials from auditory cortex and reticular formation were uniquely related to the acquired conditional or discriminative properties of the click stimulus. In the second experiment it will become apparent that they were not.

4.2 EXPERIMENT II

If the changes in acoustically evoked potentials described in the first experiment were due to acquired conditional properties of the click stimulus, they should not occur when the same conditioned response is established to a CS of another sensory modality. If, for example, a visual CS is used in conditioning an emotional response, we should not expect to find increases in the amplitudes of acoustically evoked potentials recorded during the acquisition of this behavior.

In the first phase of this experiment clicks were established as conditional stimuli in the same CER situation that was employed in the first experiment. In the second part of the experiment, following extinction of the emotional response to the click stimulus, the same behavior was reestablished with a visual CS; namely, a change in the ambient illumination of the test chamber. During this phase of the conditioning clicks were presented throughout experimental sessions. It was possible, therefore, to record click-evoked potentials during presentations of the visual stimulus to determine if there were any alterations in auditory potentials as the behavior was brought under control of the photic stimulus. It became quite apparent that click-evoked potentials were altered by these procedures in much the same way they were when clicks were employed as the CS in the first part of the experiment.

4.2.1 Methods

Three rats, S1, S2, and S3, were used in this experiment. Monopolar ball-tip electrodes were implanted bilaterally on the dura over auditory cortex.

Bar-pressing was established and maintained as in the first experiment. When this behavior had become reasonably stable, clicks were introduced for the first time.

Unlike the other experiments described in this report, this one did not employ an extensive habituation period prior to the commencement of conditioning. Two subjects, S2 and S3, were exposed to continuous clicks, presented at 1/sec, for approximately an hour during the last preconditioning session. No clicks were presented to S1 before the first conditioning trial.

A CER was then established under conditions quite like those described in the first experiment. One-minute trains of 1/sec clicks constituted the CS. The UCS was an unavoidable shock delivered to the feet through the grid floor. Approximately 10 trials were presented in each experimental session, although in several instances as few as five trials were given in sessions cut short of excessive "freezing" by the subjects.

Four conditioning sessions were followed by three days of extinction. The CER with

the click CS was then reconditioned and extinguished two more times. Following the last extinction of the emotional response to the click CS, 1/sec clicks were presented in one session, throughout the experimental period. Food reinforcements were the only other stimuli presented during this session. On the day that followed, the clicks were presented in the same way during the entire session, but a CER was once again established, this time with a visual CS. Lights in the test chamber were turned off for one minute, and this stimulus was followed by shock. In succeeding sessions the conditioned response to the visual stimulus was extinguished, then reconditioned and extinguished two more times. The number of sessions devoted to each change in procedure varied slightly for the individual subjects, but successive reconditionings required only a day or two. Extinction periods ranged from 3 to 5 days.

Throughout the procedures just described, click-evoked potentials were recorded only during click or photic CS periods. Following these procedures, the CER was once more established with the visual CS, and provisions were made to record click-evoked potentials during one-minute control periods that immediately preceded each CS, as well as during CS presentations.

4.2.2 Results

Cortical click-evoked potentials underwent systematic changes in waveform during the first conditioning and extinction periods that were due, apparently, to the omission of an extended habituation period. One feature of these changes in waveform is illustrated in Fig. 8. Average evoked responses from one subject are shown for alternate

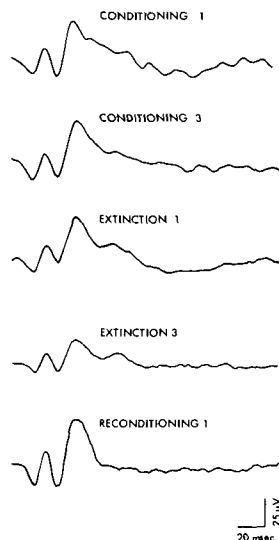


Fig. 8. Average click-evoked cortical responses from S2 for selected sessions of first conditioning and extinction periods. Sessions are noted above the traces. A gradual diminution of a late slow negative wave results in a "sharpening" of the negative peak at approximately 45 msec. Averages were computed from approximately 500 evoked potentials.

days of conditioning and extinction periods and for the first reconditioning session. In the first few sessions the late negative wave with a peak at approximately 45 msec was followed by a slow negative potential so that the peak at 45 msec appeared to have a

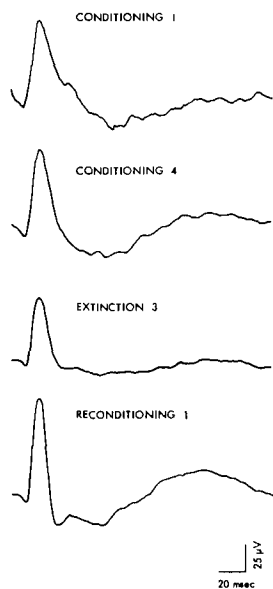


Fig. 9. Average click-evoked cortical responses from S1 presented as in Fig. 8. Gradual increase in positive component with peak at 30 msec, not seen as such until the last trace, yields "sharpening" of the first negative wave.

slow falling phase. This slow negative potential showed an orderly diminution in successive sessions of both conditioning and extinction periods. By the first day of reconditioning it was essentially gone, and the negative peak at 45 msec appeared much sharper. Subject S3 showed precisely the same pattern of change.

The second feature of the change in waveform can be seen in Fig. 9, in which average cortical responses from S1 are presented. Here the cortical potentials had a somewhat different form initially than those of the other subjects. The positive peak at approximately 30 msec was not apparent through most of this period and did not become so until the first day of reconditioning. The "sharpening" of the first negative wave that is apparent in the potentials of Fig. 9 was

due presumably to the gradual increase in this positive component. In later conditioning sessions it became even more prominent. In other experiments we have seen both kinds of changes during extended habituation periods: the diminution of the late slow negativity and the growth of the second positive wave. Both changes produce a "sharpening" of all components of cortical evoked responses.

Changes in waveform that occurred in the first 8-10 experimental sessions did not obscure the general changes in amplitude of cortical responses. During conditioning click-evoked responses were large. Amplitudes decreased during extinction and grew again with reconditioning. This pattern was maintained throughout the experiment. An over-all view of the changes in amplitude of the late components of cortical responses can be seen in Fig. 10. Mean amplitudes have been plotted as a function of daily sessions in which the CER was reconditioned and extinguished several times, first with a click CS and later with a photic CS. The plots begin with the final extinction session following the initial conditioning, i. e., after the changes in waveform were, for the most part, accomplished. Amplitudes have not been plotted as relative changes, as they are in the rest of this report, because a rational, stable reference was not available. The behavioral index introduced in the first experiment is shown in the lower graphs.

In spite of some irregularities, especially in behavioral measures for S1, it is apparent that the conditioned suppression of bar-pressing was accompanied by increases in amplitudes of late cortical potentials. With extinction of the emotional response,

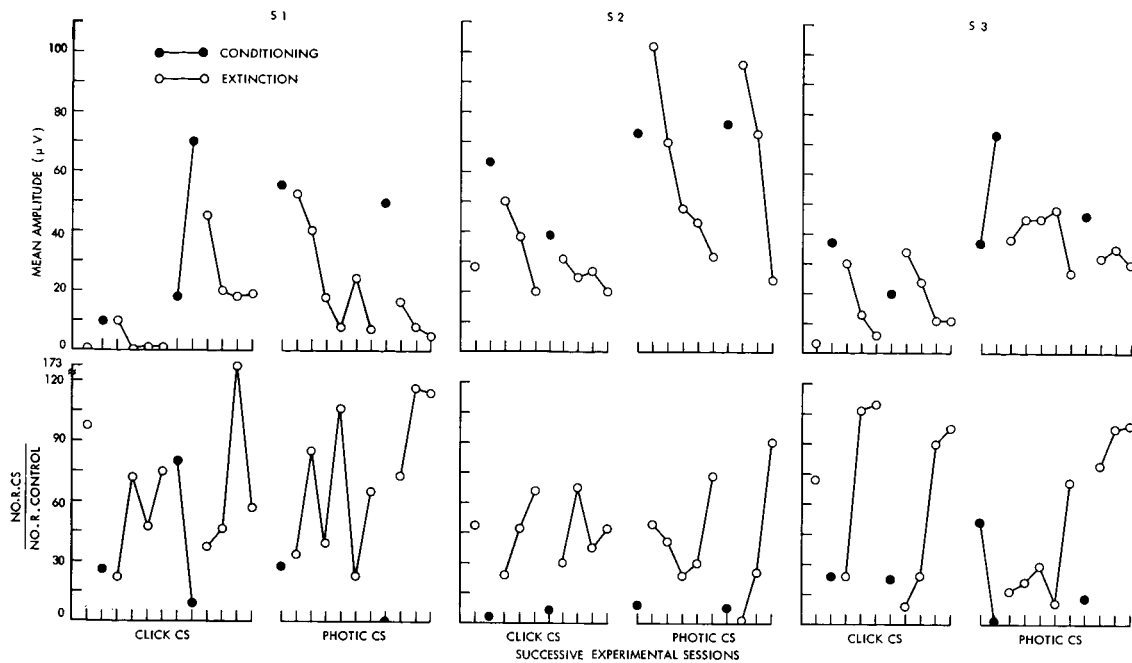


Fig. 10. Upper: Mean amplitudes of late components of click-evoked cortical potentials plotted for successive reconditioning and extinction sessions in CER situation, first with click CS, then with photic CS. Lower: Behavioral index showing conditioned suppression of bar-pressing in conditioning sessions (filled circles) and during extinction of response (open circles).

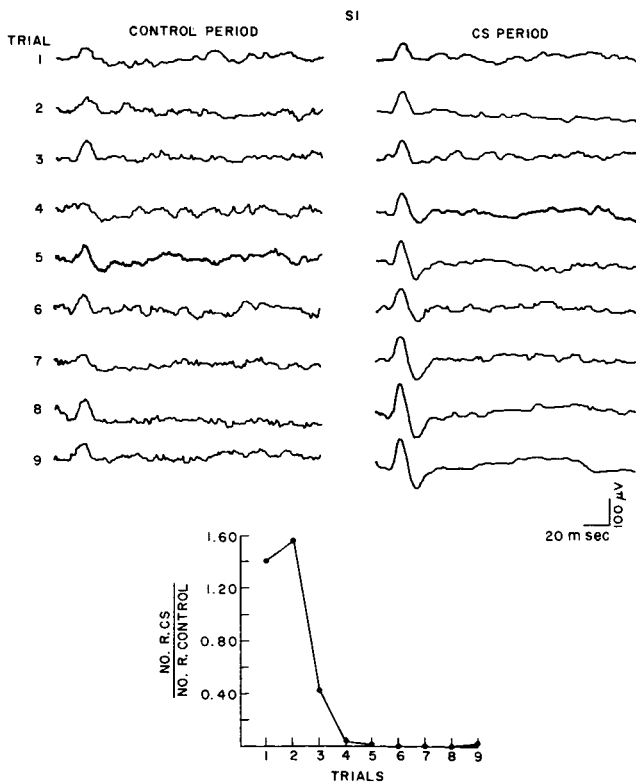


Fig. 11. Average click-evoked cortical potentials from successive trials of reconditioning session with photic CS for subject S1. Reconditioning of CER is shown in the behavioral index in the lower graph.

amplitudes returned to relatively low levels. The course of the changes in neuroelectric and behavioral measures was remarkably similar in some instances, e. g., in the plots for S3.

It is apparent in Fig. 10 that the changes in auditory potentials were not dependent upon establishment of the click as a CS. Amplitudes of click-evoked potentials showed similar increases when the CER was elicited by a change in ambient illumination.

This can be seen in another way in Fig. 11. Data presented here were obtained from the final reconditioning session in which the photic stimulus was employed as CS. Click-evoked potentials were recorded during CS presentations and during control periods immediately preceding them. Average evoked responses from both control and CS periods are shown for each conditioning trial, and the changes in behavior are shown in the lower graph. Conditioned suppression of bar-pressing was established quite rapidly, and this was undoubtedly due to the subject's extensive experience in this situation. It was rather complete by the fourth trial, and it can be seen that cortical potentials recorded in CS periods were noticeably larger at this point. They continued to grow in the trials that followed. In contrast, evoked potentials recorded during control periods showed no such systematic change and remained relatively small throughout the session.

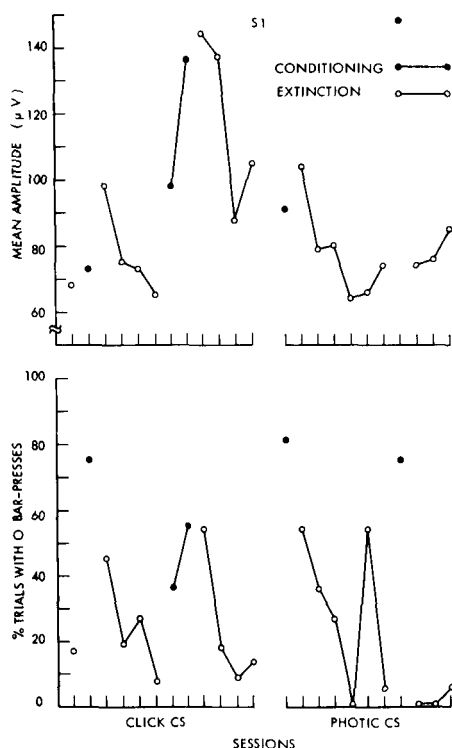


Fig. 12. Upper: Mean amplitudes of early components of click-evoked cortical potentials plotted as a function of successive reconditioning (filled circles) and extinction (open circles) sessions for S1. Lower: Percentage of trials in each session in which bar-pressing was completely suppressed (0 bar presses) during CS presentations.

Changes in click-evoked cortical potentials found in this experiment were generally reflected in all components of the evoked response. For the most part, amplitude changes in the early components were quite parallel to those in the late components,

much more so than they were in the first experiment. An example of the changes in peak-to-peak amplitudes of the initial surface positive and first surface negative potentials can be seen in Fig. 12. A different behavioral index has been employed in the lower part of this figure; namely, the percentage of trials in each session during which bar-pressing was completely suppressed. This behavioral measure provided "smoother" curves for S1 whose bar-pressing behavior was quite erratic during CS periods. With the exception of one data point, the changes in this behavioral index and the amplitude changes in early components of cortical responses appear quite parallel.

4.2.3 Discussion

Increases in the amplitudes of cortical click-evoked potentials were clearly correlated with the conditioned changes in behavior, but it became apparent in this experiment that the changes were not related to acquired conditional properties of the click stimulus. Similar changes in auditory potentials were just as obvious when the CER was elicited by a visual CS. The data strongly suggest that alterations in acoustically evoked potentials during aversive conditioning are related to some more general factor or factors that were correlated in this experiment with the occurrence of the conditioned emotional response.

The changes in waveforms of cortical responses seen in the initial stages of this experiment have not been encountered during conditioning in other experiments when extended habituation periods preceded conditioning. We have, however, observed such changes in evoked potentials recorded during habituation procedures. These facts seem to indicate that changes in sensory evoked potentials related to habituation procedures on the one hand, and to conditioning operations on the other are not simply the reverse of one another. They are apparently due to processes which are at least partially independent and may in some circumstances operate concurrently.

4.3 EXPERIMENT III

The purpose of this experiment was threefold: (i) The second experiment showed that increases in amplitudes of auditory cortical potentials were correlated with conditioned changes in behavior when a visual stimulus served as the conditional one. It was conceivable, however, that these alterations were related to the conditioning history of the subjects. In the first phase of that experiment, clicks had served as the CS. To evaluate this possibility, a photic CS was employed in the first conditioning of subjects in the present experiment, and click-evoked potentials were recorded throughout this period. (ii) Early components of cortical evoked responses were found to increase during conditioning in both experiments described above. This suggested that stimulus variables might be operative under the conditions of our experiments and that changes in evoked activity might have been due to changes in the acoustic input. Teas and Kiang⁷⁴ have shown that the primary components of auditory cortical evoked potentials in the unanesthetized cat are sensitive to stimulus parameters, while the later components appear to

be influenced by more complex variables, including level of arousal. Stimulus variables were also suspect, because of repeated demonstrations that with free-field sound stimulation orientation of the head is important in determining effective sound-pressure levels.^{60,71,76} Movement-related variables (to be discussed in greater detail in later experiments) may also serve to modify the input to the central auditory system. In view of these considerations, it seemed advisable to measure the input to the central auditory system. To this end, click-evoked potentials from the auditory nerve were recorded during conditioning. (iii) An effort was also made in this experiment to record evoked responses from the medial geniculate body. Throughout these experiments we have encountered difficulties in recording satisfactory evoked potentials from the medial geniculate. In part these have been due to difficulties in achieving good electrode placements, but for reasons that we do not understand, electrodes accurately placed have often yielded poor evoked potentials. Others have noted difficulties in recording evoked potentials from the medial geniculate^{1,55} and the fragility of medial geniculate potentials.⁶⁸

4.3.1 Methods

Four rats were employed. Ball-tip electrodes were implanted extradurally over the auditory cortex of both hemispheres. Electrodes were also implanted bilaterally in ventral cochlear nuclei and in the region of the medial geniculate body. In all 4 subjects at least one electrode was placed within the medial geniculate, but satisfactory evoked potentials were recorded from only two subjects. One electrode in RM-27 was placed in the reticular formation just medial to the geniculate body. This electrode yielded potentials like those recorded from reticular formation in the first experiment.

Animals were trained to press the bar in the usual way, and the behavior was maintained on the same reinforcement schedule employed previously. In 11 preconditioning sessions clicks were presented at a rate of 1/sec throughout each experimental period. Several alterations in the stimulus situation were made during the first 7 days. Evoked responses recorded during the last 4 days of the preconditioning period appeared stable, and conditioning was begun on the twelfth day of click stimulation.

The visual CS consisted of an increase in the ambient illumination of the test chamber for a period of 1 minute. An increase in illumination served as a control for possible sensory interaction effects in the second experiment in which a decrease in illumination was employed as the CS. During conditioning the photic CS was, of course, followed by an unavoidable shock to the feet. Subject RM-26 was given 9 days of conditioning; subjects RM-27 and RM-28 were given 12. The electrode assembly on RM-29 became detached after only 8 days of conditioning, and the animal was sacrificed at that time. Although incomplete, data from this subject have been included with the others. For subjects that completed the experiment, conditioning was followed by 5 days of extinction and 3 reconditioning sessions.

