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Operant Conditioning of Central Nervous System Electrical Activity: Implications for Research on Brain Stimulation Reward

A Thesis

by

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ABSTRACT

Dopaminergic blocking-agents have been known to suppress intracranial self-stimulation, but whether the suppression results from a reduction in the rewarding value of stimulation or from motor deficits has remained controversial. I have resolved this controversy by developing an operant technique minimally dependent on motor activity. I trained rats to perform a bar-holding response for 3 s, or to produce hippocampal theta waves for 3 s when the bar was retracted. Decamethonium bromide (a muscle relaxant) reduced bar-holding without affecting theta production for brain stimulation, whereas atropine (a cholinergic blocking-agent) abolished theta production without suppressing bar-holding. Pimozide (a dopaminergic blocking-agent) reduced both bar-holding and theta production for stimulation, though rats were still capable of making the theta response at a rate comparable to the preinjection rate. Dopaminergic blocking at low doses reduces the rewarding value of brain stimulation at the level of the lateral hypothalamus. The method reported in this thesis has wide applicability.

ABBREVIATIONS

BSR: Brain Stimulation Reward

EEG: Electroencephalogram

ESB: Electrical Stimulation of the Brain

ICSS: Intracranial Self-Stimulation

LH: Lateral Hypothalamus

MFB: Medial Forebrain Bundle

RSA: Rhythmical Slow Activity; theta

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"Sennichi no kingaku yori ichi nichi no meishō"

INTRODUCTION

BRAIN STIMULATION REWARD

Olds and Milner's (1954) discovery that rats would perform tasks like pressing a bar or running a maze in order to deliver electrical stimulation to certain sites in their own brains provided a new method for investigating reward processes. Significantly, not all electrode sites support intracranial self-stimulation (ICSS). The rewarding effect of electrical stimulation of the brain (ESB) is not a general phenomenon arising from the electrical stimulation of any neural tissue. The specificity of the rewarding effect suggests that ESB may be activating an important aspect of the actual function of the stimulated structures. Presumably, the neural mechanisms underlying brain stimulation reward (BSR) are directly related to the mechanisms that mediate natural reinforcers. It has been hoped that, by understanding the processes which control BSR, the processes underlying all rewards can be revealed. This assumption has been the driving force behind most of the work seeking to explore and explain the neural bases of rewarding brain stimulation.

It was once thought that there was one common reward substrate underlying self-stimulation, a 'pleasure-centre' (Olds, 1956; Miller, 1957). Anatomical mapping studies, seeking to locate the reinforcing mechanisms, have since identified approximately three dozen different brain sites which support ICSS. These areas include: the septum (Olds & Milner, 1954), the hippocampus (Ursin, Urdin, & Olds, 1966), the lateral hypothalamus (Olds, 1962), the ventral tegmentum (Ward, 1960), the

prefrontal cortex (Routtenberg & Sloan, 1972), the median raphe (Miliaressis, Bouchard, & Jacobowitz, 1975), the cerebellum (Ball, Micco, & Berntson, 1974), and the habenula (Sutherland & Nakajima, 1981). With such widely distributed loci, the concept of a single centre mediating all reward was clearly inadequate. Instead of continuing to concentrate on single neurons or nuclei, researchers shifted their attention to the task of linking these structures into a framework that is meaningful as a neural substrate of reinforcement. The diffuse anatomical nature of many fibre pathways made them the leading candidates as the seat of a 'reward system'.

Distinct fibre tracts can be differentiated in a number of ways: their individual morphology, axon diameter, connection with different neural structures, and the type of neurotransmitter the neurons release. Fluorescent histochemical evidence strongly suggests that there is a positive relationship between areas which are innervated by catecholaminergic neurons and sites which support ICSS (Ungerstedt, 1971; Clavier & Routtenberg, 1974; Lindvall & Björklund, 1974; Lindvall, Björklund, & Divac, 1978; Corbett & Wise, 1980). Therefore, it is quite logical that research workers began to look for a specific transmitter for reward. Since catecholamines seemed to be the best candidates (Stein, 1962; German & Bowden, 1974; Wise, 1978), debate raged over whether norepinephrine (Stein & Wise, 1969; Wise & Stein, 1969; Stein & Wise, 1971; Stein & Wise, 1973) or dopamine (Lippa, Antelman, Fisher, & Canfield, 1973; Yokel & Wise, 1975; Wise, 1980) was the crucial link in the reward system.

Recently, a number of researchers have formally proposed that there

may, indeed, be more than one system mediating reward and that different neural components may be the bases for qualitative differences between types of reward (Phillips, 1984, Wise & Bozarth, 1984). For example, the pleasure one gets from eating food when hungry is quite different from the pleasure encountered after a good night's sleep or during sexual contact.

To understand the mechanisms involved in the reward process, it is extremely important first to delineate each of the anatomical components of the reinforcement system(s) and then to determine the physiological dynamics of the system(s). The type of questions asked would be: What areas if any, are independent from what other areas? How do related areas interact? Are related areas mutually facilitatory or are they antagonistic?

PHARMACOLOGY

Pharmacological manipulation is one of the best ways to uncover these relations given the individual neurochemical natures of the structures involved. If a drug is chosen adequately, it can block the influence of one of the components specifically and the alteration in the function of the unaffected areas can be analyzed. In order to locate precise sites and manipulate explicit interstructural relationships, however, it is crucial to distinguish between the specific actions of drugs on reward mechanisms and their more general effects on the rest of the nervous system.

Among various agents, neuroleptic drugs play a very important role in the study of BSR. These drugs, which ameliorate symptoms of psychotic

disorders such as schizophrenia, block postsynaptic receptors for catecholamines, particularly dopamine, and also have profound effects on ICSS. It is the pharmacological, biochemical, and anatomical links between these three phenomena which may provide for a better understanding of the mechanisms responsible for the clinical disorders when the processes of BSR are clearly defined.

Various pharmacological agents can increase or decrease the number of responses an animal will produce in order to earn some reward. A long-standing controversy exists concerning whether these changes in performance represent alterations in the rewarding value of the reinforcer (Valenstein, 1964, Wise, 1982, Liebman, 1983). For instance, a drug may suppress responding by interfering with motor activity or sensory capacity even if it has no effect on the magnitude of the reward. It is difficult to interpret whether an experimental manipulation (e.g. drug or lesion) has produced a change in the rewarding magnitude of ESB, altered the animal's capacity to respond, or both.

Perhaps the controversy surrounding the effect of the dopaminergic receptor-blocker pimozide on operant responding best typifies these interpretive difficulties. Pimozide, a neuroleptic used as a maintenance treatment for schizophrenics (McCreadie, Dingwall, Wiles, & Heykants, 1980), attenuates rewarded responding for ESB (Fouriezos & Wise, 1976; Fouriezos, Hansson, & Wise, 1978). Although there is evidence that low doses of pimozide can attenuate responding without causing concurrent motor impairment or a decreased level of general arousal (see Wise, 1982 for a detailed review) some researchers feel that this interpretation is not compelling (Ettenberg, 1982; Freed & Zec, 1982; Koob, 1982). What is

needed, they claim, to unequivocally demonstrate that performance capacity is intact, is an experimental preparation which results in an increase in the number of target responses as a result of pimozide treatment. It seems surprising that these researchers should demand that response rate be the critical criterion for demonstrating a distinction between reward and performance deficits considering the history this measure has of being susceptible to varying interpretations.

PERFORMANCE AND REWARD DEFICITS

High stimulation intensities often result in motor artifacts that make it difficult for a rat to respond at high rates. Armed with this observation, Valenstein (1964) entered the first formal caveat concerning the use of response rate as a measure of the strength of BSR. He noted that, when given a choice between two stimulation intensities, rats often show a preference for the higher level of ESB even though the number of responses they make to earn that level of ESB may be smaller (Hodos & Valenstein, 1962). Likewise, higher intensity stimulation, which supports a lower rate of bar-pressing, may prove to be the more effective competitor against other forms of reinforcement such as water or shock avoidance (Valenstein & Beer, 1962). Valenstein concluded that an operational definition of reward magnitude based upon response rate is misleading.

An experiment by Hawkins & Pliskoff (1964) is interesting in this context. They required rats to press one lever on a variable-interval schedule to earn access to a second lever which produced ESB on a continuous reinforcement schedule. They found that, as the stimulation

intensities increased, the bar-pressing rate on the first lever continued to increase after responding on the second lever had reached a peak. The experimenters interpreted that the response rate on the first bar confirmed that response rate on the second bar was not an accurate measure of the reward value of the ESB earned. They then proposed that response rate cannot be used to assess BSR adequately, if a continuous reinforcement schedule is used. Their conclusion is unduly conservative and ignores the implication which may provide a solution to the problem of the confounding influence of adjunctive motor disruption at high stimulation intensities.

Experimental manipulations of general reward value certainly would not rearrange the intensity/reward hierarchy associated with one stimulation site. Therefore, the determination of which intensity of stimulation at one electrode site is more rewarding seems to be a very limited question, to which the answer has already been determined. Most ESB studies use a fixed intensity of stimulation and compare performances before and after treatment. Response rate becomes difficult to interpret when stimulation becomes so intense as to produce motor effects which interfere with responding. Therefore, the experimental stimulation intensity must be selected so that it does not exceed that which results in the maximum response rate. As long as the intensity remains fixed at a level safely below that which supports maximum responding, it is hard to understand how a stimulation-induced motor artifact could occur to obscure decrements or enhancements of reward.

There is a ceiling to the absolute speed at which any response can be performed but, if the baseline is chosen carefully, using intermediate

stimulation intensities so that there is latitude for change in response rate in either direction, this limitation can also be reasonably eliminated.

