# FLIGHT BEHAVIOUR ELICITED BY ELECTRICAL STIMULATION OF THE HYPOTHALAMUS AND MIDBRAIN IN RATS: ESCAPE AND AVOIDANCE PROPERTIES

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ROBERT JOHN CLARKE

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Department of Psychiatry ( heurological facines)

The University of British Columbia Vancouver 8, Canada

Date

## ABSTRACT

Emotional, motivational, or species-specific behaviour can be elicited by intracranial electrical stimulation (ICS) in unanesthetized and unrestrained animals with chronically implanted electrodes. The purpose of this investigation was to describe and quantify, using an escape and avoidance task, a behaviour called flight, using rats as the experimental animal. An enclosed test box was used that had a hole in one wall covered by a moveable clear plastic plate. With the interior light on and exterior lights off, the hole represented the only opening in the box. Flight was then operationally defined as plate-pushing in response to ICS (escape response). It was found that only 25% of rats which showed manifestations of flight on pre-test screening would perform the escape response. After establishing reliable escape, the rats were given the opportunity to avoid ICS, at the threshold voltage for escape, by responding to a signal (bell, light or click) predicting the occurrence of ICS. In over 200 trials there were at most only 10% avoidances and no tendency for faster responding. A current explanation for this, proposed by W. W. Roberts, was tested by allowing these rats to press a bar for brief ICS at the voltage used in avoidance. Only 40% of the subjects would self-stimulate. These, and other results from the literature suggest that rewarding onset of ICS, as in the Roberts hypothesis, is insufficient to explain the lack of avoidance. The electrode sites producing escape were found to be in the central gray of the midbrain, and in both the medial and lateral divisions of the middle to posterior hypothalamus near the fornix. The sites producing similar behavioural manifestations but not escape were found to be in the same regions of the hypothalamus and midbrain.

ii

# TABLE OF CONTENTS

	Page	
Abstract	ii	
Table of Contents	iii	
List of Tables	iv	
List of Figures	v	
Acknowledgement		
Introduction		
Definition of theories (a) Emotion (b) Motivation	1 1 5	
Research leading to the present investigation	9	
(a) Description: effects and location	9	
(b) Quantification of ICS behaviour	14	
(c) Conditioning	21	
Methods		
Subjects	22	
Surgery	22	
Apparatus	23	
Procedure	28	
(a) Screening	28	
(b) Escape training	28	
(c) Avoidance training	30	
(e) Histology	30	
Results		
Stimulation effects	32	
Escape	35	
Avoidance	40	
Self-stimulation	44	
Histology	44	
Discussion		
References		

# LIST OF TABLES

•

Table		Page
I	Type and frequency of stimulation effects in hypothalamus and midbrain	34
II	Behaviour, location, threshold and number of trials for escape subjects	36
III	Mean response time per session ( <u>+</u> standard deviation) for each subject and WS modality	42
IV	Average bar pressing rate with and without ICS at the voltage indicated	45

•

iv

# LIST OF FIGURES

Figure	· · · · · · · · ·	Page
1	Side view of one wall of the plate box	25
2	Semischematic diagram of the escape training apparatus	26
3	Semischematic diagram of the avoidance training apparatus	27
4	Mean escape time versus stimulating voltage for subjects 43, 48, 50 and 56	38
5	Escape latency as a function of time for subjects 48 and 56	39
6	Mean latency ( <u>+</u> standard deviation) per session for all subjects as a function of the number of training sessions	41
7	Location of electrodes producing escape by plate-pushing	46
8	Location of electrodes failing to produce • escape by plate-pushing	47

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## INTRODUCTION

A new understanding of the neural mechanisms of emotional and motivated behaviour has been brought about through the use of electrodes chronically implanted in the brains of unanesthetized and unrestrained animals. It was found that electrical stimulation of discrete brain areas (intracranial stimulation, ICS) could induce complex behaviours resembling those seen during normal emotional and motivational states. This lead to the development of a method to quantify this behaviour and to determine its properties with respect to naturally elicited states.

## Definitions and theories.

The concepts of emotion and motivation are complex and the difficulty of providing an adequate definition has been quite apparent in recent reviews (Brady, 1960; Grossman, 1967; Goldstein, 1968). Of particular interest here is a concept that is relevant to how an organism survives in its environment. Most theoretical explanations have three components: initiating stimuli, central state, response. For each theory, the definition follows from the emphasis placed on one or more components.

(a) Emotion.

There have been definitions of emotion in ages past. Bindra (1970) in a historical review of emotion, and Masserman (1941) in his introduction have indicated that since the Greek philosophers, man has been aware of his "passions" and has attempted to localize them

- 1 -

to such regions as the heart, the pineal body or the ventricles. The modern story of emotions is considered by most people to begin with the ideas of William James which were published in his "Principles of Psychology" in 1890. He recognized that emotion had two aspects: the experiential and the expressive; the former being the subjective feelings, the latter the autonomic and somatic changes. The third component of the theory was the "exciting fact". According to James the order of events was: exciting fact, expression, experience. Such a counterintuitive approach ensured that the theory would be remembered for years to come. A similar peripheral theory of emotion was proposed by Carl Lange at the same time. These theories are known collectively as the James-Lange theory and the implications of it are still a matter of controversy (Fehr and Stern, 1970; Valins, 1970).

Although James' original formulation was in introspective terminology and thus untestable, considerable research involving peripheral manifestations of emotion was stimulated. This research necessarily involves human subjects because a verbal report as to how the subject "feels" is needed. Yet due to possible confusion between the concepts of experience and expression, or a disregard for the difference, many experimenters have inferred the presence of affect in animal subjects (Goldstein, 1968). It is clear then that animals should not be used as subjects in experiments testing the theory that emotional experience is due to the feedback of peripheral behavioural information.

The central mechanisms of emotional experience and expression, have been accented in several theories. Cannon (1927, 1931) brought

- 2 -

out a thalamic theory as an alternative to that of James-Lange. Cannon recognized that experience and expression were separate, attributing these to activity in the thalamus. He postulated the thalamus as a "center" of emotion which added an "emotional quale" to the incoming sensory stimuli on their way to the cortex. Disinhibition of the thalamus by the cortex caused the expression to occur through autonomic and somatic pathways near the hypothalamus.

One of the main points of Cannon's theory is the cortical inhibition of the thalamus. Arnold (1950, 1960) in her theory, saw this as being an excitatory connection. This theory was considerably more complex than Cannon's since it attempted to reconcile not only central and peripheral theories (i.e. James-Lange) but all the experimental evidence, of which there was a considerable amount at that time. Furthermore, she attempts to attribute various emotional reactions to specific parts of the brain. Hebb's theory is even more speculative and hypothetical than Arnold's, and Lindsley's accounts better the experimental findings (Goldstein, 1968). Hebb formulated a theory about hypothetical neural mechanisms which when disrupted produced emotion. Lindsley's activation theory summarizes the relationship between the electrical activity of the brain and emotional arousal.

Besides Cannon's theory, the most influential theory of emotion has been that of James Papez (1937). Papez was an anatomist and while looking for a relationship among the structures in the medial wall of the hemispheres formulated a relationship between these structures

- 3 -

and the available evidence on emotion. He considered the cortex of the cingulate gyrus as the place mediating emotional experience. The impulses reached the cingulate gyrus by way of the hypothalamus and went out again the same way. The role of the hypothalamus in the expression of emotion was emphasized in addition to its many reciprocal connections to structures involved in emotional experience. MacLean (1949) enlarged the anatomical bounds of Papez's concept and agreed that the hypothalamus was an essential part of the effector mechanism of emotion. In addition to the structures commonly regarded as part of the limbic system or "visceral brain" as he called it, MacLean (1955) suggested that the central gray of the brainstem was "interdependent" on the limbic system with regard to emotional processes.

The evidence for all these central theories was derived at first from ablation studies on animals and clinical observations on man. The first experiments were transections of the brainstem at various levels done by Goltz, Woodworth and Sherrington, Dusser de Barenne and Cannon (Brady, 1960). These transections produced rage responses which were better integrated with the diencephalon intact than with only the midbrain intact. It seemed that as one progressed rostrally in the brainstem, the autonomic components, at least, of the rage response became more complete. Bard (1928) determined that the structure essential for well coordinated and directed rage behaviour was the hypothalamus. Other emotional behaviours as the result of ablation were reported by Klüver and Bucy (1939) for temporal lobe lesions in monkeys. There were many

- 4 -

other examples of both limbic and cortical structures which when removed or damaged produced changes in behaviour and emotionality (Grossman, 1967).

