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SUBCORTICAL RADIO STIMULATION IN THE CHIMPANZEE

José M. R. Delgado, M.D.
et al.
Yale University

January 1969

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6571st Aeromedical Research Laboratory
Aerospace Medical Division
Air Force Systems Command
Holloman Air Force Base, New Mexico

Animals used in this study were handled in accordance with the "Guide for Laboratory Animal Facilities and Care" prepared by the National Academy of Sciences - National Research Council and in accordance with the Secretary of Agriculture Standards in "Laboratory Animal Welfare" (Federal Register, Vol 32, No. 37, February 24, 1967).

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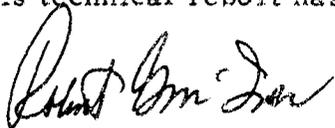
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FOREWORD

This study was carried out at the Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut during the period of 1 November 1967 to 1 June 1968 under Contract No. F29-600-67-C-0058 Project and Task Number 6892/02.

Co-authors of this report are R. J. Bradley, V. S. Johnston and G. Weiss of Yale University and Jan D. Wallace, Captain, USAF, MC, 6571st Aeromedical Research Laboratory, Holloman, AFB, New Mexico.

This technical report has been reviewed and approved for publication.



ROBERT G. McIVER, Lt Colonel, USAF, MC
Commander

ABSTRACT

The purpose of this study was to determine if conditioned suppression as demonstrated by Estes and Skinner (8) could be replicated in the chimpanzee using electrical stimulation of the brain as both aversive and pre-aversive stimuli. Stimulation was delivered by means of a miniature multichannel stimulator attached to the cranium and activated by radio. A fixed intensity pre-aversive stimulation and several intensities of aversive stimulation were superimposed on a FR 30 schedule for food reinforcement. The progress of this experiment had much in common with the outcome of a classical Estes-Skinner paradigm.

INTRODUCTION

As early as 1933 Loucks (1) demonstrated the feasibility of using cerebral stimulation as a conditioned stimulus (CS). Since that time a number of research strategies have been employed to exploit this procedure. These may be collated under four headings:

1. Mapping the areas of the CNS where stimulation will produce an adequate conditioned stimulus (2, 3).
2. Finding the degree to which the conditioned behavior may generalize to new stimulus parameters, to points other than the structure under examination, or to peripheral stimulation (3, 4).
3. Understanding the relationship between this centrally mediated stimulus and normal environmental inputs (5).
4. Investigating the extent to which the acquired properties of a central stimulation may be influenced by other central stimuli, peripheral stimuli, surgical lesions (6), or pharmacological agents (7).

The present report is an attempt to extend the range of behavioral paradigms to which this technique may be applied and describes the establishment of a Conditioned Emotional Response (CER) using two central stimuli. The phenomenon, often operationally defined as "Conditioned Suppression", was first reported by Estes and Skinner (8). They maintained lever-pressing in the rat by a food reinforcement schedule and found that response rate decreased during a stimulus which ended with an unavoidable foot-shock.

In this investigation multi-channel radio transmission was used to deliver both the conditioned stimulus (CS) and unconditioned stimulus (UCS) in the unrestrained chimpanzee.

METHOD

A. Subjects

The subjects in this study were two juvenile male chimpanzees: No. 687, 17.02 Kg (37.5 lbs); No. 688, 16.34 Kg (36.0 lbs). They were naive experimental animals and prior to behavioral training each had a total of 100 cerebral electrodes implanted in a variety of subcortical structures (9).

B. Apparatus

The test chamber was of fiber-glass construction and measured 3 meters by 2 meters by 2 meters. The front wall was made of plate glass and in one side wall was a retractible lever and food pellet dispenser. The chamber was situated in a large sound-proofed, radio frequency-screened room. Radio stimulation was achieved by means of two identical 3-channel radio stimulators previously described (9).

The unit, measuring 37mm by 30mm by 14mm, was screwed onto the electrode platform in animal No. 687 and placed in a box of similar dimensions anchored to the cranium of animal No. 688. A 7 v mercury battery contained in the unit provided sufficient power for one week of normal use.