To summarize, there are three performance artifacts which may confound the interpretation of response rate as a measure of the rewarding value of ESB: stimulation-induced motor artifacts, maximum capacity for response execution, and the performance change induced by experimental treatments. The first two of these difficulties can be reasonably controlled by selecting stimulation intensities that support less than the maximum possible response rate. The treatment-induced performance artifacts cannot be controlled by a minor modification of procedures. Perhaps the best way to control them is to adopt a new type of response which is not as sensitive to these side effects as are the traditional operant tasks (e.g. bar-pressing, maze-running).

OPERANT CONDITIONING OF HIPPOCAMPAL THETA ACTIVITY

For almost thirty years, various forms of cortical activity have been used as conditioned responses in instrumental and classical learning experiments (see Schaefer & Engel, 1973 for a bibliography of studies published up to 1972). This work includes the operant control of: cortical EEG activity like alpha waves (Hart, 1968) and beta waves (Beatty, 1971), sensorimotor cortex EEG spindles (Wyrwicka & Sterman, 1968), cortical unit activity (Fetz, 1969), early and late components of visual cortex evoked responses (Fox & Rudell, 1970), and behaviour-evoked brain potentials (Rosenfeld & Fox, 1971). Since then, the technique has been demonstrated to have clinical applications. Epileptic patients can

operantly condition their EEG activity as an anticonvulsant procedure (Cott, Pavlosky, & Black, 1979; Lubar, Shabsin, Natelson, Holder, Whitsett, Pamplin, & Krulikowski, 1981) while quadriplegic patients have been able to modulate short-latency cervical somatosensory evoked potentials resulting in altered sensory function (Finley, 1983).

Manipulating various aspects of EEG activity seems to be a fairly simple response to learn. Even postcollicular, pretrigeminal cerveau isolé rats acquired EEG-derived responses to earn rewarding ESB or escape aversive brain stimulation (Keene & Keene, 1977). Operant conditioning of hippocampal theta waves has been developed in the same context. Black and his colleagues (Dalton, 1969; Black, Young, & Batenchuk, 1970; Black, 1971) trained both dogs and rats to produce bursts of theta. Glazer (1974) also trained hungry rats to produce hippocampal theta to earn food.

Hippocampal theta has been designated as electrical activity occurring in the 4-12 Hz range. Vanderwolf (1975) separated this range into two components which were behaviourally and pharmacologically distinct. Hippocampal rhythmical slow activity (RSA) of the 7-12 Hz range appears when an animal is engaged in one set of activities, which Vanderwolf labelled Type 1 behaviour. Type 1 behaviour includes "walking, running, jumping, rearing, swimming, digging, manipulation of objects with the forelimbs, isolated movements of the head or one limb, and shifts of posture" (Vanderwolf, 1975). The slower portion of the RSA range (4-7 Hz) occurred as an antecedent to Type 1 behaviour and often appeared during the behavioural immobility which preceded movement. What Green & Arduini (1954) referred to as 'aroused' hippocampal activity

includes both ranges of RSA. A second set of behaviours, which Vanderwolf called Type 2, was usually accompanied by large amplitude irregular activity and was thus unrelated to theta. It should be noted, however, that animals with hippocampal ablations, and thus no place to produce theta, are quite capable of making Type 1 responses and manage to get along without any overt motor deficits. Therefore, theta waves are not a necessary condition for the occurrence of Type 1 behaviour.

These frequency-related components of RSA differ pharmacologically. The slower range is abolished by atropine sulphate and is called 'atropine-sensitive'. The faster frequency component and Type 1 behaviour are unaffected by the same treatment and are therefore referred to as 'atropine-resistant'. Administration of phenothiazines decreases and amphetamine increases the likelihood of occurrence of Type 1 behaviour and the corresponding atropine-resistant RSA. The higher frequency theta always accompanied Type 1 behaviour and Vanderwolf could not eliminate one without also eliminating the other by any pharmacological manipulation. Since theta activity invariably occurred when the animals performed Type 1 behaviours, phenothiazines did not block theta production directly by antagonizing dopamine receptors. Instead, the reduction of the probability of Type 1 behaviour indirectly decreased the amount of theta generated.

Black and his colleagues used a bandpass filter to analyze the animals' EEG activity and produce pulses which corresponded to single waves in the frequency range of 4-6 Hz above a preset amplitude. A basic theta response consisted of 4 of these pulses produced in a second or less. For example, Dalton (1969) required dogs to produce 7 of these

responses in 15 s in order to avoid painful shocks. This meant that they only had to produce between 4.7-7.0 s of theta activity during this interval and the production did not have to be continuous. Similarly, Black (1971) trained his animals to produce 15 of these bursts in order to earn the reward although each burst only had to be composed of 3 or 4 pulses. Glazer (1974) required only 3 successive cycles of 7.5-8.5 Hz activity, a 0.4-s response, to qualify as a theta response. Significantly, his rats had to interrupt their theta production, between successive responses, with short bursts of non-theta activity in order to continue earning food. It is important to note that, in all of the above-mentioned studies, theta activity could be generated in short bursts. It is doubtful, however, that only a few waves of activity in the theta frequency range are psychologically meaningful. Natural RSA usually occurs for long (1-100 s) uninterrupted bouts (Vanderwolf, 1975).

The most important difference between these studies and the present work arises from a difference in the purpose of the experiments. The present study does not intend to demonstrate a novel type of learning, as did Black (1972). Black wished to ask if there were differences in the type of neural process that could be operantly controlled compared to that which is susceptible only to other forms of indirect control such as the action of drugs or electrical stimulation. In addition, he wished to know if there were differences between the types of control that the methods exerted. In his study, therefore, it was important to rule out any possibility that the operant control of theta production was not mediated by inconspicuous skeletal muscular activity.

STATEMENT OF PURPOSE

My objective was to develop an experimental technique capable of testing modifications in the rewarding value of brain stimulation without motor deficits. This objective was achieved through the operant conditioning of central nervous system activity, i.e., hippocampal theta waves.

I chose the theta wave as a response for a number of reasons. First, it is resistant to pharmacological manipulations. There was a body of literature describing pharmacological attempts to block atropine-resistant RSA. In fact, catecholamine depletion through intraventricular injections of 6-hydroxydopamine did not abolish either type of theta (Whishaw, Robinson, Schallert, DeRyck, & Ramirez, 1978). Second, theta waves could be produced when an animal was paralyzed (Whishaw, Bland, Robinson, & Vanderwolf, 1976). Since I wished to use a response that was minimally dependent upon motor activity, hippocampal theta seemed ideal.

I decided to require the rats to produce a train of waves and arbitrarily chose 3 s as the required duration. This seemed an unambiguous response that was reasonable to expect an animal to produce. Theta activity is fairly easy to identify when it is produced. Its near sinusoidal appearance is quite striking and lends itself to objective evaluation and electronic detection.

In summary, the purpose of the present study is: 1) to demonstrate that rats can be trained to produce a clear theta response, 2) to indicate that this response is less susceptible to motor and general performance deficits, and 3) to test the utility of this new method in

resolving the motor versus reward controversy surrounding the effect of pimozide on ICSS.

METHODS

SUBJECTS

All male Long-Evans hooded rats used in this project were obtained from Quebec Breeding Farms and weighed 350-500 g at the time of surgery. The rats were housed individually in stainless-steel hanging cages. The temperature-controlled colony room was maintained under a 14:10 hr light/dark regime. Purina Lab Chow and tap water were available ad libitum in the home cages.

SURGERY

Under sodium pentobarbital anaesthesia (Somnotol, 65 mg/kg i.p.), four bipolar electrodes were implanted using standard stereotaxic techniques. The electrodes consisted of twisted Type 304 stainless-steel wire (0.2 mm diameter) insulated with Formex 89 except at the cross-section of each tip. Stimulating electrode tips were cut level and separated by approximately 0.5 mm. Recording electrode tips were staggered vertically so that the tips were separated by approximately 1.0 mm. One of the anchoring screws served as the indifferent electrode. Male Amphenol pins were soldered to one end of the wires and snapped into threaded McIntyre plugs. Dental acrylic, which gripped several watch screws that had been threaded into the bone, anchored the whole assembly to the skull. With the incisor bar set at +0.5 mm the following

co-ordinates for the LH-MFB electrodes were used: 0.5 mm posterior to Bregma, 1.8 mm lateral to the midline, and 8.0-8.5 mm ventral to dura. With the skull approximately horizontal, co-ordinates for the hippocampal electrodes were: 4.0 mm posterior to Bregma, 2.5 mm lateral to the midline, and 2.7 mm ventral to dura.

DRUGS

Pimozide (McNeil Pharmaceutical (Canada) Ltd.) was dissolved in a heated 0.3% solution of DL-tartaric acid (Sigma) at a concentration of 0.5 mg/ml. Atropine Sulphate (British Drug Houses Ltd.) was dissolved in distilled water at a concentration of 100 mg/ml. Decamethonium Bromide (Sigma) was dissolved in distilled water at a concentration of 1.5 mg/ml.

APPARATUS

Stimulation

A Grass S9 square wave stimulator, with a 100 kOhm resister in series with the rat, produced 0.5-s trains of 100 Hz biphasic 0.5 ms pulses. Stimulation intensity was modified by increasing or decreasing the voltage output of the stimulator. Except during training, programmable Grason-Stadler relay rack equipment delivered all stimulation, timed the sessions, and recorded the rats' responses on counters automatically.

