ELECTRICAL SELF-STIMULATION OF THE BRAIN IN MAN[1]

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At a symposium concerning depth electrode studies in animals and man in New Orleans in 1952, the Tulane investigators described (and illustrated with films of patients treated between 1950-1952) a pleasurable response with stimulation of specific regions of the brain(5). The pleasurable response to stimulation of some deep regions of the brain, first observed with electrical stimulation to the septal region, has proved a consistent finding in continuing studies(6, 7, 12). Since 1952 we have reported various aspects of the phenomenon including demonstration of relief of physical pain by stimulation to this pleasure-yielding area of the brain(11).

With the introduction of ingenious techniques for self-stimulation by Olds (14-17), the need to depend largely upon verbal reports of the subjective response was eliminated and it was possible to study apparent reward and aversive areas of the brain in animals. Subjective data, of course, were lacking in the animal studies.

During the last few years the Tulane researchers have incorporated and modified some animal intracranial self-stimulation (ICSS) methods for human investigation, permitting extension of the pleasurable phenomenon studies in man. An ICSS study recently published(3) was designed to explore human behavior under strict laboratory conditions of the type characteristically employed in animal studies. A study has also been described in which a patient was equipped with a small portable self-stimulator with 3 buttons, permitting delivery of electrical stimuli of fixed parameters to any one of 3 brain sites(8). The primary motivation in these studies, as in all depth electrode studies in man at Tulane, was therapeutic(5).

Study of reward areas in the brain of man, including use of induced reward for therapeutic purposes, is extensive and complex. This presentation will focus on a description of the subjective responses of two patients treated by the self-stimulation technique. Their reports provide information concerning the reasons for repeated ICSS—information that is not available from animal studies.

MATERIAL AND METHODS

Two patients were used in the study. Patient No. B-7, age 28, with a diagnosis of narcolepsy and cataplexy, had failed to respond to conventional treatments. He had electrodes implanted by the method developed in our laboratory(1, 2) into 14 predetermined brain regions and fixed to remain in exact position for prolonged study. These small silver ball electrodes (most of those used in this study consisted of 3 leads each separated by 2 mm.) were placed into the right anterior and posterior septal region, left anterior and posterior septal region, right anterior hypothalamus, mid-line mesencephalic tegmentum, left anterior and posterior hippocampus, left anterior and posterior caudate nucleus and over the right frontal cortex, right and left mid-temporal cortex, and left anterior temporal cortex.

Patient No. B-10, age 25, a psychomotor epileptic with episodic brief periods of impulsive behavior uncontrolled with the usual treatments, had 51 leads implanted into 17 brain sites: left and right centromedian, left caudate nucleus, right ventricle, left and right hippocampus, mid-line mesencephalic tegmentum, left and right septal region, left amygdaloid nucleus, left paraolfactory area, and over the left

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At the time of presentation, a 16 mm. sound film was shown demonstrating the effects of stimulation by the transistorized portable self-stimulator to a number of specific regions of the brain in Patients No. B-7 and No. B-10. The two subjects were interviewed to obtain subjective descriptions of the effects of stimulation.

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and right temporal cortex, left and right occipital cortex, and left and right frontal cortex. Twenty-four leads were of stainless steel .003 inch in diameter coated with Teflon; 27 were the small silver ball type electrode.[4]

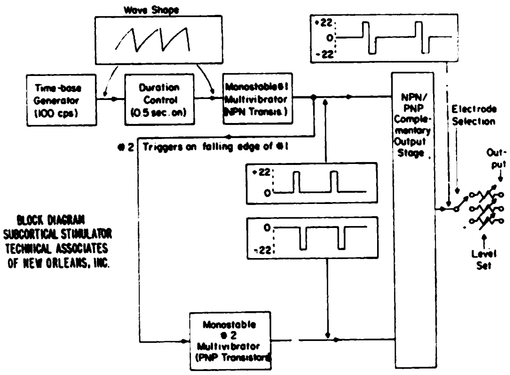
ICSS studies were not initiated until a minimal period of 6 months following operation, assuring elimination of any variables introduced by operative trauma, *e.g.*, edema, anesthetic effects.