Frequency, pulse width, and intensity of stimulation (constant current output) could be varied independently on all three channels by an RF transmitter located in an adjoining room but connected to a slave antenna suspended over the experimental chamber. Reinforcement contingencies and transmitter operation were controlled by solid-state programming modules also located in the adjoining room. Responses were counted by digital impulse counters and a cumulative recorder provided a continuous display of lever-pressing behavior. Closed-circuit television was used to monitor the experiment.

By use of an oscilloscope and a standard resistance the radio stimulators were calibrated within the experimental chamber where they were to be in operation. Intensity of stimulation was controlled by sub-carrier frequency; therefore strength of signal received by the radio stimulator was of limited consequence. However, it is necessary to sample the field strength in all parts of the experimental chamber to ensure the absence of nodes. The antenna configurations in this study were arranged to give a node-free experimental space.

C. Procedures

Using the above technology it was only necessary for the experimenter to handle the animals in order to change batteries or alter the connections between the channels of the radio stimulator and specific subcortical electrodes. Standard reinforcement procedures were used to train both chimpanzees to enter their respective restraining chairs on request and sit quietly and cooperatively while the experimenter worked on the implants (i. e., changed batteries or electrode contacts).

1. Reinforcement Value of Subcortical Stimulation

To evaluate the reinforcing properties of stimulation of subcortical loci the following technique was employed. Both animals were trained to lever-press on Fixed Ratio 10 (i. e. 10 lever-presses produced one food pellet) and then a mixed schedule was introduced. Such a procedure involved the consecutive presentation of four non-discriminated components, each lasting 10 minutes. In order that breaks in lever-pressing performance should not interfere with the order of component presentation, a further contingency was instigated. One component changed to the next component only when a 10-minute timer had timed out and a lever-press had then been made.

The order of components was as follows:

- a. Fixed Ratio 10 (Food)
- b. Extinction
- c. Fixed Ratio 10 (Food)
- d. Fixed Ratio 10 (Stimulation)

i. e. , four 10-minute periods producing a 40-minute cycle.

A daily session contained four such cycles, occupying a total of 160 minutes. Component d was similar to components a and c except that a 1-second brain stimulation was substituted for food reinforcement. Stimulation was delivered by radio as described, and intensity was set at motor threshold. Stimulation parameters were held constant at 1.0 sec pulse train duration, 100pps and 0.5 msec pulse width (square wave, monopolar).

Many electrode placements were tested in each animal as a basis for further experimentation. However, for the purpose of this study, two sites were selected in each animal. It was hypothesized that stimulation via these two electrodes would act as CS and UCS.

The electrode placements chosen, together with their reinforcement values, are summarized in the table on the following page. Reinforcing properties may be estimated by comparing average response rates during the "FR 10 STIMULATION" and "EXTINCTION" components.

If stimulation of a point in the brain has positive reinforcing properties, then, by definition, there should be a high response rate during "FR 10 STIMULATION". Similarly, a negative reinforcement value is defined by response rates well below "EXTINCTION" values.

A neutral point would support a response output which would not differ significantly from that obtained during "EXTINCTION". Using this rationale a negative reinforcing stimulation point was chosen as UCS in each animal. The CS was positive reinforcing for animal No. 687 and neutral for animal No. 688.

2. Conditioned Suppression

Both chimpanzees are stabilized on FR 30 for food reinforcement until reliable rates were achieved. Then subcortical stimulation, at the chosen CS location, was introduced for periods of 90 seconds. Such stimulation was intermittent with 1 second stimulation "on", alternating with 8 seconds "off", for the entire 90 seconds. The parameters were always 100pps, 0.5 msec pulse duration (square wave, monopolar). Eight 90-second-stimulus presentations occurred in an 80-minute daily session.

