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Studies of the Electrical Parameters and Behavioral Effects of an EEG "Siezure Discharge"

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Nemastrina monkeys with multiple electrodes implanted in the amygdoloid area of the brain were used to study the relationship of electrical seizures and overt behavior. The electrical seizures were produced by long duration electrical pulses administered through the implanted electrodes. There appears to be no relationship between this kind of electrical seizure and lever pressing performance. Relationships between depth EEG, depth impedance, DC potential and surface EEG are observed and as a consequence some ideas concerning the genesis of the electroencephalogram are put forth.

The present research had its origin in some observations made several years ago while we were studying the behavioral effects of stimulation of the reticular and limbic systems of the brain. During one of these experiments we used a repetitive pulse having a long duty cycle, ie, the stimulus assumed the character of a briefly interrupted DC current. The consequence of this stimulation was an electrographic "storm"—a series of high-amplitude slow waves (often in the theta range).

We repeated the experiment numerous times[1, 2, 3] on a dozen monkeys and always obtained some type of seizure discharge, which often persisted as long as two hours. The EEG "storm" was always delayed in its appearance until after the 10 seconds of stimulation, the delay on occasion being several minutes in length.

The animals used were monkeys which had been trained to perform an "oddity" task. They had learned to select an odd object from a set of three (two alike and one different) over 90% of the time and they maintained this performance during the electrographic storms.

In some monkeys with multiple electrode placement, the seizure would be recorded in one pair of electrodes then appear later in another pair of electrodes that had not been stimulated. In

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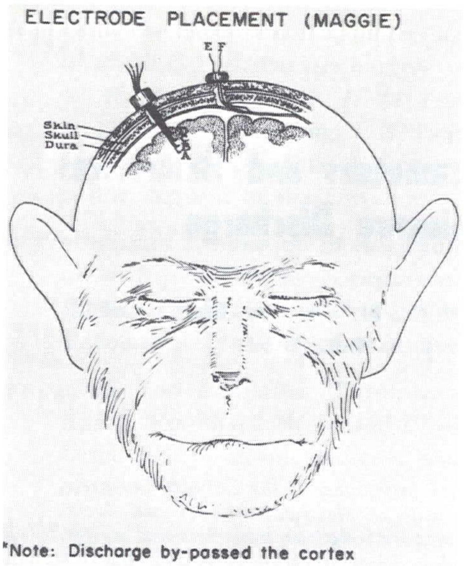


Figure 1
Electrode Placement (Maggie)

one case[3] we placed a pair of electrodes on the surface of the dura, and a few centimeters away we implanted an electrode with two pairs of contacts (Fig 1). The superficial pair was placed in the parietal region of the cerebral cortex and the deep pair in the white matter beneath this cortex. Stimulation of the surface of the dura was followed by several minutes of the electrical storm confined to the dural electrodes (Fig 2). It stopped in the dural electrodes, then appeared in the electrodes buried in the white matter of the parietal lobe, but did not appear in the cortical electrodes which were in between. It persisted in the parietal electrodes for almost an hour, gradually slowing its frequency but not changing in amplitude (Fig 3).

Another aspect of our investigation was the media in which the discharge could occur. Would stimulation of substances besides brain tissue produce the same effects? This question was of special significance because of our findings that the discharge would shift from one electrode to another. The media investigated were gelatin, blood, and human spinal fluid. We could produce electrical storms in these media (Fig 4), but not in simple saline solutions.

A search of the literature for other reports of this effect was not very rewarding. Sem-Jacobson[4] had observed a similar phenomenon while stimulating and recording from egg albumin. Heath[5] had observed similar discharges from the septal region of humans having implanted electrodes. We could find no discussions which might explain possible mechanisms which could account for our results.

In recent experiments we have performed parametric analyses of electrical characteristics of the stimulus and we have emphasized behavioral correlations. We attempted to record, simultaneously, the firing of individual neurons, the depth EEG from a localized area of the brain, the impedance characteristics from this area and the DC potential between this area and the surface of the head. The interrelationships of these phenomena with behavior as measured by lever-pressing tasks were also studied.