Recording

Carried by shielded cable (Microdot), hippocampal electrical activity passed through a 9-channel mercury swivel to a Grass Model 79C EEG/Polygraph and was recorded on paper. The filters of the Grass 7P511 EEG Data Amplifiers were set at low and high half-amplitude cut-off frequencies of 1 Hz and 1 kHz, respectively. All experimental procedures took place inside a shielded room.

Spectral Frequency Analysis

The filtered signal could be registered on magnetic tape with an FM tape recorder (Hewlett-Packard 3960 Instrumentation Recorder). A PDP-11/34, using a Fortran Program, performed the off-line analysis. Tape speed during recording and playback was 15/16 inches per second and the sampling rate was 50 Hz. A 12-Bit analog-to-digital converter transformed the signal. For the Fast Fourier Transformation (FFT), 256 points were calculated every 5.12 s for a range of 0-25 Hz over a 5.12-min sample. These points were then averaged to produce 128 values for the frequencies of 1-25 Hz and these values were plotted to produce spectral frequency profiles for each sample.

Theta Trigger

The theta trigger, a custom-designed, solid-state device, comprising a band-pass filter and a configuration of integrated circuits, analyzed hippocampal theta on-line and defined theta waves in this study. To do this, the trigger detected a signal falling within a defined frequency range that was maintained between some selected minimum and maximum amplitude (voltage) for some preset duration (Circuit diagram in Appendix

A). In the present experiments, the output of the bandpass had to stay within the preset voltage limits for a full .3 s to qualify as a legitimate theta response. The theta trigger could automatically count the number of theta trains produced and, if desired, drive the stimulator to deliver one train of stimulation immediately after the rat produced each continuous 3-s train of hippocampal theta.

Multiple responses could be continuous. That is, an uninterupted 6-s train of the appropriate amplitude would count as two theta responses. A 5-s train, on the other hand, would only count as one. Amplitude did not compensate for duration, but an unfiltered signal with a high enough amplitude could feasibly compensate for frequency. Fortunately, naturally produced, high-frequency EEG activity is usually low voltage and the low frequency, high amplitude signals, in addition to being extremely rare, would either exceed the upper voltage limit or be sufficiently slow so that the the trigger would reset between waves and thus they would not qualify as theta according to the continuity criterion.

The frequency centre and range, duration of the required train, and limiting voltages were set in such a way that the criteria defining a theta response were equal for all animals. The difference in original EEG amplitude produced the only variance in ease of responding between individual rats and this was minimized by adjusting the gain on the polygraph preamplifiers. Figure 1 presents examples of theta and non-theta EEG activity.

PROCEDURE

Screening

Initial screening took place in a standard operant chamber (28 cm x 20 cm x 20 cm high) equipped with a bar (5 cm wide) protruding 2 cm from the middle of one wall 7 cm above the floor which consisted of small (3.5 mm diam.) transverse stainless steel rods placed about 10 mm apart. Each rat was allowed 15 min to acclimatize itself to being attached to the cable and to explore the experimental chamber. Since hippocampal theta was typically generated in abundance while the rat was making its initial exploration of the chamber, the gain of the polygraph was adjusted during this period so that the output of the bandpass, recorded on paper, was approximately 5 mV (10 mm) during theta production. Baseline production of theta could then be monitored during the subsequent sessions. The range of average amplitude for theta trains across rats was 0.5-2.0 mV.

During the screening portion of the session, the rats initially received low intensity (20uA) stimulation which progressively increased in 20uA increments until the rat made the characteristic forward searching motion typically associated with rewarding MFB stimulation. If the rat responded aversively to the stimulation (leaping, screaming, or circling), it was eliminated from the experiment. The present study only included rats with good rewarding electrodes.

When an appropriate stimulation intensity had been established, the rat was trained to press the bar through standard operant conditioning procedures using rewarded successive approximations to the desired response.

Testing

Testing was carried out in a rectangular shuttlebox (18 cm wide x 80 cm long x 42 cm high) with a retractable lever at each end. The floor, like that of the operant chamber used in training, consisted of metal rods and had been constructed in halves so that, when the rat was on either side of the chamber, one of two microswitches would be depressed by the rat's weight. Each microswitch activated a separate electronic timer and pen on an event recorder, that also kept track of bar-holds and theta trains on paper. If the rat stood in the middle of the box, equidistant from the two ends, both microswitches were depressed. In this case, both electronic timers stopped. Since each pen remained deflected for the duration that its corresponding microswitch was depressed, the amount of time the rat spent in the middle could be determined by examining the output of the event recorder. In some conditions, a metal barrier could be placed in the box so that the rat was restricted to one end of the shuttlebox rather than having access to the whole chamber.

SECTION 1: OPERANT CONTROL OF THETA PRODUCTION

EXPERIMENT 1: THETA RESPONSE TRAINING

The purpose of the first experiment was to demonstrate that rats were capable of learning to produce continuous 3-s trains of theta in order to earn rewarding ESB. Unlike the Glazer (1974) study, the rats in the present experiment could produce long trains of theta and receive ESB every 3 s without having to generate non-theta frequencies between

responses.

Since it was important to compare this new task with a more traditional operant, the same rats were also trained to perform a modified bar-press task. In order to make the two tasks as equivalent as possible, the task required the rat to press the bar down and keep it depressed for 3 s. Like theta production, subsequent bar-holds could be continuous. That is, holding the bar down for 12 s, uninterrupted, counted as 4 responses. In this way, the maximum reinforcement density was identical for each operant, theta and bar-hold.

Procedure

Determination of Baseline Performance. After the initial screening session each rat was placed in the testing apparatus for 1/2 hr daily for 4 days. During this baseline period, the number of 3-s theta trains and 3-s bar-holds were recorded. No stimulation was delivered at any time. Once the baseline had been established for each type of response, each animal received a response training session in which bar-holding and theta train production were shaped using standard operant procedures.

Bar Holding Training. After the initial bar-press training, the task requirements were changed so that the rat had to hold the bar depressed for gradually increasing intervals before it earned ESB. Eventually, the rat had to hold the bar down for 3 s to earn a 0.5-s train of stimulation. Stimulation intensity sometimes had to be adjusted at this point to sustain bar-holding. The stimulation intensity determined at this stage was used for all further training and testing. When the rat had produced 100 consecutive 3-s bar-holds, it was transfered to an open field.

Theta Production Training. Theta training took place in an elevated open field (30 cm x 30 cm x 40 cm high). For the first 10 min of the hour session, the gain from the polygraph was increased so that a signal with an amplitude that would not normally activate the trigger would be sufficient to earn the rat ESB. As the rat increased its rate of responding over the session, the polygraph gain was reduced back to the level determined during screening, thus requiring a higher amplitude response to trigger ESB. Since the frequency of theta production usually increased whenever a rat was introduced into a new environment for the first time, the animal was essentially able to train itself. After this single screening and initial training session, no further priming or shaping occurred and the rat had to initiate responding on its own.

Response Acquisition. The type of reponse that could earn the rat ESB during each subsequent daily 30-min session alternated between days. Half of the rats spent their first session producing theta while the others were required to hold the bar. Three types of responses were recorded: the number of theta trains produced to earn ESB (rewarded theta), the number of bar-holds, and the number of theta trains that did not earn ESB that were produced when the bar was available (unrewarded theta).

Results and Discussion

Figure 2 shows the mean number of each of the 3 types of responses made by the 5 rats during each daily 30-min session and clearly demonstrates rapid learning. On the first day of training there were no significant differences between the number of bar-holding ($\bar{x}$=90) and both rewarded ($\bar{x}$=60) and unrewarded theta ($\bar{x}$=67) responses, $F(2,8)=0.32$. Over

the next three sessions, both bar-holding and rewarded theta progressively increased, attaining means of 246 and 179 responses, respectively. In contrast, the unrewarded theta, which occurred during the periods when bar-holding was rewarded, decreased to a mean of 43 responses. Bar-holding ($F(3,12)=6.65$, $p=.01$) and rewarded theta ($F(3,12)=4.86$, $p=.02$) increased significantly from Day 1 to Day 4, but unrewarded theta did not ($F(3,12)=0.78$). Therefore, it is clear that rats can increase their production of hippocampal theta in order to earn rewarding ESB.

If electrical stimulation itself produced theta trains, one would expect that the unrewarded theta would also show a parallel increase with the augmented incidence of bar-holding. The fact that the frequency of unrewarded theta declined, indicates that the increase in rewarded theta was not an artifact of the electrical stimulation. Similarly, one can conclude that rewarding ESB does not merely cause an increase in the general propensity of the hippocampus to produce theta.

EXPERIMENT 2: SUPERSTITIOUS RESPONDING

Even though there eventually was a distinct dissociation between the amount of rewarded and unrewarded theta produced, the number of theta trains recorded while the rat was bar-holding was higher than the initial baseline rate. LH stimulation can induce theta but the duration of this electrically-evoked activity does not usually outlast the driving stimulation. Since the rewarding trains only lasted 0.5 s, it is unlikely that they are responsible for producing the increased amount of theta that I recorded. It is imperative, nevertheless, to demonstrate

that the overall increase in RSA was not an artifact of LH stimulation and to present an alternate explanation. My explanation is that the augmented baseline level of theta responding is a superstitious behaviour.

Unlike many of the other traditional operants, bar-holding and theta production are not mutually exclusive activities. Since they can be performed concurrently, the theta production could be reinforced adventitiously by the ESB that the rat was earning by holding the bar. If this were the case, it seems reasonable to suspect that the effect should be symmetrical. In other words, if only theta trains could earn ESB and the bar was made available, the rat should continue to bar-hold, albeit at a reduced rate, even though holding the bar had no effect on the probability of the delivery of ESB. Therefore, I designed Experiment 2 in order to demonstrate superstitious bar-holding responses while the animals are reinforced for the theta response. So, in Experiment 2, I left the bar available to the rat even though only theta trains could activate the stimulator. In this way, it would be possible to demonstrate that the ESB earned while producing theta would be sufficient to maintain superstitious bar-holding at some low rate above that expected if the rat were receiving no stimulation at all.

