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D.C. POTENTIAL CHANGES FROM AUDITORY CORTEX OF CAT

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INTRODUCTION

POTENTIAL CHANGES in the central nervous system with a time course too slow to be investigated by conventional capacity-coupled amplifiers may play a significant role in brain function. These so-called D.C. or slow potential changes can be recorded only with stable non-polarizable electrodes and direct-coupled amplifiers. It has been suggested that slow changes play an important role in neuronal function (2, 7), cortical activation (1, 4, 19) and sensory discrimination (14). Whether these theories prove to be true or false, the D.C. changes are interesting in their own right.

Although the number of reports dealing with D.C. potentials in the central nervous system is rapidly increasing, only a few investigators so far have dealt with cortical potential changes incident to stimulation with sound or light. Caton's report of 1887 (5) was the earliest paper dealing with these questions, and although a few papers (mentioned in 1) appeared during the intervening 60 years, the pertinent literature begins with an abstract by Libet and Kahn (18) who recorded between the cerebral cortex and the periosteum in the cat and found baseline shifts following stimulation of the somesthetic and auditory systems. A particularly interesting series of papers has been published by Köhler and his colleagues (13-17). They have recorded D.C. shifts in response to the introduction of an object in the visual field from the visual cortex of cat and monkey (16) and from the scalp of man (13, 14). They also report similar responses to various sounds from the auditory cortex of the cat (15) and from the scalp of man (17). Recently Arduini *et al.* (1) described sustained negative shifts (referred to the eye socket) from the auditory cortex of curarized cats when a loud whistle was sounded.

The purpose of this report is to describe changes in D.C. activity in the auditory cortex of the cat incident to stimulation with sounds; and to set forth the conditions under which such responses can be reliably obtained.

METHOD

Experiments were carried out in 30 cats weighing between 2.5 kg. and 3.5 kg. The recording system consisted of a Grass Model 5 polygraph equipped with Grass 5P1 D.C. preamplifiers. The preamplifiers were chopper-stabilized at 120 c./sec. and had an input impedance of over 300 K Ω . The overall frequency response of the system (including pens)

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was down 10% at 10 c./sec. and 33% at 40 c./sec. with a rise time of 20 msec. (5%–95%). Beckman No. 270 calomel half cells were found to be satisfactory non-polarizable electrodes if pairs linked with a low resistance connection were stored with the tips immersed in saturated KCl solution. The electrodes were connected to the preparation by a salt bridge of 5% NaCl in 1% agar-agar. Polyethylene tubing was filled with this mixture as a warm solution. Upon cooling a gel formed and the salt bridges could be stored for weeks in a refrigerator. PE-60 or PE-90 tubing was customarily employed; thus the contact points had a diameter well under 1 mm. The impedance of such an electrode with a 4 inch salt bridge was approximately 15 K Ω .

The complete recording system with the electrode-salt bridge pairs shorted in normal saline had a noise level of 5 μ V., drift of less than 10 μ V. per minute, and an inter-electrode potential difference of 50–250 μ V. Although for convenience we will speak of "active" and "reference" electrodes, neither the preparation nor the amplifiers were grounded. The cat was within a shielded room.

Signals from an audio oscillator, white noise generator or pulse generator (for 1 msec. clicks), were fed into a loudspeaker via a calibrated attenuator. The loudspeaker was positioned directly over the cat's head. Intensity was usually about 80 db (above 0.0002 dynes cm.²), measured at the level of the external auditory meatus with a General Radio sound level meter.

Anesthesia was induced in the first 25 cats by a 15–20 mg./kg. dose of thiopental injected intravenously by percutaneous venepuncture and maintained on 1.5–2 mg./kg. doses of thiopental i.v. as required to inhibit movement. Incision sites were infiltrated with 0.5% lidocaine with epinephrine and this was supplemented with a topical anesthetic cream at the end of the operation. A tracheotomy was performed. Access to the middle ectosylvian gyrus was obtained by trephining a hole $\frac{1}{8}$ inch in diameter, which was tapped for just over one turn with a #24 bottoming tap foreshortened so as not to injure the dura or underlying brain. A nylon or lucite plug 0.5–0.75 inch long, with matching thread, was screwed into the defect and the muscle and skin brought up and closed around the plug. The dura was left intact.