Further evidence for the role of brain structures in emotion was derived from studies in which discrete areas of the brain were stimulated electrically. This technique which has done so much to provide information on the brain was popularized by the Nobel Prize winner W. R. Hess (1954). By localizing the electrode tip, he and his coworkers were able to map most of the brain with respect to the stimulating effects. The hypothalamus and vicinity were found to produce, on stimulation, responses such as fear and anger. This and subsequent studies found that stimulation of the hypothalamus produced not only emotional responses such as rage and fear but also motivational behaviour such as feeding, drinking and copulating (Grossman, 1967; Thompson, 1967).

(b) Motivation.

In the past emotional states such as anger, fear, joy, depression, have been considered conceptually apart from motivational states such as hunger, thirst, sexual desire and maternal care (Bindra, 1969). Emotions tend to be unorganized, involve high levels of arousal and occur irregularly due to chance external factors. Bindra has shown that there are more similarities than differences between the two concepts and has proposed a theory to explain them on the basis of a common construct called "central motive state".

- 5 -

The current view is to consider emotion as a special class of motivated behaviour (Milner, 1970). Milner defines motivation as "certain hypothetical states of the nervous system that determine what actions the organism will perform at any moment" (p. 297). The example given is of a dog which eats because it is hungry. Hunger, the central state, is a form of motivation in this case. Another example is a dog which runs because it is afraid. Fear is the central state and is a form of motivation. This central state can be operationally defined by quantifying the actions of the animal when it obtains food or runs to a safe place. As with emotion, there is a tendency to imply a central subjective state in addition to any behavioural meaning. Milner suggests that the term emotion should be reserved for the introspected central states with the hope that the difference between subjective state and overt behaviour would be made clear by the terminology.

Stellar's (1960) view of motivation is in terms of drive, goaldirected activity and satiation. Satiety is the reduction of motivated behaviour following the achievement of a goal. Drive is the intensity of motivated behaviour. The other term is self-explanatory. The experimental measure of these involves consummatory behaviour under various conditions. This terminology has been developed because the typical examples of consummatory behaviour have been eating and drinking. The concept has been extended to include also such behaviour as the avoidance of noxious stimulation.

- 6 -

Stellar has suggested a neural mechanism for motivated behaviour. His earlier theory (1954) stresses heavily the role of the hypothalamus. This is due to the strong evidence for a lateral excitatory and medial inhibitory hypothalamic system in the regulation of food intake. Stellar, using this model, generalized it to include other motivated behaviour and added enough factors to make it work and account for available evidence. His more recent paper (1960) reiterates the role of the hypothalamus and acknowledges even more factors which act on the system. One of these factors is learning, and how previously neutral stimuli can become associated with the arousal of motivation.

The role of stimuli in motivation has yet to be considered. In addition to behaviour, which can be measured, and the hypothetical central state defined as motivation by this measurement there is a stimulus (or stimuli) which initiates them. Some theories explain emotion and motivation on the basis of the stimuli which elicit them. Hammond (1970) specified these stimuli as either rewards or punishments or the absence of them. They can also be stimuli which can predict the occurrence of reward or punishment. This is accomplished by learning. The responses produced by such stimuli are classified as either approach or withdrawal. The neural basis of such a theory has been well investigated since the discovery (Olds and Milner, 1954; Olds, 1962) of areas of the brain where ICS is rewarding or punishing.

Another view of emotion and motivation has been proposed by ethologists and some investigators of the neural aspects of behaviour. Their

- 7 -

basic ideas are the same but the terminology is different. Brown (1969) questions the usefulness of the term "emotion" to describe behaviour in animals such as jellyfish, insects or frogs (for example) even though such behaviour may be functionally equivalent to a human's. All animals have some mechanisms which enable them to survive in their environment. The simplest mechanism is a reflex. It is an important determinant of behaviour in animals with primitive nervous systems. In animals higher in the phylogenetic scale, with better developed nervous systems, complex adaptive behaviours occur in addition to simple reflexes. Within a given species these behaviour patterns are consistent and the name speciestypical behaviour has been applied to them.

The study of behaviour in a wide range of species has helped the understanding of the neural organization of such behaviour. Just as the nervous system gets more complex as you go up the phylogenetic scale, so it does when you go from lower to higher levels in a given species (Brown, 1969). The example cited by Brown is the stimulation of a motor neuron in the Octopus, giving an arm movement. Stimulation at progressively higher levels gives movement of all arms, placing arms in attention position, and finally the attention position including other parts of the body. Another example is the previously mentioned studies on brain transected animals which indicated progressively greater organization of behaviour from the spinal cord up to the forebrain. The best examples, however, have come from the behaviours produced by the electrical stimulation of localized areas of the brain in animals from bullfrogs to

- 8 -

man (Doty, 1969). Here complex behaviours produced by ICS have included eating, drinking, gnawing, hoarding, attack, sexual behaviour, object carrying and maternal behaviour (Valenstein, Cox and Kakolewski, 1969, 1970).

## Research leading to the present investigation.

Early attempts at outlining the neural mechanisms of behaviour involved stimulation of the brain with observation of the effects. By identifying the stimulation sites, maps were made and structures identified with particular effects. Concern over whether certain effects resembled natural behaviour or not lead to first the quantification of ICS induced behaviour and then to the application of learning principles.

(a) Description: effects and location.

In 1927, W. R. Hess reported his discovery of centrally induced emotional behaviour to the German Physiological Society (Akert, 1961). It was clear then that electrical stimulation of a discrete area of the brain could initiate the neural activity involved in the coordination of complex motor behaviour. Hess called it affective defense and was able to correlate it with brain structures. In the region of the perifornical nucleus in cats near the descending column of the fornix in the hypothalamus, he obtained a defense reaction which resembled the behaviour of a normal cat confronted by a dog. It included assumption of a defense position, angry vocalizations, retraction of the ears, dilatation of pupils, hissing, spitting and a well directed attack.

- 9 -

Other components are lashing tail, unsheathing claws, defecation, urination, salivation, piloerection, sweating of the footpads, respiratory activation and retraction of the nictitating membrane (Akert, 1961). Not obvious in the unanesthetized, behaving animal are muscle dilatation, increased blood pressure and vasoconstriction of blood vessels in skin and intestines (Abrahams, Hilton and Zbrozyna, 1960).

Hunsperger (1956) using Hess' method investigated more fully these affective reactions, extending the anatomical boundaries and discriminating more details of the behaviour. He distinguished between affective defense, as described above, and flight, which has many of the same components but leads to running instead of attack. Affective defence was obtained from two central zones: the perifornical region of the rostral hypothalamus as described above, and the middle portion of the midbrain central gray. These two zones are embedded in an unbroken field extending from the gray matter of the preoptic area back to central gray of the midbrain. From this peripheral zone the flight reaction is obtained. This simple correlation of stimulation locus with stimulation effect is complicated by the strength of stimulation variable. There are mixed effects at the borders of these zones, of course, but an increase of voltage will tend to reverse the threshold behaviour. Strong stimulation of the central zones may cause the cat to suddenly jump off the table, and strong stimulation of the peripheral zone can evoke an affective defence reaction.

- 10 -

Subsequent papers by Hunsperger (Fernandez de Molina and Hunsperger, 1959, 1962; Hunsperger, 1963) have reiterated his view of the organization of affective reactions and have extended the system into the amygdala. He has also attempted to resolve the mixed effects into their components by using threshold stimulation and a very small stimulation electrode (Brown, Hunsperger and Rosvold, 1969a,b). Using this method, a growling reaction, a hissing reaction and two types of flight were produced. His flight type "a" is characterized by the cat looking about "as if in search of an exit" and then jumping from the table. Flight type "b" consists of exploration and sniffing of the surroundings followed by jumping off the table. Flight types "a" and "b" were obtained from the intermediate zone and caudo-lateral hypothalamus respectively. Suprathreshold stimulation still gave mixed effects but they conclude that the predominant characteristic of the response depends on the stimulation locus.

