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SENSORY NEUROPHYSIOLOGY AND REACTION TIME PERFORMANCE IN NONHUMAN PRIMATES * †

INTRODUCTION

It was clear from the conference that information is rapidly accumulating on sensory behavior in animals. Psychophysical relationships between stimulus and response parameters recently derived from animal subjects have been shown to be as reliable and precise as those obtained from man. Moreover, through analysis of these stimulus-response functions we are acquiring a better understanding of the influence of various stimulus parameters on behavior. One of the basic themes of the conference concerned the extension of our understanding of sensory functions to include the role of afferent neural structures in behavior. Contemporary behavioral procedures yielding psychophysical functions in animals provide a vehicle for such an extension. Simply stated, this approach suggests that we begin to study afferent neural activity in behaviorally trained animals from which precise measures of psychophysical relationships may be concurrently obtained.

Classical sensory neurophysiology is based upon techniques and measures of neural function which may be extended and applied to behaving animals. When appropriately employed, these electrophysiologic measures are stable, based upon known principles of neural function, and backed by a baseline of observations necessary for the evaluation of such data. However, just as the precision and

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* This work was supported in part by PHS grants NB 08181, FR 00166, and NB 05077 from the National Institutes of Health.

† We wish to acknowledge our appreciation to Dr. Dwight Sutton for reading this manuscript and for his helpful comments.

stability of behavioral measures are based upon restricted sets of procedures, these electrophysiologic measures are only appropriately employed with a restricted set of methods.

In the past, methods that have yielded precise and stable measures of electrophysiologic activity have been incompatible with behavioral experimentation. Factors involved in many electrophysiologic studies include anesthesia, paralysis, artificial respiration, pneumothorax, some reduction in cerebrospinal fluid volume, and exposure of neural structures. A behavioral analysis of sensory function under such conditions is impossible.

A dichotomy in the approach and methodology for analyzing "sensory functions" in behavioral and physiologic studies has evolved and endured as a consequence of the difference in immediate objectives of these disciplines. We suggest that an approach to the study of sensory function which embodies but one of these viewpoints is unnecessarily limited. Moreover, such a traditional attitude has resulted in an artificial division of the available knowledge of sensory functions into two categories: (1) knowledge of neuronal response properties, and (2) knowledge of behavioral function. This division can and should be eliminated. The student of psychophysical behavior often wishes to explain the "mechanism" underlying a particular behavioral response. Similarly, students of central neural function often feel compelled to speculate on the behavioral implications of their observations. These parallel but independent approaches do not presently permit unqualified translation between electrophysiology and behavior. A better understanding of sensory processes will be based upon elimination of this dichotomy.

EXPERIMENTAL APPROACHES TO THE PROBLEM OF COMBINING ELECTROPHYSIOLOGIC AND BEHAVIORAL DATA

Recent attempts to bridge this division have taken several forms. Three different approaches will be considered. The first approach is based upon attempts to compare electrophysiologic data from animal experiments directly with behavioral data obtained from man; the second has evolved from the simultaneous evaluation of electrophysiologic and behavioral activity in man; and the third consists of simultaneous studies of electrophysiologic and behavioral responsiveness in animals.

RELATION OF ANIMAL ELECTROPHYSIOLOGIC DATA TO HUMAN BEHAVIORAL DATA

The first approach, utilized in many cases by physiologists, attempts to relate animal neurophysiologic data to behavioral observations made on humans by other investigators. For example, comparisons have been made showing that neurophysiologic functions relating latency or frequency of firing of single afferent cells to stimulus intensity have parallels with behavioral functions relating latency

of motor response or rate of response to stimulus intensity. Moreover, extension of this approach has led to comparisons between intensity of neural responses from animals and behavioral functions based upon verbal magnitude estimations in man.

It is difficult at this time to justify the comparison of very diverse measures of neuronal and behavioral responsiveness suggested by some investigators (e.g., the rate of cell firing in animals and verbal magnitude estimations in man; Mountcastle et al., 1966; Werner and Mountcastle, 1965). Even though some strikingly similar relations have been observed, the disparate procedures involved in the neural and behavioral observations greatly restrict the validity of these comparisons. Any conclusion based upon a similarity in neuronal and behavioral activity observed from two such different procedures and preparations must be based upon the assumption that the neuronal activity observed in the acute animal preparation is similar to activity existing unobserved in the behaving human. Evidence is available which indicates that neuronal activity is dependent upon the physiologic state of the preparation, as might be induced by a particular type and dose of anesthetic. Moreover, neural responsiveness will vary with levels of attentiveness and wakefulness. Such differences are represented in the extreme by acute animal studies of physiologic function and human behavioral studies such as those referenced above.

ELECTROPHYSIOLOGIC AND BEHAVIORAL DATA IN HUMANS

A second approach in psychophysiology is provided by attempts to record electrophysiologic data simultaneously with behavioral responses in humans. Aside from social and moral limitations on the physiologic techniques that can be employed and the mechanisms which can be explored with humans, the technical difficulties encountered in attempting to record minute potentials from the nervous system through overlying tissue imposes major restrictions on this approach. In one respect, these difficulties have been overcome through the use of computer-summing devices (Barlow and Brazier, 1954; Clark et al., 1961; Brazier et al., 1961). Thus, through repeated observations of episodes of neural activity immediately following a stimulus, digitizing the voltage changes and arithmetically summing them, time-locked changes in voltage add, whereas random changes in voltage tend to average out. Hence, presumably such devices allow us to greatly increase the signal-to-noise ratio of our final record.

There are, however, some major physiologic problems of interpretation introduced by the use of such instruments. It is currently difficult to independently specify properties of observed summed or averaged responses that are neurophysiologically significant. Thus, it is difficult to determine which properties of the summed response to evaluate and compare to our measure of behavioral performance. These difficulties result from observations that: (1) this procedure may introduce distortion into the physiologic record; (2) it is sometimes difficult

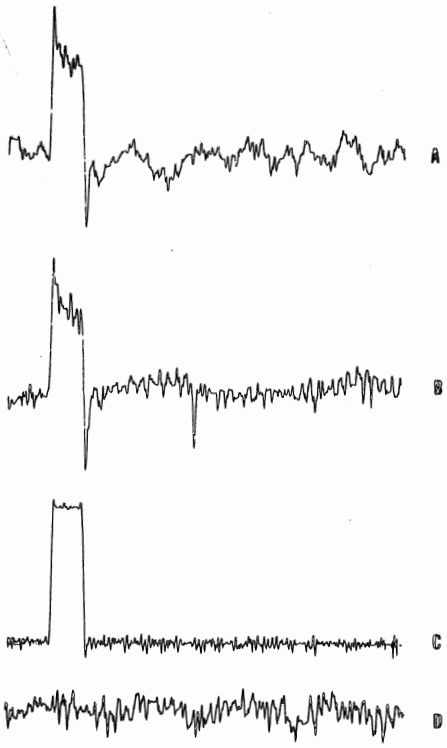

Fig. 1. Summed responses (500 trials) recorded across the third digit of the ipsilateral (A) and contralateral (B) hand to a 1-volt square pulse (C) applied unilaterally across the first digit. Amplitude of record C printout reduced by 10:1. (D) Control record from contralateral hand, with resistor across active lead.

or impossible to specify the origin of the averaged electrophysiologic response; and (3) there is little basis for evaluating long latency potentials usually observed from humans with this procedure.