Responses during each 90-second period of intermittent stimulation were counted and the total was divided by the number of responses during the 90 seconds immediately preceding the stimulation period. This provided a measure of any change in behavior during stimulation, and is called a suppression ratio. A suppression ratio greater than 1.0 would indicate an increase in response rate during the stimulation, and a ratio smaller than 1.0 would be produced by some degree of response suppression during the stimulation period. Complete suppression (i. e., no responding during the stimulation.) would be indicated by a zero suppression ratio.

The CS intensity for animal No. 687 was 1.0 ma and for animal No. 688 1.2 ma. Neither of these values produced any observable motor response as both points were stimulated at intensities well below the previously determined motor threshold.

CS presentations were continued for 10 daily sessions. For both chimpanzees the CS next ended with a 0.5 second unavoidable negative brain stimulation (UCS). As for CS stimulation, UCS parameters were 100pps, 0.5 msec pulse duration. For seven sessions the UCS intensity was 0.05 ma for animal No. 687 and 0.35 ma for animal No. 688. Following this, five consecutive sessions were given at each of the stimulation intensities given below:

Animal No. 687 0.10 ma, 0.15 ma, 0.02 ma, 0.25 ma, 0.30 ma
Animal No. 688 0.04 ma, 0.45 ma, 0.50 ma, 0.55 ma, 0.60 ma

TABLE

MEAN RESPONSES PER MINUTE		Extinction	R 10 Stimulation	Electrode Placement		Stimulation Intensity In ma	Stimulation Response	Reinforcement Value	Experimental Function	
FR 10 Food	No.			AP	LAT					HC
128.1	No. 688	58.3	145.0	A25	R5	40	1.50	Head Turn to right	Positive	CS
140.3	No.	37.1	4.6	P5	L5	55	0.15	Vocalization	Negative	UCS
152.6	No. 687	71.5	53.0	A26	L9	52	1.80	L. Eye lid Up	Neutral	CS
162.5	No.	38.4	2.4	P5	L4	46	0.45	Vocalization	Negative	UCS

Actual stereotaxic placement and experimental evaluation of the electrodes used in this study. Animals No. 687 and No. 688 are still participating in experiments but the following tentative electrode locations are offered.

Animal No. 687 CS - Head of Caudate Nucleus
UCS - Reticular Formation

Animal No. 688 CS - Putamen
UCS - Reticular Formation

Vertical co-ordinate HC is the distance in mm below cortex.

Note that the underlined UCS intensities are those described in the table; i. e., vocalization threshold.

RESULTS

Figure 1 presents segments of typical cumulative records obtained during a session before CS presentation, during CS habituation, and after complete suppression. The baseline behavior is representative of that under FR 30, with animal No. 688 showing slightly higher rates than animal No. 687. The response rate is either at a high terminal rate or zero, as described previously by Ferster and Skinner (10). The most regular period of zero responding usually occurs immediately after a reinforcement is presented and is defined as the "post-reinforcement pause" (10, 11). However this pause is rarely seen in Figure 1 and there is a remarkable consistency in rate.

During the initial presentation of CS trials, one of the animals, No. 687, showed transient unconditioned suppression but this was undetectable by the third daily session. Figure 1 shows that before the UCS was introduced the behavior of both animals was not measurably affected by the CS alone.

Figure 2 shows chimpanzee No. 687 immediately after the delivery of the initial 1-second component of CS stimulation. This transient orienting response occurred occasionally during the early stages of experimentation. The stimulator which can be seen attached on top of the implant was well tolerated by the animal.

Figure 3 shows the mean suppression ratios and baseline response rates over the last two sessions at each UCS intensity. Since the stimulation was superimposed eight times in each session, these means were calculated from sixteen 90-second periods for both animals. Those intensities of UCS stimulation producing vocalization were correlated with complete suppression. As UCS intensity was decreased, suppression also decreased. In the case of No. 688 this decline was an all or none phenomenon, although No. 687 demonstrated a more linear relationship between suppression ratio and UCS intensity.