Yasukochi (1960) obtained a type "a" flight response from the anterior hypothalamus which he labelled as fear or anxiety. A flight type "b" response was obtained from the posterior hypothalamus. This behaviour is sufficiently vague that several words could describe it. Yasukochi uses "yearning" or "curiosity". He notes that some cats when stimulated in a "fear" region would attempt to escape through any small hole in their cage. Glusman and Roizin (1960) also describe flight responses which include carefully organized attempts to escape

- 11 -

from an enclosure if an opening was provided. Some animals also searched and explored the cage before escaping. At higher current intensities an aggressive response was changed to "violent panicky flight", a result similar to Hunsperger's. Also in agreement with him were the histological localization of the stimulating electrodes.

Romaniuk (1963, 1965, 1967) disagreed with the above formulation in two respects. He did not obtain flight from high intensity stimulation of a rage point. Only the latency and intensity of the response were changed and not the nature of the response. He also did not obtain the same localization within the hypothalamus. He found a dorsalventral division between flight and rage. This was especially prominent in the medial hypothalamus where the typical rage response is obtained from the ventromedial nucleus.

Both the hypothalamus and midbrain were investigated by Skultety (1963), in an attempt to replicate Hunsperger's 1956 results. Flight is defined as "agitated scurrying about the box" and attempts to get out of the box. These effects were obtained from the hypothalamus but not from the rostral midbrain, below the superior colliculus. Flight was obtained, however, from the central gray in the caudal midbrain. It was characterized only by attempts by the cat to escape from the apparatus. There were no searching movements.

In the experiments reported so far, the experimental animal has been the cat. Although patterns of aggressive-defensive behaviour can

- 12 -

be obtained by electrical stimulation of the brains of frogs, alligators and wild ducks (Doty, 1969) the discussion will be restricted to mammals. An exploratory escape-like locomotion with elements of a search for an escape route was obtained in the opossum by Roberts, Steinberg and Means (1967). Traczyk (cited in Balinska, Romaniuk and Wyrwicka, 1964) obtained a flight reaction by stimulating the hypothalamus of rabbits. Rabbits have also been used in the study of drugs on ICS induced aggressive-defensive reactions (Val'dman and Kozlovskaya, 1970; Silvestrini, 1958). Fear, defense and rage have been obtained in dogs by Fonberg (1967). In the monkey, Delgado, Rosvold and Looney (1956) described a fear response. One of their electrodes was near the central gray of the midbrain. In man there have been many reports of subjective emotional experiences from stimulation of many areas of the brain. For example, Sano et al (1970) have reported feelings of intense horror on stimulating the posterior hypothalamus. Spiegel, Kletzkin and Szekely (1954) and Nashold, Wilson and Slaughter (1969) summarize reports of pain on stimulation of the midbrain tectum and central gray. Heath and Mickle (1960) report anxiety and discomfort from the rostral hypothalamus and tension and rage from the caudal diencephalon and mesencephalic tegmentum. In rats rage type responses have been described to a great extent (for example, Panksepp and Trowill, 1969; Panksepp, 1971) but explicit descriptions of a flight response are difficult to find. The flight response, in the form described in cats does appear in experiments where the hypothalamus of the rat is stimulated for some other purpose.

- 13 -

In that case flight is labelled under the general heading of "other effects" (Woodworth, 1971; Vergnes and Karli, 1970).

(b) Quantification of ICS behaviour.

The terminology used has varied from author to author. Such terms as alarm reaction, rage, aggressive-defensive reactions, affective defense, attack, threat, flight, fear, escape, agonistic behaviour, emotional reactions, species specific defence reaction and stimulusbound behaviour have all been used to describe the results of stimulating the hypothalamus, mesencephalon and other parts of the brain. Some responses are so general that there are a host of words to describe This is true for the sniffing, exploration, curiosity, general acit. tivity and general locomotion obtained at most points in the hypothalamus. There is obviously a need to evaluate and quantify these behaviours systematically. This is done by providing suitable environmental objects on which the animal can act. A simple example is eating produced by the availability of food coupled with hypothalamic stimulation (Margules and Olds, 1962).

A similar example has already been provided with respect to affective behaviour. It is noted in most papers that the cat, besides looking ferocious, will also attack the experimenter or a stuffed model cat (Brown et al, 1969a,b). Similarly with flight, part of the definition is that the animal will attempt to escape from wherever it is by whatever means available. This can be observed in almost any test situation but it is still a crude method of evaluating behaviour.

- 14 -

It is usually sufficient to characterize the effects of ICS by providing an environmental object on which the animal can act. The strength of response can be measured and is usually the time required for a particular response. Wasman and Flynn (1962) for example provided their cats with a rat to attack. The latency to initial movement and attack latency were recorded. In addition, the attack behaviour was rated by the experimenter and an independent observer, a technique used by Roberts (1958 a) to separate his cats into alarm and flight groups. Renfrew (1969) provided his monkeys with a rubber hose to attack and the number of bites made was automatically recorded.

The measure of flight has been done similarly. The animal is provided with a means of escape and the latency to do so is recorded. In the same manner as for attack, the latency to initial movement may be recorded (Siegel and Skog, 1970) or the time required to perform a certain response may be recorded. There have been three basic responses used: shuttle-box running, maze running, and plate-pushing. Coupled with these, many studies have also determined the threshold current necessary to produce a response or have studied the effect of stimulus parameters (Renfrew, 1969; Bower, 1959).

The most common method of measuring flight is the use of a two compartment box or shuttle-box. Flight is then defined as the crossing of the barrier between the two compartments. A system of photo-cells

- 15 -

can then detect the crossing and with a clock in the circuit, can measure escape latency and terminate ICS (Stokman and Glusman, 1968). This method has been used with cats by Stokman and Glusman (1969, 1970), Roberts (1958a,b), Cohen, Brown and Brown (1957), and Brown and Cohen (1959); and with rats by Stein (1965), Mogenson (1962), Cox (1967), and Wolfle et al (1971). Another method is to provide a runway or maze through which the cat (Roberts, 1958a,b) or rat (Bower and Miller, 1958) can escape. Again, appropriate use of photo-cells allows the measurement of running time and also terminates ICS.

Delgado, Roberts and Miller (1954) trained their cats to escape from foot shock by rotating a paddle wheel and then substituted ICS for foot shock. Nakao (1958) used this method but instead of the wheel used a paddle covering a hole in the testing chamber. He noticed that cats which had not been pretrained with foot shock would press the paddle to terminate ICS only if they showed manifestations of flight. They learned to push the paddle after accidentally pushing it in attemp-Nakao obtained paddle-pushing from stiting to escape from the box. mulation of flight areas in the hypothalamus and in the midbrain (Nakao, Yoshida and Sasaki, 1968). Using the same plate-pushing technique, also in cats, Wada and Matsuda (1970) and Wada et al (1970) found that not all points that produced flight or escape behaviour would, on testing in the plate box, lead to plate-pushing. Therefore a definition of flight based on the plate-pushing task is more exclusive since it eliminates responses such as general locomotion which would not be excluded

- 16 -

in a shuttlebox or runway task. It has not yet been determined in the rat how many points giving similar behaviour are capable of producing a plate-pushing response.

(c) Conditioning.

Most investigators have implied, on the basis of their observations and/or measurements of ICS induced behaviours, that they are not merely stereotyped motor acts but are the outcome of a central motivational state. One of the properties of motivated behaviour is that it can be influenced by learning. This enables an animal, for example, to avoid a situation that has been previously associated with some danger (Milner, 1970). To further characterize the properties of ICS induced behaviours there have been numerous attempts to condition them to neutral stimuli, and to compare the results of ICS with "natural" motivational stimuli such as footshock. The original purpose in doing so was to determine whether or not ICS produced an emotional experience in addition to emotional behaviour (Masserman, 1941).

Masserman (1941, 1943) reasoned that if ICS of the hypothalamus was accompanied by a meaningful subjective experience then the animal could learn to respond to a signal which predicted the occurrence of ICS. After numerous pairings of various stimuli with hypothalamic ICS he succeeded in conditioning only some autonomic effects in some cats even though ICS was producing rage responses. Using footshock instead of ICS he did obtain a conditioned response. Since Masserman's work

- 17 -

there have been several studies which have and have not obtained conditioning of ICS induced behaviour.