The procedure of averaging physiologic potentials includes mechanisms for distorting or masking characteristics of the neural response. Given any variability in the response, the process of summing can produce an averaged response with amplitude, latency, or wave form different than any individual evoked response. As a consequence of such treatment, confusion arises in regard to the evaluation of characteristics of the response.

Furthermore, these devices are capable of summing very small time-locked potentials generated far from the recording electrodes. Figure 1 illustrates such a summed recording generated in response to repetitive 1-volt pulses applied across one finger. Responses were recorded from an adjacent finger of the ipsilateral hand (A) and from the contralateral hand (B). There is little amplitude difference between the summed responses. The major reduction in voltage probably occurs across the skin. This example illustrates some of the difficulties that may be encountered in specifying the origin of potentials recorded with such instruments.

Moreover, the analysis of the long latency neural responses commonly studied in human preparations introduces problems of interpretation. In many studies, analyses have been made showing evoked responses with initial latencies from 80 to 800 msec. From purely behavioral considerations, the immediate role such responses may play in overt performance is questionable. We know that behavioral responses reflecting parameters of the sensory stimulus may be elicited in less time than that necessary to evoke neural activity of such latencies. The physiologic basis for such long latency potentials is poorly understood. Again, it is difficult to provide an adequate independent justification for selecting a particular property or set of properties of the neural response as relevant to a behavioral response.

ELECTROPHYSIOLOGIC AND BEHAVIORAL DATA IN ANIMALS

Many of these difficulties of interpretation of neural activity may be overcome by using techniques for recording neural activity in unanesthetized animals with chronic indwelling electrodes and by studying short-latency evoked potentials with physiologic properties which are better understood. Combining chronic electrophysiologic techniques with behavioral conditioning procedures for deriving precise measures of sensory performance in animals provides a third, and perhaps most effective, alternative approach for the study of afferent neural processes involved in stimulus-dependent behavior.

BASIC PROBLEMS IN NEURONAL AND PSYCHOPHYSICAL ANALYSIS

It is evident that in the design of an experiment aimed at recording precise, concurrent measures of neurophysiologic and behavioral responsiveness we must consider factors which are specifically relevant to a combined behavioral and neurophysiologic investigation. We must also consider more traditional factors relevant to each area separately.

BEHAVIORAL ANALYSIS

Behavioral considerations were discussed throughout the conference. The procedures and principles of behavioral analysis described there and in this book are indeed applicable to chronic electrophysiologic-behavioral studies of sensory function. The unsophisticated application of behavioral techniques in electrophysiologic studies is of questionable value.

An obvious but often overlooked point is that the measures of performance selected must be clearly identified as a meaningful measure of sensory behavior. As a case in point, the isolated observation of responses following repeated onset

of a light does not necessarily allow us to assume that the light was exerting a controlling influence on the performance. Behavioral analysis is necessary for the demonstration of specific stimulus control. Such an analysis may take one of a number of directions; the level of evaluation depends upon the precision of the measure of behavior we wish to obtain.

In general, we wish to demonstrate the modification of the behavioral response with variation in stimulus parameters. For example, we may evaluate the changes in the probability of a response following specific changes in stimulus conditions. Sufficient information of basic principles of behavior currently exists to allow the measurement of changes in behavior and the evaluation of the relevance of these changes—the specification of stimulus control.

In studies where a careful analysis of behavior and its relation to experimentally produced changes in stimulation has been ignored in favor of more casual observation, any contribution to an integrated electrophysiologic-behavioral analysis is not possible. Such informal observations of behavior have in the past appeared as an afterthought appended to a physiologic study. They may be of some value to the physiologic findings but their functional interpretation is as difficult for the psychologist as the long latency summed gross potential is for the physiologist.

PHYSIOLOGIC FACTORS

This illustration raises questions relevant to physiologic factors which must be considered in such studies. At this time, the most meaningful measures of neural activity are those obtained with single cell recording techniques. Since our understanding of current generation and volume conduction in the central nervous system is limited, interpretation of gross potentials in general is somewhat difficult. Of the gross potentials resulting from afferent stimulation, perhaps the best understood is the primary evoked potential. Extensive research has been performed on this potential regarding its origin and generation (Purpura, 1959; Towe, 1966; Biedenbach and Stevens, 1969a, 1969b; C. F. Stevens, 1969). In addition, extensive baseline information exists on the characteristics and properties of primary evoked responses in acute preparations (i.e., anesthetized and surgically prepared animals). Studies have dealt with changes in evoked responses accompanying changes in the physiologic state of the preparation, recording site, stimulus parameters, and so forth. Such basic information on the characteristics of physiologic measures is essential for the adequate interpretation of data obtained with these measures and their appropriate use in the study of sensory processes.

Concurrent analyses of physiologic and behavioral measures require careful consideration of the entire range of procedures employed. Techniques from each area can be powerful when properly used. To stress one at the expense of the other may produce confounding interactions. For example, spurious changes in electrophysiologic activity may well result from such unmonitored or unconsidered changes in a behavioral situation as a variation in the state of deprivation or satiation of a subject during an experimental session. Such interactions handi-

cap our evaluation of the data as they relate to physiologic function, to behavioral function, or to combined functional processes.

Aside from the interactions stressed above, technical problems are introduced in electrophysiologic-behavioral investigations due to the physical interaction of the different procedures and technology employed. For example, electromechanical behavioral equipment produces transient voltage pulses which are often amplified and recorded along with the physiologic signals of interest. Wires leading to and from implanted electrodes limit movement of the subject. Another problem, which at times is more subtle and difficult to recognize and control, results from the fact that muscle potentials may be recorded over large distances. This is the case even when differential electrodes implanted deep in the brain are used. A behavioral response which requires minimal movement of the subject or which occurs at a time separated from the measures of neural activity is indicated in such cases.

THE REACTION TIME TASK

The behavioral situations and techniques discussed in this conference would seem eminently appropriate for a concomitant physiologic-behavioral study of sensory processes. However, many have been directed at the investigation of behavior related to threshold levels of stimulation. Physiologic information available to date and our current views of neuronal function suggest that stimuli near threshold or small changes in the values of stimuli produce minimal changes in neural activity. The recording and analysis of such small changes in an unanesthetized preparation is technically difficult if not currently impossible.

In Chapter 13 by Dr. Moody, "threshold studies" were distinguished from "suprathreshold studies." As an example of a "suprathreshold study," Dr. Moody described the reaction time (RT) task. This task, designed for the study of sensory behavior with respect to suprathreshold stimulation, seems appropriate for the study of electrophysiologic correlates of behavior. Moreover, a number of characteristics of this task make it particularly suitable for a behavioral-physiologic study.

Let us briefly consider this behavioral task; the training procedures are relatively easy. The performance elicited is stable and quantifiable. The task is relatively simple; hence, it may be hoped that the neural circuits involved in performance of this task are also simple. Furthermore, a variety of stimulus intensities may be studied. In fact, the intensity range of stimuli employed may cover the dynamic range of the system investigated. Many characteristics of RT performance, such as latency-intensity relations, have been shown to be comparable across the mammalian species up to and including man. Thus, both general properties of sensory function and specific relationships that we obtain in regard to sensory processes involved in performance of this task may apply to man. Finally, and of great importance, it may be noted that the measure of the animal's performance and neural activity are temporally quantifiable. This pro-

vides a meaningful basis for comparison and may eventually provide a basis for the establishment of causal relationships between neural activity and behavior (Evarts, 1966).