The effects of the conditioned suppression procedure on the baseline response rates are also graphed in Figure 3. The measures used in this calculation were provided by the counts of responses during the 90-second period immediately before the period of CS stimulation. However, these samples appeared typical of the behavior

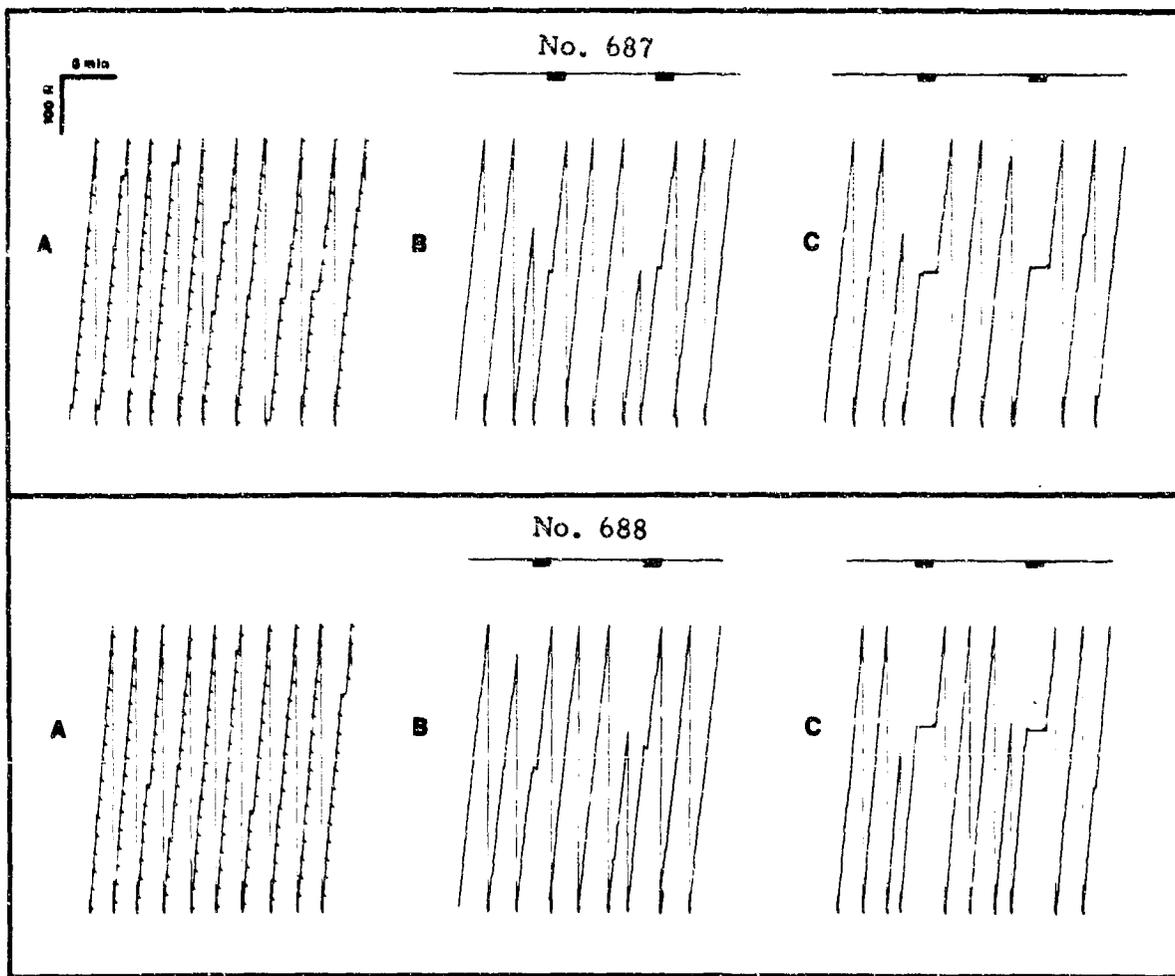


Figure 1. Sample Cumulative Records of Fixed Ratio 30 Baseline for Food Pellet Reinforcement. (A- Sessions before CS presentation, B- CS presentation, C- CS followed by UCS producing complete suppression. In record A downward deflections of the pen signify reinforcement. No reinforcements are shown during stimulation sessions; i.e., B and C. The pen was deflected down during the CS period and reset to zero 90 seconds prior to the onset of CS stimulation. All stimulations are shown on the event marker.)

