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28 January 1963

Intracranial Self-Stimulation in Man

Abstract. *Intracranial self-stimulation techniques, modified for use with neuropsychiatric patients, provide data suggestive of positive and negative reinforcing properties of brief electrical stimulation to various subcortical structures of the human brain.*

Olds and Milner (*1*) first demonstrated in 1954 that rats will press a lever in order to obtain brief electrical stimulation to various subcortical regions via permanently implanted electrodes. Subsequently, this finding has been replicated many times in rats, and the species generality of the phenomenon has been extended in controlled studies to include the goldfish, guinea pig, bottlenose dolphin, cat, dog, goat, and monkey. These and other data relating to the reinforcing properties of electrical stimulation to certain brain areas have been comprehensively reviewed in a recent article by Olds (*2*).

Since Heath's initial observations (*3*), several reports have appeared describing subjective experiences of an apparently pleasurable nature accompanying electrical stimulation of deep structures in the human brain (*4–6*). Only two previous attempts have been made, however, to employ intracranial self-stimulation (ICSS) techniques with human subjects. Sem-Jacobsen and Torkildsen (*5*) report that patients have stimulated their own brains by means of a button switch wired into the stimulation circuit, and Heath (*7*), prior to this research, equipped a patient with a small portable self-stimulator with three buttons which permitted delivery of electrical stimuli of fixed parameters to any of three subcortical sites.

The present study represents an exploratory attempt to investigate human ICSS behavior under strict laboratory conditions such as have been characteristically employed in animal studies. A full report of results to date is in preparation. The present report summarizes some of the major findings.

In the series of depth electrode studies at Tulane (*3, 8, 9*), the primary motivation has always been therapeutic. Only patients who have failed to respond satisfactorily to existing therapies have been studied and treated with these techniques. Electroencephalographic recordings from depth electrodes permit more exact localization of disordered function. More information thus becomes available concerning the nature of the disease processes under study, and more precision is possible when intervention, surgical or other, is indicated, as, for example, in epilepsy and other neurological disorders. With schizophrenic patients, focal electrical stimulation to selected subcortical sites has been shown to produce at least temporary therapeutic benefit (*3, 5, 8*) and, in the Tulane studies, stimulation of activating and "pleasure-inducing" regions has particularly benefited retarded, anhedonic, chronic schizophrenic patients. A vast number of animal ICSS data attest to the powerful reinforcing properties of intracranial stimulation and its consequent efficacy in the modification of behavior (*2*). Moreover, some of these data (see, for example, *10*) implicate abnormal functioning of brain "reward systems" as a primary factor in certain mental disorders, demonstrate the unique value of ICSS techniques in elucidating central effects of psychoactive drugs, and promise eventual pharmacological control of reward-system function in man. The potential usefulness of ICSS procedures in the study and treatment of disordered human behavior is readily apparent. The present research was designed to explore ICSS techniques and to provide preliminary data on effective stimulus parameters and brain "reward" areas in man.

Findings presented here were obtained from a chronic catatonic schizophrenic patient (No. B-12) with multiple depth electrodes in place for 4 months prior to this study. Implanted electrodes were of two types: the "regular" single silver ball (*8*), and a stainless steel array providing multiple contact points (*11*). A roentgenographic, stereotaxic technique was employed for accurate implantation and subsequent maintenance of the electrodes (*12*). Patient B-12 is a 35-year-old male with a history of schizophrenia since childhood who has been continuously hospitalized without improvement for the past 9 years. Among other symptoms, he displays a marked tendency toward perseverative behavior which limited ICSS techniques suitable for use with him.

During experimental sessions the subject was seated alone in a soundproof room with a large lever and a hand button available to him. All stimulation, recording, and control apparatus was housed in an adjoining room from which the subject could be observed through a one-way–vision window. Communication with the subject was by means of an intercom system. For all work reported here, the stimulating wave form was a monophasic rectangular pulse of 0.2 msec duration, delivered at 100 pulses per second for a fixed stimulus train of 0.5 second. Stimulation was provided by a Grass S-4 stimulator through a stimulus isolation unit and stimulus monitoring device to the subject. Unless otherwise specified, stimulation was bipolar between electrodes 4 mm apart. The lever and hand button allowed the subject to stimulate his own brain. Functioning of these switches, however, could be controlled by the experimenters to provide current with one device and not the other, or currents of different intensity with the two devices. No visual or auditory cues which might signify such changes were available to the subject.