The last five animals were prepared in two steps. They were anesthetized with 36 mg./kg. of pentobarbital i.p., the plug put in the skull and an intravenous catheter left in place. No tracheotomy was performed. On the first or second post-operative day, when the animals were walking and behaving normally, they were sedated with a small dose (3–5 mg./kg.) of thiopental via the catheter and maintained on 1–2 mg. of thiopental i.v. every few minutes in order to reduce movement. Although more elaborate, the chronic preparation was found more convenient since the level of anesthesia was more easily controlled. A very light stage of anesthesia and a warm, moist cortex were found to be essential for success in the experiments. The plug used to close the skull defect was drilled lengthwise with holes just large enough to admit the polyethylene tubing salt bridges and a thermistor probe by means of which the temperature of the dura was monitored. With the salt bridges placed on the dura, the sources of instability were numerous. However, for the short period of time when sounds were made (10 sec. or less) drifts were not troublesome. It should be noted that we have not been concerned with the large (1–20 mV.) resting and injury potentials which were balanced out (8), but with the much smaller changes in potential difference associated with auditory stimulation.

RESULTS

Changes in D.C. potential associated with auditory stimulation were recorded from 20 of the 30 cats. The possibility that these potential changes might have been artifacts due to movement or anesthesia was considered. Changes associated with movement were easily distinguished from the changes related to auditory stimulation. Moreover, the D.C. response to sound was also present in an animal prepared under thiopental and maintained on tubocurarine and local anesthesia. The second possibility—that these D.C. changes may in some obscure way be related to thiopental anes-

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thetia—seems unlikely in view of the fact that D.C. changes in response to sound were also elicited in an *encéphale isolé* preparation.

The differences in temperature, anesthesia and spontaneous electrical activity between the 20 successful and 10 unsuccessful experiments serve as the basis of our discussion of the conditions under which one may reliably record this phenomenon.

Form of response

With the active electrode on the dura overlying the middle ectosylvian gyrus, the response to a continuous sound (*i.e.*, one with a duration of 1–10 sec.) took the form of a surface-negative change in D.C. potential which appeared just following the evoked response, concomitantly with the regularization and acceleration of the cortical rhythm described by Bremer (3). The change in D.C. level was surface-negative with the reference electrode on the frontal periosteum, the cut edge of the skin of the neck or on the dura overlying non-auditory cortex. Hereafter this surface-negative change in D.C. level will, for brevity, be called a *shift*. Such shifts have been elicited with white noise, tones with a frequency of from 100 c./sec. to 9,000 c./sec. and 1 msec. clicks repeated 5–1000 times/sec. In these experiments frequency was varied over a range of 100–9000 c./sec. and clicks over a range of 1–1000 clicks/sec. in a search for maximum response. In addition it was noted that almost any sound audible to the experimenter might produce a shift; *e.g.*, a whistle, speech, the barely audible sound of a telephone in an adjoining room.

Three common forms of the response are illustrated in Figs. 1 and 2. Typically the initial positive wave of the classic evoked response was seen, followed by an abrupt surface-negative shift. The amplitude of the negative shift remained fairly constant until the end of the continuous sound of 2–8 sec. duration. At the end of the sound the pen fell promptly to the baseline, often with an overshoot forming a short positive wave. The regularization and acceleration of the cortical rhythm appeared with the shift and ceased with the end of the shift (Fig. 1A, B). Mean latency of onset for 47 such shifts was 110 msec.; mean peak latency, measured from the onset of auditory stimulation to the point at which maximum amplitude was reached, was 174 msec. and mean amplitude was 106 μ V. No relation was found between latency and type of stimulus. The range for a given value of a given stimulus was quite wide—often nearly as wide as the range for all types of stimuli.

A common variation of form of response was one in which the shift appeared promptly and rose abruptly but returned to the baseline before the end of the stimulus (Fig. 1C, D). After the D.C. level had returned to the baseline the regularization and acceleration of the EEG ordinarily continued until the end of the sound. However, on occasion this too would disappear (*cf.* 3, p. 73). Early decay to the baseline was the rule with longer periods of stimulation, becoming more common with sounds lasting over 5 sec. Length of stimulation did not appear to be the only factor, however, since early re-