Procedure

Two rats were used to demonstrate the difference in bar-holding during a non-contingent reward condition and a non-reward (extinction) condition. Each of the two sessions lasted 1.5 hr and took place inside the testing apparatus with the restricting barrier in place. In the rewarded theta session, the bar had been disconnected from the stimulator

although it remained available to the rat to hold. After the usual 5-min habituation period, the rat could only earn ESB by producing theta trains. During the non-reward session, the stimulator was turned off so that neither response resulted in ESB. Both the number of theta trains generated and the number of times the bar was held down for 3 s were recorded.

Results and Discussion

Figure 3 depicts the mean frequency of bar-holding during non-contingent reward and the non-reward extinction sessions. Although bar-holding did not result in ESB, the rat continued to respond over the session if it concurrently received ESB for producing theta. When neither response resulted in ESB, bar-holding quickly extinguished. The counters only recorded complete, continuous 3-s bar-holds. I did observe, however, that the rat actually pressed the bar many more times. Often the rat released the bar, immediately after receiving a theta-contingent train of ESB, thus interupting the bar-hold. Therefore, the data reported represent a conservative estimate of the actual amount of superstitious responding which occurred.

It may be argued that the operant conditioning of a response could result in an increase in the propensity of the response to be produced and thus lead to a higher post-training baseline. For example, Segal (1962) found that response rates consistently remained above previously established operant levels after just one session in which the animals received food reinforcement. Although this is a reasonable assumption, it does not account for the steady rate of responding which persisted for the entire non-contingent reward session of Experiment 2. During the

non-reward session, the bar-holding was quickly extinguished.

As predicted, the ESB earned by producing theta was able to maintain superstitious bar-holding. In Experiment 1, therefore, the slightly elevated levels of unrewarded theta production during bar-holding must have resulted from response perseveration maintained by adventitious reinforcement. Corroborating this conclusion are two further observations. First, subsequent subjects learned each type of response successively rather than in the alternating fashion described in Experiment 1. The elevated theta production was most pronounced in those rats that learned the theta response first. Second, it was not apparent at all in those rats initially trained to bar-hold until after the theta production training. Therefore, the increase in theta was not a direct result of either the bar-pressing or the LH stimulation but a superstitious response reinforced by the ESB earned by bar-holding.

EXPERIMENT 3: DISCRIMINATION TRAINING

Although it is clear that rats can increase their production of hippocampal theta if rewarded with ESB, the conclusion that they are, indeed, using theta production as an instrument for earning ESB would be more convincing if they could demonstrate discriminative responding. Therefore, when a rat demonstrated bar-holding and theta production reliably, it was subjected to a discrimination learning schedule using light (S^+) as a positive and darkness (S^-) as a negative stimulus.

Procedure

Each of 6 rats was run for 3 hr daily. All of them had been trained as in Experiment 1 to bar-hold (more than 100 times for each of 4 consecutive 15-min intervals over 2 days) and to produce theta (over 50 responses per 15-min period). A session consisted of a series of 15-min trials which alternated between lights on (S+) and lights off (dim red light:S-). Before the session began, the rat spent a 5-min habituation period in the test apparatus under S- conditions. During this first series of sessions, the rat could only earn ESB by bar-holding when the light was on. When the rat performed 80% or more of its responses during S+ for 3 consecutive days, it was considered to have learned the discrimination.

A second series of daily discrimination training sessions was then initiated and continued until 80% or greater of the rat's theta production occurred during S+. During this series, the bar was withdrawn and the rat could only earn ESB by producing theta trains.

In order to demonstrate that theta production was actually under the operant control of the rats and was not an artifact of the sensory processing associated with a lighted environment, two additional rats were initially trained to discriminate light/dark with the opposite association. In other words, this group was trained to respond when the light was off.

Results and Discussion

Figure 4 shows the learning of the dark/light discrimination. All rats rapidly acquired the ability to produce their responses during the appropriate portion of the daily session and reached the criterion level

by the fourth daily session. The proportion of both bar-holding ($F(3,15)=4.75$, $p=.02$) and rewarded theta production ($F(3,15)=9.37$, $p<.01$) that occurred during S+ increased significantly over the four training sessions. Unrewarded theta production during S+ did not change significantly and remained at chance levels, $F(3,15)=0.73$. Bar-holding generally attained a higher level of discrimination than did theta production, but this can be attributed to the higher baseline rate of theta.

Again, if the increased theta production that was observed was merely an artifact of the LH stimulation, one would expect that there would be a large disparity between the number of theta responses produced during S+ and S- right from the first session. The mean numbers of each type of response produced during the first session did not differ significantly, $F(2,10)=1.32$. An analysis of variance indicated a significant difference between tasks during the fourth session, $F(2,10)=7.33$, $p=.01$.

Five of the rats learned the light/dark discrimination with the bar-holding task first. Even with this previous experience with the same discrimination, the number of theta responses was about equal during both stimulus conditions for the initial portion of the first session. The discrimination was then acquired rapidly, but progressively. The rats that learned the discrimination with opposite stimulus conditions showed identical acquisition rates. Therefore, the magnitude of theta production is not a product of the presence or absence of light. These results indicate that the increased theta production during S+ represents true instrumental learning and is not an artifact of ESB.

Figure 5 shows spectral frequency profiles of the EEG activity produced during the different phases of the session once the discrimination had been successfully acquired for both tasks. During S- the frequency profile is typically multimodal with the majority of activity occurring between 1-7 Hz in approximately equal proportions. During S+, almost all of the hippocampal electrical activity is concentrated between 7.5-8 Hz, evidenced by a sharp peak in the profile. These frequency characteristics suggest that the electrical activity produced by the rat's hippocampus is the higher frequency theta corresponding to the atropine-resistant component associated with Type 1 behaviour.

SECTION 2: PERFORMANCE DEFICITS

EXPERIMENT 4: RESPONSE/INTENSITY FUNCTION

Experiments 1-3 demonstrated that hippocampal theta waves can be operantly conditioned and can be brought under stimulus control. The following study was designed to compare rewarded theta production and bar-holding at different stimulation intensities since high-intensity ESB causes motor artifacts that disrupt bar-pressing and make decrements in performance difficult to interpret. The stimulation intensity used to reinforce both responses in these experiments was determined by its ability to sustain bar-holding, therefore, it would be difficult to interpret differential changes between the two types of response without knowing if they were maintained by relatively equivalent reward magnitudes. In Experiment 4, reward magnitude was operationally defined

as the ratio of the response rate at some fixed voltage over the maximum response rate. As discussed earlier, this definition was only valid for voltages less than or equal to that which sustains the maximum response rate.

If one stimulation intensity maintained bar-holding at 80% of its maximum while only sustaining theta production at 20% of its maximum, the same degree of reduction in reward magnitude could possibly abolish one response while only slightly affecting the other. To understand this relationship is, therefore, of paramount importance for the interpretation of any subsequent dissociations between the responses.

Procedure

To determine how the rate of responding varied with stimulation intensity, two rats responded for different voltages of ESB which changed every 15 min to form an ascending and descending series of intensities. Only responses occurring during the last 10 min of each interval were recorded to minimize any carry-over from the preceeding stimulation intensity. The ascending series and descending series were separated by a 5-min time-out period. Two of these series were performed for each type of response with the type of response alternating between sessions. A 15-min time-out period separated each session. Intensities ranged from 25-225% of the voltage determined to sustain bar-holding, in increments of 25%.

Results and Discussion

Figure 6 depicts the results for one of the rats. The other rat showed the same pattern of responding. Bar-holding displayed an

inverted-"U" function similar to that reported for bar-pressing (Valenstein & Beer, 1962; Hawkins & Pliskoff, 1964). A maximum of 150 responses was reached between 100-150% of the rat's usual stimulation intensity before showing a steady decline. In contrast, theta production continued to increase with stimulation intensity until apparently reaching an asymptote of 90 responses at 175% of the usual stimulation intensity and maintaining it to 225%, the maximum intensity tested. Therefore, the intensity/response function is different for each response.

There are a number of conclusions that can be drawn from these data. First, the usual stimulation intensity determined during screening maintained bar-holding at 67% of the maximum bar-holding rate while only supporting theta production at 48% of its maximum potential rate. If response threshold is defined as the minimum stimulation necessary to support responding at a rate above baseline then, using unrewarded production as baseline, the theta response was much closer to its threshold at 100% of the stimulation intensity determined during bar-holding training. It should be noted, as discussed in Experiment 2, a baseline estimated from unrewarded theta production accompanying rewarded bar-holding may be high because of superstitious responses.

If the rate-intensity functions were equivalent in configuration this would allow the prediction that the theta response should be more susceptible to decreases in reward magnitude. The two functions are markedly different, however, and the curve associated with bar-holding is much more leptokurtic. Therefore, each small difference in stimulation intensity results in a much larger change in the rate of bar-holding than

it does in altering the rate of theta production.

Second, if the stimulation intensity were responsible for the increase in theta production, the unrewarded theta accompanying bar-holding should have shown a corresponding increase. Unrewarded theta production remained stable for the full range of intensities tested despite the marked increase and subsequent decrease in bar-holding and the progressively increasing stimulation intensity. For example, the numbers of unrewarded theta trains produced at 100% and 175% of the training stimulation intensity, which supported bar-holding at about the same rate (98 responses and 94 responses, respectively), were comparable (30 responses and 35 responses, respectively). Therefore, neither the number of bar-holds nor the intensity of ESB affected the rate of unrewarded theta production.