Materials and Methods

Physiological Recording Techniques. Two types of microelectrodes were used, glass-coated platinum-tungsten wire sharpened to a 1μ tip diameter and 3M KCl-filled glass pipettes. The latter proved the more consistent in their recording characteristics and thus were used in most of the experiments. The electrodes were connected to a Keithley electrometer, monitored on an

EEG "Seizure Discharge"

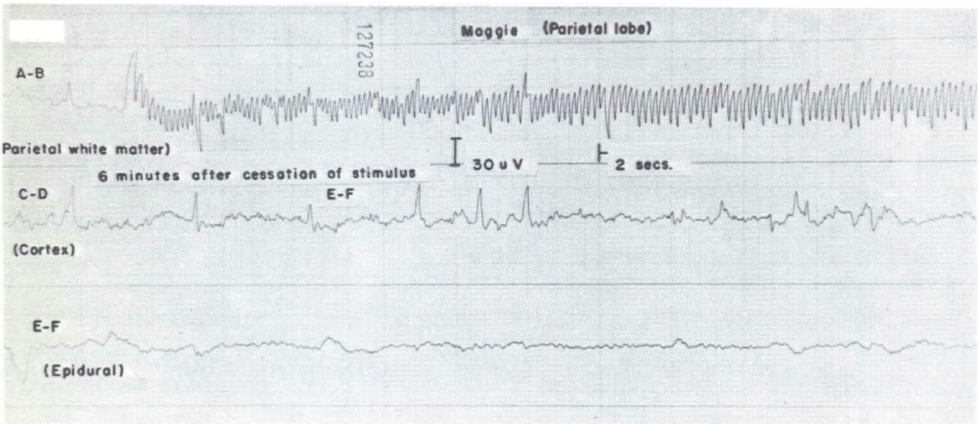


Figure 2
Post-stimulus Discharge (Maggie)