Throughout conditioning, extinction, and reconditioning, click-evoked potentials were

recorded during 1-minute control periods immediately preceding each CS and during the 1-minute CS presentations.

4.3.2 Results

Increases in amplitudes of cortical evoked potentials were again seen with the establishment of a CER to a visual CS. This can be seen in Fig. 13 where average evoked responses from one cortical electrode in each subject are presented. The data were

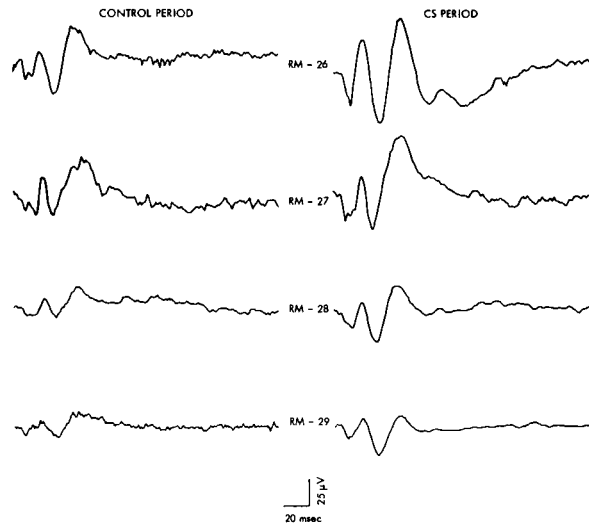


Fig. 13. Average click-evoked cortical potentials from last conditioning session for all 4 subjects. Each average was computed from 550 evoked potentials.

taken from the last day of conditioning. As in previous experiments, the most impressive changes involved the late components. It is clear, however, that the primary components were also increased. Cortical potentials from the opposite hemisphere in each subject evidenced the same kinds of changes.

Evoked responses from the medial geniculate body also increased in amplitude as the CER was established. Examples of these changes can be seen in the upper part of Fig. 14.

An over-all view of the changes in evoked responses of cortex and medial geniculate body is shown in Figs. 15 and 16. Amplitudes have been plotted as differences between potentials recorded during CS periods and those recorded during control periods. Differences are expressed as percentages of control-response amplitudes. A few data points are missing in these curves. Intermittent problems with electrode leads made the data from several sessions unusable.

Although the curves are marred by some irregular data points, it seems clear that click-evoked responses recorded during photic CS presentations were generally much larger than control responses during conditioning. The differences tended to diminish

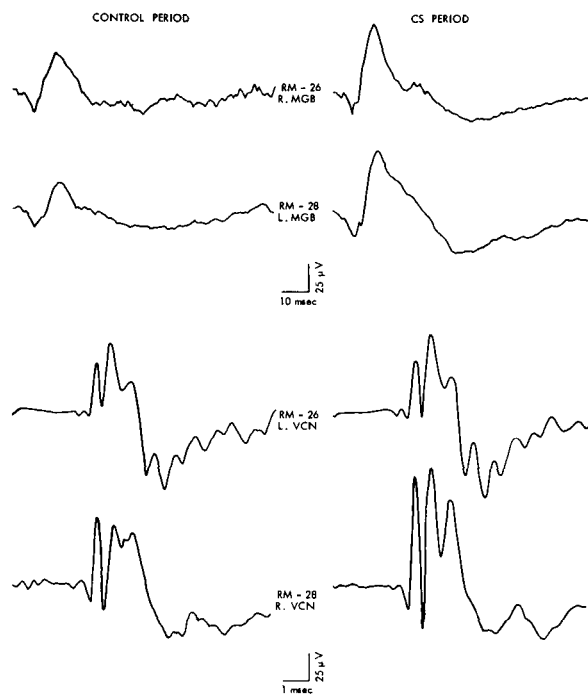


Fig. 14. Average click-evoked potentials recorded from medial geniculate body and ventral cochlear nucleus in 2 subjects on the last day of conditioning. Averages were computed from 550 evoked potentials. Note difference in time scales for MGB and VCN potentials.

during extinction and reappeared with reconditioning. Large increases in amplitude were not seen until the sixth day of conditioning, nor was the suppression of bar-pressing very dramatic until that time. Intensity of the shock UCS was increased during the first 6 days of conditioning when it became apparent that the initial shock intensity was not adequate to achieve a strong CER.

Evoked potentials recorded from the reticular formation in subject RM-27 evidenced similar changes. This can be seen in Fig. 15, in which amplitudes of evoked responses from reticular formation have been plotted in lieu of comparable measures of geniculate potentials.

Potentials recorded from ventral cochlear nucleus presented a most irregular picture. This is apparent in Fig. 14, in which average evoked responses are shown with geniculate potentials from the same subjects. Cochlear nucleus potentials from RM-26 did not appear to be larger during CS periods than they were in control periods. On the other hand, the potentials shown for RM-28 were clearly larger during CS presentations; however, differences of this kind in the data from RM-28 were most variable and seemed to show little correlation with the more systematic changes in late components of cortical and geniculate responses.

Rather surprisingly, amplitudes of potentials recorded from the cochlear nucleus evidenced no consistent relationships with amplitudes of early components of cortical

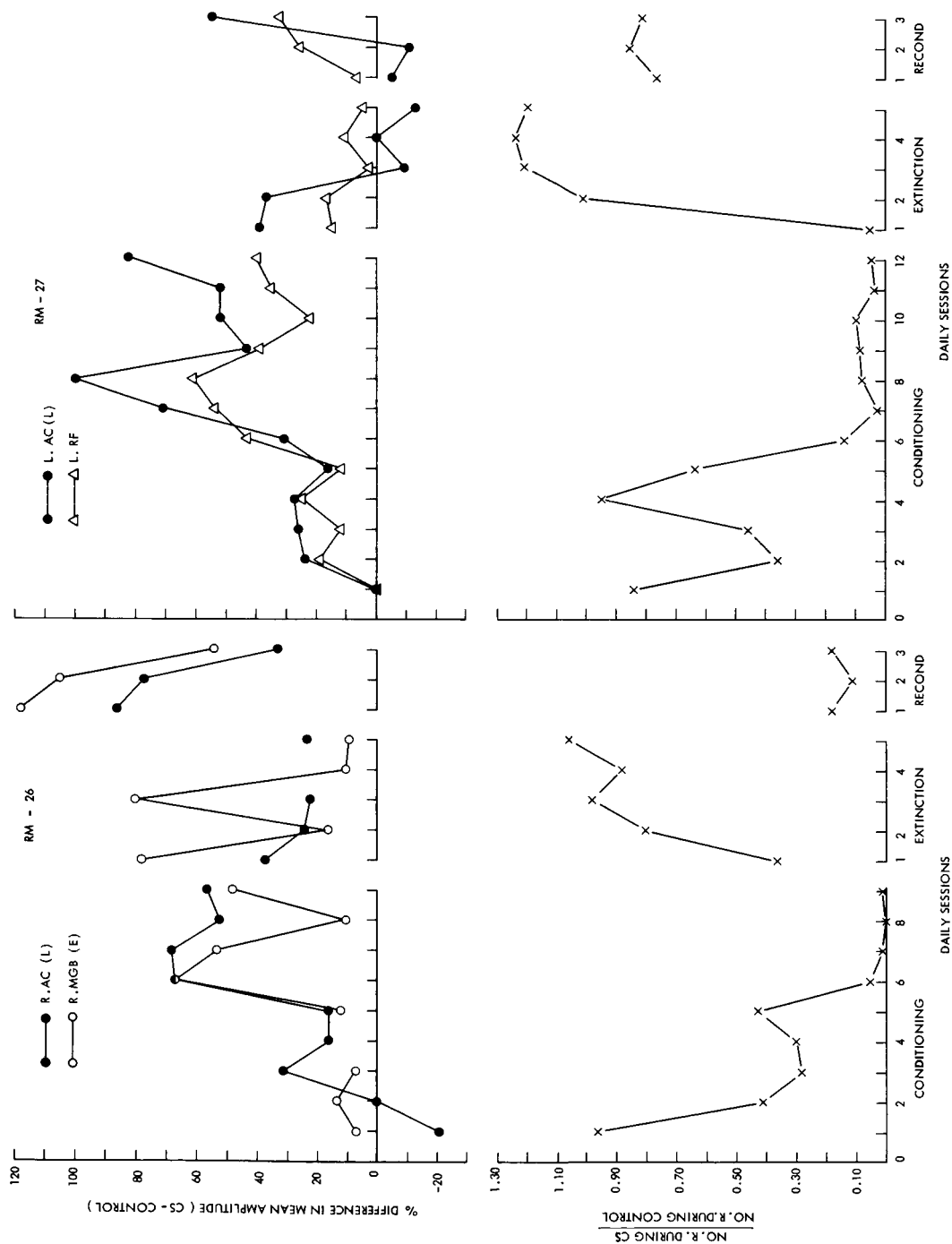


Fig. 15. Relative differences in mean amplitudes of click-evoked potentials recorded during CS and control periods of daily experimental sessions. Amplitudes of late components of cortical responses are shown for both subjects, changes in medial geniculate potentials for RM-26, and changes in responses of mesencephalic reticular formation for RM-27. Behavioral index employed in previous figures is plotted in the lower graphs.

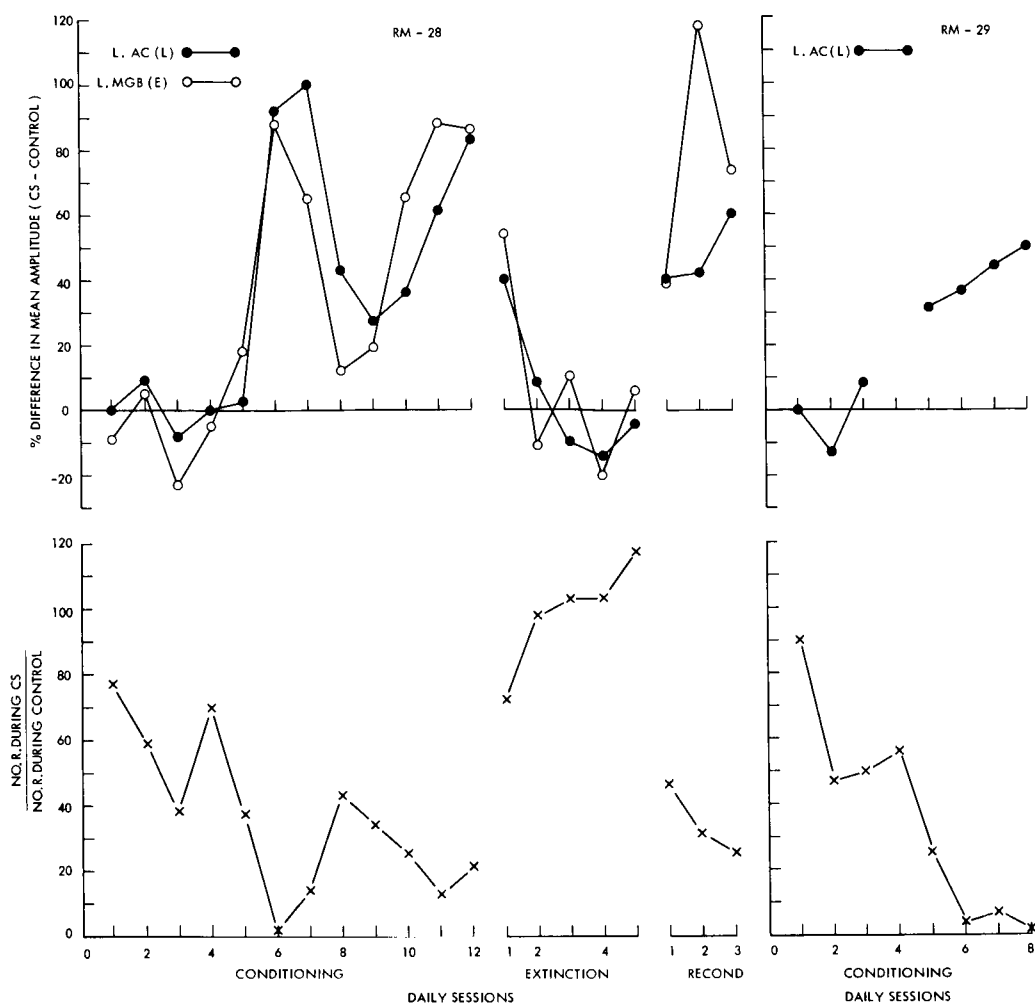


Fig. 16. Relative differences in mean amplitudes of click-evoked potentials presented as in Fig. 15. Amplitudes of late components of cortical responses are shown for both subjects, changes in medial geniculate potentials for RM-26.

and geniculate responses. This is shown in Fig. 17. Here we have plotted the amplitudes of the earliest component of the cochlear nucleus potentials, which were almost certainly due to auditory nerve activity. Plotted also are peak-to-peak amplitudes of the early components of cortical potentials from the same subject. In other respects the graphs are like those presented above. It is clear from Fig. 17 that large changes in the early cortical responses were not accompanied by similar changes in contralateral eighth-nerve responses, not at least during the initial conditioning. It should also be noted that changes in the early cortical responses were, at best, roughly correlated with changes in the late components. A comparison of the curves in Fig. 17 with those in Fig. 15 for the same subject will reveal this.

Additional examples of the changes in eighth-nerve responses are shown in Fig. 18.

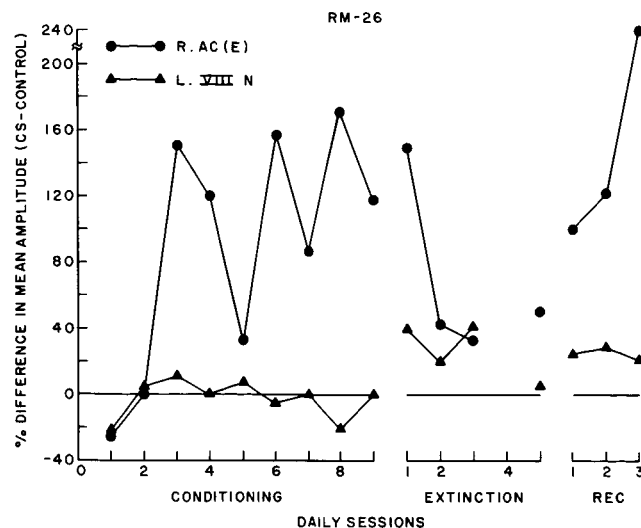


Fig. 17. Relative differences in mean amplitudes of click-evoked potentials recorded during CS and control periods of daily experimental sessions for subject RM-26. Changes in early components of cortical responses are contrasted with relatively stable amplitudes of eighth-nerve potentials during conditioning period.

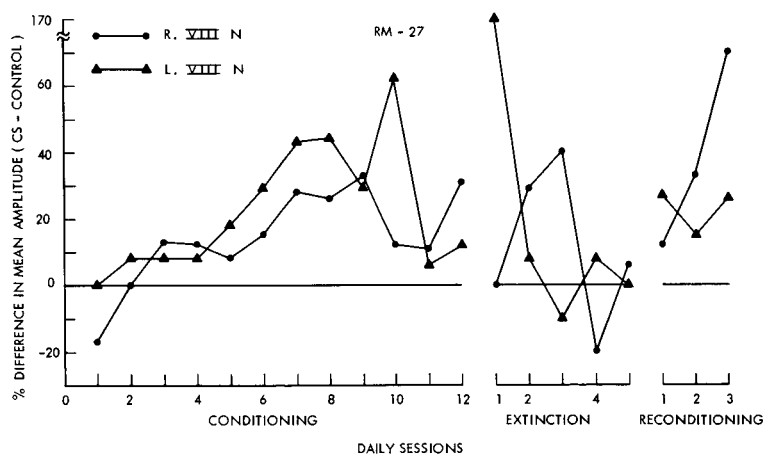


Fig. 18. Relative differences in mean amplitudes of click-evoked eighth-nerve responses recorded in CS and control periods from RM-27.

Relative changes in amplitude have been plotted for eighth-nerve responses recorded from left and right cochlear nuclei in RM-27. The curves reveal trends similar to those seen in potentials recorded from more central sites, but the variability in eighth-nerve potentials weakened the correlations between peripheral and central responses.

4.3.3 Discussion

Click-evoked potentials are clearly altered when a conditioned emotional response is established with a visual CS. These alterations are not dependent upon any prior

conditioning in which clicks have served as conditional stimuli, nor are they a function of the direction of change in the photic stimulus. An increase or decrease in ambient illumination served equally well as conditional stimuli in this and the previous experiment, and changes in click-evoked potentials were correlated with the acquisition of a CER under both conditions. The conclusion seems inescapable, therefore, that changes in click-evoked potentials which are found when clicks are employed as conditional stimuli are not related to acquired conditional properties of the auditory stimulus. To put it another way, the changes are not related to any neural mechanisms underlying conditioning; they appear to be a function of some more general change in the nervous system.

We were rather surprised to find that changes in early components of cortical responses, which were not consistently related to the conditioned changes in behavior, were not closely related either to the changes in eighth-nerve and cochlear-nucleus responses. All of these potentials were appreciably altered during conditioning, but the changes appeared to be largely independent. Because, in some cases at least, the eighth-nerve responses did undergo significant increases during conditioning, we cannot rule out stimulus variables as confounding factors in this experimental situation. But it is clear that the systematic changes in amplitudes of late cortical potentials were not dependent upon changes in the input to the central nervous system. Nor were they dependent upon parallel changes in the early components of the same responses.

4.4 EXPERIMENT IV

The changes in acoustically evoked potentials described above have been attributed to some general change in the organism during conditioning. There are two obvious possibilities. The first is the emotional response itself. Anxiety or fear is an extremely generalized reaction with many response components. These include alterations in cardiac and respiratory rates, piloerection, several important glandular responses and, very often, quite dramatic changes in skeletal-muscular behavior. It would not seem strange, therefore, to find that sensory activity in the C.N.S. is also altered in the frightened animal.

A demonstration that fear was the critical factor requires, at the very least, elimination of the second possibility, namely, a radical reduction in the amount of movement that typically is an important component of the conditioned emotional response. The frightened rat in CER situations often "freezes" in the presence of the CS. There are several reasons why this elimination of nearly all movement might in itself account for the increases in sensory evoked potentials.