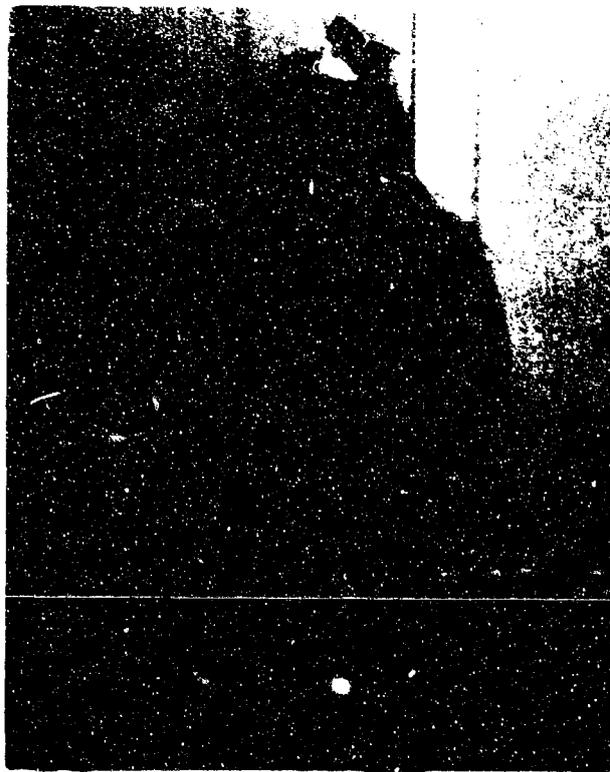


Figure 2. Chimpanzee No. 687 Attending to the Initial 1-Second Component of CS Subcortical Stimulation.