In contrast to Masserman's findings, pairing of ICS with neutral stimuli has produced a conditioned response to the stimuli alone (Nakao, 1958). It has also been noticed that dogs showed conditioned responses to the apparatus after receiving hypothalamic stimulation in it (Fonberg, 1967). Cats have shown active avoidance of a distinctive compartment where they received ICS and have shown passive avoidance of a food tray (Nakao, 1958; Delgado et al, 1954). Ross et al (1965) on pairing midbrain ICS in cats with a tone or clicks obtained first an attentional and then an emotional conditioned response which resembled flight obtained from the hypothalamus. In all of these situations, the animal has no control over the occurrence of ICS.

The more typical experimental situation, as discussed above, is to have some action of the animal terminate (escape from) ICS. The animal can then be provided with a warning stimulus (bell, light, etc.) to see if it can avoid ICS by responding to the warning stimulus. Fonberg (1967) found that dogs would avoid ICS producing "fear-flight" but not rage by performing a leg flexion during the warning stimulus. Romaniuk (1964) stimulating flight points in cats obtained the conditioned avoidance response of raising on their hind legs. Ross et al (1965) in addition to the unavoidable ICS situation discussed previously, allowed their cats to avoid ICS by producing an "emotional conditioned response" to a warning signal.

- 18 -

Using a shuttle-box response (Cohen et al, 1957; Brown and Cohen, 1959) or paddle-wheel turning (Delgado et al, 1954), avoidance to ICS was obtained. Roberts (1958a) using both a shuttle-box and T-maze obtained avoidance from "alarm" points but not from flight points. Stokman and Glusman (1970) also failed to obtain avoidance from flight points in the hypothalamus. Wada and Matsuda (1970) failed to obtain avoidance from hypothalamic ICS in a plate-pushing situation whereas Nakao (1958) did obtain it. Wada et al (1970) noted a difference between hypothalamic and midbrain ICS in its ability to produce avoidance.

In rats, only Mogenson (1962) was able to obtain two-way active avoidance. Even then only two of his three animals would do it. Wolfle et al (1971) obtained some one-way avoidance but not two-way. Stein (1965), Cox (1967) and Johnson and Levy (1969) also failed to obtain two-way shuttle-box avoidance with either hypothalamic or midbrain ICS. In a T-maze situation Bower and Miller (1958) found that rats remained in the start box until the onset of hypothalamic ICS. Since rats have not been trained to date on a plate-pushing task it is not known whether this measure of "flight" would produce avoidance if a warning stimulus was provided.

A current explanation for failure of an animal to avoid a stimulus that it will terminate has been proposed by Roberts (1958a). He proposed that the onset of ICS was rewarding and that its continuation became aversive. Therefore the animal would be rewarded for

- 19 -

waiting for ICS onset and then would rapidly turn it off to avoid punishment. Roberts tested this hypothesis (1958b) and provided some support for his view. Bower and Miller (1958) pretested their rats with several measures of rewarding ICS effects and found on subsequent avoidance training a failure to avoid. Brown and Cohen (1959) however, obtained both approach and avoidance at the same hypothalamic site, a result contrary to that predicted by Roberts' hypothesis. Their ICS effects were similar to that which Roberts describes as "alarm" and which he found produced avoidance and showed little reward effects. Roberts admits (1958b) that there is considerable overlap in reward areas and flight areas. Nevertheless, it seems that flight areas tend also to be rewarding.

That this is an oversimplification is shown not only by experiments where approach could not be obtained from points that did not produce avoidance (Wada and Matsuda, 1970) but also from the results of stimulating the midbrain. Although there are some reports of reward areas in the midbrain (Cooper and Taylor, 1967; Mayer et al, 1971), the area in and around the central gray is considered to be involved with pain and aversion (Olds and Olds, 1963; Routtenberg, 1970; Spiegel et al, 1954). If Roberts' hypothesis were true, and if midbrain stimulation is aversive, then there would be more reports of avoidance of midbrain ICS.

- 20 -

(d) Summary.

A variety of behaviours described as emotional or motivational have been produced by ICS presumably by direct activation of neurons involved in the postulated central state which governs natural behaviour. One such behaviour has been described as flight. It can be elicited from areas of the hypothalamus (HYP) and midbrain (MB) of cats. In addition to some autonomic effects, the main characteristic of this behaviour is the search for an exit from an enclosure. This part of the behaviour pattern has been used to measure ICS induced flight by means of an enclosure with a small hole. When the cat tries to get out the ICS is terminated (escape). When a warning signal (WS) is provided the cat may or may not terminate the WS (avoidance). Since there is some controversy in the literature over the properties of HYP and MB ICS that produce flight and since the plate-pushing method has not been applied in species other than the cat, the present study was undertaken to determine the following:

1. Description of flight in rats produced by HYP and MB ICS.

- Quantification of the flight response using a platepushing task.
- 3. Determine if the rat will avoid HYP and/or MB ICS.

4. Test the Roberts hypothesis using a self-stimulation task.

 Anatomical organization of flight behaviour as defined above.

- 21 -

## METHOD

## Subjects.

The subjects (S) were 30 male and female hooded rats obtained from Blue Spruce Farms (New York). They were housed individually in an airconditioned (25<sup>°</sup>C) room with a 12-12 light-dark cycle. Food (Purina Rat Chow) and water were available ad libitum. At the time of surgery their weight was 250-400 grams.

## Surgery.

The electrodes were stainless steel wires (0.19 millimeters diameter) insulated with glass capillary tubing after the method of Nakao (1958). Overall diameter of the insulated electrode was approximately 0.30 mm. Only the cross section of the tip was exposed. All electrodes were checked for integrity prior to implantation.

The rats were anesthetized with Nembutal (60 mg/kg) and placed in a Kopf stereotaxic instrument. After exposing the calvarium, four stainless steel machine screws were installed as anchors for the dental cement. One to four electrodes were then implanted at various HYP and MB sites chosen from the atlas of König and Klippel (1963). A wire attached to one of the anchoring screws was the indifferent electrode. The electrode wires were then joined to amphenol male pins (220-P02) embedded in an amphenol connector strip (221-1260). The entire assembly was molded into the completed plug through the use of dental acrylic cement. Aseptic technique was used throughout; post-operative recovery was uneventful and no infection was noticed. At least one week was allowed before testing.

## Apparatus.

Monopolar stimulation was provided by a Grass S4 stimulator set to deliver monophasic square wave pulses, 1 msec in duration, at a rate of 100 pulses per second. Voltages ranged from 0.5 to 3 volts (V) with most values falling between 0.8 and 1.5V. The depth electrode was negative. Stimulation was conducted to the animal by means of 5 lightweight flexible wires ending in an amphenol connector strip (221-1160) with amphenol female pins (220-S02).

There were basically 3 pieces of apparatus: an observation chamber, a plate-box for escape and avoidance and a self-stimulation box. For observation of ICS induced behaviour a large box (61 x 61 x 71 cm) was used initially, followed by a smaller box (30 x 30 x 60 cm). The small box was enclosed on all sides and top with brown fibre-board except for a hinged Plexiglas front through which the S entered and left. Electrode wires entered through a hole in the roof of the box. For these observations the S was connected directly to the stimulator.

The plate-box had the same composition and interior dimensions as the small observation box with the following modifications. The Plexiglas door was replaced by a one-way viewing mirror that was fixed as part of the wall. The top of the box was then the only access into and out of the box. The top was tight fitting and was equipped with a 60 watt light bulb enclosed externally such that all the light was directed into the box through a piece of translucent paper. High on

- 23 -

the wall opposite the mirror was a 4 inch speaker. The bottom of the box was a grid of 1/8 inch brass rods spaced 5/8 inch (1.58 cm) center to center and raised about 2 cm above the floor. The main feature of the box was a 4 x 4 cm window covered by a Plexiglas plate (Figure 1) located on the wall adjacent to the mirror. The plate was flush with the inside wall and a movement of the plate outward of about 0.6 cm closed a microswitch. When the S was in the box the room lights were out and the box light was on, enabling the experimenter to observe S without S being able to see out.

When S was being tested for plate-pushing, S was connected to the stimulator via a switching unit (Figure 2) which started both the ICS and a clock (Industrial Timer Corporation) which measured latency for plate-pushing to the nearest 0.01 second. ICS could be stopped either by S pressing the plate or by the experimenter.