Stimuli were delivered from a specially constructed transistorized self-contained unit[5] which was worn on the patient's belt. The unit generated a pre-set train of bi-directional stimulus pulses each time that one of the 3 control buttons was depressed. Each button directed the pulse train to a different electrode pair permitting the operator a possible selection of cerebral sites. A mechanical counter was coupled to each button to record the total number of stimuli directed toward a given area. An internal timer limited each pulse train to 0.5 second for each depression, thereby prohibiting the operator from obtaining continuous stimuli merely by keeping the button depressed. An additional feature of the unit provided 3 separate level potentiometers to give wide-range control of stimuli for each electrode pair.

Circuit details. To minimize the effects of dc polarization, a bi-directional pulse was chosen (Fig. 1). This pulse permitted restoration of the dc level to zero after each 1.0 millisecond stimulus and maintenance at zero during the entire dead time of 10 milliseconds.

A silicon unijunction timing circuit generated the basic 10 millisecond interval. The output from the unijunction transistor was gated off after 0.5 second operation by a diode gate driven from an R-G charging circuit. When the diode gate was open, the unijunction transistor generator drove two complementary one-shot multivibrators operated serially, permitting the falling edge of the first to trigger the second. The two multivibrators had equal periods of 0.5 millisecond. The multivibrator timing circuits saturated complementary output transistors which fed voltage to the load through isolating capacitors.

FIGURE 1
Circuit Diagram for Transistorized Intracranial Self-stimulator



The stimuli were mono-polar; the indifferent pole was a plate strapped to the subject's leg.

Studies conducted on the two patients differed somewhat because of therapeutic considerations. For studies with Patient No. B-7, the narcoleptic, the 3 buttons of the unit were attached to electrodes in the septal region, hippocampus, and mesencephalic tegmentum, and he was free to stimulate any of these sites as he chose. The patient wore the stimulator for a period of 17 weeks. Before he was equipped with the unit, baseline data concerning the time he spent sleeping during an arbitrary 6-hour period each day were charted by specified ward personnel. These data were later compared with sleeping time following attachment of the unit. This study was basically therapeutic (treatment results will be presented elsewhere) but from the experimental design we were able to obtain considerable subjective data regarding the effects of ICSS to several regions of the brain.

With Patient No. B-10, the psychomotor epileptic, a number of different experimental designs were employed to investigate the effects of ICSS. For illustrative purposes, the results of one study are presented herein as background for a descrip-

[4] Stainless steel array constructed of No. 316 stainless steel wire, .003 inch in diameter, with quad Teflon-coated leads and 6 contact points 2 mm. apart. Electrode designed and fabricated by Henry A. Schryver, 110 W. Packard St., Fort Wayne, Indiana.

[5] Technical Associates of New Orleans.

tion of the subjective responses. In the first part of the study a total of 17 different cerebral regions were stimulated. They were selected at random, the unit design permitting 3 sites to be hooked up at any one time. Each electrode was made available to the patient for stimulation for a minimal period of 2 hours. Various combinations of 3 sites were arranged. The purpose in making stimulation to different combinations of sites available was based on well-documented animal studies which indicate that rate of stimulation at a given site will vary somewhat depending upon the site stimulated beforehand. Data are presented in terms of the hourly stimulation to a given site as recorded with the automatic counter of the unit. Additionally, the same site of the brain was attached to different buttons to determine if the patient would relate a response to a given button. He reported, however, a consistent response to stimulation of a given electrode regardless of the button to which it was attached.

In the second part of the study the 3 sites of the brain which the subject had elected to stimulate most frequently during the first part of the study were compared over a 6-hour period.

RESULTS

Patient No. B-7. After randomly exploring the effects of stimulation with presses of each of the 3 buttons, Patient No. B-7 almost exclusively pressed the septal button (Fig. 2).