The RT paradigm has an extensive history of use in studies of neural processes related to sensory behavior. Early work related to RT and its neurophysiologic processes varied over a wide range bearing on questions extending from the velocity of conduction in peripheral sensory nerves (Helmholtz, 1853) through the analysis of biophysical properties of neural excitation (Woodrow, 1915).

Following the observations by Maskelyne, the Royal Astronomer at Greenwich, of differences between observers' estimates of the time of stellar transits, the suggestion was made by Nicholi (Herman, 1879) that these discrepancies might be due to differences in conduction velocity in the individuals' nervous systems. Helmholtz (1853) attempted to use the RT technique to measure conduction velocity in human sensory nerves, and he reported RTs to stimulation of "the great toe" to be about 20 msec longer than those to stimulation of the "ear or the face." Cattell and Dolley (1895), however, failed to confirm Helmholtz's observations. Cattell's results indicated that the RT situation was ineffective for measuring neural conduction time in man. Although he attempted to control all possible variables in the experimental situation, he repeatedly found large variations in the time of the reaction. Cattell suggested that the variability was due to the central connections involved as well as the qualitative differences in the sensations aroused at the different points of stimulation.

The differences in the data derived by these early investigators are not too surprising since many factors are now known to influence RT. It is well known that RT depends on stimulus intensity. Froeberg (1907) was one of the first to report this experimental relationship. More recent investigators (Bartlett and MacLeod, 1954; Stebbins and Miller, 1964) have confirmed these findings by Froeberg and extended these observations to animals: with attenuation of intensity of the stimulus to near threshold values, response latency and variability increase. This latency-intensity (L-I) relationship, and the psychophysical functions which may be derived from it, are discussed in detail in Chapter 13 by Dr. Moody.

Recent physiologic studies using the RT task have relied on the observation of averaged cortical evoked responses in humans. Dustman (1965) has reported that wave component latencies of the averaged evoked potential are positively correlated with RTs; shorter averaged evoked potential latencies tended to be related to shorter RTs. Haider et al. (1964) reported that as the subjects' vigilance (as indicated by detection of dim flashes) diminished, RTs increased and amplitude of visual evoked long latency potentials decreased. Morrell and Morrell (1966) reported that amplitudes of visual evoked responses were correlated with RTs; the more intense the photic stimulus, the larger the evoked potential and the shorter the RTs. As previously discussed, technical and theoretical difficulties related to the observation of long latency computer-averaged evoked potentials make interpretation of these results difficult. However, these findings do support the suggestion that the use of the RT task in animals, coupled with more direct electrophysiologic procedures for monitoring neural activity, may indeed provide a fruitful approach for the study of neural processes involved in sensory behavior.

REACTION TIME IN NONHUMAN PRIMATES

The research to be discussed is based upon the study of certain central neural processes involved in RT performance in nonhuman primates. Observations of visual and auditory neural function and behavior will be described below.

EXPERIMENTAL METHODS

Behavioral aspects of this preparation were detailed in the preceding chapter. For the study of visual processes, monkeys restrained in chairs were trained to press a telegraph key to the onset of a clearly audible 1-kHz tone, to hold down the key for a variable foreperiod, and to release the key to the onset of a neon light. Release of the key in the presence of the tone and light was followed by delivery of a 190 mg banana flavored pellet (Ciba). Both light and speaker were mounted on the upper plate of the restraining chair, approximately 10 cm in front of the monkey's eyes. The light was mounted behind a ground glass diffusion filter and viewed through a 1 cm hole in the stimulus display box. In the auditory situation, the animals' heads were further restrained and Permoflux earphones (PDR-600) were fitted directly over the external auditory meatus. The behavioral preparation is similar to that illustrated in Figure 2 of Chapter 3. The animals were trained to press a key following onset of the light and to release the key upon presentation of a pure tone delivered through the earspeakers. In the visual experiments, the intertrial interval was 30 seconds and the foreperiod varied from 0 to 5 seconds. In the later auditory experiments, the foreperiod range was changed to vary between 1 and 4 seconds and the intertrial interval was reduced to 10 seconds. In both cases, initiation of a trial was dependent upon the absence of key presses for a period equal to the minimum intertrial interval. All subjects were trained with a contingency for differential reinforcement of brief latency responses (Miller et al., 1966).

A diagrammatic representation of the arrangement of the behavioral and electrophysiologic equipment is shown in Figure 2. In the visual experiments, relay and solid-state (BRS) logic units were used to program automatically the conditioning procedures and to record behavioral performance. For the auditory studies, solid state circuitry and a Digital Equipment Corporation (PDP-8) computer were used to program the conditioning procedures and to measure behavior. This means of control permitted automatic variation of the parameters of the tone stimulus during each experimental session. The latency of key release following tone onset was punched on paper tape by the computer for off-line analysis.

Details of the stimulus generation and calibration procedures are given elsewhere. (For visual experiments, see Miller, 1965; Miller and Glickstein, 1967; for the auditory experiments, see Stebbins et al., 1966, and Chapter 3.) Visual stimuli

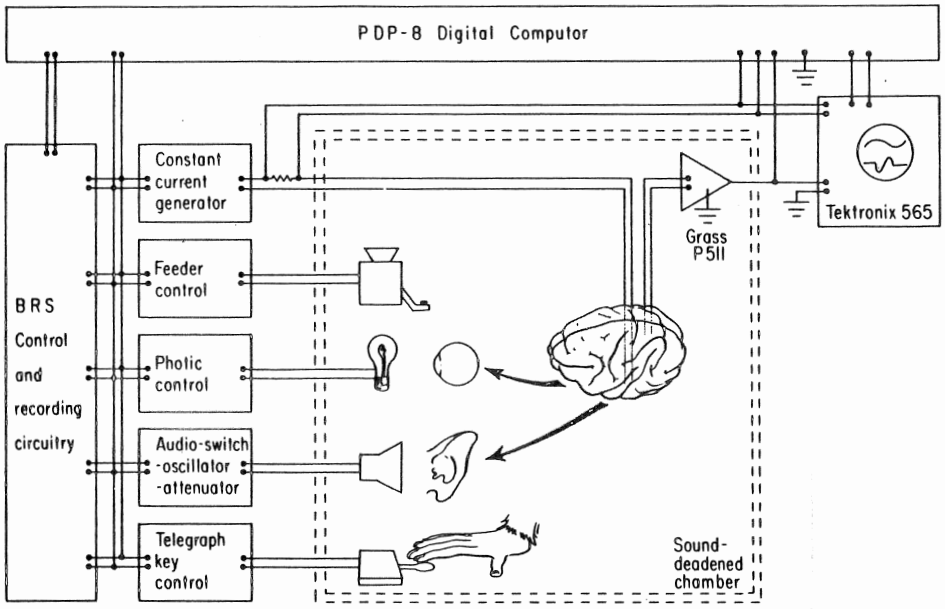

Fig. 2. Diagrammatic representation of arrangement of behavioral and electrophysiological apparatus.

were varied in log units from a maximum intensity of 8 ft-c. The tone was electrically switched with a rise and fall time of 5 msec. Intensities of all tones were measured with a calibrated probe tube and a condenser microphone. Tone intensities are given in dB re 0.0002 dynes/cm^2.