In our earliest work with a single lever it was noted that while the subject would lever-press at a steady rate for stimulation to various brain sites, the current could be turned off entirely and he would continue lever-pressing at the same rate (for as many as 2000 responses) until told to stop. Such data obviously justified no conclusions as to reinforcing or "rewarding" properties of the stimulation, but did underscore the need for stringent controls in brain stimulation work with human subjects. Three additional techniques have produced reliable evidence of reinforcing effects of ICSS in man. We have called these the *three current levels, free choice,* and *forced choice* procedures.

The *three current levels* method utilized a single lever. Subject was instructed to respond to a tone signal by pressing the lever (self-stimulating). If he felt nothing or if the stimulus felt neither "good" nor "bad," he was to press three times; if it felt "bad," he was to press less than three times; if it felt "good," he was to press repeatedly as long as he wished or until told to stop (arbitrarily after ten responses). After extensive exploration of a given electrode site for preliminary determination of rewarding and aversive current levels, an experimental series was conducted as follows: prior to each tone cue, the current was set at one of three predetermined levels, namely, zero current, the "rewarding" level, or the "aversive" level. Presentation of these currents was on a random basis for a total of 60 trials, 20 at each current level. The number of responses served as the criterion measure.

With this technique, clear evidence of rewarding and aversive properties of intracranial stimulation at varying intensities of current was obtained for the caudate nucleus, amygdala, intralaminar thalamic nuclei, and middle hypothalamus. Rewarding effects in the absence of a higher aversive level were found for the electrode pair tested in the septal area.

It should be noted that the terms "rewarding" and "aversive" as used in this report bear no necessary relation to the patient's subjective response to stimulation. Rather, they are defined operationally by the preferential lever-pressing behavior of the subject.

The free choice and forced choice methods were employed as an independent check on the above findings and for the testing of additional brain sites. With these techniques both the lever and hand button were used. In the *free choice* procedure, the subject was told that he might shift at will from the lever to the button or vice versa. A rewarding current was made available with one of these devices and either an aversive current or zero current with the other. In the course of the subject's responding, these current conditions were reversed by the experimenters so that the current previously available on the lever was now on the button, and vice versa. In addition, the current was sometimes switched off entirely. Because of the subject's marked tendency to respond perseveratively for zero current, most attempts to control his behavior under conditions of rewarding current versus no current were unsuccessful. Figure 1 illustrates one of the few successes with the free choice procedure. These are cumulative response records obtained with self-stimulation of the amygdala. The saw-tooth chart displays a continuous record of the subject's responding. Each "tooth" represents roughly 500 responses with the vertical lines indicating automatic reset of the pen. The steepness of the curves reflects response rate (in this case, about 40 per minute).

It will be noted in the top record that the subject initially stayed with the lever which was delivering reward current except for seven brief shifts to the aversive button and back. When the current was turned off, however, he continued as before to respond at the same rate. With the original conditions reversed, he quickly switched to the button, and when they were again reversed, he again responded appropriately. The lower record shows his responding for the reward current versus zero current. Again, responding was appropriate. It is of interest that the introduction of an attractive tray of food produced no break in responding, although the subject had been without food for 7 hours, was noted to glance repeatedly at the tray, and later indicated that he knew he could have stopped to eat if he wished. Even under these conditions he continued to respond without change in rate after the current was turned off, until finally instructed to stop, at which point he ate heartily.