For the avoidance training another switching unit was used (Figure 3). It allowed a 5 sec. WS followed by a 0.5 sec. pause, followed by ICS for up to approximately 10 sec. The clock measured from WS onset.

The WS were bells, lights and clicks. The light was a 60 watt desk lamp that was placed just under the top of the box. The bell was an electric (6V) doorbell producing 100 decibels. It was placed on a shelf 1 meter away from the box. The clicks were generated by a Grass S4 stimulator at a rate of 5/sec., amplified and fed to the speaker in the box. In all cases the intensity was sufficient to produce an initial startle response in all S.

- 24 -

Figure 1 Side view of one wall of the plate box. Shown in the clear plastic plate which when moved 0.6 cm to the right closes the switch. Scale: full size.

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Figure 2 Semischematic diagram of the escape training apparatus. The clock and ICS are started by the experimenter and terminated by S. The number of ICS presentations is automatically counted.

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Figure 3 Semischematic diagram of the avoidance training apparatus. The sequence 5 sec. WS, 0.5 sec. delay, ICS is initiated by start and is terminated by a plate-push by S. Timing is from WS onset and all plate-pushes are recorded.

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The self-stimulation test again used the 30 x 30 x 60 cm fibreboard box with a Plexiglas door and the addition of a bar 2 x 10 cm located 12 cm above the floor in the wall adjacent to the door. Depression of the bar by 0.4 cm closed a switch which initiated a 0.25 sec. train of pulses from the stimulator. Switching and timing was done by a Neuropsych Corporation unit. Number of bar presses was recorded on a digital counter.

#### Procedure.

(a) Screening.

After recovery from surgery S were brought to the testing area on one or two occasions to familiarize them with the procedure of connecting to the stimulator. This facilitated subsequent handling. On being placed in the observation box a few minutes was allowed for exploration, then ICS was administered starting with 0.5V and increasing in 0.1V increments until the stimulation effect was characterized. Stimulation never exceeded 4V. If there were more than one electrode per animal then the most anterior ones were tested first. The stimulation effect and the voltage producing it were recorded. It was noted that all of the effects obtained in the large observation box could be seen in the small box. Consequently, most screening was done there. Some of the later S's were screened directly in the plate-box.

(b) Escape training.

After screening, S were tested in the plate-box to see if they would escape from (i.e. terminate) ICS by pushing the plate. The

- 28 -

group tested here was smaller than the original group due to the exclusion of S which showed no effect or only stereotyped motor movements such as head turning, eye blinking, circling movements or isolated limb movements. Various current intensities were used and if a response was made, the time was recorded. Stimulation rarely exceeded 30 sec. duration. If some responses were made, that point was tested on the following days to see if it became an established response. Usually, however, it became apparent in the first few trials whether or not a S would push the plate. Following the selection of S and electrode sites that produced plate-pushing, further training was undertaken in daily sessions in order to establish a stable response and to determine the threshold for the response. ICS was given every 60 sec.

### (c) Avoidance training.

Once the escape response was being produced reliably, S was given an opportunity to avoid ICS. The 5 sec. WS was a bell, light or 5/sec click which was presented alone at first to insure that they caused no plate-pushing. The WS was then paired with HYP or MB ICS. There was a 0.5 sec. delay between offset of WS and onset of ICS. Each presentation of WS and ICS constituted a trial. Trials were given every 60 sec. For each WS modality 200 trials were given over 8 to 10 daily sessions. There was usually at least one week between modalities. The order of WS modalities varied from one S to another. The time from WS onset to the plate-pushing response was recorded. The maximum time

- 29 -

was 16 sec. at which time the ICS was automatically terminated. The current used was normally just above the threshold for the escape response. A score of 16 for a trial resulted in the voltage being raised by 0.1V to insure that S would make a response within 16 sec.

(d) Self-stimulation.

After completion of the avoidance training S were placed in the self-stimulation apparatus for 30 minutes each day for several days. The number of bar presses for each 15 minute period were recorded. On some days S received no stimulation and on the remaining days received stimulation at the setting used in avoidance training. Stimulation and non-stimulation days were presented in random order. There were at least 3 days of stimulation. Some of the earlier S were trained for self-stimulation before screening. This consisted of daily.halfhour sessions in the box with current available at various levels. Those S not pressing the bar were given "free" ICS in an effort to induce responding.

(e) Histology.

At the completion of all testing S were anesthetized with Nembutal and after clamping the abdominal aorta and cutting the vena cava, physiological saline followed by 10% formalin was perfused through the heart. After soaking in formalin overnight the brain was removed after drilling the dental cement away from the anchoring screws and removing the electrodes. The electrodes were checked again for integrity. The brains

- 30 -

were blocked in paraffin and cut in  $10 \mu$  sections for staining with Luxol Fast Blue and Cresyl Violet (Klüver and Barrera, 1953). The stimulation sites were taken to be the area immediately under the point of deepest penetration of the electrode. The structure at this point was determined by comparison with the atlas of König and Klippel (1963) and where possible, by comparison with the nuclear structures given in the atlas of Christ (1969).

#### RESULTS

## Stimulation effects.

The 30 S were implanted with a total of 81 electrodes (50 HYP, 31 MB). Five S were eliminated from the study at the beginning due to dislodging of the electrodes or breaking of the pin connectors. Throughout the study the number of S was reduced for these reasons. There were also some deaths due to respiratory infection and one unexplained death. Stimulation effects were obtained from 25 S having a total of 67 electrode sites (42 HYP, 25 MB).

Of these 67 sites tested for stimulation effect 22 (33%) produced forced motor movements or had high thresholds. The effects included head turning, body twisting, eye blinking, isolated limb movement and turning in circles. Head movements were the most frequent effect. The remaining 45 points were considered as giving positive results. In order to facilitate description these positive effects were arbitrarily divided into 3 classes; activity, locomotion and running.

The first class could be described as general activity increases, exploration, curiosity and sniffing. This frequently resembled the exploratory activity on initial placement in the apparatus. This activity was restricted to one area at a time. After exploration of that area, the next one was looked at so that eventually the entire apparatus was explored. The second pattern of behaviour, locomotion, was similar with the exception that S explored or searched the apparatus quickly by either

- 32 -

walking or running from one point to the other. In the large test chamber S moved along the walls in a predominant clockwise or counterclockwise direction, usually pausing at the corners to look around or sniff. Other S just walked or ran in a general circular pattern. There was some jumping, usually at the corners of the box.

The third class of behaviour was called episodic running behaviour (ERB). It was very similar to the wild, frantic running and jumping seen during an audiogenic seizure, hence the designation ERB. Typically this was an all-or-none phenomenon in that the S either sat motionless or burst into frantic running when a certain current threshold was passed. In some S this threshold, electrically or behaviourally, was not as sharp. At current levels below the ERB threshold S would run intermittently or dart rapidly from one point to another. Even though these motor effects were quite spectacular, the current producing them was not different from that producing other behaviours.

Table I shows the number of electrode sites producing these three classes of behaviour. It also classifies the response according to the stimulation site. In spite of the arbitrary nature of the classification it is clear that ERB was obtained mostly from the MB while the other behaviours were obtained from the HYP. The ERB obtained from the HYP resembled fast running and jumping more than it resembled the explosive running obtained from the MB. Hypothalamic ERB also did not have such a sharp threshold. Some S in the locomotion category, parti-

- 33 -

# <u>Table I</u>

Type and frequency of stimulation effects in hypothalamus and midbrain.

Effect	НҮР	МВ
Activity	13	1
Locomotion	10	2
ERB	4	15

- 34 -

cularly those showing walking or running, would at higher current levels produce ERB. Similarly increased stimulation of an "activity" site could produce "locomotion". In all three categories some S showed behaviour indicative of an attempt to get out of the apparatus. This included jumping towards the open top of the box or pushing on a corner of the plastic door (the corner opposite the hinges).