Carmel and Starr¹² have shown that in unanesthetized cats many kinds of body movements are accompanied by contractions of the middle-ear muscles. It has also been demonstrated that contractions of the middle-ear muscles often accompany eye movements and other body movements during paradoxical sleep, as well as in waking states.^{4, 5, 19} Contractions of the middle-ear muscles are known to attenuate the acoustic input to the cochlea.^{21, 28, 31} If the reduction in general body movement associated with the conditioned suppression of bar-pressing

is accompanied by a reduction in the activity of middle-ear muscles, one would expect an increase in amplitudes of auditory potentials when a CER occurs.

Movement has been implicated in another way as a variable affecting acoustically evoked potentials. Starr⁷³ has presented evidence suggesting that reductions in auditory cortical potentials related to movement are not due solely to middle-ear mechanisms. Starr found that by cutting middle-ear muscles reductions in evoked responses from subcortical auditory sites during movement were eliminated, but cortical potentials continued to show reductions when the cat subjects moved. This suggested the operation of some central mechanism.

Still another way that movement can affect acoustically evoked potentials is through the noise it creates, noise that can serve as a masking stimulus. In experiments reported here, an effort was made to eliminate apparatus noise, but the elimination of all noise associated with body movements is impossible.

In view of these considerations it seemed possible that the reduction in movement that often accompanies a CER might itself be sufficient to account for the increased amplitudes of click-evoked potentials. We have already noted that Galambos, Sheatz, and Vernier³⁰ have reported augmented amplitudes of click-evoked potentials in Flax-edilized cats during conditioning, and that Moushegian et al.⁶³ have found similar increases following section of the middle-ear muscles. There was reason to believe, therefore, that the changes in auditory potentials described above could not be accounted for solely in terms of movement or movement-related variables. Nevertheless, it seemed advisable to determine what role, if any, movement might play in the CER situation.

Electrical stimulation of peripheral sites in the auditory projection seemed to offer a suitable way to bypass peripheral auditory mechanisms that might be operative during movement. Cutting middle-ear muscles in the rat seemed too difficult to do well, and such an operation would eliminate only one of the mechanisms involved in the modification of auditory activity during movement. Electrical stimulation offered an added advantage by making it possible to provide a constant input to the auditory system in the form of constant current pulses. As we could not be certain that stimulus variables had played no role in altering evoked potentials in previous experiments, this advantage seemed important. In the experiment described below, electrically evoked potentials were recorded from several auditory structures during the acquisition of a conditioned emotional response.

4.4.1 Methods

Six rats were employed in this experiment. In three, bipolar stimulating electrodes were implanted in the cochlear nucleus. Electrodes were made of twisted pairs of teflon-insulated stainless-steel wire, 0.005 in. in diameter. The distance between exposed tips was 1 mm. Examination of the brain at the end of the experiment showed that electrodes had been placed in the ventral cochlear nucleus in subjects RM-33 and RM-36, and slightly dorsal to the dorsal cochlear nucleus in RM-35.

In three animals, RM-38, RM-39, RM-40, stimulating electrodes were implanted in the cochlea. This was done in an effort to obtain an input to the central auditory system that better approximated the input evoked by click stimulation. In these animals the tympanic bulla of one ear was opened, and the tympanic membrane, the ossicles, and muscles of the middle ear were removed to expose the cochlea. The 1-mm etched tips of two electrodes were inserted through small holes in adjacent turns of the cochlea and cemented there. The entire middle ear was filled with dental cement, and electrode leads were led subcutaneously to the connector on top of the skull.

Two structures were damaged during implantation of the cochlear stimulating electrodes: the facial nerve and the pterygopalatine portion of the internal carotid artery. Injury to the seventh nerve resulted in left facial palsies in all three subjects. Damage of the artery in two subjects led to ischemia of the ipsilateral retina and blindness in that eye. Wound infections also occurred in the same two subjects, RM-38 and RM-40, but responded well to antibiotic therapy and drainage. During the conditioning phase of the experiment behavior of the animals was normal, except for an unusual orientation of the head caused, presumably, by the unilateral blindness.

Electrodes were also implanted bilaterally in the usual way over auditory cortex. In 4 subjects deep monopolar electrodes were placed in anterior parts of the inferior colliculus contralateral to the stimulated side. Two subjects carried similar electrodes in the region of the contralateral lateral lemniscus.

One subject with cochlear stimulating electrodes, RM-39, completed the experiment, but an infiltration of tissue between skull and electrode assembly had slowly lifted the assembly from the skull. There was a progressive diminution of cortical responses recorded from this animal, as well as some minor changes in potentials recorded from inferior colliculus.

The apparatus and behavioral procedures were quite similar to those employed in the previous experiment. A 1-minute increase in ambient illumination of the test chamber served as the CS for a CER. Electrical stimulation of the cochlea or the cochlear nucleus was employed in place of click stimuli. The electrical stimulus was presented at a rate of 1/sec throughout experimental sessions, as the clicks had been in the previous experiment. The electrical stimulus consisted of a 0.1-msec square pulse applied to the electrodes through an isolation transformer and a 1-k Ω series resistor. Current levels were adjusted for individual subjects to evoke small but measurable potentials. Currents varied from 34 μ A to 200 μ A. Electrode impedances ranged from 23 k Ω to 73 k Ω . Stimulus currents were monitored throughout daily sessions and were found to be quite stable over the course of the experiment.

Following the stabilization of bar-pressing, electrical stimulation of the auditory system was introduced during 5-7 preconditioning sessions. Although stimuli were presented throughout each of these sessions, evoked potentials were sampled only during fourteen 1-minute periods. These procedures were followed by conditioning which lasted 6-8 days. This in turn was followed by 4-5 days of extinction. Finally,

the animals were reconditioned in 2-3 sessions. In all but the preconditioning sessions, electrically evoked responses were recorded during CS presentations and 1-minute control periods preceding them.

The three subjects with intact middle ears were then given 7 additional days of conditioning. In the first 6 of these the level of the background masking noise was varied in order to determine whether changes in acoustic input had any effect upon electrically evoked potentials. Noise levels employed were 10 db and 20 db above and 10 db below the level employed during most of the experiment. In the final session, click stimulation was employed to determine the nature of click-evoked potentials from the several electrode sites. Click-evoked potentials were recorded from all electrodes, including those in the cochlear nucleus, and were found to be quite like those recorded from similar placements in other animals in this series of experiments.

Body movements were monitored during some sessions. A simple accelerometer was mounted on the electrode connector for this purpose. It consisted of a bar of piezoelectric crystal taken from an ordinary phonograph cartridge. One end was attached to the connector, and the free end supported a small lead weight. Any movement that we could detect by watching the animals led to the mechanical distortion of the crystal. Potentials generated by these distortions were amplified and recorded. The device provided a crude but sensitive indicator of movement.

4.4.2 Results

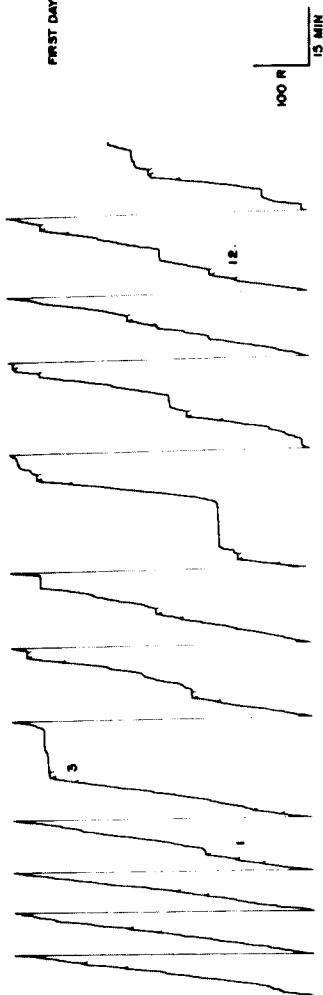
The movement indicator provided a graphic demonstration of the radical reduction in movement that is typically part of the conditioned emotional response. This can be seen in Fig. 19. The cumulative response record and movement records from selected trials of the first conditioning session are presented for subject RM-38. The movement records are simply pen records of voltages recorded from the accelerometer. It is apparent in both measures that the CER developed rapidly. It is also clear from the movement records that the rat barely moved during the twelfth trial, nor did he in later trials. This pattern of behavior has been seen in most, but not all, subjects in these experiments.

Cortical potentials evoked by electrical stimulation of the cochlear nucleus differed appreciably in the 3 subjects stimulated this way. This is apparent in Fig. 20, in which average evoked responses from the last reconditioning session are presented. It is also apparent that the responses of RM-35 and RM-36 were appreciably different from click-evoked cortical potentials recorded in our other experiments. This is not surprising, in view of the great difference in the modes of stimulation.

Cortical responses were clearly altered by the conditioning operations. In general, the potentials were larger in CS periods when the conditioned response was well established. But in this instance, some changes in waveform were too complex to justify such a simple description of the changes brought about through conditioning. Note, for example, in the responses from RM-35 the diminution of the first negative peak in CS periods

RM 38

FIRST DAY OF CONDITIONING

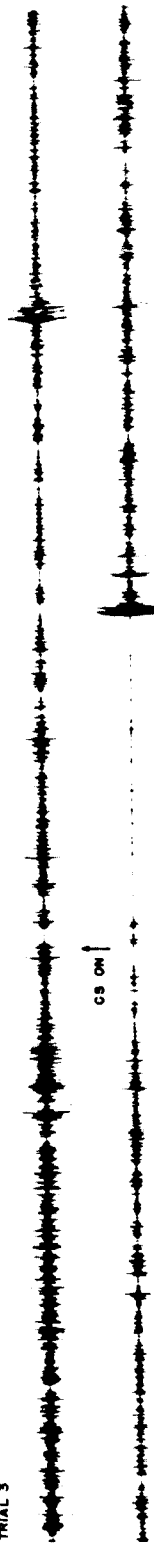


TRIAL 1



CS OFF
SHOCK

TRIAL 3



CS OFF
SHOCK

TRIAL 12



CS OFF
SHOCK

Fig. 19. Cumulative response record from first conditioning session and records of movement from selected trials for subject RM-38. First pip of each trial on cumulative response curves indicates beginning of the control period, second pip CS onset, third pip CS termination and shock UCS. Voltages in movement records from accelerometer on rat's head.

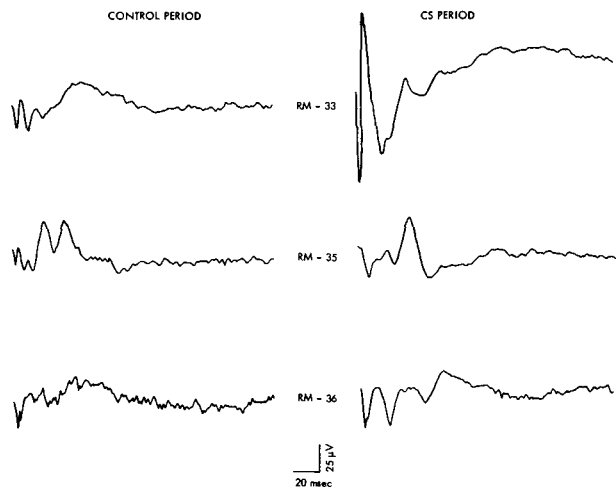


Fig. 20.

Average cortical potentials evoked by electrical stimulation of cochlear nucleus in last reconditioning session for three subjects. Responses are from cortex contralateral to the side of stimulation and were computed from approximately 500 evoked potentials. Traces begin 2 msec after stimulus onset.

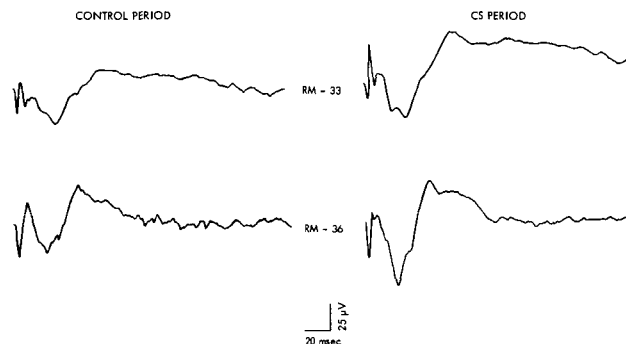


Fig. 21. Average responses recorded from ipsilateral cortex of two subjects in last reconditioning session. Potentials evoked by electrical stimulation of cochlear nucleus. Averages computed from approximately 500 evoked potentials. Traces begin 2 msec after stimulus onset.

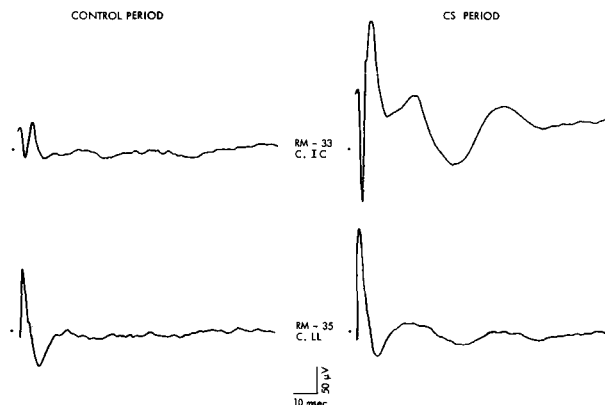


Fig. 22. Average responses to electrical stimulation of cochlear nucleus recorded from contralateral inferior colliculus of subject RM-33 and contralateral lateral lemniscus of RM-35 during last reconditioning session. Traces begin 2 msec after stimulus onset.

that accompanied increases in the later negative and positive waves. With so few subjects it is impossible to analyze these patterns of change. Different as the potentials may have been, it is important that they did show changes with the acquisition of the CER. This can also be seen in Fig. 21 where potentials recorded from ipsilateral cortex are presented for two subjects that had sizable ipsilateral responses.

Oddly enough, potentials recorded from contralateral inferior colliculus in two subjects and lateral lemniscus in the third did not differ significantly from click-evoked potentials recorded from these or other subjects in this study. Examples of these potentials are presented in Fig. 22. The collicular potentials from RM-33 underwent large increases in all components during conditioning. Increases in potentials recorded

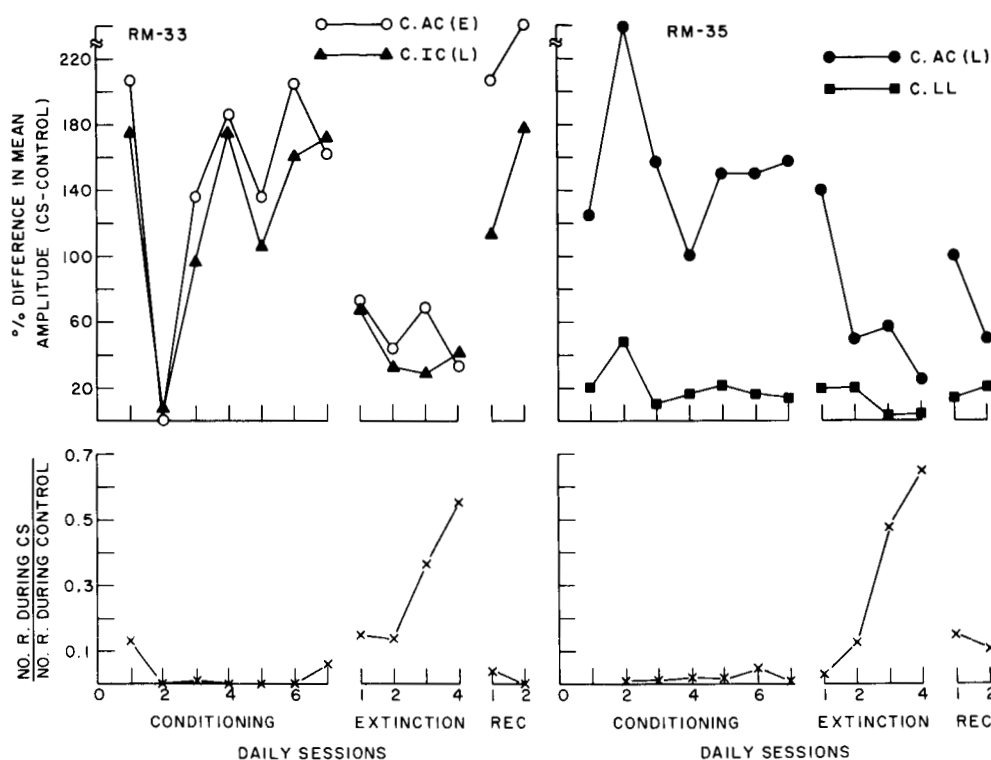


Fig. 23. Differences in mean amplitudes of electrically evoked potentials recorded during CS and control periods of successive experimental sessions. Changes in late components of cortical responses are shown for both subjects, changes in late components of inferior colliculus responses for RM-33, and changes in responses from lateral lemniscus for RM-35. Potentials evoked by electrical stimulation of contralateral cochlear nucleus. Behavioral changes plotted as usual in the lower graphs. Behavioral response counts are not available for RM-35 in first conditioning session.

from lateral lemniscus were much less dramatic, though quite consistent.

The relative magnitudes of changes in auditory potentials is more easily seen in Fig. 23, in which day-by-day changes have been plotted as in previous experiments.

The striking feature of these curves is that several large changes in amplitude were not associated with fluctuations in the behavioral index. On the second day of conditioning, for example, cortical and collicular potentials from RM-33 were of approximately the same amplitude during control and CS periods. Evoked responses in both conditions were very large, and on this day the animal "froze" throughout most of the session. We shall return to this observation presently.