After preliminary training, platinum-iridium bipolar electrodes were implanted in the CNS of monkeys under aseptic conditions. In the visual experiment, electrodes were implanted stereotaxically in the lateral geniculate nucleus (LGN) and, under direct visualization of the fissural pattern, in the macular area of the visual cortex (Talbot and Marshall, 1941; Daniel and Whitteridge, 1961). Monkeys in the auditory experiment received electrodes directed at the auditory cortex (Ades and Felder, 1945). In addition, control electrodes were implanted in cortical sites outside primary sensory areas.

Figure 3 shows the electrode assembly placed in visual cortex of one monkey. The electrodes projected 1.5 to 2.0 cm into visual cortex. The exposed tips (1 mm^2) were separated by approximately 2 mm. Other cortical implants, including those for association cortex and auditory cortex, were similar to those pictured in Figure 3. Electrodes for auditory cortex projected 4 to 5.5 mm from the stabilization plate of the assembly. These electrodes were introduced into the primary auditory area from the lateral surface of the superior temporal gyrus. As many as nine electrodes were included in one auditory cortex assembly. Paired bipolar electrodes, with exposed tips separated by 1.5 mm in the dorsal-ventral plane, were used for thalamic placements.

These electrodes were used to deliver direct electrical stimulation to, and to

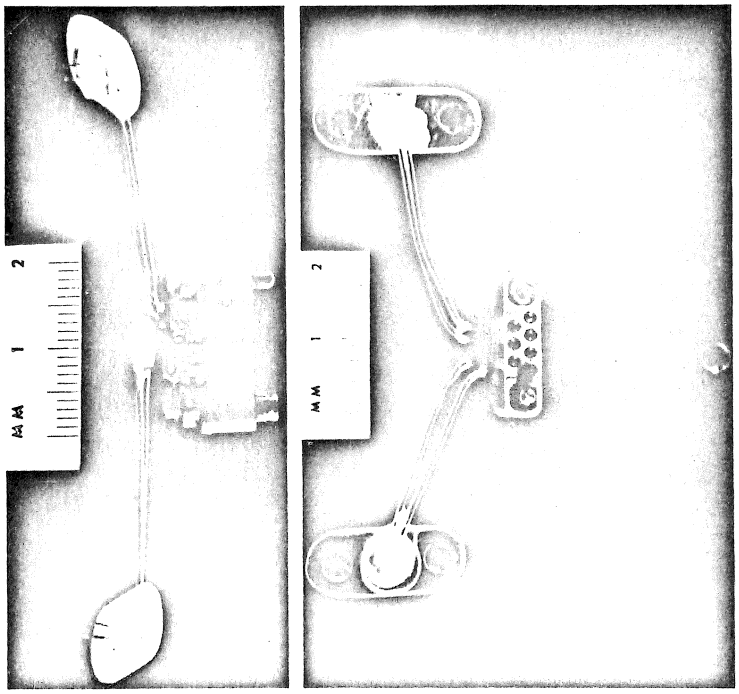

Fig. 3. Electrode assembly for bipolar, bilateral stimulation and recording in visual cortex. The assembly is a modified design of one described by Doty et al., (1956).

record from, structures along the classical auditory and visual pathways. Intracranial stimulation was provided by a constant current generator designed in our laboratory. The output was a 60-Hz sine wave, continuously variable from 1 to 1,000 μa (rms). The system provided isolation of 1×10^{12} ohms to ground and a minimum output impedance of 2×10^5 ohms. We have used this stimulation in monkeys being tested over a 2-year period and have found no obvious histologic changes in the tissue between the tips of the stimulating electrodes attributable to the use of this stimulation. (See Fig. 12a, Miller and Glickstein, 1967.) All neural potentials were recorded differentially with standard electrophysiologic equipment, including Grass P511 preamplifiers and a 565 Tektronix oscilloscope. Frequency response of the system was limited by low and high half-amplitude filters set at 3 Hz and 2 kHz.

EXPERIMENTAL RESULTS AND DISCUSSION

Given an experimental preparation in which the subjects were trained to stable performance in the RT task and implanted with nonpolarizable bipolar electrodes in the afferent systems, a number of experimental questions pertinent to the role of afferent system control of this behavior could be answered. Our first

questions took two forms. One concerned the effects of introducing direct electrical stimulation of the afferent sensory pathways on RT performance. The second concerned the relationship between afferent neural and behavioral responsiveness to peripheral stimulation.

Following recovery from surgery, the subjects were reintroduced into the behavioral situation. Determination was then made of appropriate current intensities to pass between pairs of the implanted bipolar electrodes. For animals in the visual experiment, this determination was not difficult. The intensity of manually presented stimulus pulses was increased to a point at which the monkey began to exhibit visual orientation responses. With cortical stimulation these responses were consistently directed to within a few degrees of the "foveal gaze." The subjects were then tested in the standard RT experiment with peripheral stimulation. Concomitant with the onset of the key release stimulus, electrical stimulation was delivered to the central nervous system. Like the peripheral stimulus, the electrical stimulation remained on until the key release occurred.

Observations made on the first visual RT monkey with electrodes in the macular cortex are representative of our findings. Over a period of approximately 40 trials following introduction of the central stimulation, intensity of the peripheral stimulation was decreased. At first, RTs increased as the intensity of photic stimulation decreased. However, by the time the intensity of the visual stimulus was reduced by 4 log units (though still at least 2 log units above threshold), RTs no longer increased but instead came under the control of the central stimulation. In other monkeys, using initially higher intensities of central stimulation, transfer was accomplished in fewer trials. In our most recent monkey trained in the auditory experiment and tested with electrical stimulation of the auditory cortex, transfer from peripheral to central stimulus control was completed in fewer than 10 trials presented over a 2-minute period.

On the other hand, maximum intensity electrical stimulation of frontal and parietal association cortices (1,000 μa) was ineffective in eliciting a key release response, with over 500 trials, in monkeys trained in the visual RT experiments. In one visual RT animal, an electrode pair directed at the LGN was later found to have one pole near the capsule of fibers medial to and surrounding the LGN and one pole 3 mm medial in the thalamus (across part of the medial geniculate nucleus). Stimulation between these points was ineffective in eliciting an RT response.

Characteristics of the RT response to effective central stimulation were similar to those observed with peripheral stimulation. General behavior was similar in the RT situation with either peripheral or central stimuli in all but one monkey. This one subject, with electrodes in the LGN, demonstrated an increase in variability of response latency at high intensities of central stimulation. The subject's behavior became generally unstable and the monkey stopped performing in the RT task with high intensity central stimulation. On the basis of the anatomy of the base of the brain in the region of the LGN, it is likely that high intensities of stimulation resulted in current spread to pain receptors in the dura underlying the LGN, thus eliciting behavior incompatible with stable RT performance.

The similarity in the behavioral responsiveness to peripheral and central

stimulation and the rapidity of transfer to central stimulation of the afferent pathway may be interpreted to suggest that the primary afferent paths of the visual and auditory system are indeed involved in this behavior, and further indicate that there is at least some basic similarity between the effects of incoming neural activity evoked by peripheral stimulation and that initiated by direct electrical stimulation.