### Escape.

From the group of 45 positive sites as determined above, 31 were tested in the plate-box to see if ICS would produce plate-pushing. Where negative and positive sites occurred in the same animal, both were tested. Successful plate-pushing was obtained from 7 (23%) of the positive sites. This represents 10% of the sites or 25% of the animals that were screened. Each S varied in the number of ICS presentations required to establish plate-pushing. Subjects with MB electrodes pushed it on the first trial while those with HYP electrodes took up to 5 trials. In all cases the area of the plate was the center of attention for those S that later pushed it. Subjects also varied in the total number of trials given. Table II summarizes the behaviour of the plate-pushers (as classified above), the electrode site, the threshold for platepushing and the number of escape trials.

Escape latencies were at first quite variable and remained that way until an optimum voltage was determined. Too low a voltage would not produce plate-pushing and too high a voltage disrupted performance

- 35 -

# <u>Table II</u>

Behaviour, location, threshold and number of trials for escape subjects.

Effect	Rat	Location of	Threshold	Number of
	number	electrode	(volts)	escape trials
Activity	47	НҮР	0.6	235
	48	НҮР	0.6	20
Locomotion	43	НҮР	0.8	325
	50	НҮР	0.9	145
	61	НҮР	1.0	30
ERB	48	MB	1.0	300
	56	MB	. 1.10	55

usually by producing gnawing or wild running. Figure 4 shows the relationship of voltage to latency for 4 sites. In general, increased voltage produced faster responding. For S # 43 the disrupting effect of higher voltage is clearly seen. For # 56 the best response was produced by 1.10V. The 1 sec. latency is maximum that S is physically capable of performing. The method used by each subject in platepushing also contributed to variation in latencies. On some trials S would circle the box before pressing (# 43, 61, 47), jump in two corners before pressing (# 47), gnaw (# 43, 61), or perform a stereotyped head and neck movement ( 48 HYP ). Extensive training was given to S 43 and 47 to reduce these behaviours. Circling before pressing persisted but at reduced frequency. The response from the MB rats was quite characteristic. At below threshold levels they sat quietly and at above threshold levels responded (sometimes after a short latent period) with a direct and lightning fast movement. Hypothalamic responses were slower and more deliberate.

Another source of variation was changing thresholds. A within session change was most conspicuous in the case of the MB electrodes in S 48 and 56. Subject # 48 would not respond to less than 1.40V at the beginning of a session but by the end, would respond to 1.0V. This is also shown by the decreased latency over trials at a given voltage as shown in Figure 5. This pattern persisted throughout 300 escape trials. Subject # 56 behaved in an opposite manner; latency

- 37 -

Figure 4 Mean escape time versus stimulating voltage for subjects
43, 48, 50 and 56. The means are based on 5 to 10
consecutive one minute trials.
Ordinate: mean escape time (sec.);
Abscissa: voltage.

38

MEAN ESCAPE TIME (SEC)



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Figure 5 Escape latency as a function of time for subjects 48 and 56. The presentation of voltages is in the order listed.

39







increased within a session. It was necessary to increase voltage during a session or, for a given voltage, latencies progressively increased (Figure 5). This was more obvious in blocks of 10 or 20 trials. For both S however there was a current level which produced reliable performance.

## Avoidance.

Five of the 7 escape points were used in avoidance training. Subjects 47 and 48 (HYP) were excluded because of rapidly deteriorating performance and motor side effects respectively. In spite of adequate responding to ICS and 200 to 600 pairings with various warning stimuli, all S failed to avoid ICS. One S (# 43) made 12 avoidances in 200 trials, two made 3 (# 50, 61) and two made no avoidance responses (# 48, 56). When the total number of avoidance trials is considered the maximum avoidance rate was 3%. In considering individual sessions of 20 trials, the maximum avoidance rate was 20% and this occurred only once. There was no tendency for S as a group to improve over sessions (Figure 6).

The order of WS modalities presented to each S and the average response time for each session (with its standard deviation) are presented in Table III. To be noted is the variation within a session and variation among sessions. Among sessions there is no tendency to respond faster for any site or modality with the possible exception of 56L. When responding was the fastest and with the least variability (48C) the escape latency was never faster than the l sec. maximum that this S would per-

- 40 -

Figure 6 Mean latency (<u>+</u> standard deviation) per session for all subjects as a function of the number of training sessions. The dotted line represents the response time required for it to be considered an avoidance.

41



# <u>Table III</u>

Mean response time per session (<u>+</u> standard deviation) for each subject and WS modality.

S No.	WS	DAYS									
		1	2	3	4	5	6	7	8	9	10
43 (HYP)	L	13.18+3.02	12.00 <u>+</u> 2.88	8.29 <u>+</u> 1.16	9.94 <u>+</u> 3.33	10.49+3.03	9.66 <u>+</u> 3.54	8.73 <u>+</u> 2.54	8.98 <u>+</u> 3.43	9.78 <u>+</u> 2.46	9.55 <u>+</u> 2.44
	В	9.42 <u>+</u> 3.99	10.56+3.60	9.08+3.45	9.99 <u>+</u> 3.78	9.50 <u>+</u> 5.15	9.69 <u>+</u> 4.23	10.10 <u>+</u> 2.48	8.51 <u>+</u> 1.09	10.00 <u>+</u> 3.06	-
	с	7.72 <u>+</u> 1.44	9.08+2.15	7.88 <u>+</u> 1.80	10.38 <u>+</u> 2.49	7.67 <u>+</u> 1.36	8.29 <u>+</u> 1.85	7.56 <u>+</u> 1.34	8.62 <u>+</u> 1.77	7.60 <u>+</u> 1.33	8.08 <u>+</u> 1.58
48 (MB)	L	6.66 <u>+</u> 0.20	8.18+0.67	10.84+1.73	11.06+3.27	9.48 <u>+</u> 2.60	9.00 <u>+</u> 1.22	9.60 <u>+</u> 1.13	7.46+0.63	10.27 <u>+</u> 2.69	-
	В	8.50 <u>+</u> 1.06	6.91 <u>+</u> 0.58	7.88 <u>+</u> 1.04	10.31 <u>+</u> 1.50	8.74 <u>+</u> 2.25	7.90 <u>+</u> 0.83	8.39 <u>+</u> 0.91	10.17 <u>+</u> 1.11	9.02 <u>+</u> 1.02	-
	с	6.70 <u>+</u> 0.11	6.53 <u>+</u> 0.25	6.60 <u>+</u> 0.16	6.51 <u>+</u> 0.11	6.55 <u>+</u> 0.17	6.54 <u>+</u> 0.11	6.53 <u>+</u> 0.15	6.52 <u>+</u> 0.12	6.52 <u>+</u> 0.16	6.56 <u>+</u> 0.13
50 (HYP)	В	11.62 <u>+</u> 1.19	10.51 <u>+</u> 1.90	9.79 <u>+</u> 1.55	10.59 <u>+</u> 1.08	10.85+2.33	9.80 <u>+</u> 4.23	11.06 <u>+</u> 1.27	10.31 <u>+</u> 0.91	10.41 <u>+</u> 1.11	-
	L	7.77 <u>+</u> 0.74	7.64 <u>+</u> 0.63	7.67 <u>+</u> 0.66	8.61 <u>+</u> 0.65	8.72 <u>+</u> 0.72	8.28 <u>+</u> 0.75	7.81 <u>+</u> 0.45	7.75 <u>+</u> 0.54	7.52 <u>+</u> 0.62	7.95 <u>+</u> 0.81
56 (MB)	В	7.00 <u>+</u> 0.81	6.81 <u>+</u> 0.38	8.44+2.40	8.09 <u>+</u> 2.50	8.44+2.44	9.71 <u>+</u> 3.60	8.13 <u>+</u> 2.51	7.05 <u>+</u> 0.42	-	-
	L	9.47 <u>+</u> 2.11	9.33 <u>+</u> 3.77	9.06 <u>+</u> 3.20	6.79 <u>+</u> 0.39	6.62 <u>+</u> 0.15	8.29 <u>+</u> 1.69	6.78 <u>+</u> 0.37	7.68 <u>+</u> 0.89	7.57 <u>+</u> 1.25	8.04 <u>+</u> 1.05
61 (HYP)	L	9.89 <u>+</u> 4.48	11.09 <u>+</u> 2.73	10.27 <u>+</u> 2.89	10.82 <u>+</u> 3.11	12.46+2.37	11.60 <u>+</u> 3.75	12.52 <u>+</u> 3.12	9.82 <u>+</u> 3.75	11.87 <u>+</u> 3.60	-

42

form without a WS. Subjects with longer and more variable latencies continued to perform in this way with a slight decrement over sessions in some cases. Over sessions and modalities there was a general tendency for the required voltage to increase. Within session variability was generally larger for long latencies (43L) and smaller for short latency responses (48C). This in turn was related to the voltage and the threshold changes mentioned previously for escape. In contrast to most of the escape sessions, an effort was made to maintain a steady voltage. Progressive increases in latency within a session up to the maximum allowed necessitated the raising of the voltage to maintain a response thus producing a higher mean and standard deviation. Two S showed faster responses within a session (43,48). Other inconsistencies in response which also occurred for escape contributed to variation here also.