Auditory potentials in three subjects receiving stimulation of the cochlea were also larger in CS periods when the conditioned response was established. Potentials recorded from contralateral cortex and inferior colliculus are shown for subjects RM-38 and RM-40 in Fig. 24. Increases in the amplitudes of late components of all responses are

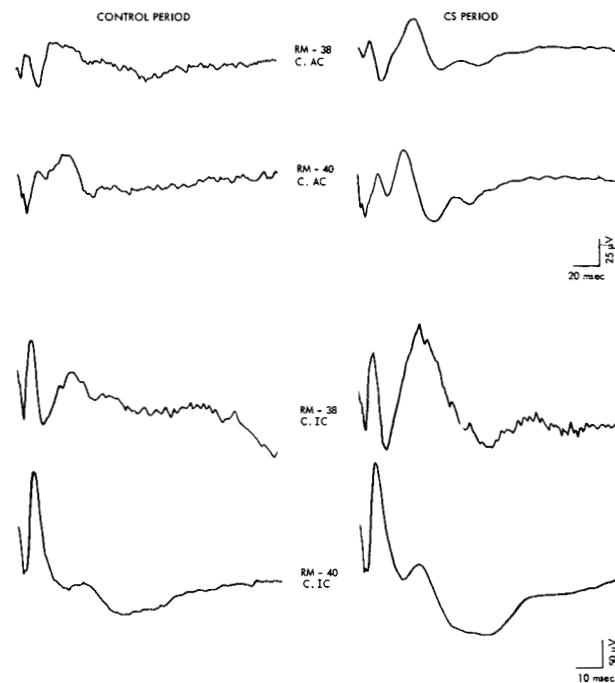


Fig. 24. Average evoked responses recorded from contralateral auditory cortex and inferior colliculus in two subjects during last reconditioning session. Potentials evoked by electrical stimuli applied within the cochlea. Averages computed from approximately 500 evoked potentials. Traces begin 2 msec after stimulus onset.

quite apparent. Similar changes were seen in evoked potentials from RM-39, but progressive alterations resulting from movement of the electrode assembly rendered the data unsuitable for presentation. It should also be noted that cortical and collicular potentials, evoked by electrical stimuli applied within the cochlea were generally quite similar to click-evoked potentials recorded from these structures throughout this investigation.

Changes in the amplitudes of cortical and collicular potentials have been plotted in Fig. 25 in the usual manner. Several features of the data are illustrated here. Late components of potentials recorded from inferior colliculus underwent significant changes during conditioning, extinction and reconditioning, as can be seen in the curves for RM-38; however, early components of these responses showed little evidence of change. This is apparent in the plots for RM-40. The patterns of change in late components of both cortical and collicular responses are of particular interest. During extinction and

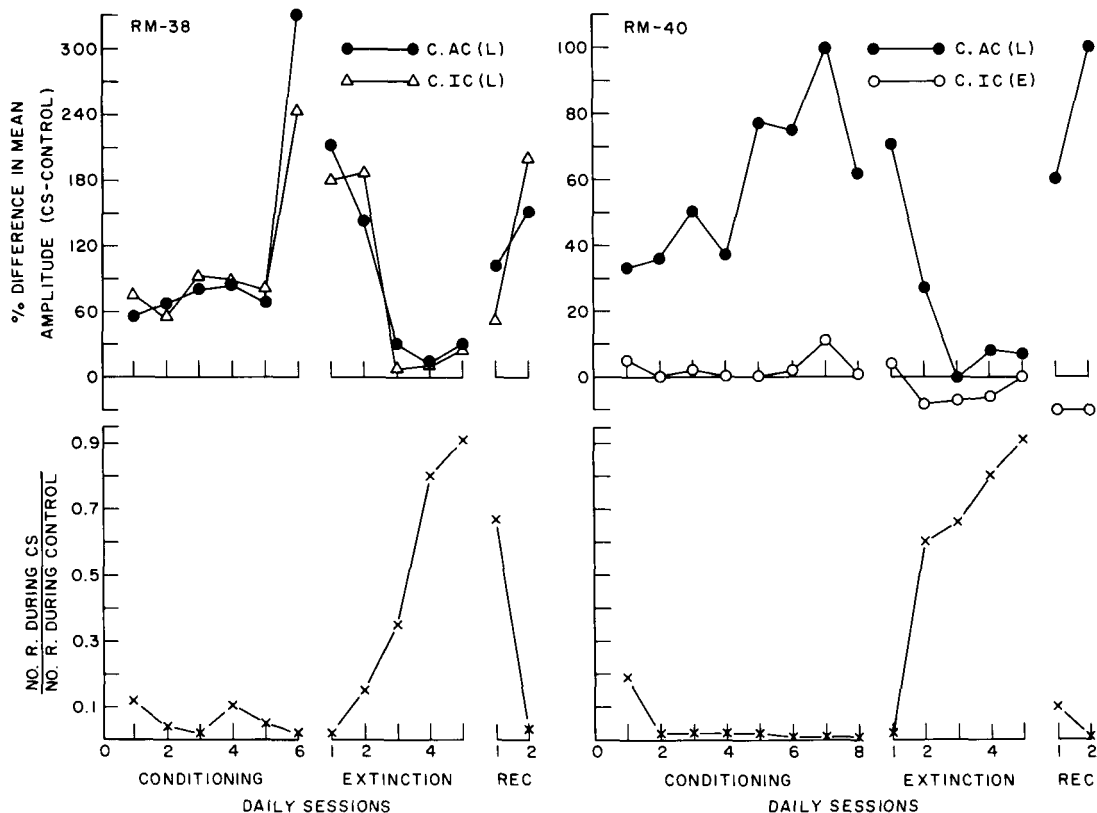


Fig. 25. Relative differences in amplitudes of both cortical and inferior colliculus potentials recorded during CS and control periods. Potentials evoked by electrical stimuli applied within the cochlea. Measure of late components of cortical potentials for RM-38 taken from second negative peak to third positive peak. Changes in late components of IC potentials are shown for RM-38, changes in early components for RM-40. Behavioral index shown in lower graphs.

reconditioning, relative differences in amplitude of potentials recorded during CS and control periods seemed directly related to strength of the CER. But during the initial conditioning period large changes in the measure of relative amplitudes were not associated with comparable changes in the behavioral index. In particular, the large increase on the sixth day of conditioning in the amplitude measure for both cortical and collicular potentials in RM-38, and the progressive increase in the measure of cortical potentials

in RM-40, were certainly not predictable from the behavioral measure that we have employed. This points to a weakness in this measure, i. e., it is insensitive to changes in behavior during control periods when bar-pressing in CS periods has been suppressed. More important are the discrepancies between behavioral index and measure of evoked potentials which point to significant aspects of the changes in behavior and evoked potentials during aversive conditioning.

In the upper portion of Fig. 26 mean amplitudes of late cortical potentials from RM-38 have been plotted separately for daily control and CS periods. Also plotted are amplitudes of potentials recorded in 5 preconditioning sessions. In the lower portion of

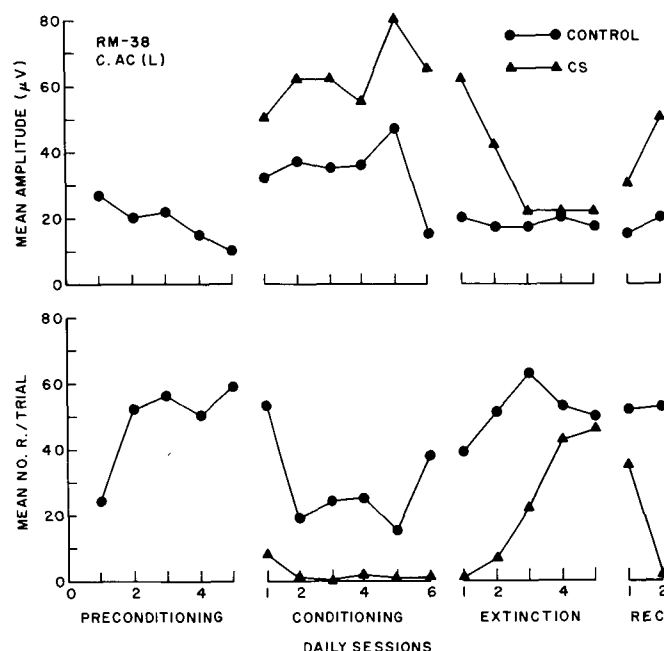


Fig. 26. Upper: Mean absolute amplitudes of late components of electrically evoked cortical responses plotted separately for CS and control periods as a function of experimental sessions. Control data from 5 preconditioning sessions are also included.

Lower: Mean number of bar-presses per trial plotted separately for CS and control periods in successive daily sessions. No CS presentations in preconditioning period.

the figure, the mean number of bar-presses that occurred in the same periods are plotted separately. Note, first of all, that with the commencement of conditioning there was an appreciable increase in the potentials recorded during control periods. This increase was maintained until the last day of conditioning and was associated with a significant reduction in bar-pressing during control periods. If the suppression of bar-pressing can be taken as an indicant of fear under these kinds of experimental conditions (and there is every reason to believe that it can), then the animal was frightened not only

during CS presentations, but also in the absence of the CS. Not until the last day of conditioning was the animal sufficiently at ease in the absence of the CS that bar-pressing assumed rates comparable to those in preconditioning sessions, i. e., before the introduction of shock. With this increase in bar-pressing evoked potentials decreased in amplitude during control periods, though not very much during CS periods, thereby yielding the large amplitude difference that was seen in Fig. 25 for the last day of conditioning. With extinction and reconditioning there was very little change in behavior or cortical potentials during control periods, except perhaps in the final return of bar-pressing rates to those of preconditioning sessions. Differences in evoked responses and behavior during these phases of the experiment reflected, therefore, the changes found in CS periods.

We have already hinted at a similar explanation for the apparently wayward data points in the curves for RM-33 shown in Fig. 23. On the second day of conditioning, RM-33 bar-pressed in only 2 of 10 control periods, and was obviously frightened throughout most of the session. Evoked potentials were appropriately large with the occurrence

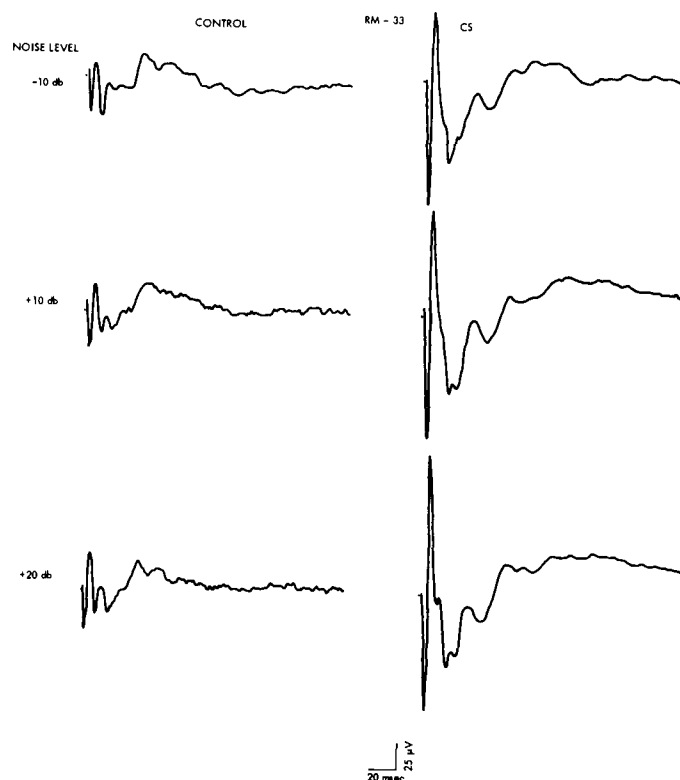


Fig. 27. Averages of cortical potentials evoked by electrical stimulation of ventral cochlear nucleus in RM-33 during 3 conditioning sessions with different levels of background noise. Noise levels referred to level employed in principal part of the experiment. Each average computed from approximately 500 evoked potentials. Traces begin 2 msec after stimulus onset.

of conditioned or unconditioned fear.

Variations in the level of background masking noise over a 30-db range affected the electrically evoked potentials in only minor ways and did not systematically influence the amplitude increases during CS presentations. This is readily seen in Fig. 27, where average evoked cortical responses from three sessions are presented for RM-33. Conditioning was continued in these sessions, and for each day the noise level indicated in Fig. 27 was employed throughout the experimental session. The data indicate that possible alterations in the acoustic environment that might have been correlated with conditioned changes in behavior had little, if any, significance in this situation. It should perhaps be noted that the 20-db noise level was sufficiently loud to depress markedly bar-pressing rates in all three subjects.

4.4.3 Discussion

Data presented above would seem to eliminate two factors that might possibly have accounted for changes in acoustically evoked potentials in CER situations: (i) differences in activity of middle-ear muscles associated with differences in amount of movement during control and CS periods, (ii) alterations in the acoustic input related to movement or other factors. The use of electrical stimuli removed any possibility that uncontrolled, but systematic, fluctuations in stimulus intensity were responsible for the changes in evoked potentials. Moreover, the demonstration that orderly changes in evoked potentials were independent of large variations in background noise would seem to rule out an explanation in terms of this variable. Although this finding cannot be generalized to conditions of physiological acoustic stimulation, other data indicate that amplitude increases in acoustically evoked potentials when a rat freezes are not due to reductions in background noise. Teas and Kiang⁷⁴ have shown that reductions affect early, as well as late, components of click-evoked cortical potentials. But we have seen that increases in the amplitudes of late components during conditioning are not necessarily accompanied by increases in the early cortical responses. Data from a later experiment will also be relevant to this point.

It was also shown that the amplitude increases in auditory responses were not dependent upon the occurrence of a conditioned emotional response. With the introduction of shock there was a general depression of bar-pressing behavior and a concurrent increase in evoked potentials in both control and CS periods. This certainly points to a relationship between fear and an increase in sensory evoked potentials. Insofar as the mode of stimulation ruled out stimulus and movement-related variables, the relationship between fear and augmented evoked potentials is not mitigated by the correlation of fear and "freezing."

Inconsistencies in the patterns of change in early components of cortical potentials were seen in this experiment, as they were in previous ones. Data from several subjects showed increases in amplitudes of early components that were highly correlated with changes in late cortical components. Records from other subjects, however,

showed an inverse relationship between early and late components with reductions in early components during conditioning. We are unable to account for the extreme variability encountered in the early cortical responses. It was characteristic of cortical potentials recorded in this entire series of experiments. Use of electrical stimulation has ruled out the explanation we had previously entertained, namely, that the inconsistencies were related to uncontrolled stimulus variables. In any case, it is again apparent that the changes in late components of the cortical responses were not dependent upon similar changes in early components.

4.5 EXPERIMENT V

Peripheral auditory mechanisms operative during movement were neutralized in the previous experiment through the use of electrical stimulation. But electrical stimulation of more peripheral parts of the auditory system could not rule out centrally mediated changes in evoked potentials related to movement. We have already noted that Starr⁷³ has reported evidence suggesting that some reductions in auditory cortical potentials during movement may be related to central mechanisms. This required that we seek a way to determine whether central factors involved in movement were at all responsible for the modification of acoustically evoked potentials during aversive conditioning.

The most straightforward solution to this problem would seem to require the elimination of differences in amounts of movement that occur during appetitive control and aversive conditioning procedures. In this experiment we attempted to do this by training rats to bar-press at equal rates under two components of a multiple schedule of reinforcement.²³ One component was a Variable Interval (VI) food-reinforcement schedule. The other was a Sidman avoidance schedule.⁷⁰ Under the schedule of food reinforcement, animals worked as they did in control periods of the CER situation. Under the avoidance schedule, rats were presumably frightened as they were in CS periods of the CER situation, but they also moved to avoid shock. This approach was based on the assumption that equal rates of bar-pressing under the two conditions would roughly equate amounts of movement during periods when the animals were or were not frightened. This assumption was incorrect, and the experiment did not accomplish what we had intended. Nevertheless, it is of interest for the very reason that it failed. Moreover, it extends the findings from CER experiments to another aversive conditioning paradigm.

4.5.1 Methods

The desired behavior under the multiple schedule of reinforcement was obtained in only 2 subjects. The experiment was terminated before 2 additional subjects reached the desired level of performance. One subject (S16) whose performance was satisfactory had been a subject in Experiment I. The other was prepared for this experiment with electrodes over auditory cortex of both hemispheres and with deep electrodes in reticular formation, medial geniculate body, and ventral cochlear nucleus.

Training procedures and training periods were different for the 2 subjects, and there is no need to describe these in detail. Under the final conditions of the experiment, bar-pressing was maintained on a multiple schedule of reinforcement. One component of this schedule was a VI 30-sec food-reinforcement schedule; the other was a Sidman avoidance schedule with a 2-sec shock-shock interval and an 8-sec or 10-sec response-shock interval. For S18, a drl condition (differential reinforcement of low rates) of 3 seconds was added to the VI schedule of food reinforcement in some sessions to reduce response rates. For S16, 10-minute periods of each schedule alternated in experimental sessions that were approximately 3 hours long. For S18, 20-minute periods were used in sessions that were approximately 6 hours long. Ambient illumination of the test chamber was appreciably increased when the Sidman avoidance schedule was in effect.

Clicks were presented at a rate of 1/sec throughout each experimental session. Again, the clicks were simply a part of the background "noise" and were not relevant to the behavior. Potentials evoked by clicks were recorded in groups of 100, beginning at the half-way mark (5 or 10 min) of each reinforcement period. Five to seven such samples were obtained for each component of the multiple schedule in an experimental session. Shock presentations during avoidance periods led to blocking of the amplifiers. Clicks presented in an 8-sec period following shock were not marked on tape. Similarly, stimulus pulses were not recorded for 8 seconds following each food reinforcement.

4.5.2 Results

Click-evoked potentials recorded from auditory cortex, medial geniculate body, and reticular formation were larger when the animals bar-pressed to avoid shock than they were when the subjects worked on the schedule of food reinforcement at comparable response rates. An example of this is shown in Fig. 28. Average evoked responses from three electrodes in S16 are presented for both components of the multiple schedule. The potentials were recorded in the session for which the cumulative response record is presented at the upper part of the figure. It can be seen that bar-pressing rates were roughly equal for most of the session. The potentials were actually sampled in 7 periods of each schedule, beginning with the second period of food reinforcement. Consequently, the sampling was complete before the large differences in response rates developed at the end of the session. The total number of bar-presses emitted during the sampling periods was 223 for the VI component, and 240 for the Sidman avoidance schedule. Increases in amplitudes of evoked potentials recorded from cortex and reticular formation were comparable to those found for the same subject in the CER situation. In this case, too, potentials recorded from ventral cochlear nucleus did not evidence an increase in amplitude.