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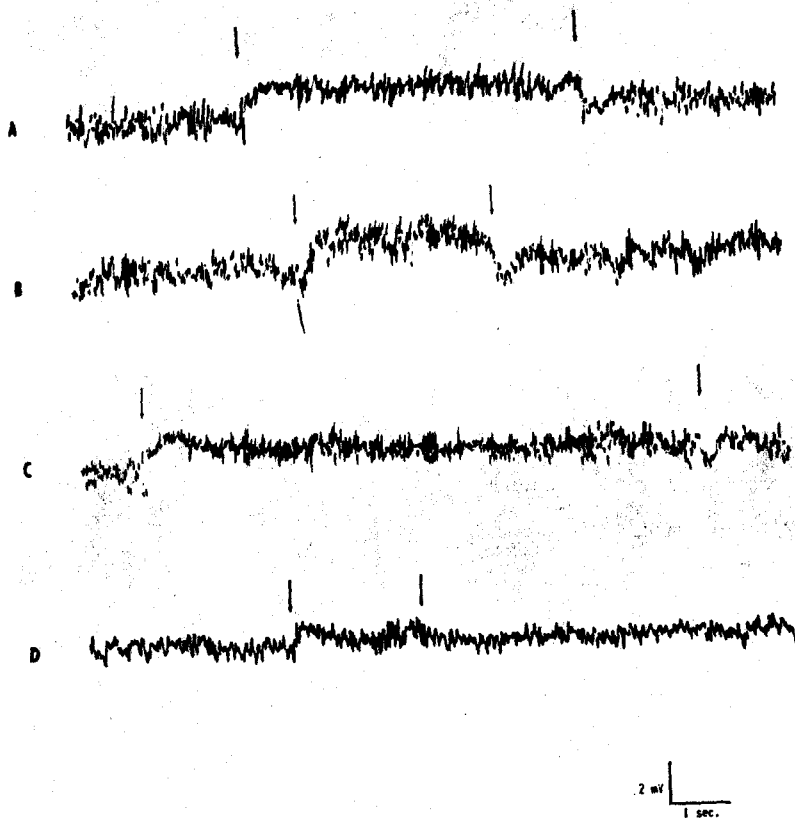


FIG. 1. D. C. responses from auditory area in response to auditory stimulation. "Active electrode" on dura overlying middle ectosylvian gyrus; other electrode on frontal perosteum. Upward deflection indicates dura negative with respect to bone. A: shift in response to white noise. B: different cat, shift in response to tone of 4000 c./sec. C: same cat as in A, shift in response to white noise returning to baseline before end of auditory stimulation. D: response to 50 clicks/sec. returning to baseline before end of stimulation.

turn to the baseline was often seen with periods of stimulation lasting only 2 or 3 sec. (Fig. 1D). Early return to the baseline was also more common when the preparation was in poor condition. A less common variation was one in which the shift took place gradually, or after an unusual delay (Fig. 2A). Although the latency might be abnormally long, what was striking here was the absence of an abrupt rise. Occasionally such a shift would appear to be overcoming a prolonged initial positivity; a few times the positivity persisted so long as to lead to the impression of a diphasic response. On rare occasions a shift was seen which lasted 1-10 sec. after the end of the stimulus (Fig. 3). Such a response was usually seen under conditions associated with a slower spontaneous EEG.