One such variation mentioned previously was the stereotyped response such as circling before responding. This also occurred here but it was noted that on some trials a preparatory response was made. This was obvious in the case of the S that circled. They would come to the plate in preparation for ICS at which time they responded without circling. Such preparatory responses were occurring at a maximum of 50% of the time but usually less. The behaviour of the MB subjects was interesting in that # 56 always stayed near the plate and # 48 always faced the wall opposite the plate. Both responded quickly and directly but produced variable latencies at times due to a strong effect of a small change of voltage on the response time near the threshold.

- 43 -

## Self-stimulation.

Table IV summarizes the results for the 5 S used in the avoidance training. Most bar-presses occurred within 5 min. of being placed in the box. After S had explored the box they remained inactive throughout most of the remaining time. This behaviour was generally the same when ICS was available. For S 43 and 50 the rate with stimulation was significantly above the non-stimulation rate as determined by a Mann-Whitney U-test (Sokal and Rohlf, 1969). That the apparatus was capable of generating high bar-press rates for ICS is shown by the rates of up to 2800/30 min.obtained from another electrode site in # 50. Similar high rates were obtained from other S which were tested before the platepushing test.

### Histology.

The stimulation sites for S which were tested for plate-pushing were plotted on diagrams of coronal sections from the atlas of König and Klippel (1963). Figure 7 shows the location of electrodes which produced plate-pushing. Figure 8a and 8b shows the HYP and MB sites respectively which did not. Successful escape was produced by electrodes in the MB central gray (483, 563) and in the HYP near the fornix. One site was medial to the fornix in the dorsomedial nucleus (505) and the rest were located lateral to the fornix in the region of the medial forebrain bundle (MFB) in the lateral hypothalamus (475, 614) and bordering on the fields of Forel and zona incerta (435, 485). Figure 8 shows

- 44 -

# Table IV

Average bar pressing rate with and without ICS at the voltage indicated.

Dot	Flootuodo	Average rate/30 min	Average rate/30 min	
no.	site	No stimulation	Stimulation	Voltage
43	НҮР	5	38 *	1.20
48	MB	8	12	1.40
50	НҮР	24	54 *	1.0
56	МВ	14	19	1.50
61	НҮР	16	15	1.20

\* Significantly above no stimulation rate ( p < 0.05, 1-tailed Mann-Whitney U-test ).

Location of electrodes producing escape by platepushing. Sites are identified by the subject number and the pin number of the electrode. Solid circles signify a locomotion stimulation effect and solid squares represent an ERB effect. The antero-posterior coordinate from these sections from the atlas of König and Klippel (1963) are given in the upper left of each section.

Figure 7





Figure 8 Location of electrodes failing to produce escape by plate-pushing:

- (a) Hypothalamus
- (b) Midbrain

Same designation as for Figure 7 with the addition of an open circle to represent forced motor movements. Sites 472 and 452 are open circles located in the cerebral aqueduct.









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that some of the electrodes having extrapyramidal or no effect were located outside the brain, in the cerebral aqueduct or in subthalamic structures. However, many of the sites producing locomotion or ERB were located in structures apparently identical to those producing similar effects and escape as shown in Figure 7.

#### DISCUSSION

The main stimulation effect obtained from the HYP and MB could be called simply motor activity. More specifically, three classes of behaviour were distinguished: forced motor movements, locomotion, and wild-running. Forced motor movements are of interest mainly to those studying the central control of motor systems (Koella, 1969) but they occur frequently as an additional behaviour or a "side-effect" of stimulation. Most studies report these effects as such. It has been noted that these effects can interfere with the performance being evaluated (Mogenson, 1962). It was observed here both the motor effects which did not elicit subsequent plate-pushing and those which were superimposed on a plate-pushing behaviour. Wild running, frequently obtained from the MB was labelled episodic running behaviour (ERB) due to its resemblance to part of an audiogenic seizure (Wada and Ikeda, 1966). It has also been called rapid intermittent locomotion (Woodworth, 1971). It is usually difficult to control and so is included with the motor effects as a reason for screening the S from an experiment (Cox, 1967). There are cases, particularly in the HYP where a reduced current produces less than wild running. Such S are likely to succeed in a shuttle-box or runway task.

The third class of behaviour identified in this study was locomotion which varied from slow walking to less than frantic running. The speed at which this is done is proportional to the current intensity. Such behaviour is ideally suited for shuttlebox and runway tasks since the forward locomotion would eventually get the animal to the "off" side. In

- 49 -

its less intense form it resembles exploratory activity. In line with the ethological approach to behaviour it can be noted that the exploratory activity seen here and elsewhere (Roberts, 1969; Valenstein et al, 1970) is a species-specific behaviour in the rat and that the running along the wall of the test box seen here resembles the species-specific thigmotaxic response (Barnett, 1963). Roberts (1969, 1970) and Valenstein et al (1970) note that exploratory locomotion is seen in the absence of environmental stimuli with which S can interact or when a goal directed consummatory response (such as eating, drinking or gnawing) has not yet been established. It seems then, that ICS induced exploration is a behaviour waiting to happen, given appropriate environmental circumstances.

In the screening procedure used here such conditions were available to a certain extent. Some S behaved as if they were trying to get out of the box either by jumping in the corners or trying to widen the crack in the door. The frantic searching, darting, running movements of some S could also be interpreted as flight, perhaps more appropriately than the other since this is the kind of behaviour that would benefit the animal in a real life-threatening situation. The plate-box provides a more appropriate environment for the S to display flight behaviour and it was found that some rats would push the plate to terminate ICS. The rat's behaviour is, therefore, similar to that described as flight in cats (Roberts, 1958a; Skultety, 1963) and produces plate-pushing as in cats (Nakao, 1958; Wada and Matsuda, 1970; Wada et al, 1970). Qualitatively the two classes of flight distinguished, locomotion and ERB, are comparable with Yasukochi's "fear" and "yearning" and Brown et al (1969a)

- 50 -

type "b" and type "a" flight responses respectively. The description of Brown et al in cats corresponds quite closely with the behaviour observed here; i.e. quiet, deliberate flight and rapid, agitated, aroused flight. Analogous with flight Flynn et al (1970) found a "quiet biting attack" and "affective attack" in cats. Even though these behaviours are qualitatively different, their outcome in terms of either flight or attack is the same. Once again it must be stressed that appropriate environmental objects must be present for these behaviours to be shown.

A further observation, made in cats by Wada and Matsuda (1970), Wada et al (1970) and in rats in the present study, was that not all points showing manifestations of searching or flight would produce escape in the plate-box. Only 50% of the cats and 25% of the rats would escape. This is not unreasonable in view of the fact that most of the rats' behaviour is subject to large amounts of interpretation and that the exploratory behaviour commonly seen can be prerequisite to any number of responses if a goal object is present (Valenstein et al, 1970). The plate-box situation can presumably select only those behaviours related to flight as defined by attempts of the S to remove themselves from the apparatus. The alternative, which might be called non-specific selection of a platepushing response, is unlikely in view of the inability of the escape response even after extensive training to transfer to another electrode in the same animal; and the observation that only one of a pair of closely spaced electrodes produced escape in spite of the otherwise identical stimulation effects for both. In this latter situation it is particularly

- 51 -

obvious that the plate-pushing test is more discriminative than a shuttle-box test since both behaviours (forward locomotion) would give good performance in the shuttle-box or in a runway.