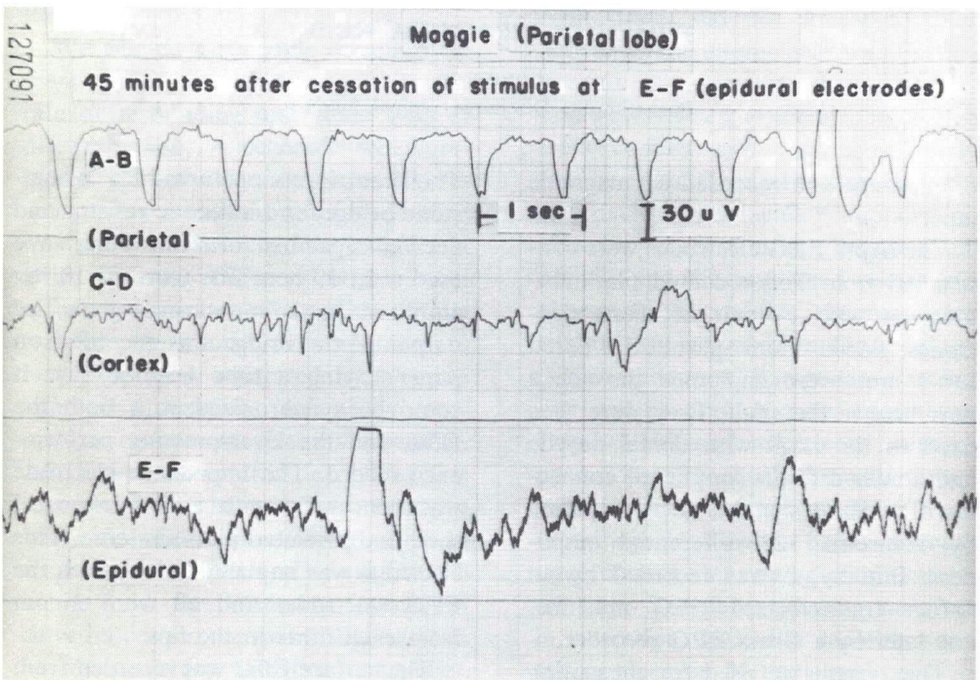
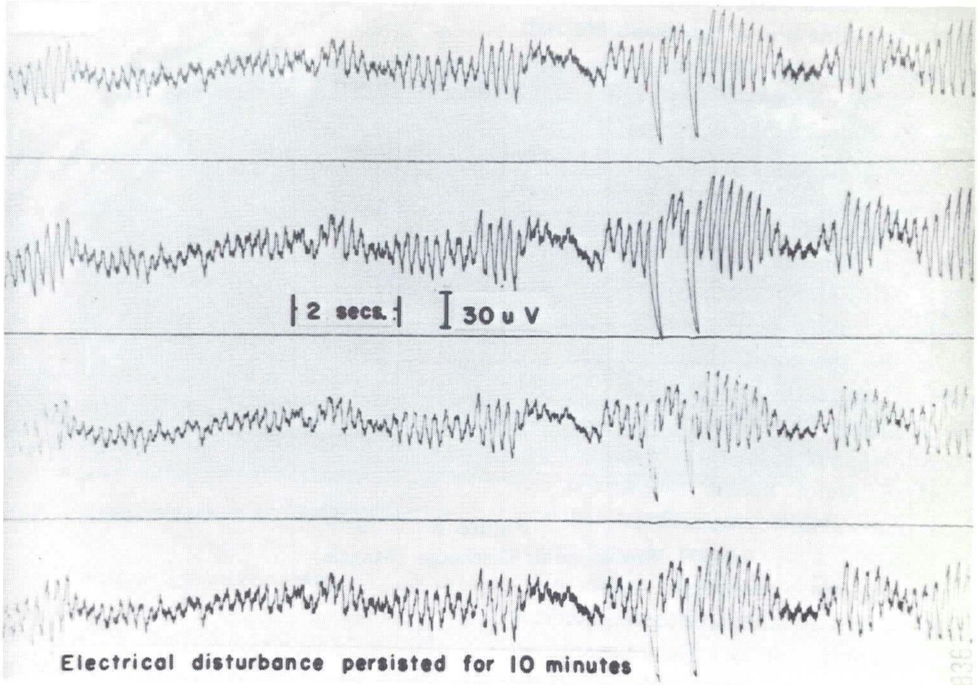


Figure 3
Post-stimulus Discharge (late stage)



HUMAN CEREBROSPINAL FLUID

Figure 4
Post-stimulus Discharge (spinal fluid)

oscilloscope and recorded on magnetic tape.

The depth EEG electrodes were constructed from Teflon-coated platinum-tungsten wire. A pair of these electrodes, placed 2 mm apart at tips bared for 1 mm, were implanted through a burr hole in the skull. They were then fixed to the skull with dental acrylic and attached to an Amphenol connector. The EEG signal was preamplified by Tektronix 122 differential amplifiers. Initially, it was recorded by an Offner transistorized EEG machine, and later by a Grass EEG recorder.

The system we used for measuring brain impedance is similar to the one described by Adey, Kado and Didio.[6] The brain forms one arm of a Wheatstone bridge, and a decade resistor and decade capacitor form the other. We used a 1,000 herz sine wave of 10 mv amplitude as the measuring signal. The output of the bridge was recorded on paper having a time line, so that it could be synchronized with both the EEG and the lever-pressing performance record. The impedance electrode was concentric with a stainless steel shell and insulated platinum core. This electrode was implanted along with the EEG electrodes and all were 2 mm from each other at the tips.

The surface EEG was recorded from stainless steel screws which were embedded in the skull. Also, the DC potential between the depth electrodes and the screws in the skull was recorded.

Behavioral Techniques. For the behavioral evaluation we used techniques established in the field of operant conditioning. Such techniques are appropriate because we wished to develop a stable pattern of response which would allow an almost continuous evaluation of the animal's performance.