We next looked for measurable differences in the responses to peripheral versus cortical stimulation. Hopefully, with a relatively invariant behavioral measure such as response latency, small differences in performance may be demonstrated. It was necessary to equate behaviorally the intensities of the peripheral and central stimulation if they were to be compared. Latency-intensity (L-I) functions to both classes of stimuli were examined in the visual and auditory RT task. For peripheral and central stimulation in both systems at high intensities, the RT function approximates a minimal latency asymptote and varies little over a wide range of stimulus intensities. This finding justifies comparison of RTs to peripheral and electrical stimulation at high intensities.

Figures 4 and 5 illustrate the L-I functions obtained with peripheral and cortical stimulation in the visual and auditory RT experiments. At high stimulation intensities, a consistent reduction in response latency of 30 and 15 msec was observed with cortical stimulation in the visual and auditory experiments respec-

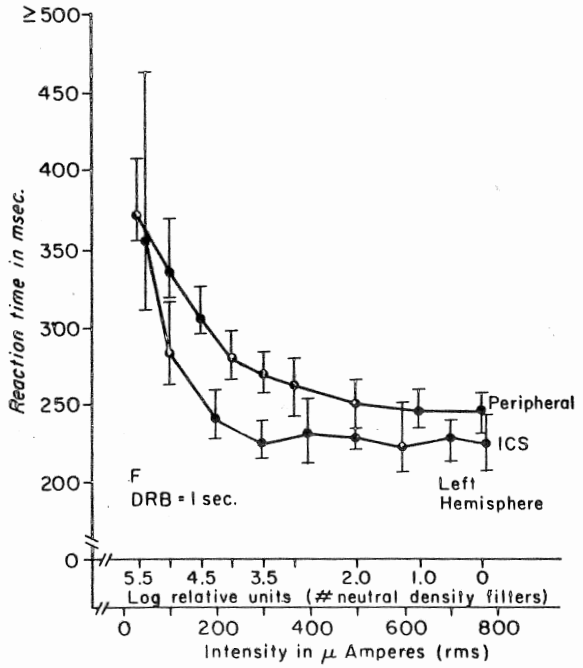

Fig. 4. Comparison of RT to photic and visual cortex stimulation. Medians and interquartile ranges are plotted. Each point is based on at least 50 trials. (From Miller and Glickstein, 1967. J. **Neurophysiol.**, 30:399–414. Copyright 1967 by the American Physiological Society.)

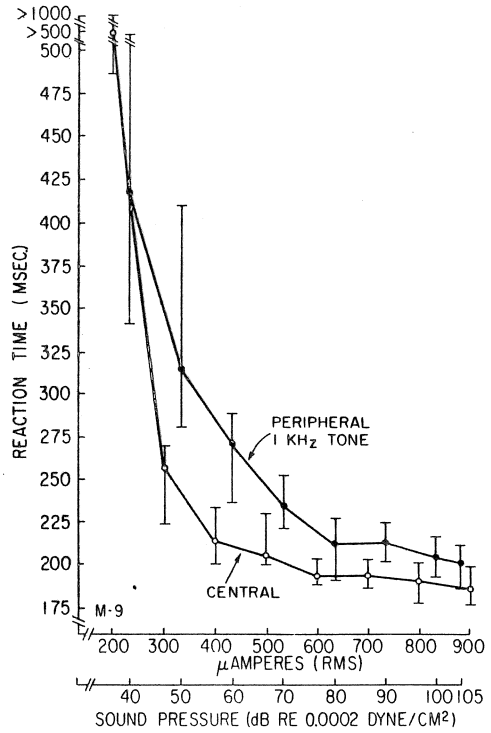

Fig. 5. Comparison of RT to acoustic and auditory cortex stimulation. Medians and interquartile ranges are plotted. (From Miller et al., 1969. **Science**, 163:592–594. Copyright 1969 by the American Association for the Advancement of Science.)

tively. These shifts in response latency are approximately the same as the latencies of the primary evoked potentials recorded in unanesthetized primates to photic stimulation and anesthetized animals to auditory stimulation. Moreover, in an animal in which RTs to direct electrical stimulation of the LGN were compared with photic stimulation, a reduction of approximately 20 msec was observed.

These findings are consistent with the view that the afferent sensory pathway is in series with the motor system in RT performance. Direct stimulation of LGN apparently acts to "short-cut" transmission of visually evoked impulses through retina, optic nerve, and tract. Stimulation of the macular cortex appears to result in a bypass of processes at the retina and eliminates transmission times to the cortex. Findings in the auditory experiments may also reflect general properties of afferent systems involved in determination of RT performance.

These latency shifts have been compared above to latencies of primary evoked potentials in the visual and auditory systems. This relationship would be more impressive had it been based upon direct observations of evoked potentials made in the same monkeys when performing the RT task. With this in mind, an attempt was made to record evoked potentials from the macular cortex through the electrodes used for stimulation in animals performing in the visual RT experiment.

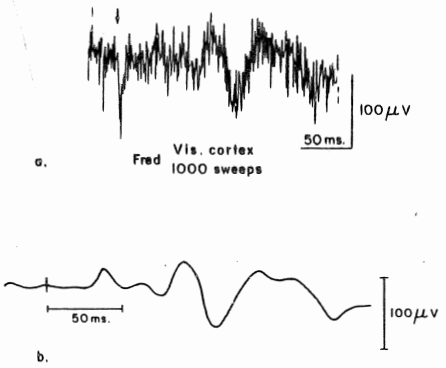

Fig. 6. Evoked potentials from visual cortex.
a. Recording of neural activity summed by a computer of average transients during first 200 msec. after photic stimulation. Negative deflections upward. Sum of 1000 sweeps. Arrow indicates onset of visual stimulus. (From Miller and Glickstein, 1967. **J. Neurophysiol.**, 30:399–414. Copyright 1967 by the American Physiological Society.)
b. Filtered, extended hand tracing of response in a.

Attempts to record evoked potentials from the visual system were somewhat less successful than originally hoped. With the use of a computer of average transients, a reproducible potential was obtained from one monkey (Fig. 6). The record is the sum of 1,000 trials. A major deflection occurred with a latency of approximately 80 msec. There was a small consistent potential (possibly equivalent to the primary) observed with a 30-msec latency. This finding, coupled with the findings of others (Hughes, 1964; Doty et al., 1964), suggests that visual evoked cortical potentials in the unanesthetized monkey may be demonstrable only with flash stimuli of very high intensities.

The indicated presence of an evoked potential with a latency of 30 msec supports our interpretation of the effect of cortical stimulation on RT performance. The use, however, of a summing device in recording this potential restricts the evaluation of this observation. Attempts to record evoked potentials from the stimulating electrodes in the auditory cortex were more successful. Figure 7 illustrates the potentials evoked by bursts of white noise and a 1-kHz tone at various intensities. Each record is composed of five superimposed traces. At high intensities of stimulation, the initial evoked response latency was approximately 15 msec. This correspondence between the latency of the evoked potential and the parallel changes in RTs with cortical and acoustic stimulation provides further corroborating evidence for the suggestion that the afferent pathways play a direct and perhaps controlling role in RT performance.