In Fig. 29 are plotted the relative differences in amplitude of potentials recorded from 5 electrodes in S18. Data are presented from 4 successive daily sessions and for 2 additional sessions run several weeks later. In the lower part of the figure, the mean number of bar-presses per recording period under each schedule is shown for the same

experimental sessions. It is apparent that differences in evoked-response amplitudes were related to the animal's activity in periods of food reinforcement. In the second session bar-pressing rates were very low during the VI drl component, and differences

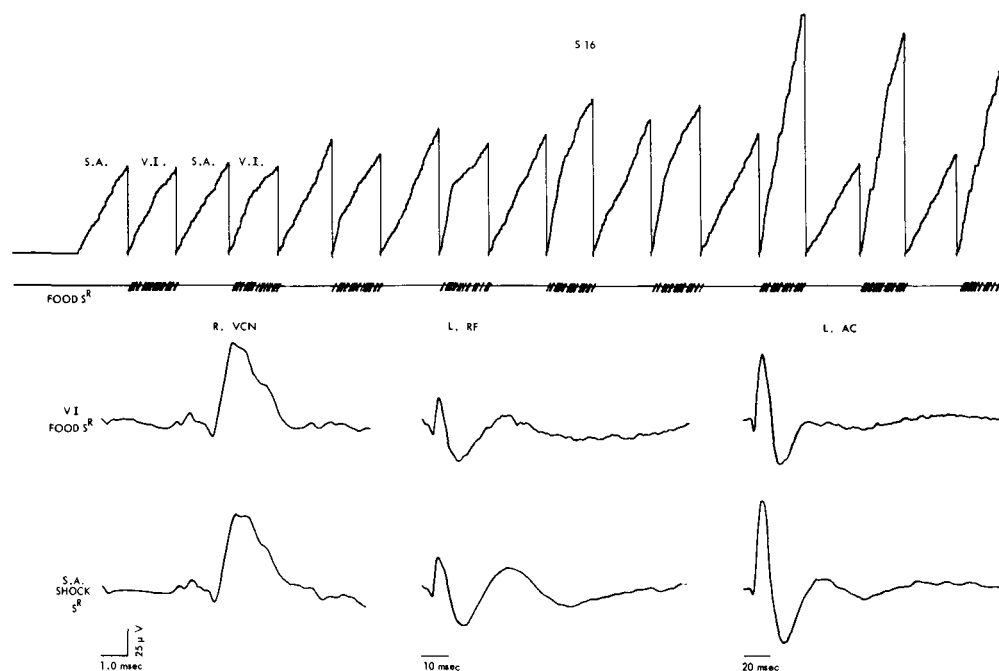


Fig. 28. Cumulative response record at top shows bar-pressing of S16 under multiple schedule of reinforcement (mult VI 30 sec Avoidance RS 10 SS 2). Average evoked responses at bottom recorded from right ventral cochlear nucleus (R. VCN), left reticular formation (L. RF), and left auditory cortex (L. AC) computed from 550 evoked potentials recorded during 7 periods of each schedule beginning with the second period of food reinforcement.

in amplitude were much reduced. This was also true for the first of the two later recording sessions. Over-all response rates and observation of the animal were sufficient to indicate that the rat was generally frightened throughout both sessions. Potentials recorded during periods of food reinforcement were much increased in the same sessions, thereby accounting for the reductions in amplitude differences shown in Fig. 29.

The last two sessions for which data are presented in Fig. 30 were run for the purpose of obtaining records of the subject's movement. The accelerometer described earlier was employed for this purpose. In Fig. 30 movement records are presented in the lower portion of the figure for one recording period of each schedule condition. The cumulative response record for the entire session is shown in the upper portion. Response rates during the VI drl component actually exceeded those found under the avoidance component in this session. But it is clear from the movement records that

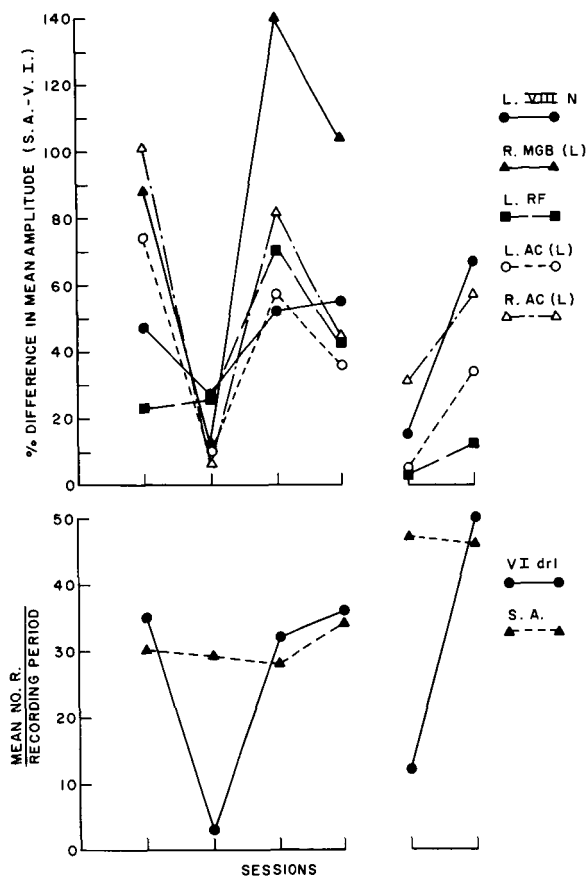


Fig. 29. Upper: Relative differences in mean amplitudes of click-evoked potentials recorded during two components of multiple schedule of reinforcement plotted for 6 experimental sessions.

Lower: Mean number of bar-presses emitted during periods of each component of multiple schedule when evoked potentials were recorded. Last 2 sessions 2 weeks after first 4 sessions. (S.A., Sidman avoidance component; VI drl, Variable Interval differential reinforcement of low rate schedule of food reinforcement.)

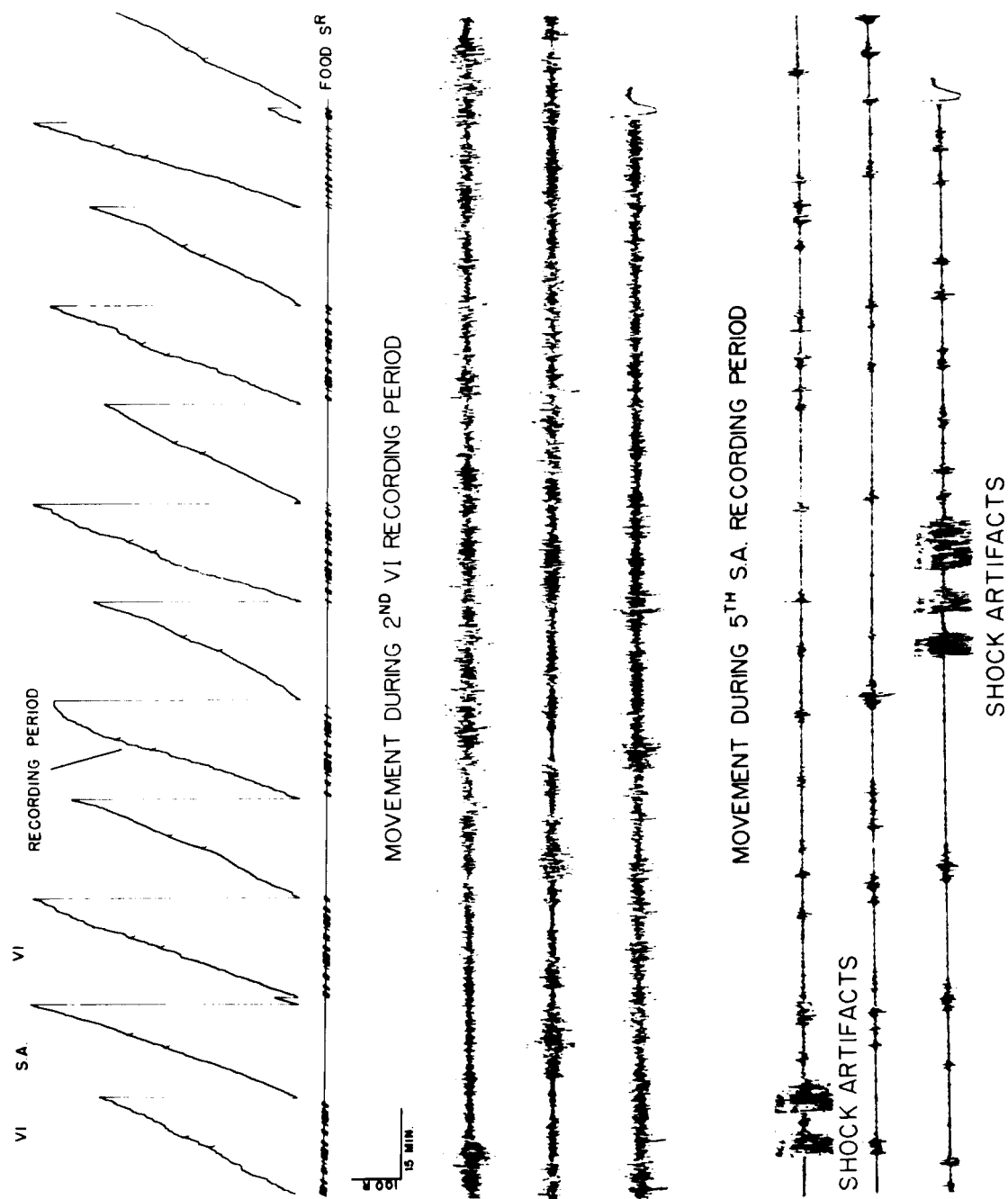


Fig. 30. Cumulative response record at the top shows comparable rates of bar-pressing by S18 under two components of multiple schedule of reinforcement, one aversive (S.A.), one appetitive (VI drl). Movement records from accelerometer on rat's head are shown for one recording period in each component of the schedule.

comparable bar-pressing rates are not necessarily indicative of comparable amounts of general bodily movement. There was much less movement during the aversive

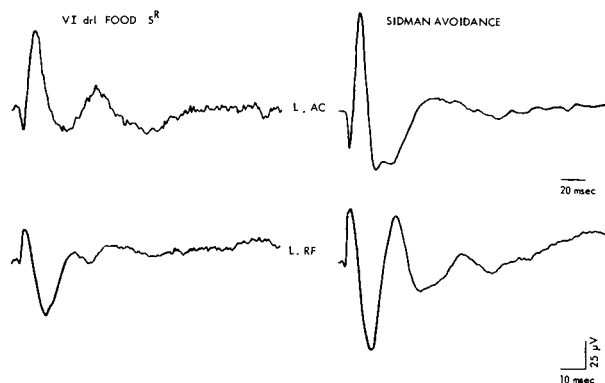


Fig. 31.

Average evoked responses from left auditory cortex (L.AC) and left reticular formation (L.RF) obtained from the same session for which behavioral data are presented in Fig. 30. Each average computed from 600 evoked potentials.

component of the multiple schedule than there was during the appetitive component.

Potentials recorded from two electrodes in the session for which behavioral data are shown in Fig. 30 are presented in Fig. 31. There would seem to be little doubt that sensory evoked potentials in the frightened rat, moving only to avoid shock, are appreciably larger than those recorded when the animal is very active and working for food.

4.5.3 Discussion

The behavioral techniques employed in this experiment did not eliminate the high correlation between the occurrence of an emotional response and a reduction in general bodily movement. Consequently, the larger evoked responses recorded during the aversive component of the multiple schedule cannot be unequivocally related to fear or anxiety. Nevertheless, in this experiment we have another instance of alterations in sensory evoked potentials related to some behavioral change effected through aversive conditioning techniques. At the very least, the data indicate that changes in sensory activity described in previous experiments were not peculiar to the conditioned emotional response situation. The changes may occur under conditions permitting the animal to avoid the noxious stimulation. Moreover, the occurrence of some behavioral activity is not sufficient to eliminate these changes.

Behavioral data presented above indicate that the topography of a behavioral response is affected by the kinds of conditioning procedures employed to obtain the response. In so doing, they emphasize the need for more complete descriptions of behavior in electrophysiological studies of conditioning.

4.6 EXPERIMENT VI

In the preceding experiment an attempt was made to eliminate differences in the amounts of movement that were typical of control and CS conditions in CER situations by increasing the amount of movement during the aversive CS condition. In the present

experiment the opposite approach was taken; rats were trained to sit motionless during control periods.

A restraining device was employed that from the outset severely limited movement. The device has been described in detail elsewhere.⁴⁰ Briefly, it consisted of a small cagelike structure just large enough to accommodate a rat. Animals were secured in the restrainer by means of a plastic collar that was worn for the duration of the experiment. In other experiments rats have been trained to bar-press under these conditions of partial restraint, but in this experiment the bar was removed and rats were trained to sit motionless. This situation differed from the usual CER situation, in that "holding still" for a period of 4 seconds constituted a response rather than a bar-press. When the holding-still behavior had been stabilized, an emotional response was conditioned in the usual way. Briefly, the procedures provided a situation in which alert animals were motionless a large part of the time while "working" for food. The freezing that occurred during an emotional response did not represent a radical change in skeletal-muscular behavior.

Another technique was available as a control for residual differences in amounts of movement during control and CS conditions, namely, the sampling of evoked potentials only in periods of no movement under both conditions.

We would like to note here that in an earlier experiment concerned with changes in evoked potentials during conditioning, partially restrained rats were employed in a CER situation. When bar-pressing in the restrainer had become stable, trains of clicks were introduced, first in habituation sessions and later as conditional stimuli. Following conditioning, the CER was extinguished and reconditioned. Finally, a visual stimulus was employed as the CS, and click-evoked potentials were monitored as the same

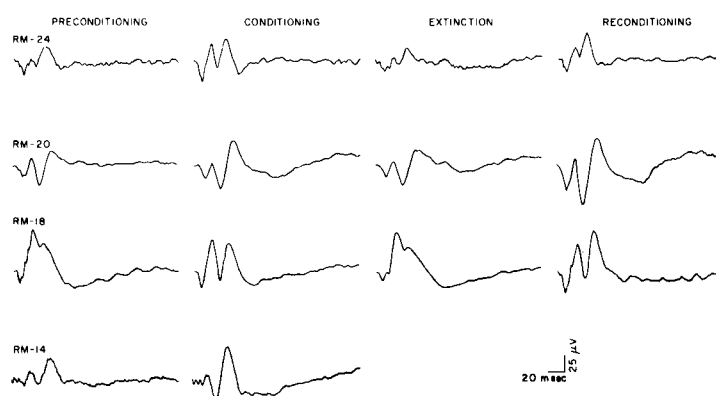


Fig. 32. Average click-evoked cortical responses recorded from 4 subjects in CER situation in which animals were restrained in special apparatus that permitted bar-pressing. Trains of 60 clicks, presented at 1/sec, served as CS. Averages from each stage of the experiment computed from 600 evoked potentials. RM-14 did not complete the experiment.

behavioral changes were brought under control of another sensory modality. The experiment has been described in detail by Mark.⁵⁸ The results were quite consistent with the data presented above. A brief summary of the findings is presented in Fig. 32. Average cortical evoked responses are shown for the 4 subjects at each stage of the experiment in which clicks served as CS. Cortical responses underwent considerable increases with acquisition of the CER, diminished to preconditioning levels during extinction, and grew again with reconditioning. It is apparent in Fig. 32 that late components of the cortical potentials were again the most labile. Evoked responses recorded from anterior portions of the medial geniculate body in several subjects underwent similar changes, but the changes were relatively small. Although this experiment could not rule out movement as the explanation of changes in auditory potentials, it suggested that the explanation could not be found in gross bodily movements or general orientation of the animals with respect to the stimulus. In the experiment described below, evoked potentials from restrained rats were altered during aversive conditioning when nearly all movement was eliminated.

4.6.1 Methods

Electrodes were implanted in 6 rats at the following locations: auditory cortex, medial geniculate body, inferior colliculus, and ventral cochlear nucleus. One subject, S32, lost its electrode assembly on the fourth day of conditioning. Data from S32 were consistent with those from the other animals, but will not be considered here. Of 5 animals that completed the experiment, 3 had medial geniculate electrodes that yielded satisfactory potentials. Four had electrodes from which typically large collicular potentials were recorded. All subjects had at least one electrode in the ventral cochlear nucleus. For some unknown reason, cortical potentials from both hemispheres of S33 showed a progressive deterioration during the conditioning phase of the experiment. Consequently, complete cortical data are available for only 4 subjects. It should perhaps be mentioned that 2 additional subjects were employed in a pilot study, and data from those animals support the findings of the principal experiment.

Two to three weeks after the implanting operation, the animals were adapted to the restrainer in 4-6 daily sessions. During this period, they were given food only while they were restrained for approximately 3 hours each day.

In the next stage of the experiment, the animals were trained to sit motionless. This required from 9 to 16 days. In the terminal stage of this training, a response was defined as holding still for 4 sec, and was maintained on a VI 25-sec schedule of food reinforcement. To accomplish this, the output from the accelerometer was integrated, and the integrated voltage was led to a level detector and switching circuit. The system was adjusted empirically so that the switch was triggered whenever the animal showed the slightest movement. The device was very sensitive to chewing movements and other small head movements that were difficult to see.

After being trained to sit still, the rats were exposed to clicks in 14 preconditioning

sessions. In the last 4 sessions, clicks were presented at 1/sec throughout each one. In the last two of these, the visual CS, an increase in ambient illumination lasting 1 minute, was presented 13-14 times in each session. Click-evoked potentials were recorded during the 1-minute CS presentations and during 1-min control periods that fell midway between CS periods. No food reinforcements were presented in either control or CS periods that were separated in this experiment so that subjects might not discriminate the relatively long periods of no-reinforcement resulting from having them contiguous.

Eight days of conditioning followed in which the visual CS was followed by shock to the tail. All recording conditions were like those in the immediately preceding control sessions. Conditioning was followed by 5 days of extinction and 2 days of reconditioning.

In all sessions a stimulus marker for every stimulus was recorded on one tape channel in the usual way. In some sessions only those stimuli presented when the subjects were motionless, and had been so for at least 1 second, were marked on another tape channel. It was possible thereby to compare average evoked responses derived from periods of no movement with the complete samples from some sessions. The sampling procedure was not employed throughout the experiment because it required an additional tape channel and therefore eliminated data from one electrode.