The behavioral apparatus was secured to the restraining chair and consisted of a response lever and a food cup where banana pellets were delivered. There was a light illuminating the chamber and also a light which could illuminate the food cup. The monkey was trained to press the lever according to a certain schedule in order to receive the reinforcement, which was the delivery of a food pellet into the cup.

We wanted a schedule of reinforcement which would ensure a steady rate of responding and some type of discrimination. A schedule which required the monkey to space his responses by a certain amount of time was chosen. The schedule is called a DRL, meaning Differential Reinforcement of Lowrates. According to the schedule the monkey was required to emit responses separated by a minimum time duration, such as five seconds, in order to receive reinforcement. All responses emitted less than five seconds after the previous response were classified as incorrect. Correct responses were followed by a light flash at the food cup. When the animal received a certain number of light flashes he was rewarded with the food pellet.

At the present time, the EEG and behavior are recorded with a seven-track digital tape recorder. Thus, we have a synchronized record ready for analysis by a digital computer of depth EEG, surface EEG, and performance of a lever-pressing task.

Results

Electrical Parameters of Stimulation. As an economy measure, rats and cats instead of monkeys were used to develop the technique of micro-electrode recording. Nineteen rats and 13 cats were used in logging over 100 hours of microelectrode recording. The results of the experiments with unit potentials were largely unrewarding. Post-stimulus discharges at the EEG depth electrodes were brief when they occurred. This has been generally true of all our experiments with rats and cats, but not with monkeys. Even without the discharge, stimulation through the macroelectrodes did not appear to affect activity in the microelectrodes. Further, because of movement during respiration (even when artificial), microelectrode contact with a given cell could not be maintained. In summary, this approach could neither support nor disavow a relationship between unit activity and the prolonged seizure discharge. In view of this, the micro-electrodes were not used in the monkeys.

Experiments with impedance recording have been much more informative. Depth EEG and impedance were recorded simultaneously from the amygdaloid nucleus of the monkey. These recordings, six to eight hours in length, were done under resting conditions on 63 days. The lever-pressing task was in operation while the recording was taking place on 31 days, and on 19 of these the monkeys were stimulated through the depth EEG electrodes. The

10 seconds of stimulation was with a 400 herz square wave pulse having a duty cycle of 80%. The voltage varied between 8 and 14 volts because we tried to maintain the stimulus current between 3 and 4 milliamps.

The resting impedance in each monkey varied from day to day. Recordings made within 48 hours after implantation of the electrodes showed a resistance around 50 K ohms with a capacitance of 2,000 picofarads. Over a period of about two months, the daily impedance varied over a resistance range of 19.2K to 100K ohms, and a capacitance range of 4,800 to 1,100 picofarads.

Occasionally during the first moments of the lever-pressing task, there would be a slight change in the impedance but it would soon return to the resting level. This also occurred with the presentation of a new object to the monkey, such as some food or a toy. Repeated presentation of these same objects had no further effect. It would appear that some alerting phenomenon is related to impedance change.

With electrical stimulation of the brain, the impedance varied in its response. On four occasions there was no lasting change; on three occasions the resistive component increased and the capacitive component decreased, and on four other occasions the reverse happened: the resistance decreased and the capacitance increased. When the EEG "seizure discharge" was obtained, the impedance showed long lasting changes. In Fig 5, the resistance is shown to decrease and the capacitance is shown to increase.

As yet, even during the presence of the electrical "seizure discharge," we have observed no changes in the DC potential between the depth electrode and the scalp electrodes related either to the lever-pressing task or stimulation.

Behavioral Correlations. Figure 6 illustrates some of the patterns of responding found for different second-order schedules. A key is provided in the upper right corner. The top line records the lever responses. A downward deflection indicates when the lever was pressed, and that the pen stayed down until the lever was released. Thus the length of this deflection indicates the duration of the response. A deflection of the middle line occurred whenever the response met the time requirement and so was followed by a light. The bottom line indicates food pellet delivery. A dot has been placed in the records below any response which occurred before the minimum time was up. Thus, the dots indicate responses considered as errors.