The question should be raised whether the application of cortical stimulation introduces unknown qualitative differences into the RT situation and whether such differences may affect a change in response latency independent of any spe-

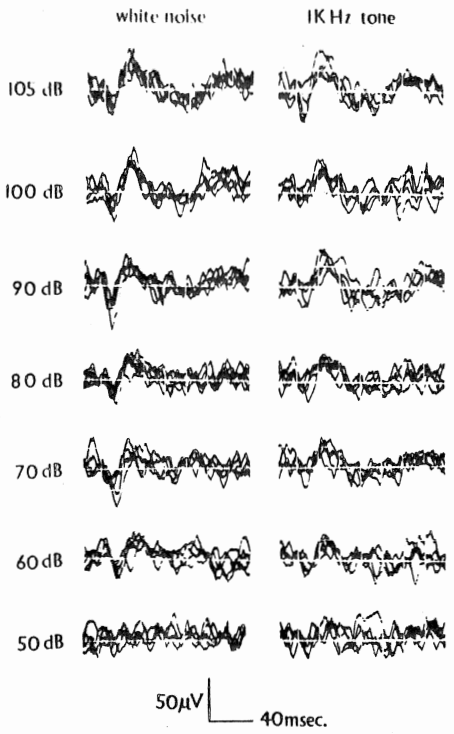

Fig. 7. Evoked potentials from auditory cortex to white noise and a 1 kHz tone at differing intensities. Each response represents the superposition of five traces.

cific sensory role of the afferent system in this task. Observations which oppose this interpretation are:

1. The ease of transfer of the behavioral response from peripheral to central stimulation of appropriate cortical sites.
2. The lack of transfer of the behavioral response to electrical stimulation of sites in association cortex.
3. The difference in magnitude of behavioral response latency changes with central stimulation in the auditory and visual systems.
4. The agreement of these RT differences with initial latency of the peripherally evoked cortical potentials.

The form and time course of the evoked potentials (Fig. 7) are similar to those expected of acoustically evoked "primary" cortical potentials. The initial latency of this potential showed little if any consistent variation with changes in the intensity of the stimulation. If this potential is indeed the "primary" response, one questions this lack of change in initial latency. Such changes are a known property of cortical evoked primaries. A possible explanation for this finding follows from the observation that primary evoked responses show most rapid latency changes at or near threshold levels of stimulation; at higher intensity levels, latency changes may be minimal. It may be that the intensities employed in this

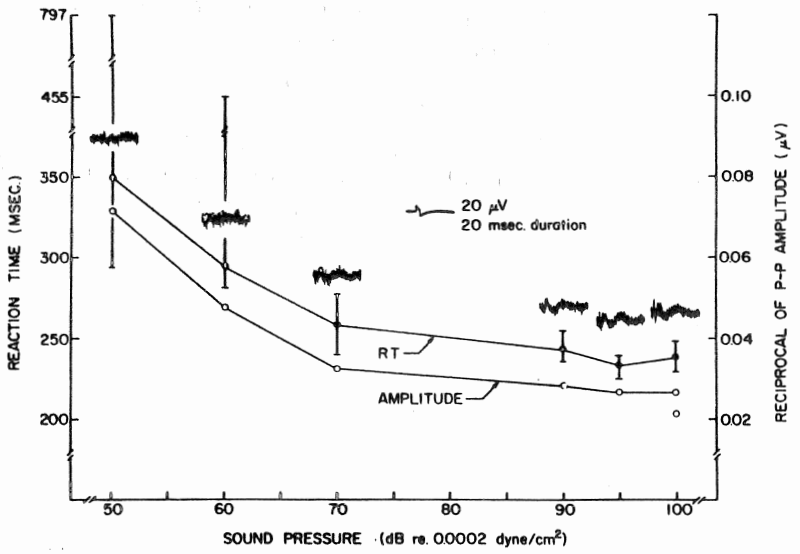

Fig. 8. Median RTs and reciprocals of the peak-to-peak amplitude of evoked potentials recorded simultaneously from one monkey. Each point is based upon 25 trials. An example set of five superimposed evoked responses is included for each stimulus intensity. Stimulus was a 1 kHz pure tone.

investigation are already at a level producing only minimal latency changes in the electrophysiologic response.

An additional property expected of the primary potential is that of change of amplitude with changes in stimulus intensity. Such changes are evident in Figure 7. Moreover, this variation in amplitude of the evoked potential may be examined in light of variations in behavioral response latencies observed with changes in stimulus intensity. Figure 8 illustrates the relation between reciprocals of the peak-to-peak amplitude of the evoked potential and RTs to a 1-kHz tone in one monkey. Figure 9 illustrates a similar finding to a 250-Hz and an 8-kHz tone in another monkey.[1] In both Figures 8 and 9 it is evident that as intensity of auditory stimulation increases, peak-to-peak amplitude of the evoked cortical response increases and RT decreases.

A correlation between latency shifts of both the neural and behavioral responses was expected with changes in intensity of acoustic stimulation. The lack of such a relationship between latency of the neural response and stimulus intensity plus the observation of corresponding variation between neural response amplitude and behavioral response latency requires some consideration. First,

[1] During these experiments, electrophysiologic signals from the preamplifiers were also transferred to the analog-to-digital converter of the PDP-8 computer for on-line analysis. The computer was programmed first to sample (at 4 kHz) a 100-msec episode of cortical activity starting from the onset of the tone, and then to determine the latencies of the first positive-going peak and the first negative-going peak, and the peak-to-peak amplitude of the signal. This procedure was followed for each evoked potential. Statistics based upon these individual measurements were then calculated.

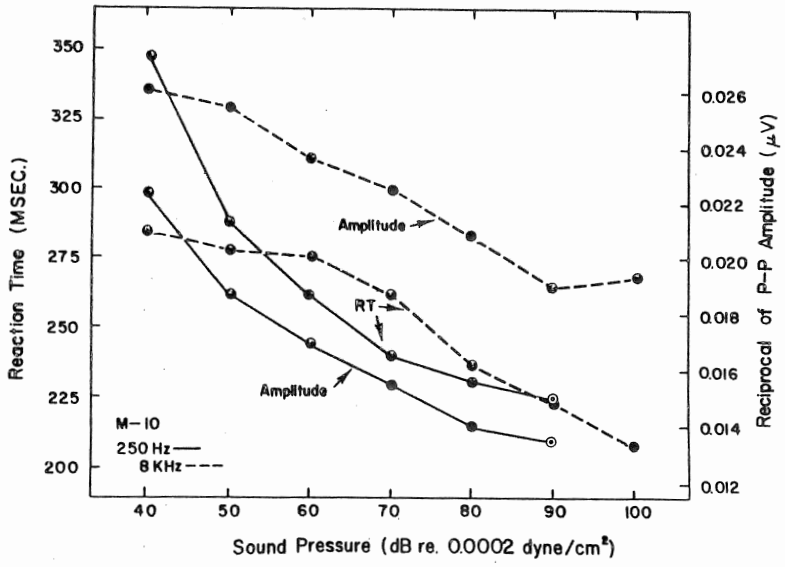

Fig. 9. Median RTs and reciprocals of the peak-to-peak amplitude of evoked potentials recorded simultaneously from one monkey. Measurements were taken to 250 Hz and 8 kHz pure tones at various sound pressure levels. (From Miller et al., 1969. **Science**, 163:592–594. Copyright 1969 by the American Association for the Advancement of Science.)

in regard to latency changes of the evoked potential, it has been suggested that the intensities employed in this investigation were at a sufficiently high level to produce only minimal changes in latency. As activity continues through the synaptic system involved in this behavior, latency dispersion would account for the latency changes observed in the RTs. Secondly, we know that the speed of conduction through a synaptic system is based upon, among other properties, synchrony of the neural activity (Towe and Kennedy, 1961). Thus, if amplitude of evoked potential reflects amount or synchrony of neural activity, one basic property of the synaptic system includes the mechanism for transforming such amplitude differences into latency differences. This property may reflect the basis for the observed close relationship between amplitude of evoked potential and the behavioral response latency, and may in part determine the role of sensory cortex in RT behavior.

