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AVERAGE RESPONSES TO CLICKS IN MAN RECORDED BY SCALP ELECTRODES

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Abstract

Electric potentials were recorded from scalp electrodes in response to different sensory stimuli and, in particular, to clicks. These electric responses are usually too small to be detected in the electroencephalogram. The use of an average-response computer enables us to study those components of the responses that are time-locked to the delivery of sensory stimuli. The present study deals with the characterization of average responses to acoustic-click stimuli in man. These responses were compared with evoked responses in subhuman species, and tentatively identified as "secondary" responses.

First, we investigated the effects of the biological structures that separate the brain from a recording site on the scalp. We concluded that average responses recorded on the scalp reflect average responses that can be recorded on the cortex directly beneath. Then, we investigated various characteristics of average responses to clicks. We determined the places on the scalp from which these responses can be recorded and the changes in the waveform of the average responses that occur as a function of changes in stimulus parameters. Our findings parallel certain findings on click responses obtained from the cortex of experimental animals.

In a series of control experiments, we eliminated the possibility that the average responses that we recorded from human scalp were produced by generators outside the brain.

We conclude that the average click responses obtained from the human scalp are probably "secondary" cortical responses. This conclusion is based, in part, on two series of experiments: One in which the effects of multisensory stimulation were investigated, and another in which the effects of sleep upon average responses to clicks were studied.

The last section of this report contains data obtained from two types of experiment in which these responses were related to the performance of certain sensory tasks. In the first type, the responses became detectable at stimulus intensities close to the subject's absolute "psychophysical threshold." In the second type, the amplitude and waveform of these average responses were found to remain essentially invariant, regardless of whether the subject was performing a specific auditory or visual task.

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GLOSSARY

Term	Definition
Correlation Function	The mathematical definition of the correlation function R(τ) is the expected value or statistical average of $x(t) \cdot x(t+\tau)$. The statistical average, in turn, is defined in terms of the whole ensemble of output waveforms that could be generated by the random process. However, the random process in the model in Section III generates not an ensemble of outputs, but only a single one. To obtain the autocorrelation function of this single output, we must make the ergodic hypothesis. That is, we assume that the wave shape under consideration is "typical" of the random process outputs and that time averages along the single sample output are the same as statistical averages computed on all possible outputs of the random process. More specifically, we assume that $R(\tau) = E[x(t)x(t+\tau)] = \lim\limits_{T \to \infty} \frac{1}{T} \int_{-T/2}^{T/2} x(t)\,x(t+\tau)\,dt.$
EEG	The abbreviation of electroencephalogram, is used in this study to refer to the electrical activity recorded with scalp electrodes, and is used interchangeably with such expressions as "extracranially recorded potentials" and "potentials recorded with scalp electrodes."
Electrophysiological Threshold	The lowest intensity of sensory stimuli at which evoked "responses" (defined by the experimenter) are "consistently" (also defined by the experimenter) detectable
Evoked Response	Generally considered to be the electric potentials produced in a preparation (or subject) by the presentation of a stimulus to it
Intensity Function	A graph presenting the amplitude of evoked responses as a function of stimulus intensity
K-complex	A monophasic, biphasic or triphasic evoked response recorded from human subjects that is characterized chiefly by its long onset latency (approximately 100 msec) and by the fact that it can be recorded from extensive portions of the scalp
Noise Level	A measure of the approximate peak-to-peak amplitude of the "ripple-voltage" component of an average response, and hence a measure of the uncertainty in the amplitude of the average response. (See section 3.2 for a more complete discussion.)

GLOSSARY (continued)

Primary Response	A response evoked by a single-modality stimulus in the corresponding "classical projection areas" of the cortex
Psychophysical Threshold	The lowest intensity of sensory stimuli at which a human subject "consistently" (defined by the experimenter) reports that he is able to detect the stimuli. Actual values of psychophysical threshold to clicks given in this study are based on measurements taken once (or several times) during an eight-month period (the method is described in section 3. 1)
Secondary Response	Also called "widespread response," a response evoked by a single-modality stimulus in cortical areas other than the corresponding projection areas (See section 1. 1c.)
Sign Convention	A change in recorded electric potential for which the active electrode is negative with respect to the reference electrode is plotted upwards in all figures in this study (except for Fig. 19).
Spontaneous Activity	Electric activity that exists in the absence of deliberate sensory stimulation. In the model used for average responses recorded from human scalp (see section 3. 2), the spontaneous activity was assumed to be completely independent of deliberate sensory stimulation.
Wide-sense Stationary Random Process	A random process whose sample functions have a time-invariant mean and variance, even though the probability density may change with time. See Communications Biophysics Group of Research Laboratory of Electronics and W. M. Siebert (87) for a brief introductory treatment of random processes and suggested readings.

I. INTRODUCTION: EVOKED RESPONSES RECORDED FROM MAMMALIAN BRAINS

The electrical behavior of the nervous systems of the higher mammals has been under extensive investigation since cathode-ray oscilloscopes came into widespread use. The early experimenters recorded this electrical activity with rather large electrodes from animals that were deeply anesthetized and surgically prepared. The experimental procedures have been gradually refined so that at the present time experimeters can record the activity of single cells with implanted microelectrodes while the host animal is awake and alert.

The extension of these techniques to human subjects, obviously, has been restricted and only very limited intercranial investigations have been carried out on humans. As a natural consequence, the activity recorded by electrodes located on the scalps of subjects has been the primary source of direct information about the electrical activity of the normal human brain. Usually, the recorded activity is so complex that specific electrical events evoked by sensory stimuli are not observable and only the gross overall patterns have been studied. However, with the development of new data-processing techniques, small response events evoked by specific stimuli may be consistently detected in the EEG. It is these small response events recorded from the human scalp with which this study is concerned.

One difficulty in the interpretation of the EEG is that it is by no means clear just what activity of the brain has been recorded by the scalp electrodes. The separation of the scalp from the active sites means that no single point of the brain is very close to a scalp electrode. Rather, a considerable area of cortical surface is almost equidistant from such an electrode, a spatial arrangement which means that the potentials produced in an extended volume of the cortical mantle will be recorded at the scalp. In addition to cortically produced activity, subcortical activity may contribute to the EEG. Spread of electrical activity from other, more distant, parts of the body may also be a contributing factor. However, due to the fact that the cortex is much closer to the scalp than other parts of the brain, it is expected that cortically produced potentials will make up a preponderant part of the activity recorded by scalp electrodes. Also, since the cortical mantle essentially covers the rest of the brain, subcortically produced potentials that are recordable at the scalp will also be recordable on the cortex. With the expectation, then, that evoked potentials that can be recorded from the cortex will be reflected in the responses recorded from the scalp, let us turn our attention first to the cortex. Because of the known similarities between the cortices of man and other mammals, such as the cat and the monkey, the many experiments performed on the cortices of these experimental animals are of great interest and provide a natural starting point for this investigation. Since acoustic stimuli were employed almost exclusively in this study, we shall concentrate our attention upon the experiments involving responses evoked by auditory stimuli.

1.1 EVOKED RESPONSES RECORDED FROM THE CEREBRAL CORTEX OF THE CAT

The extent of cerebral cortex associated with the auditory system is not clearly understood. Different investigators have described different cortical regions and subregions as being related to auditory and other types of stimuli; these descriptions depend upon the particular treatment of the experimental animal. A schematic diagram of the cat's cortex as seen from the left side is shown in Fig. 1 and the cortical locations from which investigators have reported evoked responses to various types of sensory stimuli are indicated in Fig. 2.

a. Evoked Responses Recorded under Deep Barbiturate Anesthesia

A typical experiment has been reported by Walzl and Woolsey (1). Examining cats under heavy pentobarbital anesthesia, they recorded click responses from a fairly well-localized region, bounded dorsally by the suprasylvian sulcus and extending in the ventral direction. This area is of particular interest because it contains most of the cortical projections of the medial geniculate body, a thalamic nucleus known to be of primary importance in the auditory system. Consequently, this cortical area, shown in Fig. 2, is sometimes referred to as the "auditory projection cortex." Other workers, using the

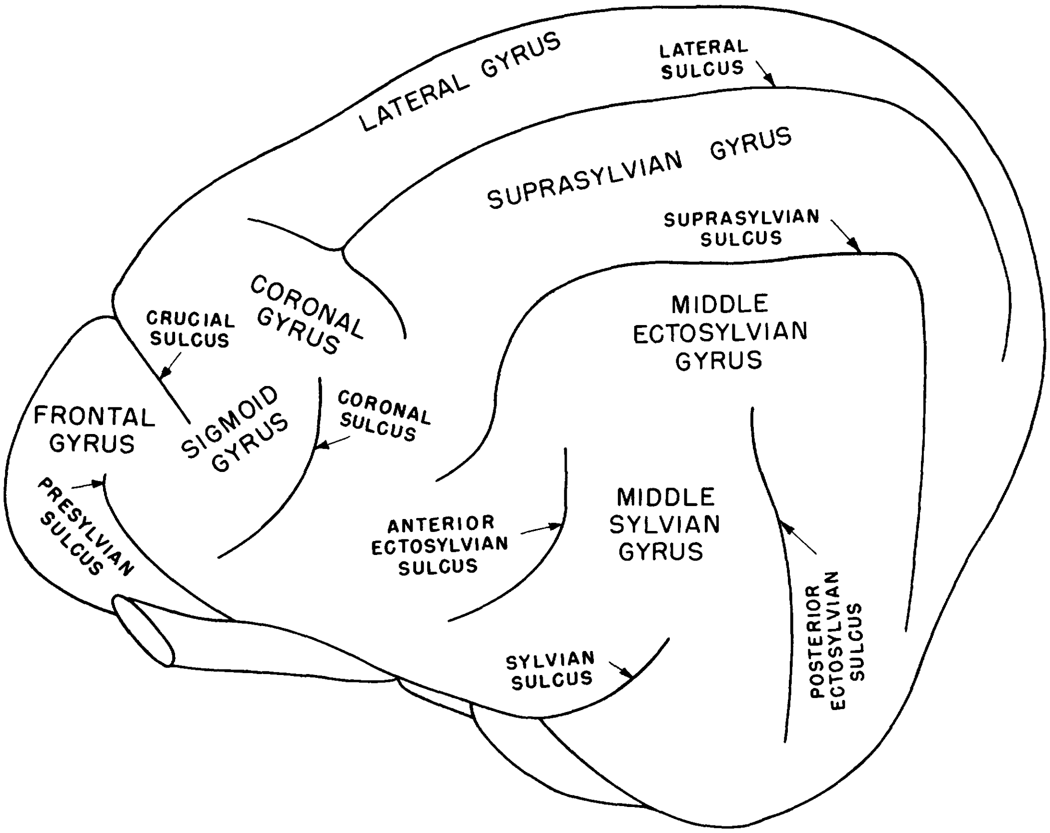


Fig. 1. Schematic diagram of the cerebral cortex of the cat showing the sulci and gyri.

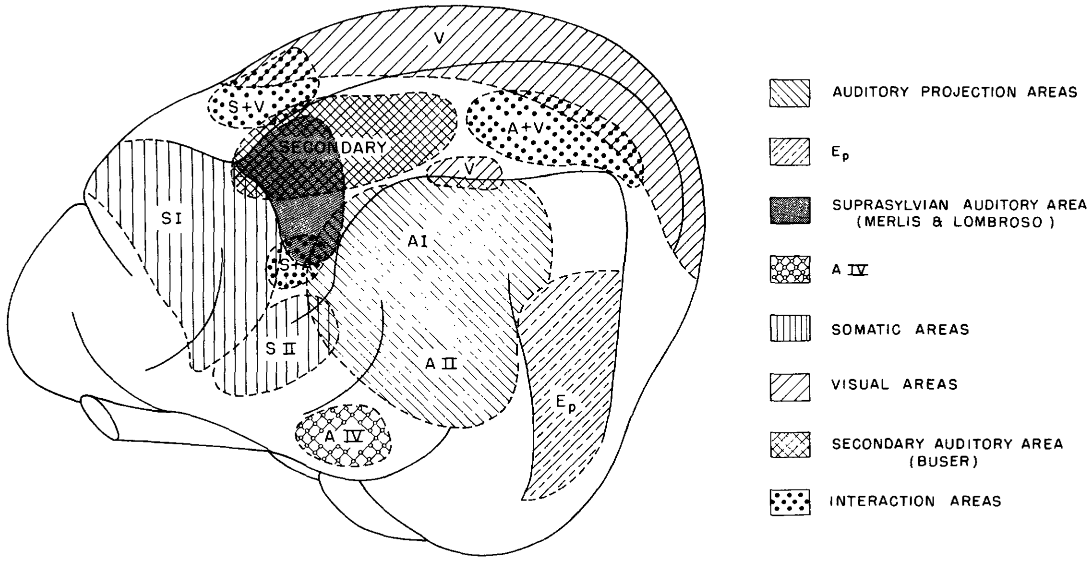


Fig. 2. Schematic diagram of the cerebral cortex of the cat showing various regions from which evoked responses to sensory stimuli have been observed.

criterion of tonotopic organization, have further divided this region into two major areas, called AI and AII. Both of these auditory projection areas, however, constitute the locus of responsive cortex that is usually reported by workers using click stimuli. Kiang (2), using several different techniques, has shown that there are indeed functional differences between AI and AII, although his delineation of the two areas is different from that of most workers.

A second type of evoked response was reported in 1943 by Ades (3). After first mapping the responsive area to click stimuli, Ades put small patches of strychnine on this responsive area and subsequently observed responses in the posterior ectosylvian gyrus, an area that lies outside the responsive area that was first mapped. Usually, a still unresponsive area separated this strychnine-activated area, labeled "Ep" in Fig. 2, from the projection areas. In present usage, the term "classical auditory cortex" usually refers to the combination of the three areas, AI, AII, and Ep.

The area near the rostral tip of the anterior suprasylvian sulcus is characterized by sensitivity to both acoustic and somatic stimulation. It must also be noted that responses to excitation of the contralateral vestibular nerve may be recorded in this vicinity (4). The fact that at least three separate types of stimuli can evoke responses from the same area has led some writers to differentiate it from the other auditory areas and to give it the special designation AIII (5) (not shown in Fig. 2).

Adrian (6) was among the first to record cortical potentials evoked by somatic stimuli. Under moderately deep anesthesia, induced by several chemical agents, he used touch, pressure, and movement to evoke electrical potentials. The locus of responsive points found by Adrian, as well as by others, is shown in Fig. 2 as areas

SI and SII. Analogously to what happens in the auditory system, the "primary somatic cortex" is not uniform in its responses. Very briefly, mechanical stimulation of the posterior parts of the animal's body gives largest responses in the rostral part of SI, while stimulation of the anterior parts of the body gives largest responses in the ventral portions of SI. The fact that SII contains a different somatotopic organization and that it is sometimes separated from SI by a band of unresponsive cortex has justified its separate designation.

The cortex of deeply anesthetized animals has also been examined for responses to light flashes. Marshall, Talbot, and Ades (7) outlined the "visual areas" shown in Fig. 2 as responsive to brief light flashes. In addition, they note a localized responsive area bordering on the suprasylvian sulcus. Doty (8), also recording from cats anesthetized with nembutal, recorded responses over essentially the same areas found by Marshall. Also, Doty subdivides the total responsive area on the basis of differences in waveform and latency of the evoked responses.

b. Characteristics of Click Responses Obtained from the Cat's Auditory Projection Cortex

Responses to click stimuli may be recorded from the cat's auditory projection areas by means of a wire electrode placed on the surface of the cortex. An evoked response, recorded by just such an electrode, is shown in Fig. 3. This response, which was evoked by an acoustic click (10), is typical of click responses that may be recorded from the auditory projection areas of the cat. The most characteristic deflection of the response is the large surface-positive deflection labeled "C". [The responses are necessarily recorded between two electrodes. For "monopolar" recordings, one

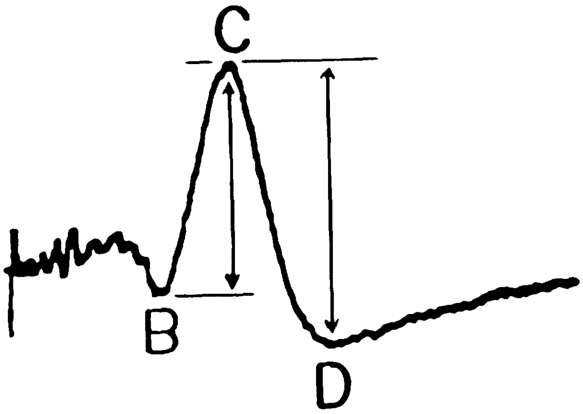


Fig. 3. Tracing of a typical response obtained from the auditory projection areas of the cat. The beginning of the trace marks the time of the stimulus: B, C and D are the peaks usually observed. The relative sizes of the three peaks vary from location to location on the cortex. (After J. Macy, Jr. (9); from data by M. Rosenzweig.)

electrode is located on the surface of the cortex and the other in a distant location. Hence, the electrical polarity of the various deflections in the cortical responses is with respect to this distant electrode, termed simply the reference electrode. "Bipolar" records, on the other hand, are recorded from two closely spaced electrodes.] The amplitude of deflection "C" may vary over wide ranges, the variation depending on the experimental conditions, but its latency, measured to the peak, is usually found to be between 8 msec and 15 msec. The negative deflection which follows, labeled "D", is much more variable in nature than the initial positive deflection and may have very different sorts of waveforms; under some experimental conditions it may not even be present. The diphasic waveform composed of components C and D together is what is usually referred to as the "diphasic" click response. The initial negative deflection, labeled "B" in Fig. 3, is quite small and is not always detectable.

The characteristics of these responses to auditory clicks have been well described by such workers as Bremer (11). He has utilized many different experimental tools to explore the nature of the electrically active sites that produce these responses. He has applied minute quantities of strychnine to the surface of the cortex, for example, and observed a remarkable increase in the amplitudes of both the initial surface-positive deflection and the following negative deflection. Since the direct effect of the strychnine was, presumably, confined to a small volume of the cortical mantle, it is suggested that the sites producing these augmented responses are located in the same volume and hence in the cortical mantle. Other techniques, such as thermocoagulation of cortical volumes and resection of the cortical mantle, were also carried out by Bremer, and led him to the conclusion that "the two components of the diphasic surface-responses of the unanesthetized acoustic area are both the expression of the reaction of cortical elements to the different impulses streaming from the thalamus" (11).

The waveforms of the cortical responses evoked by repetitions of identical click stimuli are not identical: Although the corresponding components of the various responses may have approximately the same latencies, the amplitudes are often quite different (12). To describe these responses, various statistics concerning the size of the cortical responses evoked under differing experimental conditions have been compiled. Harris (13), in one study, measured the amplitude and latency of the surface-positive deflections of responses evoked by slowly repeated clicks of various intensities. Two curves constructed from her data are shown in Fig. 4. Both the amplitude and latency of the surface-positive deflection of the click responses are plotted as functions of click intensity. From Fig. 4, we see that the amplitude of the responses evoked by 70-db clicks is quite small and that larger responses are evoked by more intense clicks. The response amplitude is seen to grow monotonically for the first 40 db above threshold ("threshold" is defined here as the stimulus intensity at which the experimenter can detect visually the presence of the evoked response 50 per cent of the time), but above 40 db the amplitude of the responses does not reflect a further increase in click intensity. Response latency, measured to the peak of the positive deflection, is also shown

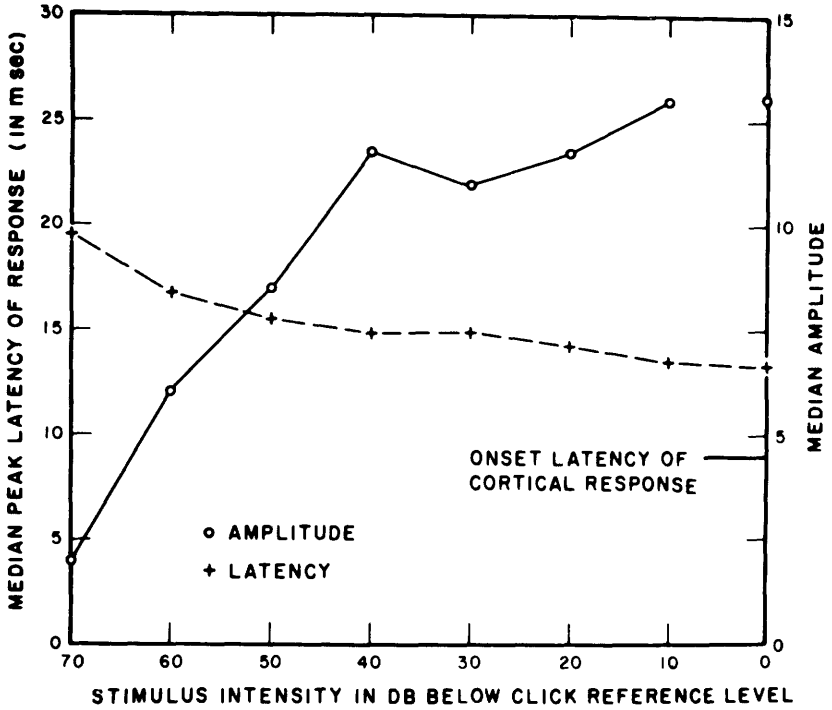


Fig. 4. Amplitude and peak latency of the surface-positive component of click responses. These responses were recorded from the auditory projection cortex of an anesthetized cat. Each point is the median value of 15 consecutive responses. The stimuli were separated by time intervals of several seconds. Monopolar recording. (After W. A. Rosenblith (14); from data by K. S. Harris (13)).

for various click intensities. Essentially constant at the higher intensities, the latency increases appreciably when the stimulus intensity approaches threshold value.

Measurements have also been made on responses evoked by more rapidly repeated stimuli. W. D. Keidel, U. O. Keidel, Kiang, and Frishkopf (15) presented clicks at the rate of 10 per second and recorded responses from the auditory projection area. In cats anesthetized with Dial anesthesia, they found that the responses to the initial clicks of a click train had larger amplitudes than "steady-state" responses evoked by later clicks in the same train. They report that the surface-positive deflection of the steady-state responses had an average amplitude that increased with click intensity. In one of the two cats used, rapid growth of the average amplitude was limited to the first 30 db above threshold intensity.

The size of the evoked responses recorded by gross electrodes from the auditory areas of the cat has been interpreted by Goldstein and Kiang (16) as reflecting the degree of synchrony of the contributing neural units. They added random noise to click stimuli and found that, as had been shown previously, the neural responses evoked by constant-intensity clicks, whether measured at the level of the auditory nerve or on the cortex, were reduced in amplitude as the intensity of the "masking" noise was increased. Now if the responses to clicks recorded by gross electrodes can be thought of as the summated effect of synchronized responses evoked from many neural units, and if the noise can be thought of as evoking the responses of neural units in a random fashion, such experimental results would be expected. For since both clicks and random noise have wideband spectra, and hence presumably excite the same populations of neural units, a click in the presence of masking noise would evoke a synchronized response from fewer units that it would in the absence of the noise. As the noise intensity is increased, more and more neural units would respond to the noise randomly and hence would not be free to contribute to a synchronized response. For very high noise levels, no detectable click response would be expected. The decrease, and eventual disappearance, of the click-response amplitude with increasing noise level, which was experimentally observed by Goldstein and Kiang, supports this interpretation. Certainly, the response to masked clicks cannot be considered as the linear combination of responses to clicks and to noise.

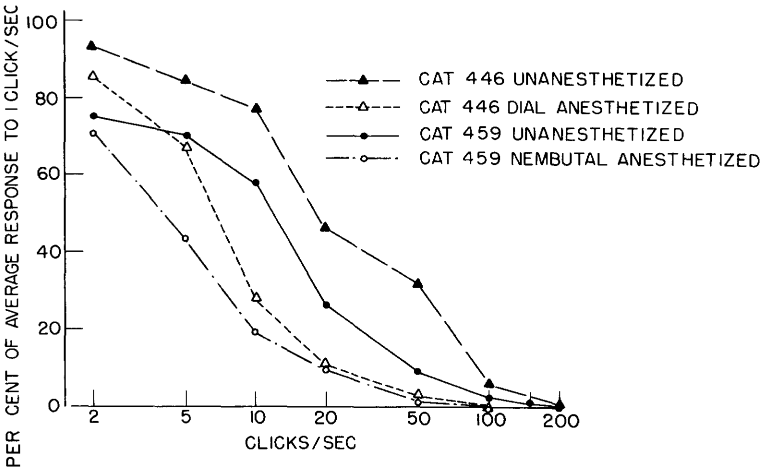


Fig. 5. Relative peak-to-peak amplitudes of average responses evoked by repeated clicks plotted as a function of repetition rate before and after anesthetization by barbiturates. Recording is from concentric bipolar electrodes in the middle ectosylvian gyrus. Stimulus intensity, 35 db above threshold intensities observed at low rates; spinal sections were utilized for immobilization. (After M. H. Goldstein, Jr., N. Y-S. Kiang, and R. M. Brown (17)).

The fact that the steady-state responses found by Keidel and his co-workers were smaller than those evoked by the initial clicks of a train indicates that the time interval between successive clicks is an important stimulus parameter. Goldstein, Kiang, and Brown (17) have investigated this parameter by studying the responses that are evoked by repetitive click stimuli presented at various rates. Figure 5 shows the relative peak-to-peak amplitude of the average responses obtained by these workers. Although the amplitude of the average cortical response decreases with rate, detectable responses are obtained for rates as high as 100 per second in the anesthetized cat, and for rates as high as 200 per second in the unanesthetized cat.

c. Evoked Responses Recorded from Other than Projection Areas of the Cortex

Most of the experiments reported above were performed on cats that had been heavily anesthetized, usually through the use of barbiturates. In addition to immobilizing the animal, the anesthesia served the function of reducing the "spontaneous" activity of the cortex so that the evoked responses could be easily detected. In recent years, it has become apparent that depth of anesthesia not only changes the spontaneous acitivity, but has also a profound effect upon the evoked responses. Not only is the amplitude and waveform of the responses changeable with depth of anesthesia, as indicated in Fig. 5 (see also figures in Goldstein et al. (17)), but the extent of cortex from which responses can be recorded is also affected.

The effect of anesthesia upon the locus of responsive cortex is well illustrated by the experiments of Lombroso and Merlis (18). From a small area of the suprasylvian gyrus, shown in Fig. 2, these experimenters recorded responses having approximately the same amplitude and latency as those recorded from the auditory projection areas. The distinctness of the two areas was indicated by a band of relatively unresponsive cortex that usually separated the two areas. The level and type of anesthesia was found to be of crucial importance. Under "light to moderate" Nembutal anesthesia, the suprasylvian responses were sometimes absent, although frequently seen. Under light Dial anesthesia, however, these responses were much more stable than they were under Nembutal. Increasing the depth of anesthesia, whether Dial or Nembutal was used, tended to abolish the suprasylvian responses. On the other hand, the responses recorded from the auditory projection areas were still observable under heavy anesthesia, although somewhat diminished in amplitude. The distinctiveness of this suprasylvian area, as compared with the projection cortex, is further indicated by the fact that its responsiveness depended greatly upon the integrity of the contralateral cochlea. Unanesthetized-curarized and encéphale isolé preparations also yielded responses from the suprasylvian cortex.

Recording from cats immobilized either by Flaxedil or by surgical sectioning of the brain stem or spinal cord, Desmedt and Mechelse (19) reported still another area that was responsive to acoustic clicks. This area, called AIV, lies ventral to the projection areas and is separated from them by an area of unresponsive cortex. The latency of the responses recorded in AIV was comparable with those recorded from the projection areas. In contrast to the projection cortex, however, area AIV also responded to light flashes, a fact that indicates that the areas probably have a difference in function.

It remained for Buser to demonstrate the true complexity of evoked response activity. Using unanesthetized cats, immobilized by Flaxedil, Buser and Borenstein (20) recorded some sort of evoked potentials from virtually all over the convexity of the cortex, no matter whether somatic shocks, acoustic clicks, or light flashes were given as the stimuli. Buser's "secondary" responses (as he calls the responses from areas other than the projection areas) were found to be more variable in nature than the "primary" responses (those recorded from the projection areas). The secondary responses usually had longer latencies and smaller amplitudes that the primary responses. Moreover, it was found that barbiturate anesthesia depressed these secondary responses, a fact that perhaps accounts for their omission in the reports of early investigators. Chloralose anesthesia, by contrast, was found to augment the secondary responses.

Buser and Borenstein also found that some cortical areas not only showed responses to the diverse stimuli employed, but exhibited clear interactions between the responses evoked by stimuli of different sensory modalities. The distinctive nature of these interactions has led to a very important characterization of the various cortical areas. Not all of the areas that responded to different sensory stimuli showed an interaction between the responses, but only certain restricted areas. Under curarization, or light chloralose anesthesia, three interaction areas were delineated (see Fig. 2). The interaction area between the auditory and visual projection areas showed interaction between responses to click and flash stimuli; the area between the primary visual and somatic areas showed interplay between flash and shock responses; and the third area exhibited interactions between shock and click response. In the interaction areas, the cortical response to a particular stimulus was always greatly inhibited by a preceding stimulus of the complementary modality. In the projection areas, however, the primary responses were little affected by preceding secondary responses, but reduced the amplitude of secondary responses that followed.

In a study in which chloralose anesthesia was used, Albe-Fessard and Rougeul (21) found further interesting results. Using electric shocks to various limbs as stimuli, they also recorded responses over a great deal of the cortical surface. Under deep chloralose, the secondary, or so-called nonspecific, responses were found to be largest in several discrete areas located along the suprasylvian gyrus and in the anterior lateral gyrus. In addition to having latencies that were 15-20 msec longer, the secondary potentials had essentially bilateral representation, with responses from symmetrical points on the two hemispheres being almost identical. This bilateralness was in clear contrast to the predominance of contralateral representation that existed in the primary somatic areas.

In another study of curarized, but unanesthetized, cat, Buser and Borenstein (22) found secondary click responses over a great deal of the suprasylvian gyrus (see Fig. 2). These secondary responses, bilateral in nature, had onset latencies that exceeded 15 msec; furthermore, the secondary responses were found to exhibit much greater variability than the responses recorded from the auditory projection areas. The largest secondary responses were seen under very light chloralose anesthesia and tended to disappear when the cortical activity showed "arousal" patterns resulting either from reticular stimulation or painful stimuli. Secondary responses were not detectable during patterns of electrocortical activity that corresponded presumably to "deep sleep," although the large amplitude of the spontaneous activity in that instance may simply have obscured the responses. It is significant to point out that large secondary responses were also obtained when the electrocortical activity was classified as "awake" activity though not as "aroused." In contrast, the primary responses recorded during all of these changes in the animal's "state," showed much less variability.

Finally, in a very recent study of cats that had been deeply anesthetized with chloralose, Thompson and Sindberg (23) found acoustic-response fields on the somatic cortex, the anterior lateral gyrus, and the middle ectosylvian gyrus. Onset latencies of 15-30 msec characterized these secondary responses. Responses with much longer latencies were also recorded from part of the visual areas.

It is plain, then, from these many experiments, that the responses evoked by auditory stimuli from the cortex of the cat can be quite complex. Not only are responses of some sort recordable from almost all points on the cortical mantle, but various cortical areas exhibit different response characteristics. The functional significance of these different areas is obscure.

1.2 EVOKED RESPONSES RECORDED FROM THE CEREBRAL CORTEX OF MAMMALS OTHER THAN THE CAT

Acoustic responses have been obtained from the brains of many other animals besides the cat. Guinea pigs, dogs, and monkeys have been among the mammals investigated, and although the morphology of their cortices is quite different, similar responses have been obtained from homologous areas in each species. Mark (24) has recorded average responses evoked by click stimuli from the cortex of the anesthetized guinea pig. The largest responses were obtained from a fairly well-localized region of cortex and had essentially the same deflections as those shown in Fig. 3. A surface-positive peak with a latency of approximately 15 msec was followed by a large negative response. The amplitude of the response components varied with click intensity: A rapid increase in component amplitudes was found for the first 20-40 db above threshold intensities. Thus the intensity function of the anesthetized guinea pig is similar to that shown for the anesthetized cat in Fig. 4. The addition of random noise reduced the amplitude of the responses evoked by clicks.

Tunturi (25) has recorded evoked responses from the cortex of the dog. Using various acoustic stimuli, he recorded responses over a cortical area homologous to that of the auditory projection areas in the cat. Surface-positive response deflections that had onset latencies of approximately 10 msec were evoked by abrupt stimuli; a surface-negative deflection followed the positive one.

Let us now turn our attention to the monkey. The brain of the monkey is morphologically more similar to the human brain than are those of the other mammals. For instance, both the monkey brain and the human brain possess well-developed temporal lobes and concomitant Sylvian fissures.

Poliak (26) has shown that the monkey's medial geniculate body projects mainly to the rostral portions of the superior temporal gyrus. Only a few fibers reach the

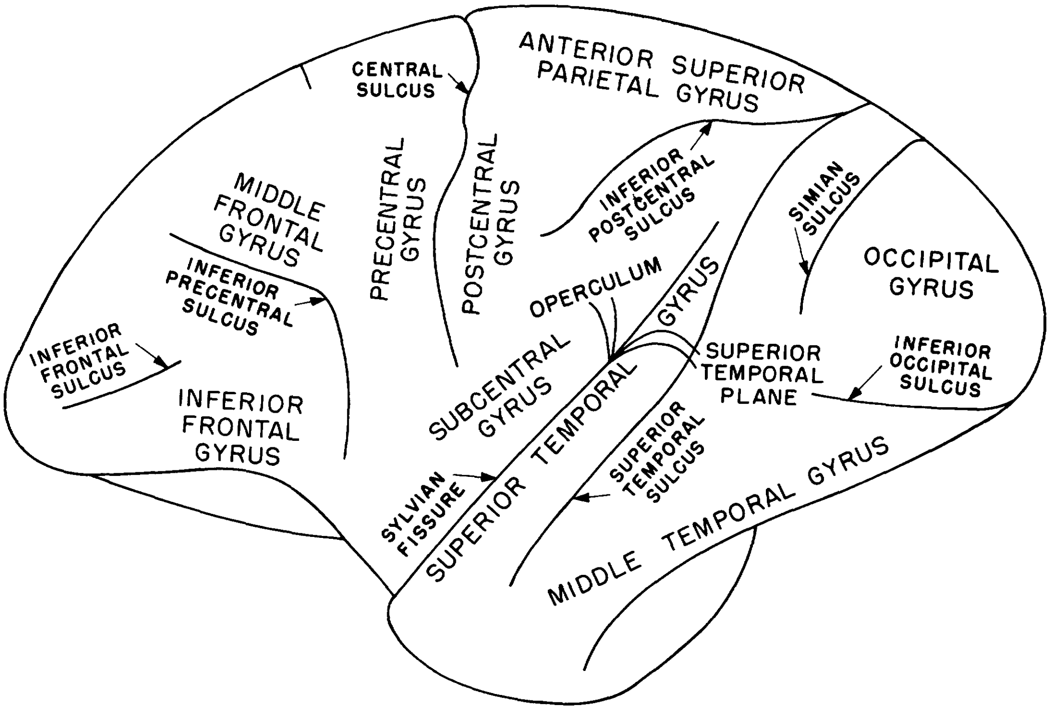


Fig. 6. Schematic diagram of the cerebral cortex of the monkey showing the sulci and gyri.

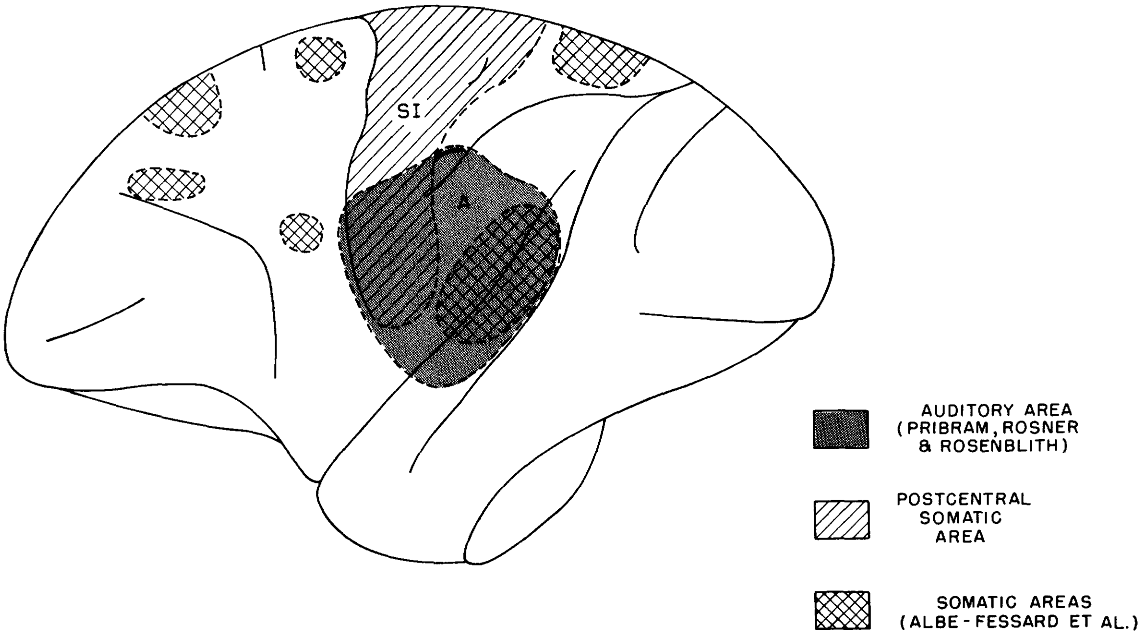


Fig. 7. Schematic diagram of the cerebral cortex of the monkey showing various regions from which evoked responses to sensory stimuli have been observed.

convexity of the temporal lobe, most of them terminating in the superior temporal plane, the portion of the gyrus which lies within the Sylvian fissure (see Fig. 6).

As with the cat, acoustic responses may be recorded from the auditory projection area. Ades and Felder (27), using deep pentobarbital anesthesia, resected the subcentral gyrus and frontal operculum and found well-localized "diphasic" responses on the superior temporal gyrus. While the responsive locus described by these workers is limited to the superior temporal plane, it covers much less area than does Poliak's projection area.

As was found in the cat, the level and type of anesthesia used is a significant factor in the electrophysiological events that are recorded from a monkey's brain. Pribram, Rosner and Rosenblith (28), in addition to recording click responses from all surfaces bounding the Sylvian fissure, found responses on a widespread area of the cortical convexity, as shown in Fig. 7. Dial, administered in large doses, was the anesthetic used, and obviously it had quite a different effect upon the monkey's cortex than did Nembutal. The peak latencies of the first positive deflection of the responses recorded by Pribram and his co-workers varied from 12 msec to 27 msec, the shortest ones being recorded on or about the projection region. Kennedy (29) has also recorded similar responses under Dial anesthesia, but feels that the mechanism generating the widespread response is different from that generating responses in the projection areas. Her conclusion is based on the fact that the application of strychnine patches, the neural isolation of the piece of cortex recorded from, and even the removal of large portions of the projection area failed to greatly influence the widespread responses.

Responses evoked by somatic stimuli have also been recorded from the monkey's cortex. One of the first of such studies was reported by Woolsey, Marshall, and Bard (30), who used deep pentobarbital anesthesia. Figure 7 shows the locus of cortex, labeled SI, from which they recorded responses to slight manipulations of the hairs and skin of the whole body. A second responsive area, analogous to that found in the cat, was also found under barbiturate anesthesia (31). This area lies on the frontal operculum of the Sylvian fissure.

As might be expected, when chloralose anesthesia is employed, responses to somatic stimuli may be recorded from a more extensive area of cortex. Albe-Fessard, Roche-Miranda, and Oswaldo-Cruz (32), using electric shock stimuli under chloralose, recorded responses from several places outside of the postcentral region, as shown in Fig. 7.

In addition to previously observed responses on the precentral gyrus, bilateral responses of short latency were recorded from an area, identified with area SII, lying partly on the superior temporal gyrus. "Nonspecific" responses were recorded from both the superior frontal gyrus and the superior parietal gyrus and showed a bilateral representation that differed plainly from the predominantly contralateral representation observed in the postcentral somatic area. In addition, the nonspecific responses exhibited longer latencies than the responses recorded from the postcentral region.

It seems, therefore, safe to conclude that the limited response areas that have previously been reported for the monkey's cortex are due, in part, to the use of anesthetics like Nembutal which suppress widespread responses. The use of chloralose, at least for the somatic system, allowed the recording of bilateral responses from areas of the cortex outside of the postcentral region. It is well to remember that the nonspecific, or secondary responses, had longer latencies than the primary responses.

Responses to sensory stimuli have thus been recorded from the cortices of many different mammals. The same diphasic response has been evoked in the auditory projection area of each species reported here: The first large deflection is surface-positive with a peak latency of approximately 15 msec, and it is followed by a negative deflection. "Secondary" responses have also been recorded from widespread areas of the monkey's and cat's cortices.

1.3 EVOKED RESPONSES RECORDED FROM MAN

Experiments recording evoked responses directly from the human brain are limited in number and scope. Yet, in conjunction with surgical procedures, electrodes have been introduced into the brains of waking subjects (33). Chatrian, Petersen, and Lazarte (34), for example, have recorded with electrodes located within the brain. Using clicks, they recorded responses from monopolar electrodes located deep within the Sylvian fissure in five patients. A deflection with a peak latency of between 8 msec and 24 msec was the first component reported. It is noteworthy that this peak latency in human subjects does not differ appreciably from that reported for the initial positive deflection in experimental animals. Other components were found to follow the earliest deflections with more or less consistency.

Most investigators, however, find it impossible to record intracranially from human subjects. Fortunately, the intactness of a subject's skull and scalp does not prevent electrophysiological investigations of the activity of his brain. For when electrodes are placed on the scalp, potentials produced by brain tissue are observed between any pair of them.

This phenomenon is well known and various characteristics of the recorded potentials provide valuable clinical clues to the localization and nature of brain abnormalities. Normally, the potentials are small, approximately 50-100 μv (peak-to-peak), and it is, in general, difficult to determine the specific parts of the brain which generate them; but useful information has been gained from study of them.

As early as 1939, H. Davis, P. A. Davis, Loomis, Harvey, and Hobart (35) reported that auditory stimuli produced electric responses that could be recorded from the scalp of certain subjects. The usual response consisted of a deflection, negative with respect to the ear-lobes or mastoid, beginning 50-100 msec after the onset or cessation of a tone. This deflection was followed by a slower positive wave. As similar responses could also be evoked by light flashes and electric shocks, these responses were not considered to reflect the activity of the auditory cortex directly. It was found that as the subject went to sleep, these responses, which were called "K-complexes," grew larger;

amplitudes as large as 100 μv were sometimes obtained.

However, the presence of the continual activity that is recorded by scalp electrodes, whether or not the subject is being stimulated deliberately, not only makes it difficult to characterize responses to specific stimuli, but may even prevent their detection. For, if electrical activity unrelated to the sensory stimuli presented is much greater than the responses evoked, the responses will not even be seen in the usual displays.

Various methods have been employed in an attempt to resolve small specific responses out of the more general EEG activity. Dawson (36) and others have attempted resolution of specific responses by photographic means. With this technique, extracranial potentials following each stimulus are recorded photographically. These individual photographs are then superimposed and the whole set of them re-photographed. Waveforms that consistently occur after each stimulus tend to "reinforce" themselves on the photographic plate, and form heavy lines. Time-locked responses then become observable even in the midst of comparatively large amounts of unrelated activity. Time-locked responses have also been obtained by electronic averaging computers such as the Average Response Computer built by Barlow (37). Digital averaging machines, one example of which is the ARC-1 (38), developed at Lincoln Laboratory, M. I. T., and in use, at present, in the Communications Biophysics Group, of the Research Laboratory of Electronics, M. I. T., are also being used to detect specific responses in the recorded EEG activity.

Using his photographic superposition technique, Dawson (36) succeeded in detecting extracranial responses to electric stimulation of the ulnar nerve. His responses were reported to be recordable from small regions of the scalp lying approximately over the central sulcus. Stimulation of the nerve, first at the wrist, and then at the elbow, resulted in a decrease in onset latency of 6 msec, a time interval that corresponds to the conduction time required for nerve pulses to travel from the wrist to the elbow. When the thigh was stimulated, the locus of responses shifted toward the midline, in accord with the accepted map of the somato-sensory cortex in man (39). For stimulation of the elbow, the response, 20 μv with respect to a distant electrode, was initially positive with an average onset latency of 20 msec.

Bates (40), using the same photographic averaging technique, recorded extracranial responses beginning 20-35 msec after rapid hand movements. In another study, using the same technique, Larsson (41) systematically studied extracranially recorded responses to electric stimulation of the ulnar nerve. He found a well-localized response, onset latency approximately 20 msec, as well as a later, more widespread response with an onset latency of approximately 100 msec. The early response, identified with the activity of the sensory-motor cortex, was unaltered at stimulus rates up to 20 per second, whereas the later response disappeared for rates greater than 5 per second.

Responses of the visual system in man have also been recorded with the use of electrodes placed on the scalp. Cobb and Morton (42), using photographic averaging techniques, obtained responses to intense flashes from the occipital region of the scalp.

These responses had onset latencies of approximately 25 msec. Brazier (43), using an average response computer, obtained average responses to light flashes that were characterized by onset latencies of approximately 30 msec. Cobb and Dawson (44), also using an electronic averaging device, obtained average responses to brief flashes of high-intensity light from the occipital region. Here again, onset latencies of approximately 25 msec were reported. Abe (45), extending Dawson's photographic averaging technique to the auditory system, reported click responses of relatively long latency from all over the human scalp.

One of the most interesting studies of average responses was done by Calvet and his co-workers (46). These investigators modulated the intensity of an oscilloscope trace by applying the potentials recorded from the scalp to the control grid of the cathode-ray tube. They used a standard sweep, triggered by the stimuli, and photographed each trace. The individual traces were then superimposed photographically and a photocell translated the intensities on the composite photograph into a line graph of amplitude vs time. Average responses to visual, somatic, and auditory stimuli were found in this way. The auditory responses that are of most interest here were recorded from widespread locations on the scalp. The onset latencies were from 15 msec to 25 msec, and the amplitudes were found to grow with intensity. For rates of more than 2-3 per second, the amplitude of these responses was reported to decrease.

Finally, average responses have been recorded from human scalp in our laboratory with the use of the ARC-1 computer (38). Using click stimuli, Geisler, Frischkopf, and Rosenblith (47), have found widespread responses having a peak latency of approximately 30 msec. These responses were first detected near the subject's psychophysical threshold, and were found to vary in amplitude with the intensity and rate of the clicks.

1.4 THE PURPOSE OF THIS STUDY

The need for a systematic study of responses recorded from the human brain is clear. Since the use of intracranial electrodes is plainly out of the question, we have used the averaging technique, which provides us with the needed experimental tool whereby average evoked responses can be extracted from the potentials recorded with scalp electrodes.

It is the purpose of this study to continue the investigation (47), already begun, into the characteristics of average responses evoked by various patterns of click stimuli. We have systematically manipulated such experimental parameters as electrode location, and the rate and intensity of the click stimuli. The systematic changes in the average responses that were obtained under these differing conditions, although of interest in themselves, gain in significance when they are compared with responses obtained from experimental animals. The primary aim of the present study, therefore, is the characterization of the average responses obtained from the human scalp and their identification in terms of the responses that have been recorded from lower mammals.

Psychophysical data obtained from human subjects are plentiful but, because of obvious difficulties, comparatively little is known about electrophysiological correlates of human sensory performance. However, the method of averaging provides a mean of obtaining evoked responses from normal, alert humans. To discover correlations that may exist between evoked-response data recorded from the scalp of a human subject and psychophysical data obtained from the same observer, is, therefore, a further aim of this study.

II. ELECTRIC POTENTIALS RECORDED FROM THE SCALP

The usefulness of electroencephalography stems from the fact that the electrical activity recorded from the scalp of human subjects reflects, in some sense, the activity of the brain beneath. Electrically active sites in the brain set up potential fields that, because of the finite conductivity of the brain and its physiological surroundings, extend even to the surface of the scalp. Yet electrodes on the surface of the scalp are separated from the active sites by the many layers of dura, skull, muscle and scalp. Unfortunately the effects of these layers, which have different conductivities, are little understood and it becomes difficult to specify the quantitative relationships between the potential fields recorded at the scalp and the fields that actually exist in the brain.

Some insight into the nature of the fields generated within the brain has been gained by the use of implanted electrodes. Many hospitals, in conjunction with treatment of certain patients, routinely record potentials from the depths of the human brain. Yet the electrical activity which is recorded is so complex in nature that it is difficult to interpret. First of all, it is difficult to specify the correlations that exist between potentials that are recorded from different electrodes within the brain. Second, even if such correlations could be found, the locus of active sites producing the correlated activity would be unknown.

Unlike most patients, however, those with certain types of epilepsy are well suited for an investigation of electrical fields set up in the head. The unique quality of the potentials recorded from these subjects is the presence of sporadic events that have huge, easily identifiable wave shapes. These events are of such magnitude that the fields set up by them may often be detected by quite distant electrodes. The measurement of the amplitude of such events at various places inside and on the head should provide an indication of the potential fields set up in the head by the active epileptic sites.

Abraham and Ajmone-Marsan (43) have conducted just such an investigation. Using subjects who had previously been diagnosed as "temporal lobe" epileptics, these experimenters recorded simultaneously from electrodes located on the scalp, on the cortex (extradural), and in the cortical depths.

Epileptic discharges were recorded from these various electrodes and compared with one another. Since "primary" epileptic discharges may cause "secondary" discharges in other parts of the brain, it is necessary to exercise care in determining the potentials that are due simply to the fields of the primary discharges. Hence, taking care to include only those epileptic abnormalities that were synchronously recorded from the various electrodes and were similar to one another in wave shape, these experimenters found that specific waveforms recorded from the scalp did indeed reflect cortical epileptic potentials when such activity was spread over an appreciable area of cortex. A ratio of 5 to 1 was often observed between the amplitudes recorded with cortical and scalp electrodes, but larger amplitude ratios were frequently seen. In fact, when the epileptic discharge was recorded from only one of two closely spaced cortical electrodes, a fact that indicates a discharge sharply localized on the cortex, the potentials recorded from the scalp electrodes did not even show a corresponding event. These authors concluded that the extent of the area of cortex from which epileptic potentials may be recorded is an important determinant of the potential fields recorded at the scalp. They also recorded the epileptic events with depth electrodes and observed amplitudes comparable with those of the corresponding events recorded from the scalp.

In other attempts to characterize the potential fields in the head, mathematical models have been developed. Brazier (49) has used the model of a voltage dipole immersed in a sphere of homogeneous conducting material and has calculated the potential fields that exist on the surface of the sphere because of the presence of the dipole. Although clinically useful interpretations of scalp potentials have been gained by such models, their applicability is limited because the different layers overlying the brain have not been taken into account.

These studies have provided some insight into the nature of the electric fields existing within the heads of human subjects, but the information provided by scalp potentials about the electric fields existing within the heads of human subjects is still rudimentary.

This section deals with two different investigations that were undertaken to describe further the nature of the potential fields existing in the head. A mathematical model, which takes into account the different layers of conducting media surrounding the brain, will be presented first. Experimental data in the form of average evoked responses obtained from various locations in the heads of monkeys will then be reported and general conclusions drawn.