The first record is a sample of how "Slick" responded on a schedule in which three responses spaced at least five seconds apart were required for a pellet delivery. Note that the responses vary somewhat in duration, although frequency of reinforcement is fairly constant.

The second record shows responses on a schedule with a shorter time limit between responses. Here "Samantha" is required to make five responses spaced at least two seconds apart. It can be seen that the responses occur at a higher rate than on the first record. There is also much less variation in response duration.

We are continuing our program with "Samantha" who is now on the schedule shown in the third record. Here the time between responses is the same

EEG "Seizure Discharge"

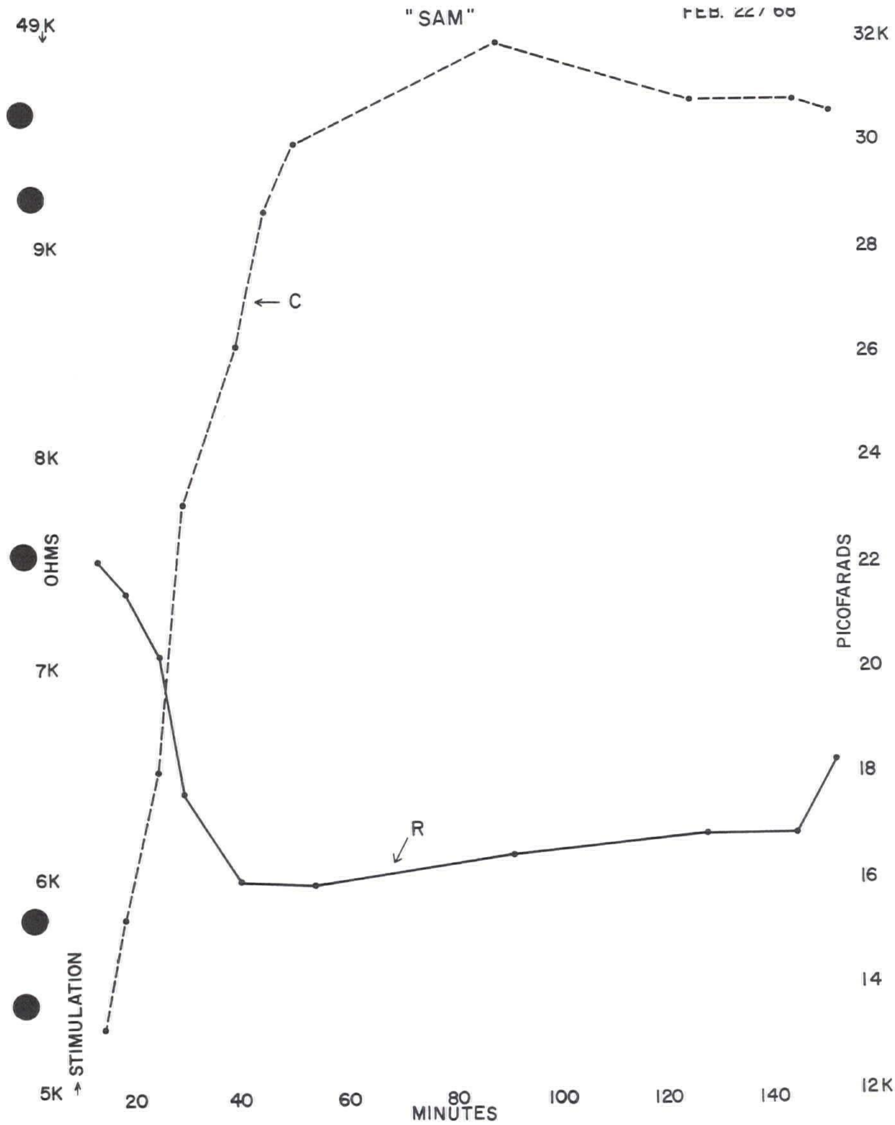


Figure 5
Post-stimulus Impedance (capacitance and resistance)