FUTURE INVESTIGATION

ORGANIZATION OF AUDITORY CORTEX

Future investigation of the role of the afferent sensory path in behavior may take a number of directions. One question of some interest concerns the observed difference that exists between the slopes of the evoked potential amplitude-intensity functions in Figure 9. Such differences have been consistently observed

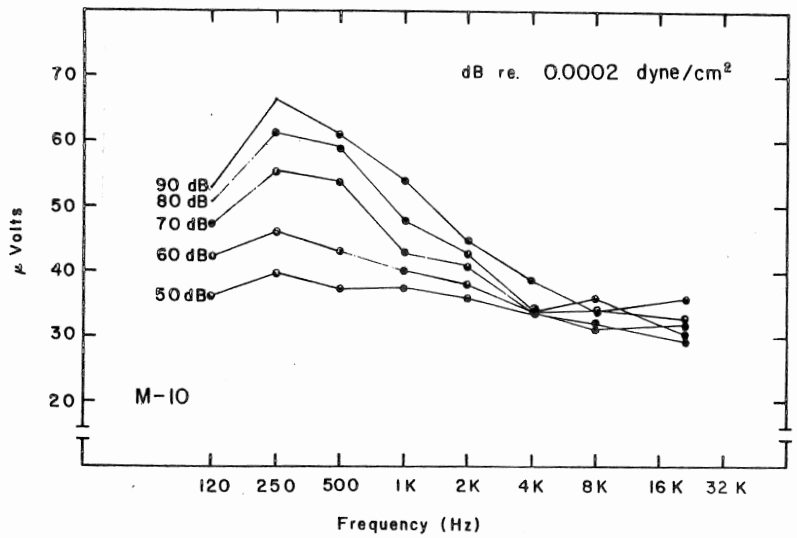

Fig. 10. Equal intensity function derived from amplitude-intensity measurements of evoked potentials observed to various frequencies of pure tone stimulation. Each point was obtained by finding that amplitude of the amplitude-intensity function elicited by a tone of a given intensity.

for all frequencies tested at all recording sites examined. They have been studied by comparing the amplitude of the responses evoked at the different frequencies with a fixed intensity of stimulation. From such an analysis, a family of curves has been obtained (Fig. 10). Each curve represents the amplitude function across frequency for a particular intensity of stimulation. These curves suggest that at this particular recording site, the cortical tissue was maximally responsive to a specific frequency of auditory stimulation.

This observation, illustrated in Figure 10, may be viewed from a different point. Rather than evaluating the response amplitude elicited by stimulation at a given intensity, we may determine the intensity of various pure tones necessary to produce a primary evoked response of a given amplitude. The results from such an analysis of the data are shown in Figure 11a. These curves suggest that at this recording site the tissue was maximally sensitive to a particular frequency of stimulation.

A similar analysis of evoked potentials recorded from adjacent tissue of the auditory cortex in the same animal has been made. The results of the analysis are illustrated in Figure 11b. In comparing this tissue with that represented in Figure 11a, one notes a clear similarity; however, this tissue appeared maximally sensitive to a lower frequency of stimulation.[2] The different curves illustrated in this figure were obtained at different recording sites. Each site appears to have a most effective frequency of stimulation. These observations appear to be in

[2] Our stimulating system did not permit examination of a response to a 30-Hz tone. Thus, from this data, it is not known whether the functions would have continued to decrease.

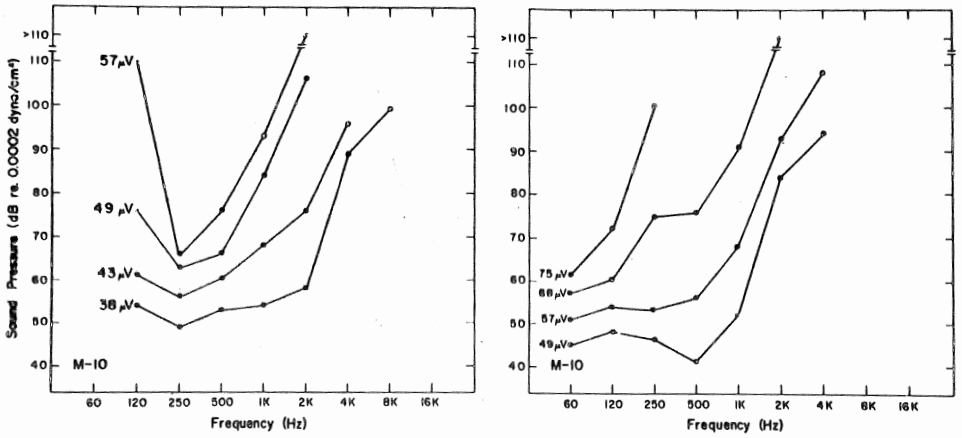

Fig. 11. Equal amplitude functions, derived from amplitude-intensity measurements of the evoked potentials observed to various frequencies of pure tone stimulation. Each point on each curve was obtained by finding that intensity of the amplitude-intensity function capable of eliciting a potential of a given amplitude. The differences in A and B result from different recording sites in the same monkey.

agreement with tonotopic maps of the primary auditory cortex in anesthetized monkeys (Kennedy, 1955), cats (Woolsey, 1961), and dogs (Tunturi, 1962).

On the basis of our current data this conclusion is not definite. Extensive study of this tissue and histologic determination of the specific loci of the electrode tips is certainly necessary. In addition, at most cortical sites examined to date, low frequencies (below 1 kHz) have been most effective in producing a primary evoked response. At one site in one monkey, a 2-kHz tone was found best. Note that all recordings discussed have been made differentially. This procedure was utilized to minimize artifacts from animal movements and from the acoustic stimulation system. This procedure imposes a restriction on the interpretation of such findings as a "most effective frequency" for different recording sites. One problem is the evaluation of the contribution of the tissue around each electrode tip to the evoked potential. With baseline information on the characteristics of this potential which, hopefully, will allow us to recognize and control artifacts, it is now possible to extend our observations to the properties of monopolar recorded potentials.

FREQUENCY DISCRIMINATION

This examination of monopolar recorded potentials is one of the current directions of work in our laboratories. This research, moreover, must include the analysis of this observation of a "most effective frequency" relative to behavioral performance. Human psychophysical studies have demonstrated that differential frequency discrimination thresholds are lowest at high intensities of stimulation. No direct findings from neurophysiologic investigations are available to explain

this psychophysical relationship. In fact, the frequency-restricted responsiveness of single auditory cells which has formed a basis for speculation of neural mechanisms underlying frequency coding in the auditory system suggests, if anything, that individual cells should be most sensitive to changes in frequency at low intensity stimulation. (See, however, Hind et al., 1967.) A possible mechanism may be suggested on the basis of data illustrated in Figure 11. It is clear that as we examine the activity generated at either of these two cortical sites, the frequency range of tonal stimuli capable of eliciting high amplitude activity is less than the range capable of eliciting low amplitude activity. This observation is consistent with the suggestion that a particular point on the cortex may be more selectively responsive to particular frequencies of stimulation at high intensity levels than at low intensities of stimulation. This finding agrees with the behavioral observation in man on frequency discrimination at high intensities of stimulation.