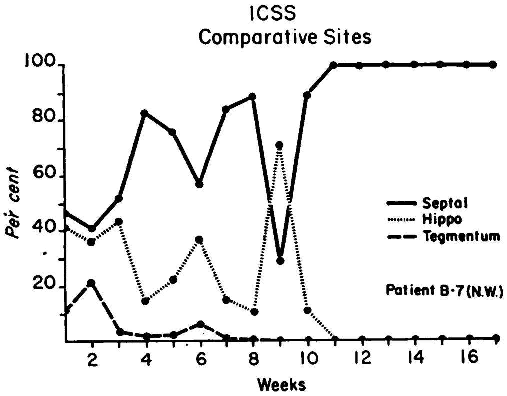
Stimulation to the mesencephalic tegmentum resulted in a prompt alerting, but was quite aversive. The patient, complaining of intense discomfort and looking fearful, requested that the stimulus not be repeated. To make certain that the region was not stimulated, he ingeniously modified a hair pin to fit under the button which directed a pulse train to the mesencephalic tegmentum so it could not be depressed.

Hippocampal stimulation was mildly rewarding.

Stimulation to the septal region was the most rewarding of the stimulations and, additionally, it alerted the patient, thereby combatting the narcolepsy. By virtue of his ability to control symptoms with the stimu-

FIGURE 2

Comparative Sites, ICSS. Frequency of Stimulation to Various Intracranial Sites Expressed in Percentages in Patient with Narcolepsy and Cataplexy



lator, he was employed part-time, while wearing the unit, as an entertainer in a night club.

The patient's narcolepsy was severe. He would move from an alert state into a deep sleep in the matter of a second. Recognizing that button pressing promptly awakened him, fellow patients and friends occasionally resorted to pushing the button if he fell asleep so rapidly that he was unable to stimulate himself.

The patient, in explaining why he pressed the septal button with such frequency, stated that the feeling was "good"; it was as if he were building up to a sexual orgasm. He reported that he was unable to achieve the orgastic end point, however, explaining that his frequent, sometimes frantic, pushing of the button was an attempt to reach the end point. This futile effort was frustrating at times and described by him on these occasions as a "nervous feeling."

Patient No. B-10. Studies conducted on the psychomotor epileptic patient were more varied and provided more information concerning subjective responses. The average number of button presses per hour for various regions of the brain is listed in Tables 1 and 2. Regions of the brain are listed in order of the frequency with which they were selectively stimulated by the subject. A summary of the principal subjective feelings is given.

The button most frequently pushed provided a stimulus to the centromedian thala-

TABLE 1
ICSS in Man
Reward (?) Sites

REGION STIMULATED	AVERAGE/HOUR	SUBJECTIVE RESPONSE
L. Centromedian	488.8	Partial memory recall; anger and frustration
R.P. Septal	394.9	"Feel great"; sexual thoughts; elimination of "bad" thoughts
L. Caudate	373.0	Cool taste; "like it OK"
Mesenceph. Teg.	280.0	"Drunk feeling"; "happy button"; elimination of "bad" thoughts
A. Amygdala	257.9	Indifferent feeling; somewhat pleasant, but feeling not intense
P. Amygdala	224.0	Moderately rewarding; increase of current requested

TABLE 2
ICSS in Man
Aversive Sites

REGION STIMULATED	AVERAGE/HOUR	SUBJECTIVE RESPONSE
R. Hippocampus	1.77	Strongly aversive; "feel sick all over"
L. Paraolfactory	0.36	Moderately aversive
R. Parietal Cortex	0.50	No significant subjective response
R. Frontal Cortex	0.00	
R. Occipital Cortex	0.00	
R. Temporal Cortex	0.00	

mus. This stimulus did not, however, induce the most pleasurable response; in fact, it induced irritability. The subject reported that he was almost able to recall a memory during this stimulation, but he could not quite grasp it. The frequent self-stimulations were an endeavor to bring this elusive memory into clear focus.