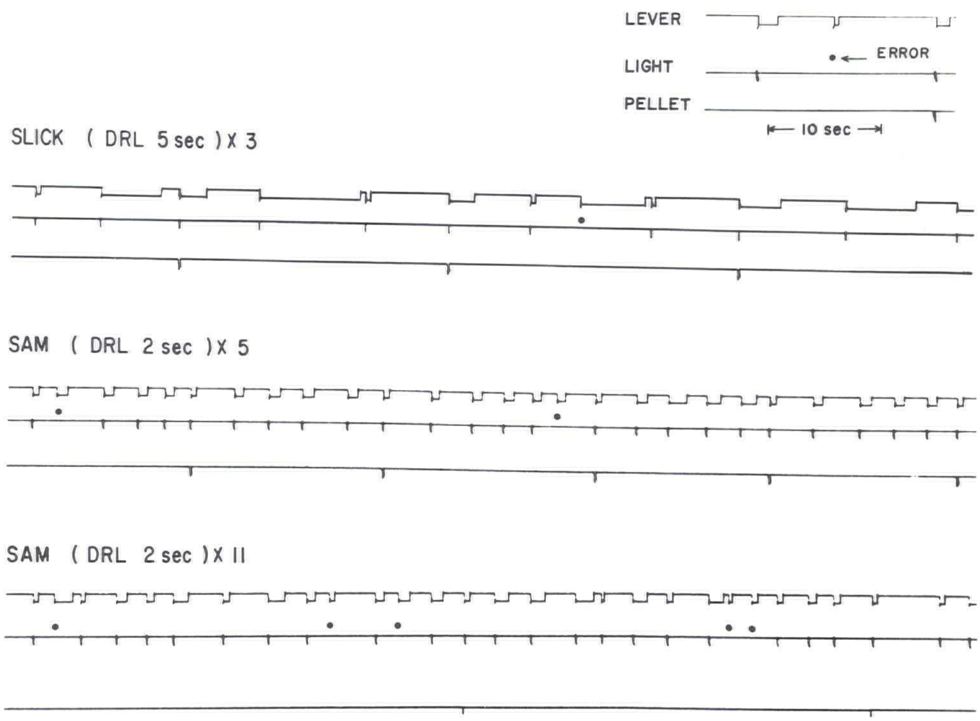


Figure 6
Control Behavior Patterns

as above, (two seconds) but the required number has been increased from 5 to 11. Response is still well-maintained although there is a slight increase in errors.

The monkey "Slick," received electrical stimulations of various voltages ranging from 1.5 to 12.0 v each lasting for ten seconds. Stimulation values from 1.5 to 5.0 v had no reliable disruptive effect upon "Slick's" behavior. A value of 5.5 v consistently resulted in a pause of at least 30 seconds. Following stimulation values ranging from 8 to 12 v, the monkey stopped responding for at least five minutes. He was observed making clonic movements during and after stimulation. A graph showing the effect of a 12-v stimulation on the number of responses is seen in Fig 7. Each bar of the graph represents the number of responses for each successive 30-second period. Correct responses (those followed by a light) are plotted above the horizontal line and incorrect responses below the line. Results for a control session are included for comparison. No responses were recorded for more than five minutes after stimulation.

Samantha has been stimulated twice with values of 8.0 volts, while performance on the reinforcement schedule was recorded. Both times she began responding within six or seven seconds following termination of the stimula-