4.6.2 Results

The kind of behavior generated by the conditioning procedures described above can be seen in the cumulative response records of Fig. 33. In the absence of the CS,

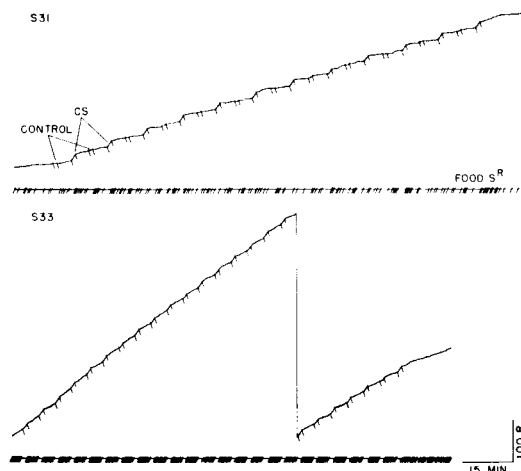


Fig. 33. Cumulative response records of 2 subjects showing "holding-still" behavior in special "CER" situation with restrained rats. Response defined as holding still for 4 sec. Visual CS followed by shock to tail. Alternate control and CS periods marked by pairs of pips on response curves.

response rates for S31 were among the lowest in the group. In the presence of the CS the frightened animal "froze," as did all subjects, and there was a very noticeable increase in the rate of the "holding-still" response. A marked change in rate of responding is not so apparent in the record for S33. Except for chewing, this subject moved little at any time, and response rates were altered only slightly during CS

periods. In this situation, then, the emotional response was not indicated by the suppression of some operant behavior, but rather by an increase in response rates during CS presentations.

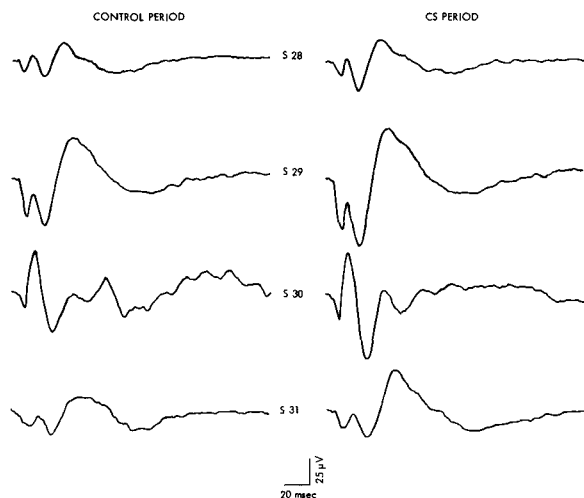


Fig. 34.

Average click-evoked cortical potentials obtained from periods of no movement during control and photic CS conditions after establishment of CER in 4 restrained subjects. Averages computed from 350-600 evoked potentials.

Cortical evoked potentials underwent changes during conditioning that were similar to those found in earlier experiments. Examples of the changes can be seen in Fig. 34, where average cortical evoked responses from one conditioning session are presented. These potentials are from the session in which the largest differences occurred, and the averages were computed from potentials recorded only when the subjects were not moving. The most conspicuous differences were again in the late components. Relative changes in amplitude over the course of the experiment are shown in Fig. 35. Curves in the upper portion of the figure show changes in the late components. The same behavioral index employed in previous experiments has been plotted in the middle portion of Fig. 35, and peak-to-peak measures of the early components are presented in the lower graphs. In each case comparisons based on no-movement samples are presented for all sessions in which the selective sampling procedure was employed.

Increases in the amplitudes of late cortical potentials clearly paralleled the behavioral changes in S28 and S30. There were no systematic differences in the measures derived from no-movement samples and those based on responses to every stimulus presentation. Movement that did occur in this situation apparently had little effect on the auditory potentials. The occasional large discrepancy between the no-movement and complete samples indicate that sampling errors and other errors of measurement can be appreciable in situations of this kind.

Irregular patterns of change were once more encountered in the early components of the cortical potentials. There were few consistencies either within or between subjects. Data from S30, for example, gave no indication of any systematic changes in amplitude.

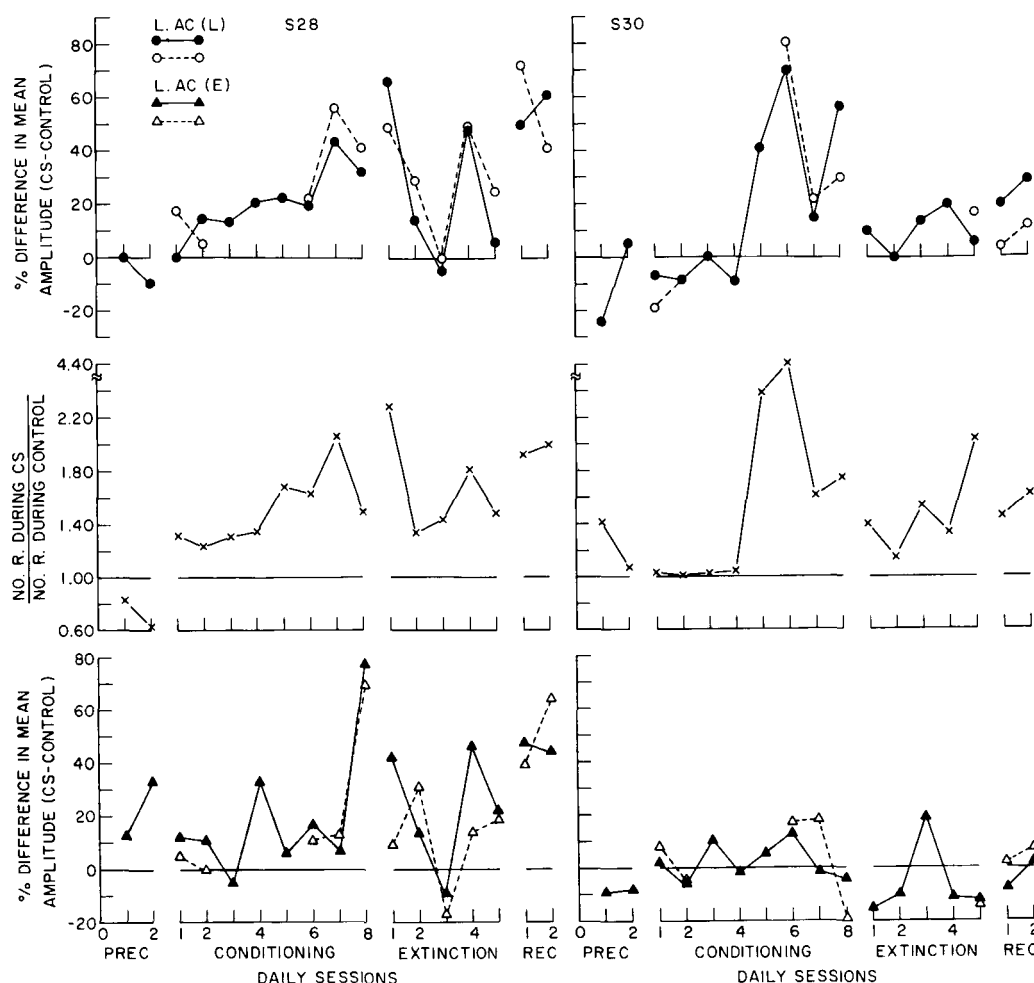


Fig. 35. Upper: Relative differences in mean amplitudes of late components of click-evoked cortical potentials recorded from 2 subjects during control and photic CS periods. Mean amplitudes of potentials recorded while subjects were motionless (unfilled symbols) are compared with mean amplitudes of all evoked responses recorded during each condition (filled symbols).
 Middle: Changes in holding-still response shown in same behavioral index employed for bar-pressing behavior throughout the report.
 Lower: Relative differences in mean amplitudes of early components of cortical evoked potentials shown as in the upper graphs for late components.

On the other hand, the early cortical potentials from S28 showed changes quite parallel to those of the late components during extinction, although no such simple relationship was apparent during the initial conditioning.

Late components of evoked responses from electrodes in anterior portions of the inferior colliculus increased in amplitude during conditioning, as they had in the experiment with electrical stimulation. With one exception, the early components did not undergo similar changes. Average evoked responses comparable to the cortical potentials in Fig. 34 are presented in Fig. 36. Early collicular potentials from S33 were



Fig. 36. Average click-evoked potentials recorded from inferior colliculus in 4 subjects during control and photic CS periods in one conditioning session. Averages based on 350-600 evoked potentials recorded when rats were motionless.

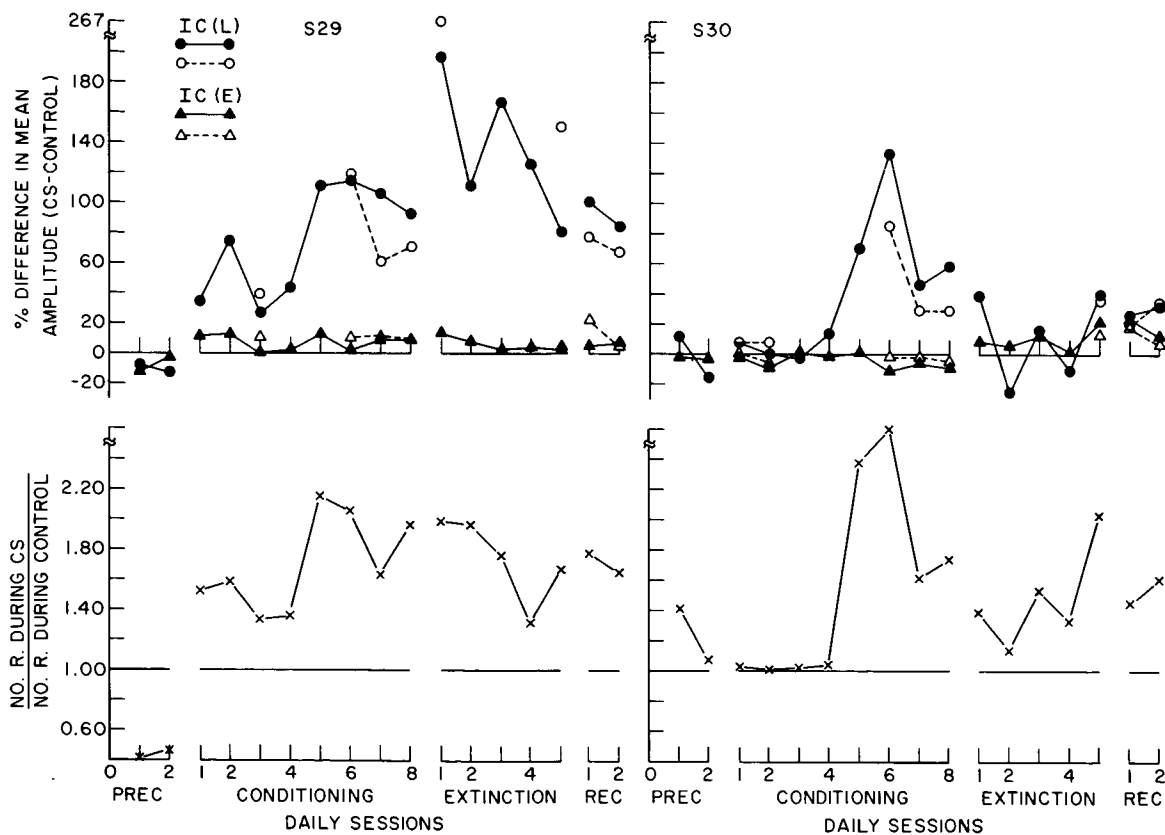


Fig. 37. Relative differences in mean amplitudes of both early and late components of click-evoked potentials recorded from inferior colliculus during control and photic CS periods of daily experimental sessions. Amplitude measures based on no-movement samples (unfilled symbols) are compared with those based on potentials evoked by all stimuli (filled symbols). Behavioral changes are plotted in the lower graphs.

consistently larger during conditioning, and the waveform of these potentials differed slightly from that of the potentials in other subjects. There was no obvious difference in electrode location to account for this discrepancy.

Relative differences in amplitude of potentials recorded in control and CS periods have been plotted for both early and late components of the collicular potentials in Fig. 37. For S30, increases in late components during CS periods were highly correlated with the conditioned behavioral changes. Although the correlation seemed somewhat lower for S29, there was little doubt that the late potentials were generally larger

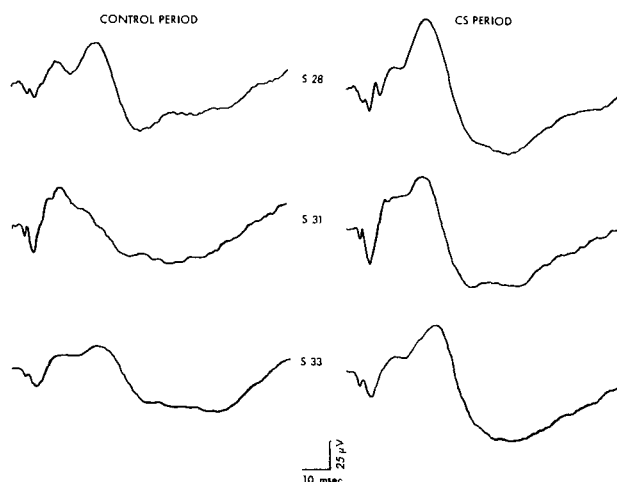


Fig. 38. Average click-evoked potentials recorded from medial geniculate body in 3 subjects during control and photic CS periods of one conditioning session. Averages based on 350-600 evoked potentials recorded when rats were motionless.

during CS presentations. In both subjects amplitudes of the early components showed only minor fluctuations during the experiment.

Evoked potentials recorded from medial geniculate revealed patterns of change very similar to those seen in cortical responses. Late components increased appreciably during conditioning. This is readily apparent in Fig. 38. At times, the early components seemed to show similar trends, but the amplitude increases were considerably smaller. This can be seen in the curves for S33 in Fig. 39. At best, these changes were of the order of 30 per cent and showed few consistencies either within or between subjects. Note in the curves for S33 the very small behavioral changes that, nevertheless, were accompanied by relatively large increases in the late potentials recorded from the medial geniculate.

As in previous experiments, evoked potentials recorded from ventral cochlear nucleus exhibited no consistent patterns of change during conditioning. This was true for both the earliest response components that can be attributed to auditory nerve and for the later nuclear potentials. Examples of the potentials

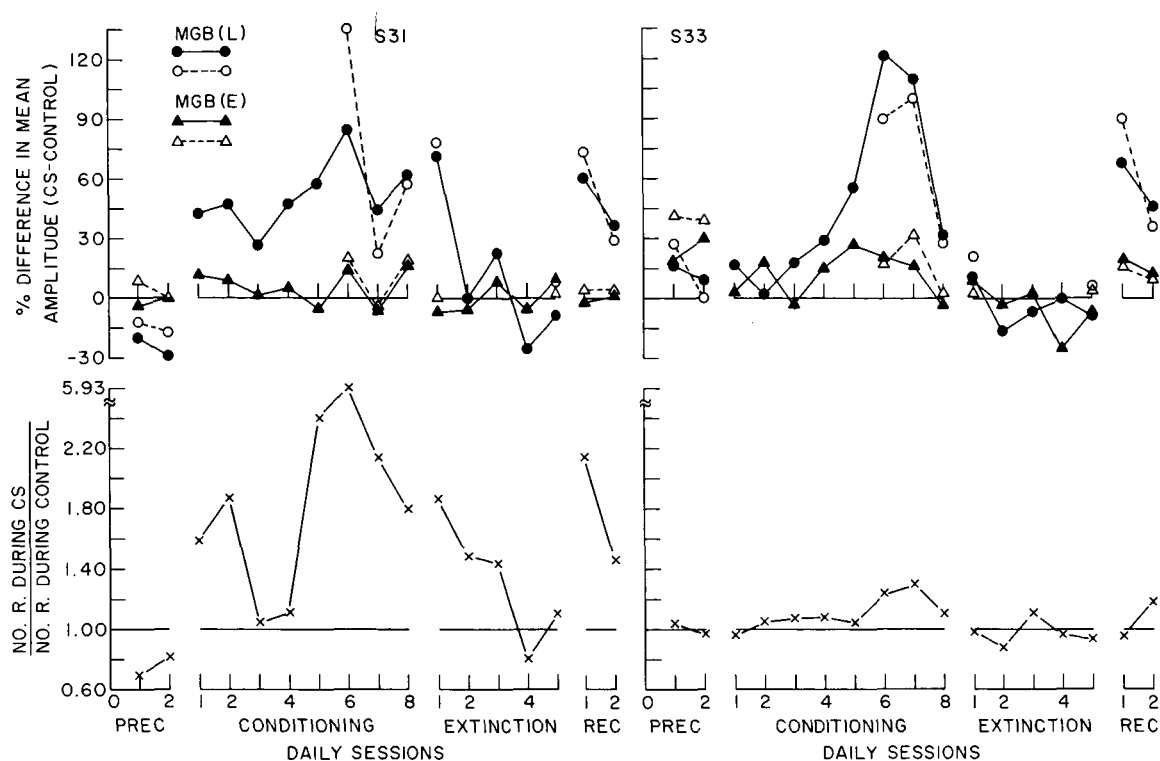


Fig. 39. Relative differences in mean amplitudes of both early and late components of click-evoked potentials recorded from medial geniculate body during control and photic CS periods of daily experimental sessions. Plots are comparable to those for inferior colliculus potentials in Fig. 37. Filled symbols indicate means based on all evoked potentials recorded in each session; unfilled symbols indicate means of no-movement samples.

are shown in Fig. 40, where day-to-day changes in amplitude have also been plotted in the usual way. Cochlear-nucleus potentials in S33 showed increases during conditioning which more or less paralleled the changes in potentials recorded from more central locations. Such changes are not apparent in the plots for S30 and S31. If there was any change in the potentials from S31, it was in the opposite direction. These potentials, incidentally, were much like those described for S14 and S16 in the first experiment reported here. The latter were also recorded from the lateral surface of the ventral cochlear nucleus and showed similar decreases during conditioning. The eighth-nerve component of evoked potentials from S30 and S33 showed rather orderly increases during conditioning, but changes like this were not apparent in the records from other subjects.