The patient most consistently reported pleasurable feelings with stimulation to two electrodes in the septal region and one in the mesencephalic tegmentum. With the pleasurable response to septal stimuli, he frequently produced associations in the sexual area. Actual content varied considerably, but regardless of his baseline emotional state and the subject under discussion in the room, the stimulation was accompanied by the patient's introduction of a sexual subject, usually with a broad grin. When questioned about this, he would say, "I don't know why that came to mind—I just happened to think of it." The "happy feelings" with mesencephalic stimulation were not accompanied by sexual thoughts.

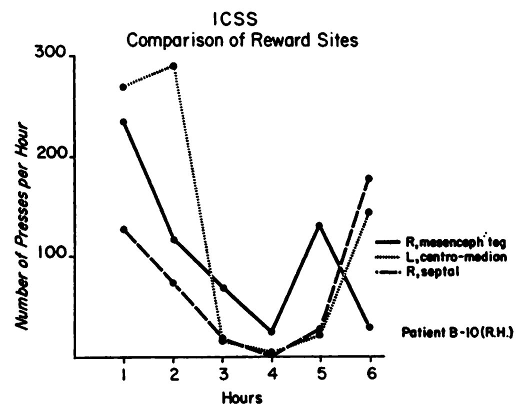
Patient No. B-10 also described as "good," but somewhat less in pleasurable-yielding quality, stimuli to two sites, the amygdaloid nucleus and the caudate nucleus. Several other septal electrodes and one other electrode in the amygdaloid nucleus were stimulated a moderate number of times. His reports concerning these stimulations suggested a lesser magnitude of pleasurable response, but definitely not an unpleasant feeling.

Minimal positive response was obtained with stimulation of several other septal electrodes. The most aversive response ("sick feeling") was obtained with stimulation to one hippocampal electrode and one lead in the paraolfactory area. With stimulation of the latter lead, he complained of light flashes, apparently due to spread to the optic nerve, and of general discomfort.

No consistent changes, either significantly aversive or rewarding, were displayed with stimulation to any of 12 cortical leads dispersed widely over the cortical surface, including the frontal, temporal, occipital, and parietal lobes.

In the second part of the study the 3 electrodes which were stimulated most during the first phase of the study were attached to the 3 buttons. The sites of these electrodes were the centromedian thalamus, the septal region, and the mesencephalic tegmentum. Data indicated that the combination of sites available influenced the number of times that a given region of the brain was stimulated (Fig. 3). When coupled with the subjective reports, the data also suggested that the over-all state of the subject at a given moment was an influential determinant for selecting the region to be stimulated. For example, the centromedian thalamus was stimulated up to 1,100 times per hour when in combination with relatively inactive sites of stimulation and only a maximum of 290 times per hour when in combination with two other highly rewarding areas, the septal region and the mesencephalic tegmentum.

FIGURE 3
Comparison of Frequency of Stimulation to Reward Sites in the Brain of Patient with Psychomotor Epilepsy



The patient noted that the frustration and anger resulting from stimulation of the centromedian thalamus was alleviated with stimulation to the septal region and to the mesencephalic tegmentum. As Figure 3 indicates, the patient during the first two hours stimulated the centromedian thalamus most frequently. This was associated with discomfort in his attempt to recapture a fleeting memory. He reported that stimulation of the other areas relieved this discomfort. There was little activity during the next two hours. Toward the end of the study, in the 5th and 6th hours, stimulation to septal and tegmental leads increased. During the 5th hour, the mesencephalic tegmentum was stimulated most frequently; during the 6th hour, the septal lead was stimulated most frequently. The patient evolved a pattern coupling the stimulus to the centromedian thalamus (which stirred his curiosity concerning the memory) with stimuli to the more pleasurable areas to lessen the feeling of frustration.[6]

DISCUSSION

Changes in parameters of stimuli to a given region of the brain, including current intensity, wave form, pulse width, and frequency, in many instances altered the patients' responses. This has similarly been reported with animal ICSS.