2.1 MATHEMATICAL MODEL OF ELECTRIC POTENTIALS EXISTING IN THE HEAD

a. Formulation of the Model

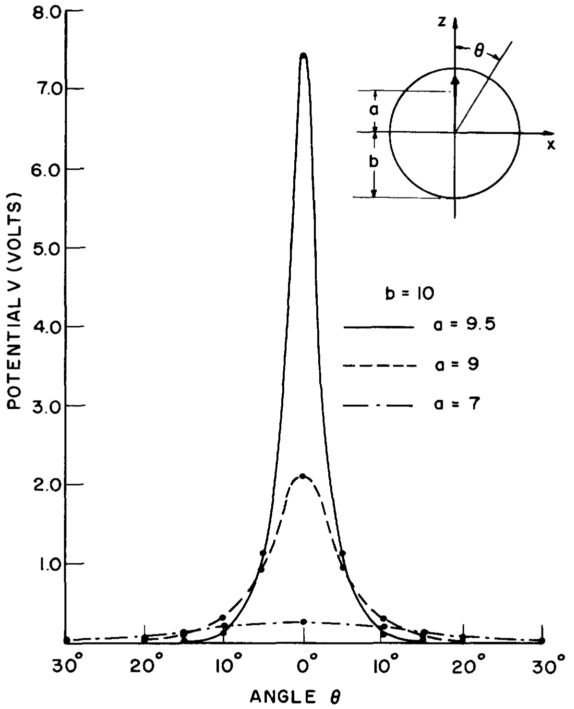
In a mathematical description of the potential fields set up in the head the nature of the electrically active sites within the brain must first be known. Therefore, as a first step let us consider the electric generators located within the brain. And because the cortex is closest to the scalp, let us direct our attention to the generators located in the cortical mantle of the brain and neglect, for the moment, the midbrain and other underlying structures.

The nature of the electrical activity evoked within the cortical mantle is described in the work of Bishop and Clare (50). Working on cats, these experimenters inserted very fine electrodes into and through the mantle of the striate cortex and recorded potentials evoked by stimulation of the optic nerve. The response of the cortex to electric pulse stimulation of the optic nerve were measured between two electrodes, one on the surface of the cortex, and the other directly underneath it, just below the cortical mantle. This cortical response consisted typically of from three to five successive surface-positive spikes and an underlying slower wave of approximately 5-msec duration, also surface positive. A surface-negative wave and other components followed to make up the total response. Of special interest are the potentials obtained by these investigators from tiny bipolar electrodes, which had between 0.1 mm and 0.2 mm vertical separation between the electrodes. As these electrodes were lowered vertically through the cortex, different components of the evoked response were seen to vary in amplitude independently. Near the cortical surface, the bipolar electrode did not record the first spikes, but large-amplitude fifth spikes were seen. Near the bottom of the cortical mantle, on the other hand, the first spikes of the responses were large, the fifth spikes small. Such potential distributions could not be the result of electrical fields induced by distant sites, and hence the cortex must contain the active sites. Other measurements reported in this same work confirm the observation that different components of the evoked responses to optic-nerve stimulation are generated at different, but overlapping, depths within the cortex. This conclusion may also be extended to the auditory projection cortex of cats; on the basis of his work, Bremer (11) has concluded that the "diphasic" cortical response to clicks is produced in the cortical mantle.

A mathematical representation for these active sites within the cortex is the model of a volume distribution of dipoles. These dipoles would all be oriented perpendicularly to the cortical surface, and different volumes of dipoles would produce different components of the total response. All of the dipoles producing a single component would be fixed in spatial distribution and orientation but would be synchronously varying in amplitude. The potentials produced inside the cortex by such distributions of dipoles could be made to match closely the experimentally observed potentials.

We are particularly interested in the fields produced at the surface of the scalp, however, and are therefore more interested in the potentials existing outside of the cortex than within it. Since dipole distributions within the cortical mantle are adequate models for the active sites as measured inside the cortex, they are certainly adequate models for these cortical generators as measured by the fields produced in the conducting media surrounding the cortex. Moreover, the cortex is physically so thin that for the calculation of potential fields as far distant from the cortical mantle as the scalp, two-dimensional dipole sheets would probably be adequate models of the active cortical sites. Unhappily, the mathematical complexity involved in the use of even geometrically simple dipole sheets is great. We, therefore, shall adopt the model of a single equivalent dipole for the active sites in the cortex. Such a model is certainly not realistic but does approximate the activity of a small area of the cortical mantle, particularly if that cortical area is more or less planar in nature.

The active sites in subcortical structures are not so easily localized as they are in the cortical mantle, and so are more difficult to represent by equivalent dipole volumes. On the other hand, these subcortical sites are located farther from the surface of the scalp than is the cortex, so that an equivalent dipole model for them may be quite adequate, at least as measured by the fields produced at the scalp.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7.0
6.0
5.0
4.0
3.0
2.0
1.0
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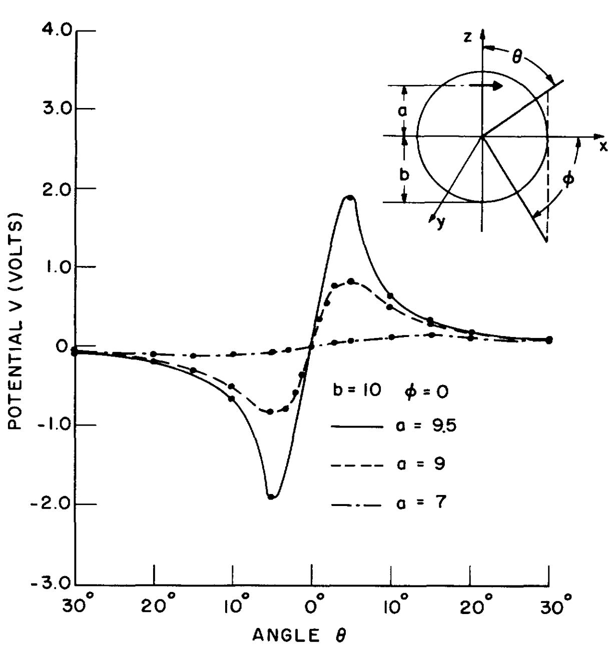
30°
20°
10°
0°
10°
20°
30°
ANGLE θ
z
θ
a
b
x
b = 10
a = 9.5
a = 9
a = 7

(a)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-3.0
POTENTIAL V (VOLTS)
30°
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0°
10°
20°
30°
ANGLE θ
z
θ
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b
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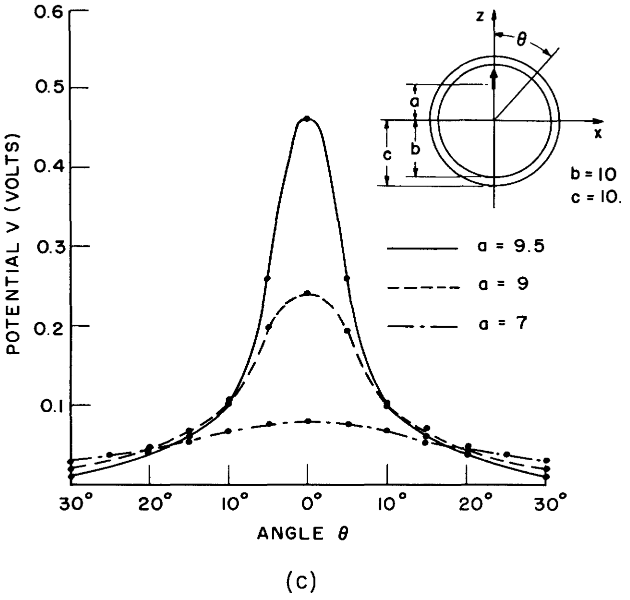
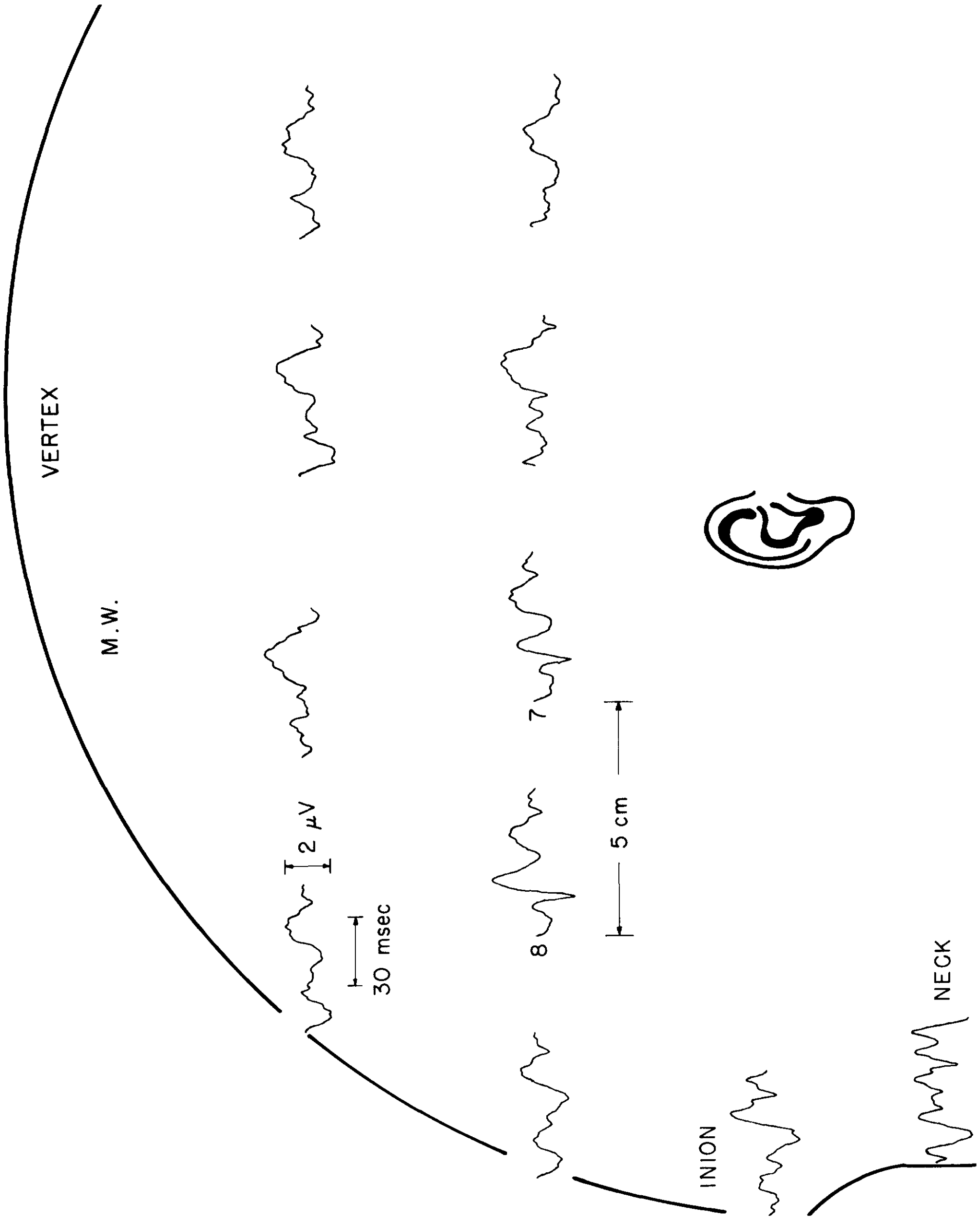
ϕ
b = 10 ϕ = 0
a = 9.5
a = 9
a = 7

(b)


0.6
0.5
0.4
0.3
0.2
0.1
POTENTIAL V (VOLTS)
30°
20°
10°
0°
10°
20°
30°
ANGLE θ
z
θ
a
b
c
x
b = 10
c = 10.
a = 9.5
a = 9
a = 7

(c)

Fig. 21g. Average responses to contralateral clicks recorded from various scalp electrodes (Subject, M. W., H-596). Stimulus conditions: clicks, left ear, -45 db, 15/sec. Response conditions: reference electrode, nose; number of responses, 2000.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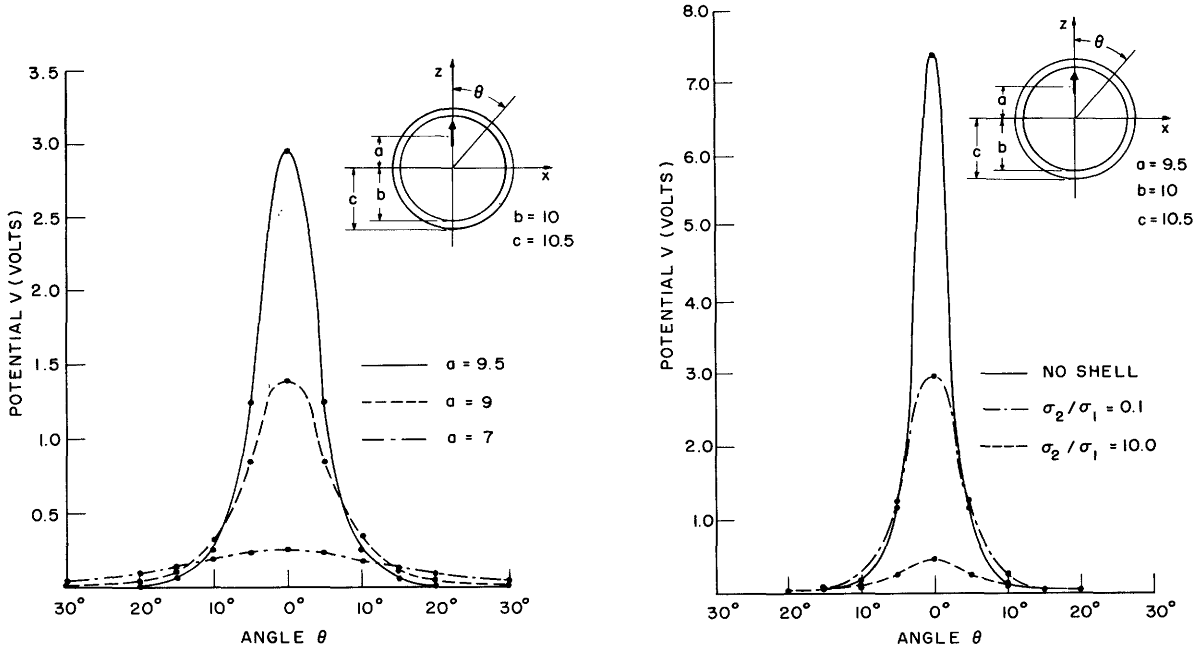
M.W.
2 μV
30 msec
8
7
5 cm
INION
NECK



(d)

(e)

Fig. 8. (a) Potential fields that exist on the surface of a homogeneous conducting sphere caused by a radially oriented dipole located at different points along the Z-axis. Each point on the curves was computed from Eq. 1 with enough terms of the Legendre expansion used to achieve at least two-place accuracy. (b) Potential fields that exist on the surface of a homogeneous conducting sphere caused by a tangentially oriented dipole located at different points along the Z-axis. Each point on the curves was computed from Eq. 2 to at least two-place accuracy. (c) Potential fields that exist on the outer surface of a sphere-shell configuration caused by a radially oriented dipole located at different points along the Z-axis. The conductivity, σ_2, of the homogeneous conducting shell is 10 times the conductivity, σ_1, of the homogeneous sphere. Each point on the curves was computed from Eq. 3 to at least two-place accuracy. (d) Same potential fields as in (c). The conductivity, σ_2, of the homogeneous conducting shell is 1/10 the conductivity, σ_1, of the homogeneous sphere. Each point on the curves was computed as in (c). (e) Summary of potential fields that exist on the outer surface of various sphere-shell configurations caused by a fixed, radially oriented dipole. With no shell, the field existing at the surface of the sphere is shown. With shell, the field existing at the shell's outer surface is shown. The homogeneous shell has a conductivity, σ_2, and the homogeneous sphere has a conductivity, σ_1.

For our purposes, then, we shall adopt the single equivalent dipole representation for all of the generators of evoked potentials measured at the scalp. For the rest of the mathematical formulation, we shall represent the brain by a sphere of uniform conductivity. As we have pointed out, the layers surrounding the brain are far from homogeneous, with such diverse substances as skull and cerebrospinal fluid present. To take into account the effect of these various layers of differing conductivity that overlie the brain, we shall surround our conducting sphere with a shell of variable conductivity.

b. Calculation of Potential Fields

(Formulas and numerical calculations used in this section were supplied by Dr. George L. Gerstein.)

Let us first consider a unit dipole immersed in an isolated sphere of radius "b". If the dipole is oriented along the Z-axis at a distance "a" from the origin (see insert of Fig. 8a) the potential field at the surface of the sphere is found to be

$$V_1(r=b) = \frac{1}{ab} \sum_{n=0}^{\infty} (2n+1)\left(\frac{a}{b}\right)^n P_n(\cos\theta) \tag{1}$$

where the $P_n(\cos\theta)$ are ordinary Legendre polynomials. (See the Appendix for the derivation of this formula.) Numerical calculations of this function V_1 for various values of "a" have been made and are plotted in Fig. 8a.

As noted by others who have used this model (49), the potentials induced on the surface for different values of "a" differ both in amplitude and in spatial distribution. The largest and most sharply localized potentials are observed when the dipole is nearest the surface.

If the dipole is oriented 90° clockwise in the XZ-plane, as shown in the insert of Fig. 8b, the potential induced on the surface is given by

$$V_2(r=b) = \frac{1}{ab} \sum_{n=1}^{\infty} \frac{2n+1}{n} \left(\frac{a}{b}\right)^n P_n^1(\cos\theta)\cos\phi \tag{2}$$

where the P_n^1 are associated Legendre polynomials. Calculations of this potential distribution were made for various values of "a" and are shown in Fig. 8b. Note that although the potential distribution is considerably different from that produced by the Z-oriented dipole, here again the dipole closest to the surface induces the largest, most sharply localized potential distribution on the surface.

As we have pointed out, the brain is normally surrounded by layers of different material. The cerebrospinal fluid bathing the cortex is a relatively good conductor, while the skull is a relatively poor conductor. To take such layers into consideration, let us surround our conducting sphere with a shell of conducting material having a different conductivity. A unit dipole located within the sphere and oriented along the Z-axis will induce a potential distribution V_3 on the outside of the shell:

$$V_3(r=c) = \sum_{n=0}^{\infty} \frac{a^{n-1} c^n (2n+1)^2 P_n(\cos\theta)}{(n+1) b^{n+1}(1-\sigma_2/\sigma_1) + nc^{2n+1}(1+\sigma_2/\sigma_1) + \sigma_2/\sigma_1 c^{2n+1}} \tag{3}$$

where σ_1 and σ_2 are the conductivities of the sphere and of the shell, respectively.

Figure 8c shows the potential distribution V_3 evaluated for various values of "a" under the condition that the conducting shell have a conductivity that is 10 times that of the conductivity of the sphere. This particular model approximates the presence of a layer of cerebrospinal fluid overlying the brain, for cerebrospinal fluid has roughly 5 to 10 times the conductivity of cortical matter (51). The skull, on the other hand, has lower conductivity than cortical matter, and hence the model in this case would include a shell of less highly conductive material. Figure 8d shows the potential distribution V_3 evaluated for various values of "a" when $\sigma_2/\sigma_1 = 0.1$.

In each case, notice that the potential field on the outside of the shell is lower in amplitude than that found on the surface of the isolated sphere. But the high-conductivity shell causes appreciably more attenuation of the dipole field than the shell of lower conductivity. To further emphasize these quantitative relationships, the potential fields produced by a dipole 9.5 units from the origin, for all three cases considered, are plotted in Fig. 8e. When the shell of lower conductivity is introduced, the maximum amplitude on the outer surface is approximately 40 per cent of the maximum amplitude recorded with no shell. In contrast, the maximum amplitude recorded from the surface of the higher conductivity shell is only approximately 6 per cent of the maximum recorded with no shell. Figure 8e also shows that the higher conductivity shell causes more angular "spread" of the potential fields than does the other shell.

The effects of rotating the dipole to a tangentially directed orientation have also been calculated. For this orientation of the dipole, the potential fields at the surface of either type of shell are lower in amplitude than those existing on the surface of the isolated sphere. But lower amplitudes and wider angular "spread" are seen on the surface of the more highly conducting shell. Since potential fields caused by dipoles in any orientation may be calculated from a suitable superposition of tangentially and radially oriented dipole fields, it is clear that surrounding a sphere with a shell of any nature generally reduces the dipole fields recordable from the outer surface. If the shell is of a material that is more highly conductive than the inner sphere, greater attenuation and "spread" of the fields occur than if the shell were of lower conductivity than the inner sphere.

2.2 EXPERIMENTAL INVESTIGATION OF ELECTRIC POTENTIALS EXISTING IN THE HEAD

In order to assess the actual relation of potentials recorded from the scalp to those existing on the cortex, a series of experiments was carried out on cynomolgous monkeys. Monkeys were chosen as the experimental animals because of certain similarities between their brains and skulls and those of humans. For instance, the brains of both monkey and man have well-defined temporal lobes, and the auditory projection areas of both species lie within the Sylvian fissure.

These experiments were devoted to an investigation of the potentials that can be recorded from the exposed surface of a monkey's head as various layers (scalp, skull, etc.) which enclose the brain are removed. Repeated click stimuli were used to evoke deflections in the potentials recorded simultaneously from various electrode pairs. Averaging techniques (see Section III) were used to reduce the effect of the potentials that were not time-locked to the stimuli.

a. Experimental Design

Two experiments involving different monkeys are reported here. At the beginning of the first experiment Monkey A was anesthetized with Dial anesthetic. (It should be noted that although the anesthetic will undoubtedly affect the potentials evoked by the clicks, it should not change the influence of the various layers upon potential fields set up by active sites in the brain.) After the administration of the anesthetic, the monkey was tied to an animal board and his head was shaved. A headholder, utilizing three prongs, was then used to immobilize the monkey's head. One prong was imbedded in each cheekbone, and the third was imbedded in the back of the skull. The two prongs imbedded in the cheekbones were electrically connected to the metal animal board and served as the ground electrode. The third prong was electrically isolated. A short tube leading from a PDR-10 earphone was loosely fitted in the external meatus of the left ear. The acoustic clicks used were generated by the delivery of 0.1-msec square waves to the earphone. The amplifiers that were used are described in Section III. The responses obtained during most of the experiments were so small that they were undetectable by visual examination of the recorded potentials. Averaging of responses was performed, therefore, in order to reduce the effect of potentials that are not time-locked to the stimuli. The results, consequently, are all presented in the form of average responses.

In the first experiment, responses to clicks were first obtained from the surface of Monkey A's scalp with the use of small solder electrodes, attached to the scalp with ordinary electrode paste. After a suitable number of responses had been recorded, the solder electrodes were removed, and needle electrodes, insulated except at the tip, were inserted through the scalp and imbedded in the skull directly beneath the sites of the solder electrodes. Clicks were again delivered to the animal and responses were recorded. The untimely death of Monkey A terminated the first experiment at this point.

The second experiment was performed on Monkey S under essentially the same experimental conditions as those of the first experiment. Potentials were obtained from electrodes on the exposed surface of the monkey's head as various layers were stripped away. (The surgery was performed by Dr. Nelson Y-S. Kiang.) Care was taken at each level to record at points lying directly underneath the electrode locations that had been used on the outer layers. First, responses were recorded from needle electrodes imbedded in the skull, both before and after the scalp and muscle overlying the skull had been removed. Next, small holes were drilled through the skull and platinum spring electrodes were used to record responses from the exposed spots of dura. The next step was the removal of a piece of the skull, the reflection of dura, and the recording of responses directly from the pial surface of the cortex. A coating of warm mineral oil was used to protect the cortex from the effects of drying. The final step in the experiment was the recording of responses from the exposed auditory cortex following subpial resection of the subcentral gyrus and the frontal operculum.

b. Experimental Results

Figure 9 shows the average responses recorded from electrodes on the surface of Monkey A's head. These responses are grouped in pairs, each pair being recorded from electrodes that lay along a line perpendicular to the surface of the head. The top response of each pair was recorded with a scalp electrode, and the lower one was recorded from a needle electrode imbedded in the skull directly beneath the site of the

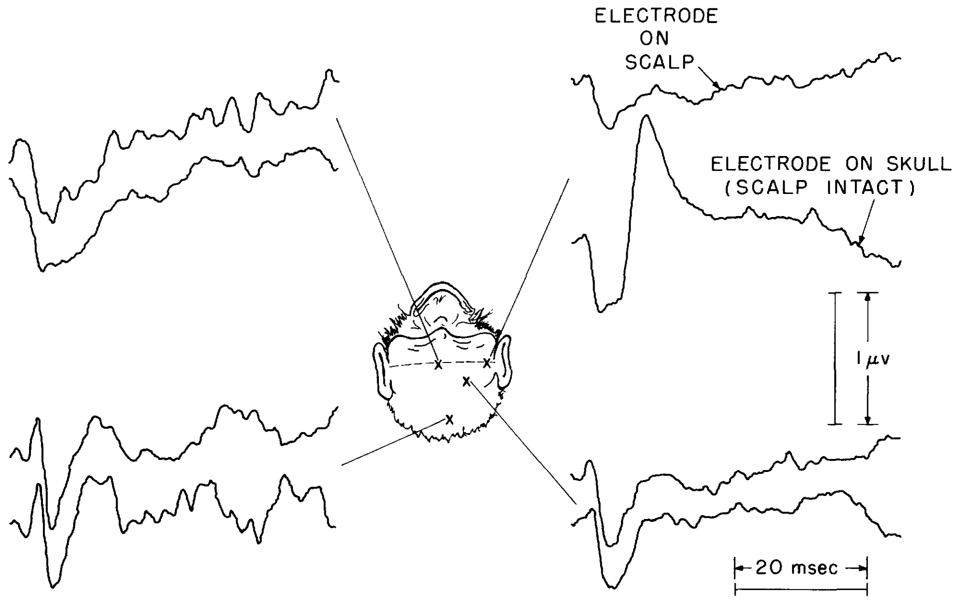


Fig. 9. Average responses to clicks obtained from electrodes on the head of Monkey A(M-5). Each pair of average responses was recorded from electrodes located along a line perpendicular to the surface of the scalp: top response, by a solder-blob electrode on the scalp; bottom response, by a needle electrode on the skull directly beneath. The ground electrode was used as reference. Each trace is the average of 900 responses; at each level, the responses of the 4 electrodes were recorded simultaneously. Clicks presented periodically at the rate of 10/sec; click intensity, approximately 20 db above average response threshold measured with the solder-blob electrodes. (In this and the rest of the figures, upward deflection indicates negativity with respect to the reference electrode.) Dial anesthesia.

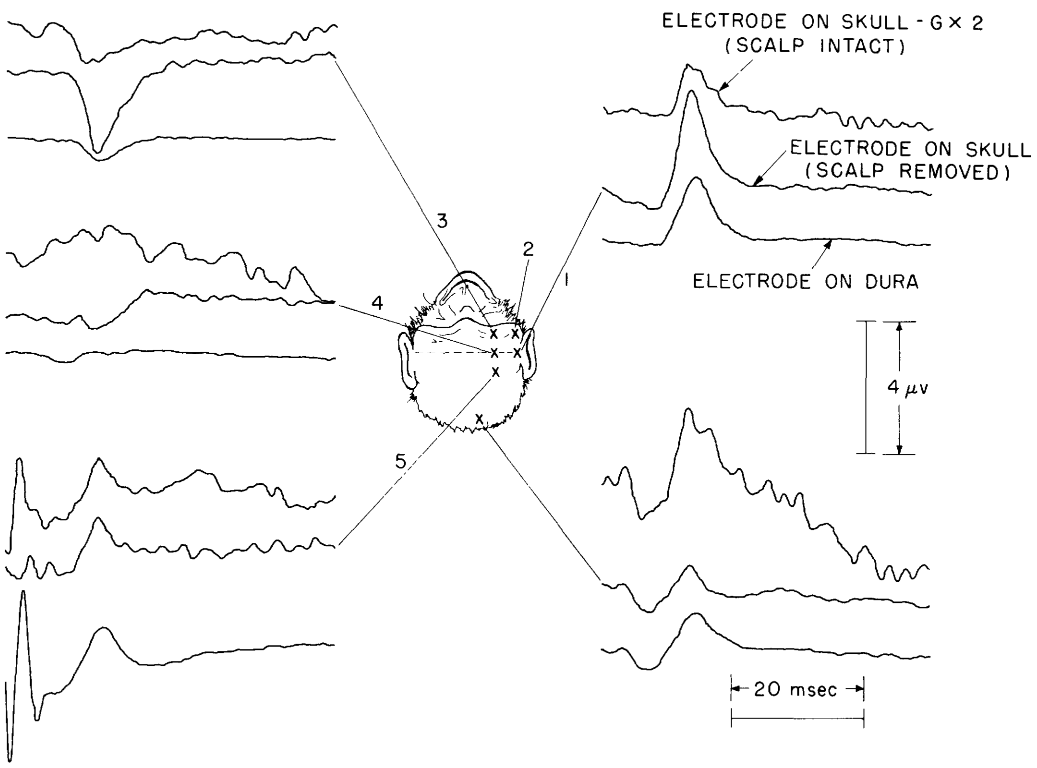


Fig. 10. Average responses to clicks obtained from various electrodes on the head of Monkey S(M-6). Each group of average responses was recorded from electrodes located along a perpendicular to the surface: top response, by a needle electrode on the skull inserted through the scalp; middle response, by the same electrode on the exposed skull; and bottom response by a platinum-wire electrode on dura. At each level electrode 2 was used as reference electrode. Each curve is the average of 900 responses; at each level the responses of the 5 electrodes were recorded simultaneously. The responses obtained with the scalp intact are shown at G × 2. Clicks were presented at a rate of 5/sec; click intensity, approximately 20 db above average response threshold as measured on the skull. Dial anesthesia.

solder electrode. From Fig. 9, we see that the pair of responses recorded from the temporal region are quite different from one another, the average response recorded by the needle electrode being much larger than the one recorded with the surface electrode. The responses recorded from the other regions, on the other hand, show a similar wave shape whether recorded from the surface of the scalp or from underneath it.

Average responses obtained from Monkey S are shown in Figs. 10 and 11. In Fig. 10 the responses that were recorded from points along the same perpendicular are grouped together: The upper trace of each group shows the responses obtained with needle electrodes on the skull, inserted through the scalp; the middle trace shows responses obtained with these same needle electrodes when all of the tissue overlying the skull had been removed; and the lower trace records responses obtained from spots of exposed dura. Notice the similarity between the wave shape of the three responses obtained from each location, although the different layers do have an effect upon the magnitudes of the responses. The removal of muscle and scalp is seen to cause an appreciable increase in the amplitude of the potentials recorded, while removal of the skull does not have such a marked effect.

Figure 11 shows the responses recorded from the dural and pial surfaces of the brain. The top response of each pair shows the responses recorded from the dura through holes in the skull, the bottom trace shows the responses obtained from the same locations after more of the skull and the dura were removed. In contradistinction to the responses recorded in Fig. 10, these responses were obtained with respect to the ground electrode. The removal of the dura causes the rather dramatic change in the response recorded at location 2, but aside from a slight increase in magnitude, the responses obtained from the other locations are relatively unchanged.

Many other points on the pia were recorded from, and a summary map of the responses obtained from the exposed cortex is shown in Fig. 12. Average responses were recorded from all of the cortical points that were explored and show, as first

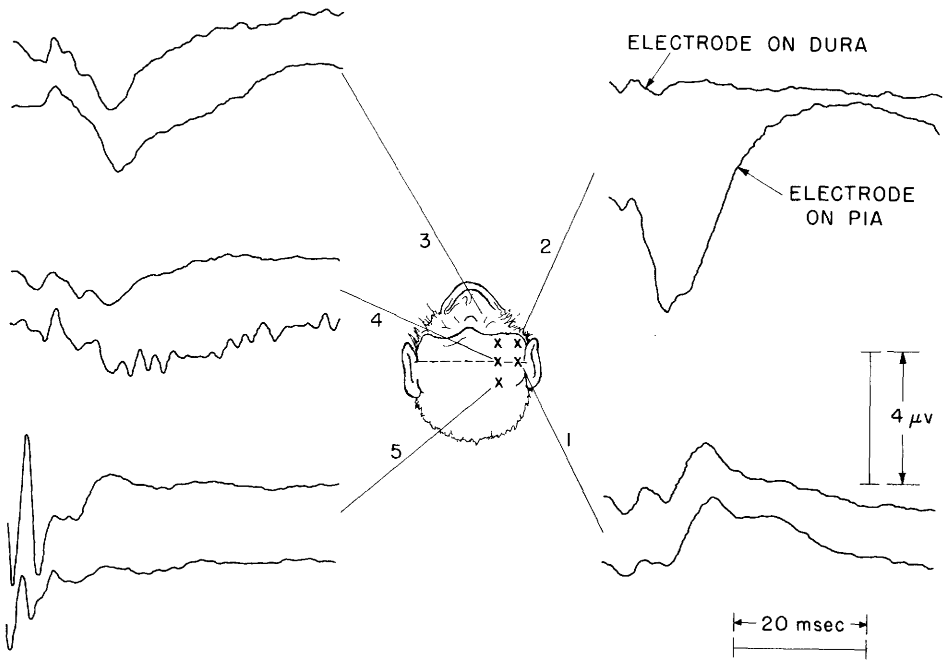


Fig. 11. Average responses to clicks obtained from various electrodes on the head of Monkey S(M-6). The top response in each pair was recorded from the dural surface; the corresponding lower response from the pial surface directly beneath, after dural reflection. Platinum-wire electrodes were used at both levels. The ground electrode was used as reference. With the following exception, responses of all electrodes placed on any one layer were recorded simultaneously: The dural response of electrode 2 was computed by averaging 900 responses (whose average is shown in Fig. 10) recorded between electrode 2 and the occipital electrode and 900 responses recorded (simultaneously with the other responses whose averages are shown in this figure) between the occipital electrode and ground. Otherwise, the number of responses was 900. Same stimulus conditions as in Fig. 10.

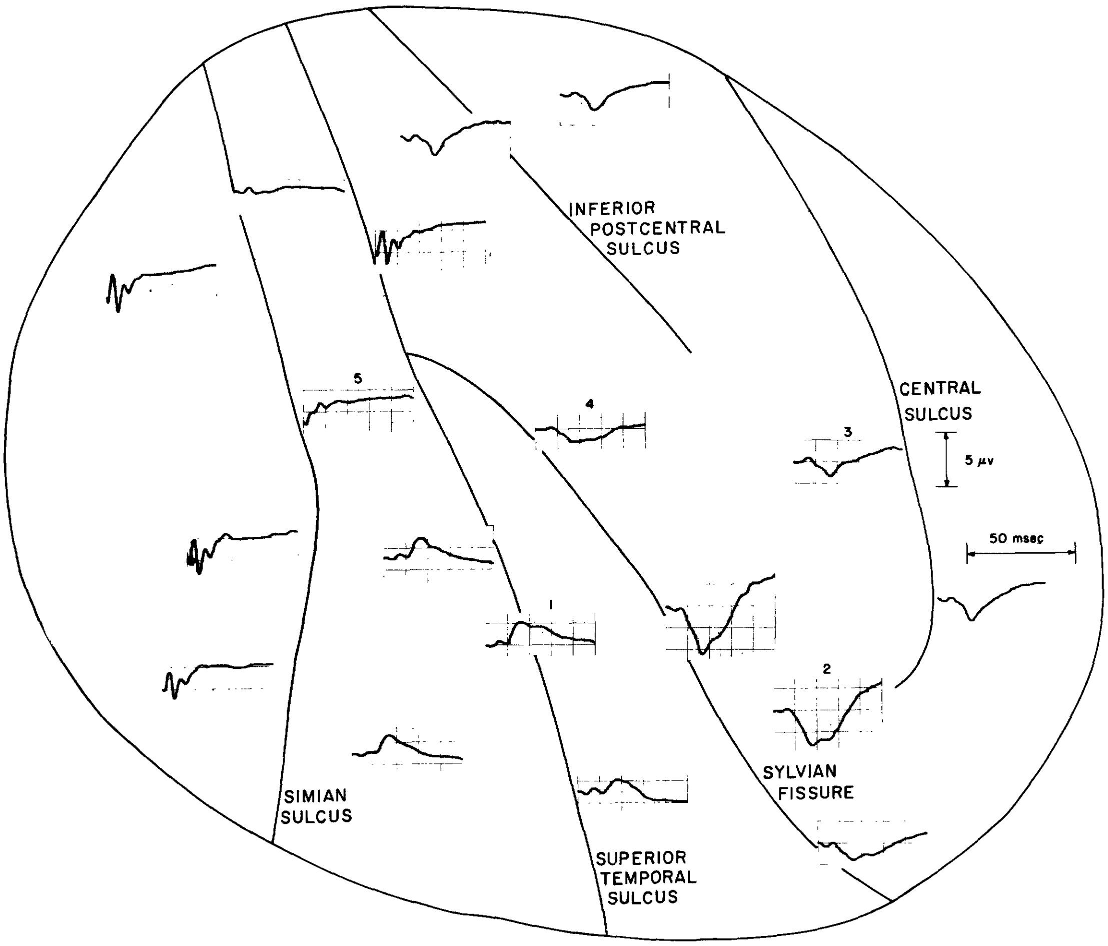


Fig. 12. Average responses obtained at various points on the exposed pial surface of Monkey S(M-6). Each response is the average of 900 responses. Numbered electrode sites are those shown in Fig. 11 (approximately 1 cm apart). Same experimental conditions as in Fig. 11. The outside line shows the extent of brain exposed. Dial anesthesia.

mentioned by Pribram, Rosner, and Rosenblith (28), the wide extent of cortex from which auditory responses may be recorded. The final recordings in the experiment were obtained from the exposed auditory cortex by needle electrodes and showed average responses having much the same shape as those recorded from electrode 2 of Fig. 12, but with amplitudes ranging up to 70 μv.

2.3 CONCLUSION

The first point to be made in the comparison of the experimental and mathematical results obtained is that the average evoked response, even in an anesthetized animal, does not really have a dipolelike field distribution. Reference to Fig. 12 shows that although average responses were obtained from many points on the cortex, the wave shapes were different at many of the points. A true dipole, in comparison, would give rise to responses having identical wave shapes throughout the volume. Moreover, the data in Fig. 12 also show that the amplitude of the average response does not, in all cases, decrease with increasing distance from the point of maximal response. A dipole field, on the other hand, would show just such a progressive decrease.

In spite of the fact that the single dipole equivalent for the active sites of an evoked response is not realistic, the mathematical data need not be discarded. From the mathematical model, it was found that, for a fixed dipole, the potential field existing on the surface of a layer of conductive material surrounding the central sphere had lower amplitude than the potential field existing on the surface of the sphere by itself. Moreover, a shell of conductivity higher than that of the sphere was found to have more of a reducing and "smearing" effect upon the potential field than a shell of lower conductivity. By extrapolation, it would be expected that the potential field produced by a dipole sheet, a more realistic model for active sites in the cortex, would be more altered by the more highly conducting layer than by the layer of lower conductivity. From the mathematical model, then, we would predict that the more highly conducting layers surrounding the brain would have the greatest effect upon the potential fields measured at the outside surface.

The experimental data support this prediction. Figure 11 shows, for instance, average responses recorded from similar locations on the dural surface and on the pial surface when the dura with its cerebrospinal fluid undercoating was removed. The responses recorded by the dural electrodes were little lower in amplitude than those recorded on the pia, and the huge response recorded at location 2 on the pia was not even recordable from the electrode at the same location on the intact dura. Figure 12 shows that the responses recorded at location 2 were well localized on the pial surface, since electrodes located only a centimeter away in several directions recorded very different wave shapes. In contrast, the response wave shapes recorded at the other numbered locations were recordable over more widespread areas. Figure 9 shows a large well-localized response that was recorded from the skull underneath the layers of muscle and scalp. An electrode located directly above on the surface, however, recorded only a small response that looks rather like the other responses recorded on the surface. The fact that potential fields recorded from underneath a highly conductive layer may be undetected on the surface of the layer is good evidence for the attenuating properties of highly conductive layers. Also, in accord with our general prediction, the potentials recorded from over and under the skull, which is presumably not as good a conductor as the underlying media, are not too dissimilar.

These results are in agreement with those found by Abraham and Ajmone-Marsan (48) in their study on epileptic subjects. They noted that potentials recorded from the scalp did indeed reflect epileptic discharges that were spread over an appreciable area of underlying cortex. However, when an epileptic discharge was recorded from only one of two closely spaced dural electrodes (a fact that indicates a sharply localized discharge on the cortex), a corresponding event was not visually detectable in the potentials recorded by the scalp electrodes.

In another study on human patients, Cobb and Sears (51) studied potentials recorded from scalp electrodes placed on the operated side of hemispherectomized patients. They replaced approximately half of the cerebrospinal fluid in the hemispherectomy cavity with air and studied the potentials produced by the remaining brain matter that was now distant from the electrodes. For head orientations in which the active brain matter was separated from the scalp electrodes by an appreciable quantity of cerebrospinal fluid, the recorded potentials were smaller than those recorded in positions when the injected air replaced the fluid. The attenuating effect of a layer of cerebrospinal fluid upon potential fields produced in the human brain is clearly shown by these results.

In conclusion, then, it has been demonstrated that average responses recorded from the pial surface of monkey cortex are faithfully reflected at the surface of the scalp, as long as the potential fields evoked by the stimuli are not too sharply localized. These sharply localized potential fields are attenuated and "smeared" by both the dural and the scalp layers, and may be practically undetectable (by our present methods) at the surface of the scalp. These attenuating effects were paralleled in the mathematical model by the attenuating and "smearing" influence of the various layers upon the dipole potential fields existing on the outer surface. By extension of these results to humans, we therefore expect that average responses obtained from the scalp of human subjects will indeed reflect the activity existing in the brain beneath. The various layers separating the scalp electrodes from the cortex will attenuate and smear the potential fields produced in the brain. But nevertheless we may expect average responses on the scalp to mirror the average responses actually existing on the surface of the cortex directly beneath.

III. BASIC EXPERIMENTAL AND DATA-PROCESSING TECHNIQUES

Evoked responses to acoustic stimuli are not ordinarily detectable upon a visual examination of the electric potentials recorded from the scalp of a human subject. In this study, we have used the technique, which will be discussed in section 3.2, of averaging responses to many identical stimuli in order to detect these responses. The particular acoustic stimuli used almost exclusively in these experiments were clicks, since we wished to evoke responses as large as possible, and clicks are known to activate many neural units synchronously (16). Electric potentials were recorded from the scalp of subjects during presentation of the clicks, and average responses to the clicks were then computed from the recorded EEG potentials. These average responses form the basic data presented in this study.

3.1 BASIC EXPERIMENTAL TECHNIQUES

a. Basic Equipment

All of the experiments in this study were conducted in an electrically shielded, soundproof, anechoic chamber, which was maintained at approximately constant temperature. The sound-absorbing Fiberglas wedges that cover all six surfaces of the room may be seen in the background of Fig. 14.

The click stimuli utilized were produced by 0.1-msec pulses that were generated by a Grason-Stadler (Model 876-S-1) click generator and applied to an earphone through a MacIntosh 20-watt amplifier. An attenuator circuit permitted control of the click amplitudes in steps of 1 db; 0 db corresponded to 4.4 ± 0.4 volts across the earphone. In a few experiments, random noise was added to the electrical pulses through a resistive mixer network. The noise was generated by a General Radio (Model 1390-A) Random-Noise Generator. Whenever it was used in this study, the electrical noise covered the frequency band of from 30 cps to 20 kcps. During most of our experiments matched PDR-10 earphones were used. These earphones had an effective bandpass which approximately covered the range 100 cps-7 kcps. During some of the experiments a single Audivox hearing-aid earphone (Model 9C) with ear plugs of graduated size was used. This earphone had an effective bandpass extending from 500 cps to 7 kcps. The 9C earphone was used only occasionally, and unless otherwise specified, the PDR-10 earphones were used.

Occasionally, we used electric-shock stimuli. The electric stimulator used was a high-impedance source designed and built in our laboratory. (The stimulator was designed by Robert M. Brown.) The stimulator applied 0.5-msec pulses to the subject through a General Radio isolation transformer (Model 289A). Over a range of load resistances ranging from 500 ohms to 80 kilohms, the source, as seen at the output terminals of the transformer, had an equivalent output resistance that was relatively constant at 130 kilohms. A high output resistance was desirable because electric current is thought to excite the nerves, and the resistance between the electrical contacts on the subject may change with time. Hence, a current source that is insensitive to load resistance was needed. When the load resistance of our stimulator was changed from 50 kilohms to 20 kilohms, a current increase of 20 per cent was sustained. We did not, therefore, have a constant-current source, but the adequacy of the device was indicated by the usual reports from subjects that there was relatively little change in the subjective impression of similar shocks applied during the course of a particular experiment. Current calibration was made at various dial settings by using a 50-kilohm test resistor. The shape of the voltage pulse applied to test resistors greater than 15 kilohms was quite a reasonable facsimile of a square pulse.

The recording of potentials from the scalp of a human subject involves the establishment of good electrical contact between the scalp and the electrode. Some EEG investigators simply use small needle electrodes that penetrate the skin and make contact with the conductive tissue beneath the surface. But for those who use surface electrodes, good electrical contact with the scalp, coated as it is with body deposits, is a bit of a problem. The first step is usually the cleaning of a small area of the scalp by a degreasing agent such as alcohol. Then an electrode is placed over the spot, and secured to the scalp by one of the many methods that have been developed. Some sort of conducting paste or jelly must be inserted between the scalp and the electrode in order

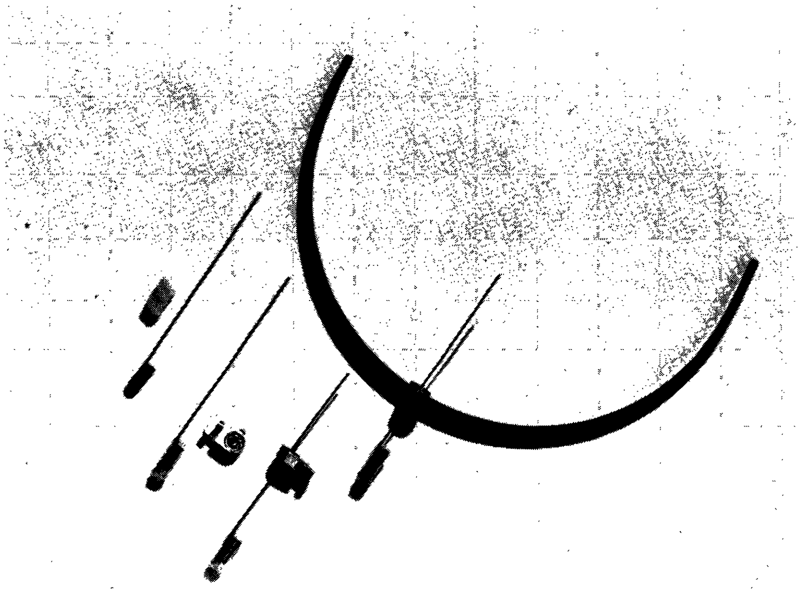


Fig. 13. Successive stages in the construction of the electrodes used in this study. From left to right: A piece of sponge rubber and a copper cylinder on the end of a brass rod (rod approximately 4 in. long) are glued together and covered with a cylinder of plastic. The rod fits into a ball-and-socket joint which, in turn, is mounted on a plastic band. Electric contact to amplifier inputs is finally made through a metal piece inserted between the socket holder and the plastic band.

to insure good electrical contact between them.

One commonly used electrode is simply a blob of solder attached to the end of a wire. We have used this kind of electrode only occasionally, for we have had difficulty in attaching it firmly to the scalp. Rather, a new type of electrode system, utilizing Grass ball-and-socket joints, was developed. (The aid of Margaret Z. Freeman and of the machine shop of the Research Laboratory of Electronics, under the supervision of John B. Keefe, in the development of this electrode system is gratefully acknowledged.) As seen in Fig. 13, the ball of a joint was free to rotate within its socket, and had a hole through the middle, into which the shaft of an electrode fitted. The electrode shaft fitted the hole snugly, so that the static friction between the ball and the shaft held the shaft firmly. The friction was not so great, however, as to prevent movement of the shaft if sufficient pressure were exerted. In order to put these electrodes within reach of the scalp, the ball-and-socket joints were mounted on plastic bands that spanned the head. The bands, in turn, were affixed either to a pair of earphones, as shown in Fig. 14, or to a simple headpiece that encircled the head. The bands could be rotated about a single axis and the ball-and-socket joints themselves could be moved along the plastic bands. Judicious jockeying, therefore, allowed an electrode to be located at almost any point on the scalp.

The electrodes themselves were composed of a brass electrode shaft, a thin copper cylinder attached to the shaft, and a piece of sponge rubber carefully glued to the cylinder (see Fig. 13). A small flexible plastic cylinder was the "skin" of the electrode. To

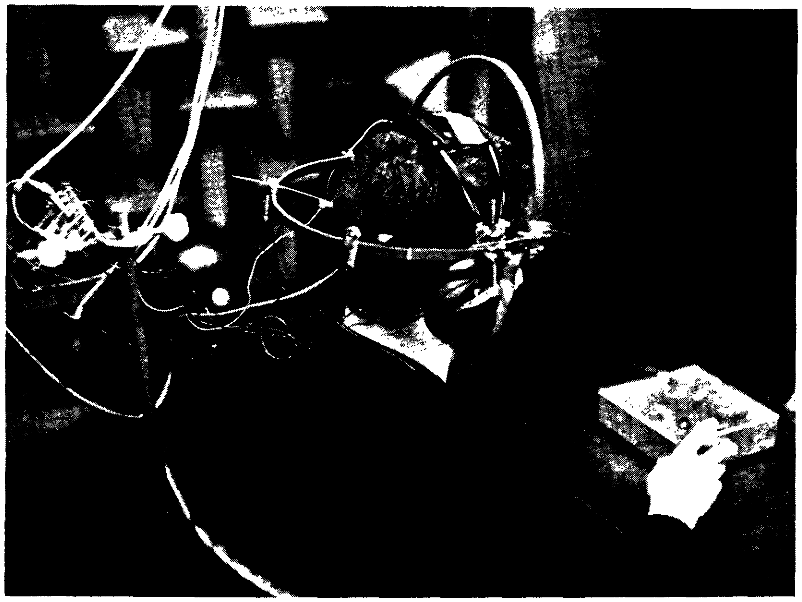


Fig. 14. PDR-10 earphones and scalp electrodes in place on a subject's head. Subject is sitting in the experimental room (the sound-absorbing Fiberglas wedges can be seen on the wall in the background). Amplifier inputs can be seen in upper left-hand corner. The signaling box in front of the subject is of the type used to measure psychophysical thresholds.

apply these electrodes, the desired spots on the scalp were first cleansed. Then a blob of conducting paste (Sanborn "Redux") was put on the spots and the sponge electrodes, previously soaked in saline, positioned firmly against the scalp at these spots. If the sponges became dry, additional saline was dripped in through the open back of each electrode. Unless otherwise specified, these electrodes were used throughout this study.

The outputs of the scalp electrodes were amplified by a bank of six (Offner Model 142) high-gain differential amplifiers with a maximum gain of approximately 120 db. The frequency response of these amplifiers is variable and can be extended to cover the range 0.5-7000 cps between cutoff points, although the normally employed passband was 8-600 cps.

The amplified EEG potentials, together with time markers synchronized to the various stimuli presented to the subject, were recorded on magnetic tape by a tape system that utilized a modified Ampex (Model 1100) FM seven-channel tape recorder. At the recording speed of 1 7/8 inches per second that was normally used, potentials from dc to greater than 300 cps were recorded.