The irregularities in evoked potentials recorded from cochlear nucleus are undoubtedly due, in part at least, to differences in electrode placements. But it seems unlikely that this is the sole explanation. In S29, evoked potentials recorded from cochlear nucleus were quite like those recorded from S30. Electrode placements were nearly identical. There was no evidence, however, of

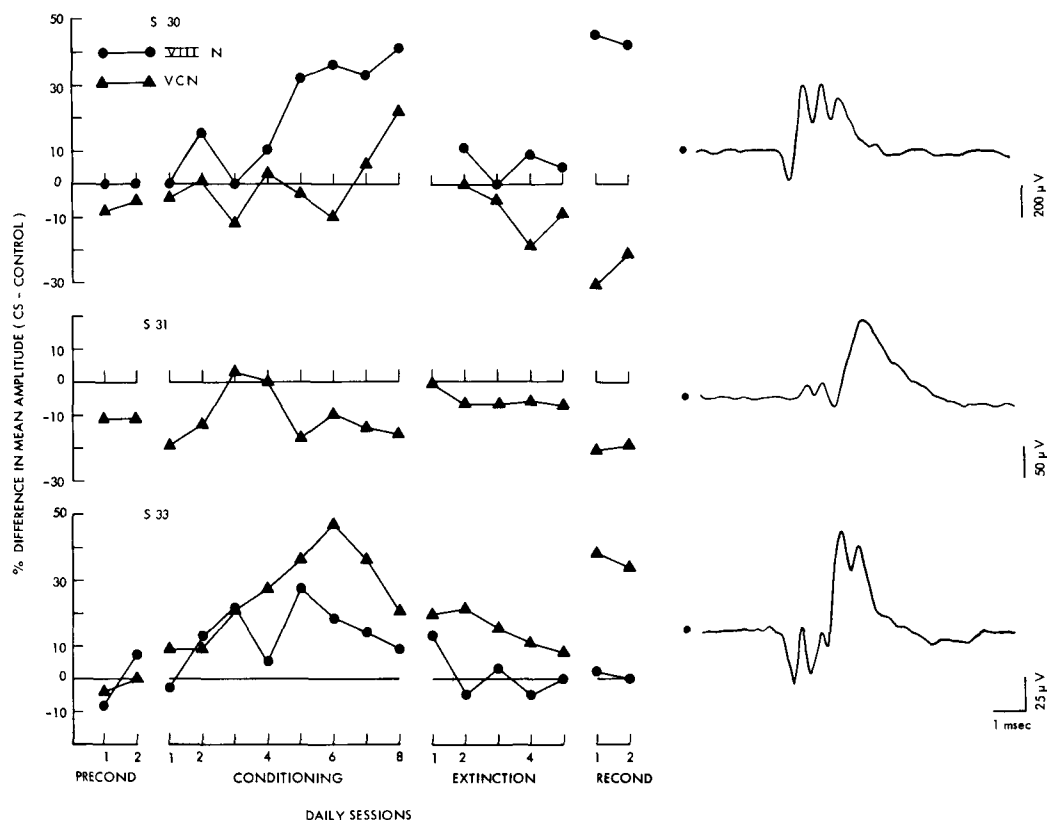


Fig. 40. Relative differences in mean amplitudes of both eighth-nerve and cochlear-nucleus components of click-evoked potentials recorded from ventral cochlear nucleus during control and photic CS periods of daily experimental sessions. Examples of potentials from which amplitude measures were derived are shown on the right. Dots at beginning of these traces indicate time of click onset.

any systematic change in the data from S29.

In all of the graphs above we have again plotted changes in amplitude as relative differences between potentials recorded in CS and control periods for each experimental session. Plots of this kind tend to emphasize the correlations between conditioned changes in behavior and increases in evoked-response amplitudes. But we have already noted (see Fig. 26 for Experiment IV) that this way of looking at the data obscures an important aspect of the changes in evoked potentials. When electric shocks are first introduced at the outset of conditioning, evoked responses from both control and CS periods typically show large increases. Before there is evidence that the emotional response has been conditioned and is discriminative (i. e., occurs only with CS presentations), there is abundant evidence that the subjects are generally frightened. Examples of this can be seen in Fig. 41. Here, mean absolute amplitudes of late cortical and geniculate potentials have been plotted separately for control and CS periods as a function of daily sessions. Also shown are the total behavioral response counts from recording periods for each condition. Data from S28 were selected because the relative

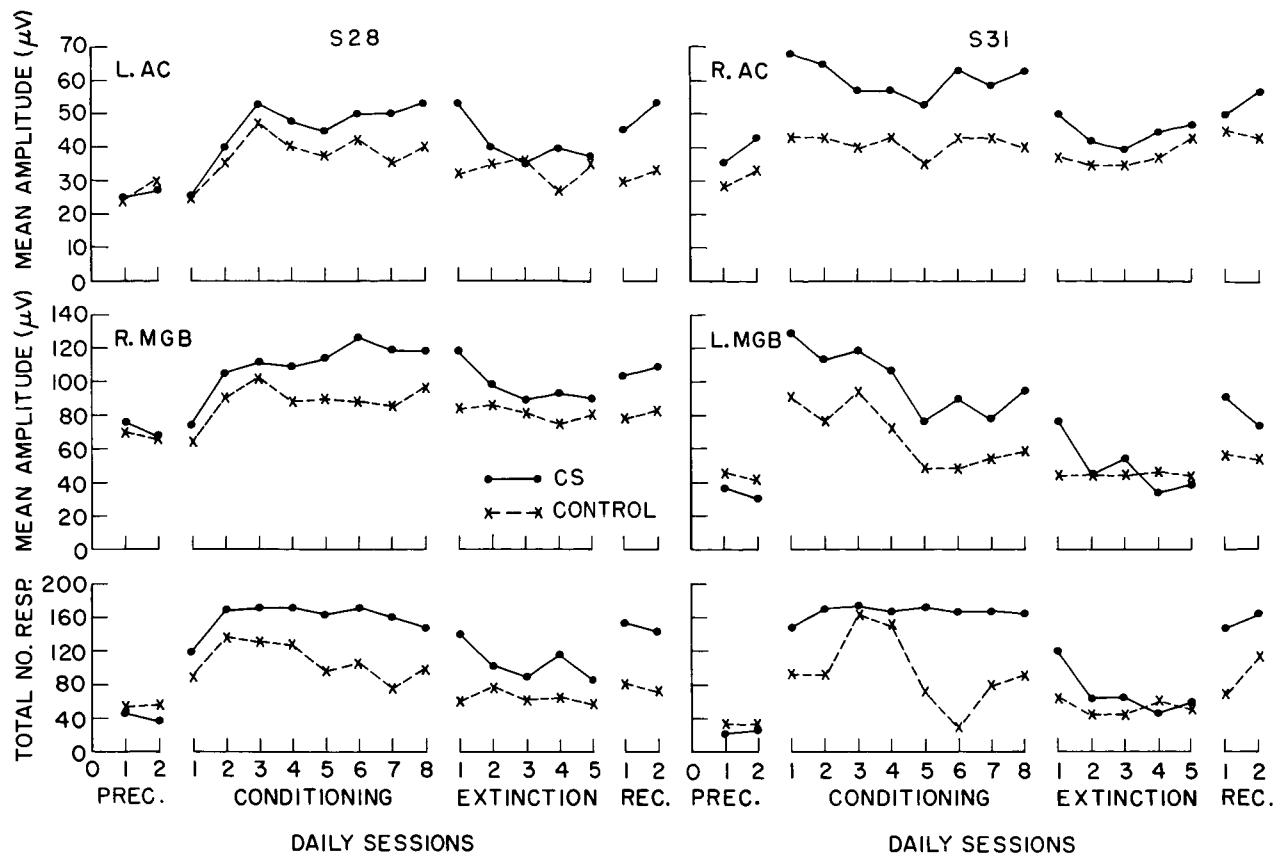


Fig. 41. Mean absolute amplitudes of late components of click-evoked potentials recorded from auditory cortex (upper) and medial geniculate (middle) plotted separately for control and photic CS periods as a function of daily sessions. Lower graphs show for both control and CS conditions the total number of behavioral responses (holding still) emitted during recording periods.

changes in amplitude were found to be highly correlated with the conditioned changes in behavior. Data from S31 represent the opposite case. It is apparent in the plots for both subjects that behavioral response rates and amplitudes of evoked potentials increased in the first few conditioning sessions, not only in CS periods, but also in control periods. In the behavioral measures from S28, the curves for control periods show an orderly decline, thereby indicating that the emotional response has become discriminative. During extinction, a decrease in potentials recorded during CS periods constituted the principal change in evoked potentials under that procedure. The picture is somewhat more complicated for S31, but the general pattern is clear. Evoked potentials recorded during aversive conditioning exhibit changes not only with the occurrence of conditioned fear responses, but during unconditioned fear responses, too.

4.6.3 Discussion

It now seems reasonable to conclude that differences in amount of movement cannot account for the changes in evoked potentials recorded from central auditory structures

during aversive conditioning. In the present experiment gross differences in movement were eliminated through behavioral techniques, and selective sampling of potentials from periods of no movement served as a control for residual differences. It seems most probable, therefore, that the observed alterations in acoustically evoked potentials were related to fear, elicited first as an unconditioned response and later as a conditioned one. This hypothesis is quite compatible with results from all of our own experiments, and all of the published work that we know of. It will be amplified in our final discussion.

The behavioral situation employed in the present experiment seems to have much in common with behavioral conditions that have characterized most studies of evoked potentials and conditioning. Animals sitting rather quietly were simply presented with trains of sensory stimuli that were followed by a noxious unconditional stimulus. But in the

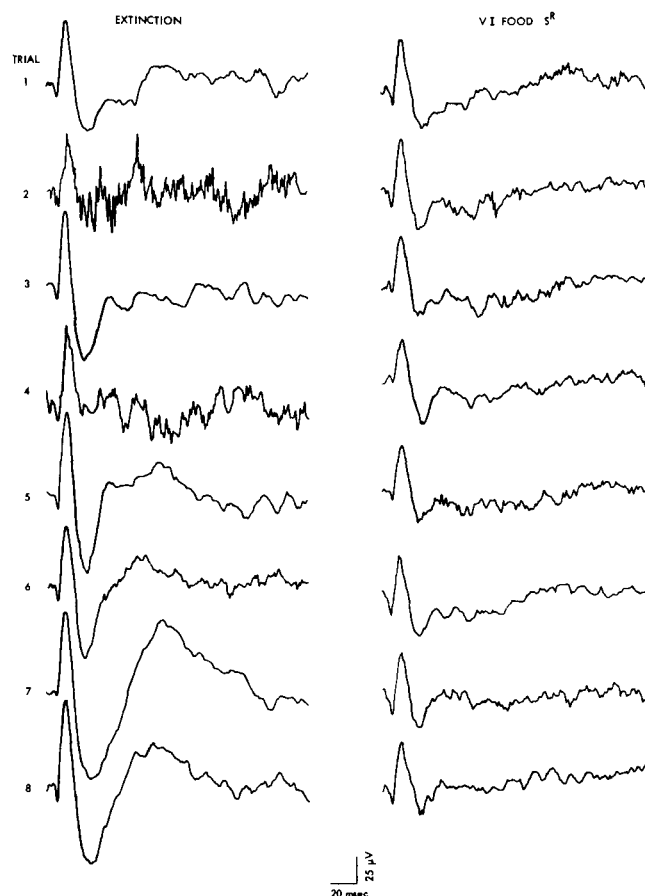


Fig. 42. Averages of 50 click-evoked cortical potentials recorded from subject S25 during control periods of successive conditioning trials. Potentials at left recorded from session with no behavioral control during control periods (holding-still response in extinction); those at right from earlier session in which holding-still response was maintained on VI schedule of food reinforcement.

present experiment, subjects were sitting quietly under conditions of behavioral control. Hungry alert animals were "working" under a schedule of food reinforcement. Their relatively constant performance throughout experimental sessions (after the initial disturbances related to the introduction of shock) was indicative of stable behavioral conditions suitable for recording baseline evoked potentials. The importance of achieving behavioral control during preconditioning or other control periods is illustrated in Fig. 42. These data were obtained from subject S25, one of the animals in the pilot study for the present experiment. Average evoked cortical potentials shown in the left column were obtained from a conditioning session like those described above for the restrained animals, except that reinforcement of the holding-still response was withheld for the entire session, i. e., the response was under extinction. This procedure was employed to ascertain if the holding still was largely under control of the food reinforcer. It became immediately obvious in behavioral data that it was.

The average responses in Fig. 42 are averages of 50 evoked potentials taken only from control periods of successive trials. The great variability in responses taken from the session in which the holding-still behavior was extinguished is immediately obvious. The very noisy potentials of the second and fourth trials were due to the subject's chewing on metal supports of the restrainer. The large change in late components in trials 7 and 8 reflect the fact that the animal was dozing. Contrast these irregularities with the relatively stable averages recorded in control periods of an earlier conditioning session in which the usual reinforcement procedures were in effect. Whenever we have attempted to record evoked potentials under conditions of no behavioral control, we have encountered variability like that of the potentials from the extinction session of Fig. 42. It has caused us great concern about the so-called habituated evoked responses that have commonly constituted the baseline data in most studies of evoked potentials and conditioning. Common sampling practices are also brought into question by the inherent variability of evoked potentials recorded under conditions of no behavioral control.

V. SUMMARY OF EXPERIMENTAL WORK AND DISCUSSION

A summary of the experimental work presented here is complicated by the fact that what seemed true for late components of auditory evoked potentials was not necessarily so for the early components. Irregular patterns of change and many inconsistencies were encountered in early components of evoked potentials recorded from central auditory structures. Similar irregularities were found in the more peripheral activity recorded from ventral cochlear nucleus. It will be convenient to consider this problem first, so that the following summary need be concerned only with the systematic changes in late components of acoustically evoked potentials.

5.1 EARLY COMPONENTS OF AUDITORY EVOKED POTENTIALS

In our earlier experiments, in which movement-related variables were undoubtedly operative, relatively large increases in early components of cortical and medial geniculate potentials were frequently seen during conditioning. Similar increases were sometimes found in eighth-nerve and cochlear-nucleus responses. Such changes were not entirely consistent between subjects or within the same subject. Moreover, the changes in early components did not necessarily parallel the changes in late components that were systematically related to the changes in behavior. In later experiments, when efforts were made to eliminate the movement factor, there was still evidence of change in the early components. Changes that did occur, however, generally seemed smaller and less frequent.

The data suggest that movement-related variables may have been partly responsible for the large-amplitude increases in early components found in CER situations with unrestrained rats and physiological acoustic stimulation. A word of caution is in order here, for it is not clear that the later experiments differed from the earlier ones only with respect to the control of movement. But the fact remains that when some control of movement variables was achieved, changes in the early components of auditory evoked potentials seemed more the exception than the rule.

As we have already noted, it seems unlikely that changes in the early components can be explained as a result of poor stimulus control. Similar irregular patterns of change were found in potentials evoked by electrical stimulation. Moreover, variations in effective sound-pressure levels could have been no more than trivial in the last experiment with restrained subjects. Another finding that argues against a simple stimulus interpretation of changes in early cortical potentials is that such changes did not depend upon similar changes in potentials from more peripheral structures, including auditory nerve. Eighth-nerve responses were sometimes quite stable, while early components of cortical potentials underwent appreciable alterations. The same arguments make it exceedingly unlikely that the irregular patterns of change in early components are to be explained in terms of middle ear muscle activity.

Regrettably, few conclusions can be drawn about the changes in early components of

evoked potentials recorded from the classical auditory system. This includes, of course, the potentials recorded from VCN, both eighth-nerve and cochlear-nucleus components. They sometimes exhibit increased amplitudes when rats are frightened, but the correlation seemed much too low to indicate any simple relationships between the behavioral and electrophysiological events. But one point is clear: The changes in early components of auditory evoked responses that occur during aversive conditioning are not related to acquired conditional or discriminative properties of the auditory stimulus. Moreover, the systematic changes in late components of the potentials are not dependent upon changes in the components that precede them.

5.2 LATE COMPONENTS OF AUDITORY EVOKED POTENTIALS

The analysis of alterations in late components of evoked potentials recorded from central auditory structures now seems reasonably straightforward, for in this case the changes were systematically and consistently related to measurable alterations in behavior. Experiments described above reveal the following facts about the late components of click-evoked potentials recorded from central auditory structures:

1. Increases in amplitude of evoked potentials recorded from auditory cortex, medial geniculate body, and inferior colliculus occur with the establishment of a conditioned emotional response. Similar increases occur in potentials recorded from mesencephalic reticular formation.
2. Quite comparable increases in acoustically evoked potentials are found when the same conditioned behavior is brought under control of a photic CS. The photic stimulus may be an increase or decrease of illumination. Moreover, these changes in click-evoked potentials do not require a previous conditioning history in which clicks have been employed as CS.
3. The amplitude increases are not specific to the CER situation, since comparable changes were found during Sidman avoidance conditioning.
4. Increased amplitudes were found in CER situations with both restrained and unrestrained subjects.
5. Potentials evoked in central auditory structures by electrical stimuli applied to cochlear nucleus or within the cochlea revealed the same amplitude increases during acquisition of a CER.
6. Elimination of differences in amounts of movement that were typical of control and CS periods in most experiments did not eliminate the increases in evoked potentials during aversive conditioning.
7. Unconditioned fear, evidenced by behavioral measures obtained during control periods (i. e., in the absence of the CS), was accompanied by comparable increases in amplitude of click-evoked potentials.

In our opinion, the most parsimonious and reasonable explanation of these facts is that amplitude increases in acoustically evoked potentials recorded from central auditory structures and reticular formation during aversive conditioning are due to fear,

fear which is first elicited by noxious unconditional stimuli, and later as a conditioned response. Certainly there is no reason to believe that the changes in evoked potentials were related to acquired discriminative or conditional properties of the acoustic stimulus. In fact, the demonstration that this is so proved to be relatively trivial. Acoustically evoked potentials were readily changed by conditioning procedures that made no use of the auditory stimulus, and the changes were quite comparable to those seen when the auditory stimulus was employed as the CS. Our principal task in this analysis was to determine what role, if any, movement or movement-related variables played in the observed amplitude increases. The use of electrical stimuli in one experiment served as a control for the more conspicuous variables related to movement, namely, the peripheral factors such as activity of the middle ear muscles, noise generated by movement, and fluctuations in stimulus intensity. With the elimination of nearly all movement by means of behavioral methods, and with the complete elimination of movement through the selective sampling of evoked potentials, data from our final experiment indicate that increased amplitudes of click-evoked potentials during aversive conditioning were not due to "central" factors, or indeed, to any other factors related to movement.