Effective click repetition rate for shift. In any one animal there was found

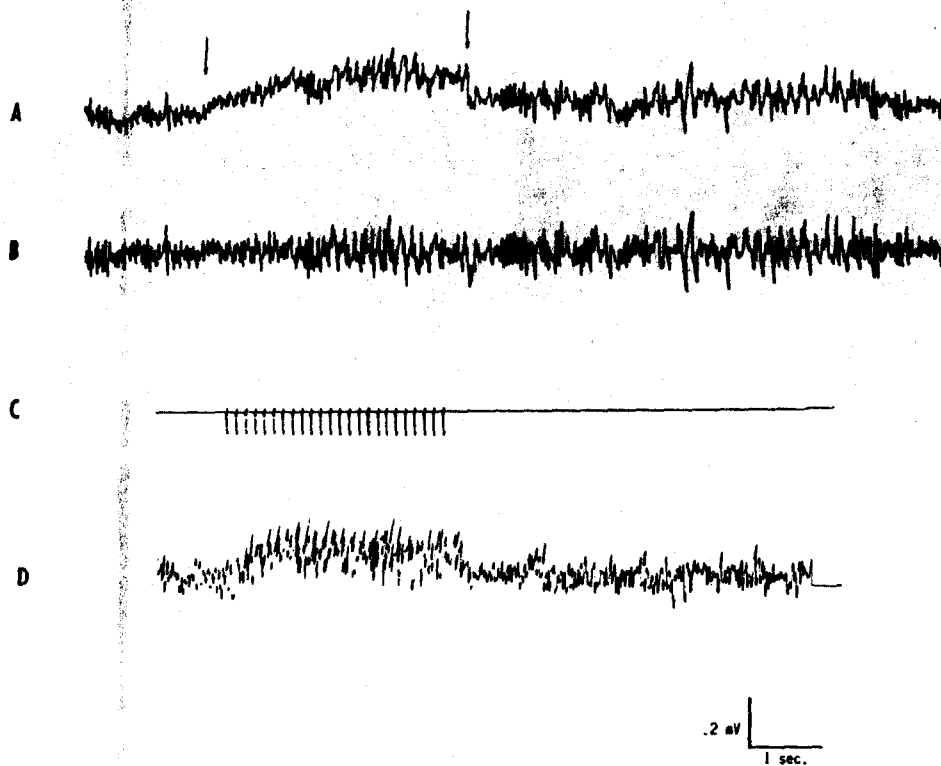


FIG. 2. Responses from auditory area in response to auditory stimulation. Same conditions as Fig. 1. A: lack of abrupt rise of shift in response to tone of 700 c./sec. B: D.C. change not revealed by R-C coupled amplifier recording simultaneously with A from same electrodes (time constant 0.1 sec.). C, D: "staircase" development of D.C. shift in response to 8 clicks/sec.

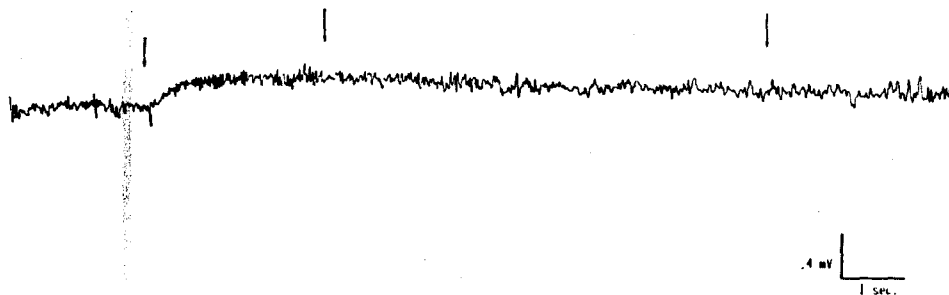


FIG. 3. Sustained potential shift in response to white noise. Same conditions as in Fig. 1. Note that regularization and acceleration of background rhythm ceases with end of sound. Two arrows to left indicate duration of auditory stimulation; arrow to right marks return of D.C. level to baseline.

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to be a certain repetition rate of clicks which resulted in the development of a shift. The repetition rate threshold (i.e., the minimal rate at which shifts developed) was determined in 12 animals. The mean was 11.5 clicks/sec. with a standard deviation of 3.8 over a range of 5 to 19 clicks/sec. In determining these values the threshold was taken as the number of clicks/sec. which reliably produced a surface-negative shift. In these cases the shift was not abrupt but arose slowly, as if each click built upon the effect of the previous one. This "staircase" effect is illustrated in Fig. 2D.

Conditions influencing responsiveness

Habituation. If the sounds used to stimulate the cat were repeated at short intervals, more often than once each minute, the shifts we have been describing became smaller or did not appear. However, after a rest of a few minutes, the shifts were again elicited in full strength. If only one type of stimulus had been used for a while, e.g., pure tones, it often became difficult to obtain shifts. If, however, a different type of sound was made, e.g., white noise or clicks, the shifts were seen again. After an hour or more in which the various types of sounds were presented over and over again, shifts might not appear in response to any of them. However, if keys were jangled, a musical instrument sounded or some other novel noise presented, again shifts were recorded.

Anesthesia. The slow shifts we have been describing were seen best when the animal was at a very light level of anesthesia. *Behaviorally*, the cats were capable of pricking up their ears to an unexpected sound, of purposeful struggle rather than a simple withdrawal reflex to pain. They were lighter than the level characterized by spontaneous drifting eye motion, and the animal's eyes would often follow the experimenter's movements. *Electrically*, the spontaneous electrical activity of the middle ectosylvian gyrus was in the range of 20-30 c./sec., 75-125 μ V. peak to peak (on the dura), not infrequently superimposed on a very slow, 0.3-0.75 c./sec. low-voltage (50 μ V. on the dura) rhythm. The EEG activity of a nonauditory area, monitored on the dura overlying the lateral gyrus was slower; 15-20 c./sec., 50-75 μ V. activity was dominant with occasional runs of 3-5 c./sec. activity about 100 μ V. peak to peak.