Most importantly, since the rat continued to earn ESB by producing theta at high stimulation intensities at which bar-holding had completely ceased, one must assume the stimulation was rewarding. The reduction in bar-holding could be attributed to the motor artifact produced by the stimulation, similar to that discussed by Valenstein (1964), which interfered with the rat's ability to press the bar. Stimulation onset at high intensities typically caused the rat to suddenly jerk backwards. This motion became more violent as ESB intensity increased until the rat was no longer able to maintain contact with the bar after reward delivery. As the motor effect increased, the rat was thrust further and further from the bar and took progressively longer to recover between responses. The theta response, however, was less susceptible to this performance impairment than was bar-holding since the rat could produce

RSA from wherever it was and the same violent motor activity accompanying high intensity ESB did not disrupt theta production.

EXPERIMENT 5: ATROPINE & DECAMETHONIUM BROMIDE

The purpose of this experiment was to demonstrate that performance deficits associated with bar-holding could be differentiated from those associated with theta production. Since curarized animals had learned to produce theta waves reliably (Dalton, 1969; Black, Young, & Batenchuk, 1970), this response, in contrast to manipulating a bar, running a maze, tail wiggling, and other traditional operants, must require very little skeletal muscle activity, if it requires any at all. Neuromuscular blocking-agents, which exert their primary effect outside of the central nervous system, should impair motor function without hampering theta production.

Experiment 5 employed one of these agents, decamethonium bromide, to attempt to create a deficit in bar-holding. Unlike tubocurarine, decamethonium, a depolarizing neuromuscular blocking-agent, has a higher affinity for limb muscles than it has for the muscles which support respiration. The rats received half of the dosage reported to produce 90-100% neuromuscular blockade (Zaimis, 1953). At this dosage the rats were unable to stand upright, but were able to maintain respiration without a respirator. Thus, the rats do not have to suffer from apnea or from the discomfort of a respirator mask which distracts them and disrupts their performance of the task at hand.

Although Vanderwolf (1975) found that atropine did not abolish the 7-12 Hz RSA, atropinization did increase the occurrence of

high-frequency, low amplitude electrical activity that disrupted the long, uninterrupted trains of naturally-occurring theta waves. If atropine has a similar effect on rewarded theta production, and impairs the rat's ability to produce continuous 3-s trains, it could be used to create a theta response performance deficit without impairing bar-holding. Atropine is not known to cause any form of muscular paralysis and, in fact, has been reported to accelerate bar-pressing for ESB (Wauquier, 1976).

Procedure

Each rat was placed in the operant chamber and, after a 5-min desensitization period with the lights out, the white light came on and the rat could respond appropriately to earn ESB for 1/2 hr. If the response rate was relatively stable over this period, the rat was injected with either the experimental drug (atropine sulphate or decamethonium bromide) or an equivalent volume of the vehicle, and a 5-min time-out (S-) period took place. After the time-out, the lights came back on and the rat could resume responding for the next 2 hr. The type of response required to earn ESB (bar-holding or theta production) alternated between sessions but remained constant within a session. A minimum of 24 hr elapsed between sessions.

Following the same experimental procedure, I tested 2 additional rats that had only been trained to perform the standard bar-press (i.e., one press produced one 0.5-s train of ESB) in order to compare the alterations produced by the drugs in bar-holding and theta production with a more traditional response.

Results and Discussion

Decamethonium caused a decrease in bar-holding ($F(1,2)=31.39$, $p=.03$) and bar-pressing ($F(1,1)=180.28$, $p=.05$) without significantly altering the rats' ability to produce theta trains for ESB ($F(1,2)=0.08$). These differences are quite apparent in Figure 7A. Drugged rats showed marked mustular flaccidity which interfered with their ability to stand. Following the injection, a rat would usually begin bar-holding but, as the drug reached the period of its maximum effectiveness, the rat experienced increased difficulty in maintaining a regular response rate. Eventually, its paw would slide from the bar and the rat would then remain with its abdomen resting on the floor of the chamber with its limbs hanging down between the bars. As the drug's effects gradually wore off, the rat progressively increased responding until it had completely recovered and had returned to its baseline rate. This partial paralysis did not prevent the rats from earning ESB by producing theta. These results are in agreement with the findings of Black and his colleagues using tubocurarine. One can reasonably conclude, therefore, that the theta response is not significantly altered by a drug which merely causes motor impairment.

Atropine, as illustrated in Figure 7B, abolished theta production ($F(1,1)=268.96$, $p=.04$) while sparing bar-holding ($F(1,1)=0.13$). Examination of the EEG activity revealed that theta waves were still being produced but, as expected, short bursts of high-frequency, low amplitude activity occurred frequently enough to disrupt the rat's ability to produce continuous theta trains. Although the rat squealed whenever I approached it, bar-holding persisted steadily at its baseline

rate. Therefore, atropine injections selectively interfered with performance of the theta response.

In summary, these pharmacological manipulations have demonstrated distinctive performance deficits associated with each of the two types of response.

SECTION 3: REWARD AND PERFORMANCE DEFICITS DISSOCIATED

EXPERIMENT 6: RESPONDING DECREASED BY PIMOZIDE

Pimozide has been known to produce motor impairment at high doses. As stated earlier, a controversy exists about whether the ability of pimozide to reduce rewarded responding at low doses (0.5 mg/kg or less) is due solely to its performance-blocking capacity or can be attributed to its ability to diminish the hedonic impact of the reinforcer. Experiment 6 addresses this question by testing if pimozide would affect bar-holding and theta production differentially.

Procedure

Since there is a significant delay between the time of pimozide injection and the period of its maximum effect (Atalay & Wise, 1983), I used the same experimental procedure employed in Experiment 5 with the following modification: pimozide (0.5 mg/kg, i.p.) was injected 4 hr before the experimental session. The same procedure was then followed during the actual experiment as had been employed with the other drugs except that physiological saline was administered after the first half-hour to control for any possible disrupting effects of the intrasession injection.

Results and Discussion

Figure 8 represents the mean number of responses of two animals. Pimozide abolished both types of responses that earned ESB very rapidly after the start of the session. ($F(1,1)=8665.63$, $p=.01$). Initial responding usually began at a level comparable to the rates produced during control sessions but quickly declined over the first 5 min. Observation of the rat's behaviour under the influence of this relatively low dose of pimozide suggested that the animal was not overtly impaired, unlike the obvious muscular flacidity apparent under decamethonium. If pimozide merely caused a motor deficit, one would expect that theta production for ESB would continue. There was no clear indication that the pimozide caused a general sedative effect or reduced the rat's overall level of arousal; the rat's regular degree of spontaneous movement continued throughout the period of response suppression. Unfortunately, the present experiment was not designed to make an objective evaluation of all these possible general effects of pimozide.

EXPERIMENT 7: REWARD DEFICIT CAUSED BY PIMOZIDE

One of the distinctive characteristics of theta production as a response is that, when it is used in conjunction with another task, such as bar-holding, it can be monitored while the second response is being reinforced. In this way, the animal's capacity to produce the EEG response can be confirmed in a situation in which the reward was not contingent upon the response without the additional complication of response extinction. This experiment exploited this quality of the theta response to better determine the effect of pimozide on responding for

ESB.

Procedure

Each session was run in two phases. During Phase 1, each of the two rats tested was restricted to one end of the shuttlebox for 2.5 hrs. Task requirements to earn ESB alternated between bar-holding and theta production every 15 min. A 5-min period of darkness separated Phase 1 and 2.

In Phase 2, the barrier was removed and the rat was allowed free access to the whole shuttlebox for 1 hr with each response associated with a separate end. Every 15 min the responses alternated between ends. Daily control sessions were repeated until the rats demonstrated a clear preference for either bar-holding or theta production (>80% time spent on the preferred side). Pimozide (0.5 mg/kg, i.p.) or an equivalent volume of the pimozide vehicle (0.3 % tartaric acid) was injected 4 hours before the testing session.

Results and Discussion

Figure 9A shows that, as expected, pimozide reduced the frequency of both bar-holding and theta production for ESB ($F(1,1)=3898.99$, $p<.01$). Hippocampal activity during the periods when the bar was available indicated that unrewarded theta wave production was not similarly depressed by pimozide. In fact, not only was the unrewarded production of theta under pimozide equal to that during the control sessions, it had the capacity to increase, as is clearly seen in Figure 9B. Therefore, pimozide did not suppress the rat's capacity to produce hippocampal theta waves.

Although, on the surface, the discrepancy between unrewarded theta production with and without pimozide may seem just cause for concern, the explanation is relatively simple. In the control situation, the rat was spending almost all of the session holding the bar to earn ESB and produced the baseline rate of theta. As bar-holding occupied less of the rat's time in the pimozide condition, the rat began moving about the chamber, apparently exploring, and this activity was accompanied by theta.

When allowed to express a preference, this rat spent most of the time bar-holding and followed the availability of the lever as it changed from side to side every 15 min. After pimozide, the rat moved to the bar and pressed for about 2 min before ceasing to respond. When the bar became available on the other side of the box, the rat approached it and responded for another 2 min before stopping. For the remainder of the session, the rat moved around the shuttlebox but did not show a preference for either side.

Since the rat displayed no noticeable signs of sedation or catalepsy, it does not seem likely that pimozide reduced responding by depressing the rat's general state of arousal. In fact, the number of times the rat shuttled from one side of the chamber to the other increased under the influence of pimozide.