The ARC-1, a digital average response computer (38), was used to compute most of the average responses shown in this study. ARC is a high-speed, transistorized, special-purpose digital computer that has a magnetic-core memory. The speed with which ARC was able to compute average responses, and the fact that it computed a "running" average response as the data were fed in, meant that the computer could be used "on-line." That is, average responses were computed from the EEG data during the actual presentation of the stimuli to the subject, instead of after the experiment was all over. The value of obtaining the average responses during the experiment was great. First, since click responses were not usually detectable in the normally recorded EEG, average responses obtained during an experiment insured the integrity of the stimulating systems. Second, prompt notification that the average responses evoked by two supposedly identical patterns of stimuli were quite different led to an immediate investigation into possible causes of the change. The disadvantages of being informed of such response changes after the experiment is over are obvious. Third, the effects of systematic variation of stimulus parameters upon the average response waveforms were more accurately determined by "on-line" computation. For, in a range of stimulus values which evoked greatly differing wave shapes, small increments of change in the stimuli were needed to show the progressive changes that occurred in the responses; for ranges of stimuli which evoked essentially identical responses, fine increments were not needed. Hence, average responses actually obtained during an experiment led to more judicious manipulation of the stimulus parameters. This study could not have been accomplished nearly as quickly, surely or completely without the use of the ARC computer.

In Section V, measurements of scalp displacements will be reported. The measuring device used is shown in Fig. 15. A ceramic phonograph cartridge (Astatic Model 53-25) was used as the basic transducer. The cartridge, fitted with a wire replacement for the

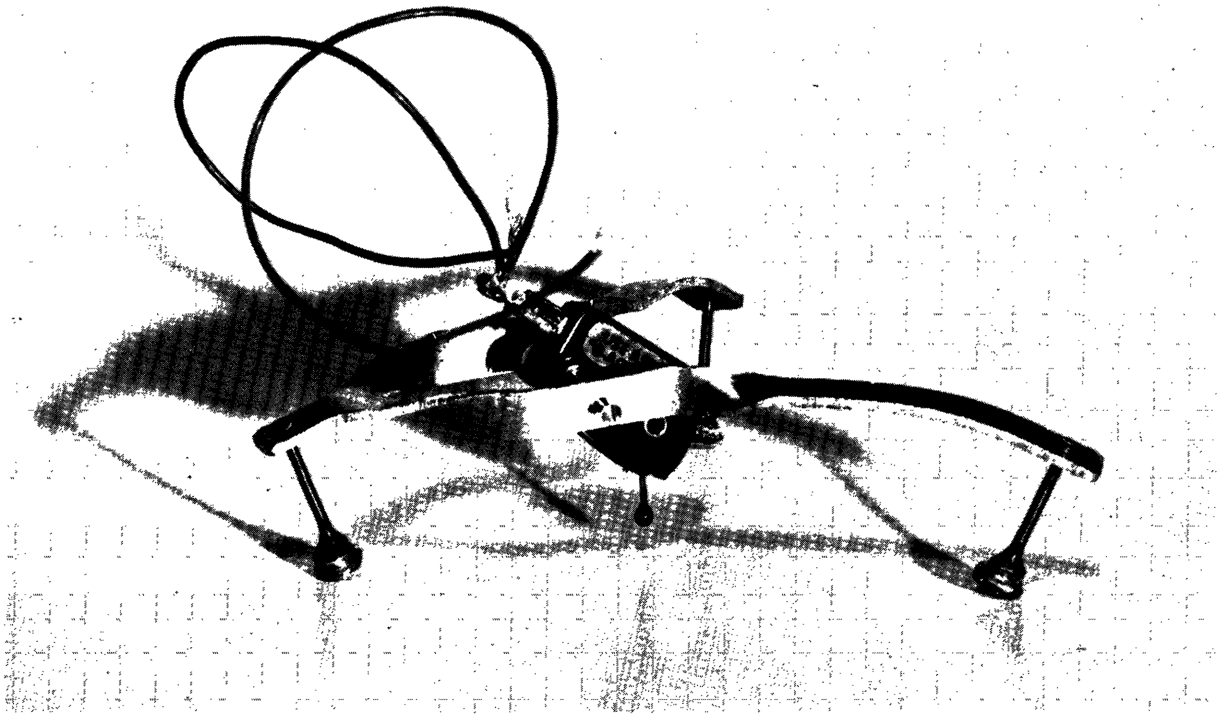


Fig. 15. Phonograph cartridge used to measure scalp displacement, mounted on its frame. The feet of the mounting frame are approximately 8 cm apart and all feet are approximately 5 cm equidistant from the tip of the wire. The precautionary measure of coating the tip of the wire with a blob of insulation was taken to insure that no electric potentials on the scalp were introduced into the cartridge.

phonograph needle, was mounted on a frame. The mounting frame was cut from sheet aluminum and was fastened directly to the scalp with collodion by means of three "feet." The tip of the wire was also affixed to the scalp by a drop of collodion. The output of the cartridge was amplified to useful levels by one of the differential amplifiers already described. The device was calibrated by affixing the wire tip to a paper straw, which, in turn, was attached to the center of a small loud-speaker. (This method of calibration was suggested by Dr. George L. Gerstein.) The displacement of the wire tip for various inputs to the loud-speaker was directly observed and measured under stroboscopic illumination. A 50-cps sine wave, essentially undistorted at the cartridge output, was the calibrating signal used. Other observations showed that the cartridge measured displacement directly, in the range of frequencies in which we were interested. The good sensitivity of the device was indicated by the fact that it clearly recorded, when a subject was talking, scalp displacements having the fundamental frequency of his speech.

b. Basic Experimental Procedure

Throughout the whole investigation, experiments were conducted on one subject at a time. At the beginning of each experiment, the recording electrodes and stimulating devices were applied to the subject and he was positioned in the anechoic chamber. Then, trains of periodically repeated clicks were presented to the subject through an earphone. The clicks within any one train were all of the same intensity and were presented at a single repetition rate; the clicks in different trains had different parameters. The electric potentials obtained from the various pairs of electrodes were continuously recorded on the magnetic tape during the presentation of the stimuli. The output of one or two of the electrode pairs was monitored on an oscilloscope and "on-line" average responses were computed by the ARC. Most of the experiments lasted approximately two hours, so periodic checks were made to insure that the subject was both comfortable and alert. The experiments were numbered sequentially.

During most of the experiments, the subject was provided with a specific task to keep him awake and alert. Most subjects were able to concentrate quite well on reading and so were provided with reading matter and instructed to read while in the chamber. One subject found it easier to concentrate on a chess game, so a chess set and a partner, carefully instructed to be very quiet, were usually provided for him. The instructions usually given to the subjects were to sit as quietly as possible and to concentrate on their appointed task without paying particular heed to the various stimuli presented. Subjects would occasionally become so engrossed in their tasks that they were almost unaware of the stimuli that had been given to them. Usually, however, they reported that they were vaguely "aware" of the stimuli.

Psychophysical judgments on various stimuli were obtained from our subjects on several occasions with the use of techniques that are in common usage.

Threshold intensities for click trains were obtained by a straightforward application of the method of limits (52). First, the intensity of an audible train of clicks delivered at a constant rate, 15 per second, was lowered in steps of 1 db. The subject pressed a button as long as he heard the clicks and released the button when he could no longer hear them. The intensity of the clicks was reduced still further and then raised in steps of 1 db until the subject signaled that he heard the clicks by pressing the button again. The intensity was increased still further, and then again decreased in 1-db steps. The cycle was repeated several times and the arithmetic average of the various transition intensities (in db) was the value called the "psychophysical threshold."

During the collection of some of the data shown in Section VII, psychophysical judgments on the loudness of clicks were obtained. In these particular experiments, the subject was presented with short click trains, each train consisting of repetitively presented clicks having a fixed intensity; different trains contained clicks of different intensity. The subject was instructed to listen carefully to the clicks of each train and to place the loudness of the clicks in that train into one of five possible categories, ranging from loudest to softest (53). Then after each train was terminated, the subject was to register his judgment by pressing the appropriate button on a box that was supplied. The essential feature of the box was a row of five buttons. The left-hand button represented the softest category, and the right-hand button, the loudest; and the other three buttons, intermediate categories. The only label was an arrow, marked with the words "increasing loudness" which pointed from left to right. Judgments were continually observed and recorded on the magnetic tape for permanent record.

3.2 BASIC DATA-PROCESSING TECHNIQUE: AVERAGING

A "typical" electric response evoked from mammalian auditory projection areas has been shown in Section I. When the animal is deeply anesthetized, the responses evoked by repetitive stimuli are very similar in waveform, and any one of the responses may be selected as a typical response. In more lightly anesthetized animals, or in those that are unanesthetized, the responses to repeated presentations of identical stimuli may be quite different (12). In order to characterize these variable responses, the experimenter either performs some data processing himself, by deciding what is a typical response, or statistical measures of the data are computed (12, 13). When recording with electrodes on the human scalp, the variability of evoked responses is even greater; responses to sensory stimuli are often not even detected. Yet small average responses to sensory stimuli have been computed from EEG data in which no single evoked responses were visually detectable. Undoubtedly, small responses are often present in the EEG but are completely hidden in the activity ("spontaneous activity") which exists regardless of the presence or absence of deliberate stimulation.

Such problems are familiar to those interested in the transmission of signals. For, a signal is inevitably distorted in transmission, and the receiver is, therefore, left with some uncertainty about the signal sent. In order to reduce the signal distortions encountered in transmission, various techniques have been evolved. Perhaps the simplest of these methods is averaging. A signal is transmitted over and over again, and if a time marker, synchronized with each repetition of the signal, is available to the receiver, he is capable of averaging them and obtaining a more faithful representation of the transmitted signal than could be obtained from a single transmission.

a. A Mathematical Model for Averaging

Before we apply this promising technique to bioelectric signals, let us explore more quantitatively the effects of averaging upon transmitted signals. For our mathematical model, let us assume that the received waveform $f(t)$ is the sum of two independent waveforms, the transmitted waveform $s(t)$ plus an additive noise waveform $n(t)$ picked up in transit. The transmitted waveform is composed of repetitions of the same signal, as shown in Fig. 16a, and let us make the further assumption that the noise waveform is produced by a wide-sense stationary random process with a mean $E(n)$ and a variance $\sigma^2(n)$.

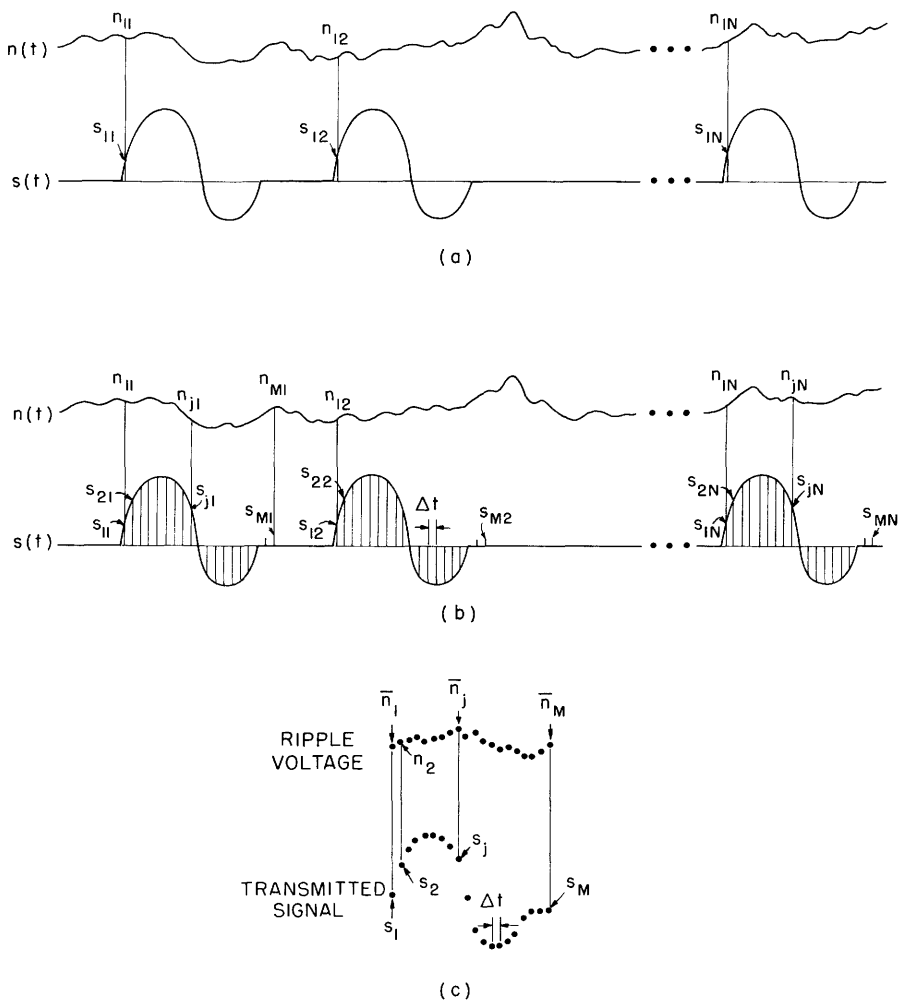


Fig. 16. (a) Component parts of the received waveform f(t). The received waveform f(t) is the sum of the random noise waveform n(t), and the transmitted waveform s(t). Samples n_{1k}; k = 1, 2 ... N are uncorrelated, although time-locked to repetitions of the signal. (b) Sampling of the component parts of the received waveform f(t). M periodic samples, time-locked to the signal onset, are taken during each repetition of the signal. (c) Component parts of the average transmission. The average transmission is the sum of the ripple voltage and an individual transmitted signal.

If we assume that the receiver also has information concerning the onset of each signal repetition, then we may specify the following operation. We take N samples, subject to the two restrictions that sample instants must be time-locked to the signal waveform and still give uncorrelated samples of the noise. Such samples are indicated in Fig. 16a. The mean of these samples is calculated to be

$$\bar{f}_1 = \frac{1}{N}\sum_{k=1}^{N} f_{1k} = \frac{1}{N}\sum_{k=1}^{N} (s_{1k}+n_{1k})$$

$$\bar{f}_1 = \frac{1}{N}\sum_{k=1}^{N} s_{1k} + \frac{1}{N}\sum_{k=1}^{N} n_{1k} = \bar{s}_1 + \bar{n}_1 \tag{4}$$

Here, the bar indicates sample mean.

But since the sample mean $\bar{s}_1$ has the same value, s_1, as any sample s_{1k}, we may rewrite the equation,

$$\bar{f}_1 = s_1 + \bar{n}_1 \tag{5}$$

The expected value, or statistical average, of the sample mean is then found to be

$$E(\bar{f}_1) = s_1 + E(\bar{n}_1) = s_1 + E(n) \tag{6}$$

If we make the reasonable assumption that the mean value of the noise is zero, we have

$$E(\bar{f}_1) = s_1 \tag{7}$$

To compute the variance of the sample mean, we have, by definition,

$$\sigma^2(\bar{f}_1) = \frac{1}{N^2} \sum_{k=1}^{N} \sum_{p=1}^{N} E(f_{1k} f_{1p}) - E^2(\bar{f}_1) \tag{8}$$

Since we have specified uncorrelated samples of n(t),

$$E(f_{1k} f_{1p}) = E(f_{1k})\, E(f_{1p}), \quad p \neq k \tag{9}$$

Therefore, we have

$$\sigma^2(\bar{f}_1) = \frac{1}{N^2} \sum_{k=1}^{N} E\left(f_{1k}^2\right) - \frac{1}{N} E^2(f_{1k})$$

$$\sigma^2(\bar{f}_1) = \frac{1}{N^2} \sum_{k=1}^{N} E\left(s_{1k}^2 + 2 s_{1k} n_{1k} + n_{1k}^2\right) - \frac{1}{N} E^2(s_1) \tag{10}$$

and thus

$$\sigma^2(\bar{f}_1) = \frac{1}{N^2} \sum_{k=1}^{N} \left[E\left(s_{1k}^2\right) - E^2(s_{1k})\right] + \frac{1}{N^2} \sum_{k=1}^{N} E\left(n_{1k}^2\right) \tag{11}$$

But since the signal sample is perfectly specified, the variance of the signal term is zero and

$$\sigma^2(\bar{f}_1) = \frac{1}{N} E\left(n_1^2\right) = \frac{1}{N} \sigma^2(n_1) = \frac{1}{N} \sigma^2(n) \tag{12}$$

We see, therefore, that the expected value of the sample mean is just the value of the desired signal, and that the variance of the sample mean (a measure of the uncertainty of the sample mean about the desired value) is $(1/N)\, \sigma^2(n)$.

If we had only taken a single sample f_1 from the family of N samples just considered, we would find that its expected value is also s_1:

$$f_{1k} = s_{1k} + n_{1k} \tag{13}$$

and therefore,

$$E(f_{1k}) = E(s_{1k}) + E(n_{1k}) = s_1 \tag{14}$$

The variance, on the other hand, is found to be

$$\sigma^2(f_1) = E\left(f_{1k}^2\right) - E^2(f_1)$$

$$= E\left(s_{1k}^2+2s_{1k}n_{1k}+n_{1k}^2\right) - E^2(f_{1k}) \tag{15}$$

$$\sigma^2(f_1) = \left[E\left(s_{1k}^2\right)-E^2(s_{1k})\right] + E\left(n_{1k}^2\right) \tag{16}$$

Again, since the signal is perfectly specified, the only term contributing to the sample variance is the noise term and therefore

$$\sigma^2(f_{1k}) = E\left(n_{1k}^2\right) = \sigma^2(n) \tag{17}$$

The expected value of the single sample is s_1, as found for the averaged case, but the variance about the mean for this single sample is $\sigma^2(n)$.

By averaging, therefore, we obtain the same expected value s_1 for the average of N samples as for the single sample. However, the variance of the sample average about the expected value is only 1/Nth that of the single sample. One often-used measure of the uncertainty of a signal in the presence of additive noise is the signal-to-noise ratio. The signal value, obviously, is s_1. Let us take the standard deviation of the noise as the measure of the noise. For a single sample, then, the ratio is equal to $s_1/\sigma(n)$. If, on the other hand, we average N samples, the signal-to-noise ratio is $s_1\sqrt{N}/\sigma(n)$. And so, subject to the previous assumptions and definitions, we have improved the signal-to-noise ratio by $\sqrt{N}$ in averaging N samples.

If we are interested not only in a single point of the signal, but in the complete wave shape, the obvious thing to do is to sample, not once for each signal but periodically, enought times M to specify the signal waveform. If, with reference to Fig. 16b, we take only samples f_{1k}, $k = 1, 2 \ldots N$, the previous considerations hold, and the standard deviation around the expected value s_1 will be $\sqrt{N}$ smaller for the averaged samples than for a single sample f_{1k}. For, simply by sampling at other points, we have not changed conditions at these original sample points. In similar fashion, the statistical average of the N samples f_{jk}, $k = 1, 2 \ldots N$, will be s_j, and the standard deviation about this value will be $\sqrt{N}$ smaller for $\bar{f}_j$ than for a single sample f_{jk}. Any point of the average transmission, therefore, has the expected value of the corresponding point on the signal and varies about that value, with a standard deviation that decreases as the square root of the number of transmissions averaged. The average transmission, therefore, is the sum of a typical signal and a "ripple voltage" caused by the noise. These two components of the average transmission are shown in Fig. 16c. In order to get an accurate estimate of the signal at each sample point, and hence an accurate estimate of the whole signal, no matter how small, we have only to average enough uncorrelated transmissions to make the ripple voltage small compared with the signal.

The difficulty with the direct application of these mathematical conclusions to electric potentials recorded from the human scalp is that we do not know that the potentials recorded with scalp electrodes satisfy the restrictions placed on the mathematical model. It is true that Weiss (55), on the basis of amplitude histograms computed from the spontaneous EEG activity of human subjects, could not discard the hypothesis that the data were generated by a Gaussian noise source. But on the other hand, spontaneous activity recorded from the human scalp over long periods of time cannot be considered stationary, even in the wide sense, because of the differing characteristics observed during different "states" of the subject. For example, gross changes are noticed in the characteristics of a subject's EEG as he goes to sleep (see Section VI). Perhaps smaller changes are occurring all of the time. In addition, it is well known that systematic changes in evoked responses occur when long trains of monotonous stimuli are presented to awake animals (56). And as a final point, it must be noted that the model of identical responses added to a random-noise background does not adequately describe auditory responses evoked from anesthetized dog cortex (57) (see reference to Tunturi's measurements in sec. 3.2b).

It is not suggested, therefore, that potentials recorded from the human scalp actually satisfy all of the assumptions used in the mathematical analysis given above. Nevertheless, as a model, we shall consider the potentials recorded from human scalp to be composed of spontaneous activity and evoked responses. The spontaneous activity will be considered as the output of a wide-sense stationary noise generator, and the successive responses evoked by repetitions of identical stimuli will be considered to be identically the same and to be added to the spontaneous activity. The degree to which the model successfully predicts the behavior of the average responses is the degree to which the model is justified.

b. Experimental Test of the Model

In order to estimate the validity of the model that we have chosen for averaging, let us consider the characteristics of the electric potentials recorded from the scalp of one of our subjects, A. T. The data to be discussed were obtained during a routine experiment in which the subject sat in the experimental chamber and played chess.

Let us turn our attention to the component of the EEG potentials which we have called the spontaneous activity. Since this spontaneous activity has been assumed to exist whether or not stimuli are presented to the subject, we could presumably examine its characteristics by studying the EEG potentials recorded in the absence of deliberate sensory stimulation. However, deliberate stimulation may change the "state" of the subject, and thereby change the statistical characteristics of his EEG potentials; it would be better to study the behavior of the spontaneous activity while the subject is actually being stimulated. Fortunately, this condition is approximately realizable, since the EEG potentials recorded during the presentation of click stimuli are found experimentally to be much greater than the average potentials evoked by the clicks. The contribution of the individual evoked responses to the total recorded potentials, therefore, will probably be very small, and we may ignore the evoked responses as long as we do not average them. Accordingly, in order to study our subject's spontaneous activity, we shall investigate EEG potentials that were recorded from him while he was being presented with click stimuli.

Two restrictions placed on the mathematical model were that the statistical mean of the noise be zero and that any two samples of the noise, n_{jk} and n_{jp}, taken during different individual evoked responses, must be uncorrelated. To test the model fairly, we should impose the same restrictions upon the experimentally obtained spontaneous activity. Because the EEG potentials were recorded through an ac-coupled amplifier and because the spontaneous activity is assumed to be by far the largest component of the EEG potentials, we may assume that the statistical mean of the recorded spontaneous activity was effectively zero. But in order to satisfy the restrictions of uncorrelated samples, we must refer to the autocorrelation function $R(\tau)$.

The infinite time sample required to compute the time autocorrelation function of any physically realizable source is unattainable and therefore we are never able to calculate $R(\tau)$ directly. It has been shown, however, that the finite-time autocorrelation

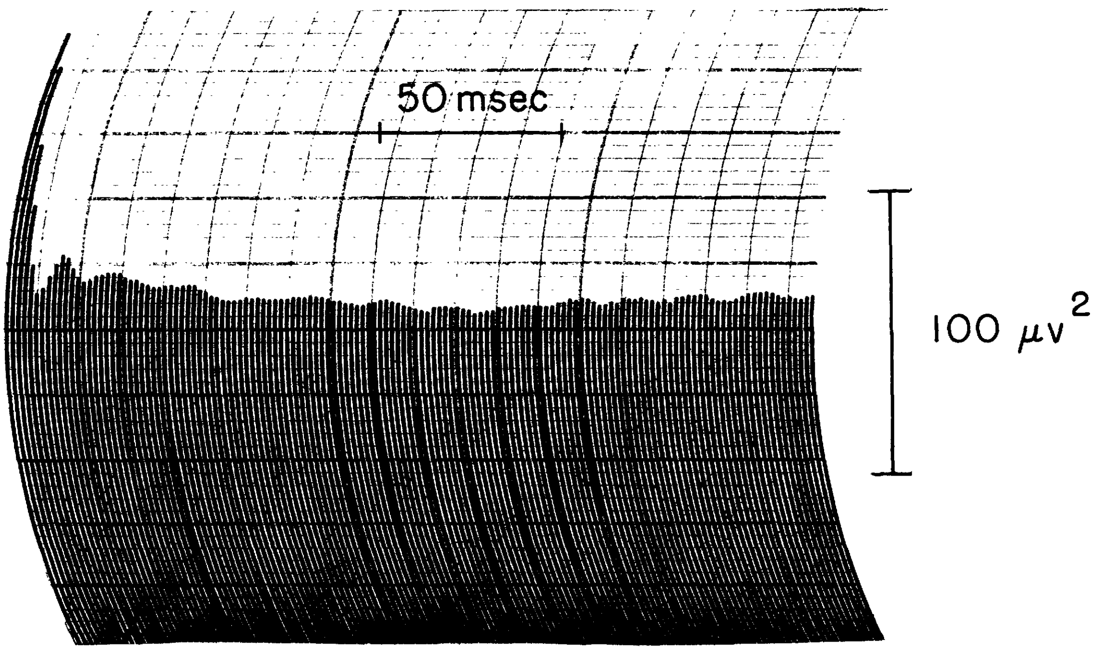


Fig. 17. Autocorrelogram of 6 minutes of EEG recording. Subject (A. T., H-582) was awake and playing chess. Click stimuli at a rate of 5/sec were continuously presented to the subject. Click intensity, −40 db; recording electrodes, 6 and 8 (see Fig. 21d for location of electrodes).

$$R(T, \tau) = \frac{1}{T} \int_0^T x(t)\, x(t+\tau)\, dt \qquad (T \text{ is finite}) \qquad (18)$$

is a consistent estimate of the autocorrelation function and converges in the mean to $R(\tau)$, as T approaches infinity (55). In other words, $R(T, \tau)$ is an estimate of $R(\tau)$, with the same expected value as $R(\tau)$, and becomes a better and better estimate as the sample length T is increased. It is possible, therefore, to estimate $R(\tau)$ by computing a finite-time autocorrelogram from the recorded experimental data. Figure 17 shows such a correlogram computed from 6 minutes of continuous electrical activity recorded from the scalp of the subject. (Computation was done on the CBG correlator (58). As used, it had a bandwidth extending from dc to approximately 80 cps.) Notice that appreciable correlation is absent for τ greater than 75 msec. (The absence of noticeable correlation for $\tau = 200$ msec is ample justification for our assumption that the evoked responses are very small compared to the spontaneous activity.) Although this correlogram was computed from a short time sample, let us assume that it is a good estimate of the autocorrelation function $R(\tau)$ of an imaginary, infinitely long record from which we have taken this 6-minute sample. Hence, we conclude that samples of these EEG data taken more than 75 msec apart may be considered as uncorrelated. The condition that corresponding samples of the spontaneous activity taken during different individual evoked responses be uncorrelated will, therefore, certainly be satisfied by these data, for a click rate of only 5 per second was used.

Getting on now to the actual testing of the model, we see that Eq. 12 predicts that the variance of any point in an average response will decrease inversely with the number of responses, N, that are averaged. Furthermore, our model predicts that these individual point variances, and hence the whole ripple voltage, will be contributed solely by the spontaneous activity. We should, therefore, be able to study the behavior of the ripple voltage by averaging the recorded EEG potentials with the use of time markers that are not consistently related in time to the presentation of the actual stimuli. Experimental ripple voltages obtained by averaging various numbers of epochs (An epoch is the section of recorded EEG potentials, following a single time marker, over which we sample periodically. An epoch is a response if the time marker is synchronized to a stimulus presentation.) were computed in this manner and are shown in Fig. 18.

Notice that the amplitudes of the various deflections observed in the ripple voltages do indeed decrease as the number of the epochs that were averaged increases.

Quantitatively, the model predicts that the variance of any point in the ripple voltage will drop off inversely as the number of averaged epochs N. But in order to test the appropriateness of the model for quantitatively describing the characteristics of experimental ripple voltages, we are again faced with an estimation problem. We do not know the variance of a particular point in the ripple voltage, nor can we compute it exactly. For, variance is defined in terms of a statistical measure of a whole ensemble, and we have only a few sample points. Hence, we can compute only an estimate. As a first

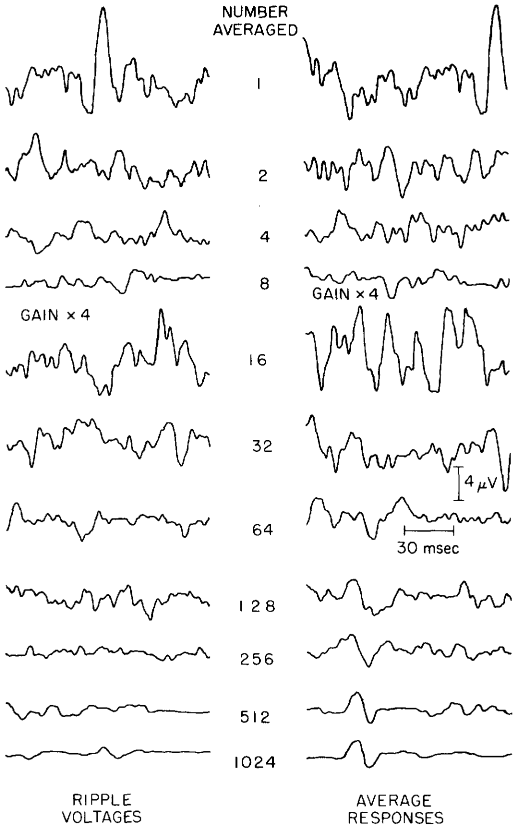


Fig. 18. Average epochs obtained from the EEG potentials of a subject stimulated with periodically presented clicks. Each curve is the computed average of 2^n epochs. Left column: computed by using periodic time markers (rate, approximately 5.2/sec) not synchronized to the stimulus presentations (rate, 5/sec). Right column: computed by using time markers synchronized to the stimulus presentations. The averages in each column were computed from successive sections of EEG data. Corresponding curves in both columns refer to same number of averaged epochs and were computed from the same sections of EEG data. The gain is increased by 4 for all curves below "G X 4". Each curve was constructed by joining M separate points (M=250). The data were taken from the EEG potentials used in the computation of Fig. 17. Upward deflection indicates negativity at electrode 8.

step, we shall compute the mean of the variances of the 250 individual points that make up each ripple voltage. For according to the model, this mean variance, $\sigma^2_M(N) = \frac{1}{M}\sum_{j=1}^{M} \bar{f}_j^2$, can be shown to be a consistent estimate of the variance of any single point f_j in the ripple voltage. Table I lists the mean variances computed from each of the ripple voltages shown in Fig. 18.

According to Eq. 12, the variance of one point in the ripple multiplied by N, the number of epochs averaged, is just equal to the variance of a point in a single epoch. It follows that because each of the ripple voltages in Fig. 18 was computed from a separate section of the EEG data, that we have 11 independent estimates of the variance of a point

Table I. Measures computed from the ripple voltages of Fig. 18.

Number of Epochs Averaged N	Mean Variance of the Ripple Voltage $\sigma^2_M(N) = \frac{1}{M}\sum_{j=1}^{M} \bar{f}_j^2$; M = 250	Decrease in Mean Variance Obtained by Averaging $\sigma^2(1)/\sigma^2_M(N)$
1	94797	0.82
2	32800	2.4
4	14366	5.4
8	5776.9	13.5
16	3794.0	20.6
32	2004.0	39.0
64	634.02	123.
128	798.10	97.9
256	208.61	374.
512	243.55	321.
1024	146.22	534.

in the spontaneous activity. The mean of these 11 estimates, labeled $\sigma^2(1)$, is 78,134 (in arbitrary units), and is our final estimate of the variance of a point in the spontaneous activity. This number forms the basis for the computation of the numbers shown in the third column of Table I. Each number in that column is simply the dividend obtained when $\sigma^2(1)$ is divided by the corresponding number in the second column, the mean variance $\sigma^2_M(N)$. These numbers are, therefore, an estimate of the decrease in the variance of a single point in the average epoch obtained by averaging N times.

The expected value of the ratio in each case is N, and the fit between the predicted and observed ratios is only fair. Perhaps the musculature of the head and neck was active and contributed electrical potentials to the EEG which were not statistically similar to the potentials produced in the brain. In any case, it is true that the mean variance of the experimental ripple voltage is decreased by a factor approximately equal to the number of epochs averaged.

If now the timing pulses are synchronized with the actual click stimuli, the model predicts that the behavior of the ripple will be unchanged, but in each case will simply be added to a typical response. Therefore, as the number of responses N is increased, the experimentally obtained average response should become a better and better estimate of an individual response. Of course, we do not know the actual wave shape of an individual response, so we cannot evaluate directly the exactness of our various estimates. The effect of the spontaneous activity, however, should decrease as the number of responses N is increased. The right column of Fig. 18 shows average responses to 2^n clicks, computed from the corresponding sections of EEG potentials used in the calculation of the various ripple curves. Each average response, therefore, was computed from a separate section of the EEG. Notice that as the number of responses is increased, each average response resembles the previous one more and more. Moreover, the spurious potentials (potentials that do not repeat from curve to curve) are of approximately the same magnitude as the deflections in the corresponding ripple voltage. Such behavior is certainly compatible with the model.

The average transmission in the model was shown to be the sum of the ripple voltage and the signal waveform. That is, any point of the average transmission $\bar{f}_j$ was found to equal $s_j + \bar{n}_j$. Therefore, the expected value of $\bar{f}_j$ was s_j and the variance about this value was found to be simply the variance $\sigma^2(\bar{n})$ of the ripple voltage. Hence, the model predicts that the statistical variance, and hence also the sample variance, of any single point, $\bar{f}_j$, in the average transmission will be independent of j.

In order to test this prediction of the model, sample standard deviations were computed from the experimentally obtained responses and are displayed in Fig. 19. (These curves were computed on the TX-0 computer, with the use of a program written by Charles E. Molnar.) The top curve in each column is the average response, the sequence of sample means $\bar{f}_j$; $j = 1, 2 \ldots M$. The bottom curve in each column is the sequence of sample standard deviations, $\sigma_N(f_j) = \left(\frac{1}{N}\sum_{k=1}^{N} f_{jk}^2 - \bar{f}_j^2\right)^{1/2}$; $j = 1, 2 \ldots M$. It is clear that, in accord with the model, there is no observable dependence of the sample standard deviation $\sigma_N(f_j)$ upon j, that is, there is no observable dependence upon the time at which the sample j was taken in each response.

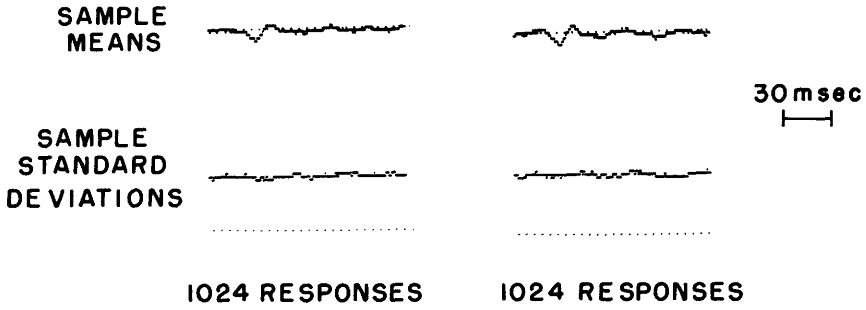


Fig. 19. Sample means and sample standard deviations obtained from EEG potentials. The upper curves are average responses; each point is the mean of 1024 samples taken at a fixed time after consecutive stimulus presentations. Each point on the lower curves is the standard deviation of these 1024 samples. The standard deviation and mean are shown on the same amplitude scale. The zero lines are shown dotted; the interval between dots is 5 msec. These curves were computed from the EEG data used in the computation of Fig. 17. The left column was computed from data used in the calculation of the upper curves of Fig. 18; the right column was computed from approximately the same data used in the calculation of the lowest pair of curves in Fig. 18. (Downward deflection indicates negativity at electrode 8.)

Tunturi (57) has made similar measurements on the evoked responses obtained from anesthetized dog cortex. He used a brief acoustic stimulus and recorded the evoked potentials photographically. Periodic samplings were made of each response, and sample means and sample standard deviations were computed for corresponding sample points of the responses. Under conditions of normal anesthesia, the standard deviations computed by Tunturi showed a marked degree of dependence upon the time of stimulus presentation: For sample points lying within the initial surface-positive deflection, the standard deviation was sometimes twice that of points lying elsewhere along the response Such response behavior shows that an individual evoked response cannot be considered as an unchanging response simply added to a background of spontaneous activity. Evoked responses obtained from the anesthetized dog, therefore, do not satisfy the model that we have proposed, for it has been shown that acoustic stimulation changes the pattern of variability of the sample points as well as their mean.

Perhaps click stimulation also induces some variability in the samples taken of human EEG potentials, but it is undetectable in the presence of other sources of variability which are independent of the stimuli. The term "spontaneous activity," therefore, becomes justified when applied to human EEG, in the sense that the variability in the average responses is due to activity not time-locked to the stimuli.

c. Conclusion: Appropriateness of the Model

The suggested model, therefore, is able to successfully describe several characteristics of the average responses computed from potentials recorded from human scalp. First, the mean variances of points in the experimentally obtained ripple voltages are shown to decrease approximately proportionally to the number of epochs N that are averaged. Second, a more and more consistent waveform is seen in the average responses as more and more responses are averaged. Third, the sample variance of points f_{jk}; $k = 1, 2 \ldots N$, is found to be independent of j, and hence independent of the time of stimulus presentations.

We shall, therefore, adopt the proposed mathematical model as an adequate description of the way in which the effect of spontaneous activity recorded from the human scalp is reduced by averaging. We are not suggesting that the recorded potentials actually satisfy the assumptions used to construct the model, but only that the model is able to successfully predict certain characteristics of average responses.

IV. AVERAGE RESPONSES TO CLICKS OBTAINED FROM HUMAN SCALP

In a recent study of the K-complex (henceforth referred to as the "K-component"), Roth, Shaw, and Green (59) stated that these particular response components were visually discernible in the EEG of all subjects when they were in light sleep. These experimenters, however, were able to find visually discernible responses in only 20 per cent of their awake subjects. The small percentage of awake subjects in whom these response components were detected could reflect the actual percentage of awake subjects from whom the K-components were evoked. On the other hand, perhaps these K-components were actually evoked from a high percentage of awake subjects, but were usually too small to be detected in the presence of the spontaneous activity. One possible experimental technique for choosing one of these alternatives might be the application of averaging, which was shown in Section III to reduce the effect of the spontaneous activity recorded from human scalp.

Figure 20 shows results obtained by just such an application of averaging. Periodically repeated clicks were presented to an awake subject at repetition rates varying from 0.3 per second to 10 per second. For none of these stimulus rates were responses discernible from a visual examination of the EEG record. But after averaging, very clear responses were obtained. The right column of Fig. 20 presents these average responses on a time scale that is suitable for observation of the K-component; responses with latency characteristics similar to the K-component are indeed observed for the low rates of stimulation. Notice the large peaks at approximately 70 msec and 140 msec. As the rate of click stimulation is increased, these peaks decrease in size and essentially disappear for the higher rates. By way of comparison, Larsson (41), using somatic stimulation, has reported responses with the latency characteristics of the K-component and notes that they disappear for stimulus rates higher than 5 per second. It is clear, then, that responses to clicks were indeed evoked from subject E. F., even though individual responses were not detectable from a visual examination of his EEG potentials.

A close examination of the average responses in the right column of Fig. 20 reveals that there are, in addition to the long-latency K-components, response components that have relatively short latencies. These short-latency components are more easily seen in the left-hand curves, which are the same average responses as the corresponding ones in the right-hand column, but are shown on an expanded time scale. The most consistent feature of the responses in the left column is a deflection with a peak latency of approximately 30 msec. This peak is relatively independent of click rate, and is seen even at the click rate of 10 per second.

The latency of the 30-msec deflections, although a little longer than that of the earliest evoked activity usually recorded from the primary projection areas of the mammalian cortex, is approximately the latency of responses obtained from secondary areas of the cortex (see Section I). The identification and description of our 30-msec responses, therefore, becomes of some interest. For, while there exists a large body of data

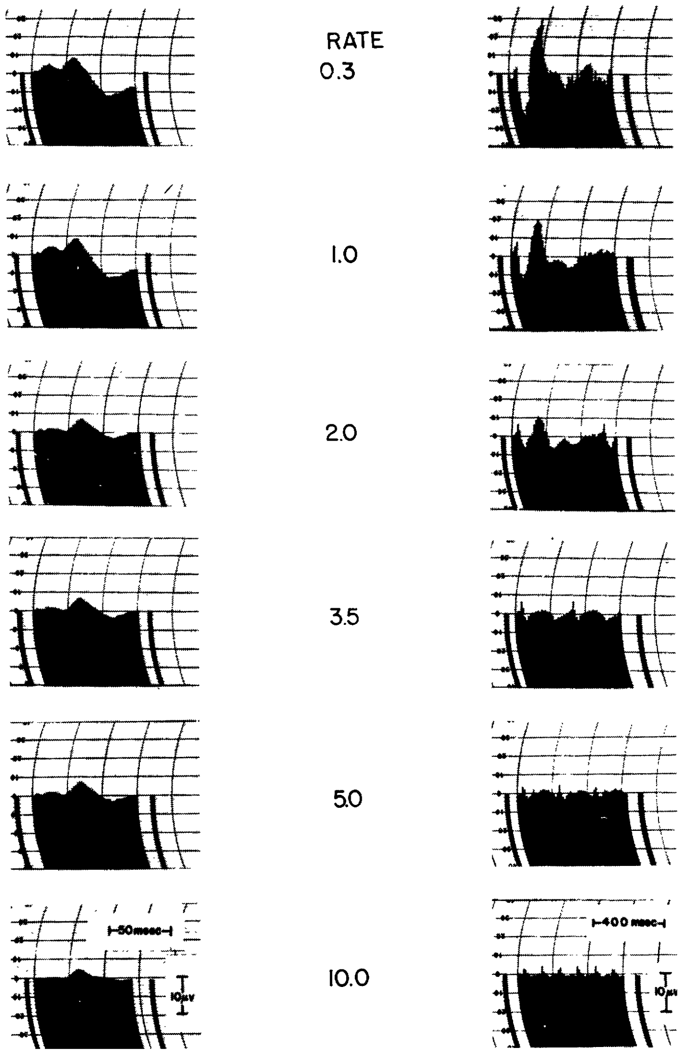


Fig. 20. Average responses to clicks as a function of click rate (Subject, E. F., H-436). Stimulus conditions: periodically repeated clicks delivered to the left ear at approximately −30 db. Response conditions: the active electrode was on the mastoid process; the reference electrode, at the vertex; number of responses averaged, 250 times the rate, varying from 75 at 0.3/sec to 2500 at 10/sec. (In this and in the rest of the figures, downward deflection denotes positivity of the active electrode with respect to the reference electrode.)

describing the cortical responses recorded from higher mammals, there have been few systematic electrophysiological studies of the normal human brain. It should be quite interesting to compare the characteristics of the average evoked responses obtained from the human scalp with the more extensively studied evoked responses obtained from the brains of experimental animals.

With the motivation then of utilizing the existing framework of electrophysiological data obtained from animals, we have concentrated our study upon the earliest electrical events that are detectable on the outside of the human scalp following the presentation of acoustic clicks.

4.1 AVERAGE RESPONSES RECORDED FROM DIFFERENT ELECTRODE LOCATIONS ON THE HUMAN SCALP

The data discussed in Section II indicate that average responses obtained from the scalp do indeed reflect the average responses recordable on the cortex directly beneath. A knowledge of the particular electrode locations on the human scalp from which responses might be obtained, therefore, would provide us with information about the locus of cortex from which response activity could be recorded. And knowledge of the cortical regions from which average responses could be obtained should be of value in determining the nature and origin of the responses. As a first step, therefore, we shall determine the distribution of electrode locations on the scalp from which various average response components may be obtained.

One point that needs to be discussed first concerns the location of the "reference" electrode. As stated in Section III, differential amplifiers were utilized throughout our study. This type of amplifier, which amplifies the potential differences that exist between its two input leads, requires both of these leads to be in contact with the body of the subject (or preparation). For "monopolar" recording, one lead is connected to the "active" electrode, and the other connected to a place that (one hopes) is completely unaffected by the electrical events under investigation. If, however, the second lead is not truly "indifferent" to these events, then its activity will also contribute to the amplifier's output, which will then no longer show potentials recorded by the active electrode only.

For the recording of response activity from the brain of a human subject, a reference electrode placed anywhere on the head is close to the active sources and may not be truly indifferent. But electrodes placed below the neck usually show quite large heartbeat potentials that are undesirable on a reference lead. It has been found, however, that heartbeat potentials recorded from the back and the front of the body can be used to partially cancel one another, and that a simple potentiometer can be used to balance out most of the effect of the heartbeats (60). One terminal of the potentiometer is attached to the subject's chest, another to his back, and the middle terminal, the slidewire terminal, is used as the reference point. The potentiometer is then adjusted until minimum heartbeat potentials are observed at the slidewire terminal, a point which thereby becomes relatively uncontaminated either by potentials related to heartbeats or to brain activity.

Figure 21a shows the average responses recorded from various points on the scalp of subject O.G. with respect to such a neck-chest reference electrode. Notice that the responses, although they are recorded from the whole electrode array, are largest in the occipital regions.

Unfortunately, the neck-chest electrode is difficult to apply, and excessive muscle potentials are sometimes introduced by it. A different reference location is, therefore, desirable, and the tip of the nose, which is fairly well removed from the brain, was finally chosen as the most convenient reference point.

Figure 21b shows average responses recorded from the same points on the subject's scalp as in Fig. 21a; however, an electrode on the tip of the nose is used as the reference electrode. It is clear that the average responses shown in the two pictures are different, undoubtedly due to the fact that the nose electrode also records response activity. However, a negative response component with a peak at 30 msec is seen in Fig. 21a and 21b, and the general distribution on the scalp of this 30-msec component is more or less unaffected by changing the reference point. Although the shifting of the reference electrode from the body to the nose of subject O. G. had a marked effect upon his response waveforms, the same shift of the reference electrode of other subjects caused much less effect upon their recorded response waveforms.

Figure 21c shows the distribution of average responses on the scalp of subject W. P. The preponderant localization of these responses in the occipital region is quite marked in this subject; the amplitude of his responses is almost the largest recorded from any of our subjects.

Figure 21d and 21e shows the average responses recorded from the scalp of another subject, A. T., when clicks were presented to his left and right ears separately. For this subject, also, the larger responses were recorded from the more posterior electrodes; the temporal and frontal electrodes show very small responses. Note especially that regardless of whether ipsilateral or contralateral stimulation was used, responses recorded from the same electrode have approximately the same waveshape and amplitude.

Figure 21f shows the widespread average responses recorded from the scalp of subject M. E. The deflections shown for electrodes 3 and 6 may be spurious, as they have not been seen in similar experiments on this same subject. However, even for this subject, response amplitudes are greatest in the occipital regions.

All of the response distributions considered thus far show a similar pattern. Each subject exhibits a fairly widespread response whose most prominent component is a negative deflection having a peak latency of approximately 30 msec; the amplitude of this 30-msec component is larger when recorded from the posterior electrodes. The fact that both left and right ear stimulation evoked essentially the same type of response from subject A. T. (Fig. 21d and 21e) has already been noted. This figure, together with data obtained from experiments in which responses to monaural clicks were obtained simultaneously from symmetrical points on opposite sides of the head, indicates that these responses are evoked bilaterally: that is, small differences in amplitude are the only readily detectable differences between ipsilateral and contralateral responses.

Figure 21g-i shows a more complicated response pattern, which contains, nevertheless, the generally observed 30-msec component. Figure 21g and 21h shows the average responses of subject M. W., which are distinguished by a well-localized positive peak that is evoked principally by contralateral stimulation. This positive deflection has a peak latency of approximately 20 msec. Subject M. W.'s responses to clicks are also shown in Fig. 21i for a lower rate of stimulus presentation. In this figure (where the contralateral and ipsilateral responses are displayed one over the other) the various

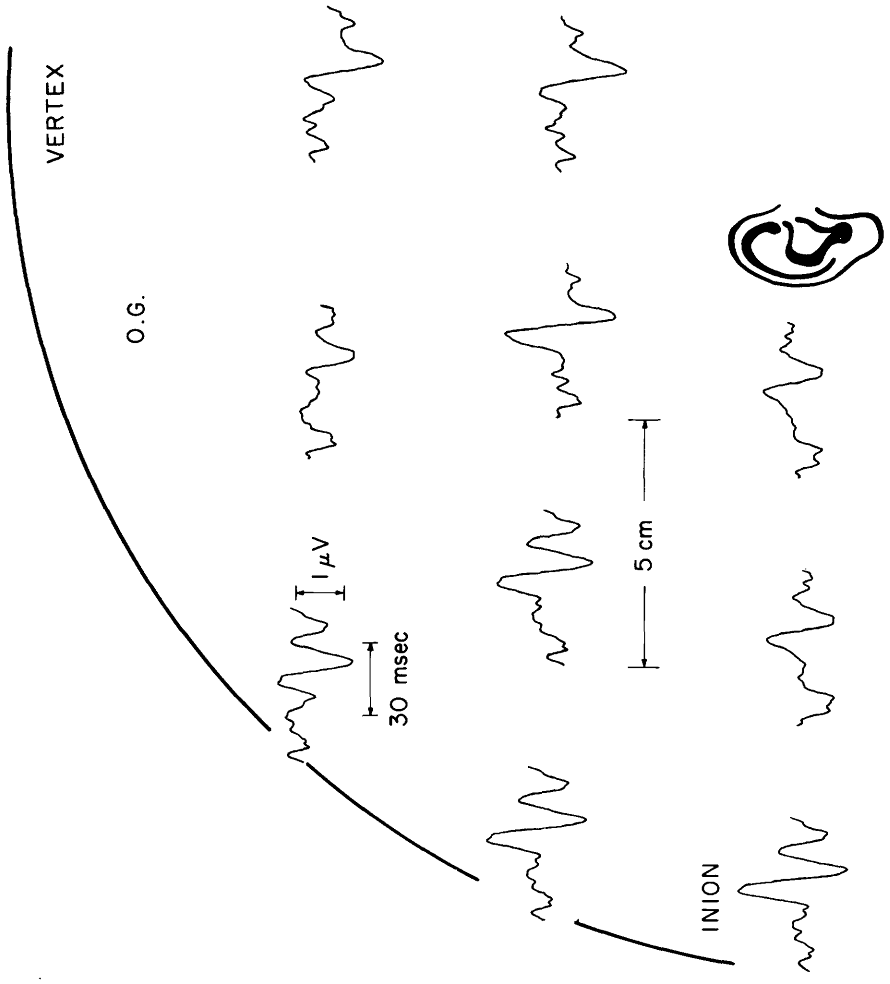

VERTEX
O.G.
1 μV
30 msec
5 cm
INION

Fig. 21a. Average responses to clicks recorded from various scalp electrodes (Subject O. G., H-512). Stimulus conditions: clicks, left ear, 10/sec, -45 db. Response conditions: reference electrode, slidewire terminal of 10 kohm potentiometer attached to neck and chest; number of responses, 2000.

[In this and in the following figures the beginning of each trace marks the approximate location of the recording electrode on the right side of the head. These electrodes were positioned on the scalp by using the following procedure, or minor modifications of it: 5-cm divisions were marked along the mid-line, anteriorly from the inion; 5-cm divisions were marked along the vertex-preauricular cavity line, medially from the preauricular cavity; and equal divisions, approximately 5 cm apart, were marked off on lines joining corresponding occipital and temporal markers.]