The *forced choice* technique was introduced to circumvent the difficulties arising from the subject's tendency to respond perseveratively for no current under free choice conditions. Instructions for this procedure were as before except that in addition to shifting at will from one device to the other, he was told that whenever a tone signal was sounded, he was to shift immediately to the other device and that he might then

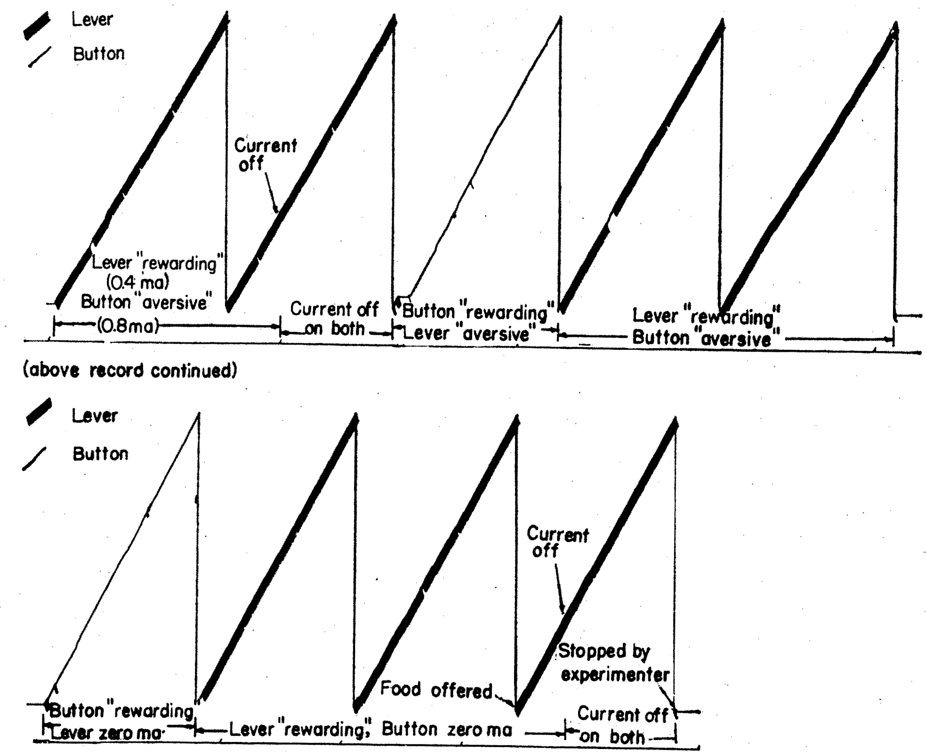

Fig. 1. Free choice ICSS responding for stimulation to the amygdala: rewarding current (0.4 ma) versus aversive current (0.8 ma) and versus zero current. Subject D.S. (No. B-12).

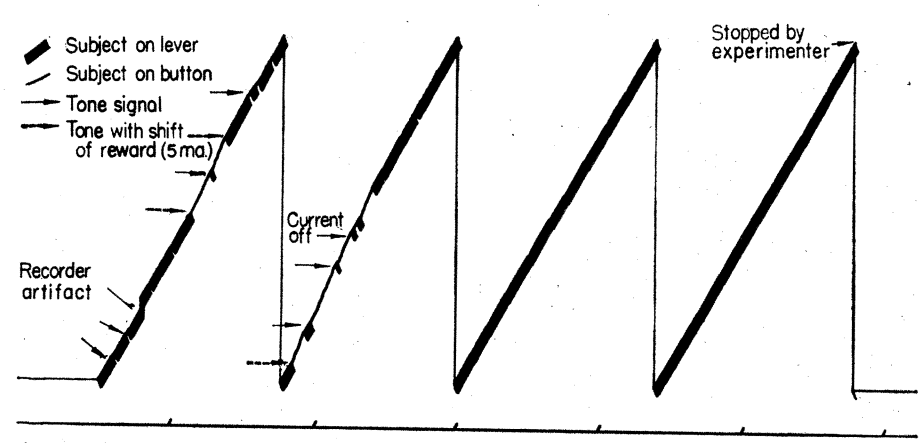

Fig. 2. Forced choice ICSS responding for stimulation to the septal area: rewarding current (5 ma) versus zero current. Subject D.S. (No. B-12).