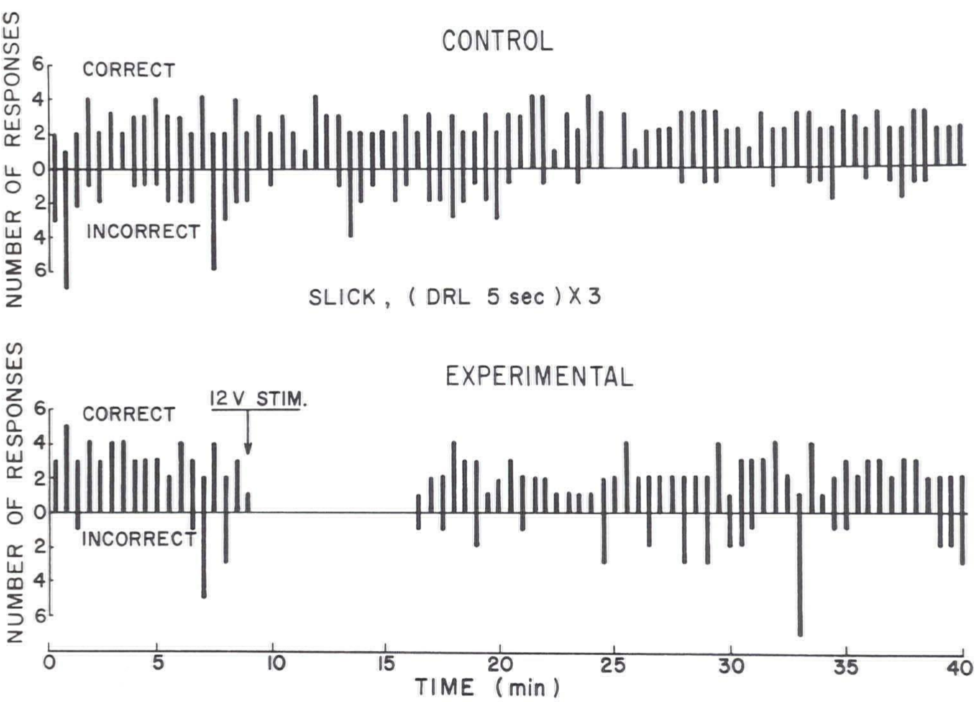


Figure 7
Post-stimulus Behavior (Slick)

tion. The results for one of these sessions are shown in Fig 8. Although the seizure discharge appeared on the EEG immediately following the stimulation, there was no marked change in responding.

Discussion

Our observations to date have led to the following conclusions: An electrical stimulus of certain parameters applied to the limbic system of the monkey brain consistently produces an electrographic seizure. The seizure is characterized by a delay in its appearance following cessation of the stimulus. This delay may vary from a few seconds to a few minutes and the seizure will subsequently persist for a time, varying from a few minutes to a few hours. The critical parameters of the stimulus appear to be a square-wave pulse with an 80% duty cycle and a current flow of at least three ma. The discharge always appeared first at the stimulated electrodes but on occasion would subsequently shift to another pair of electrodes within the brain. Some changes in brain impedance were seen during the discharge, but changes in microelectrode or DC potentials were not observed. Similar electrographic storms could be produced in several organic substances but could not be produced in a simple saline solution. No behavioral effects which could be related to the discharge