The rat's previously demonstated preference for bar-holding in the choice situation was reduced to chance levels after pimozide injections. Even though theta could be produced, no new preference emerged. If LH stimulation was aversive in combination with pimozide, the rat would have avoided that area in the chamber where it received such stimulation.

Furthermore, a preference for the side of the apparatus where the bar was available would have developed even though the bar was not used since the rat did continue to produce theta trains and they would result in aversive stimulation if emitted on the appropriate side. This did not happen. It is not likely, therefore, that pimozide caused LH stimulation to be aversive.

Thus, using the method developed in the present study, both a simple motor and a general sedative hypothesis for the effect of pimozide, at the dosage employed, on responding for ESB can be conclusively rejected. The present experiment provided evidence that pimozide reduces the rewarding value of ESB beyond any doubt that interpretation is confounded by performance impairment.

GENERAL DISCUSSION

I can conclude from the preceding experiments that rats can be trained to produce theta trains in order to earn ESB just as they can be trained to hold a bar. These two responses show strong similarities; response rate is fairly stable across sessions and the two responses can be placed under stimulus control. The most important difference between these tasks is that theta responses can be produced during severe interference with the motor system. It is also convenient that theta waves can be constantly monitored in a variety of quasi-baseline conditions. In this way, the capacity of the rat to produce theta can be confirmed without depending upon some other test.

The present series of experiments clearly demonstrated that the use of hippocampal theta waves as an operant can determine whether or not

response decrements can be attributed to motor deficits. Theta production did not decline at high ESB intensities that caused a drastic reduction in bar-holding. The theta response, therefore, is less susceptible to stimulation-induced artifacts. A paralytic agent, decamethonium bromide, impaired the rat's ability to bar-hold and even made it difficult to stand erect. Theta production, however, was not influenced at all and the rat continued to earn ESB by generating theta trains at the same rate as in the preinjection period. In contrast, atropine abolished theta responding without affecting bar-holding.

Since both responses ceased to be produced to earn ESB after pimozide injections, yet theta production clearly endured the treatment, the decrement in responding cannot be attributed to either a simple motor deficit or decreased arousal level. Thus, the method presented in this thesis, has resolved the controversy about the pimozide effect: pimozide reduces the magnitude of the rewarding effect produced by ESB.

Recently, Liebman (1983) published an extensive critique of the methodology used in ICSS studies to discriminate between reward and performance. Liebman classified a myriad of experimental techniques into 6 basic ICSS procedures. These categories include: response decrement patterns, locus of rise, differential electrode placement, stimulation parameter manipulation, self-regulation of intensity, and self-regulation of duration. Each of these techniques has its own flaws.

Among them, a method proposed by Gallistel and his colleagues (Edmonds & Gallistel, 1974; Edmonds, Stellar, & Gallistel, 1974; Gallistel, 1974; Gallistel, Stellar, & Bubis, 1974) has been widely adopted. To assess the magnitude of ESB reward, they had rats run in a

runway to gain access to BSR in the goal box. Over the session, the number of pulses in the trains of BSR of fixed duration were systematically increased. They found that there is a threshold number of pulses above which the running speed sharply increases, and called it "the locus of rise". According to them, a decrease in the magnitude of reward is reflected in a shift of the locus toward a larger number of pulses. A decrease in the maximum running speed is believed to represent a decline in response capacity. This method requires a great deal of time since a full range of stimulation intensities must be tested to produce the crucial data points. Drugs with short-lasting effects cannot be adequately tested with this technique. Precise, stable day-to-day operant baselines are essential for unequivocal interpretation with the locus of rise procedure; these may not always be possible.

The theoretical simplicity and intuitive sensibility of the locus of rise technique make it an attractive candidate for adoption. Some researchers (Colle, 1984; Miliaressis, Rompre, Philippe, & LaViolette, 1984) are not using the runway task as originally described by Edmonds & Gallistel. Instead, they have tried to employ the interpretive paradigm with another operant (e.g. bar pressing). Since, in this modified method, responding and delivery of ESB overlap the motor artifact produced at high stimulation intensities could pose a problem to the interpretation of performance versus reward deficits. Suppose a neuroleptic caused a large but pure reduction of the magnitude of reward without causing any concurrent motor difficulties. As the model predicts, a larger number of pulses will be required to produce the sharp increase in responding. This shift in threshold would be interpreted as

evidence that the rewarding value of ESB had been reduced. If, however, the number of pulses required to support a response rate equal to the maximum response rate in the control condition should interfere with the actual execution of the response, the motor deficit produced by the stimulation would produce a false ceiling response rate. This would then be misinterpreted as a motor deficit produced by the drug. In this instance, one would mistakenly conclude that the neuroleptic had both motivational and motor effects. Obviously, a response with minimum motor involvement, like theta production, would be much more resistant to this type of misinterpretation.

Human subjects are capable of a broad range of different responses. Requirements for language tasks are quite different from those for simple motor tasks. Through neuropsychological testing, the different neural substrates underlying the performance of these tasks have been delineated. Unfortunately, almost all of the tasks one can use in animal studies are the simple motor type. This limitation restricts the type of question that can be asked in the laboratory and the interpretations that can be drawn using animal subjects. If there are different systems underlying the phenomenon of reinforcement, different classes of responses may be associated preferentially with each of these systems. Just as conditioned taste aversions are more easily produced with induced sickness than with aversive shock, it may be easier to train a rat to produce theta for food than it is to train it to press a lever. Of course, it would be necessary to show that this effect was not just the result of the relative ease of performing one of the responses possibly by demonstrating that the relationship was reversed in different

circumstances. Therefore, it is essential to have truly distinctive classes of response, discriminable in quality, in order to address this issue.

Some investigators have attempted to contrast the traditional bar-press required of rats with responses like alley-running, tail-wiggling, nose-poking, and spout-licking. All of these responses are essentially motor tasks differing only in the sets of skeletal muscles involved. The operant conditioning of electrical brain activity may provide a truly distinctive type of response, especially since I have now demonstrated that it can be performed when the musculature is severely impaired. In the present study, the theta response was used to separate a change in hedonic value from possible coincidental motor deficits. Using the operant conditioning of neural activity, we can test what Ettenberg (1982) referred to as "the virtually untestable" hypothesis that an immobile animal may indeed be capable of responding.

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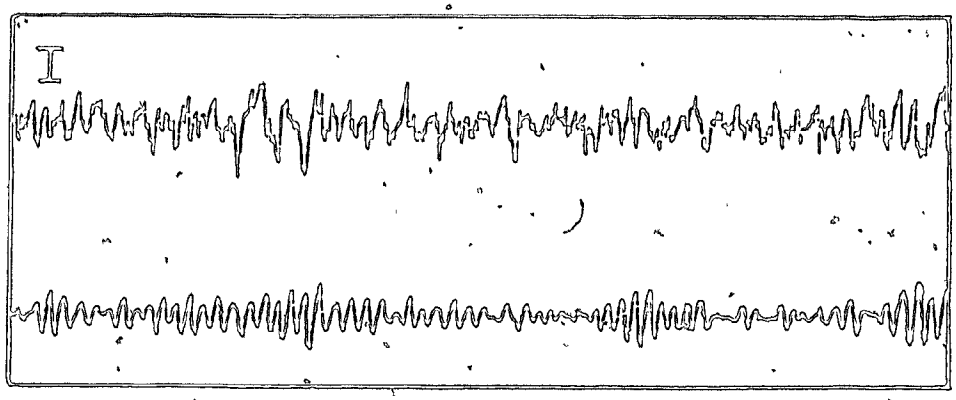
FIGURES AND FIGURE CAPTIONS

Figure 1.

Polygraph records of electrical activity from the dorsal hippocampus of a single rat being trained to produce theta trains to earn rewarding ESB. Each pair of traces represents raw (upper trace) and filtered (lower trace) EEG activity. Samples are presented from one of the baseline sessions where no ESB was available (A) and following training when the rat reliably produced 3-s trains of theta to earn 0.5 s of LH stimulation (B). Time marks are in 1-s intervals and delivery of ESB trains are indicated on time scale. Calibration bars= 100 uV.

A



B

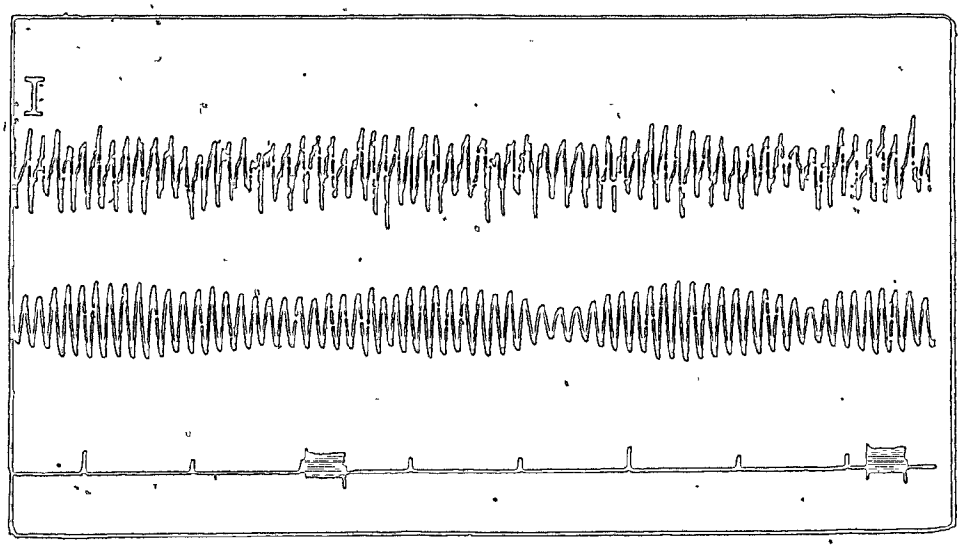


Figure 2.