Even though rats would escape from HYP and MB ICS by platepushing, none of these same rats would avoid it by responding during a signal which predicted the occurrence of ICS. Except for the report by Mogenson (1962), these results are in agreement with other attempts to produce avoidance of ICS in the rat (Stein, 1965; Cox, 1967; Bower and Miller, 1958; Johnson and Levy, 1969; Wolfle et al, 1971). They are also in agreement with Roberts' (1958a) and Wada and Matsuda's (1970) results with HYP ICS in cats. In general, the result of no avoidance is found with all types of apparatus.

Failure to produce avoidance of ICS is not a general property of all sites in the brain. Avoidance has been obtained by Nakao (1958), Cohen et al (1957), Brown and Cohen (1959), Romaniuk (1964) and Roberts (1958a) in a number of situations and using stimulation of areas similar to those failing to produce avoidance. More interesting are the cases where avoidance has been obtained from the MB but not the HYP (Wada et al, 1970) or where avoidance occurs in some animals and not others in the same experiment (Stokman and Glusman, 1970; Wolfle et al, 1971; Roberts, 1958a; Fonberg, 1967). In some cases this can be attributed to differences in stimulation effect or electrode site. Wolfle et al (1971) found differences in avoidance between sites in central gray and sites in adjacent tegmentum. Wada et al (1970), however, with all electrodes in central gray found that four out of six cats avoided WS, and Stokman and Glusman (1970) with all electrodes in HYP found that one of their four cats would avoid. Current intensity would seem to be a factor but most studies used threshold levels. In all these studies and the one reported here there is no apparent factor which might account for the differences observed.

Even though there was no tendency toward avoidance in this experiment there was an increase in preparatory responses. This has been noted in other studies as well. That the S can form an association between ICS and neutral stimuli is shown in studies where successful passive avoidance (Cox, 1967) and conditioned suppression (Wolfle et al, 1971) have been obtained. Wolfle et al also used a one-way active avoidance task and found a greater incidence of avoidance than in the two-way situation. These techniques have been used extensively to study the motivational properties of footshock. In several studies ICS has been compared with footshock.

Avoidance of footshock has been used as a control in some studies to insure that S are capable of responding. Nakao (1958) pretrained his cats with footshock and subsequently obtained avoidance of ICS. Cox (1967) comparing the two in rats found little transfer of training to the ICS task. Romaniuk (1964) found that the course of acquisition of an avoidance response was the same for footshock as it was for ICS. A comparison of footshock with ICS under contingent and non-contingent associations with the WS showed that the properties of ICS were quite different from footshock (Stokman and Glusman, 1970).

- 53 -

Just as the natural model for ICS induced eating is the eating done by a food deprived animal so the model for ICS induced flight is the behaviour induced by peripheral electrical shock. By observing that S do not avoid flight-producing ICS but do avoid footshock one might conclude that ICS does not induce a central state comparable with that produced by footshock. This conclusion should not be made without taking into consideration the fundamental differences between the two. For example, footshock can disrupt performance by eliciting competing responses such as freezing. Here pain is involved as well as any central state of fear. The animal may freeze or may run to a safe place if an opportunity is provided (Bolles, 1970). With ICS pain may or may not be involved. Delgado et al (1954, 1956) obtained avoidance from structures involved in the transmission of pain. However, ICS in the HYP is known to produce strongly rewarding effects (Olds, 1962) and a hypothesis put forward by Roberts (1958a,b) seemed to account for failure to avoid on the basis of rewarding onset of ICS.

In the present experiment self-stimulation rates were low for all S. Rates without ICS are comparable to Olds and Olds (1963) rates, but the rates with ICS are not even as high as Routtenberg's (1970) or Stein's (1965) rates for non-reward. The criterion of self-stimulation given by each author appears to be quite arbitrary. Since prior stimulation experience might have produced a lower rate in the present experiment the criterion of statistical significance was used. By this method selfstimulation was obtained from two out of three animals with HYP electrodes or two out of five total electrodes. Although bar-press rate is limited as an indicator of reward effect (Valenstein, 1964) it has been used in a number of studies which tend to support Roberts' hypothesis. The Bower and Miller study (1958) in rats used sites known to produce selfstimulation. In all experiments using the HYP it is not unreasonable to expect electrodes to give rewarding effects. More surprising are the reports of self-stimulation from the MB (Crow, 1972; Mayer et al, 1971; Cooper and Taylor, 1967) and in particular from the central gray where shuttle-box escape was obtained in the same rat (Wolfle et al, 1971). Signs of pain and fear often accompany the effect and it takes a longer period of time for it to develop. Sometimes it does not develop at all and sometimes this is in an animal that will not avoid. There are also some S which will both avoid and self-stimulate. All of Brown and Cohen's (1959) cats made approach and avoidance responses at the same site. The majority of flight points overlap with reward points but there are enough non-overlapping points in the literature and particularly in the present experiment to suggest that the Roberts hypothesis is insufficient to explain all the data. That flight and reward points have separate mechanisms but overlapping structures is suggested by recent demonstrations of differing thresholds for reward and motivational behaviours (Olds, Allan and Briese, 1971; Ball, 1970; Huston, 1971).

The HYP and MB are functionally equivalent with regard to escape and avoidance behaviour although a higher proportion of ERB was obtained from MB. Hunsperger (1956) considered the zone giving affective reactions to be continuous from the hypothalamus to the midbrain. He also considers

- 55 -

the HYP and MB areas as independent sources of behaviour since the stimulation effects of a MB site are not affected by lesions rostral The wide distribution of sites eliciting escape in the present to it. study would support the concept of an extensive system governing this type of behaviour. Sites yielding escape were found in both the lateral and medial divisions of the middle to posterior area of the HYP. There were no electrodes in the anterior HYP or in the posterior nucleus. These are the areas that have been used in cats by Nakao (1958) and Roberts (1958a) respectively. The posterior nucleus of the HYP is particularly interesting since it gradually merges with the central gray area of the MB. In spite of claims of homogeneity of neural systems, there have been very few electrodes placed in this transition zone. The lateral and dorsal boundaries of the HYP are not distinct anatomically and the lateral hypothalamic area merges with the zona incerta and fields of Forel (Nauta and Haymaker, 1969), where extrapyramidal motor effects are obtained. The main fiber system through the HYP is the medial forebrain bundle which has been associated with reward (Valenstein, 1966) while the corresponding system in the central gray area is the dorsal longitudinal fasciculus which has been associated with punishment (Olds and Olds, 1963). The MB area is also associated with the termination of pain pathways from the spinal cord (Mehler, 1966). This along with reports of pain from MB stimulation in man (Nashold et al, 1969) and pain and fear-like activity in animals make self-stimulation an unlikely combination with these in the MB yet the bar-press rates by rats indicate that they are indeed combined.

- 56 -
The involvement of pain in the MB but not the HYP seems to be a fundamental difference between the two areas but the method of bar-pressing for ICS cannot distinguish between the two. Nevertheless, the fact that S will terminate (and quickly) both HYP and MB ICS in this experiment and in others suggests that the fundamental nature of ICS is aversive. An alternative explanation is that ICS is not aversive (except at higher intensities) and is only an elicited motor behaviour which requires that the act be performed in order to be rewarding (Roberts, 1970). In line with this is the speculation that plate-pushing be considered as a type of stimulus bound consummatory behaviour in the same way that feeding behaviour has been considered (Valenstein et al, 1970; Valenstein, 1969). Valenstein's group has presented evidence showing important differences between natural and stimulus bound behaviours. One observation is that apart from any reward value of ICS, the performance of the elicited act is rewarding. This, and some additional work (Valenstein, 1971) which showed that the response induced by ICS is resistant to change after being established, could explain the failure of S to avoid in this experiment. Under the condition of the present experiment, escape responding would be maintained by the rewarding consequence of performing the plate-pushing response in the presence of ICS. Implied is that the association of the WS with the response would be less rewarding. Escape responding would also be maintained due to the fact that the response has been well established by pretraining. Even though an association may have been formed between WS and ICS, the S has been trained to respond in a fixed pattern using the cue properties (Mogenson and Morrison, 1962) of ICS.

Although Valenstein's group has accumulated evidence incompatible with the view that ICS elicits a central motivational state identical with that produced by natural stimuli, it is possible to gain access to the neural substrate underlying several species-typical behaviours. That they can be produced and directed towards appropriate goals on an interactive basis with the environment, should be enough of a similarity, given suitable means of quantification, to further our understanding of behaviour.

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