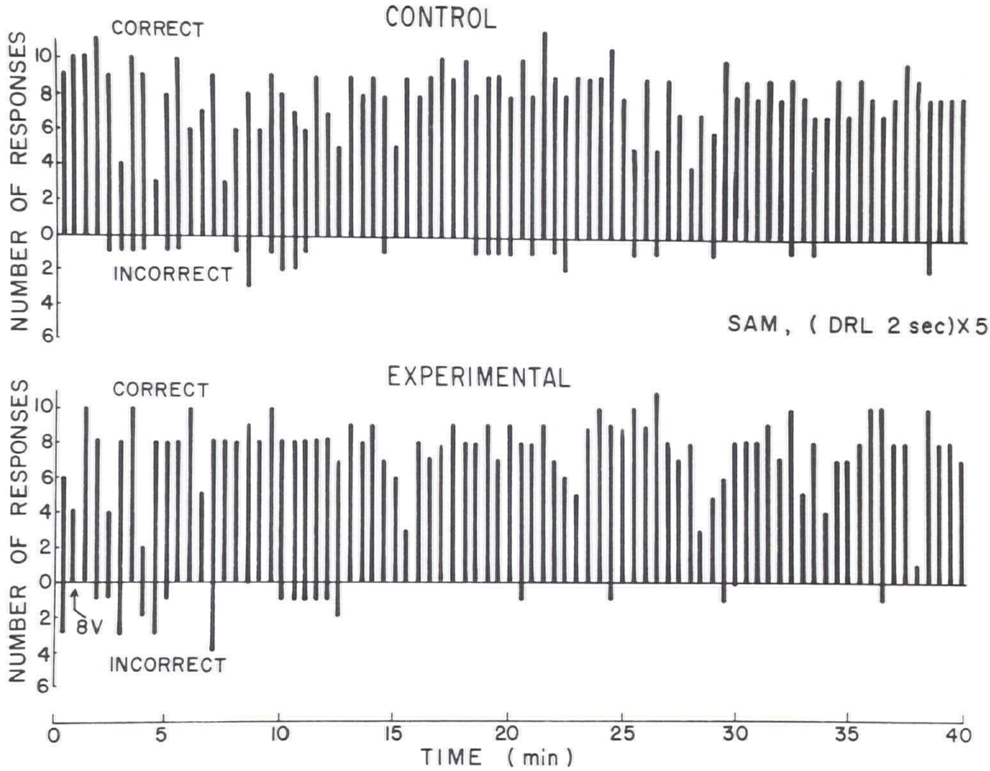


Figure 8
Post-stimulus Behavior (Sam)

itself were found either for the oddity or timing (DRL schedule) tasks.

A basic goal in these experiments was specifically to understand the mechanism underlying this electrographic seizure and more generally to understand the genesis of the EEG.

Historically, the clinical EEG was first recorded from the scalp. Relatively large-surfaced electrodes of low resistance were used as the reference points for the measurement of potential differences between various regions of the cranium. These electrodes summed the potentials generated in these regions. It was generally assumed that changes in these potentials were due primarily to the discharge of neurons and to the ebb and flow of charge in the dendritic fields. Potentials generated by electrolytes in the ventricles and eyes, blood flowing in cerebral vessels, contraction of cerebral vessels and metabolic activity of supporting cells (glial activity) seem to have received little consideration as factors in the genesis of the EEG. Furthermore, except for some polarization effects, the consequences to the EEG of physical phenomena that occur at the interface of the brain and an electrode have been generally ignored.

Although the report of our findings has been brief, it represents a considerable amount of work over a number of years. It is difficult to relate the evidence provided in this paper to the general concept of the genesis of the EEG. We can produce a dramatic "electrographic storm" in one area of the brain, yet the overall function of the brain remains unchanged. The surface EEG is not altered, the DC potential between the area of the "seizure" and the brain surface does not change, unit activity as far as can be determined does not change, and the animal's behavior does not change.

These findings have led to a reconsideration of the concept of the EEG. Rather than viewing the EEG as a representation of specific neurophysiological events we would consider it as a representation of a potential field within the brain case that has a structural and dynamic character separate from, and only indirectly related to, the anatomy and physiology of the brain whose space it shares. Certainly this field is generated by all the physiological, biochemical and physical forces at work within the brain case. However, their potentials become so integrated and summed that the resulting field achieves an independent character. The character of the field does change. Such changes may be slow or rapid, may vary in duration and may be diffuse or spatially localized. Although these field changes or perturbations reflect changes in the underlying systems, the autonomy of the field, as mentioned, may not permit direct relationships. It is possible, perhaps even probable, that the character of the field changes (wave form, spatial distribution and duration) is quite limited when compared with the almost infinite variety of change in the anatomical, physiological, and pathological character of the brain. If this is the state of affairs, then one kind of field perturbation must represent at least a class of events in the brain.

The evidence we have gathered while studying the "unique seizure discharge," added to our observations of clinical electroencephalography, does push us towards accepting this point of view. This does not mean that the EEG is without useful information. When it is considered as an electrical pattern representing the dynamic state of a complex system, then the analysis of the various pattern changes provides a moving description of the changes in the underlying system. It must be remembered, however, that it describes the dynamics of the system and not the anatomy or even the specific neurophysiology of the system. The general flow of information within the brain is regarded by many as independent from the activity of any specific neuron.

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