As anesthesia was deepened the shifts to sound decreased in amplitude, decayed rapidly and disappeared. *Pari passu* the background EEG became slower and of higher voltage. At yet a deeper level even the regularization and acceleration of the ectosylvian rhythm to continuous sounds became inconstant and disappeared and the beginning of barbiturate spindles was noted.

Temperature. Best results were obtained with a temperature, measured at the outer surface of the dura, of 38-38.5°C. Temperatures below 37°C. were usually associated with a slower EEG, indicative of deeper anesthesia and few or no shifts.

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DISCUSSION

The experiments reported, performed with a recording system having a wider frequency response, confirm and extend the findings of Köhler *et al.* (15). At present one can only speculate about possible reasons for the variation in the form of the D.C. response to continuous sounds. It may be that an early return to the baseline is a sign of "fatigue" or of "accommodation." The absence of an abrupt rise seen in some of the shifts could mean that the active cortical region initially was some distance away from the recording electrode and that as time passed activity also arose under the electrode. Köhler *et al.* (15, p. 11) originally proposed this explanation and outlined a possible underlying mechanism.

In the few observations in which the shift persisted for a long time after the end of the sound it appeared as if the shift was not associated with the sound *per se*, but with a more general arousal. Such responses were seen under conditions when shifts to sound were hard to obtain, but at a level of anesthesia where arousal was possible. Such shifts have been studied in response to stimulation of the sciatic nerve (1, 19), thalamic (4, 9), sub-cortical (10) and reticular structures (1, 4, 19).

The degree of *habituation* which the shifts to sound manifest is quite striking. Such behavior seems to be typical of the sensory portions of the nervous system, at least in awake or lightly anesthetized animals. Whitfield (20, p. 39; 21, p. 38) describes such behavior in the activity of the auditory cortex in unanesthetized intact cats. Bremer's studies of the auditory cortex of *encéphale isolé* preparations (3) also revealed such behavior. Similar habituation has been seen in the cochlear nucleus by Galambos *et al.* (6) and by Hernández-Peón *et al.* (12).

Shifts associated with repeated clicks. The experiments described here, showing that the repetition rate threshold for a shift to clicks is between 5 and 19 sec., and the "staircase" form which such a shift assumes, are strikingly similar to those reported by Goldring *et al.* (9-11) in their investigations of the negative potentials and shifts associated with thalamic stimulation and direct cortical shocks.

Neural nature of shifts. Although definite proof is lacking, it is probable that the shifts are of neural origin. The investigations of similar phenomena by Goldring *et al.* (8-11, 19), Brookhart *et al.* (4) and Arduini *et al.* (1) have clearly shown that the nervous system is capable of generating such potential changes. The fact that the shifts to auditory stimulation can be observed in paralyzed cat, *encéphale isolé* preparation and enucleated cat (15), effectively rules out peculiarities of anesthesia, eye movements or other movement artifacts as the source. Although it is possible that quite localized changes in blood flow might be associated with these shifts, the question of which is cause and which effect would still be unanswered.

It is tempting to speculate on the relationship of the shifts to four important areas of neurophysiological interest: (i) the electrophysiological ques-

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tions of dipole source and potential distribution; (ii) the relation to the functioning of central auditory mechanisms *per se*; (iii) the relation to the nature of the auditory stimulus and behavioral aspects of the stimulus situation; and (iv) the relation to arousal activity, EEG activation and the functioning of the reticular formation. At present, however, knowledge about these shifts is so limited that such speculation is deferred until more facts are at hand.

SUMMARY AND CONCLUSIONS

1. During stimulation by continuous sounds of from 1 to 10 sec. duration, D.C. shifts were recorded from the dura overlying the middle ectosylvian cortex of the cat. The shifts were surface-negative referred to the frontal periosteum, the cut edge of the skin of the neck, or the dura overlying non-auditory cortex. The magnitude of the shift was ordinarily about 100 μ V.

2. There was much variation in the temporal characteristics of the shifts. The onset was usually abrupt but frequently more gradual. The shift often persisted until the sound ended, but not infrequently it weakened or disappeared somewhat earlier. Rarely the shift persisted for some seconds after the end of the sound.

3. Single clicks did not produce a shift but rapidly repeated clicks did. At repetition rates of from 5 to 19 clicks/sec. the gradual development of a shift was seen.

4. The shifts were ordinarily accompanied by a regularization and acceleration of the spontaneous cortical activity. Although the two types of response showed remarkable similarities in behavior, they were not precisely correlated.

5. The shifts could be recorded only when the cortex was warm and moist and when the cat was almost awake. The proper conditions were described in detail and a method by which the shifts can be reliably obtained was described.

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