Mean number of each response for five rats during single, 30-min daily acquisition tests. Before acquisition bar-holding, with the accompanying unrewarded theta, and rewarded theta all occurred at about the same frequency. Over the following sessions, unrewarded theta production decreased slightly, then remained stable across sessions. In contrast, bar-holding and rewarded theta increased sharply as the rats acquired the ability to produce the correct response in order to earn rewarding ESB. The pretraining baseline level of theta production is illustrated with the horizontal line indicated with the arrow.

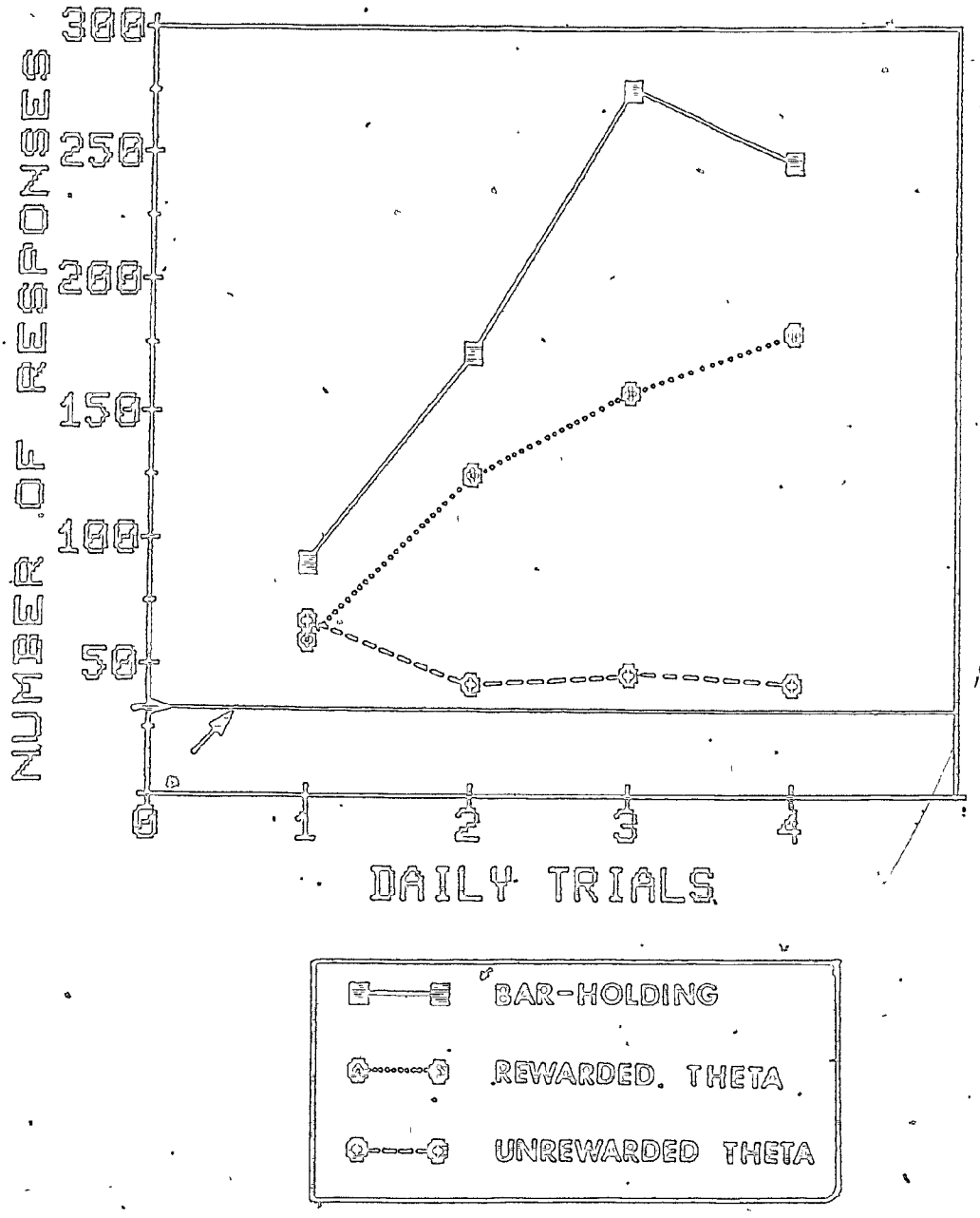
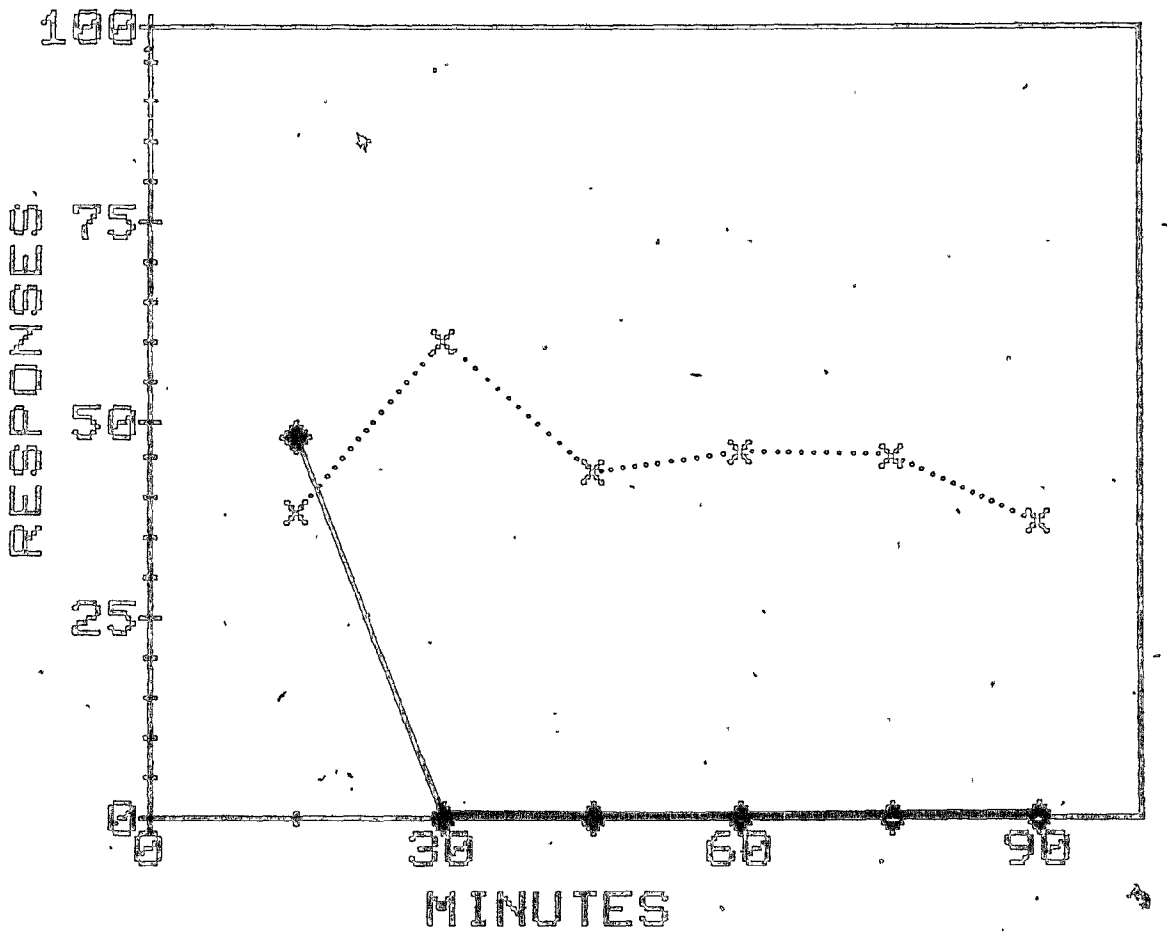

NUMBER OF RESPONSES
300
250
200
150
100
50
0
1
2
3
4
DAILY TRIALS
BAR-HOLDING
REWARDED. THETA
UNREWARDED THETA

Figure 3.

Mean number of bar-holding responses during non-contingent reward (dotted line) and non-reward/extinction (solid line) conditions for two rats. Both rats continued to bar-hold when receiving non-contingent reward but quickly stopped when the stimulator was turned off.



Non-reward

Non-contingent Reward

Figure 4.

Mean frequency of bar-holding, rewarded theta production, and unrewarded theta production during the S+ portion of each daily light/dark discrimination training session for 6 rats.