This suggestion is, of course, quite speculative and falls into the class of neurophysiologic-behavioral analyses discussed earlier in this chapter; that is, the approach of comparing physiologic data from one experiment with behavioral data from another. The neurophysiologic observations alone are of some interest. The relationship of this data to behavior requires clarification through experiments comparing simultaneously recorded neural and behavioral measures.

An initial approach to this problem and the general question of the relationship of central auditory processes to frequency discrimination behavior is under way. Stebbins and Reynolds (1964) have demonstrated the effect of differential reinforcement on RT to photic stimuli. After initial training to two photic stimuli, the introduction of a differential reinforcement contingency resulted in an increase in response latency to the unreinforced stimulus, while RTs to the reinforced stimulus remained unchanged. It would be interesting to examine the effects of such a procedure on the primary evoked potential. The behavioral observations with acoustic stimuli have been examined and similar changes in response latency to those found with photic stimuli were observed. Initial observations of auditory cortical evoked responses suggest that a decrease in evoked potential amplitude may occur to the unreinforced stimulus.[3] If this is the case, it would be important to examine various cortical sites for changes in "most effective frequency" organization. Such an investigation may be followed by analysis of lower auditory centers in an attempt to determine the level at which such modifications of the neural activity occur.

EFFECTS OF CENTRAL STIMULATION

An additional question pertaining to sensory processes which may be investigated with these procedures includes the further study of neural and behavioral responses to electrical stimulation at other sites along the afferent pathway. In the

[3] This observation, although very preliminary, receives some indirect support from the finding of a greatly reduced amplitude of the evoked potentials in our RT animals when they were relieved of the telegraph key and hence, not overtly responding to the acoustic stimulus. Until appropriate controls are investigated, however, it is clear alternative explanations for these observations are possible.

auditory system where it is possible to measure short latency activity, it would also be very useful to examine behavioral responsiveness to brief pulses of direct electrical stimulation introduced at lower auditory centers. The use of such pulses would permit a direct comparison of the cortical evoked response elicited by peripheral and central stimulation, which is impossible with 60 Hz central stimulation, and the examination of the relationship of these potentials to behavioral response properties. Moreover, Luschei (1968) has demonstrated a reduction in RTs to peripheral stimulation in primates receiving concomitant direct electrical stimulation of the brain stem. Such facilitation of peripheral stimulation by central excitation may be examined along the afferent pathway. This will yield a better understanding of the processes underlying the relationship of acoustically and centrally evoked activity to RT performance.

ANALYSIS OF SINGLE CELL ACTIVITY

Arguments have been presented for the use of measures resulting from the RT task and the observation of primary evoked potentials in this chapter. However, the analysis of single unit activity from individual cells yields a more precise and better understood measure of neural function than that resulting from analysis of gross potentials. We believe that the use of this measure in conjunction with RT performance will provide a more substantial basis for the eventual formulation of causal relationships between neural and behavioral functioning.

The all-or-nothing response of a single cell recorded from the primary auditory cortex in an unanesthetized monkey is illustrated in Figure 12. The ease of quantification of temporal characteristics of the single unit responses is readily apparent. Figure 12 is the result of an initial attempt to examine such activity in the unanesthetized primate. In this preliminary study, no attempt was made to

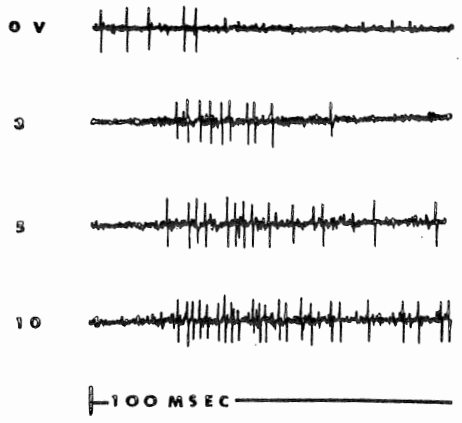

Fig. 12. Single cell activity recorded from auditory cortex of an unanesthetized monkey. Auditory stimuli were clicks of differing intensity. Voltage to speaker given at left of each trace. Vertical mark under bottom trace indicates presentation of stimulus.

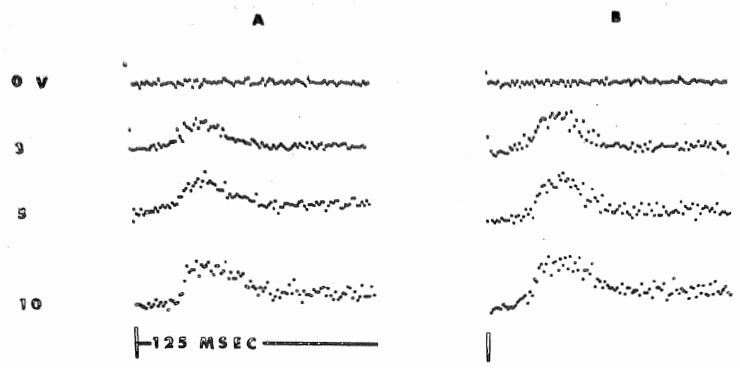

Fig. 13. Post-stimulus histograms of single cell activity from auditory cortex of unanesthetized monkey. Each histogram based upon 70 observed responses to single clicks of a given intensity. Click intensity, as voltage into speaker, is given at left of each trace. Histograms under A from observations made on cell shortly after it was isolated; those under B made four hours later.

control the behavior of the animal or to specify characteristics of the acoustic stimuli employed. The animal was seated in a primate chair placed inside a sound-deadened chamber. Clicks were delivered to the animal through a speaker mounted on the wall of the chamber. The only measure of characteristics of the clicks available is the amplitude of the voltage pulse delivered to the speaker. To date our findings are limited to observations that it is possible (1) to locate and isolate single cortical cells, (2) to evoke acoustic responses from them, and (3) to record from them long enough to study their behavior under a variety of conditions.

The observations illustrated in Figure 13 were taken from a cell that was isolated and studied for a period of 6 hours. This figure consists of poststimulus histograms generated on the basis of the response of this cell to 70 presentations of the click stimulus at four intensities. A 125-msec episode of activity was sampled following each click. Note that no time-locked change in activity was elicited when, as a control, the click intensity was set at zero volts. As the voltage increased, evoked activity increased. Concomitantly, a decrease in latency occurred with an increase in stimulus intensity. Changes in the evoked response of this unit with changes in intensity of stimulation correspond to those observed in classic electrophysiologic experiments. Stability of these observations is also illustrated in this figure. One series of measurements was taken shortly after the unit was isolated (*A*); the second measurement (*B*) was made approximately 4 hours later.

We believe that this extension of chronic neurophysiologic recording procedures and the incorporation of such techniques with concomitant measures of behavioral functioning provide a most fruitful direction for research on the role of central structures in behavioral performance. Moreover, the use of procedures and techniques that are firmly founded upon basic principles of physiology and psychology, coupled with measures of function that are precise, stable,

and quantifiable, will provide an effective vehicle for the study of neural mechanisms controlling behavior.

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