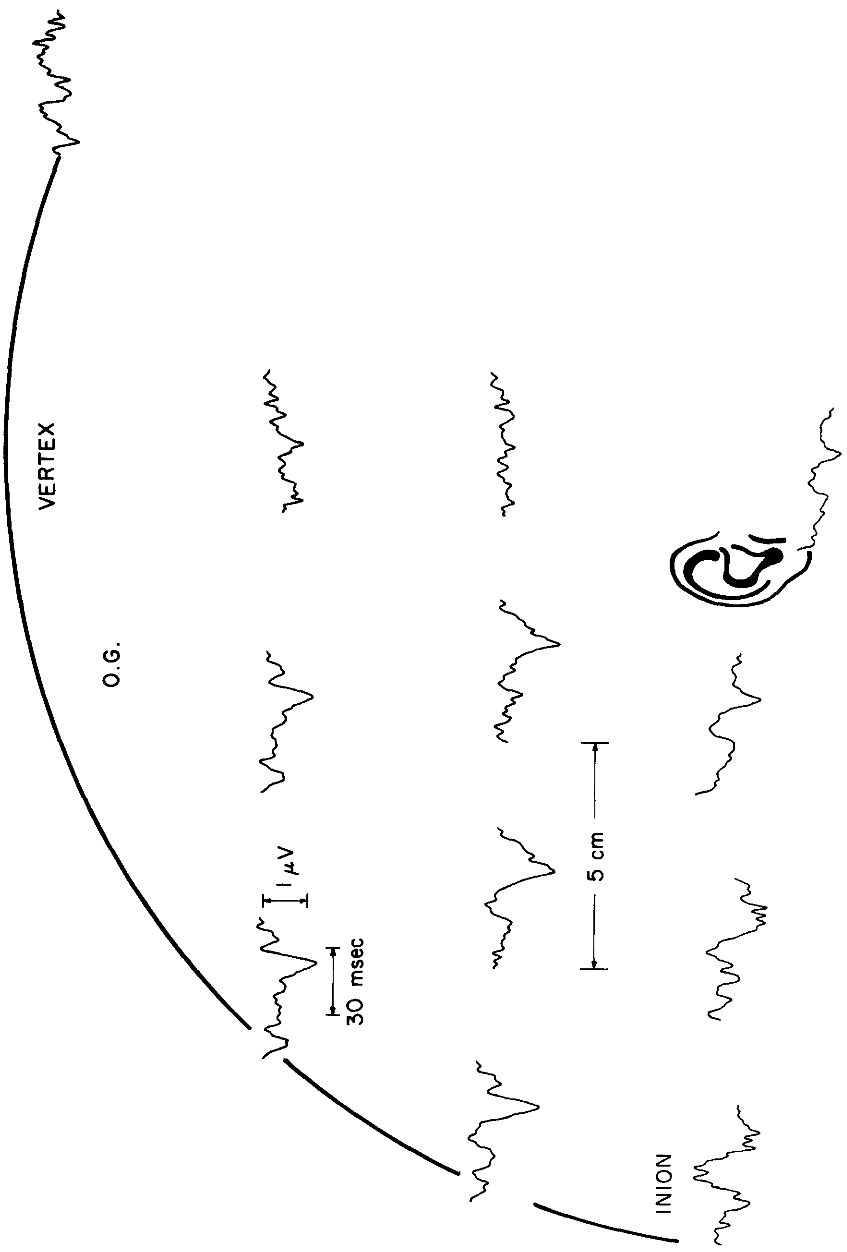

VERTEX
O.G.
1 μV
30 msec
5 cm
INION

Fig. 21b. Average click responses recorded from various scalp electrodes (Subject, O. G., H-517). Stimulus conditions: clicks, left ear, 14/sec, -45 db. Response conditions: reference electrode, nose; number of responses, 2000. Since a bank of only six amplifiers was available, the responses from all electrodes were not recorded simultaneously. [In recording data for this section, whenever more than one period of recording was needed to obtain responses from all of the electrodes on the scalp, the activity of one electrode was, unless otherwise noted, recorded throughout the entire experiment and used as a monitor. The average responses recorded from this monitor electrode were always sufficiently similar to one another that the responses obtained during different periods could be reasonably combined in one figure.]

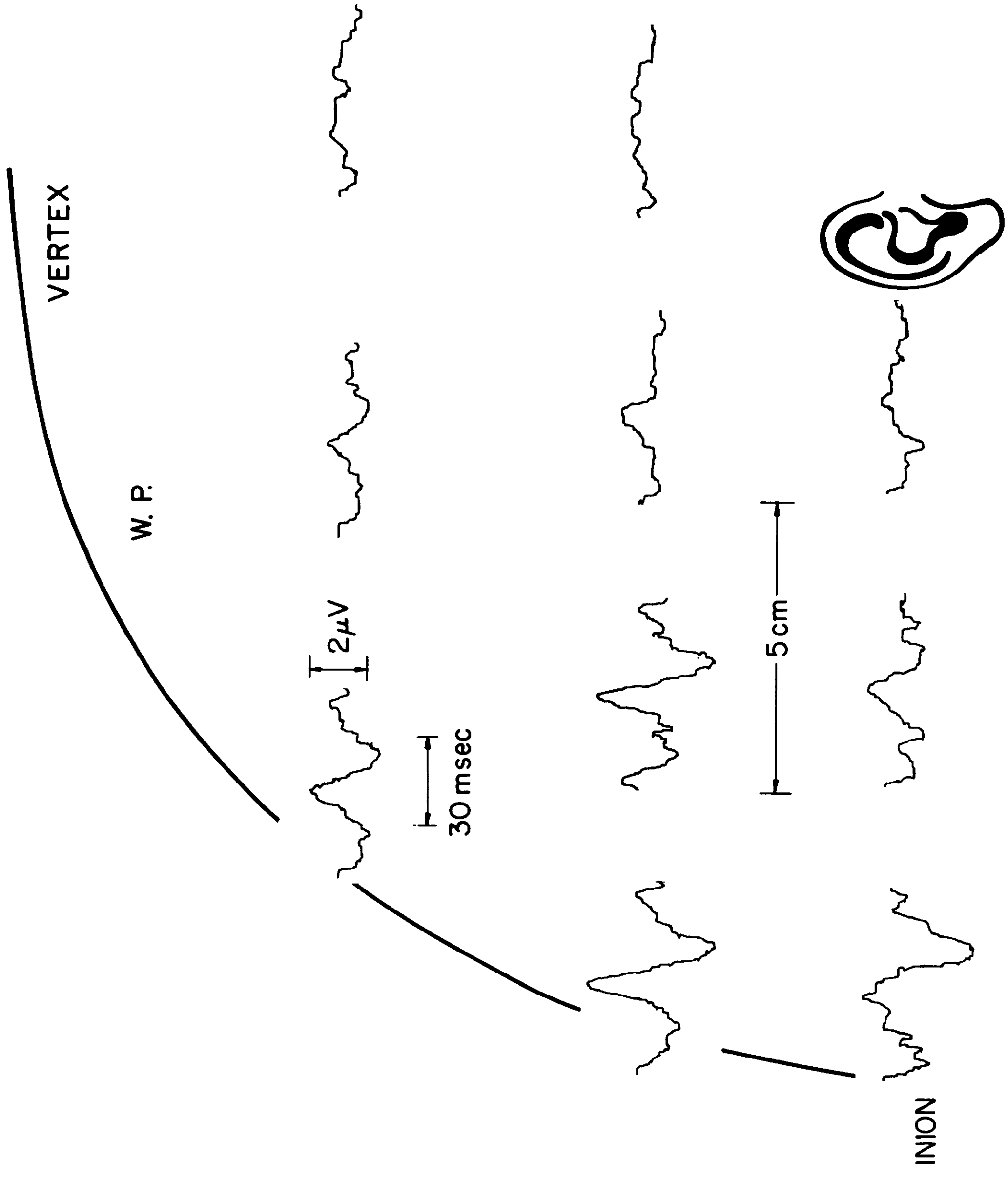

VERTEX
W. P.
2μV
30 msec
5 cm
INION

Fig. 21c. Average click responses recorded from various scalp electrodes (Subject, W. P., H-518). Stimulus conditions: clicks, left ear, -45 db, 14/sec. Response conditions: reference electrode, nose; number of responses, 2000.

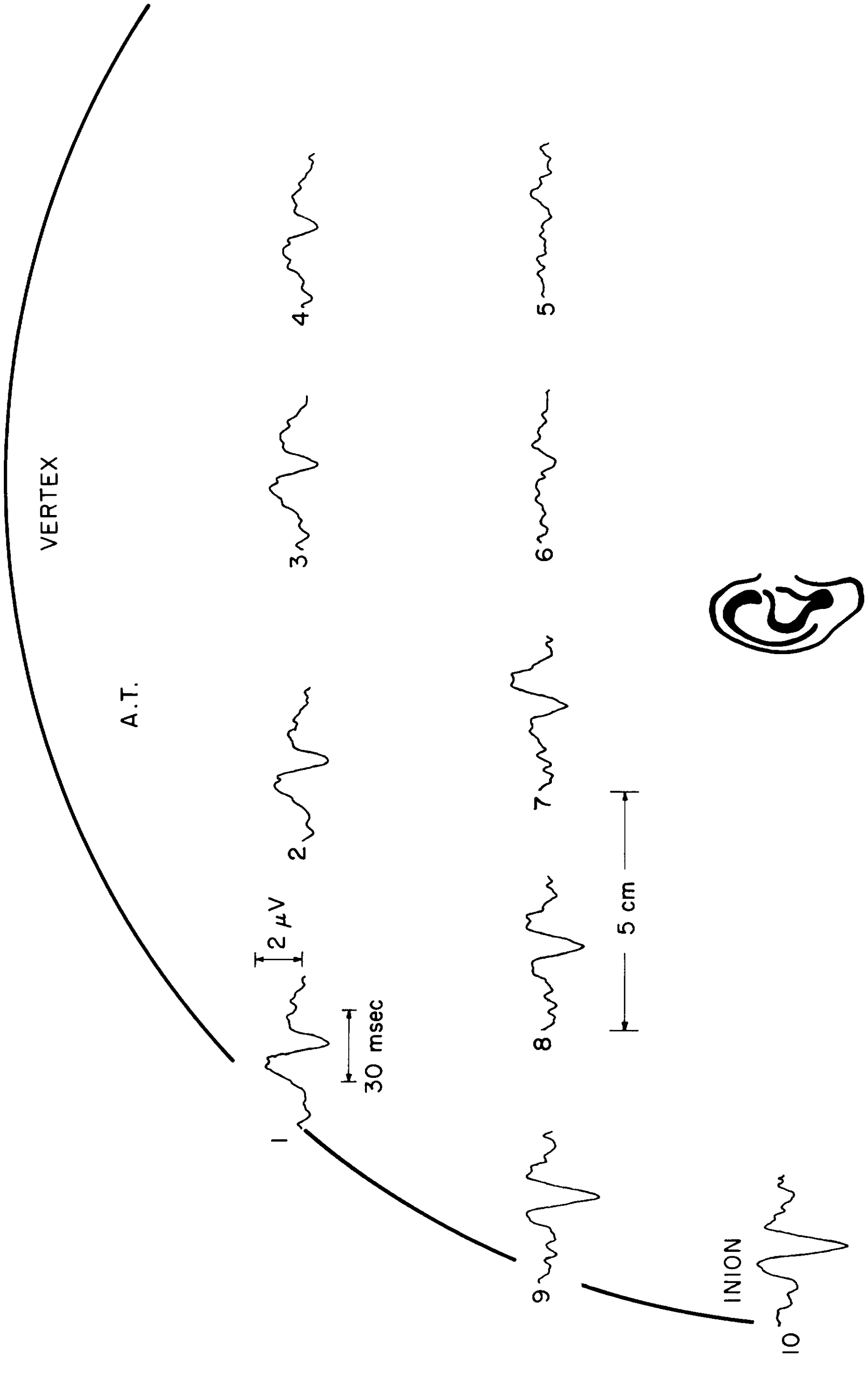
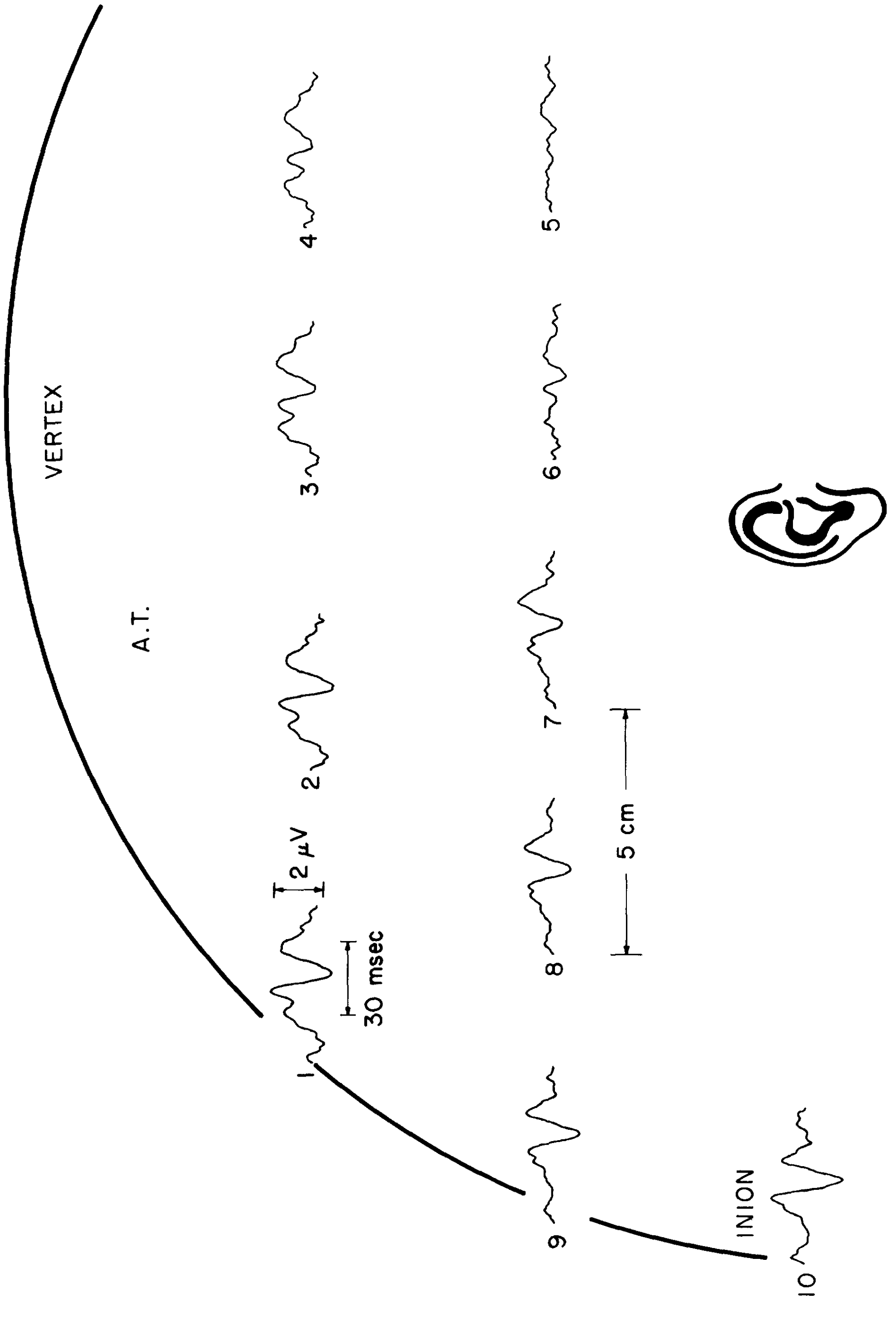

VERTEX
A.T.
2 μV
30 msec
5 cm
INION
1
2
3
4
5
6
7
8
9
10

Fig. 21d. Average responses to contralateral clicks recorded from various scalp electrodes (Subject, A. T., H-598). Stimulus conditions: clicks, left ear, −45 db, 15/sec. Response conditions: reference electrode, nose; number of responses, 4000.

The electrodes in this experiment were placed according to the description given for Fig. 21a, except that the temporal markers, although they were 5 cm apart, were located 6 cm and 11 cm medially to the preauricular cavity. [The electrode locations in this figure are numbered and will serve as the standard locations for this study. In practice, electrodes were placed within 1 cm of these numbered positions. By way of comparison with the 10-20 electrode position system of the International Federation (62), our location 1 is slightly posterior to 10-20 position Po; our location 3 corresponds closely to C4; our location 6 is a few centimeters medial from T4; and our locations 7 and 8 are in the vicinity of T6 and O2, respectively.]


VERTEX
A.T.
2 μV
30 msec
5 cm
INION
1
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9
10

Fig. 21e. Average responses to ipsilateral clicks recorded from various scalp electrodes (Subject, A. T., H-598). Stimulus conditions: identical to those of Fig. 21d, except for right ear. Response conditions: identical to those of Fig. 21d. Corresponding responses shown in Fig. 21d and 21e were recorded from the same electrodes. Responses to two trains of 2000 clicks each were averaged for each trace shown. The presentation of the click trains to left and right ears was varied quasirandomly to minimize the effect of any systematic changes in "state."

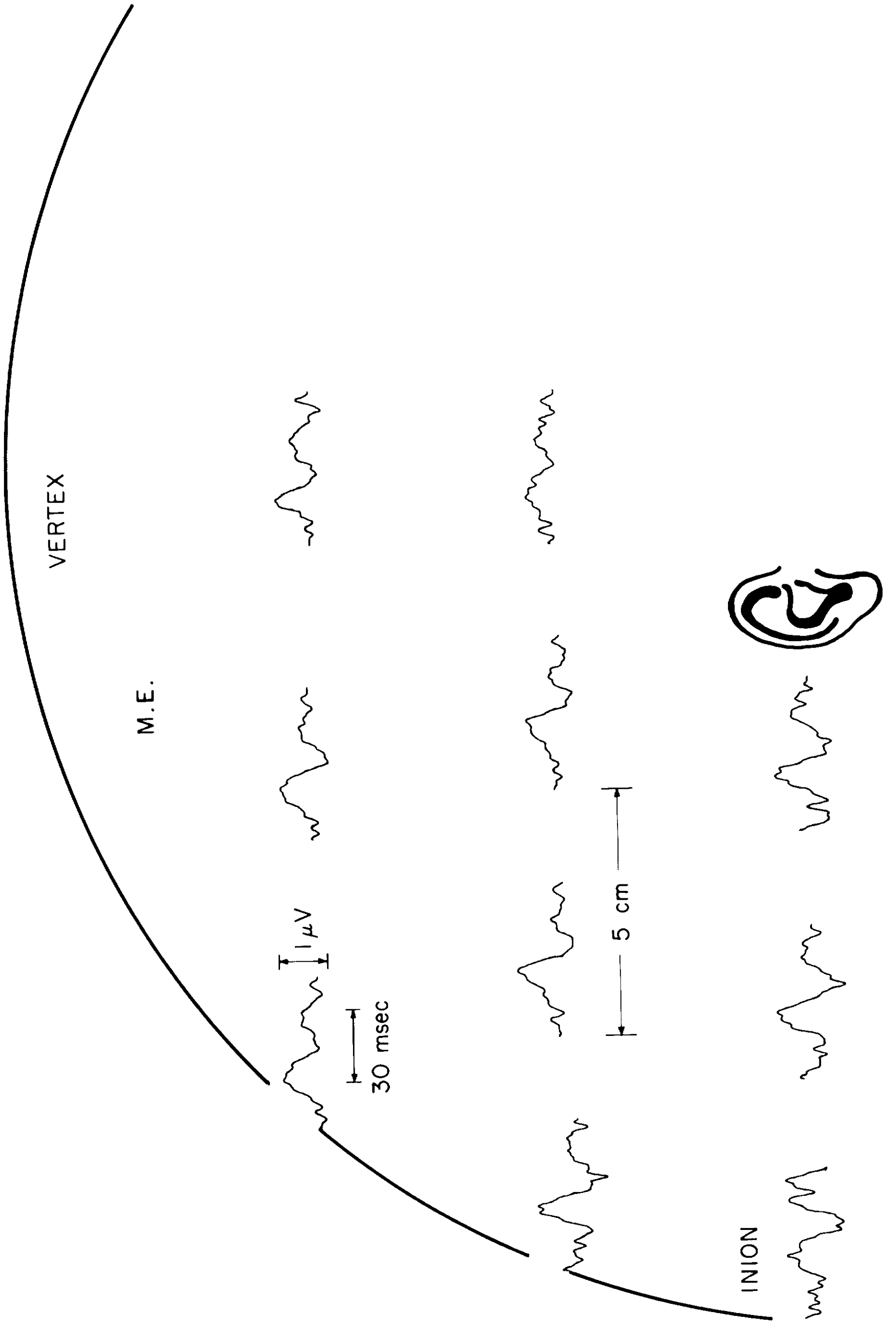

VERTEX
M.E.
1 μV
30 msec
5 cm
INION

Fig. 21f. Average click responses recorded from various scalp electrodes (Subject, M. E., H-531). Stimulus conditions: clicks, left ear, -45 db, 15/sec. Response conditions: reference electrode, nose; number of responses, 2000.

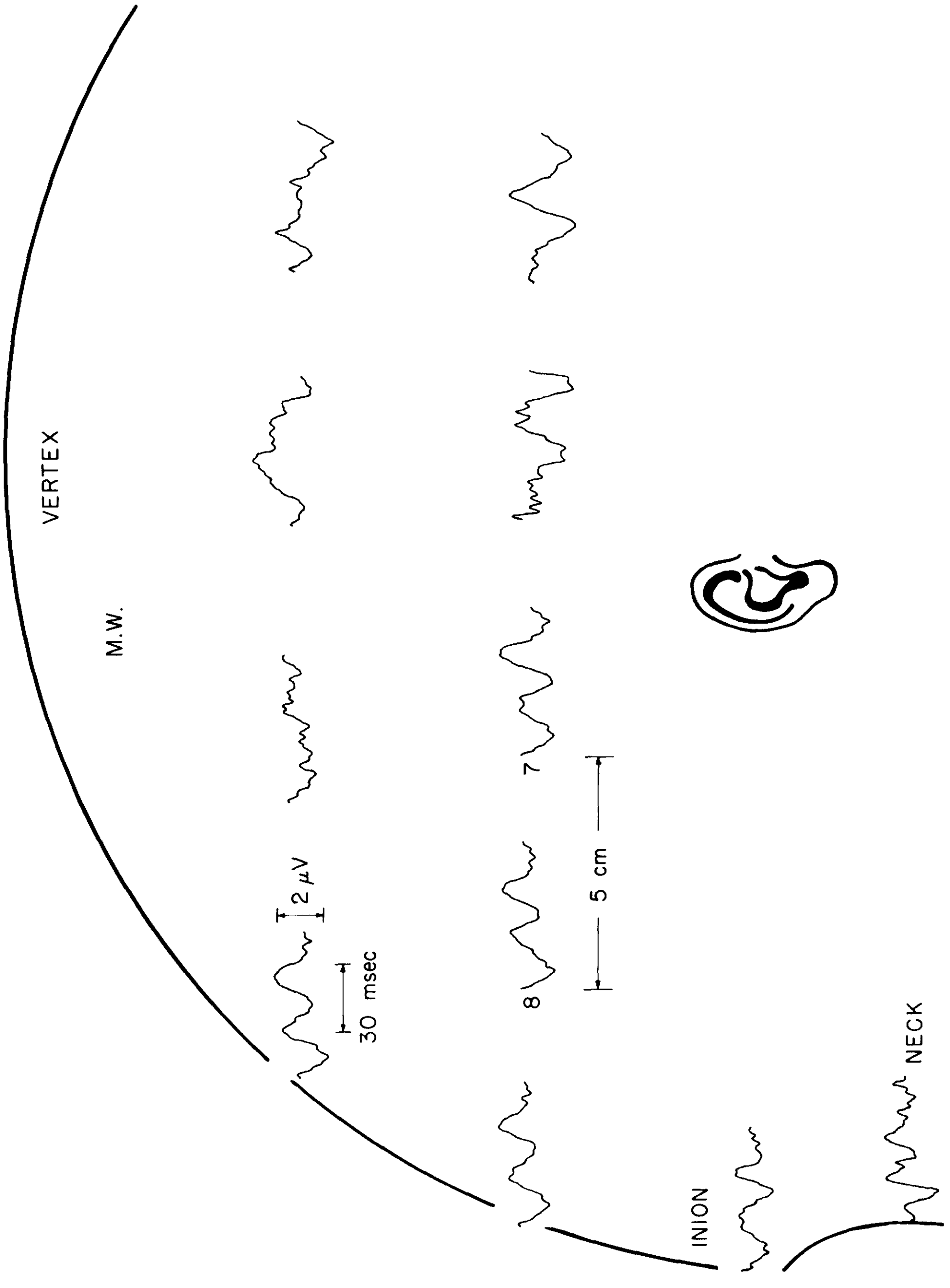

VERTEX
M.W.
2 μV
30 msec
8
7
5 cm
INION
NECK

Fig. 21h. Average responses to ipsilateral clicks recorded from various scalp electrodes (Subject, M. W., H-596). Stimulus conditions: identical to those for Fig. 21g, except to right ear. Response conditions: identical to those for Fig. 21g. In experiment H-596, the presentation of click trains (2000 clicks each) to left and right ears was varied quasi-randomly to minimize the effect of any systematic changes in "state."

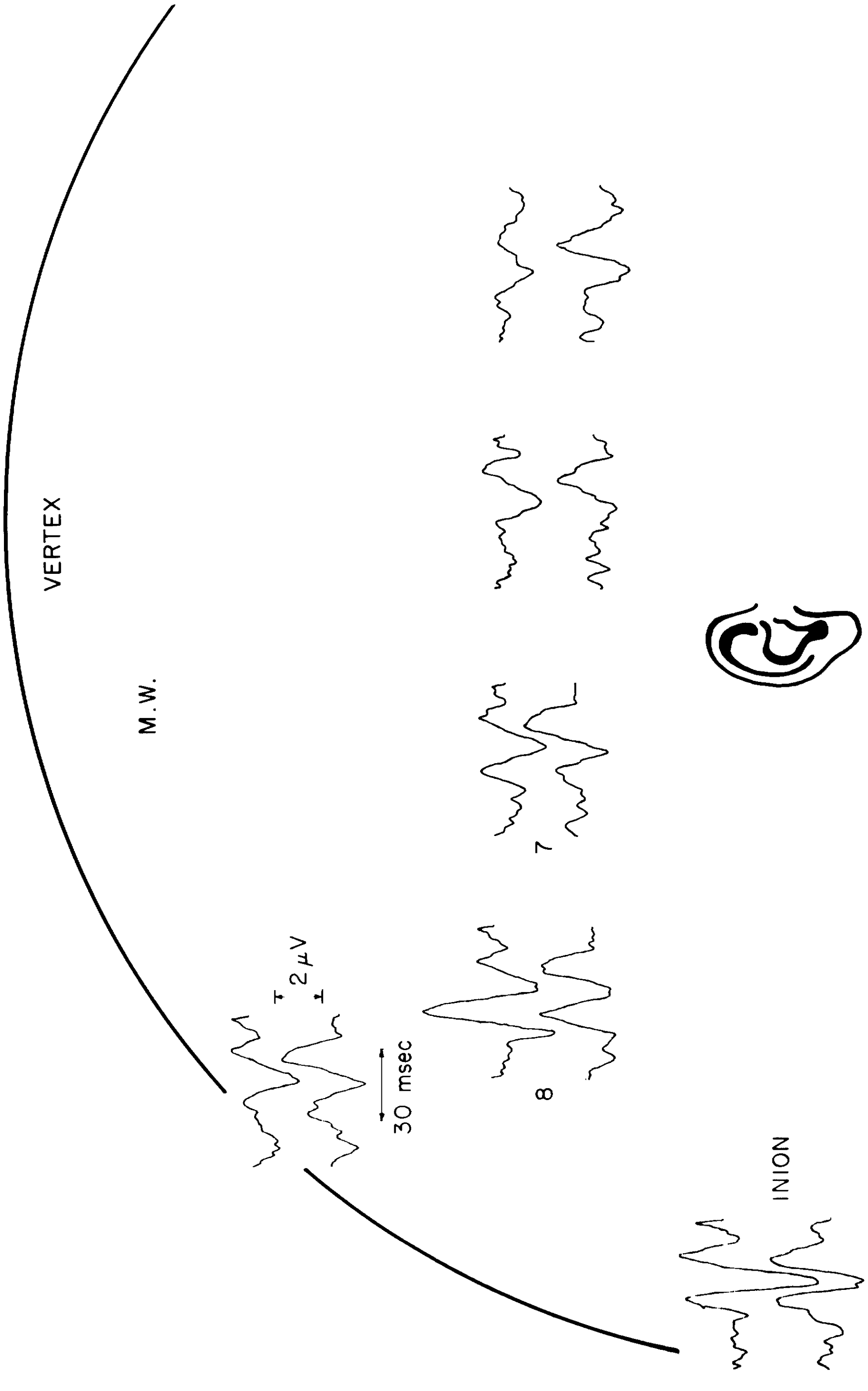

VERTEX
M.W.
2 μV
30 msec
7
8
INION

Fig. 21i. Average responses to both contralateral and ipsilateral clicks recorded from various scalp electrodes (Subject, M. W., H-600). Stimulus conditions: clicks, -45 db, 5/sec. Response conditions: each pair of responses was recorded from one electrode; the upper response was evoked by contralateral stimuli, and the lower trace by ipsilateral; reference electrode, nose; number of responses, 4000.

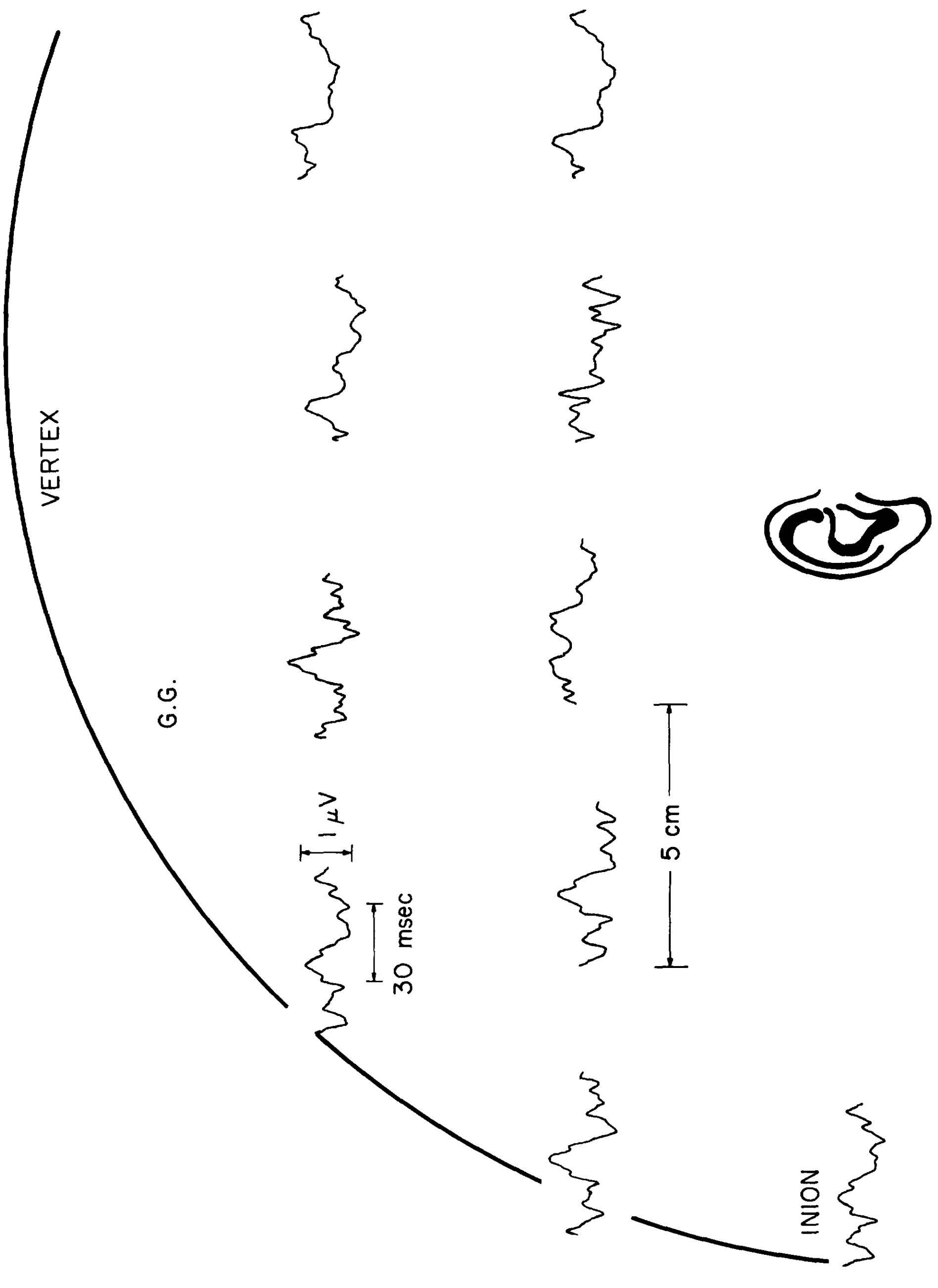

VERTEX
G.G.
1 μV
30 msec
5 cm
INION

Fig. 21j. Average responses to contralateral clicks recorded from various scalp electrodes (Subject, G. G., H-612). Stimulus conditions: clicks, left ear (9C earphone), -45 db, 15/sec. Response conditions: reference electrode, nose; number of responses, 4000. No monitoring electrode or quasirandomized click trains were used in this experiment, but average responses to identical stimuli obtained at the beginning and end of the experiment were very similar.

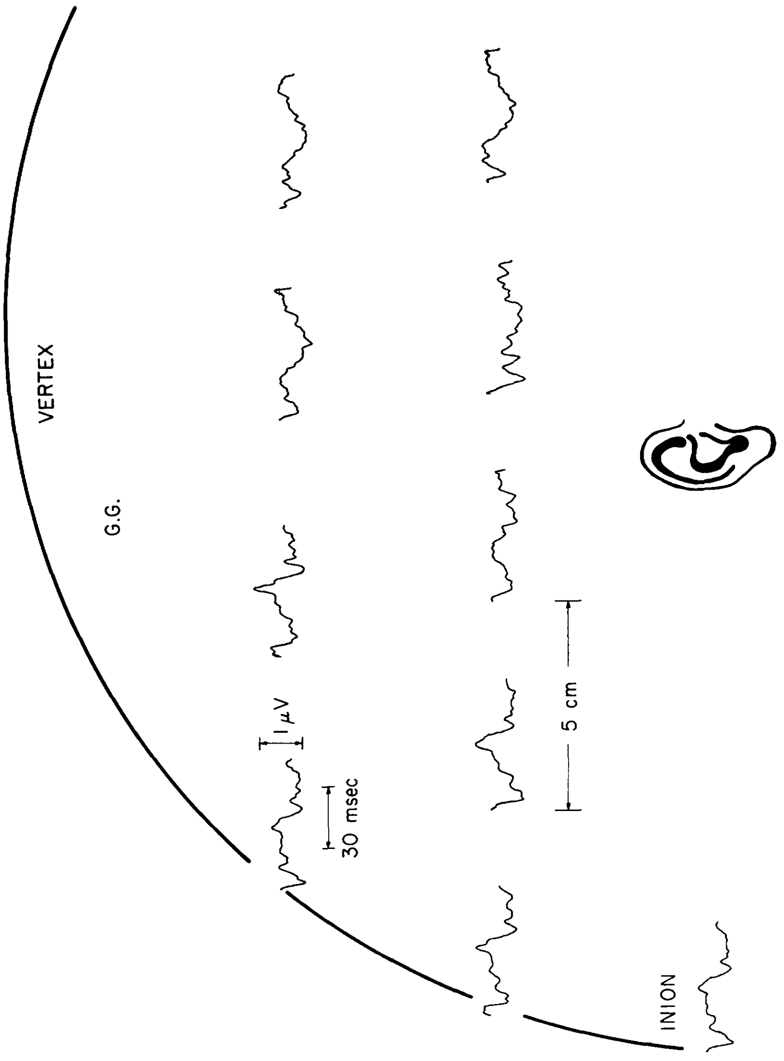

VERTEX
G.G.
1 μV
30 msec
5 cm
INION

Fig. 21k. Average responses to ipsilateral clicks recorded from various scalp electrodes (Subject, G. G., H-612). Stimulus conditions: identical to those for Fig. 21j, except to right ear. Response conditions: identical to those for Fig. 21j.

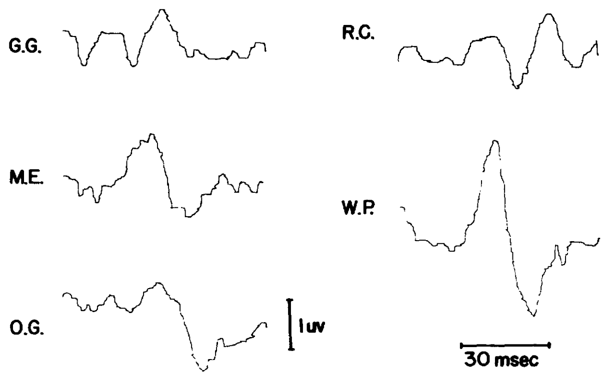


Fig. 22. Average responses to clicks obtained from 5 different subjects. Stimulus conditions: clicks, left ear, -45 db, 14/sec or 15/sec. Response conditions: active electrode, 8; reference electrode, either 6 (O.G., R.C., W.P.) or nose (M.E., G.G.). Number of responses: for M.E., 4000; for others, 8000 (H-517, -518, -519, -527, -531).

components of the responses are more clearly seen. A positive deflection of approximately 30-msec latency is seen at the frontal electrodes, with the ipsilateral response being the largest. The more posterior electrodes show a negative 30-msec deflection on both sides of the head, and electrodes 7 and 8 show the 20-msec peak evoked by contralateral stimulation.

The average responses of subject G.G. show a still different pattern. In Fig. 21j and 21k, the most obvious response component is the familiar 30-msec peak recorded by the posterior electrodes. In addition, an earlier response component, peak latency approximately 15 msec, is seen in all of the electrodes on the contralateral side. The earliest deflection evoked by contralateral stimuli has a peak latency of approximately 5 msec. Since, however, this peak has been found to exhibit quite different latencies in various experiments on this subject, it is interpreted as the onset of the 15-msec component rather than as a separate response component. The ipsilaterally observed deflections having approximately 5-msec latency, in contrast, seem to be genuine response components (see Fig. 58c).

By way of comparison between subjects, Fig. 22 shows average responses recorded from 5 different subjects. The waveforms and amplitudes are hardly identical, and yet each response, regardless of its other characteristics, has a negative peak at approximately 30 msec. This response component has been seen in all except two of the 27 subjects whom we have investigated thoroughly. The two exceptions occurred in the early stages of this study, and might yield responses if examined carefully with the improved techniques that have evolved.

4.2 CHANGES IN THE AVERAGE RESPONSES CAUSED BY VARIATION OF STIMULUS PARAMETERS

After preliminary tests, six of the subjects were selected for further investigation. The selection was made on the multiple grounds of a subject's availability, the large size or unique nature of his responses, and his ability to sit quietly and peacefully for an hour or so. Four of the subjects exhibited the ordinary 30-msec components. Subjects M.W. and G.G. were included in the experimental population because of the unusual deflections consistently seen in their responses.

a. Average Responses as a Function of Click Intensity

Preliminary experiments indicated that average responses obtained from our subjects varied with the intensity of the click stimuli presented to them. Clicks of high-intensity levels were found to evoke larger average responses than clicks of lower intensities. Furthermore, the lowest click intensities for which responses were detectable were near psychophysical threshold. On the basis of these rather qualitative observations, a systematic investigation of the effects of click intensity level upon the average evoked responses was undertaken.

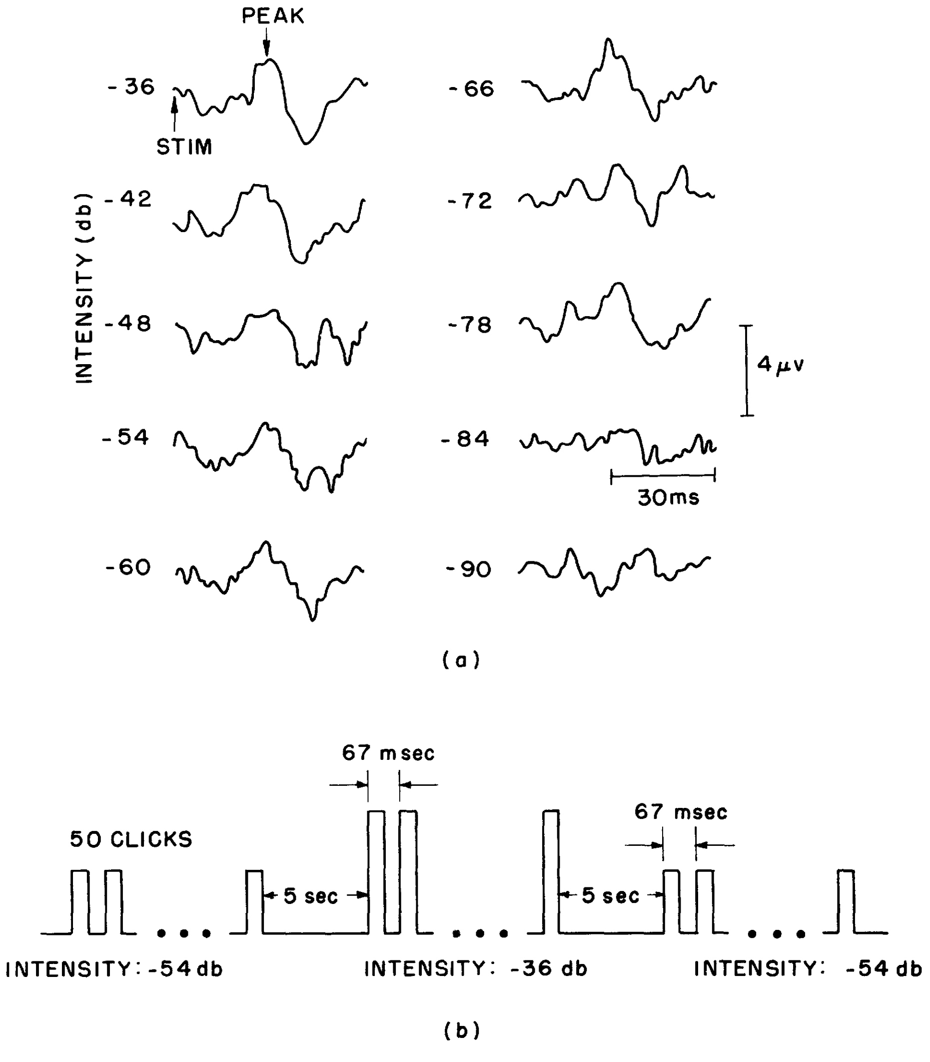


Fig. 23. (a) Average responses to clicks of various intensities (Subject, W. P., H-565). Stimulus conditions: clicks, left ear, randomized stimulus pattern (see (b)). Response conditions: active electrode 9; reference electrode, 6. Number of responses, 1000 for each intensity. (b) Schematic diagram of the stimulus pattern for presenting clicks of various intensities. Trains of clicks, each train containing 50 clicks of the same intensity, were presented to the subject. Ten different intensity levels were used; the order of their presentation was randomized. Click rate, 15/sec.

Since we must compute average responses, many identical stimuli must be presented to a subject in order to obtain the number of responses desired for averaging. Simply presenting long trains of identical clicks to the subject is risky, however, for perhaps his "state" may change during an experiment, and cause average responses to identical stimuli presented during different parts of the experiment to be quite different. And if identical stimuli may thus evoke different average responses, it would be questionable to compare average responses evoked by different stimuli. In order, therefore, to compensate for possible changes in the state of a subject over the course of an experiment, the presentation of click stimuli in these experiments was ordered in the following way.

Trains to clicks were presented to the subject's left ear, but each train was restricted to 50 clicks, all of the same intensity. The intensity of any particular train was selected randomly from 10 possible stimulus levels under the two constraints that in one complete series of trains, each intensity be presented 10 times and that every possible transition between neighboring intensity levels should occur once and only once. Clicks within each train were presented at the rate of 15 per second, and a time interval of approximately 5 seconds separated the trains from one another. (See Fig. 23b.) Two different series of trains were usually given to the subject so that a total of 200 different trains were presented during an experiment. One thousand individual click stimuli at each of the 10 intensities, therefore, were usually presented to a subject in the course of an experiment. (Occasional errors in the stimulus-generating equipment meant that a few stimuli more or less than 1000 were sometimes presented.) The average responses evoked by the 1000 clicks of each intensity level were then computed. (The computation of these averages was performed on the TX-0 computer.) Several repetitions of the experiments were performed on each of our subjects in order to demonstrate the variableness of the average responses obtainable from individual subjects. In each of the experiments on the same subject, a different random ordering of the click intensities was usually used.

Figure 23a shows the average responses to different intensity clicks recorded

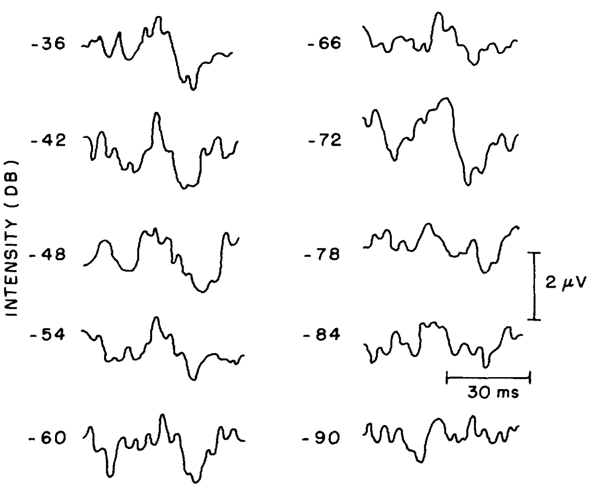


Fig. 24. Average responses to clicks of various intensities (Subject, W.P., H-577). Stimulus conditions same as in Fig. 23a. Response conditions: active electrode, 8; reference electrode, 6. Number of responses, 1000 for each intensity.

from subject W. P. For the louder clicks, clear response components are seen. The peak at 30 msec that is evoked by −36 db clicks is indicated by an arrow. Even the softest clicks are seen to evoke an average response, but of much less amplitude and slightly longer latency.

Figure 24 shows the averages of responses obtained from subject W. P. during another experiment. The responses here are considerably lower in amplitude than those in Fig. 23, but behave in the same general manner; as the stimulus intensity is decreased, the amplitude tends to decrease also. The average responses presented in Figs. 23 and 24 were purposely chosen as examples of the extreme variations in the average responses that can be evoked from the same subject by the same stimuli.

In order to quantify the data, the peak-to-peak amplitude of the average responses was chosen as a measure of the responses. To measure the amplitude of the first negative peak above the base line proved difficult, for the onset of the response, and hence the value of the base line at that instant, was by no means always clear. In one experiment (H-566), however, especially well-defined responses were obtained, and the amplitude

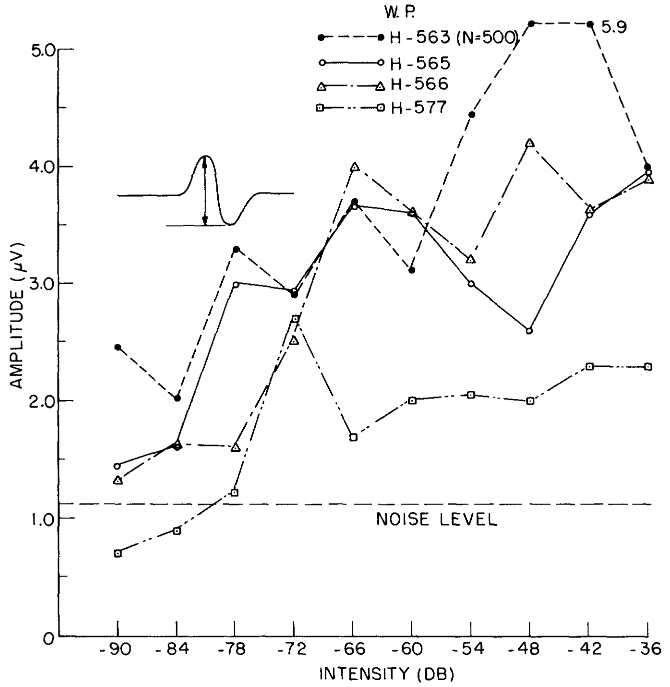


Fig. 25. Amplitude of average responses as a function of click intensity (Subject, W. P.). Each point represents the peak-to-peak amplitude of an average response; lines join data points from the same experiment. Stimulus conditions same as in Fig. 23a in all experiments. Response conditions: active electrode, either 9 (H-563, -565) or 8 (H-566, -577); reference electrode, 6. Each measured average response was computed from 1000 responses (only 500 in H-563). Subject's psychophysical threshold was −88 db. The "noise level" shown is a measure of the effect of the spontaneous activity. It is the approximate amplitude of "spurious" deflections (that is, deflections not consistently seen in the average responses) such as the peak at 5 msec in the average response to −48 db clicks in Fig. 23a.

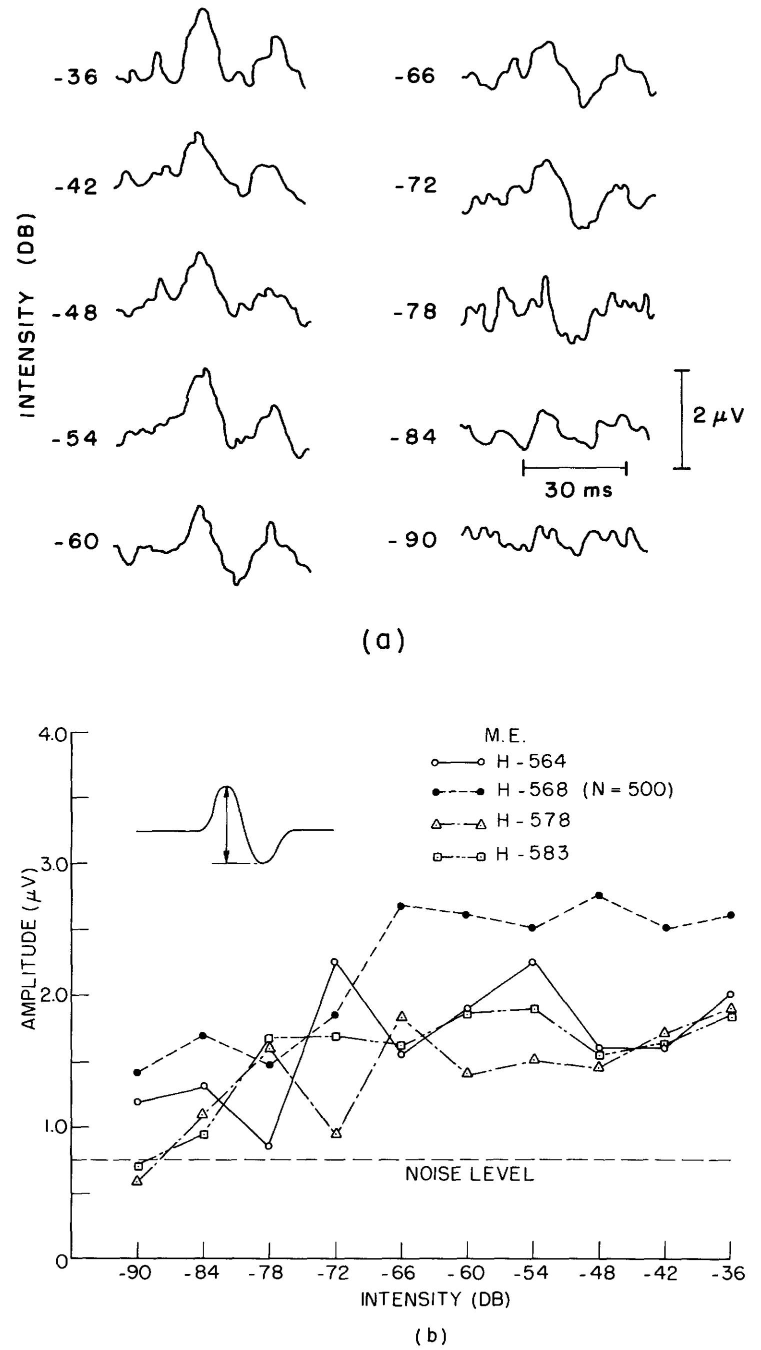


Fig. 26. (a) Average responses to clicks of various intensities (Subject, M.E., H-583). Stimulus conditions same as Fig. 23a. Response conditions: active electrode, 8; reference electrode, 6. Number of responses, 1000 for each intensity.