As we have noted in the introduction to this report, other workers have concluded that changes in sensory evoked potentials during conditioning are not related to the neural substrate of conditioning. Jasper,⁴⁹ Pickenhain and Klingberg,⁶⁷ and Gerken and Neff³⁸ have all proposed that the changes found in their experiments were related to some more general factor. Interestingly, these three experiments had two important features in common: (i) Objective measures of the animals' behavior were obtained. (ii) Avoidance conditioning paradigms were employed. (Gerken and Neff also employed Pavlovian conditioning procedures in some subjects.) Careful measurement of both behavior and evoked potentials revealed in all three cases that changes in evoked potentials were not a simple function of the strength of conditioned avoidance responses. The use of simple avoidance paradigms was, it seems, particularly suitable for revealing this discrepancy.

Since the classical work of Mowrer⁶⁵ and Miller,⁶¹ it has been widely accepted that conditioned fear frequently provides the motivational basis of avoidance behavior. Conditioning of the fear response precedes the establishment of the instrumental avoidance behavior, but when the latter has been acquired (and the subject, therefore, is no longer being shocked) signs of fear become much less apparent. Conditioning of the fear and avoidance responses do not follow the same temporal course. If increased evoked-response amplitudes in avoidance conditioning are related to fear, then one would expect an initial rise in amplitudes with the occurrence of unconditioned fear and with the conditioning of this response, before the occurrence of many avoidance responses. But with the subsequent acquisition of the avoidance behavior, amplitudes of evoked potentials should diminish with the mitigation of the fear response. In our opinion, the data presented by Jasper, and Pickenhain and Klingberg are, for the most part, consonant with this interpretation, although some explanation must be found for

the amplitude decreases in the first few conditioning trials reported by Pickenhain and Klingberg. We wonder if these were related to movement of the "disturbed" subjects. The report by Gerken and Neff that increases in evoked potentials followed the appearance of conditioned avoidance responses is rather puzzling. This conclusion, however, was based on combined data from four subjects which included measures of both early and late components. Failures to follow systematically changes in both evoked potentials and behavior in individual subjects has made most of the published data on conditioning and evoked potentials exceedingly difficult to evaluate.

We have attributed the increases in evoked potentials to fear, rather than to increased levels of vigilance or arousal because in our experiments the increases were always accompanied by measurable signs of fear. Moreover, baseline or control responses were recorded from very alert, highly motivated subjects working under schedules of food reinforcement. Anyone who has watched hungry rats work for food can testify that the animals are exceedingly "aroused" in the generally loose sense of that word. To maintain that the frightened animal is more highly aroused would seem to impart more to this rather vague concept that can be operationally justified at this time. Moreover, it is not clear that fear represents simply an extreme point on some level-of-vigilance continuum. It seems more likely that there are important qualitative differences between frightened animals on the one hand, and highly aroused animals that are not frightened on the other. The experimental definition of these differences with respect to sensory evoked potentials may prove to be exceedingly difficult. We cannot rigorously exclude the possibility that the important aspect of fear, insofar as increases in evoked potentials are concerned, is an increase in some general arousal factor. Until such time as this may be demonstrated, however, it would seem preferable to relate the changes in evoked potentials to their more obvious behavioral correlates, namely, the many reactions for which the label 'fear' serves as a convenient and meaningful short notation.

A singular failure of most conditioning studies of evoked sensory activity has been the omission of any controls for sensitization or pseudoconditioning — and continues to be if we are to judge from some very recent reports.^{9, 10} A notable exception is found in the study of Gerken and Neff³⁸ and also in the much earlier report of Buser, Jouvett and Hernández-Peón.¹¹ For several subjects, Gerken and Neff employed a common kind of control for pseudoconditioning in which presentations of CS and UCS are intermixed in "random" fashion with no consistent temporal relationships between the two stimuli. Increases in amplitudes of cortical evoked potentials were found under these conditions. The increases seem readily explained in terms of unconditioned fear elicited by the shock UCS. The data are in accordance with our own finding that acoustically evoked potentials evidence increased amplitudes before the establishment of an emotional response as a conditioned one.

In very recent experiments we have had occasion to witness increases in click-evoked potentials when rats were shocked in such a way as to preclude any possibility

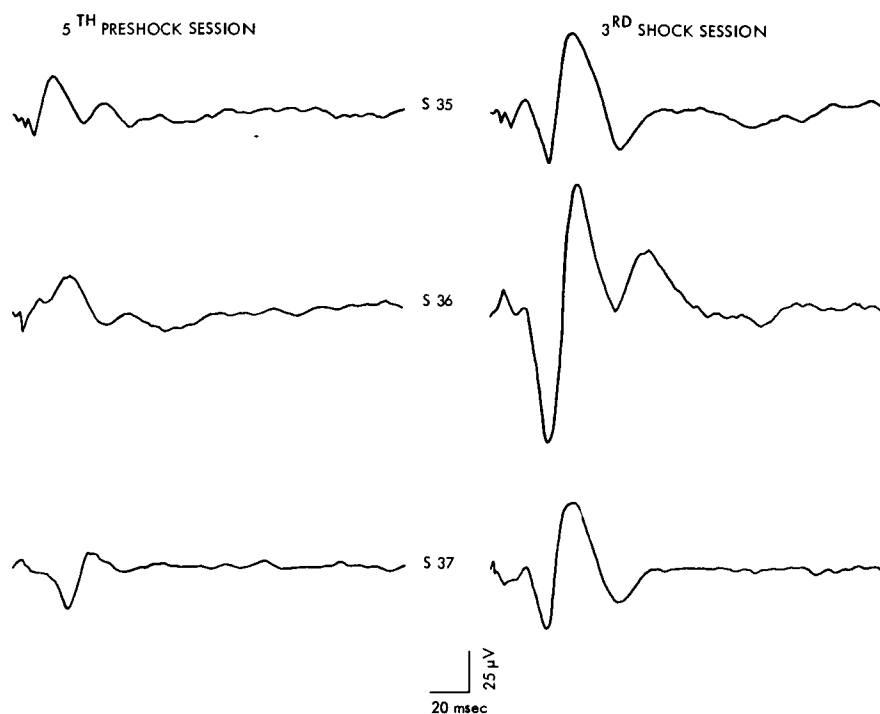


Fig. 43. Average click-evoked hippocampal potentials recorded from three subjects before presentation of any electric shocks, and during the third session in which shocks were delivered "randomly" with respect to click trains.

of conditioning. An example of such changes can be seen in Fig. 43. These data were obtained from a pilot study in which an attempt was made to determine the nature of click-evoked potentials in the hippocampus and dentate gyrus. The average evoked potentials in Fig. 43 were recorded from bipolar electrodes in hippocampus. The rats were placed in the experimental chamber and exposed to clicks in 7 three-hour daily sessions. Clicks were presented at 1/sec in 10-12 groups of 100 in each session. During three additional sessions, the animals were shocked through the grid floor of the box. Ten to twelve shocks were administered in each session at irregular times in the 10-minute intervals between trains of clicks, usually around midway through the intervals. No attempt was made to achieve behavioral control in this brief experiment, for our primary concern was with the waveform of the hippocampal response. The shocking procedure was introduced when the potentials appeared sufficiently stable to permit at least the disclosure of possible large changes.

The average responses in Fig. 43 were obtained from the fifth preshock session and on the last day of shocking. They include all evoked potentials recorded from these electrodes in each session. Data from the fifth preshock session are presented because the last two preshock sessions were used to obtain monopolar recordings. The effects of shocking were sufficiently great as to leave little doubt that noxious stimulation can bring about significant increases in acoustically evoked potentials quite independently of

any conditioning operations.

Changes in the electrical activity of auditory structures described in two recent experiments^{9, 35} appear to lend support to the idea that changes in acoustically evoked potentials in aversive conditioning situations are not related to associative factors, but to some more generalized reaction. In the most recent study, Buchwald, Halas, and Schramm⁹ employed electrodes 50 μ in diameter to record activity evoked by 1.5-sec tone bursts. These served as CS for a leg flexion response in cats. Signals from a number of electrodes in each subject were highpass-filtered so that spike potentials generated by relatively small cell populations were separated from the slow-wave responses "seen" by the same electrodes. The filtered signals were then integrated to obtain "average" responses of the multiple-unit activity. Enhancement of these responses from a number of recording sites was found during conditioning, especially in responses recorded from the classical auditory system and reticular formation. It was noted, however, that these augmented responses were not specifically correlated with the occurrence of conditioned responses, but that evoked activity generally seemed to increase during conditioning as did strength of the conditioned leg flexion. This suggests to us that the critical conditioning in this situation was the conditioning of fear. We would guess that behavioral measures of some part of the fear response, e.g., change in heart rate, would have been highly correlated with changes in the integrated multiple-unit responses.

Galín³⁵ employed similar recording techniques with a procedure in which 1-minute bursts of noise were paired with subcutaneous electric shocks to the backs of cat subjects. Potentials were recorded from a number of sites along the auditory pathways. Without considering the details of this experiment, we would simply point to the principal finding. This was a reduction in amplitude of the integrated voltages recorded during noise bursts and, interestingly, during 1-minute control periods that preceded noise presentations. The largest decrease was in the level of spontaneous activity, i.e., the activity recorded in prestimulus periods. The "evoked response," the difference between the average integrated voltages recorded in prestimulus and stimulus periods, underwent relatively minor changes. The changes which, curiously, were all reductions in amplitude were most apparent in the activity recorded from inferior colliculus. No changes were found in potentials recorded from auditory cortex or medial geniculate body. These findings are not readily incorporated with those from our own experiments or with the data from other conditioning studies of evoked sensory activity. The finding that noxious stimulation appreciably alters the spontaneous activity of sensory structures certainly suggests a significant change in "state" of the organism.

5.3 COMMENTS ON REPORTED CHANGES IN EVOKED POTENTIALS RELATED TO "ATTENTION"

In 1956, Hernández-Peón, Scherrer and Jouvét⁴⁴ reported that acoustically evoked potentials recorded from cochlear nucleus of unanesthetized cats showed reductions in

amplitude when "distracting stimuli of other sensory modalities were presented. This finding was interpreted as an indication that attending to a stimulus of one sensory modality leads to an inhibition of sensory activity in other modalities. Following this original report, a long series of papers by Hernández-Peón and various co-workers seemed to confirm this finding. Much of the work has been described in several review articles.^{42, 43} Many confirmations, too numerous to list here, were forthcoming from other laboratories throughout the world. Another finding that has often come hand-in-hand with reports that "attention" influences evoked responses is that evoked potentials "habituate," i. e., decrease in amplitude as a function of repeated stimulus presentations. Habituation effects, the changes attributed to attentional processes, and the reported increases in evoked potentials related to conditioning together have led to a rather general notion that biologically "significant" stimuli are accorded some priority by the nervous system. They evoke larger responses than do stimuli which at some given time are irrelevant or insignificant.

A detailed review of the experimental work concerned with effects of attention on sensory evoked potentials is much too large a task to initiate at this point. It should be noted, however, that not all reports have been positive. In a recent review, Horn⁴⁶ has been critical of much of the experimental work in this active research area. We introduce the problem because the principal findings from our own conditioning studies seem relevant.

The reader may recall that experiments described in this report stemmed from earlier failures to demonstrate changes in evoked potentials as stimuli were made discriminative stimuli in appetitive operant conditioning situations. By any reasonable operational criteria, it would seem that a discriminative stimulus is clearly "significant," and is a stimulus to which the animal "attends." Yet we were unable to detect any changes in click- or flash-evoked potentials as either stimulus acquired these properties. Moreover, the work described here clearly indicates that changes in evoked potentials observed in aversive conditioning situations are not related to discriminative properties of the stimuli. When rats, for example, responded to, and presumably attended to, a photic CS, click-evoked potentials did not diminish, they became larger. These findings imply that attending to a stimulus in one modality is not sufficient in itself to enhance potentials evoked by that stimulus or suppress potentials evoked by stimuli of other modalities.

How then are we to account for the repeated observations that evoked potentials recorded from sites along classical sensory pathways are reduced when "distracting" stimuli of other sensory modalities are presented? (It is probably significant that, in animal experiments at least, there has been no successful attempt to demonstrate an increase in amplitudes of evoked potentials in a given sensory system as a stimulus of the same modality becomes one to which the subject attends. See, for example, the reports by Jane, Smirnov, and Jasper,⁴⁸ and Horn.⁴⁶) We suspect that in many instances the alterations in evoked potentials observed in "attention" experiments with

animals can be attributed to uncontrolled stimulus variables and changes in "state" of the organism, but it would be presumptuous to propose that all such reports are explicable in these terms. The problem is further complicated by the fact that sensory evoked potentials recorded from the human scalp do appear to depend upon the relevance of the stimuli to tasks assigned to subjects. Among many experiments with human subjects concerned with this problem, several recent and well-designed experiments^{13,69,72} indicate that late potentials, with peak latencies typically greater than 100 msec, are larger when the stimulus becomes a critical aspect of the subject's task. There are many difficulties in drawing comparisons between the data from human and animal subjects. Perhaps the most important are the considerable differences between potentials recorded from the human scalp and those recorded from the cortical surface or from within the cortex of animal subjects. Almost certainly, evoked potentials recorded from temporal and occipital regions of the human scalp do not have their origins in primary sensory cortex. It would seem, then, that the burden of proof is with those who maintain that evoked potentials recorded from classical sensory systems are influenced by attentional processes. This will require an appropriate demonstration under experimental conditions marked by rigorous control of all variables known to influence sensory evoked potentials.

5.4 CLOSING REMARKS

This investigation was begun with the hope that significant changes in sensory evoked potentials might be found that were unequivocally related to conditioning. But the observed changes in acoustically evoked potentials could not be attributed to conditioning, and consequently shed no light on neural mechanisms underlying conditioned changes in behavior. In some sense, the changes were simply an artifact of the kinds of conditioning procedures employed.

The finding that sensory evoked potentials are appreciably modified when animals are frightened has, however, its own intrinsic interest. Why these changes occur is a question that should prove amenable to experimental analysis, for fear is reasonably susceptible to experimental control. This finding also has some practical implications for future work concerned with the neural basis of conditioning. It suggests that conditioning procedures that provoke radical changes in "state" are to be avoided, for such changes may unduly complicate the search for neuroelectric events that are uniquely related to conditioning operations.

VI. SUMMARY

Acoustically evoked potentials were recorded from unanesthetized rats in a series of experiments concerned with changes in sensory evoked potentials during conditioning. Experiments described here employed aversive conditioning procedures, principally the conditioned emotional response (CER) paradigm. Aversive conditioning techniques were adopted after repeated failures in our earlier work to find changes in cortical evoked potentials as appetitive operants were brought under stimulus control.

The principal findings from aversive conditioning experiments may be summarized as follows.

1. When clicks are established as conditional stimuli in CER situations, click-evoked potentials recorded from auditory cortex, medial geniculate body, inferior colliculus, and mesencephalic reticular formation show evidence of increases in amplitude that are strongly correlated with the conditioned suppression of bar-pressing. Only changes in the late components of potentials recorded from central auditory structures are consistently and systematically related to the conditioned behavioral changes. Early components of cortical, geniculate, and collicular evoked potentials, as well as evoked responses from auditory nerve and cochlear nucleus, often show amplitude increases, but the changes observed are not consistent from subject to subject or within the same subject. Changes in early components, therefore, do not necessarily parallel those in later components.

2. None of the changes in evoked potentials during the establishment of the CER are related to the acquired conditional or discriminative properties of the CS. Similar changes in acoustically evoked potentials occur when the CER is elicited by a photic CS.

3. Changes in click-evoked potentials during aversive conditioning are not specific to the CER situation; similar changes were found with Sidman avoidance procedures.

4. The changes could not be attributed to movement or movement-related variables. Potentials evoked in central auditory structures by electrical stimuli applied to cochlear nucleus or within the cochlea revealed similar amplitude increases during acquisition of a CER. In another experiment, behavioral methods and data sampling techniques were employed to eliminate differences in amount of movement that were typical of control and CS periods in most of our experiments. These procedures did not eliminate the increases in acoustically evoked potentials during aversive conditioning.

5. In general, whenever behavioral measures indicated that rats were frightened, late components of click-evoked potentials recorded from central auditory structures exhibited increased amplitudes, whether or not a CS was present.

We conclude that reliable alterations in sensory evoked potentials observed during aversive conditioning are related to fear, which is elicited by noxious unconditional stimuli and becomes itself a conditioned response.

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We are indebted to many people in the Research Laboratory of Electronics of the Massachusetts Institute of Technology, who in countless ways have helped to make this work possible. We can only begin to acknowledge them here.

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Time and again, we have considered ourselves fortunate in having Richard Clayton and Robert M. Brown to consult on instrumentation problems. They were always ready with practicable solutions. Thanks are due also to Arthur Berg and Jack Sears for their assistance on equipment matters.

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Ann O'Rourke did most of the histological work, and Dorothy Ippolito saw the work completed.

These are the people who were most directly involved in the execution of the research, but we are indebted to all of our colleagues in the Communications Biophysics Group. They have provided a scholarly, critical and friendly atmosphere pervaded by a collective esteem of excellence in research. We can only say "We'll try harder."

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13. ABSTRACT <p>Acoustically evoked potentials were recorded from unanesthetized rats in a series of experiments designed to study changes in evoked potentials during conditioning. It is shown that when clicks are established as conditional stimuli (CS) in conditioned emotional response (CER) situations, click-evoked potentials recorded from central auditory structures and from mesencephalic reticular formation exhibit amplitude increases. Similar increases were found with Sidman avoidance conditioning. These changes during aversive conditioning were not related to acquired discriminative properties of the acoustic stimulus, since similar changes in click-evoked potentials were found when a CER was elicited by a photic CS. The changes were shown to be independent of movement-related variables. Potentials evoked in central auditory structures by electrical stimulation of the cochlear nucleus or cochlea increased in amplitude during acquisition of a CER. In one CER situation nearly all movement was eliminated through methods of behavioral control, and data-sampling techniques provided a control for residual differences in amount of movement during CS and control periods. These procedures did not eliminate increases in click-evoked potentials during conditioning. In general, whenever behavioral measures indicated that rats were frightened, acoustically evoked potentials exhibited increased amplitudes, whether or not a CS was present, but only changes in late components of click-evoked potentials were consistently related to observed behavioral changes. We conclude that changes in evoked potentials observed during aversive conditioning are not related to the neural substrate of conditioning, but are associated with fear elicited initially as an unconditioned response to noxious stimulation and later as a conditioned response.</p>		

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