either stay with that one or return to the one he had been pressing, whichever he wished. In short, he was forced with each tone signal to "try out" the other device and decide which he preferred to use. In this procedure a rewarding current was made available on one device and zero current on the other. In conjunction with some tone signals the rewarding current would be shifted by the experimenters to the other device; at other times the tone would be given without such a change being made. A sample forced choice record is shown in Fig. 2. This record demonstrates forced choice performance with self-stimulation of the septal area at a current level of 5 ma versus no current. Both spontaneous shifts and forced shifts were followed by rapid return to the initially rewarding lever, and when the tone was associated with shift of reward, the subject's preference shifted accordingly. These data appear to provide sound evidence of the reinforcing or rewarding properties of electrical stimulation at this site. Again, however, when the current was turned off entirely, this subject vacillated back and forth a few times and then continued to press the lever without reinforcement for more than half an hour until stopped. This has been a consistent finding with this patient in all work with him to date.

Table 1 summarizes preliminary findings with respect to rewarding and aversive current levels in various subcortical structures. This material is based on data obtained through use of the three techniques described. The current levels specified should not be taken as firmly established even for this subject. They are intended rather to give a general picture of differential thresholds in the various brain areas. Brady (*13*) has shown that prior stimulation in one area can affect response rate, and presumably reward threshold, in a second area. In our exploratory work we have not adequately controlled for this variable. Also, there has been indication that sites only a few millimeters apart in the same structure may show significantly different thresholds. It would appear, however, that current requirements for both rewarding and aversive effects are generally much higher in the forebrain structures than in the hypothalamic-tegmental area. Current requirements indicated for the head of the caudate raise some question as to whether the rewarding and aversive properties in this case might have resulted from spread of the field of excitation to other structures.

The rather consistent finding of an aversive current level in the range of 25 to 100 percent above the reward level in a given brain site does not correlate well with most animal data. Olds (*2, 14*) reports similar "ambivalent" effects in rats, but these have been less widespread in terms of anatomical locus. Further research is needed to determine whether the present finding may be generalized to other human subjects.

In summary, specialized intracranial self-stimulation techniques have produced data suggestive of the presence of subcortical areas in the human brain in which brief electrical stimulation appears to have rewarding or reinforcing properties. Brain areas thus far suggested as possessing such properties are the head of the caudate nucleus, the septal area, the amygdala, the intralaminar nuclei of the thalamus, the mid-hypothalamus, the posterior hypothalamus, and the boundary of the hypothalamus-tegmentum. With our electrode placements and stimulus parameters, relatively small increases in current above the rewarding level typically produced an aversive effect. These findings are based on data obtained from one clearly nonnormal subject. Any firm conclusions must await the collection of additional data (*15, 16*).

Table 1. Comparative current intensities, in milliamperes, for "reward" and "aversive" ICSS responding with various subcortical placements: subject D.S. (No. B-12).*

Structure	"Rewarding"	"Aversive"
Caudate (head)	8.0	10.0
Septal area	3.5 and up	‡
Amygdala	0.4	0.8
Central median thalamus	1.25	2.5
Mid-hypothalamus	0.2	0.4
Posterior hypothalamus	0.5	0.7
Post. hypothalamus-tegmentum	0.5	0.7
Tegmentum	†	0.2

* Stimulus parameters: unidirectional rectangular pulses of 0.2 msec duration delivered at 100 pulse/sec. Train duration: 0.5 sec. Bipolar stimulation between electrodes 4 mm apart in all areas except caudate nucleus (monopolar) and posterior hypothalamus-tegmentum (electrodes 2 mm apart).
† Not tested below 0.2 ma (apparatus limitations).
‡ Stimulation apparently rewarding and nonaversive up to 12.5 ma. Not tested above this level.

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11 February 1963

Radiolarians: Construction of Spherical Skeleton

Abstract. *The skeleton of spherical radiolarians, which consists basically of a network of hexagonally shaped structures, also contains some non-hexagonal structures, since a network made up entirely of hexagons cannot completely cover a spherically shaped organism.*

Among the radiolaria which can be classified as spherical, probably the most perfectly shaped is *Aulonia hexagonia*. This organism has a skeleton which consists of a basically hexagonal network. Several authors have shown that a completely hexagonal [6, 3] net cannot completely cover a sphere. Thompson (*1*) states this as a consequence of Euler's rule for polyhedra, and Weyl (*2*) gives a simple proof. The [6, 3] net is one composed entirely