(b) Amplitude of average responses as a function of click intensity (Subject, M.E.). Each point represents the amplitude of an average response. Stimulus conditions same as in Fig. 23a for all experiments. Response conditions: active electrode, either 9 (H-564) or 8 (H-568, -578, -583); reference electrode, 6. Each measured average response was computed from 1000 responses (500 only in H-568). Subject's psychophysical threshold was -92 db.

from the base line to the 30-msec peak, as well as the peak-to-peak amplitude, was measured for the various responses. The respective amplitude measures were then plotted as function of intensity and, aside from an obvious disparity in absolute size, the curves did not seem to differ appreciably in shape.

Figure 25 shows these peak-to-peak measurements for four separate experiments on subject W. P. run on four different days. The subject's psychophysical threshold for clicks lies at approximately -88 db and is a significant landmark. For, up to approximately 30 db above psychophysical threshold, the average of the responses grows with increasing stimulus intensity, while for still more intense stimuli the response amplitudes show little change. These particular experiments were conducted during the course of 5 months and give an indication of the variability of average click responses evoked from human subjects.

The average responses of subject M. E. to different intensity clicks are shown in Fig. 26a. Peak-to-peak amplitude measurements of these responses, as well as of those recorded during three similar experiments, are shown in Fig. 26b. Here, again, little difference in response amplitude is seen for clicks that are more than 30 db above threshold.

Subject A. T.'s average responses to clicks of various intensities are shown in Fig. 27. Note the slight increase in latency that is seen for the responses to faint clicks. Figure 28 shows the peak-to-peak amplitudes of average responses for four different experiments on this same subject.

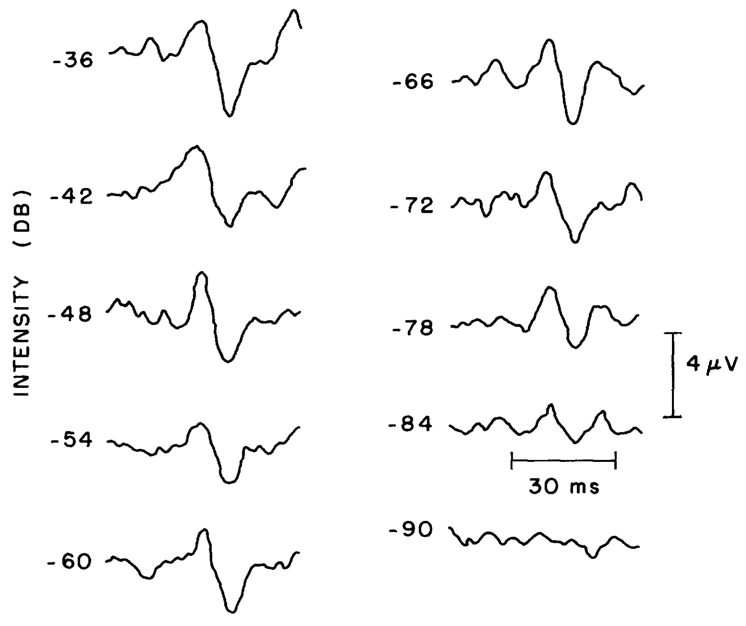


Fig. 27. Average responses to clicks of various intensities (Subject, A. T., H-585A). Stimulus conditions same as in Fig. 23a. Response conditions: active electrode, 8; reference electrode, 6. Number of responses, 1000 for each intensity.

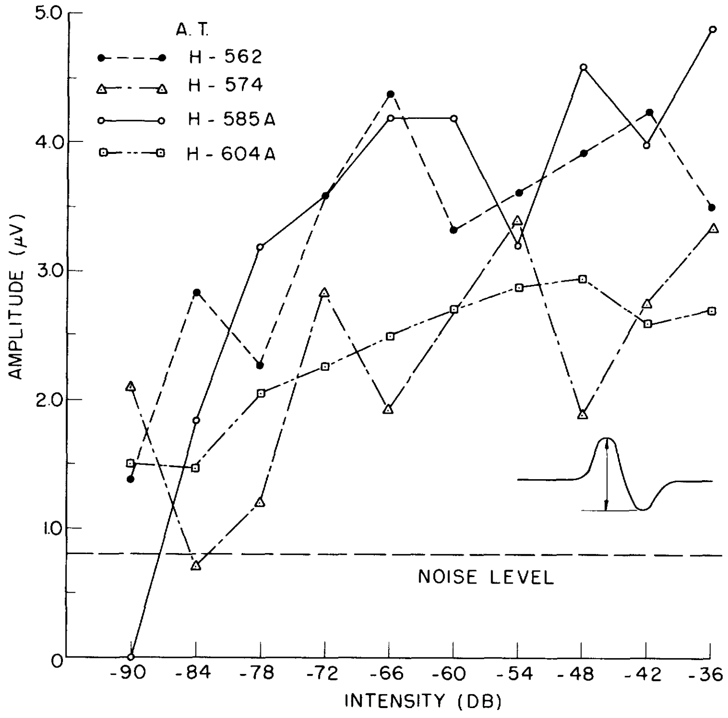


Fig. 28. Amplitude of average responses as a function of click intensity (Subject, A. T.). Each point represents the amplitude of an average response. Stimulus conditions same as in Fig. 23a for all experiments. Response conditions: active electrode, either 9 (H-562) or 8 (H-574, -585A, -604A); reference electrode, 6. Each measured average was computed from 1000 responses. Subject's psychophysical threshold was approximately −95 db.

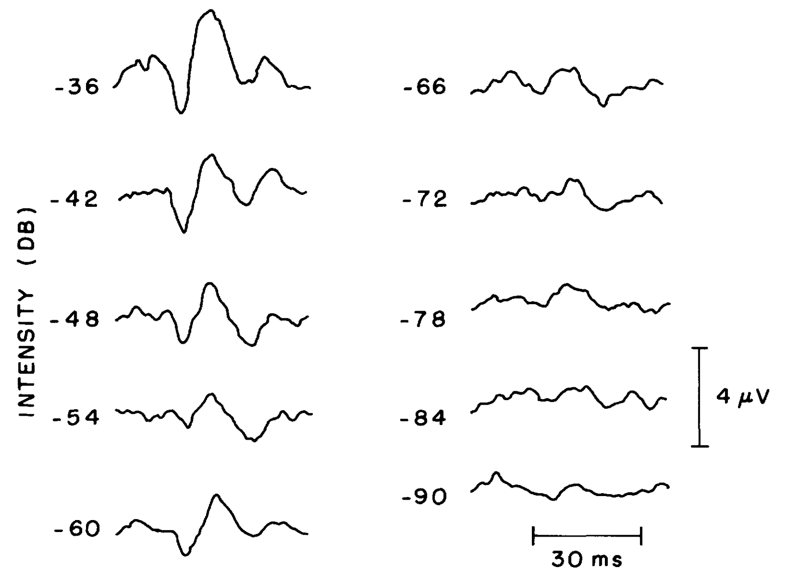


Fig. 29. Average responses to clicks of various intensities (Subject, M.W., H-584A). Stimulus conditions same as in Fig. 23a. Response conditions: active electrode, 8; reference electrode, 6. Number of responses, 1000 for each intensity.

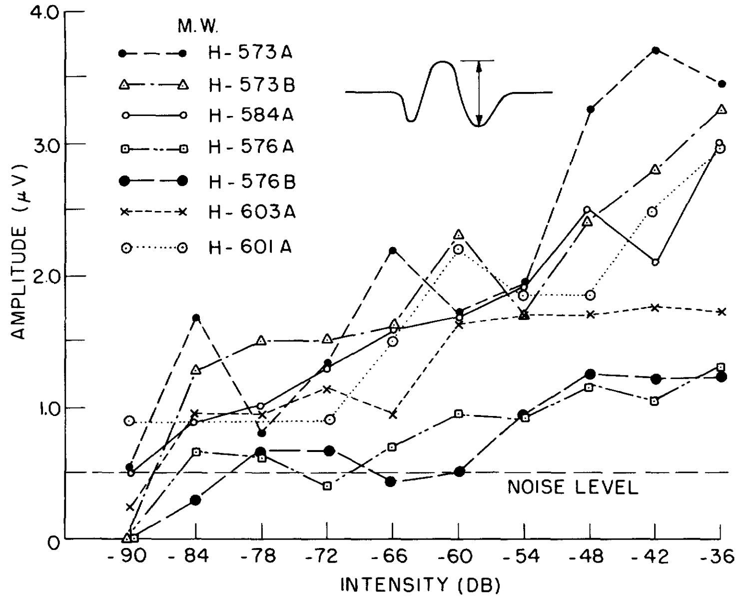


Fig. 30. Amplitude of average responses as a function of click intensity (Subject, M.W.). Each point represents the amplitude of an average response. Stimulus conditions same as in Fig. 23a for all experiments. Response conditions: active electrode, 8; reference electrode, 6. Each measured average was computed from 1000 responses. Subject's psychophysical threshold was approximately -99 db.

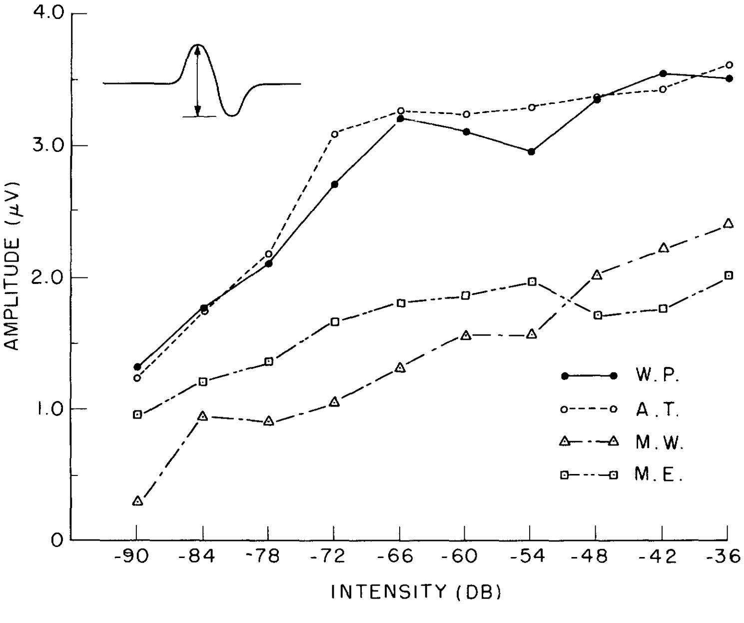


Fig. 31. Amplitude of average responses obtained from different subjects as a function of click intensity. Each point is the mean of the individual points shown at one intensity in the appropriate figure (Fig. 25, Fig. 26b, Fig. 28, or Fig. 30). The results of 7 experiments were, therefore, averaged for Subject M.W.; results of 4, for the others.

Average responses obtained from subject M. W. are shown in Fig. 29. The positive peak at 20 msec was not always well behaved, and proved to be more variable than the following negative component. The peak-to-peak amplitudes of these and similarly obtained responses are shown in Fig. 30.

The data obtained from each subject were compressed into a single curve: At each intensity, the amplitudes of the average responses obtained during the different experiments were averaged and plotted as a single value. The summary curve for each of the four subjects is plotted in Fig. 31. For three of the four curves, growth with intensity is limited approximately to the first 30 db above psychophysical threshold. Moreover, subject M. W.'s curve, which is the exceptional one, cannot be directly compared with the others, for the responses obtained from this subject contain components that are not present in the responses of the other subjects. We may suppose that the three similar curves, therefore, are typical descriptions of the way in which the amplitude of the 30-msec component varies with click intensity.

It is of interest to compare the characteristics of these average responses obtained from human subjects with those obtained from experimental animals. Figure 4 showed a typical intensity curve for responses obtained from the auditory projection areas of anesthetized cat cortex. This curve, it will be remembered, showed a rapid growth for the first 40 db above "threshold" and was very similar in shape to the curves in Fig. 31. Moreover, the increase in the peak latency of cortical responses evoked by faint clicks which was plotted in Fig. 4 is paralleled in some of our experiments by a slight increase in the peak latency of the average responses evoked by very faint clicks.

b. Average Responses as a Function of Repetition Rate

The rate at which clicks are presented to a subject has been found to have a marked effect upon the various components of the average evoked responses. The curves in Fig. 20, for example, showed that the K-components disappeared for click rates as low as 5 per second, although the 30-msec components were not greatly diminished, even at click rates of 10 per second.

In a series of experiments designed to show the effect of click rate upon the 30-msec components, long trains of clicks were presented to various subjects. The clicks in any one train were presented at the same rate; different trains contained clicks at different rates. Each train contained many clicks, and an average response was computed for each train of stimuli. The various trains, and hence the various click rates, were usually presented in a quasi-random order to minimize the effect of changes in "state." In all of these experiments, the stimulus intensity was held constant at –45 db.

The left column of Fig. 32 shows the average responses recorded from subject W. P. The 30-msec component evoked by 20/sec clicks is basically similar in shape to that of 5/sec clicks, although the amplitude is slightly less. The responses at the higher rates have a more complex waveform, for the responses evoked by successive clicks are beginning to affect one another.

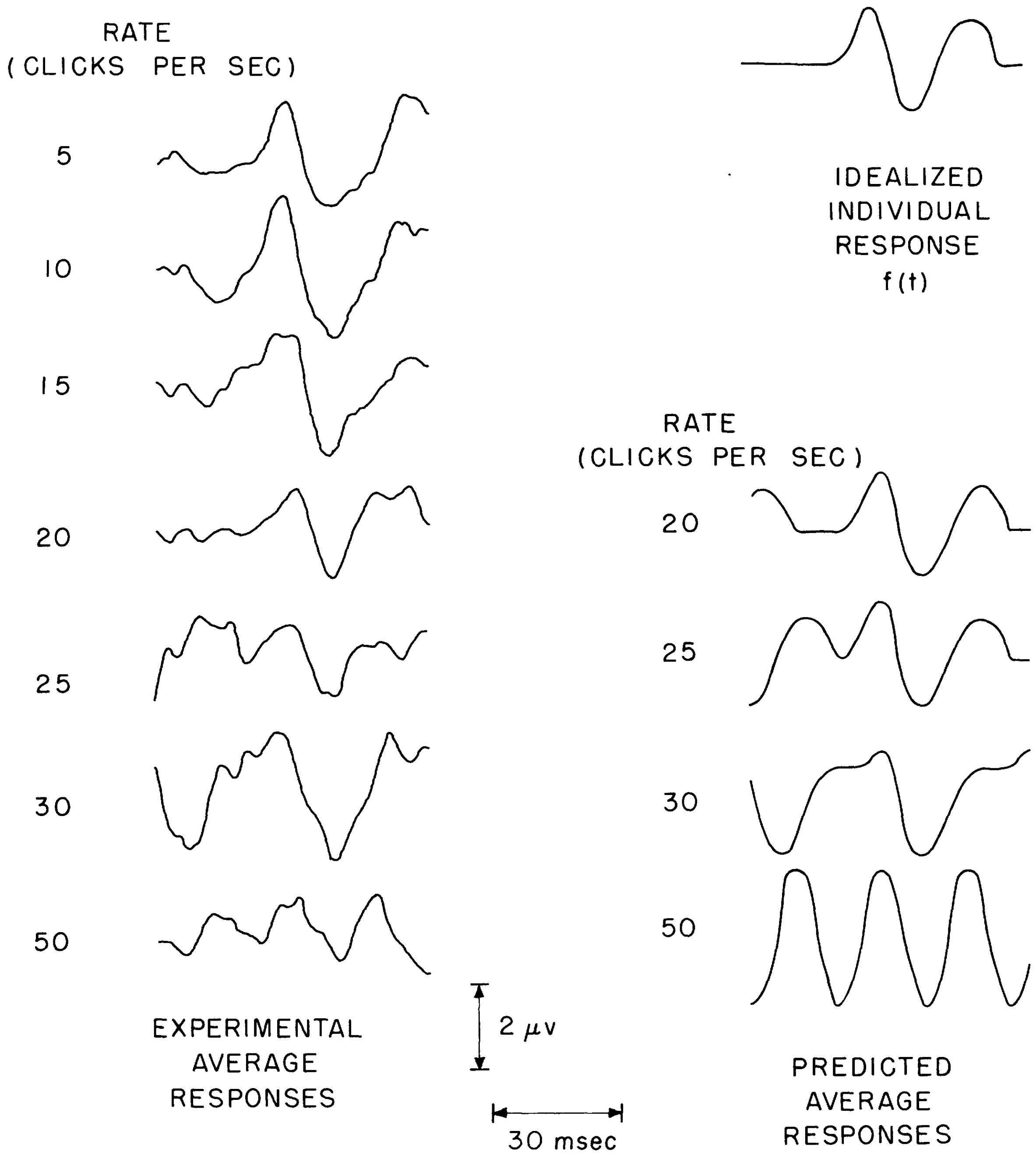


Fig. 32. Average responses to clicks presented at various rates (Subject, W. P., H-569). Left column: experimental average responses. Stimulus conditions: clicks, left ear, −45 db. Response conditions: active electrode, 8; reference electrode, 6. Number of responses, 1000 for all rates (500 only for 50/sec). Right column: the idealized individual response f(t) is a modified copy of the experimental average responses to clicks presented at low rates. Predicted average responses were constructed by the appropriate superposition of idealized individual responses, f(t).

Goldstein (61) has investigated the average responses evoked from cat cortex by clicks presented periodically at different rates. He, too, found that the average responses evoked by slowly repeated clicks were similar in shape to one another, but that more complex average waveforms were evoked by more rapidly repeated clicks. By appropriately superimposing the responses evoked by low rates of click stimulation, this experimenter was able to predict, with good accuracy, the complex wave shapes of the average responses evoked by higher rates of stimulation. The complex waveforms evoked from cat cortex by high-rate clicks, therefore, may be considered to be due to the simple overlapping of responses evoked by successive stimuli.

Let us apply this overlap model to the average responses obtained from human scalp. If we assume that responses to the successive identical stimuli of a train are identical, and that the waveform of the individual response f(t) evoked by any stimulus in a train does not change as the repetition rate of the train is changed, then the total response

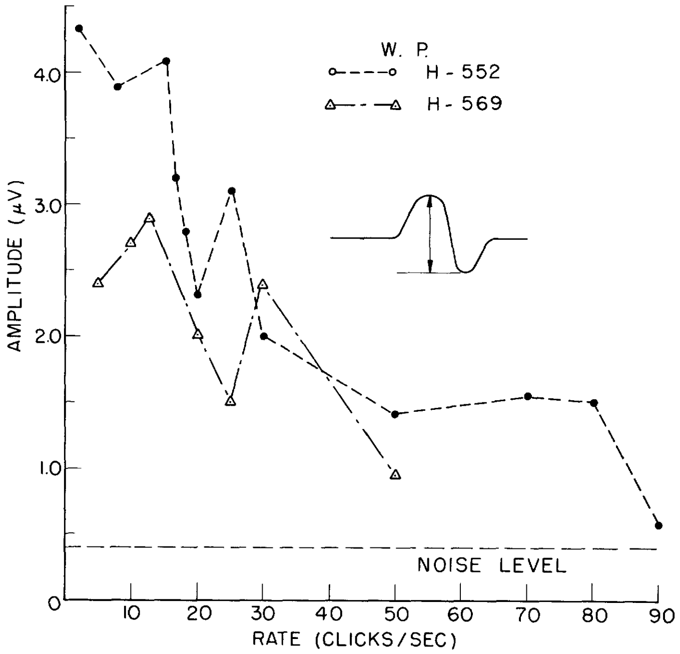


Fig. 33. Amplitude of average responses as a function of click rate (Subject, W. P.). Average responses were computed for the click trains of each experiment. Each point is the mean amplitude of all average responses obtained in the course of an experiment to clicks of the indicated rate (last train of H-552 excluded); lines join data points from the same experiment. For Figs. 33, 35, 37, and 39, the usual peak-to-peak amplitudes were measured when the average responses were clearly defined. Where overlapping occurred, the mean peak-to-peak amplitude of the periodic waveform was found. Stimulus conditions: clicks, left ear, −45 db. Response conditions: active electrode, 8; reference electrode, 6. Number of responses, 1000 for each measured average response (except N = 500 for 2/sec rate). The noise level is the approximate peak-to-peak amplitude of averages obtained (N = 1000) when clicks were withheld from the subject (H-552).

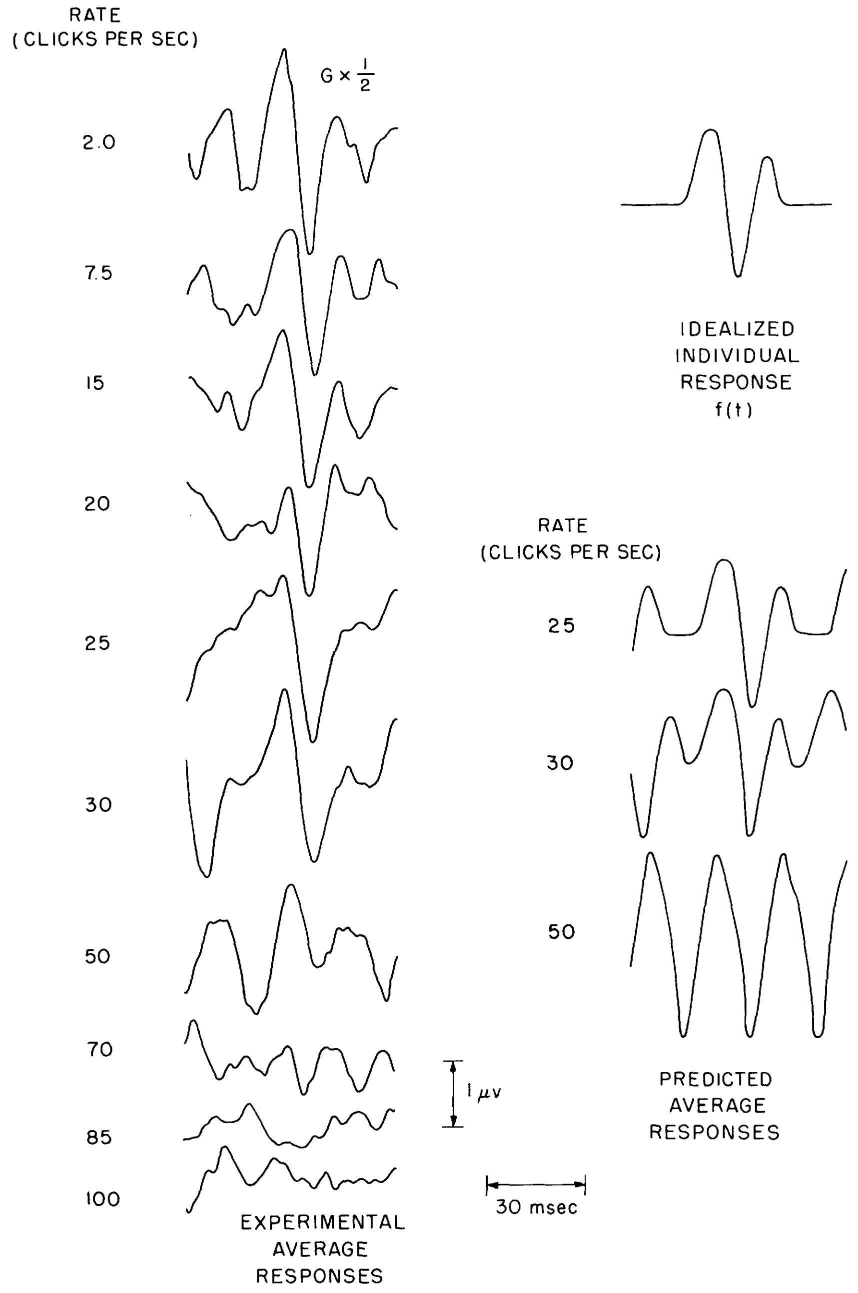


Fig. 34. Average response to clicks presented at various rates (Subject, A. T., H-572). Left column: experimental average responses. Stimulus conditions: clicks, left ear, -45 db. Response conditions: active electrode, 8; reference electrode, 6. Number of responses, 2000 for all rates (500 only for 2/sec, 1000 for 7.5/sec). Right column: idealized individual response f(t) is a copy of the experimental average responses to clicks presented at low rates. Predicted average responses were constructed by the appropriate superposition of idealized individual responses, f(t).

waveform R(t), for an infinite train of clicks is

$$R(t) = \sum_{k=-\infty}^{\infty} f(t-kT); \quad k = 0, \pm 1, \pm 2, \ldots \tag{19}$$

where T is the period of click presentation. If this period is less than the time duration of the significant components of f(t), then overlapping of successive responses will occur. The average response $\overline{f(t)}$ will be identical to one (or several) period(s) of the periodic response waveform R(t).

The wave shapes shown in the right column of Fig. 32 were constructed with the use of this model. An idealized individual response f(t) was first constructed from the average responses to low-rate clicks. Then the average responses predicted by the model were constructed by superimposing individual responses, f(t), having the indicated time relationships. The corresponding waveforms in the two columns are quite similar, although the amplitude of the predicted response for 50/sec clicks is considerably larger than the corresponding experimental response. The good agreement between the predicted and experimental waveforms indicates that the overlap model can be used to

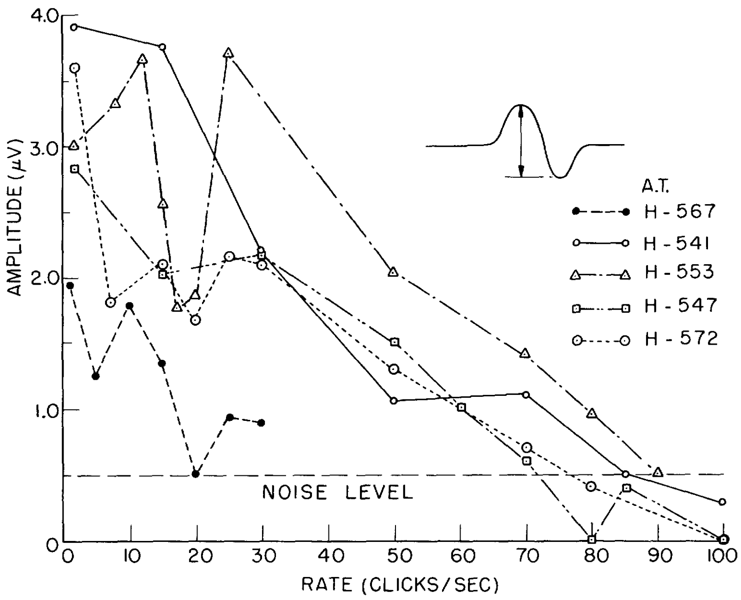


Fig. 35. Amplitude of average responses as a function of click rate (Subject, A.T.). Average responses were computed for the click trains of each experiment. Each point is the mean amplitude of all average responses obtained in the course of an experiment to clicks of the indicated rate. Stimulus conditions: clicks, left ear, −45 db. Response conditions: active electrode, 9 (H-541, -547) or 8 (H-553, -567, -572); reference electrode, 6. Number of responses, 1000 for each average response measured in H-567 and H-553; 2000 in H-541, H-547, H-572 (except N = 500 or N = 1000 at very low click rates). The "noise level" is the approximate peak-to-peak amplitude of averages (N=2000) of spontaneous activity obtained when clicks were withheld from the subject (H-541, -547).

explain the wave shapes of average responses evoked from this subject by high-rate stimuli.

Amplitudes were also measured in this experiment. Figure 33 shows how these amplitudes vary with click rate during two separate experiments on subject W. P. As the rate increases, the amplitude of the average responses decreases.

The left column of Fig. 34 shows responses obtained from another subject, A. T. Periodic activity that is time-locked to the stimuli is even detectable at the rate of 70 per second. The right column shows response waveforms predicted by the overlap model. The predicted waveforms for click rates higher than 50 per second were not computed but they would be essentially sinusoids with the same periodicity as the clicks. Here, again, there is good agreement between the curves in both columns. Figure 35 shows amplitude measurements made on responses obtained during several experiments on this same subject. It must be noted that the dip in the curves at 20 per second cannot be explained in terms of the overlap model.

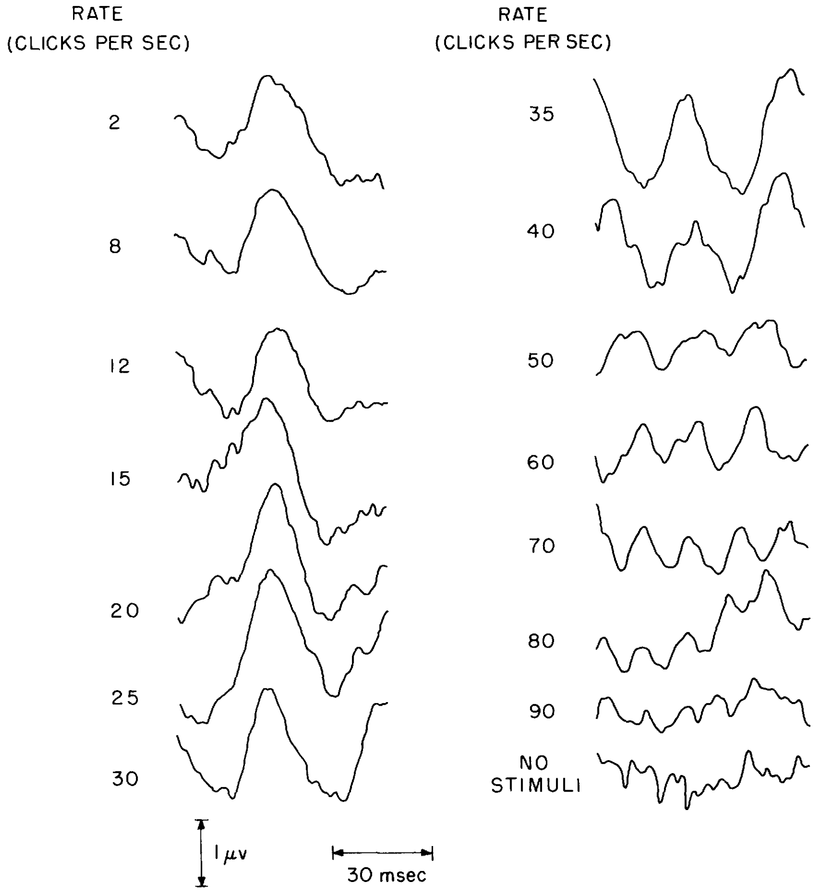


Fig. 36. Average responses to clicks presented at various rates (Subject, O. G., H-556). Stimulus conditions: clicks, left ear, −45 db. Response conditions: active electrode, 8; reference electrode, 6. Number of responses, 1000 for all rates (except N = 500 at 2/sec). Time markers at 90/sec were used to compute average labeled "no stimuli" from spontaneous activity.

Figure 36 shows that average responses are still detectable at rates of 80 per second or 90 per second for a third subject, O. G. It would be well to stress here the word "average." Note, for instance, the average response evoked by 40/sec clicks, which contains a small deflection flanked by two larger ones. This type of average response, which is occasionally seen, can perhaps be explained by a "skipping" behavior, whereby a response is evoked by approximately every other click (23). The average response of such a train of responses, then, would look like no particular individual response, for the individual responses would not be identical. Figure 37 shows a quantitative summary of this subject's responses.

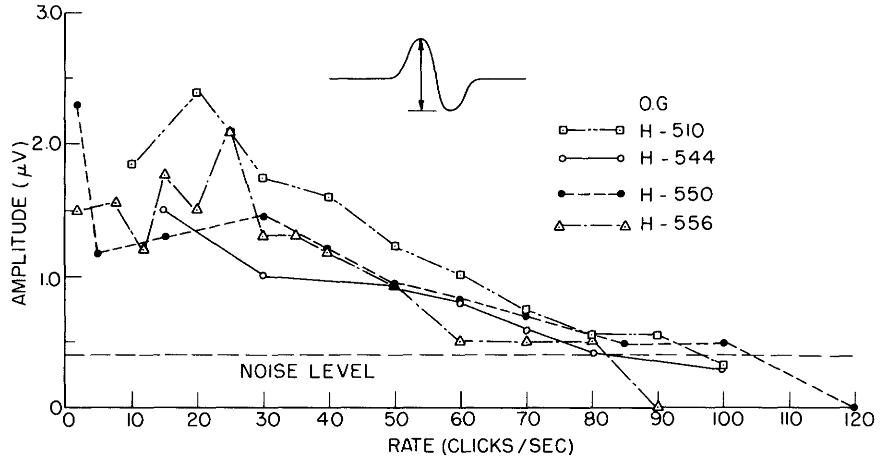


Fig. 37. Amplitude of average responses as a function of click rate (Subject, O. G.). Average responses were computed for each click train of each experiment. Each point is the mean amplitude of essentially all average responses obtained over the course of an experiment to clicks of the indicated rate. Stimulus conditions: clicks, left ear, –45 db. Response conditions: active electrode, either 9 (H-544) or 8 (H-510, -550, -556); reference electrode, 6 (except in H-510, between 6 and 3). Number of responses, at least 1000 for each average response measured (except N = 500 at low click rates). The "noise level" is the approximate peak-to-peak amplitude of averages (N=1000) obtained when clicks were withheld from the subject (H-550, -556).

The overlap model seems to apply particularly well to the average responses obtained from another subject, M. W. Figure 38 shows the experimental and predicted responses of this subject, and the similarity between the curves in the two columns is striking. Figure 39 shows the usual quantitative measurements. The increase of response amplitude in the 30-50/sec range is probably caused by the overlap of various response components, as predicted in the responses in the right column of Fig. 38. In conjunction with Fig. 39, it is interesting to note that experiment H-571 was the first experiment performed on subject M. W. Notice that the curve for H-571 compares quite closely with that for H-579, which was the fourth experiment performed on this subject. The novelty of the experimental environment to this subject during the first experiment,

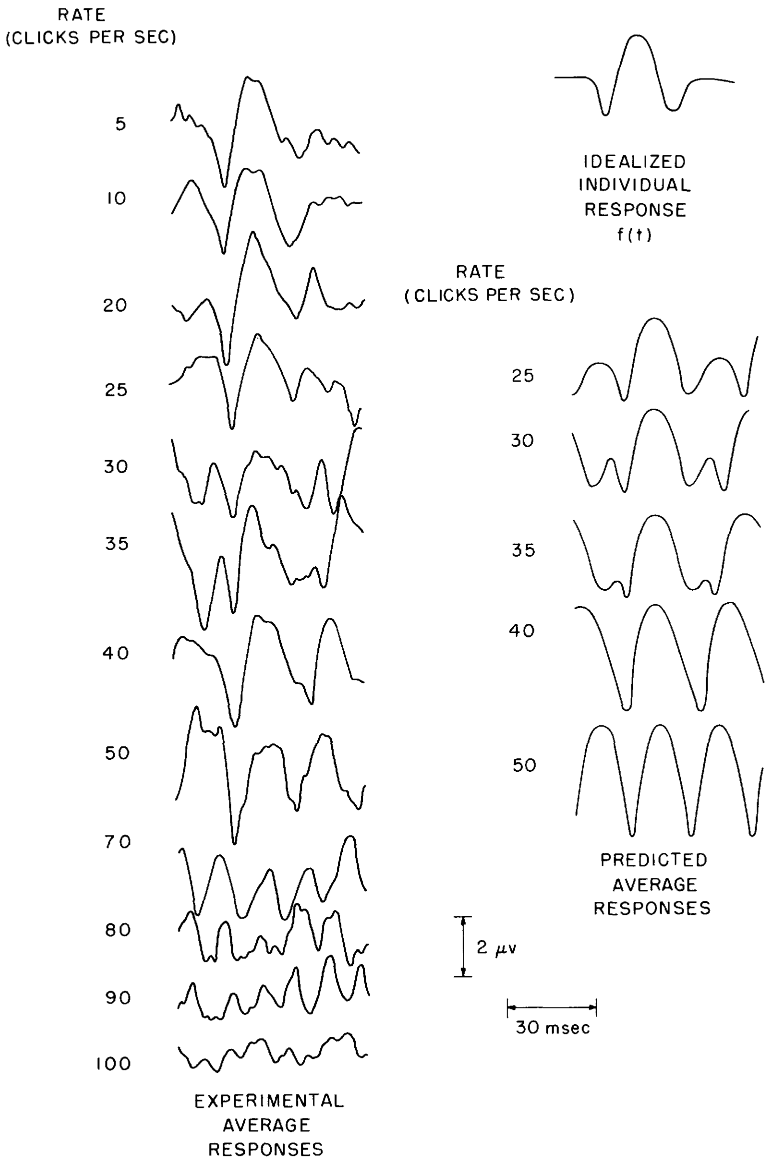


Fig. 38. Average responses to clicks presented at different rates (Subject, M. W., H-571). Left column: experimental average responses. Stimulus conditions: clicks, left ear, -45 db. Response conditions: active electrode, 8; reference electrode, 6. Number of responses, 1000 for all rates (except N = 500 at 35/sec, and N = 2000 at 100/sec). Right column: idealized individual response f(t) is a copy of the experimental average responses to clicks presented at low rates. Predicted average responses were constructed by the appropriate superposition of idealized individual responses, f(t).

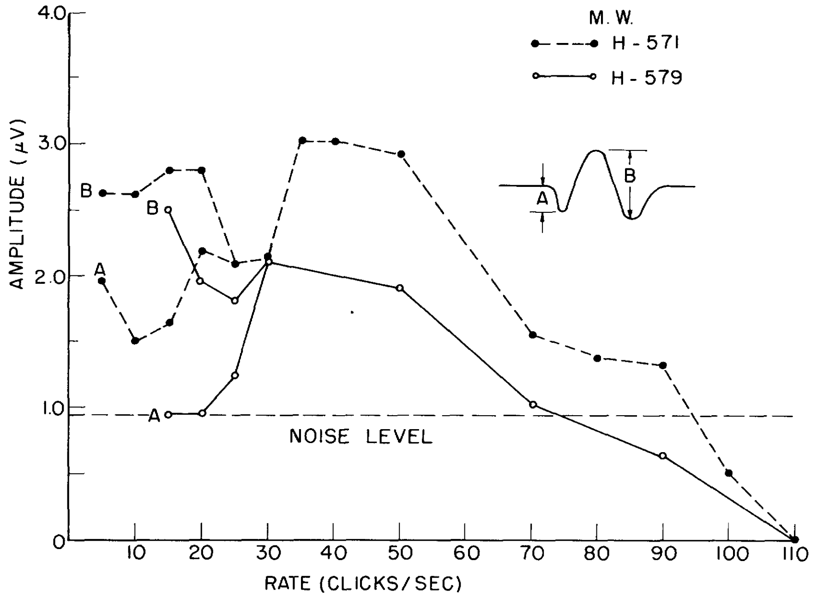


Fig. 39. Amplitude of average responses as a function of click rate (Subject, M. W.). Average responses were computed for the click trains of each experiment. Each point is the mean amplitude of all average responses obtained over the course of an experiment to clicks of the indicated rate. Stimulus conditions: clicks, left ear, -45 db. Response conditions: active electrode, 8; reference electrode, 6. Number of responses, at least 1000 for all average responses measured. The "noise level" is the approximate peak-to-peak amplitude of averages (N=1000) obtained when clicks were withheld from the subject.

therefore, does not seem to have had a significant effect upon his responses.

In summary, the average responses to repetitive click stimuli obtained from our subjects are seen to exhibit similar characteristics: Each subject exhibits responses that diminish in amplitude as the click rate is increased, and each subject exhibits detectable responses for rates up to approximately 100 per second. Moreover, the overlap model is quite successful, on the whole, in predicting the wave shape of the average responses evoked from our subjects.

By way of comparison, Fig. 5 showed that average responses obtained from the auditory cortex of the unanesthetized cat exhibit a somewhat greater dependence upon rate. For example, responses to 50/sec clicks have a smaller amplitude when compared with 2/sec responses in Fig. 5 than is observed in Fig. 35. However, the range of click rates over which responses were measurable was of the same order of magnitude in both figures. In a more directly comparable study on human subjects, it was found that click responses could be recorded from the depths of the temporal cortex and were detectable for click rates up to 100 per second (34).

4.3 SUMMARY

Average responses to clicks have been obtained from many human subjects. These responses are quite variable in nature, but all seem to possess in common a negative component with approximately a 30-msec peak latency. This 30-msec component is usually largest in the occipital regions of the scalp. The behavior of these response components, as a function of the rate and intensity at which the clicks are presented, parallels the behavior of cortical responses obtained from experimental animals.

V. CONTROL EXPERIMENTS

Responses produced in the brain are indeed reflected in the responses recorded from the intact scalp, but the converse is not necessarily true. Not all potentials recorded from the surface of the scalp necessarily reflect electrophysiological activity generated in the brain beneath. First of all, so-called stimulus artifacts, which are the electrical potentials associated with the physical generation of stimuli, may sometimes be recorded by scalp electrodes. Second, activity from distant electrophysiological sites, such as the heart, may be recorded by scalp electrodes. Third, potentials associated with movements of the musculature of the scalp and head give rise to fairly widespread electrical activity that is recordable with scalp electrodes. The possibility that the average responses that we have recorded from human scalp reflect the activity of sources other than the brain must be examined.

5.1 DEMONSTRATION OF THE ELECTROPHYSIOLOGICAL NATURE OF THE 30-msec RESPONSE COMPONENTS

In this study, the clicks have all been generated by the delivery of electrical pulses to earphones. The possibility that our averages are not physiologically produced but are simply stimulus artifacts is not very great, for although the electrical pulses used had a duration of only 0.1 msec, the peak latency of the response component most commonly recorded is 30 msec. An additional demonstration for the electrophysiological nature of these responses is provided by data from experiments involving the "masking" of clicks by random noise.

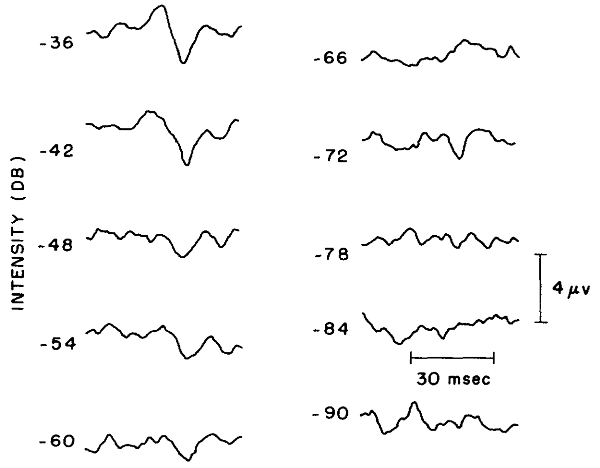


Fig. 40. Average responses to masked clicks of various intensities (Subject, A. T., H-585B). Stimulus conditions: clicks plus random noise, left ear; clicks, randomized stimulus pattern was used (see Fig. 23): random noise, rms value approximately −76 db (re 4.4 volts). Response conditions: active electrode 8; reference electrode 6; number of responses, 1000 for each intensity.

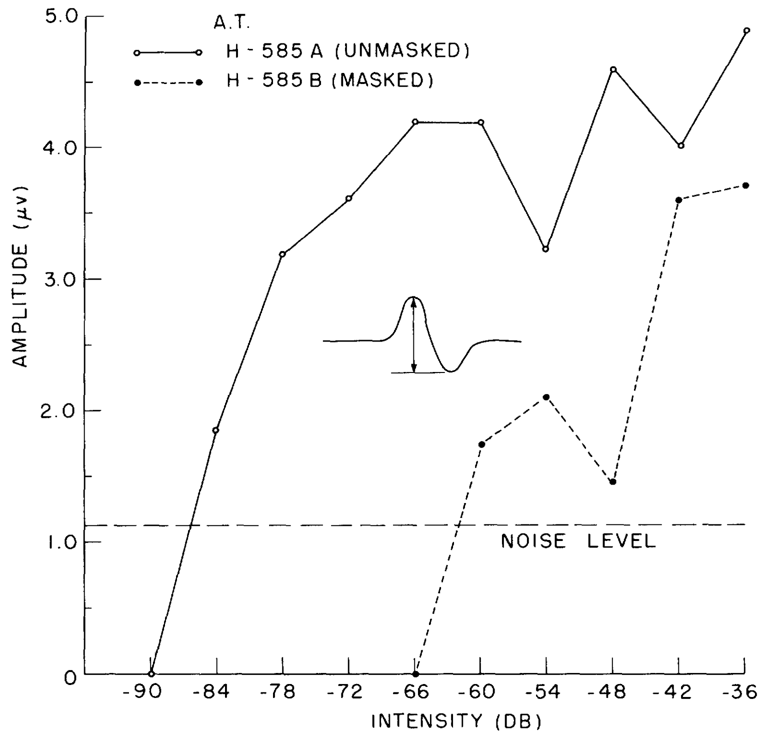


Fig. 41. Amplitude of average responses to masked and unmasked clicks as a function of click intensity (Subject, A. T., H-585). Each point represents the peak-to-peak amplitude of an average response. Stimulus conditions: clicks with and without random noise; clicks, randomized pattern used; noise, rms value approximately −76 db. Response conditions: active electrode 8; reference electrode 6; each average measured was computed from 1000 responses.

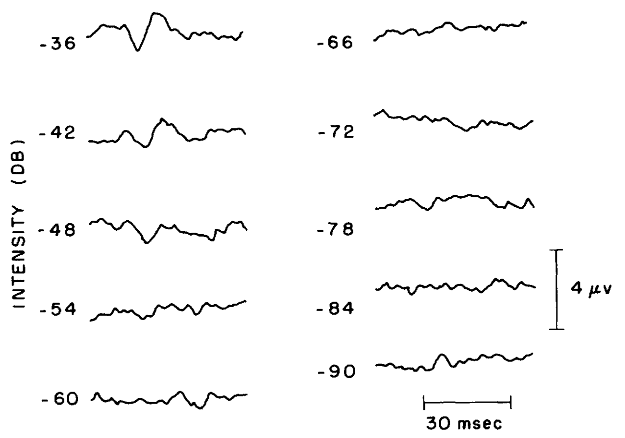


Fig. 42. Average responses to masked clicks of various intensities (Subject, M.W., H-584B). Stimulus conditions and response conditions same as for Fig. 40.

In these masking experiments, the basic click patterns utilized in the intensity experiments described in Section IV were adopted. But in addition to the clicks, a continuous background of audible wideband random noise was superimposed. If the average responses that we have recorded are due to the electrical spread of the stimulus potentials, then the addition of random noise to the clicks might produce additional variability in the average responses, but otherwise should have little effect upon them. Electrophysiological responses to masked clicks, on the other hand, should show considerable reduction of response amplitudes, at least for clicks of faint intensities. (See Section I for a more complete discussion.) Rosenblith (14) recorded, in the anesthetized cat, cortical responses evoked by masked clicks, and found that the amplitude of responses to identical click stimuli decreased as the intensity of the masking noise was increased.

Figure 40 shows the average responses evoked by masked clicks from subject A. T. Notice that responses are only seen for click intensities greater than −60 db. The peak-to-peak amplitudes of the average responses evoked in this subject by unmasked and masked clicks are shown in Fig. 41. Notice that measurable responses to the unmasked clicks were obtained even at −84 db. Although the click intensity at which responses to the masked clicks are first seen is 30 db higher than that for those evoked by unmasked clicks, the initial rate of increase with intensity for the two curves is approximately the same. A comparable experiment on subject W. P. gave qualitatively the same sort of results.

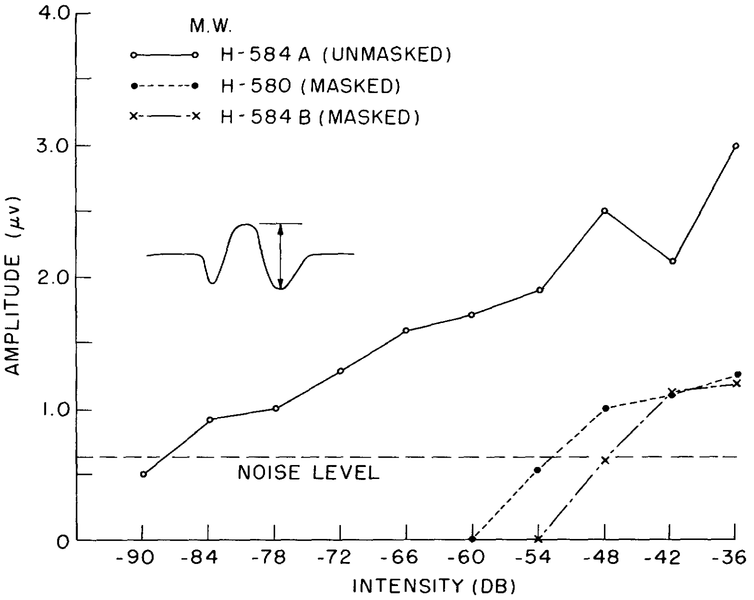


Fig. 43. Amplitude of average responses to masked and unmasked clicks as a function of click intensity (Subject, M.W.). Each point represents the amplitude of one average response. Stimulus and response conditions, same as for Fig. 41. During experiment H-580, the subject's psychophysical threshold to masked clicks was measured at approximately −66 db.

Figure 42 shows average responses recorded from subject M.W. which were evoked by click stimuli in the presence of added random noise. Figure 43 shows the peak-to-peak amplitudes of responses evoked in this subject by masked and unmasked clicks. Detectable average responses are not seen for the masked clicks until the intensity of the clicks is raised to −54 db. At higher intensities, the amplitude of masked clicks grows in a manner parallel to the growth of unmasked clicks at low intensities.

These data clearly indicate that random noise added to click stimuli causes gross changes in the average click responses recorded from the human scalp. These responses cannot be explained as the linear combination of effects resulting from the noise and from the clicks, but are understandable if we assume that the responses were produced by a limited neural population which responded to both the noise and to the clicks.

5.2 ELIMINATION OF SCALP MUSCULATURE AS THE SOURCE OF THE 30-msec RESPONSE COMPONENTS

It has been shown recently that voluntary muscle twitches can produce electrical potentials that are recordable with scalp electrodes (63). Since there are muscular events, such as eye-blink reflexes (64), which are known to follow click stimuli with short latencies, the possibility exists that some sort of muscle reflex to clicks is being evoked in our human subjects. The electrical activity of the scalp muscles must, therefore, be examined as a possible source of the average responses to clicks that we have recorded.