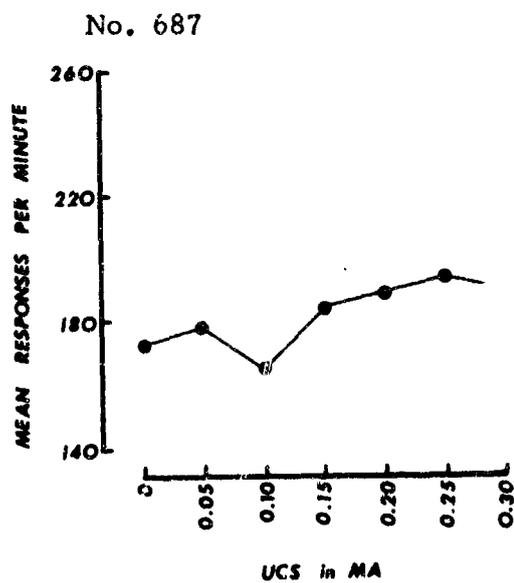
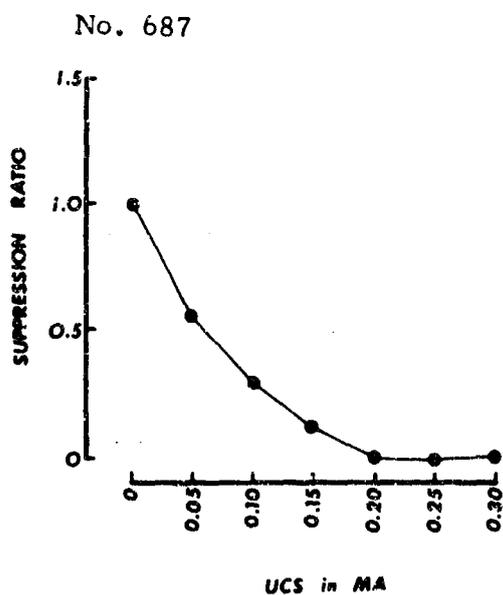
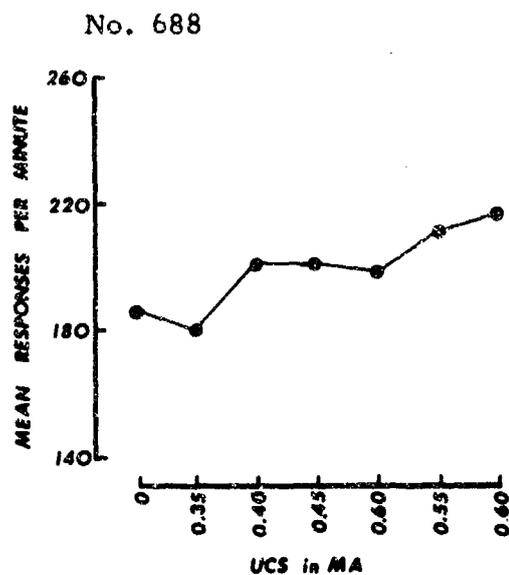
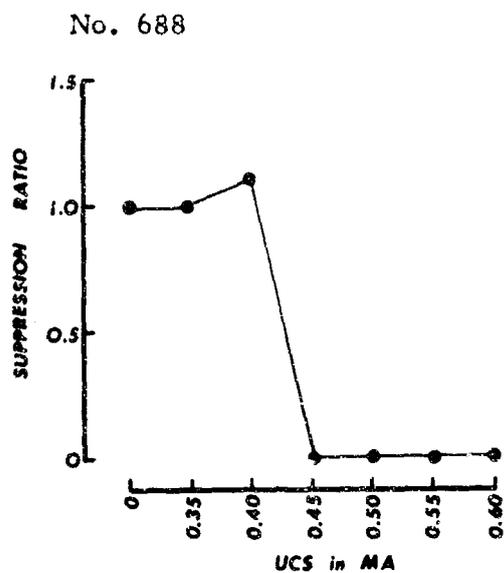


Figure 3. Mean Suppression Ratios and Baseline Response Rates Obtained Throughout the Experiment.

UCS In MA	No. 687	No. 688
No. 687 0.00	100	102
No. 688 0.00	100	102
No. 687 0.05	0.86	104
No. 688 0.35	0.86	104
No. 687 0.10	0.82	110
No. 688 0.40	0.82	110
No. 687 0.15	0.82	0.00
No. 688 0.45	0.82	0.00
No. 687 0.20	0.00	0.00
No. 688 0.50	0.00	0.00
No. 687 0.30	0.00	0.00
No. 688 0.60	0.00	0.00

Figure 4. Representative Segments of Cumulative Records.

during the entire period when the CS complex was absent. The data plotted are again the means obtained from the last two sessions at each UCS intensity. There appears to be a gradual inflation of rate as the UCS intensity is increased. When conditioned suppression became complete, the behavioral baseline was in no way affected.

Figure 4 shows representative segments of cumulative records obtained during the CS presentation with selected UCS intensities. The number in each section of this figure designates the mean suppression ratio obtained at that UCS intensity (plotted in Fig. 3). There is a slight evidence of conditioned facilitation for chimpanzee No. 688 as the UCS intensity is raised prior to complete suppression. Notable at all stages of this experiment was the immediate return to terminal rate following UCS presentation.

During complete suppression visual observation revealed that both animals would normally turn away from the lever at the first 1-second CS stimulation and remain in the far end of the experimental chamber until the UCS had been delivered.

Neither animal gave any physical indication that CS stimulation was being applied, nor was there any interference with on-going behavior other than the disruption of lever-pressing. Values of UCS below vocalization threshold all produced some signs of distress; i. e., startle response, attempt to escape, grimace or defecation.