Information acquired from the patients' reporting of their reasons for button pressing indicates that all ICSS is not solely for pleasure. The highest rate of button pressing occurred with Patient No. B-7 when he was somewhat frustrated in his pleasurable pursuit and as he attempted to achieve an orgastic end point. In Patient No. B-10 the highest rate of button pressing also occurred with frustration, but of a different type, evolving with attempts to bring into focus a vague memory that ICSS had evoked. The subject's emotional state in this instance built into strong anger. It was interesting that the patient would button press to stimulate the region within the centromedian thalamus for a prolonged period, but at a slower rate when buttons providing more pleasurable septal and tegmental stimulation were also available. Depression of the septal button, with resultant pleasant feelings, alleviated the painful

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[6] When the paper was presented, it was here that the 16 mm. sound film was shown. Clinical effects of stimulation to a variety of deep regions of the brain, as summarized herein, were demonstrated.

In the last sequence of the film, Patient No. B-10, the psychomotor epileptic, was stimulated in the septal region during a period when he was exhibiting agitated, violent psychotic behavior. The stimulus was introduced without his knowledge. Almost instantly his behavioral state changed from one of disorganization, rage, and persecution to one of happiness and mild euphoria. He described the beginning of a sexual motive state. He was unable, when questioned directly, to explain the sudden shift in his feelings and thoughts. This sequence of film was presented to demonstrate a phenomenon which appears to be consistent and which has been repeated in a large number of patients in our laboratories. This phenomenon is the ability to obliterate immediately painful emergency emotional feelings in a human subject through introduction of a pleasurable state by physical or chemical techniques.

FIGURE 4

Subcortical and Cortical Recordings from Patient with Psychomotor Epilepsy during Psychotic Episode. This Record was Obtained During the Time that the Baseline of the Last Sequence of Film (Described Herein) was Taken. Note the Predominant Spiking Localized Principally to the Septal Leads. This has Proved to be a Consistent Physiological Correlate with Psychotic Behavior

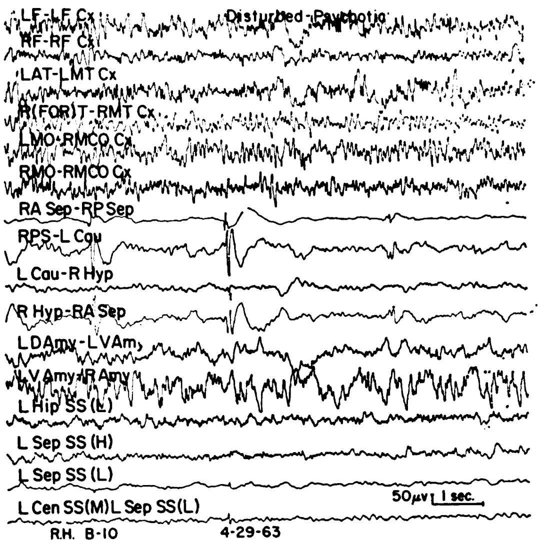
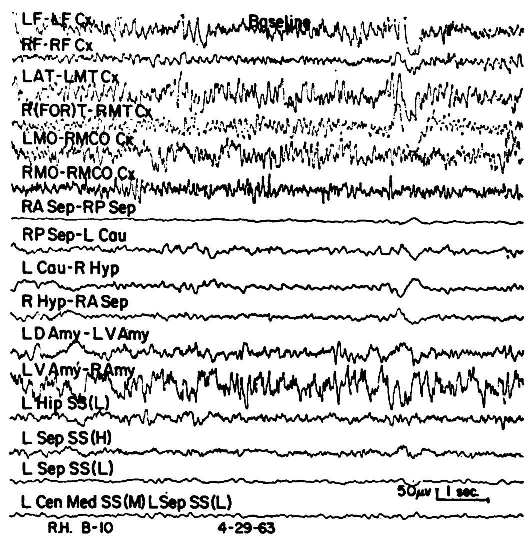


FIGURE 5

In Contrast to the Recording in Figure 4, this is a Baseline Record of the Type Displayed by the Patient with Psychomotor Epilepsy During his Usual Nonpsychotic Behavioral State



emergency state, according to the subject's report, and thereby provided him comfort to pursue his quest for the fleeting memory.