Figure 44 shows the effect that muscular activity can have upon the EEG. The traces

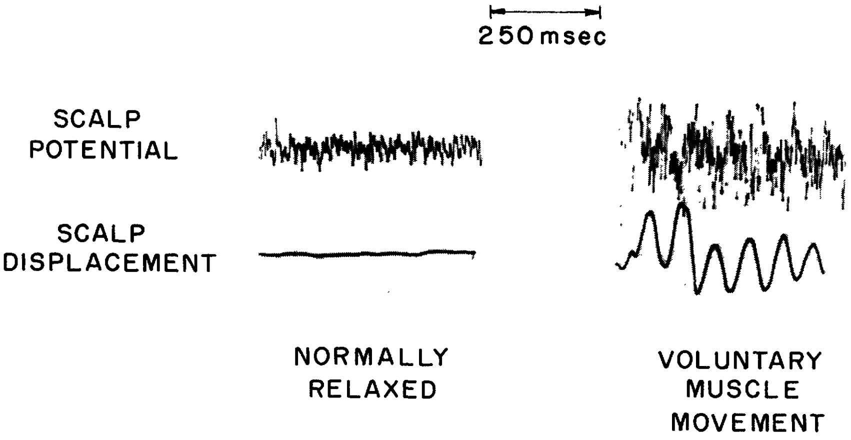


Fig. 44. Electrical potentials and physical displacements measured on the scalp (Subject, W. P., H-630). Top trace in each column shows electrical potentials recorded from scalp electrode 8 (reference electrode, nose). Bottom trace in each column was recorded simultaneously with the top trace and shows scalp displacement measured at a spot approximately 1 cm away from electrode 8. Left column: oscillograph taken while subject was sitting relaxed. Right column: oscillograph taken just after subject voluntarily tensed his jaw muscles.

in each column were obtained simultaneously and show electrical potentials and distance displacements recorded from the same area of the scalp. The data in the left column were taken while the subject was sitting, reading in a normally relaxed way. The data in the right column were taken during voluntary scalp movement. A striking increase in the electrical potentials recorded during scalp movement is seen.

It is clear that voluntary movements of the scalp muscles can have a counterpart in the electrical activity recorded from the scalp. Therefore, should scalp reflex movements that are time-locked to the click stimuli occur, we would expect that electrical activity, time-locked to the clicks, would also exist on the scalp simply because of the activity of the scalp muscles and not because of that of the underlying brain. Conversely, we would expect that any electrical events resulting from reflex activity of the scalp muscles would have time-locked counterparts in the movements of the scalp. In order, therefore, to determine whether muscular reflex activity that is time-locked to click stimuli occurs, we measured scalp displacements during the presentation of clicks to several different subjects.

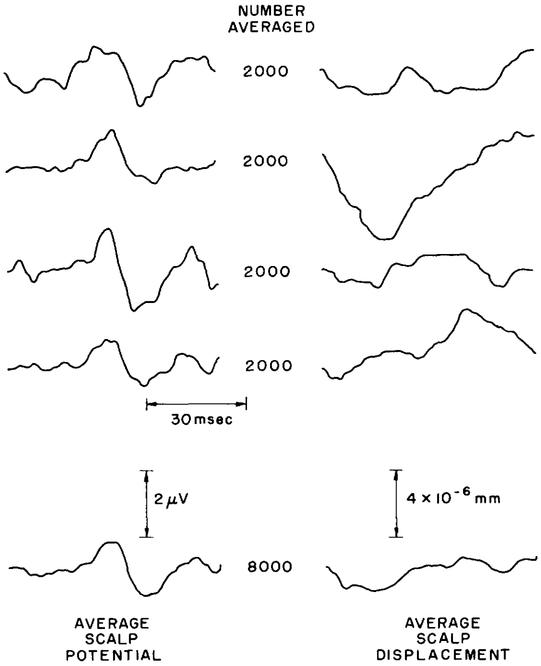
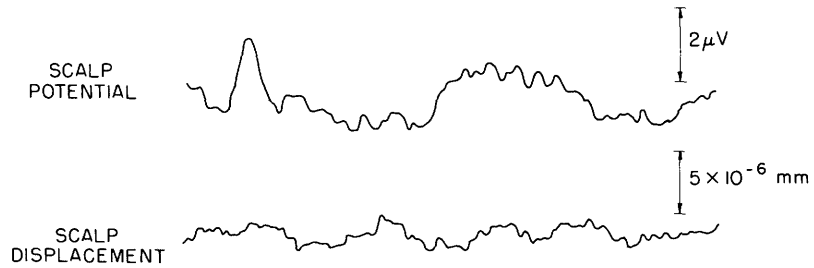


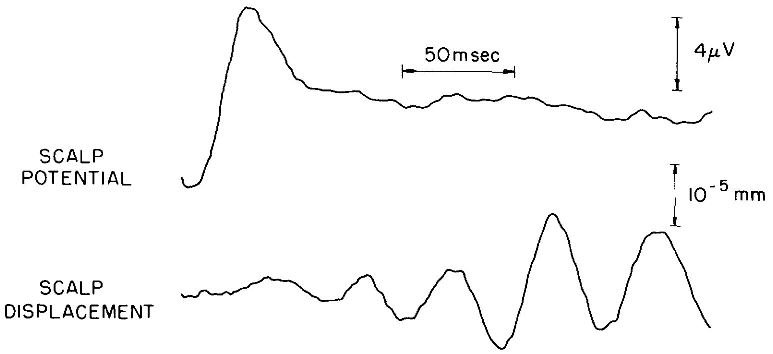
Fig. 45. Average scalp potentials and average scalp displacements to clicks (Subject, W. P., H-630). The data used to compute the averages in each row were obtained simultaneously. The data for the averages in the four top rows were obtained sequentially; the averages in the bottom row were computed from the data used in the computation of the averages in the four upper rows. Stimulus conditions: clicks, left ear, −45 db, 14.5 per second. Response conditions: traces in the left column are average electric responses recorded between electrodes 8 and nose. Traces in the right column are average scalp displacements, measured at a spot approximately 1 cm from electrode 8. Displacement calibration is only approximate.

The measuring device used was a modified phonograph cartridge mounted directly on the head. (This device, of a type previously used by Galambos, Rosenberg, and Glorig (64) to measure displacements, was completely described in Section III.) The output of the cartridge, which measured posterior-anterior displacement in the orientation that was always used, was recorded simultaneously with the output of a nearby scalp electrode. Clicks were delivered to the subject, and average responses to the clicks were computed from the amplified potentials obtained from both the scalp electrode and the phonograph cartridge.

Figure 45 shows average responses recorded from the scalp of W. P. Average responses recorded by the scalp electrode are shown in the left column and average scalp displacements are shown in the right column. Although the familiar 30-msec deflection is seen in the average EEG responses, no average scalp displacement that is time-locked to the clicks is consistently observed. It is true that deflections are seen in the



AVERAGES TIME-LOCKED TO CLICKS



AVERAGES TIME-LOCKED TO HEART BEATS

Fig. 46. Average scalp potentials and average scalp displacements (Subject, A. T., H-616). The time markers used in the computation of the two upper curves were synchronized to clicks. The two lower curves were computed from the same identical data as the upper curves, but the time markers used by ARC were synchronized to heartbeat potentials obtained from an electrode on the chest. Stimulus conditions: clicks, left ear (9C earphone), −45 db, 1 per second. Response conditions: the top trace of each pair is the average response recorded between scalp electrodes 8 and 6. The lower trace of each pair is the average scalp displacement measured at a spot approximately 1 cm from electrode 8. Number of responses, 550. Displacement calibrations are only approximate.

right-hand curves, but they are not consistently observed and are probably due to the effect of "spontaneous" scalp movements.

Figure 46 shows averages recorded from subject A. T. The upper trace shows an average response to clicks computed from the subject's scalp potentials. The usual peak at 30 msec is plainly visible, as well as a later deflection. The second trace shows the average scalp displacement that follows these same clicks; no significant deflections are seen in this trace.

The two lower traces are averages that were computed from the same sections of recorded potentials as in the upper traces except that heartbeat potentials were used as the time markers that were fed into ARC. These lower curves, then, are averages time-locked to the heartbeats rather than to clicks. The trace next to the bottom shows the average EEG potential that follows a heartbeat. The shape of this average response is almost identical to that obtained by averaging the actual heartbeat potentials, and shows that the electric fields generated by the heart may be detected, by averaging techniques, even on the scalp. The bottom trace is the average scalp displacement following heartbeat, and shows a series of comparatively large deflections. The fact that there is no electrical activity synchronized with these scalp movements is interpreted as evidence that the musculature of the scalp, although displaced, perhaps, was not actively stimulated. Hence, these average scalp displacements are probably due to the blood pulsing through the arteries of the scalp. A comparable experiment on subject M. W. gave qualitatively the same sort of results.

In the data obtained from these experiments, we have been unable to observe evidence of scalp displacements that are time-locked in a consistent manner to the delivery of click stimuli. With confidence that any electrical effects caused by the scalp muscles would have had time-locked counterparts in displacements of the scalp, we conclude that the musculature of the scalp does not contain the active sources that produce the 30-msec response components to clicks which we have recorded with scalp electrodes.

5.3 ELIMINATION OF DISTANT ELECTROPHYSIOLOGICAL SITES AS THE SOURCE OF THE 30-msec RESPONSE COMPONENTS

The detection of electric fields generated by the heart with the use of scalp electrodes illustrates the fact that there may be considerable spatial spread of electrophysiological potentials. Hence, electrical spread of the activity of such sites as the eye muscles or the neck muscles could possibly contribute to the potentials recorded on the scalp.

Reference to the average responses recorded from three separate subjects, however, quickly eliminates the possibility that distant sites are the sources. In Fig. 21g, for instance, there is a well-localized response in the occipital region: electrodes only 5 cm away from the active one (electrode 8) show little or no evidence of the positive, 20-msec peak. In Fig. 21c, although the 30-msec deflection is quite widespread, there is a marked difference in amplitudes recorded at the various electrodes. For example, notice the difference between the responses recorded from electrodes 6 and 7. The electrode 7 response has a clearly visible 30-msec peak, while the average response recorded by electrode 6 has almost no deflection at 30 msec. Finally, in Fig. 21d and 21e, electrodes 6 and 7 also show quite different deflections. For the average responses that we are recording, then, electrodes only 5 cm apart may record differently shaped average responses. Sometimes the responses recorded by one electrode completely lack a component recorded by the neighboring electrode. Such marked attenuation of response components recorded from electrodes only slightly removed from one another means that the amplitude of the recorded average responses diminishes sharply as the electrodes are moved away from the vicinity of the electrically active sites. Therefore, the nearly equal amplitudes of the 30-msec response components to clicks that are usually recorded from electrodes 1, 8, 9, and 10, preclude the possibility that we are recording electrical fields generated in such structures as the eye muscles or the neck muscles.

5.4 CONCLUSION

Stimulus artifacts, and electrophysiological sites outside of the brain have all been eliminated as sources that contribute significantly to the average responses recorded from the human scalp. Having eliminated all other possibilities, therefore, we conclude that the average responses recorded with scalp electrodes do indeed reflect activity that is recordable from the surface of the cortex itself.

Note carefully that we have not stated that these average responses are necessarily produced by active sites within the cortical mantle. The mere fact that potentials are recorded from the surface of the cortex does not imply that the electrophysiological sites producing these potentials lie within the cortex, since electrical activity produced by subcortical structures has been recorded from the surface of the cortex by several workers. Goldstein, Kiang, and Brown (17), for example, recorded small average-response components to click stimuli from cat cortex with the use of monopolar electrodes. Because these response components had an extremely short latency and duration and they were undetectable with concentric, bipolar electrodes, these authors concluded that these particular components of the average responses were probably the result of electrical spread from subcortical structures. Kennedy (29), in her study of the widespread responses originally recorded on the monkey cortex by Pribram, Rosner, and Rosenblith (28), was unable to change the waveform of these responses by the local application of drugs, by recording from a section of cortex isolated from neighboring cortex, or even by completely undercutting the isolated section of cortex from which she was recording. Such data suggest that the widespread responses recorded in the monkey constitute electrical spread from subcortical structures.

In our own experiments on human subjects, ipsilateral clicks have evoked a response component with a very short peak latency (5 msec) from subject G. G. (Figs. 21k and 58c). Surely such activity is produced by subcortical structures. Also, the widespread responses with longer latency recorded from subject O. G. (Fig. 21a) which were presumably present even on the nose, can best be explained in terms of the electrical spread of subcortical activity.

It is concluded simply that the average response components to clicks that we have recorded from the intact human scalp are produced in the brain and are recordable from the surface of the cortex.

VI. THE NATURE OF THE AVERAGE CLICK RESPONSES OBTAINED FROM THE HUMAN SCALP

The area of the human scalp from which we have been able to record the 30-msec response components to clicks is usually limited to the occipital region. This localization of responsive area is significant, since we believe that average responses recorded on the scalp reflect the average responses that are recordable from the surface of the cortex directly beneath. It follows, therefore, that there is an area of cortex in the occipital region from which responses to clicks may be recorded. Since the classical auditory projection areas in man lie within the Sylvian fissure, we conclude that the area of the cortex from which average responses to clicks are recordable is not part of the auditory projection areas. Hence, in the terminology of Section I, the 30-msec response components that we recorded are probably "secondary" in nature.

In addition to specifying the different regions of cortex from which evoked responses are recorded, cortical responses have been differentiated by many other experimental techniques. Some of these techniques involve treatment of the brain tissue itself, or the administration of drugs, and are, of course, not applicable to the present study. Fortunately, however, evoked responses have also been differentiated by several experimental techniques that can be used on normal human subjects. First, evoked responses have been found to exhibit differential effects resulting from changes in stimulus parameters. Second, the use of multisensory stimuli has proved to be a useful tool in the study of various cortical responses. Finally, the manner in which variations in the "state" of an experimental animal affects the various types of evoked responses has proved to be another method of differentiation.

The experiments reported in this section were undertaken in order to explore the nature of the response components to clicks that have been recorded from the human scalp. The data obtained support the hypothesis that we have recorded secondary cortical responses.

6.1 AVERAGE RESPONSES TO MULTISENSORY STIMULI

Buser and Borenstein (20), using multisensory stimuli on cats, have established three different types of responsive areas on the cortex: (a) the "primary," or projection areas; these areas are characterized by the relative stability of the primary responses, although they are also responsive to stimuli other than those of the primary modality. The primary responses are little affected by other sensory stimuli, but the size of the secondary responses that are recorded in these areas depends greatly upon the primary activity. (b) There are "overlap" areas in which secondary responses to stimuli of various sensory modalities can be evoked relatively independently of each other. (c) There are the "interaction" areas in which secondary responses evoked by the different modalities affect each other in more or less reciprocal fashion.

The Buser and Borenstein characterization of evoked responses in the cat suggested to us that data from similar experiments on our human subjects would be useful in determining the nature of the click responses that we had obtained. Moreover, data from preliminary experiments indicated that average responses to somatic stimuli were also recordable from our subjects. Hence, a series of experiments was undertaken to determine the effect of somatic stimulation upon the average responses to clicks recorded from the human scalp. As a first step, we obtained average responses evoked by the presentation of somatic stimuli alone.

a. Average Responses to Shock Stimuli

Responses to somatic stimuli evoked from human subjects have been reported by many workers. As early as 1950, Dawson (16), using photographic superposition techniques, recorded responses to electric shock of the wrist and hand from the human scalp. These responses contained several components, the first one being a positive deflection with a peak latency of approximately 30 msec. Other workers, such as Larsson (41), and Bates (40), have obtained similar responses to electric shock by means of photographic superposition. With the recent development of electronic averaging devices (37, 38) several other workers have reported average responses to somatic stimulation. Uttal (65) reports an average response to electrical pulse stimuli that has several components: the earliest large deflection has a latency of approximately 20 msec. Rosner (66) has also observed average responses to shock stimulation. He found that the first large component (recorded from an electrode located posterior to a scalp marking of the central sulcus) that was evoked by contralateral shock stimulation was usually a sharp negative deflection with a peak latency of approximately 22 msec; a positive deflection with a 24-msec peak latency followed.

In our laboratory, we have recorded average responses from the scalp of our subjects to various types of somatic stimuli. The tap of a reflex hammer upon the back of the hand was found to evoke average responses that were largest on the contralateral scalp, but also had appreciable ipsilateral representation. Electric shocks to the wrist and to the elbow have also been used. In the particular experiments reported here electrical shocks were applied at the wrist to activate primarily the median nerve. (See Section III for description of the electric stimulator.)

Figure 47a and 47b shows average responses to shocks recorded from various points on subject A. T.'s scalp. Two types of responses are seen in the central region in response to contralateral stimulation (Fig. 47a). The anterior electrodes recorded an initial negative peak with a latency of approximately 23 msec, followed by a positive peak at 35 msec. In contrast, the electrodes posterior to the central-sulcus marking record a more complicated waveform — a sharp negative deflection which occurs only 20 msec after stimulus delivery is followed by a positive peak at 23 msec. Several other response components follow, including a positive deflection at 45 msec. The early components of the responses recorded by electrodes B, E, and H are seen to be very small, and the two occipital electrodes record patterns that resemble those of electrodes A, F, and G.

The average responses evoked by ipsilateral stimuli are somewhat different

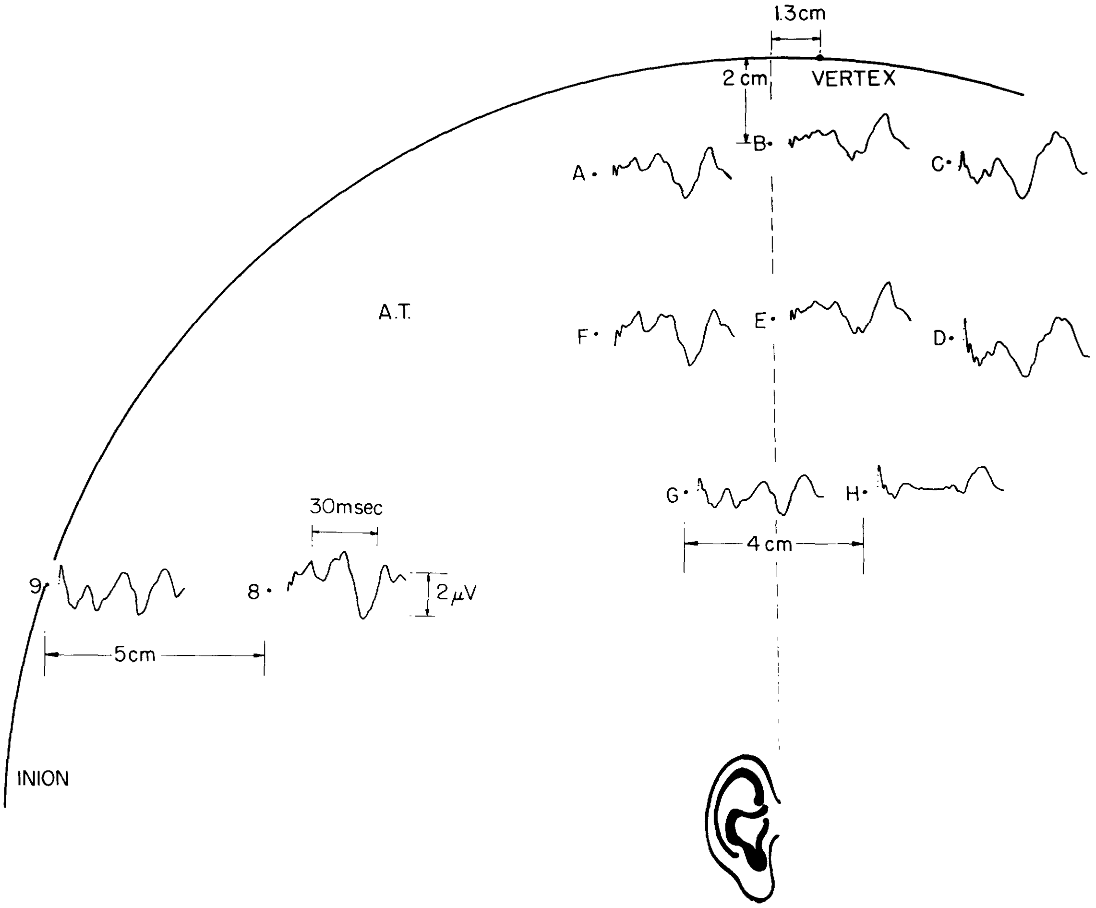


Fig. 47a. Average responses to contralateral shock stimuli recorded from various scalp electrodes (Subject, A. T., H-614). Stimulus conditions: periodic shocks at a current setting of 3.4 ma were delivered to the left wrist at a rate of 5/sec. Response conditions: reference electrode, nose. Number of responses, 1000. Responses from electrodes A, B, E, F, and 8 were recorded simultaneously. At a different time in the experiment, responses from electrodes C, D, G, H, and 9 were recorded simultaneously. Therefore, the responses of electrodes 8 and 9 were not recorded simultaneously, and although these two responses have similar components of almost identical peak latencies, they are rather different in shape. In subsequent experiments, however, little difference could be detected between average responses to contralateral shocks recorded from electrodes 8 and 9. The two occipital electrode positions, 8 and 9, have already been described. Each electrode in the central region was located 4 cm away from its nearest neighbors. By way of comparison with previous locations, electrode E is located approximately at electrode 3 (Fig. 21d). The beginning of each response (a dot) corresponds to the location of the electrode on the scalp. The dotted line approximates the line commonly accepted as lying over the central sulcus (see Grant (67)), and indeed does seem to be some sort of boundary.

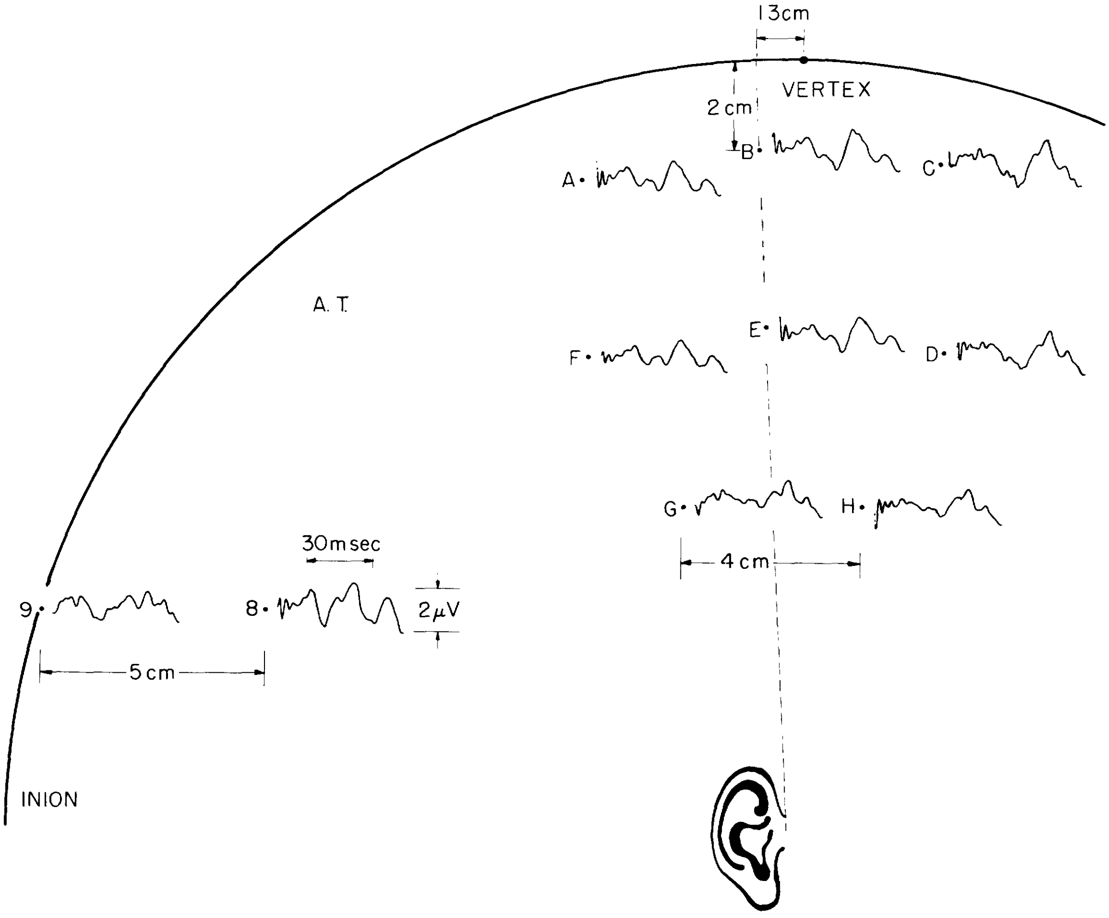


Fig. 47b. Average responses to ipsilateral shock stimuli recorded from various scalp electrodes (Subject, A. T., H-614). Stimulus conditions: periodic shocks at a current setting of 4. 2 ma were delivered to the right wrist at a rate of 5/sec. Response conditions: reference electrode, nose. Number of responses, 1000. Responses from electrodes A, B, E, F, and 8 were recorded simultaneously; responses from electrodes C, D, G, H, and 9 were also recorded simultaneously. The corresponding responses in Fig. 47a and 47b were obtained from the same electrodes during the same experiment. The shocks delivered to both contralateral and ipsilateral wrists were judged by the subject to activate the appropriate median nerve and to be of approximately equal strength. It will be noticed that the first 5-10 msec of each response has been omitted in order to avoid recording the shock artifacts, which were large as compared with the average responses.

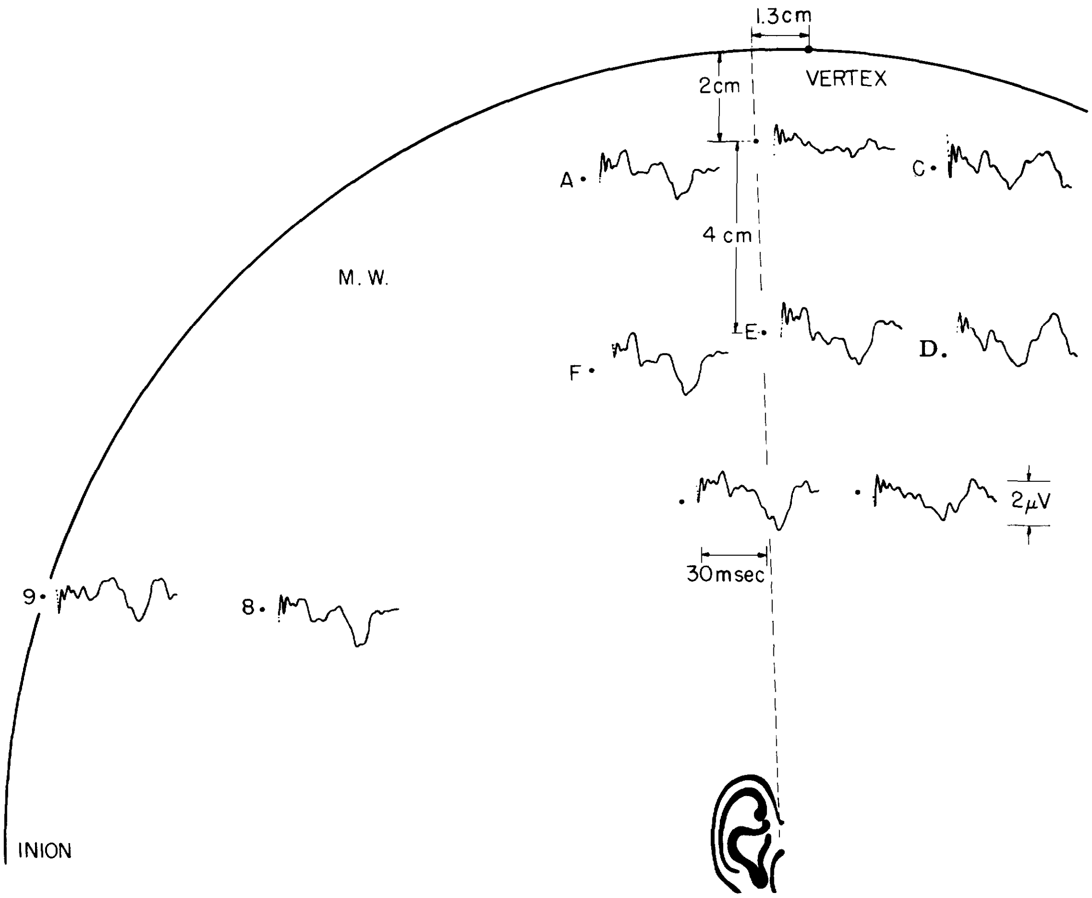


Fig. 47c. Average responses to contralateral shock stimuli recorded from various scalp electrodes (Subject, M. W., H-615). Stimulus conditions: shocks, left wrist, 4.2 ma, 5/sec. Response conditions: reference electrode, nose; number of responses, 1000.

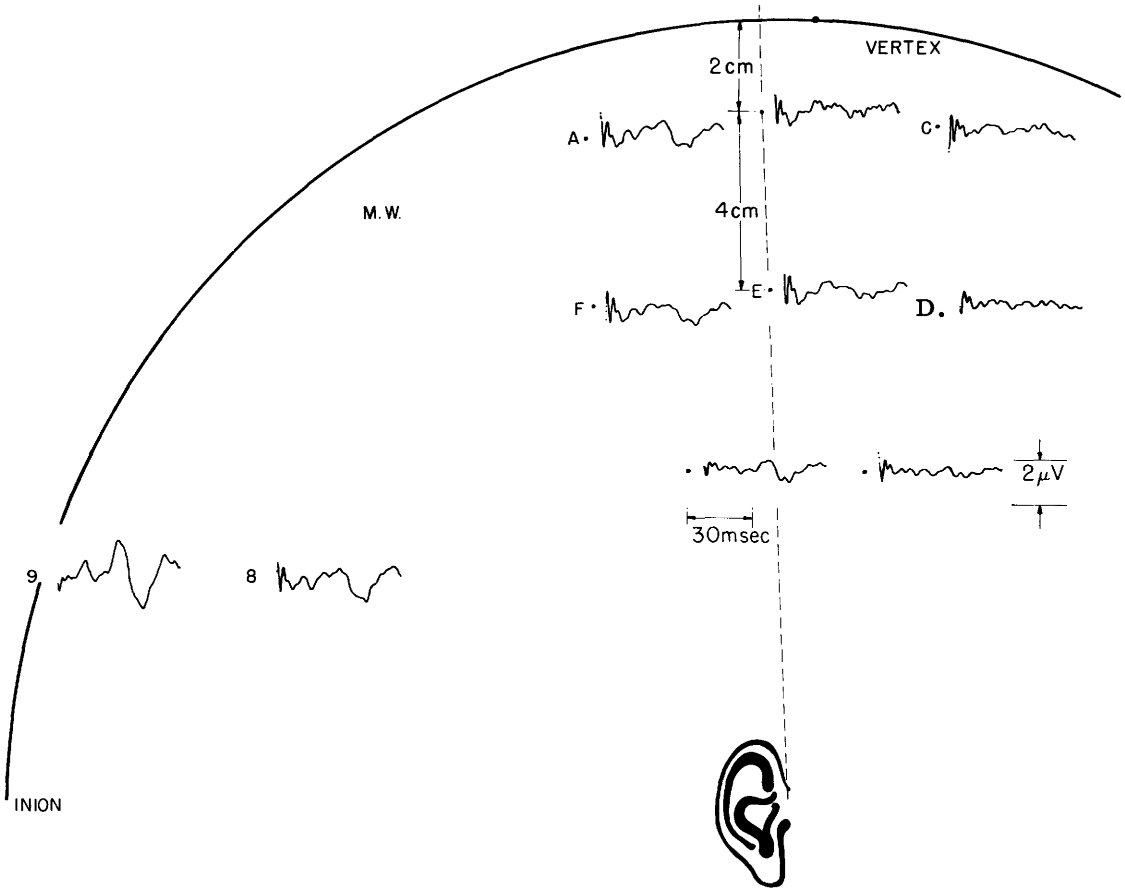


Fig. 47d. Average responses to ipsilateral shock stimuli recorded from various electrodes on the scalp (Subject, M.W., H-615). Stimulus conditions: identical to those in Fig. 47c, except that right wrist was stimulated. Response conditions: identical to Fig. 47c. The corresponding responses in Fig. 47c and 47d were obtained from the same electrodes during the same experiment. The shocks delivered to the contralateral wrist were judged by the subject to be just a little bit "weaker" than those delivered to the ipsilateral wrist.

(Fig. 47b). The central electrodes record responses that are generally of smaller amplitude than those evoked by contralateral stimuli. An initial positive component is entirely missing at electrodes C and D. It is significant that the occipital electrodes show the same type of response as that seen for contralateral stimulation, although it is smaller in amplitude.

The responses to shock evoked from subject M.W. are shown in Fig. 47c and 47d, and exhibit remarkable similarity to those of subject A.T. For contralateral stimulation (Fig. 47c), electrodes C and D record an initial negative peak at approximately 25 msec, and a later positive deflection. Electrodes A and F record an initial negative peak at 20 msec, a positive peak at 24 msec, and another positive peak at 45 msec. The two occipital electrodes show nearly identical responses resembling those recorded from electrodes A and F.

Figure 47d shows the average responses to ipsilateral shocks. The greatly diminished response activity in the central regions is a striking feature of this response pattern. Nevertheless, the responses recorded from electrodes 8 and 9 are similar to those evoked by contralateral stimuli.

A common pattern of average responses is clearly seen in these two subjects: The central electrodes record responses that vary consistently in an anterior-posterior direction. Moreover, in any particular central location, responses to contralateral shocks are larger than they are to ipsilateral ones. The responses to contralateral stimuli which we have recorded from the electrodes located posterior to the central sulcus line have, by comparison, an initial diphasic component that is very similar to the component observed by Rosner (66). The occipital electrodes, in contrast to the central ones, record quite comparable average responses both to ipsilateral and contralateral stimuli. This bilateral representation of shocks at occipital locations becomes significant when it is remembered that we have recorded bilateral responses to clicks from this same region. In the occipital region of the human scalp, therefore, there exists a broad area that exhibits responses both to clicks and to electrical shock stimuli of the hand.

b. Average Responses to Pairs of Clicks

Since we were primarily interested in the effect of somatic stimuli upon the evoked responses to clicks, stimuli of both modalities had to be presented to our subjects. Moreover, since the time interval between shock and click stimulation was thought to be a significant stimulus parameter, click and shock stimuli with different time intervals between them had to be presented. Furthermore, many individual responses to any particular shock-click pair must be averaged in order to obtain a clear response. Hence, the basic stimulus pattern used in these experiments was a series of identical shock-click pairs. These identical pairs were generated by two trains of repetitive stimuli, one of clicks and the other of shocks, which were presented to the subject at the same time, and at identically the same rate, but displaced in time with respect to each other.

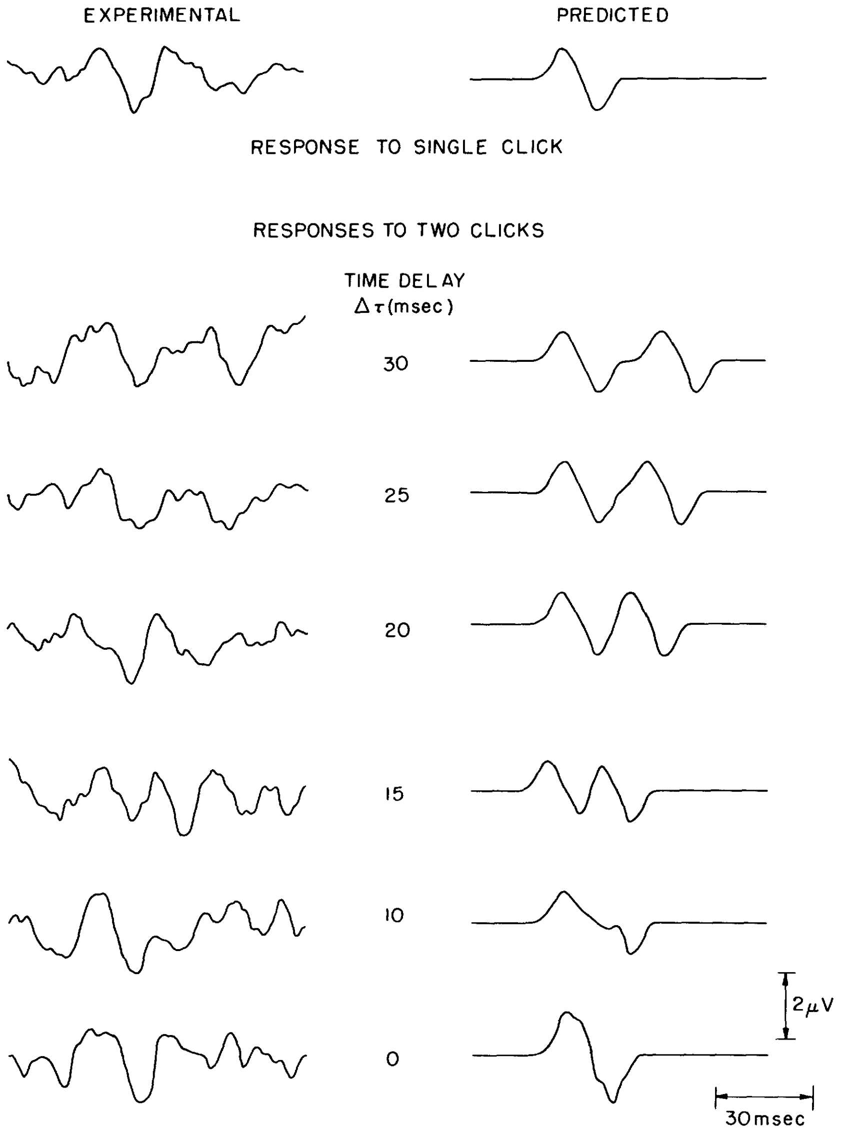


Fig. 48. Average responses to single clicks and pairs of clicks (Subject, A. T., H-623). Left column: experimentally obtained responses; single-click response is shown at the top, responses to click pairs below. Stimulus conditions: clicks, left ear (9C earphone). All clicks were -40 db and each stimulus pattern, whether a single click or a click pair, was repeated periodically at the rate of 10/sec. Response conditions: active electrode, 8; reference electrode, nose; number of responses, 1000. For each of these average responses, the time markers used by ARC were the first clicks of each pair. The time refers to the inter-click interval between the clicks of each pair. Right column: idealized single-click response, copied from the experimental response, is shown at the top; predicted responses, constructed by the appropriate superposition of two idealized single-click responses, are shown below.

The average response to any particular shock-click pair could then be simply computed from the EEG data recorded during the presentation of the shock and click trains having the appropriate time shift between them.

The stimulus patterns just proposed for the shock-click stimuli are perhaps unusual, and it was decided to apply this type of pattern first to click stimuli alone. To this end, two intercalated trains of repetitive clicks having the same intensity were simultaneously presented to the left ear of subject A. T. Each train was presented at identically the same rate (approximately 10 per second), but the two trains were displaced in time with respect to each other. The total stimulus pattern used, therefore, was a series of click pairs presented repetitively at a rate of 10 per second.

Figure 48 shows the average responses to such click pairs that were obtained from the human scalp. The top left-hand curve shows the average response to a train of single clicks, and the other curves in that column are average responses to various click pairs. The form of these average responses is best understood by consideration of the curves in the right column. The top curve in that column is a smoothed copy of the experimental average response to single clicks, in which only the earlier, more consistent response components are represented. Each of the other curves in the right column was constructed by superposing two of the idealized click responses with the indicated time interval between them. An examination of the corresponding curves in the two columns shows that although they are not identical, most of them exhibit considerable similarity.

If we use the latencies to the various peaks and the various peak-to-peak amplitudes of the two curves as criteria for comparison, we find that the experimental and predicted responses to click pairs match rather well for interclick time delays greater than 10 msec. For time delays of 5 msec and 10 msec, however, the experimental response is not well approximated by the predicted waveform. The experimental data for $\Delta\tau$'s that exceed 10 msec may, therefore, be interpreted as the superposition of independent average responses evoked by the two separate clicks of the click pair. For $\Delta\tau$'s of 10 msec and 5 msec, however, there has been "interaction" between the responses to the two trains of clicks. It is interesting to note here, by way of comparison with psychophysical data, that Rosenzweig and Rosenblith (68), report 10 msec to be the minimum time interval between the clicks in a click-pair stimulus that allows the two clicks to be perceived separately by human subjects.

c. Average Responses to Shock-Click Pairs

Interlaced trains of shock and click stimuli were presented to three different subjects, A. T., M. W., and G. G. Reference to Section IV indicates that the average responses to clicks exhibited by these three subjects cover the range of types of responses that has been reported in this study. It was hoped that the differential effects of shock stimuli upon the various types of responses to clicks would help us to distinguish and identify the different response components.

At the beginning of each experiment, trains of clicks and trains of shocks were

CLICK RESPONSE

SHOCK RESPONSE

RESPONSES TO COMBINED STIMULI

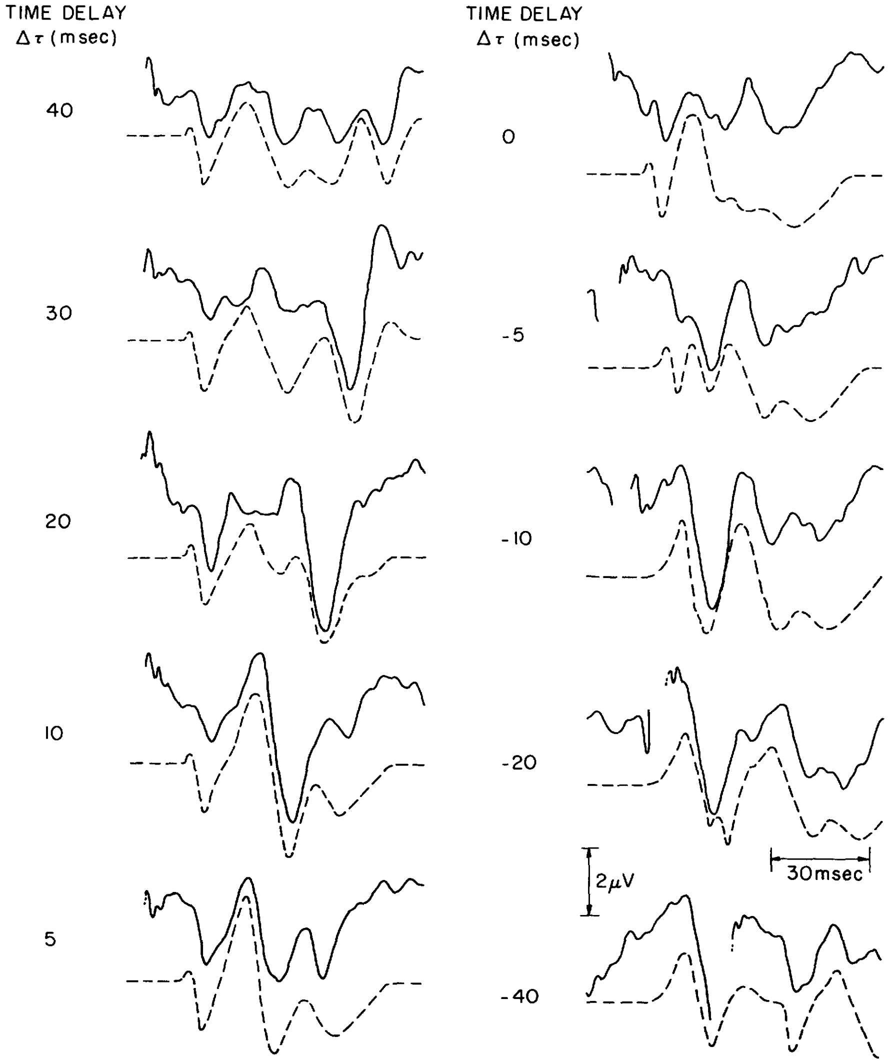


Fig. 49. Average responses to shock and click stimuli from electrode 8 (Subject, A. T., H-627). Top row: solid lines show experimentally obtained responses to shock and click stimuli presented separately at the beginning of the experiment; dotted lines show idealized copies of these experimental responses. Lower rows: solid lines show experimentally obtained responses to shock-click pairs; dotted lines show predicted responses that were constructed by the appropriate superposition of the idealized responses to the single-modality stimuli. Stimulus conditions: all shocks presented to left wrist, 4.2 ma; all clicks presented to left ear (9C earphone), –40 db; each stimulus pattern, whether a single stimulus or a shock-click pair, was repeated periodically at the rate of 10/sec. Response conditions: active electrode, 8; reference electrode, nose; number of responses, 2000. (In this and in the succeeding figures, $\Delta\tau$ is the interval by which the shock of each shock-click pair preceded the click. The time markers used by the average response computer were the first stimuli of each pair. Hence, in the average responses shown, shocks precede clicks for positive $\Delta\tau$, but trail them for negative $\Delta\tau$.)

presented to the subject separately. From the EEG data obtained during the presentation of these trains, the average responses to clicks alone and to shocks alone were determined. The rest of the experiment was divided into a series of separate "runs" involving combined shock and click stimuli. The stimulus pattern used in each run was that previously described, in which intercalated trains of clicks and shocks were delivered to the subject at the same time and at the same rate. Throughout each experiment, the shock and click stimuli were kept at the same intensity levels, so that the stimuli presented during each run consisted of repetitions of identical shock-click events. The stimuli were clearly perceptible to each subject but were not uncomfortable. Each run lasted approximately 3.5 minutes, that is, enough time for 2000 repetitions of the shock-click pair.

The repeated presentation of trains of clicks and shocks carries with it the possibility of long-range cumulative effects. Continued stimulation by clicks and shocks may lead to adaptation or potentiation effects or give rise to progressive changes in the "state" of the subject during a lengthy experiment and thus affect the responses obtained. In order to minimize the possibility of long-term adaptation, a two-minute "rest" period, during which time both clicks and shocks were withheld from the subject, separated each run. In order to minimize the effects of progressive changes in the "state" of the subject which still might have occurred in spite of our precautions, the runs were arranged in quasi-random order.

Occasionally during the course of an experiment, a stimulus pattern used during a previous run would again be presented to the subject. Also, occasionally during each experiment a train of clicks only (or a train of shocks only) would be presented to the subject. The average responses evoked by these trains of single-modality stimuli did not always match those obtained at the beginning of the experiment, a fact which indicates that certain long-term effects did indeed occur. However, the average responses obtained from the subject during the repeat runs of shock-click pairs, when compared with the responses obtained during the original runs, usually matched closely. The repeatability of the responses shown in this section is, therefore, good, unless otherwise indicated.

The solid lines in Fig. 49 show the average responses to shock and click stimuli recorded from the scalp of subject A. T. (electrode 8). The top row shows average responses evoked by trains of clicks and trains of shocks, presented separately at the beginning of the experiment, before combined shock and click stimuli had been given. The remaining average responses were evoked by combined shock-click pairs with the indicated time delay between the shock and the click.

To aid in our analysis of these responses, we have used the familiar superposition of response waveforms. The dotted lines shown directly beneath the experimental average responses in the top row are idealized copies of the experimental average responses to the single-modality stimuli. The dotted lines in the lower rows are responses constructed by the appropriate superposition of the idealized average responses to single-modality stimuli. The dotted lines are, therefore, average responses predicted by a model for which the assumption is made that the average responses evoked by shock-click

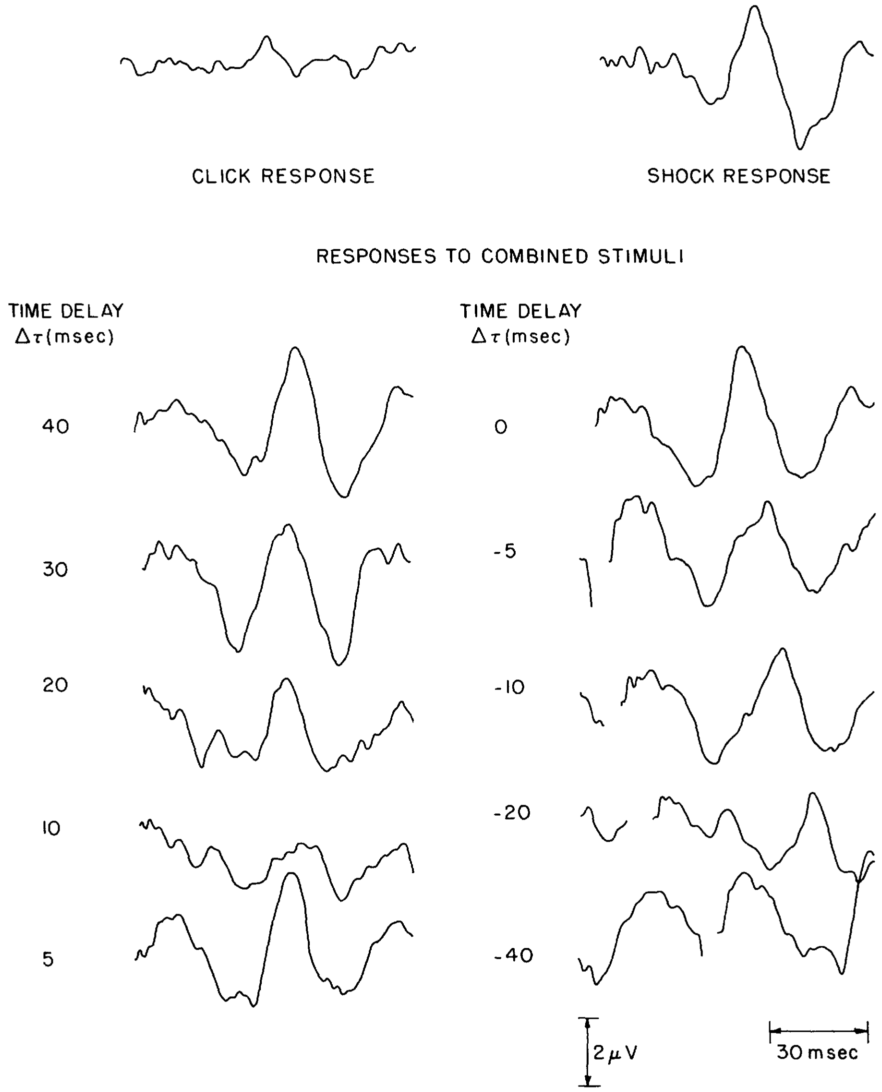
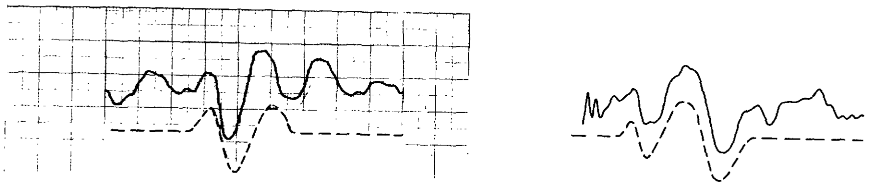


Fig. 50. Average responses to shock and click stimuli from electrode E (Subject, A. T., H-627). Same display as in Fig. 49 except that only experimentally obtained responses are shown. Stimulus conditions: the individual responses used in the computation of this figure were recorded simultaneously with those used in the computation of Fig. 49. Response conditions: active electrode, E; reference electrode, nose; number of responses, 2000. In experiment H-627, data for the average responses at Δτ's of 40, 30, −40, 0 and 5 msec were obtained during the first five runs. Succeeding runs involved stimulus patterns having the remaining values of Δτ. Subject reported that the shocks were subjectively the same strength throughout the experiment.