DISCUSSION

The present study has shown that the conditioned suppression phenomenon can be demonstrated in the chimpanzee by electrical stimulation at two distinct subcortical locations. Ease of conditioning and the reliability of stimulus control generated by such techniques would suggest some superiority to normal external stimuli.

Annau and Kamin (12) have shown that the degree of conditioned suppression is a positive function of shock intensity. This is confirmed in the present experiment using aversive brain stimulation.

Previous experiments (13, 14) have suggested that shock has an adverse effect on behavioral baselines. This disruption has also been reported when the shock was used to produce conditioned suppression in the Estes-Skinner procedure (15). The finding is not confirmed in the present experiment and baseline rates continued to rise as the UCS

intensity was increased even beyond the intensity which produced complete suppression.

Lyon (16) has described the effects of varying the point in the ratio run at which the CS is introduced. He found that pigeons continued to respond during the CS if they had already emitted a certain number of responses of the ratio requirement. This key-pecking would continue until the next reinforcement was delivered and then suppression would begin. If the CS was presented early in the ratio run there was complete suppression. The behavior of animals No. 687 and 688 supports this finding. Examples of this partial suppression can be seen in Figure 4 (No. 688, 0.45 ma, 1st sample; No. 687, 0.20 ma, 2nd sample). On these occasions the ratio run in progress at the instigation of CS stimulation has been carried on to completion; i. e., reinforcement is obtained. At higher intensities a ratio was never completed irrespective of the point in the ratio at which the CS was imposed. In this experiment, although the CS was presented randomly in relation to the FR baseline and it was not possible to quantify the ensuing ratio completion, it was felt that the critical number of responses in the ratio run would be a function of the UCS stimulation intensity.

There seems little doubt that any experiment utilizing external signals, with or without reinforcing properties, could be replicated with appropriate stimulation of the central nervous system. In general, whether we wish to control the brain or understand its function, telemetry provides the means towards an unbiased analysis. The experimental animal may be unaware that he is carrying around his own private laboratory transmitting to, and receiving information from, the experimenter. This can even be an operant laboratory as both positive and negative reinforcement may be delivered at cerebral locations in a free-ranging animal.

In terms of both end result and procedural efficiency these techniques are of unquestionable value and raise new possibilities for experimental manipulation. For example, using multi-channel radio transmission to deliver brain stimulation it would be possible to control the behavior of individuals in a colony without participation of other colony members.

Some day we may control behavior by altering the on-going activity of a nervous system based on our understanding of its function. This experiment provides a more primitive way of achieving the same end. In essence we are making use of the brain's remarkable

ability to re-organize itself in response to our artificial stimuli and reinforcement techniques.

To date, however, this type of conditioning by cerebral stimulation has yielded little real understanding of brain function. The possible participation of kinesthetic feedback from a CS-elicited motor response is still unresolved and no experiments have been carried out to demonstrate the involvement of such a CS in normal sensory pathways. The present authors have found that if a subcortical point does not produce a motor response when stimulated at some critical intensity then it does not act as a conditioned stimulus at any intensity. It is also true that this stimulation of a point which does produce a motor response may be reduced below motor threshold and still act as a conditioned stimulus.

Rutledge and Doty (6) have investigated the effects of discrete lesions upon the behavioral change mediated by cortical CS. They conclude that such a CS is elaborated principally via corticofugal fibers, thus lending no support to the Pavlovian concepts of irradiation and intracortical elaboration of CS-UCS connections. This type of experiment is fruitful because the experimenter can specify the exact cerebral input to a stimulus.

Another promising experimental area is in the comparison of various internal stimuli. In a recent study Stutz (17) has shown that stimulus generalization occurs between conditioned stimuli produced by stimulation of positive reinforcing loci, but does not occur if two electrodes differ in their reinforcing properties.

The generalization experiment offers a powerful method for isolating the neuronal mechanisms which may have been activated by a cerebral CS. The Estes-Skinner procedure will be of considerable heuristic value in such an approach to brain physiology and, as has been shown in this study, may be established by radio control in the free-ranging chimpanzee.

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