With septal stimulation in other patients, as well as the two subjects discussed here, a sexual motive state has frequently been induced in association with the pleasurable response. This sexual state has not developed in association with pleasurable feelings during stimulation to other regions. The consistent observation of a relation between sexual feelings and stimulation to the septal region has been described by MacLean in monkey experiments(13). These reports, in part, answer questions raised by Galambos regarding ICSS when he asked, "What motivates these animals to do such unheard-of-things? Is it some exquisite pleasure they receive, as several students of the problem staunchly contend, or the feeling of utter and complete well-being as others claim?"(4).

The ICSS techniques represent one of several methodologies that the Tulane researchers have used in man to investigate the pleasurable phenomenon associated with certain types of cerebral activity. These studies complement early subcortical electrical stimulation studies(5). The pleasurable response has also been induced in man with introduction of certain chemicals into specific deep brain regions(8-10). It is noteworthy that intense pleasurable responses induced with chemical stimulation of the brain occurred when a high amplitude spindling type of recording was set up in the septal region (Figs. 6 and 7).

The observation that introduction of a stimulus which induces pleasure immediately eliminates painful emergency states is quite consistent. If our psychodynamic formulations are correct, this basic observation may have widespread implication for the development of therapeutic methods to alter favorably disordered behavior.

Summary

Studies are described of two human patients under treatment with ICSS. Their subjective reports in association with stimulation to reward areas of the brain are presented. The data indicate that patients will

FIGURE 6
Baseline Record of Epileptic Patient No. B-5

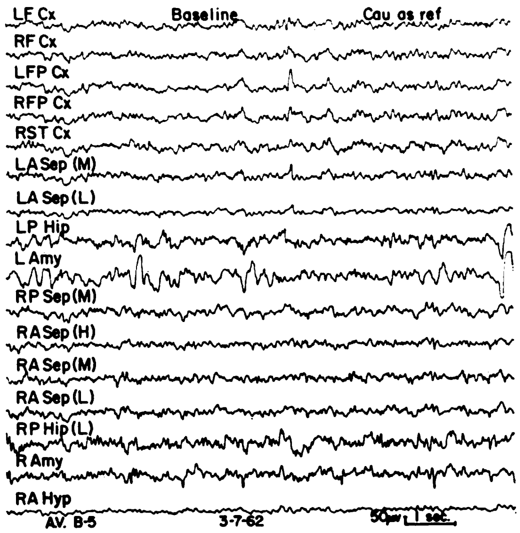
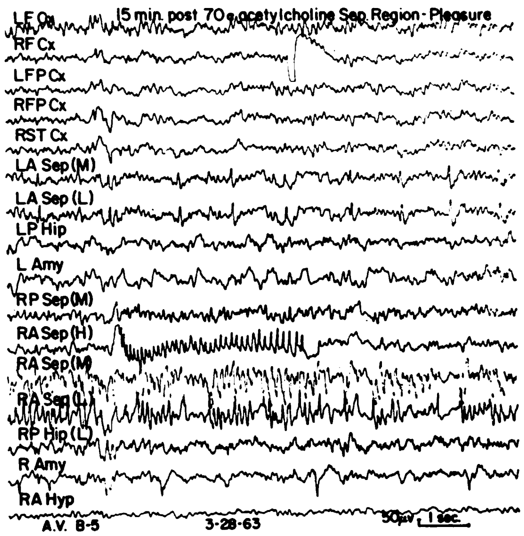


FIGURE 7
Recording from Epileptic Patient No. B-5 Following Injection of Acetylcholine into the Septal Region through Intracerebral Cannula



stimulate regions of the brain at a high frequency for reasons other than to obtain a pleasurable response. These data extend information obtained from ICSS in animals.

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