CLICK RESPONSE

SHOCK RESPONSE

RESPONSES TO COMBINED STIMULI

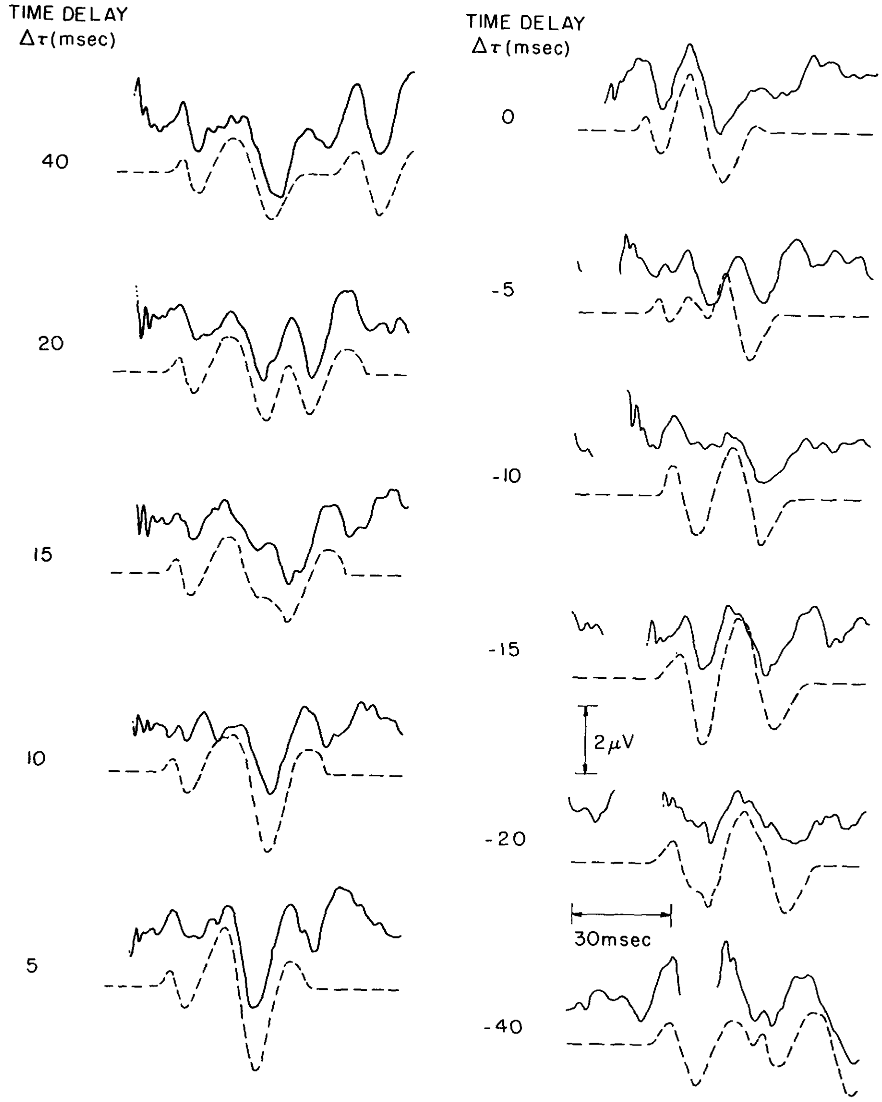


Fig. 51. Average responses to shock and click stimuli from electrode 9 (Subject, M.W., H-628). Same display as for Fig. 49. Stimulus conditions: all shocks to left wrist, 2.9 ma; all clicks to left ear (9C earphone), −40 db; each stimulus pattern, whether a single stimulus or a shock-click pair, was repeated periodically at the rate of 10/sec. Response conditions: active electrode, 9; reference electrode, nose; number of responses, 2000. The data for the average responses shown in the figure at $\Delta\tau$'s of 40, 0, −40, −5 and 5 msec were obtained during the first five runs for shock-click pairs. At this point in the experiment, the subject moved his arm and the subjective sensation of the clicks changed. The data for the average responses shown at $\Delta\tau$'s of 20, 10, −10, −20, 15 and −15 msec were obtained during the next six runs. A repeat run with $\Delta\tau = 0$ then followed, but the average responses for this run failed to match those of the second run. A rest was given and then runs with $\Delta\tau = -5$ msec and 5 msec followed. The average responses for these last two runs were an almost identical match with those of the fourth and fifth runs. Hence, some long-range effects probably influenced the responses obtained toward the end of the experiment.

pairs are just the linear superposition of the average responses evoked by the shocks and clicks separately, and hence that responses to shocks and clicks are independent.

In comparing the experimental and predicted responses to click pairs, we found that similarities in peak latencies and peak-to-peak amplitudes could be used to judge similarity between responses. Using these same criteria of comparison, we see that the experimentally obtained average response for a $\Delta\tau$ of 10 msec, for example, is quite similar to the predicted response. The same holds true for responses $\Delta\tau$'s of -10, -20, and -30 msec: The evoked responses are very similar to the predicted waveforms. By contrast, if the shocks precede the clicks by 20 msec or 30 msec, components of the average response to clicks have larger amplitudes than predicted. For interstimulus delays of 5, 0, and -5 msec, the experimental waveforms also differ considerably from the predicted ones, and thus indicate that "interaction" between responses to shocks and clicks does indeed take place. This interaction of responses for small $\Delta\tau$'s is especially significant in view of the fact that it parallels the interaction seen in this same subject for responses to click pairs with small interclick intervals (Fig. 48).

Figure 50 shows average responses recorded from electrode E during the same experiment. The fact that some of these responses, notably that for the shock-click delay of 10 msec, are much smaller than the others is not considered significant, for comparable responses obtained from preliminary experiments on this same subject showed no such variation. In spite of a certain amount of variability, it is clear that no gross interaction of responses occurs for small $\Delta\tau$'s.

Figures 51-53 show the responses to clicks and shocks recorded by different electrodes on the scalp of subject M.W. The type of display used is that of Fig. 49, and shows both experimental and predicted average responses, one under the other. It will be remembered (Fig. 21g) that M.W.'s responses to clicks were more complex than those usually obtained. In addition to the positive peak at 30 msec, which was recorded from the whole occipital region, a large deflection at 20 msec was recorded from electrode 8 in response to contralateral clicks.

Figure 51 shows the average responses recorded from electrode 9. We see that there is good agreement between the predicted and observed waveforms for $\Delta\tau$'s greater than 10 msec, $\Delta\tau$ equal to zero, and $\Delta\tau$ greater than -20 msec. The other experimental responses are not so well matched by the predicted waveforms. Thus for small $\Delta\tau$'s, particularly if the click stimuli precede the shocks, the responses to the combined stimuli cannot be considered as the superposition of the responses produced by single-modality stimuli. Rather, an interaction between the responses to different modality stimuli is clearly seen.

Figure 52 shows the responses recorded from electrode 8. The top row shows, as usual, average responses to trains of clicks and of shocks presented separately. Notice the positive peak at 20 msec which is evoked by clicks. Notice also that the average shock response is quite similar to the shock response recorded from electrode 9 (Fig. 51). When it is remembered that the responses to ipsilateral clicks are very

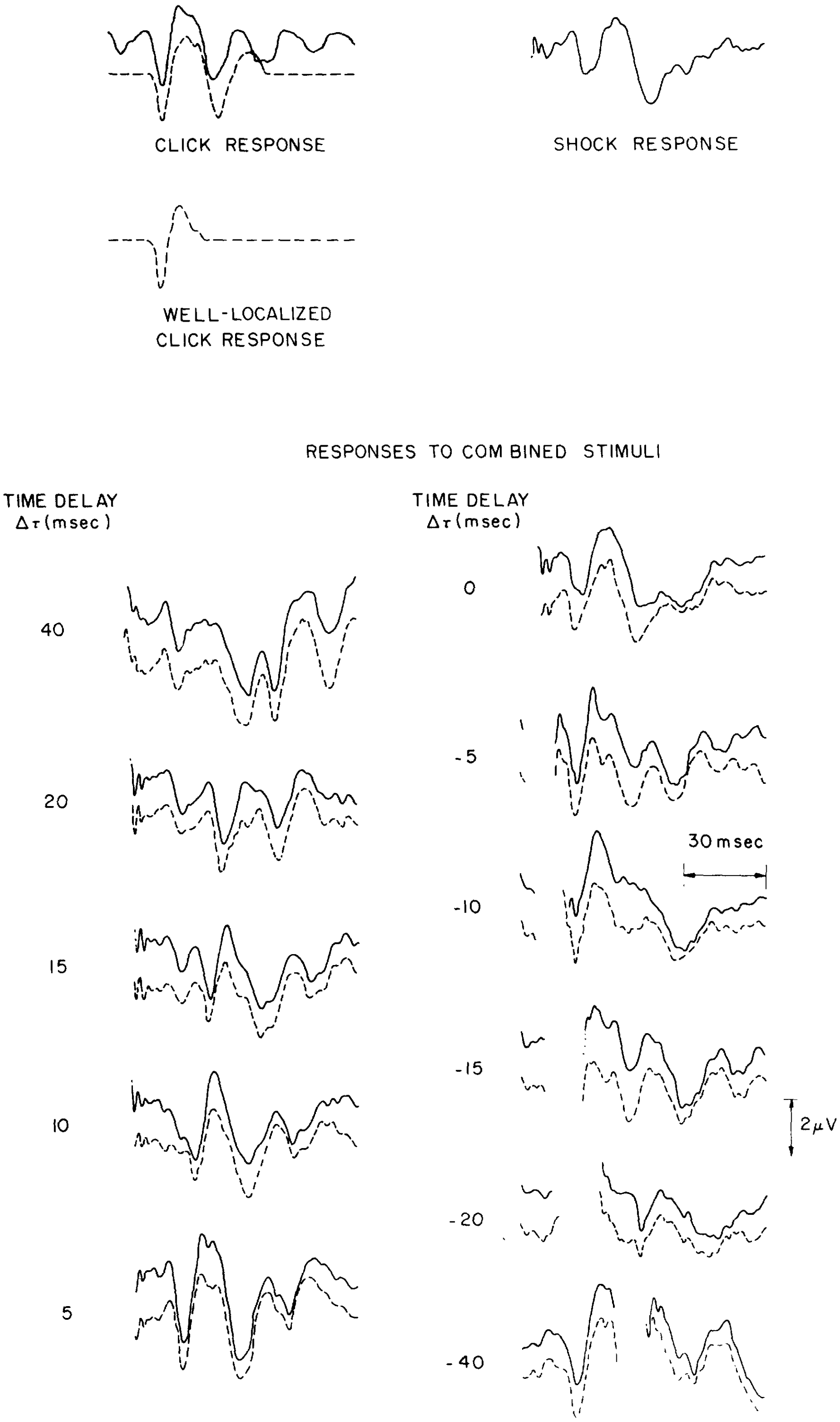


Fig. 52. Average responses to shock and click stimuli from electrode 8 (Subject, M. W., H-628). Same display as for Fig. 51 except that the idealized well-localized click response is also shown. Stimulus conditions: the individual responses used in the computation of this figure were recorded simultaneously with those used in the computation of Fig. 51. Response conditions: active electrode, 8; reference electrode, nose; number of responses, 2000.

similar at electrodes 8 and 9 for this subject (Fig. 21h) an interesting hypothesis suggests itself.

Let us suppose that we have two overlapping yet independent response areas to clicks: One is well localized and responds only to contralateral clicks; the other area we assume to be rather widespread on both sides of the head and equally responsive to clicks and shocks. On the basis of such an hypothesis, we would expect that the responses of the well-localized area to clicks would be unaffected by the shock stimuli, while the widespread area would exhibit interactions between responses to clicks and to shocks.

In order to test this model of two independent response areas, an idealized waveform of the "well-localized response" to clicks was first constructed by subtracting the idealized click response at electrode 9 from that of the idealized click response at electrode 8. This is a valid procedure, since we have assumed the "widespread click response" recorded from electrodes 8 and 9 to be nearly identical: The widespread response components should cancel each other if one electrode's response is subtracted from that of the other. The predicted response waveforms to shock-click pairs at electrode 8 were then constructed by simply superimposing the idealized well-localized response to clicks and the appropriate experimental widespread response as recorded at electrode 9. The predicted waveforms are shown as dotted lines directly beneath the corresponding responses actually obtained from electrode 8. The extraordinary agreement between the predicted and experimental waveforms, for all values of $\Delta\tau$, admirably supports our hypothesis that there is a well-localized area whose responses to clicks are independent of the responses generated by the widespread area.

Figures 53 and 54 show the average responses evoked by the shock-click pairs that were recorded from centrally located electrodes on subject M.W.'s scalp. The shock response at electrode E, shown in the top row of Fig. 53, has a waveform typical of postcentral responses (Fig. 47c). On the other hand, the shock response at electrode D, seen in Fig. 54, has a waveform that is characteristic of precentral responses.

Figure 53 shows that there is rather a complicated interaction between the shock and click responses at electrode E. For, although the experimental and predicted waveforms are somewhat similar, it is obvious that the responses interact appreciably, particularly when the shock stimuli precede the clicks. In addition, the components of the click responses for $\Delta\tau$'s of −20 msec and −40 msec are larger than predicted.

Figure 54 shows average responses recorded from electrode D which exhibit still more interaction than the responses at electrode E. Perhaps the fact that the response components evoked by the click stimuli at $\Delta\tau = -20$ and -40 msec are not augmented is most important. Apparently the potentiation of auditory responses at these values of $\Delta\tau$ is limited in this subject to postcentral responses.

The third subject, G. G., from whom average responses to shock-click pairs were recorded, exhibited still a different response pattern evoked by click stimuli alone. Peculiar to this subject was a large negative peak at approximately 15 msec; this peak was especially large in the temporal regions. In addition, an occipitally located

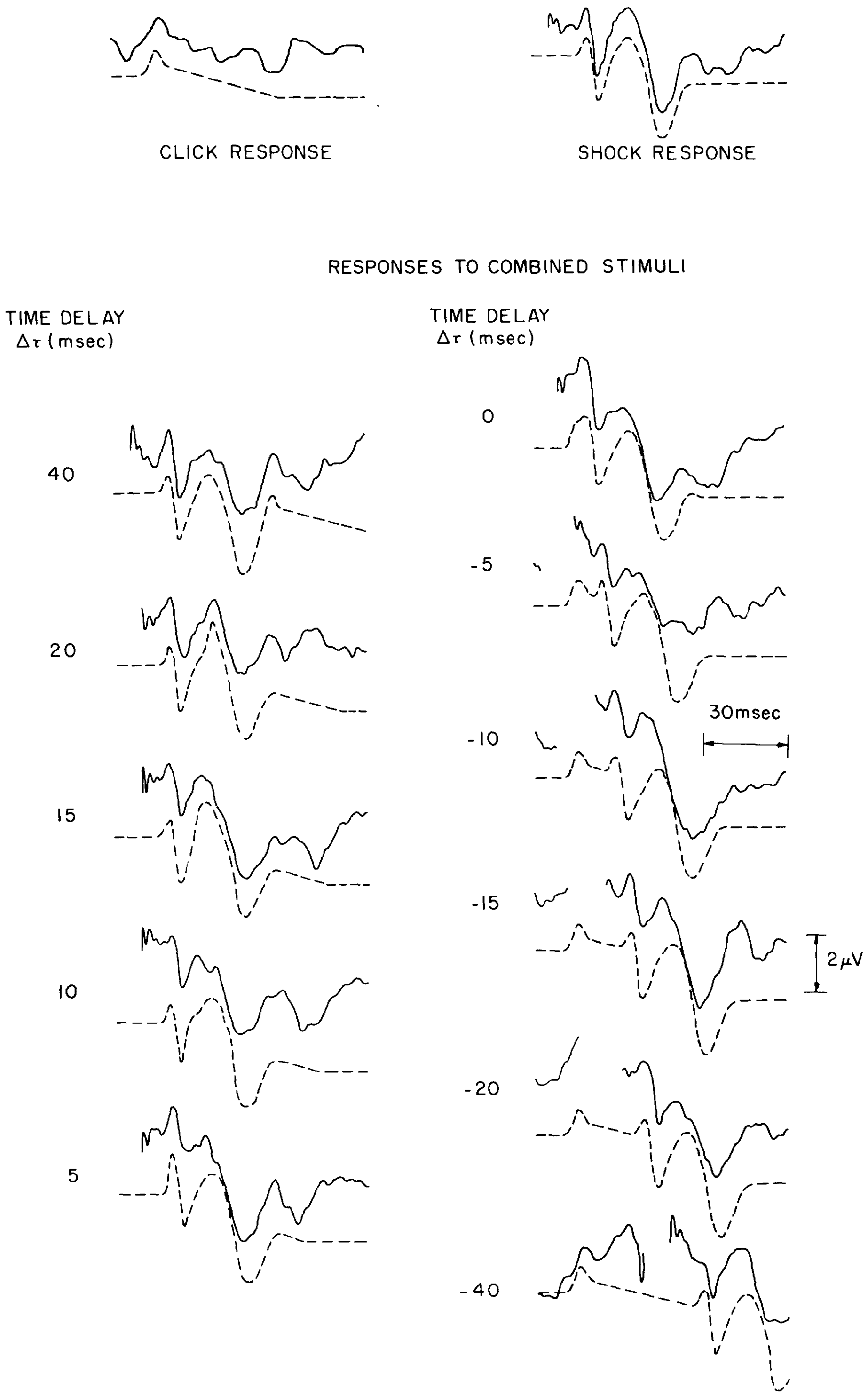


Fig. 53. Average responses to shock and click stimuli from electrode E (Subject, M.W., H-628). Same display as for Fig. 51. Stimulus conditions: the individual responses used in the computation of this figure were recorded simultaneously with those used in the computation of Fig. 51. Response conditions: active electrode, E; reference electrode, nose; number of responses, 2000.

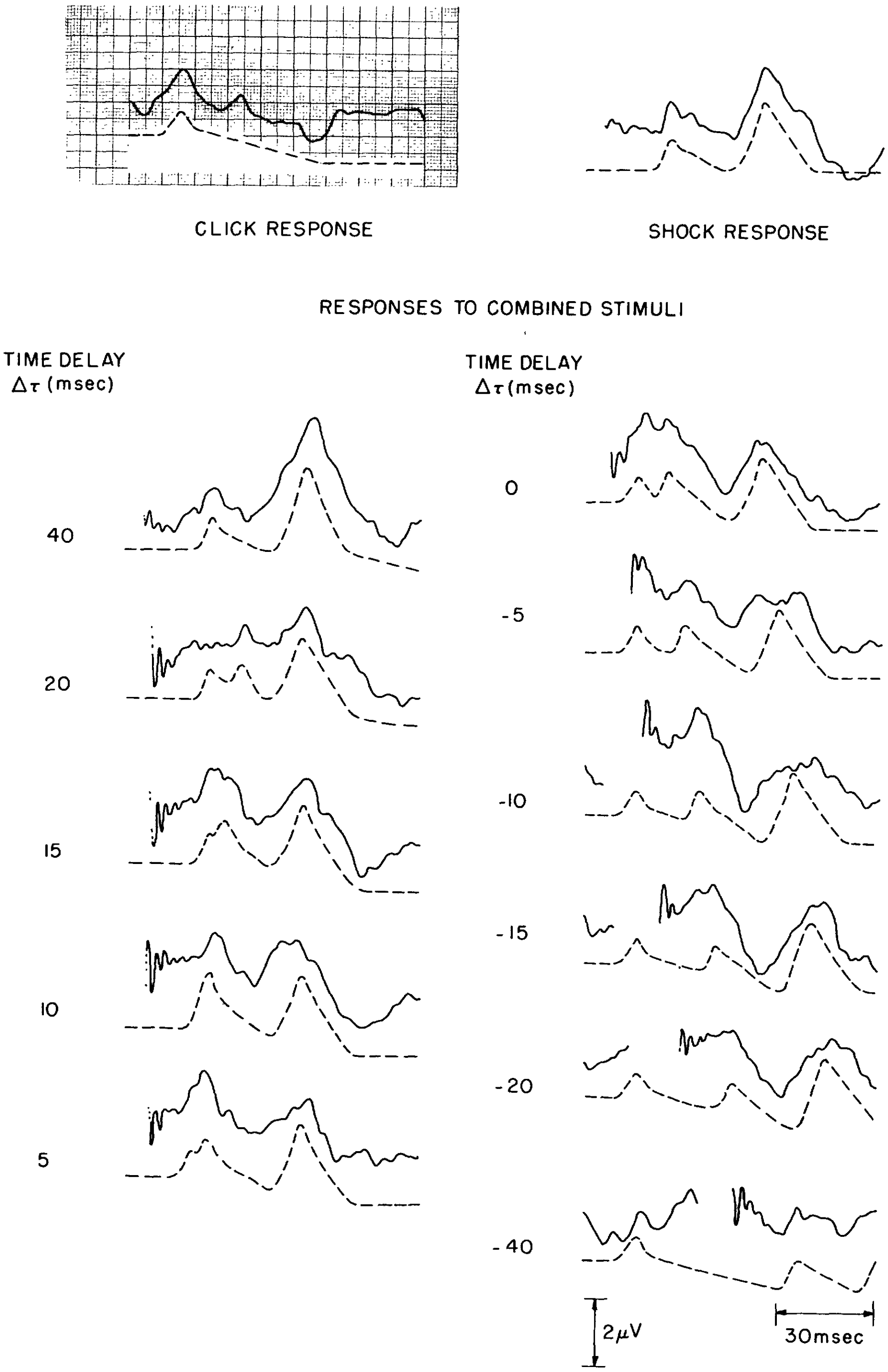


Fig. 54. Average responses to shock and click stimuli from electrode D (Subject, M. W., H-628). Same display as for Fig. 51. Stimulus conditions: the individual responses used in the computation of this figure were recorded simultaneously with those used in the computation of Fig. 51. Response conditions: active electrode, D; reference electrode, nose; number of responses, 2000.

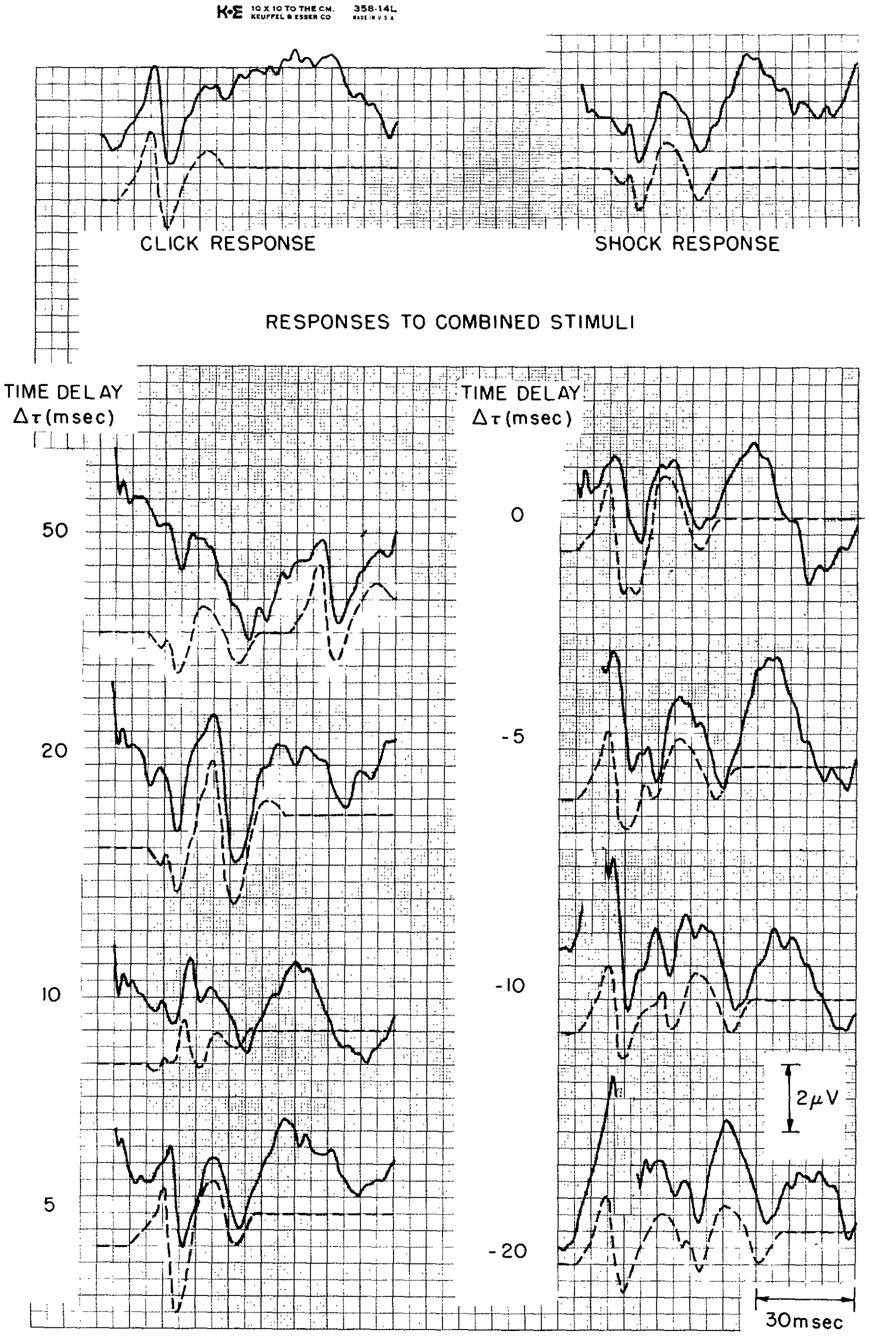


Fig. 55. Average responses to shock and click stimuli from electrode 3 (Subject, G. G., H-632). Same display as for Fig. 51. Stimulus conditions: all shocks to left wrist, 2.0 ma; all clicks to left ear (9C earphone), −40 db; each stimulus pattern, whether a simple stimulus or a shock-click pair, was repeated periodically at the rate of 10/sec. Response conditions: active electrode, 3; reference electrode, nose; number of responses, 2000.

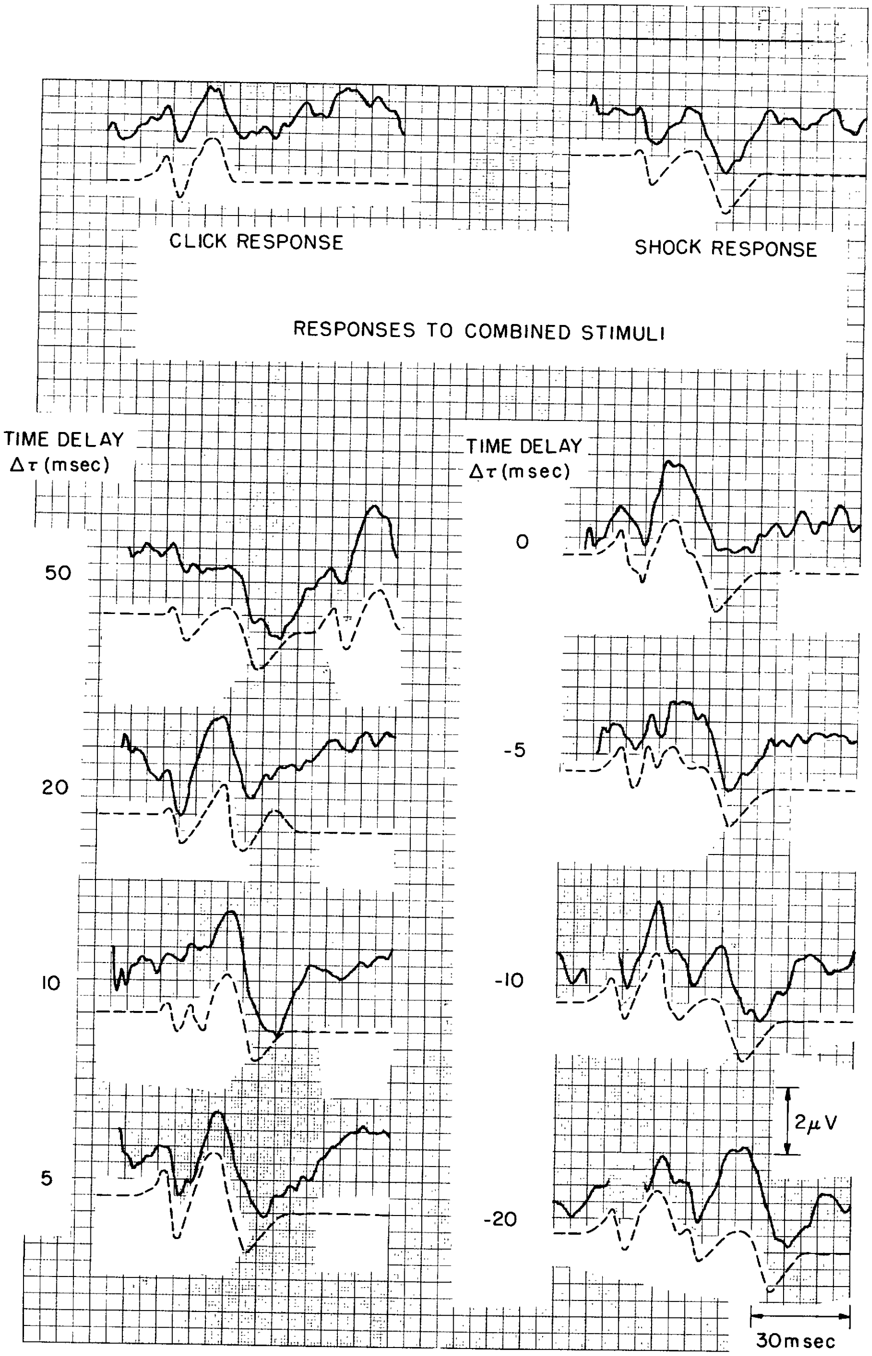


Fig. 56. Average responses to shock and click stimuli from electrode 8 (Subject, G. G., H-632). Same display as for Fig. 51. Stimulus conditions: the individual responses used in the computation of this figure were recorded simultaneously with those used in the computation of Fig. 55. Response conditions: active electrode, 8; reference electrode, nose; number of responses, 2000.

component was also observed at 30 msec (Fig. 21j).

Figure 55 shows the average responses to click and shock stimuli recorded from electrode 3, which, it may be remembered, is in the vicinity of electrode E. A complete distribution of responses to shock stimuli only was not obtained from the scalp of this subject, but the average response to shock stimuli in this figure is rather similar in waveform to the postcentral shock responses that were recorded from the other two subjects. Perhaps the most interesting effect in Fig. 55 concerns the deflections produced by clicks. For $\Delta\tau$ greater than 10 msec, the predicted waveforms closely match the experimental waveforms and the components due to the clicks may be called "normal." For $\Delta\tau = 0$, 5, or 10 msec, the response components due to the clicks are reduced in amplitude. However, when the clicks precede the shocks, the click components are again normal in size; indeed they are even potentiated. By contrast, the components of the response due to the shocks remain relatively unaffected for all $\Delta\tau$'s except perhaps for small values.

Figure 56 shows the responses recorded from electrode 8 on subject G. G.'s scalp. The average response to clicks that is peculiar to this subject is seen in the top row along with a rather typical shock response. Examination of the responses to the shock-click pairs shows generally close agreement between observed and predicted waveforms, indicating little interaction between responses. The systematic interaction found in Fig. 55 is certainly not present here.

d. Average Responses to Other Types of Multisensory Stimuli

The waveforms of the click responses obtained from our subjects were affected not only by shock stimulation but also by the presentation of other sensory stimuli. Figure 57 shows how the position of the head affected the click responses in various subjects. In the left column, click responses obtained from four different subjects, each sitting in a normal reading position are shown. The corresponding figures in the right column show responses evoked by the same acoustic stimuli, presented to the subject while his head was raised and his chin extended. The dependence of the response amplitude upon the position of the head for the first two subjects is remarkable. Definite, but more subtle changes are seen for subject M. W. Head position did not much affect the response obtained from electrode 8 on his scalp, but did have a noticeable influence upon the response recorded from electrode 9. Since the "well-localized response" is mainly observed at electrode 8 and not at electrode 9, such results indicate that the well-localized response is unchanged by the position of the head. The unchanging size of the well-localized response component is good evidence that the change in the "widespread response" was not simply due to a change in the acoustic stimuli caused by such physical changes as the bending of the external meatus or the shifting of the earphones. Lastly it must be noted that the responses evoked from subject W. R. were essentially the same no matter what position his head was in.

Light stimuli in the form of brief flashes were sometimes presented to our subjects,

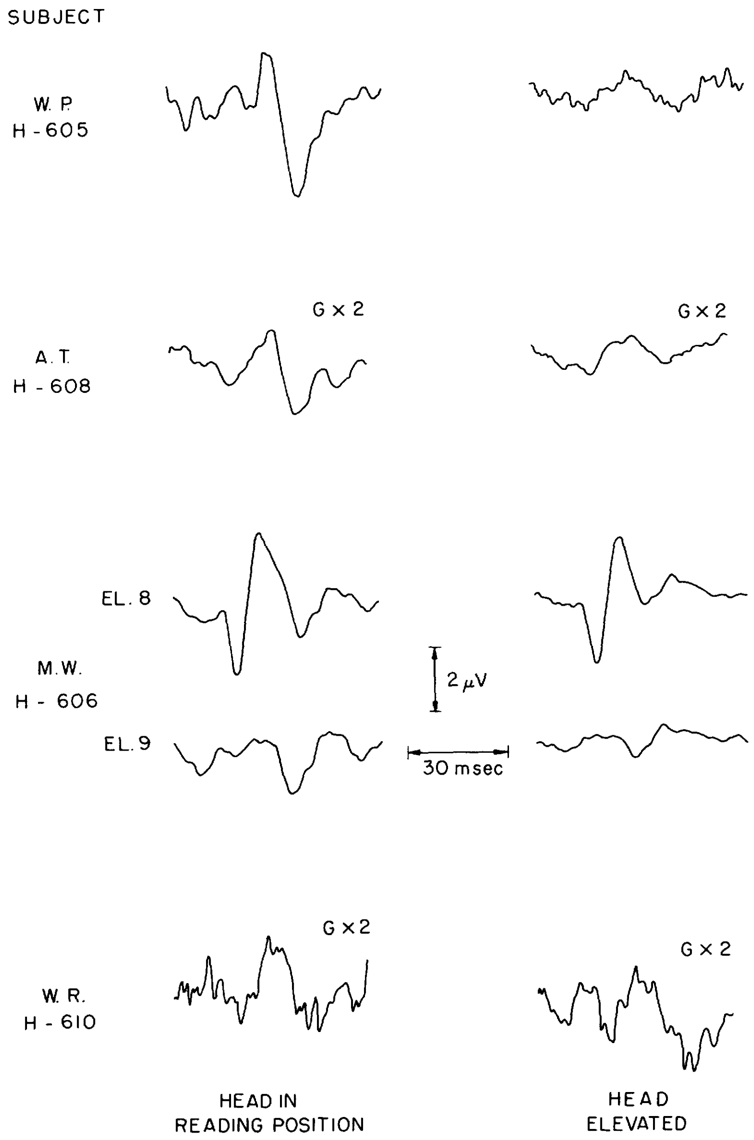


Fig. 57. Average responses to clicks for various orientations of the head. Left column: responses with head in normal reading position. Right column: responses with head raised. Subjects W. P. and M. W. used an elevated chin rest. Subjects A. T. and W. R. used voluntary control. Stimulus conditions: for all subjects, clicks, left ear, –45 db, rate 5/sec for Subject W. P., 15/sec for the others. Response conditions: active electrode, 8 (9 also for M. W.); reference electrode, either nose (M. W.) or 6 (others); number of responses, either 1000 (W. P.) or 2000 (others).

but no systematic study of responses to such flashes was undertaken. It may be stated, however, that average responses to the light flashes were obtained mainly from the occipital regions of the head and were considerably larger than those evoked by either shocks or clicks. Although multisensory stimuli involving light flashes were not systematically studied, clicks were occasionally presented to subjects in the presence and absence of light. No consistent differences in the average click responses were obtained under the two conditions.

e. Summary

Three different types of responsive areas, designated here as "primary," "overlap," and "interaction" areas, were found on the cat cortex by Buser and Borenstein (20). The responses to multisensory stimuli that we have obtained from various electrodes on the human scalp exhibit characteristics of the responses evoked from the three types of responsive area.

First, the average responses that we have obtained from the postcentral regions of human scalp behave in the manner characteristic of primary responses. Two subjects (G. G. and M. W.) displayed clear auditory responses from this postcentral region, and for these subjects the effect of shock stimuli upon the response components because of clicks was greater than the effect of the clicks upon the response components caused by the shocks. The data from subject G. G. illustrate this effect particularly clearly. For subject A. T., whose postcentral click responses were very small, click stimulation had no consistent effect upon the wave shape of the shock responses recorded by the postcentral electrode.

Second, the responses obtained from the occipital region of all three subjects show response characteristics of nonprimary or secondary responses. For subjects M.W. and A. T., the widespread responses evoked by click and shock stimuli were found to have the mutual dependence that is characteristic of responses evoked from the interaction areas. The effect that the position of the head had upon the click responses obtained from these same two subjects further illustrates the fact that their widespread responses to clicks were changeable by somatic stimulation. By contrast, subject M.W.'s well-localized responses were found to be completely independent of somatic stimulation, and thereby exhibited characteristics of responses evoked from either primary or overlap areas. Overlap characteristics are evident in the relative independence of the responses to shocks and clicks recorded from the occipital electrode of subject G. G. For all three subjects, therefore, the responses obtained with occipital electrodes displayed the characteristics of secondary responses.

Hence, we conclude that when multisensory stimuli involving clicks were used, the responses to clicks recorded from the human scalp displayed the characteristics of responses evoked from secondary cortical areas.

6.2 AVERAGE RESPONSES TO CLICKS PRESENTED DURING NATURAL SLEEP

The effect of natural sleep upon evoked responses in cats was mentioned briefly in Section I. Buser and Borenstein (22) report that during periods when the electrocortical potentials recorded were mainly slow waves (when the cat was presumably asleep), secondary responses became difficult to detect, although primary responses were still observable.

If we assume that comparable effects are present in human subjects, the effect of sleep upon average click responses recorded from the human scalp should be significant. For, if the responses recorded from the scalp are a reflection of activity within the primary auditory areas, these responses should remain detectable during sleep although their waveform might change. If, on the other hand, the responses are secondary in nature, we would expect them to be much more affected by sleep. Accordingly, we performed several experiments in which click stimuli were delivered to our subjects while they were asleep.

a. Potentials Recorded from the Scalp of Sleeping Subjects

Potentials that can be recorded from the human scalp during sleep have been the subject of investigations for many years. As early as 1937, Loomis, Harvey, and Hobart (69) described EEG potentials recorded from sleeping subjects and suggested a classification scheme for the different types of waveforms encountered. These authors suggested five categories, labeled A, B, C, D, and E, each of which was characterized by the presence or absence of certain rhythmic patterns in the EEG. Type A activity, for example, was characterized by the presence of alpha rhythm, while Type E activity exhibited "slow" waves. Bursts of 14-cps activity were labeled Type C activity, and a combination of 14-cps and slow waves characterized Type D. Type B activity had low amplitude with no particular rhythmic components. These authors associated all of the five types of EEG potentials with different stages of sleep, and described a continual shift of EEG potentials from one type of activity to another during a night of experimentation.

In a more closely controlled series of experiments, Blake and Gerard (70) also obtained EEG potentials from sleeping subjects. But, in addition, they regularly obtained a measure of the "depth" of sleep by stimulating the subject with a tone and noting the minimal intensity or duration needed to elicit either a verbal response or a spontaneous movement. The correlations between depth of sleep and EEG pattern were found to be quite good and enabled these authors to describe a typical night's sleep as follows: In the awake state, alpha activity, as well as higher frequency components, was observed. At the onset of sleep, the rhythmic activity diminished and irregular patterns of small amplitude were recorded. As slumber deepened, very regular alpha activity was sometimes observed. Deep sleep was reached, accompanied by slow waves in the EEG. After two hours, sleep became progressively lighter and rhythmic activity reappeared fitfully. During the fifth hour, sleep deepened again and slow waves reappeared.

Movements occasionally occurred and were usually succeeded by the appearance of alpha activity.

We must be cautious in our acceptance of the characterization of sleep proposed by Blake and Gerard (70), however, for recent work on cats (71) has suggested that the state of sleep characterized by irregular, electrocortical patterns of low amplitude, rather than by slow waves, is the deepest state of sleep.

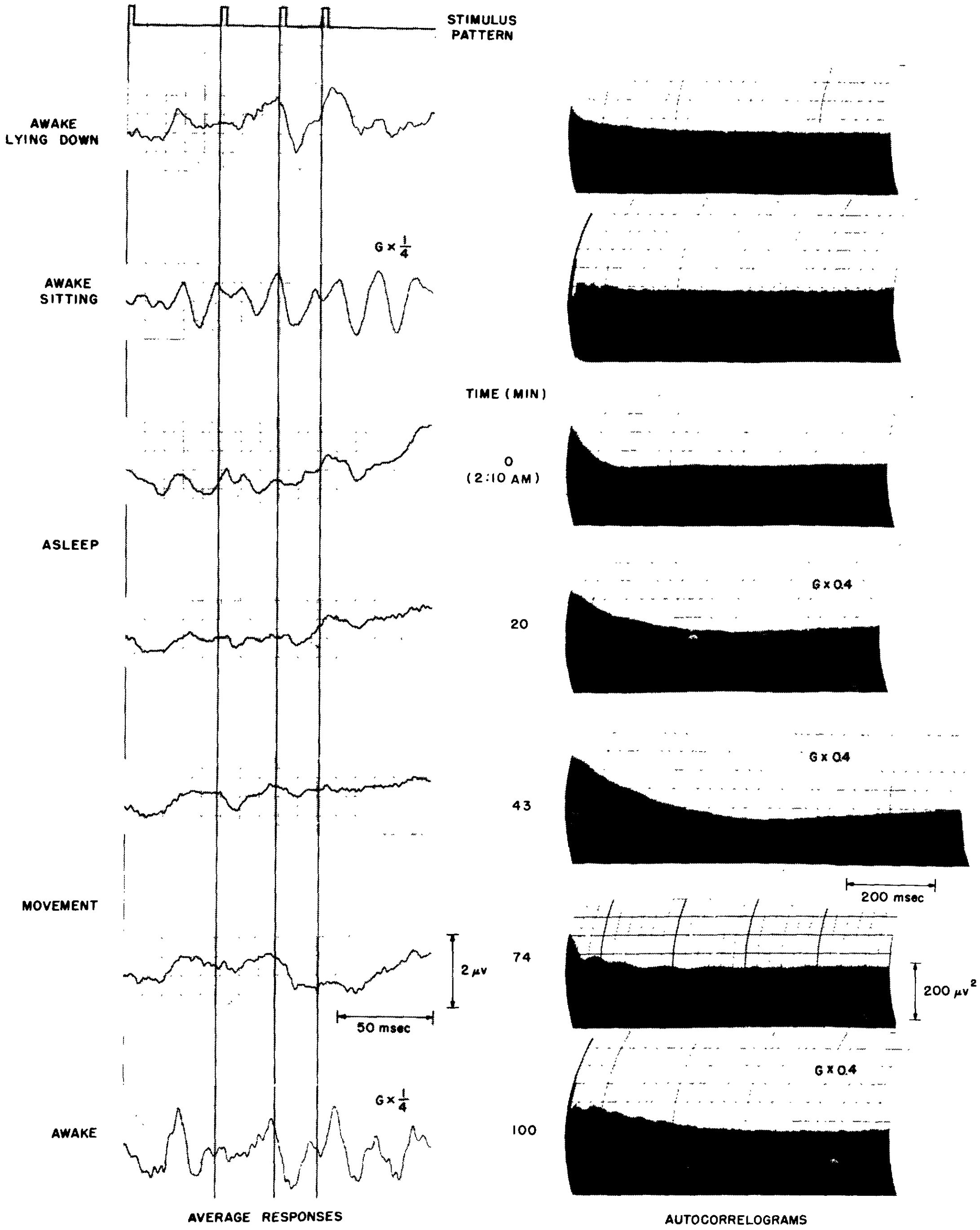
b. Design of Experiments

It is clear from the work of such investigators as Blake and Gerard (70) that sleep is not a single "state." Rather, the various measures employed by these workers indicate that a sleeping subject is in a continually changing condition. Because of this constant change in the condition of a sleeping subject, two identical stimulus trains presented at different times during a period of sleep could yield quite different average responses. It would thus be questionable to compare average responses evoked by different stimulus trains, particularly if much time had elapsed between the presentation of the different trains. Therefore, the type of stimulus presentation which involves many different stimulus trains presented sequentially was not considered particularly suitable for studying the average responses of sleeping subjects. Instead, the continued repetition of identical stimulus patterns seemed more suitable to us.

The stimulus pattern chosen for use with our sleeping subjects is shown in the upper left-hand trace of Fig. 58a. This pattern contains four clicks of equal intensity, separated by varying time delays. As can be seen, the second click occurs 50 msec after the first click, and the third and fourth clicks follow after delays of 30 msec and 20 msec, respectively. This basic pattern was repeated periodically at a rate of 5 per second, a fact which means that the first click of each pattern followed just 100 msec after the fourth click of the preceding pattern. The first click was used as the time marker presented to ARC; each average response, therefore, contains average response components evoked by each of the four clicks in the basic stimulus pattern.

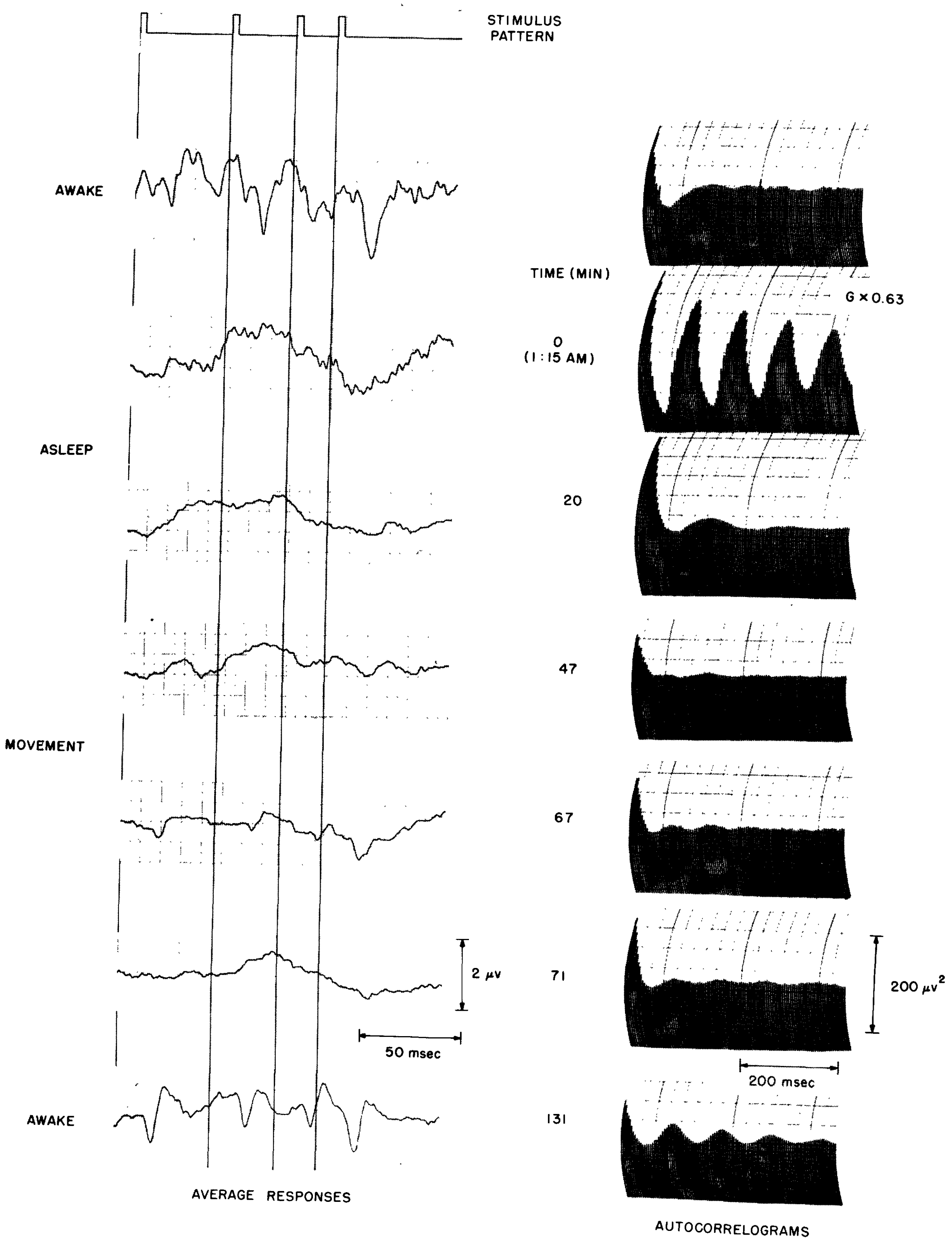
The same three subjects, A. T., M. W., and G. G., used in the experiments involving shock and click stimuli, were used in these "sleep experiments." Each of the experiments was run at night; the subjects first prepared themselves for sleep and then lay down on a cot in the soundproof chamber. Common solder-blob electrodes were used, attached to the scalp with collodion. (Since collodion does not prevent the conducting paste, bentonite, from drying out, care was exercised in exposing as little of it as possible to the air. The bentonite paste was composed of 75 parts by volume bentonite powder, 10 parts saturated $CaCl_2$ solution, and 40 parts Ringer's solution. We wish to thank Dr. John S. Barlow for this formula.) The stimuli were presented to the subjects through the 9C earphone which was firmly attached to the ear with patches of collodion. In each case, the earphone was still firmly attached at the end of the experiment.

During the experiments, the "state" of the subjects was monitored by a continuous display of the EEG potentials on an oscilloscope. Rather than reporting necessarily brief


STIMULUS PATTERN
AWAKE LYING DOWN
G × 1/4
AWAKE SITTING
TIME (MIN)
0 (2:10 AM)
ASLEEP
20
G x 0.4
43
G x 0.4
200 msec
MOVEMENT
74
2 μv
200 μv²
50 msec
G x 0.4
100
AWAKE
G × 1/4
AVERAGE RESPONSES
AUTOCORRELOGRAMS

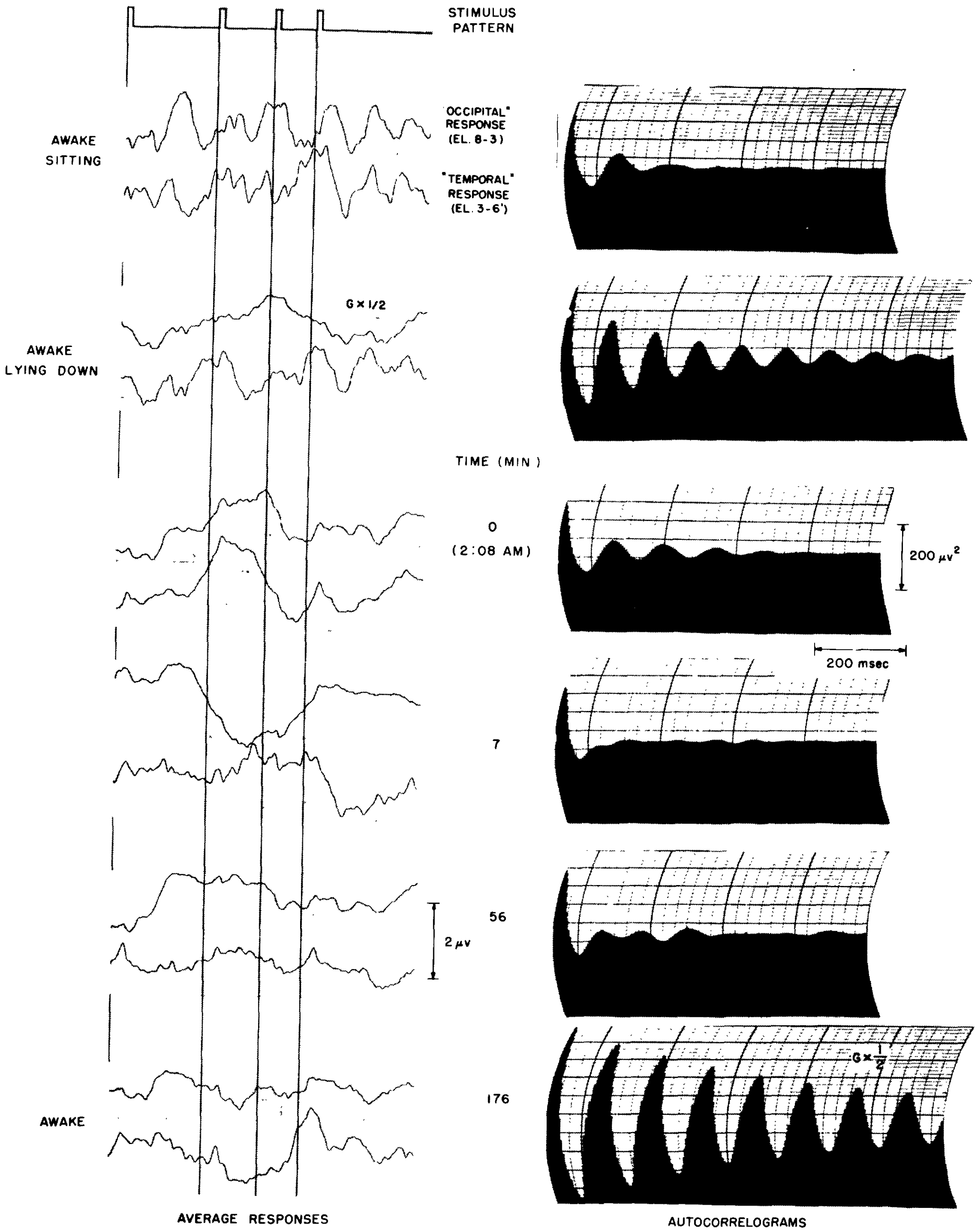
(a)

Fig. 58a. Average responses to clicks and autocorrelograms obtained from a sleeping subject (A.T., H-634). Left column: average responses to clicks. Stimulus conditions: four-click pattern shown at top of figure, left ear (9C earphone), all clicks were -55 db, pattern repeated repetitively at the rate of 5/sec. Response conditions: active electrode, 8; reference electrode, 6; number of responses, 1000; the first clicks of each four-click pattern were used as time markers for ARC. Right column: autocorrelograms computed from the same EEG data used in the computation of the corresponding average responses. Each curve is, therefore, the autocorrelogram of 3.5 minutes of data obtained from a subject stimulated with clicks. Elapsed time refers to the approximate time after the subject was instructed to sleep when the data used in the computation of the particular curves began to be recorded. In order to prevent adaptation effects, the stimuli were turned off occasionally. They were turned off for 5 minutes at time 30 minutes.


STIMULUS PATTERN
AWAKE
ASLEEP
MOVEMENT
AWAKE
TIME (MIN)
0
(1:15 AM)
20
47
67
71
131
G × 0.63
2 μv
50 msec
200 μv²
200 msec
AVERAGE RESPONSES
AUTOCORRELOGRAMS

(b)

Fig. 58b. Average responses to clicks and autocorrelograms obtained from a sleeping subject (Subject, M.W., H-624). Left column: average responses to clicks. Stimulus conditions and response conditions: same as for Fig. 58a. Right column: autocorrelograms computed from EEG data used in the computation of the corresponding average responses (T = 3.5 minutes). Elapsed time refers to the approximate time after the subject was instructed to sleep when the data used in the computation of the particular curves began to be recorded.


STIMULUS PATTERN
"OCCIPITAL" RESPONSE (EL. 8-3)
"TEMPORAL" RESPONSE (EL. 3-6')
AWAKE SITTING
AWAKE LYING DOWN
G×1/2
TIME (MIN)
0
(2:08 AM)
200 μv²
200 msec
7
56
2 μv
176
G×1/2
AWAKE
AVERAGE RESPONSES
AUTOCORRELOGRAMS

(c)

Fig. 58c. Autocorrelograms and average responses to clicks obtained from a sleeping subject (G.G., H-629). Left column: average responses to clicks. Stimulus conditions: same as for Fig. 58a. Response conditions: averages of simultaneously recorded responses from two electrode pairs are shown in each row. For upper trace of each row (the "occipital" response), active electrode, 8; reference electrode, 3; for lower trace of each row (the "temporal" response), active electrode, 3; reference electrode, 6' (electrode on left side of head, directly opposite electrode 6); number of responses, 2000. Right column: autocorrelograms computed from the first 5 minutes of the EEG potentials used in the computation of the corresponding "occipital" average responses. Elapsed time refers to the approximate time after the subject was instructed to sleep when the data used in the computation of the particular curves began to be recorded.

and incomplete visual observations made during the experiments, however, we computed autocorrelograms from the pertinent parts of the recorded EEG data. Autocorrelograms, it will be remembered from Section III, are computed from several minutes of continuous data and present a fairly convenient summary measure of these data. Rhythmic activity is especially well represented by an autocorrelogram. In addition, the mean square of the total electrical activity correlated is given directly by the ordinate of the autocorrelogram at $\Delta\tau = 0$.

c. Experimental Results

Figure 58a shows the results obtained from subject A. T. The curves in the left column are average responses. Autocorrelograms, computed from the same EEG data that were used to compute the corresponding average responses are shown in the right column. Let us first look at the curves in the second row, which summarize the data obtained from the subject when he was sitting on the cot and reading. The average response computed during this time shows a complex waveform which is, however, easily resolved when it is noted that the familiar negative deflection follows 30 msec after each click of the basic four-click pattern. In terms of the overlap model of Section IV, the responses evoked by the individual clicks simply overlap one another. The autocorrelogram $R(T, \tau)$ computed from these same data has a large value for $\tau = 0$. Since for $\tau = 0$, the ordinate is equal to the mean square of the total activity processed, the mean square of the EEG recorded from the sitting subject is large.

The data used to compute the traces shown in the top row of Fig. 58a were recorded before the data summarized in the second row were and they were obtained while the subject was lying down and reading. Notice that the average response evoked when the subject was lying down is much smaller in amplitude than that evoked while he was sitting up. This reduction in amplitude is quite striking but not unreasonable when we remember the effect of shock stimulation of the hand and the effect of head position upon the click responses for this same subject. (It should be noted that the act of lying down reduced the amplitude of subject A. T.'s average responses to clicks during the day when he was alert (H-635).) When we compare the autocorrelogram of the subject prone with that of the subject sitting, we see a marked decrease both in the ordinate for $\tau = 0$ and in the rhythmic components observed near $\tau = 0$. Since electric potentials produced by the musculature of the head and neck have been shown (Fig. 44) to contribute high-frequency components to the EEG, the correlogram of the prone subject may be interpreted as signifying that the musculature of the head and neck were then in a more relaxed state than when the subject was sitting. A parallel reduction in the mean square of the EEG potentials and in the amplitude of the average responses to clicks was once observed in this subject even while he was sitting, and suggests that the degree of tension existing in the head and neck muscles has a marked effect upon this type of responses to clicks.

The remaining rows of Fig. 58a show average responses and correlograms obtained at various times during the night. Notice that while there is a detectable average response component to the first click in all of the traces in the left column, components that are time-locked to the later clicks in the basic pattern vary throughout the experiment. The overlap model, therefore, no longer applies to the average response components evoked by any particular click of the four-click pattern, for many of these components are very much changed by the occurrence of the preceding clicks. In the stage of sleep characterized by slow components in the correlogram, response components evoked by the later clicks of the four-click stimuli are hardly detectable.

The subject moved shortly before 74 minutes. Note the appearance of rhythmic activity at a frequency of roughly 14 cps in the correlogram of data collected at 74 minutes. (Although each average response and correlogram was computed from 3.5 minutes of data, for ease of reference we shall refer only to the beginning of this 3.5-minute period.)

The data summarized in the last row were obtained after the subject had been awakened and asked to sit up on the cot and read. Both the mean square value of the EEG and the amplitude of the average of the responses obtained when the subject was awakened are greatly increased over those obtained while the subject was lying down, asleep.

Figure 58b shows data obtained from subject M. W. The first row summarizes data recorded while the subject was sitting in a chair reading. The positive deflection that follows each click of the four-click sequence at 20 msec is clearly seen, and a negative peak at approximately 30 msec follows at least the first three clicks. The waveform of the response components evoked by the first click, when compared with this subject's responses in the left column of Fig. 57, is evidence that both the well-localized and widespread responses were recorded in this subject. The autocorrelogram of these data shows a lack of rhythmic components.

The subject was then put to bed and instructed to sleep. Average responses and autocorrelograms were computed from various sections of the EEG potentials recorded from the sleeping subject. Data collected directly after the instruction "go to sleep" had been given are summarized in the second row. The correlogram shows a strong rhythmic component of alpha frequency, suggesting that the subject was in the state of light sleep, mentioned by Blake and Gerard (70), which is accompanied by especially regular alpha activity. The average responses obtained from these same data show only "hints" of response components at 20 msec.

The data collected at 20 minutes show rhythmic activity of a decreased frequency. The data collected at 47 minutes have a low mean-square value, and the average of the responses obtained at that time shows clear deflections at 30 msec, the characteristic latency of the "widespread response" in this subject.

The data collected at 67 minutes were obtained just after the subject had moved: 14-cps components are clearly seen in the correlogram and the 20-msec peaks of the "well-localized response" components are seen in the average response. The data collected at 71 minutes were obtained right after the collection of the data that are summarized in the preceding row. Although some rhythmic activity is still seen in the correlogram, no clear deflection of any type is seen in the average response.

The subject was awakened in due course and asked to lie in the dark but to keep awake. The traces in the bottom row were computed from data taken during this period. An alpha-frequency component is seen in the correlogram and distinct well-localized response components are seen to follow each of the four clicks. Widespread responses do not seem to be present. (Compare with this subject's responses in Fig. 57).

Figure 58c summarizes the data obtained from subject G. G. during sleep. The autocorrelograms show some form of rhythmic activity throughout the experiment, and thus indicate that deep sleep was probably never achieved. In fact, upon termination of the experiment, the subject reported that he had awakened once during the experiment and felt cold, and was sleeping "lightly" when the experiment was ended.

Average responses obtained from two electrode pairs are of interest in this experiment and are shown together in each row of the left column. The upper curve of each pair exhibits the 30-msec "occipital" response components common to all of our subjects; the lower curve of each pair shows the earlier contralateral response components that were observed in the temporal region of this subject.

The top row summarizes data taken when the subject was sitting quietly and reading. The correlogram shows slight alpha components and the appropriate average response components are clearly seen in each of the average responses. The subject then lay down ready for sleep, but the lights were left on and he was instructed to stay awake. The average of the "occipital" response obtained during this period is not too clear, but deflections occurring 30 msec after each of the four clicks are seen. (In a subsequent experiment this same stimulus pattern was presented to subject G. G. while he was both sitting and lying down (H-633). No significant differences were noticed in the responses obtained under these two conditions.) The "temporal" response still exhibits a large deflection after each of the four clicks.

At this point in the experiment, the subject was instructed to go to sleep and he was left in darkness. The averages of the "occipital" responses obtained during sleep all show a response component 30 msec after the first click of the four-click pattern. Response components following the later clicks of the basic pattern are, however, difficult to detect. Even in the data obtained from the "occipital" electrode at 176 minutes, after the subject had been awakened and instructed to open his eyes and stay alert, average components following the later clicks are small in amplitude. Such response behavior is very similar to that noted for the occipital response components in subject A. T.

During sleep, the 15-msec "temporal" response components following each click disappeared and a much earlier component with approximately 5-msec peak latency is seen. If it is realized that electrode 6' (the prime denotes the ipsilateral side) was the reference electrode used to record the "temporal" responses, we cannot ignore the possibility that these response components at 5 msec were contributed by the reference electrode, and hence were ipsilaterally generated. Moreover, when reference is made to Fig. 21k, it is seen that such short-latency components were indeed recorded from this subject for ipsilateral click stimulation. Finally, since electrode 3 was the reference electrode used to record the "occipital" responses, responses localized near electrode 3 would also be observed in the "occipital" responses. Early response components are, however, not seen in the "occipital" responses, and so it is concluded that the 5-msec components were recorded by electrode 6', at a location near the ipsilateral ear.

With arousal from sleep, 15-msec response components are again seen in the average "temporal" response; a particularly large one is evoked by the fourth click of the pattern.

d. Summary

The effects of sleep upon the 30-msec response components that were recorded occipitally from our three subjects are quite complex. Complete disappearance of these occipital components is observed in the responses obtained from only one subject, M.W. Yet we have seen that for each subject, sleep caused striking changes in the average responses evoked by our stimulus pattern, a group of several clicks spaced rather closely in time. We may conclude, therefore, that the effects of sleep upon the 30-msec components of the average-response are not incompatible with the identification of these 30-msec components as secondary responses. Since the behavior of the 30-msec components recorded from these three subjects, from subject A. T. in particular, is assumed to be representative for our whole experimental population, this conclusion may be tentatively extended to the 30-msec response components generally recorded from human scalp.

The effect of sleep upon the well-localized response components of subject M. W. is easier to describe: these components disappeared completely during part of the time he was asleep. The 15-msec response components recorded from subject G. G. were likewise not detectable during some stages of sleep. We conclude, therefore, that the unusual average response components observed in subjects G. G. and M. W. during sleep exhibit characteristics that are compatible with their identification as secondary responses.

6.3 CONCLUSION

Average responses to clicks have been recorded from the scalps of a number of human subjects and certain experimental facts about these responses have been established.

(a) These responses are usually found to be largest in the occipital regions of the scalp. (Indeed, for subjects A. T. and W. P., the average responses are limited essentially to the occipital regions only.)

(b) These occipitally located responses are essentially bilateral in character — clicks to either ear produce substantially equivalent average responses at corresponding points on opposite sides of the head. Since we believe that the average responses recorded from the scalp are reflections of the average responses that exist on the surface of the cortex, we may say that bilateral responses to clicks are present in the occipital regions of the cortex.

(c) The earliest component of these occipitally located responses has a peak latency of 30 msec, which is longer than that reported for the primary click responses in experimental animals but is quite comparable with peak latencies reported for secondary responses.

(d) As stimulus parameters are systematically changed, these response components at 30 msec have been found to demonstrate characteristics that resemble those of certain responses recorded from the exposed cortex of the cat. Altogether there is a strong suggestion that these click responses, which exist in regions so far removed from the auditory projection areas, which have peak latencies of 30 msec, and which are bilateral in nature, are indeed secondary responses.

The experimental results just described give still further evidence of the nature of these occipital responses. First, there is clear evidence that the average responses to clicks can be affected by the position of the head, and even by the position of the whole body. Moreover, the click responses were found to "interact" with bilateral responses evoked by shock stimulation of the wrist. Furthermore, these average responses from the human scalp changed a great deal when the subject went to sleep. The data obtained from these experiments are similar to data reported by Buser and Borenstein (20, 22) for secondary responses in the cortex of the cat.

We conclude, therefore, that the 30-msec components of the average responses to clicks that we have recorded from the human scalp are probably secondary cortical responses. The earlier response components that we recorded from subjects M. W. and G. G. show quite different characteristics, but the available evidence permits us to designate even these components as probably secondary responses. We recognize, of course, that we have studied only the short-latency components of responses that are recordable from human scalp and that we can make no statement about longer-latency components such as the K-complex.

VII. AVERAGE RESPONSE CORRELATES OF SENSORY PERFORMANCE IN MAN

The stimulus-evoked activity recorded by gross electrodes from the cerebral cortex of experimental animals was reviewed briefly in Section I. Such electrophysiological data, gathered from many parts of the brain by many different experimenters, have been rapidly accumulating during recent years. However, as discussed in Section I, the extension of these techniques to human subjects has been very limited.

Recently, data have also been accumulating concerning the ways in which various organisms handle sensory information. The ability of organisms to detect and identify physical stimuli and to make discriminations between different stimuli have been greatly clarified by extensive investigations. But because of the difficulty of communication with subhuman species, experiments in the area of sensory performance have been conducted, for the most part, on human subjects. It is true that various types of conditioning techniques have been developed for use with experimental animals which enable an experimenter to "ask" certain types of experimental questions. But such studies are still limited in scope.

The search for correlations between the sensory abilities of an organism and electrophysiological events that occur within that organism has, therefore, been quite difficult. For while most of our electrophysiological data come from such animals as guinea pig, cats, and monkeys, the sensory performance of these species is less well known than that of man. Man's sensory performance, on the other hand, has been extensively investigated, but there is a lack of electrophysiological data on humans.

Some investigators have attempted to find meaningful correlations between electrophysiological data obtained from lower animals and psychophysical data obtained from humans. Stevens and Davis (72), for example, first review the psychological responses of human observers to auditory stimuli. Then they describe possible physiological mechanisms involved in human hearing on the basis of electrophysiological data obtained mainly from experimental animals. While similar physiological mechanisms undoubtedly exist in humans and in subhuman species, a cross-species comparison needs to be made with great care.

Later investigators have measured sensory performance and electrophysiological data in the same experimental animals. Heise and Rosenblith (73), for example, measured absolute thresholds to clicks in pigeons. A "behavioral threshold" was first determined in these birds by operant conditioning techniques. Then, under anesthesia, neural potentials from the region of the cochlea were recorded. The lowest intensity at which the first neural component was detectable was termed the "electrophysiological threshold." The electrophysiological and behavioral thresholds agreed quite closely in the two pigeons on which these experimenters determined both thresholds.

A similar study was performed on cats by Hind and Schuknecht (74). These investigators first trained cats to respond to tone pips. Then after experimental surgery on the cochleas, the lowest intensities of tone pips to which the cats responded (the "behavioral thresholds"), were compared with the lowest intensities of tone pips that could consistently produce full-scale "strychnine responses" from the auditory projection cortex of the same cats (the "cortical thresholds"). The cortical thresholds, for even the most sensitive preparations, were found to be approximately 30-40 db higher than the corresponding behavioral thresholds. Such a wide discrepancy, however, does not necessarily mean that the alert animals responded to stimuli that did not evoke cortical responses from them when they were deeply anesthetized. First, the criterion for cortical threshold, which was arbitrarily set at the lowest intensity of tone pip which evoked full-scale "strychnine responses" 75 per cent of the time, may have ignored significant changes in cortical activity at lower intensities. In addition, sound-pressure levels in the behavioral test were determined by free-field measurements at the point where the cats' heads were situated during the tests; the sound levels in the cortical tests, on the other hand, were measured near the eardrums in a closed sound system. Yet, in spite of the large differences in absolute thresholds, threshold shifts caused by experimental cochlear damage, as measured by the two methods, were in many cases strikingly parallel: Elevation of threshold for particular frequency ranges was reflected in both sets of measurements.

It should be emphasized here that the electrophysiological data used in the study of Hind and Schucknecht (74) were recorded only from the auditory projection areas of the cat cortex. The function of the cortex with regard to sensory performance is, however, not well understood. Indeed, the removal of large parts of cortex from experimental animals has been shown to have relatively little effect upon the ability of the animals to perform simple discriminations of auditory stimuli. Butler, Diamond, and Neff (75) trained cats by operant conditioning techniques to discriminate between tones of different frequencies. Bilateral removal of regions AI, AII, Ep, and some neighboring cortex anterior to these regions did not impair the ability of the cats to discriminate between the tones. The effect of cortical ablation upon the ability of cats to discriminate between sounds of different intensity has been investigated by Raab and Ades (76). These experimenters trained cats to respond to intensity changes of various tone pips, and found that the removal of cortical areas that included the auditory projection areas did not affect the ability of the cats to discriminate intensity changes. Consequently, it is not certain that the cortex is the best place to "monitor" the activity of the mammalian nervous system in relation to the performance of sensory tasks.

Until the present time, few electrophysiological correlates of human sensory performance have been directly measured from the human brain. Potentials have been obtained from the scalp of many normal subjects, but the activity usually recorded is so complex that it makes interpretation difficult. Averaging techniques, however, provide a tool whereby evoked responses, which we have identified with "secondary" cortical responses (see Section VI), are now easily obtainable with scalp electrodes. Hence, experiments measuring both behavioral performance of a human and average responses evoked from his brain can now be easily conducted. To be sure, an average evoked response is only one simple measure of electrophysiological activity, but it is a measure.

As an illustration of the types of experiment that can now be performed on man, two different types of experiments measuring average evoked responses and psychophysical responses in the same human subjects are reported here. These experiments deal with the measurement of absolute thresholds and with the effect upon average responses of the "psychophysical states" of our subjects.

7.1 MEASUREMENT OF AUDITORY THRESHOLDS BY AVERAGE RESPONSE TECHNIQUES

a. Previous Electrophysiological Methods Used to Measure Auditory Thresholds

Many experimenters, particularly those who are interested in the hearing of infants and others who cannot or will not communicate, have investigated the electrophysiological correlates of hearing.

Perl, Galambos, and Glorig (77) tried to estimate the psychophysical threshold of human subjects by visually examining the potentials recorded with the use of scalp electrodes. Defining a "response" to a click as either the appearance of the K-complex or the disappearance of the alpha rhythm, Perl and his colleagues found that the lowest click intensity at which responses were evoked 20 per cent of the time was usually within 10 db of the subject's psychophysical threshold. However, the lowest intensity at which tone bursts could evoke consistent responses did not agree closely with the corresponding psychophysical thresholds.

Derbyshire, Fraser, McDermott, and Bridge (78) defined five types of changes that may occur in the EEG following the presentation of tone stimuli to dozing subjects: (a) general reduction of potential amplitude, (b) appearance of K-complex (c) appearance of high-frequency activity, (d) appearance of a few cycles of 14-cps activity, and (e) disappearance of alpha rhythm. Using the criterion that the appearance of two or more of these changes constituted a "response," they determined the lowest intensities that evoked responses 50 per cent of the time. These threshold intensities were then compared with the results of standard audiometric tests. For 22 cases, the psychophysical threshold was, on the average, 18 db lower than the electrophysiological threshold; however, there was a rather high variance. Incidentally, responses to click stimuli were also observed.

Making use of Dawson's photographic superposition technique, Suzuki and Asawa (79) also investigated extracranially recorded responses to tones in man. The waveform of the responses which they obtained suggests that they recorded the familiar K-complex. The lowest intensity at which tones could evoke detectable responses was usually within 20 db of the thresholds determined by "standard psychophysical methods."

When certain sounds are given to a human subject, the autonomic nervous system is known to react. For example, the electric potential observed between two electrodes placed on the skin shows a definite change following certain sounds, a response which is presumably mediated by the sympathetic system. Attempts have been made to use these "galvanic skin responses" as some indication of the thresholds of hearing, but reliable results are difficult to achieve. Another type of response consists of a change in the resistance measure by two electrodes placed on the skin. This change is thought to result from increased activity of the sweat glands, the increased saline in the skin under the electrodes causing a lower resistance between electrodes. One advantage of this type of response is that it can be conditioned. For instance, Hardy and Bordley (80) used a shock to condition a change in skin resistance whenever a tone was sounded. A mild shock was consistently given to the subject a few seconds after a tone was presented. Eventually a change in skin resistance was seen to follow the presentation of a sound even though the shock was withheld. When this conditioned response was firmly established, the intensity of the tone was gradually reduced until no response was seen. The lowest intensity at which a response was clearly seen was called "threshold." In a study of tests involving 89 different ears, the threshold values achieved by this galvanic skin response technique agreed within 5 db with thresholds established by routine audiometric tests.

Gersuni (81) also used conditioned-response techniques. Thresholds for tone stimuli were obtained by using conditioned skin-responses, conditioned eye-blink, and conditioned alpha-rhythm depression. These thresholds are reported to agree within 0.2 db with thresholds reported by the subjects. His results seem remarkable in view of the results reported by Hardy and Bordley (80).

Other investigators have studied rather more indirect responses. Galambos, Rosenberg, and Glorig (64), using a fine wire in contact with the eyelid, found that clicks could elicit eyeblinks with a remarkably consistent onset latency of 35-40 msec. The percentage of clicks which caused this eyeblink was found to be roughly proportional to the intensity of the clicks. The lowest intensity that elicited such eyeblinks was within 30-50 db of psychophysical threshold.

b. Experimental Results Obtained in this Study

The intensity experiments reported in Section IV give ample indication that average responses to clicks may be evoked by a wide range of stimulus intensities. The figures summarizing these experiments, Figs. 25, 26b, 28, and 30, show that for the four subjects investigated, response amplitudes decreased as the intensity of the clicks was reduced. Although it was difficult to detect even an average response to low-intensity clicks, average responses were usually seen for click intensities within 6 db of psychophysical threshold (subject M.W. furnished the exception).

A more careful study of threshold phenomena was attempted in the following experiments. First, seven intensity levels were chosen. These intensity levels were separated by 3-db steps, and the center intensity was set just at the subject's psychophysical threshold, which had been obtained at the beginning of each experiment. The stimulus sequence presented to each subject was initiated by 50 clicks presented repetitively at a rate of 15 per second and at a constant intensity level, 9 db above threshold. Then a 1.5-second pause occurred, followed by a train of 50 clicks having a common intensity,

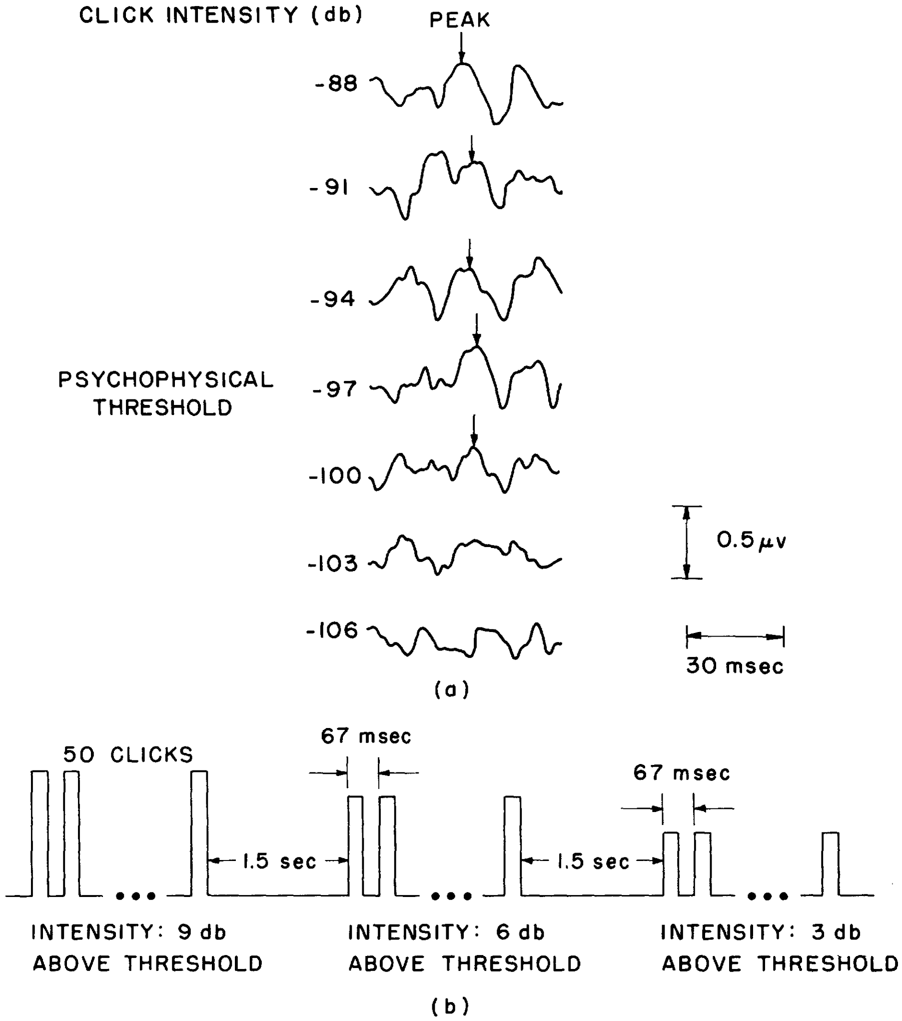


Fig. 59. (a) Average responses to click stimuli of near threshold intensity (Subject, A.T., H-594). Consistent deflections, each marked with an arrow, are seen for all intensities greater than −103 db. Response conditions: active electrode, 8; reference electrode, 6; number of responses, 2000 for each intensity.

(b) Schematic diagram of stimulus sequence used in presenting clicks of near threshold intensity. Trains of clicks, each train containing 50 clicks of the same intensity, were presented to the subject. The intensity of each train was ordered. Click rate was 15/sec.

6 db above threshold. Another pause, and then 50 more clicks; this time, all were 3 db above threshold, and so on. Each train contained 50 clicks that were 3 db lower in intensity than those in the preceding train (see Fig. 59b). The train containing clicks of the lowest intensity, 9 db below threshold, was followed first by a train identical to it, and then by six more trains. Each of these six succeeding trains contained clicks that were 3 db greater in intensity than those of the previous train. The train having clicks at an intensity 9 db above threshold marked the end of the stimulus sequence. Thus, at each of 7 levels, 100 clicks were presented during each repetition of the stimulus pattern. The basic click rate of 15 per second was preserved in all trains. The trains were all separated by pauses of 1.5 seconds. Finally, the responses to all clicks of a given intensity were averaged.

Unfortunately, the amplitudes of average responses to clicks of such low intensity were so small that even averages computed from 1000 individual click responses (10 repetitions of the total stimulus sequence) were usually not detectable above the averaged spontaneous activity. One experiment yielded results that are less variable than those obtained in the other experiments, and are shown in Fig. 59a. Consistent deflections, marked with arrows, are seen for all intensities above −103 db and are identified as responses. The slight increase in the peak latency as the click intensity decreases is interesting, for just such a latency increase is reported for primary responses to near-threshold clicks evoked from the cortex of anesthetized cats (see Fig. 4).

The use of the average responses as an objective estimation of a subject's psychophysical threshold is therefore quite promising, although two of our 27 supposedly normal subjects showed no detectable responses to quite loud clicks. Investigators at the John Tracy Clinic, in Los Angeles, are, at the present time, utilizing these average-response techniques to obtain objective measures of psychophysical threshold in children. They report very encouraging results (82), obtained with the use of a much simpler computer than the ARC-1.

7.2 AVERAGE RESPONSES AND PSYCHOPHYSICAL "STATE"

a. Previous Electrophysiological Experiments

An organism existing in the physical world is not subject to stimuli of a single modality, but is constantly bombarded by stimuli from many different sources. Some of these stimuli evoke responsive behavior from the organism, while other stimuli do not. Indeed, repetitions of the same stimulus, presented at different times, may evoke quite different behavioral responses from the same organism.

It has also been observed that electrical responses to stimuli are not invariant with respect to the "state" of the subject or animal that is being stimulated. For example, differences in general alertness or specific attention to stimuli exciting other senses can influence the responses elicited by auditory stimuli. In one study, Jouvet and Hernández-Péon (83) recorded responses to acoustic clicks from the cochlear nucleus of awake cats in different "states." These experimenters report that the recorded click responses were much smaller than usual during periods when the "attention" of the cat was diverted to nonauditory stimuli, such as pain or strong scent. In a similar study, Galambos (84) reports that click responses obtained from both the cochlear nucleus and the auditory cortex were reduced when the cat was "attending" to food.

The difficulty in this type of experiment is the inability of the experimenters to communicate directly with the experimental animal – they just cannot ask a cat to "attend" to something. Yet, the presentation of food and strong odors, which definitely change the evoked responses of experimental animals, involves very complex stimuli which may arouse the animals to a state that is not simply describable as "attending." It might be argued that perhaps operant conditioning techniques enable an experimenter to focus the "attention" of an experimental animal, but it is by no means obvious that conditioned behavioral responses insure simply the "attentiveness" of the animals to the conditioned stimuli. Even so, investigators are not agreed upon the effect of conditioning processes. Some investigators (83, 84) have reported an increase in the amplitude of evoked responses to conditioned stimuli, while another (85) has found no consistent changes.

Gershuni (81) has investigated the effect of attention in human subjects. He conditioned responses such as eyeblink and the suppression of alpha rhythm, and reports that attention to nonauditory stimuli raised the threshold for these conditioned responses to tone stimuli as much as 20-30 db.

b. Experimental Results Obtained in this Study

Using averaging techniques to obtain unconditioned evoked responses to clicks from the human scalp, we have investigated the effect of "attention" upon these responses. However, the behavioral definition of such a state remains difficult, and we cannot be satisfied with instructing human subjects to "pay attention" to various series of clicks. Instead, we conducted a series of experiments in which our subjects were required to perform one of two specific tasks while trains of acoustic clicks were presented to them.

Four subjects were used in these particular experiments, all of whom had been used as subjects in this study many times previously. Two of the subjects, W. P. and M. E., were members of the Communications Biophysics Group, of the Research Laboratory of Electronics, M. I. T., and both were experienced psychophysical subjects. The two other subjects, A. T. and M. W., were undergraduate students and were "naive" in the sense that they were not workers in this field and did not know the purpose of this study in any detail. Moreover, the two students had never acted as subjects in psychophysical experiments before participating in this study.

Each of the experiments was conducted in the following way. In part A of the experiment, the subject was seated in a normal fashion and given the standard instructions to read or play chess without worrying about the clicks. The behavior of all of the subjects seemed to be quite normal and they became interested in their reading material or in the game. The subject was then presented with clicks whose intensity varied according to

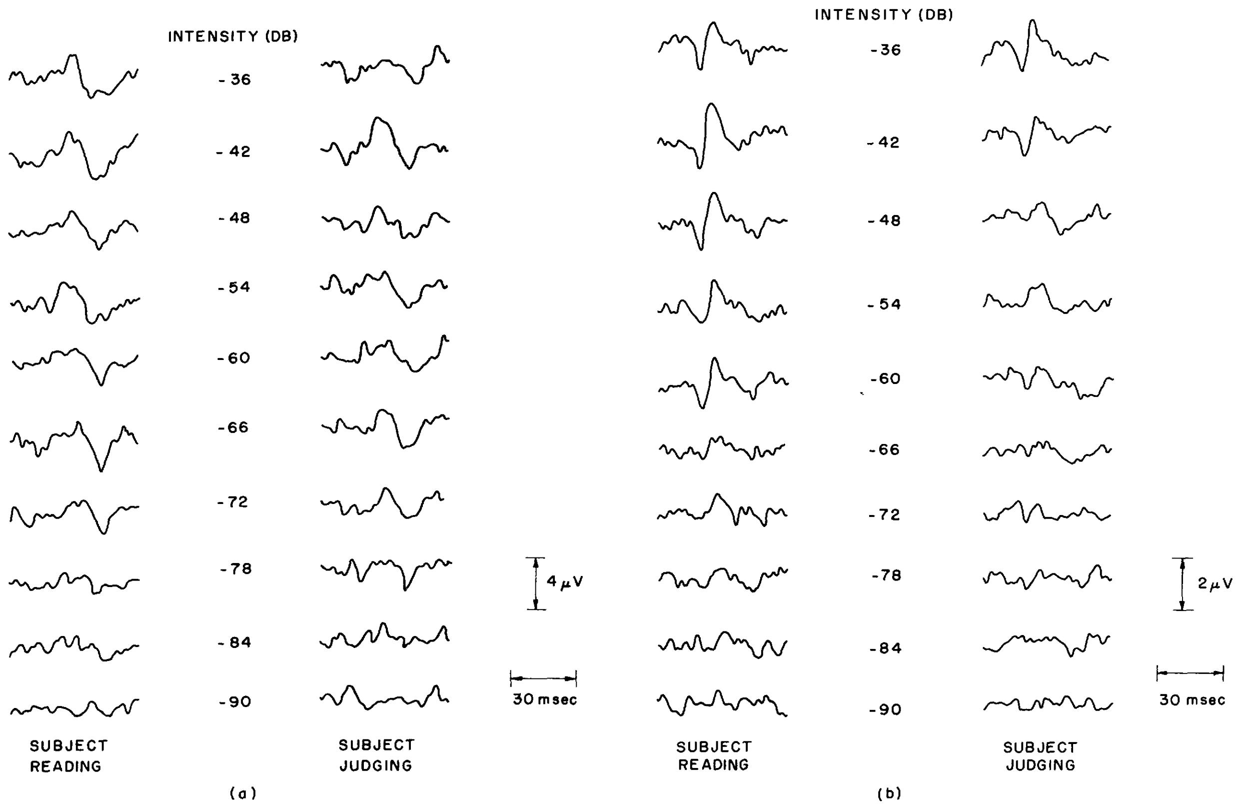


Fig. 60. (a) Average responses to clicks presented during the performance of two psychophysical tasks (Subject, W. P., H-602). Traces shown in the left column are the averages of responses obtained while the subject was reading; those in the right column are the averages of responses obtained while subject was making psychophysical judgments on the clicks. Stimulus conditions: same as Fig. 23a. Response conditions: active electrode, 8; reference electrode, 6; responses in the left column are each the average of 1000 responses, those in the right column are each the average of only 500 responses.

(b) Average responses to clicks presented during the performance of two psychophysical tasks (Subject, M. W., H-603). Display and stimulus conditions: same as for Fig. 60a. Response conditions: active electrode, 8; reference electrode, 6. Each curve in both columns is the average of 1000 responses.

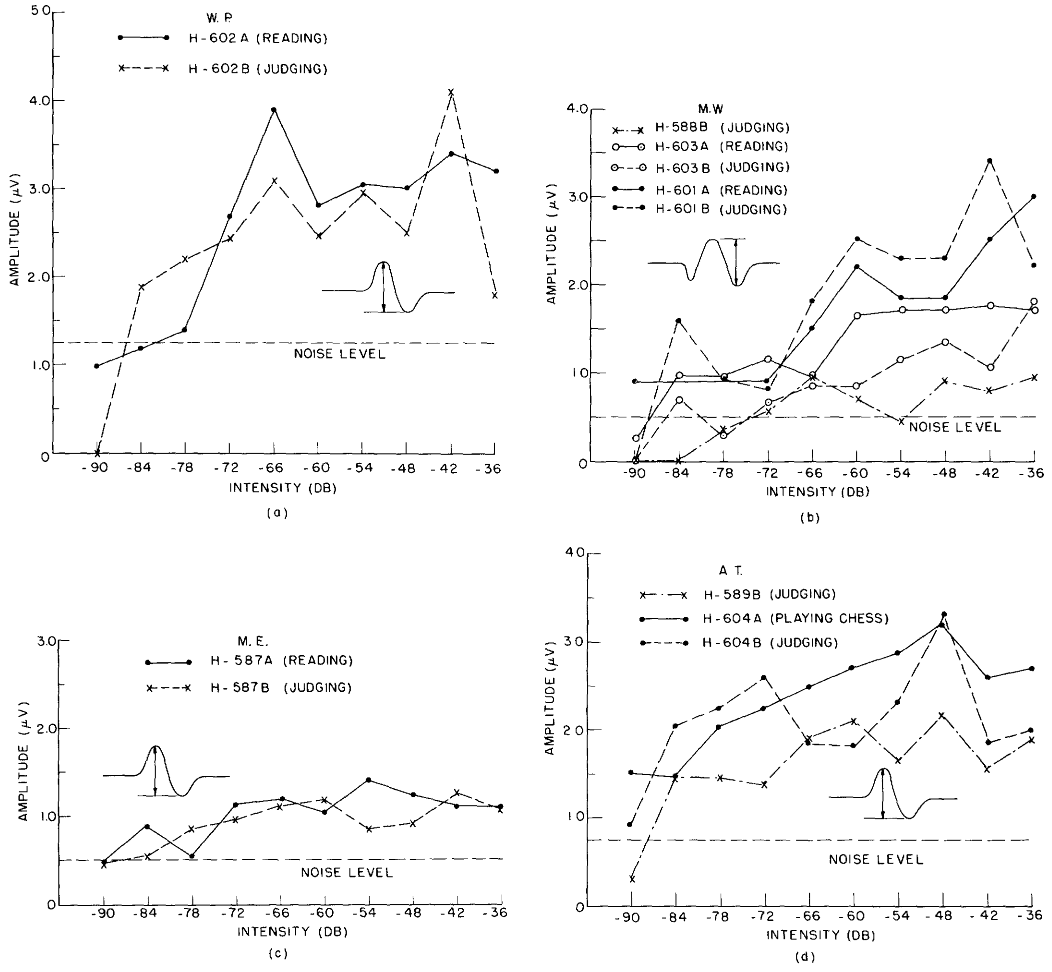


Fig. 61. (a) Amplitude of average responses as a function of click intensity for two psychophysical "states" (Subject, W. P.). Each point in the figure represents the peak-to-peak amplitude obtained from the appropriate average response in Fig. 60a.

(b) Amplitude of average responses as a function of click intensity for two psychophysical "states" (Subject, M. W.). Each point represents the peak-to-peak amplitude of an average response. Stimulus conditions: same as for Fig. 23a in all experiments. Response conditions: active electrode, 8; reference electrode, 6; each average response measured was computed from 1000 responses (500 only in H-601B).

(c) Amplitude of average responses as a function of click intensity for two psychophysical "states" (Subject, M. E.). Stimulus conditions: same as for Fig. 23a in all experiments. Response conditions: active electrode, 8' (8' is the ipsilateral counterpart of electrode 8); reference electrode, 6; each average response measured was computed from 1000 responses.

(d) Amplitude of average responses as a function of click intensity for two psychophysical "states" (Subject, A. T.). Stimulus conditions: same as for Fig. 23a for all experiments. Response conditions: active electrode, 8; reference electrode, 6; each average response measured was computed from 1000 responses.

the stimulus pattern used in the intensity experiments of Section IV. This stimulus pattern, it will be recalled, consisted of trains of 50 clicks. Each train contained clicks of constant intensity (one of 10 possible intensities) presented at a rate of 15 per second. The stimuli of part A usually consisted of 20 trains at each intensity (a total of 200 trains), presented in a random order. Therefore, 1000 clicks were presented at each intensity level.

After the completion of part A, a small signaling device (see Section III), which had previously been hidden, was placed in front of the subject. The essential part of the device was a series of five unlabeled buttons located on one side and connected by wires to the recording equipment. The subject was instructed to listen carefully to each train of clicks and then to assign it to one of five possible loudness categories (53). He was further instructed to register each judgment sometime during the 5-sec interval which separated the trains by simply depressing one of the 5 buttons, which were ordered from left to right in order of increasing loudness. The subjects were allowed to listen to a few trains and to practice making category judgments. After a brief practice period, part B of the experiment was run. In this part, the subject was presented with a stimulus pattern that was identical to that of part A, except for a different random ordering of the stimulus intensities. The judgments, which indeed covered all five categories, were observed and recorded. The experienced subjects perhaps suspected that the judgments themselves were of no particular value, but they applied themselves to the task. The inexperienced subjects, on the other hand, presumably thought that the judgments were important, an assumption that was later verified for subject A. T., who proved to be actively concerned about the consistency of his judgments. This subject also reported, incidentally, that it only took him half of a train to make up his mind about its "proper" category.

Figure 60 shows average responses of subjects W. P. and M. W., obtained during the two parts of an experiment. In Fig. 60a and 60b, the left column shows averages of responses obtained while the subject was reading, and the right column shows averages of responses obtained while the subject was making the loudness judgments. Consistent differences in waveform between corresponding responses in the two columns are not seen in either part of the figure, although W. P. was an experienced subject, and M. W. was a "naive" observer. Peak-to-peak amplitudes of these responses were measured, and are plotted in Fig. 61.

Figure 61 summarizes the data obtained from our four subjects. In the first two experiments, H-588B and H-589B (Fig. 61b and 61d), the control part A was omitted. Consequently, although the amplitudes of the average responses evoked during these first two experiments are consistently smaller than those obtained in the other experiments, definite conclusions must be based on the other complete experiments, which contained both parts A and B. In no complete experiment did the amplitude of the responses obtained under the two psychophysical "states" differ consistently: Whether he was reading (playing chess) or making loudness judgments, each subject exhibited average responses whose amplitudes as a function of intensity were similar to his own peculiar intensity functions presented in Section IV. We conclude, therefore, that the average response components to clicks that we have recorded from human scalp were not appreciably influenced by either the visual or auditory task that the subjects performed.

On the basis of the experimental data obtained from cats (Galambos (84)), perhaps our conclusion is somewhat surprising. However, direct comparisons of our experimental results with those of Galambos and others are improper because of differences in experimental design, in location of electrodes, and even, perhaps, in the particular response components under study. Differences in method also prevent direct comparison of our results with those of Gershuni (81).

7.3 SUGGESTIONS FOR FUTURE EXPERIMENTS

The two types of experiments just described are only two of many investigations that suggest themselves, once we are able to record average responses from the human scalp.

One possible area of future investigation concerns comparisons between average responses and various measures of sensory performance. For example, encouraging correlations between absolute psychophysical and electrophysiological thresholds have already been demonstrated in this study. Yet, in order to establish the usefulness and accuracy of the average evoked response threshold as an estimate of psychophysical thresholds, experiments must be tried on representative populations. Just such a research program is now under way at the John Tracy Clinic, where Lowell (82), with the use of an analog averaging device, is comparing psychophysical and average response thresholds obtained from large numbers of subjects. The onset of a tone burst is also known to elicit cortical responses in experimental animals and there is no reason to assume that tone bursts will not evoke average responses that are detectable on human scalp. If this is the case, then averaging techniques may provide an objective way of estimating a subject's sensitivity to tones of various frequencies, that is, his audiogram.

Another area of possible research concerns the sensitivity of the average response to changes in the subject's "state." We have seen in this study that the characteristics of our short-latency response components change as a subject goes to sleep. But in addition to these response components, other types of response components evoked by auditory stimuli are known to exist. As early as 1939, Davis and his co-workers (35) found that individual responses evoked by auditory stimuli could be detected in the EEG potentials recorded from sleeping subjects. These response components (K-complexes) could be evoked by slowly repeated stimuli and had latencies of approximately 100 msec. In a more recent paper, Roth, Shaw, and Green (59) reported that the K-complex could be detected by visual examination of the EEG potentials in all subjects in light sleep. They were not able to obtain responses in deep sleep, however. In an experiment performed in our laboratory, we have investigated the average K-complex evoked by clicks in a sleeping subject (86). Periodic clicks were presented to this subject at a rate of

0.75 per second and average responses were computed from his EEG potentials. Average K-complexes were detectable during the experiment and showed a progressive change in waveform as the subject went to sleep. All of these results suggest that average-response waveforms might be used as an indication of the depth of sleep in humans, and perhaps of the depth of anesthesia. To go a step farther, it would be interesting to determine whether the "state" of a subject under hypnosis is reflected in the components of average responses that are evoked by various stimuli.

Opportunity also exists for the extension of the experiments reported in this study. In Section VI, we reported, in connection with the sleep experiments, that the amplitude of the average click responses evoked in subject A. T. depended upon the position of his body. Also mentioned was the fact that the mean-square value of the EEG potentials from which these average responses were computed depended upon the position of the body. Other experiments have also suggested that, in some subjects, there is a strong correlation between the mean-square value of the EEG potentials and the amplitude of the average response computed from it. It would be interesting to investigate such relations. Extension of the experiments involving stimuli of other modalities is also possible. Average responses to shock stimuli have been obtained from scalp electrodes positioned, presumably, over the somatic projection areas and also over "secondary" cortex. The differential effect of sleep upon these primary and secondary responses would be of interest. Also, since flash, click, and shock responses can be recorded from the occipital regions of the skull, average responses evoked by multisensory stimuli would be of interest.

Another series of possible experiments involves the investigation of the average responses evoked by stimuli that are made "meaningful" to the subject by various psychophysical or conditioning techniques. In still another series of possible experiments, average responses might be obtained from babies and young children. The change of these responses as the children grow older might show interesting correlations with behavioral studies on the same children.

Finally, better electrodes, better psychophysical methods, and better control of the general experimental environment should reduce the variability of the responses recorded here and thus clarify the observations made in this study. It would, for example, be of interest to record EEG potentials in humans by means of needle electrodes, insulated except at the tip, which are imbedded in the skull. And, needless to say, it would be of great interest to record average responses to clicks directly from exposed human cortex during neurosurgery.

APPENDIX

Equation 1 is derived here as an illustration of the general methods utilized in obtaining the equations used in Section II. Legendre polynomial formulation, conveniently used to describe potentials in spherically bounded media, is employed.

The potential produced by a dipole in a conducting medium of infinite extent must be found first. Let us consider a dipole oriented along the Z-axis, that is, a positive charge q located at $Z = a + \epsilon$ and a negative charge $-q$ at $Z = a$, where ϵ is a small distance. If the distance r to an observation point P is greater than "a", the potential at P may be described as

$$V_{r>a} = \frac{q}{r} \sum_{n=0}^{\infty} \left(\frac{a+\epsilon}{r}\right)^{n} P_n(\cos\theta) - \frac{q}{r} \sum_{n=0}^{\infty} \left(\frac{a}{r}\right)^{n} P_n(\cos\theta) \qquad \text{(A-1)}$$

where the P_n are Legendre polynomials. Expanding terms, we have

$$V_{r>a} = q \sum_{n=0}^{\infty} (a^n + na^{n-1}\epsilon^n \ldots - a^n)\, r^{-n-1} P_n(\cos\theta) \qquad \text{(A-2)}$$

Since a dipole is obtained as $\epsilon \rightarrow 0$ in such a way that $q\,\epsilon \rightarrow D$, where D is the dipole moment, the field produced at point P by a dipole is

$$V_{r>a} = \frac{D}{ra} \sum_{n=0}^{\infty} n\left(\frac{a}{r}\right)^{n} P_n(\cos\theta) \qquad \text{(A-3)}$$

By a parallel development, the potential at an observation point less than "a" distant from the origin is found to be

$$V_{r<a} = \frac{D}{a^2} \sum_{n=0}^{\infty} (n+1)\left(\frac{r}{a}\right)^{n} P_n(\cos\theta) \qquad \text{(A-4)}$$

We must now determine the potential produced by a dipole in media of different conductivities that are separated by spherical boundaries. Since, in all such configurations, Laplace's equation is satisfied everywhere but at the dipole, the effect of the boundary may be represented everywhere but at the dipole by Legendre polynomials. Let us, for the moment, leave the coefficients of such polynomials unspecified.

Consider now a Z-directed dipole located at $Z = a$, immersed in a spherical medium of radius b and conductivity σ_1. Surrounding this is an infinite medium of conductivity σ_2. The potentials may be written as

$$V_{r<a} = -\frac{D}{a^2} \sum_{n=0}^{\infty} (n+1)\left(\frac{r}{a}\right)^{n} P_n(\cos\theta) + \sum_{n=0}^{\infty} A_n r^n P_n(\cos\theta) \qquad \text{(A-5)}$$

$$V_{a<r<b} = \frac{D}{ra} \sum_{n=0}^{\infty} n\left(\frac{a}{r}\right)^{n} P_n(\cos\theta) + \sum_{n=0}^{\infty} A_n r^n P_n(\cos\theta) \qquad \text{(A-6)}$$

$$V_{r>b} = B_n r^{-n-1} P_n(\cos\theta) \tag{A-7}$$

These expressions involve two sets of unknown coefficients, A_n and B_n. However, these coefficients are not arbitrary, for the dipole potential must satisfy two boundary conditions at $r = b$:

(i) The potential must be continuous.

(ii) The normal current, and hence, the normal derivative of the potential must be continuous. If these conditions are written explicitly in terms of Eqs. A-6 and A-7, the values of the A_n and B_n may be found by equating the coefficients of the various orthogonal terms of the Legendre expansion. Hence, at the interface between the two media, letting $\sigma_2 = 0$, we can show that

$$V = \frac{D}{ab} \sum_{n=0}^{\infty} (2n+1)\left(\frac{a}{b}\right)^n P_n(\cos\theta) \tag{A-8}$$

Furthermore, if the dipole movement D is arbitrarily set at unity, we have Eq. 1:

$$V(r=b) = \frac{1}{ab} \sum_{n=0}^{\infty} (2n+1)\left(\frac{a}{b}\right)^n P_n(\cos\theta)$$

As shells of different conductivities are added to this basic configuration, the same boundary conditions used in the derivation above must be met at each interface between two media of a different conductivity. The principle of solution is exactly the same, but the algebraic tedium involved is considerably increased.

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