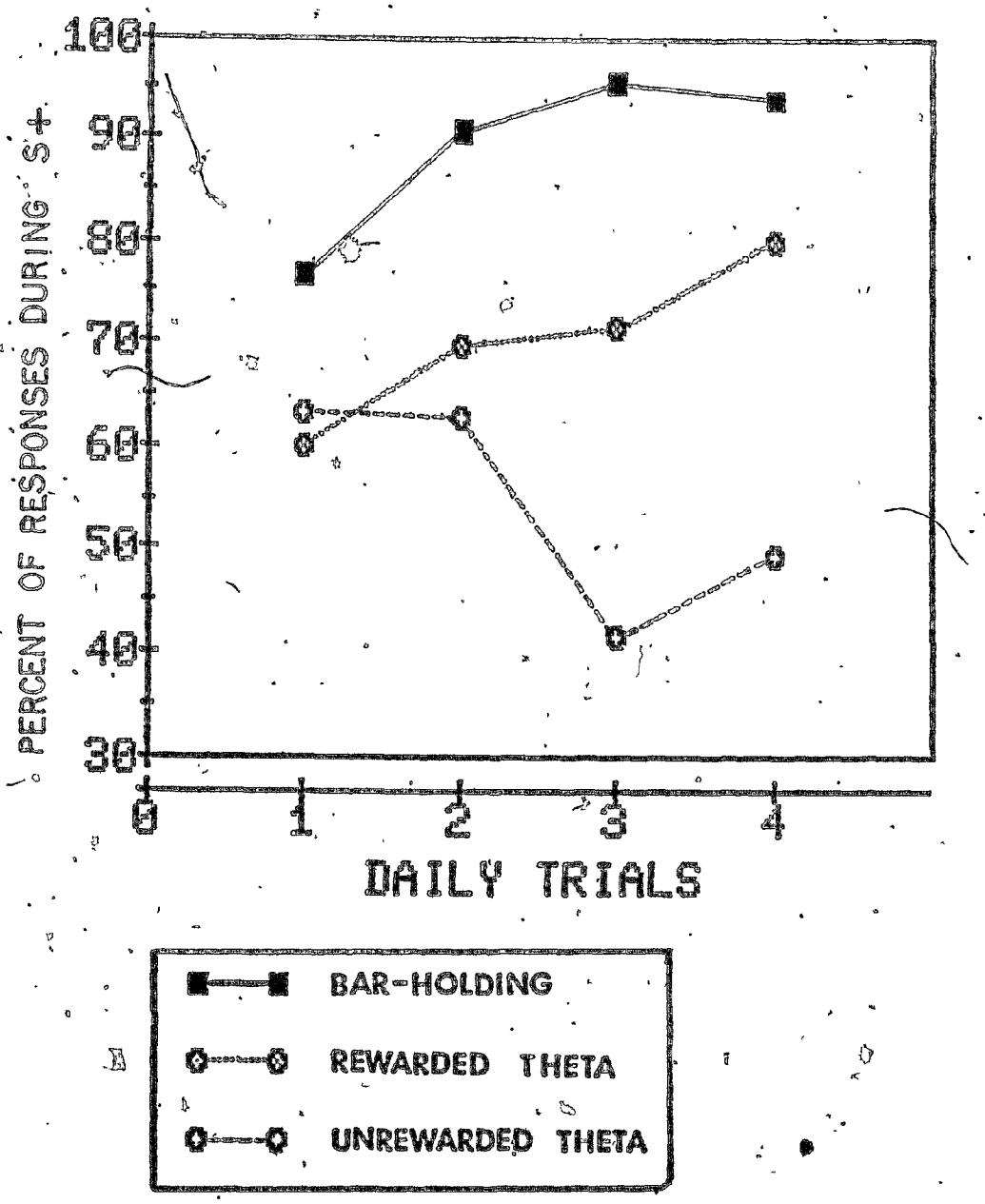
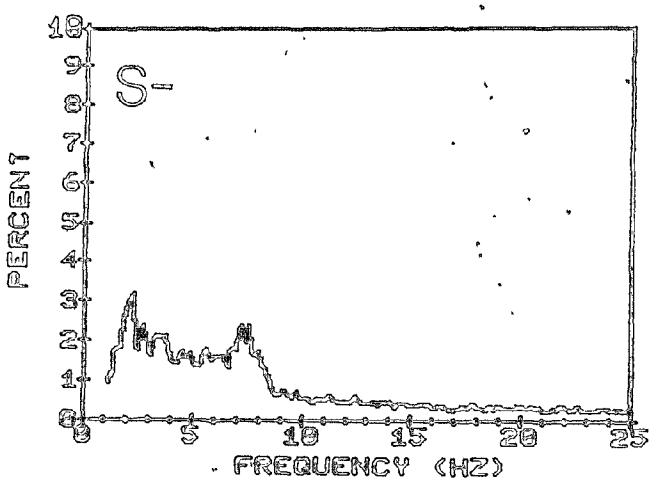

PERCENT OF RESPONSES DURING S+
100
90
80
70
60
50
40
30
0
1
2
3
4
DAILY TRIALS
BAR-HOLDING
REWARDED THETA
UNREWARDED THETA

Figure 5.

Spectral frequency profiles of hippocampal activity recorded during S- and S+ conditions for a typical rat.


S-
PERCENT
FREQUENCY (HZ)
0
1
2
3
4
5
6
7
8
9
10
0
5
10
15
20
25

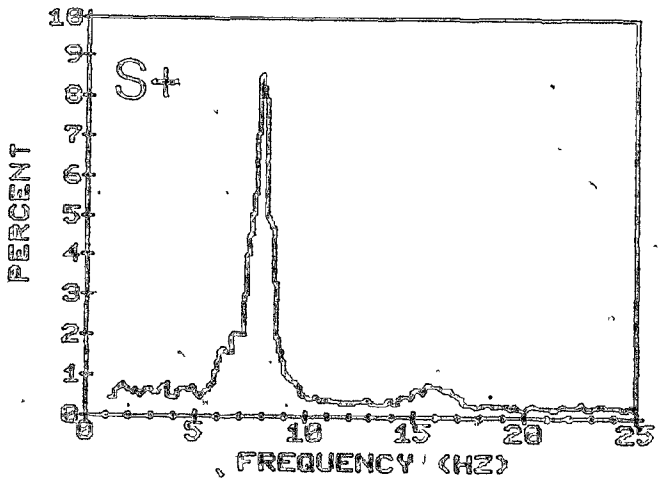

S+
PERCENT
FREQUENCY (HZ)
0
1
2
3
4
5
6
7
8
9
10
0
5
10
15
20
25

Figure 6.

Stimulation intensity/response functions for a typical rat comparing bar-holding with rewarded and unrewarded theta production.

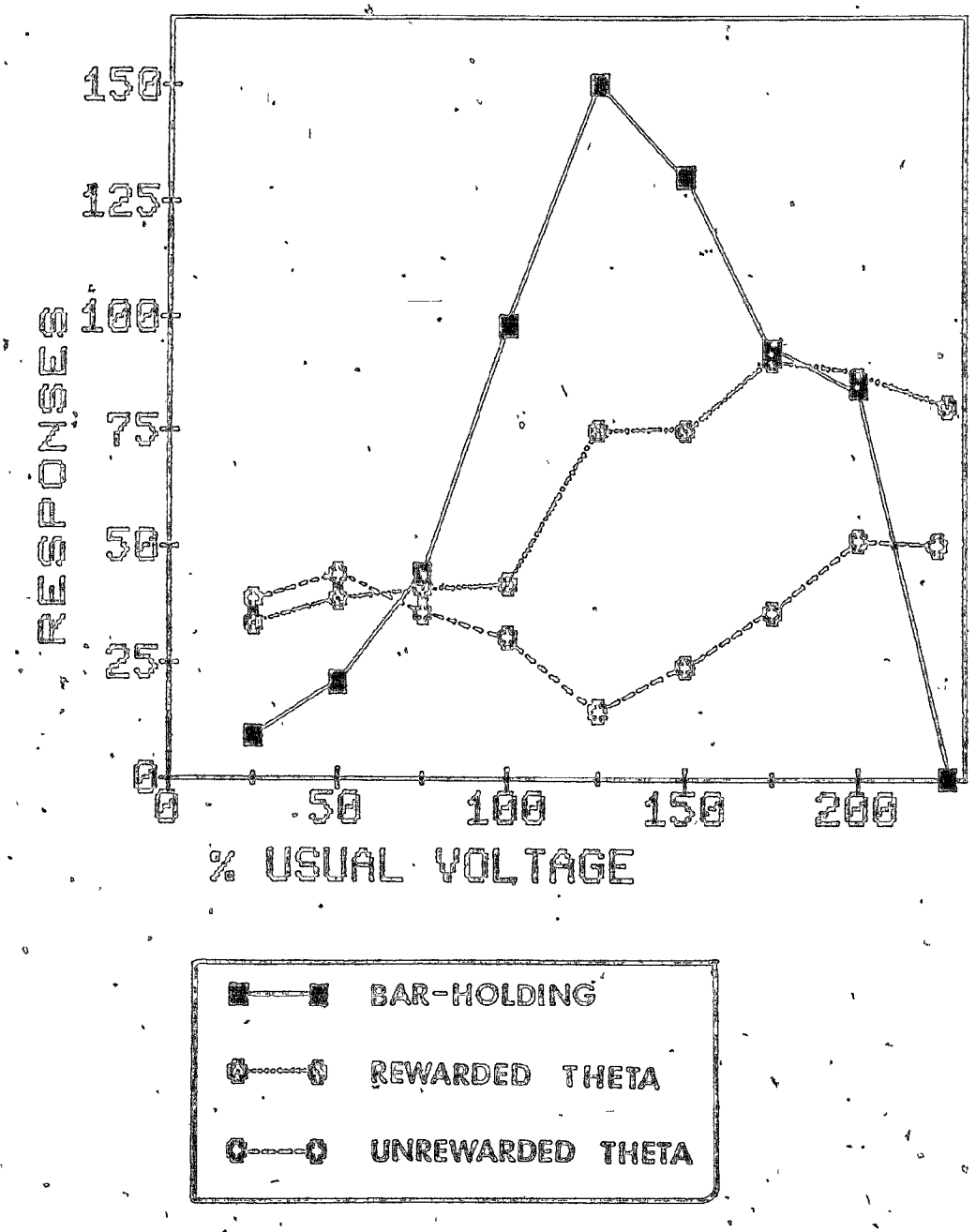

RESPONSES
150
125
100
75
50
25
0
0
50
100
150
200
% USUAL VOLTAGE
BAR-HOLDING
REWARDED THETA
UNREWARDED THETA

Figure 7.

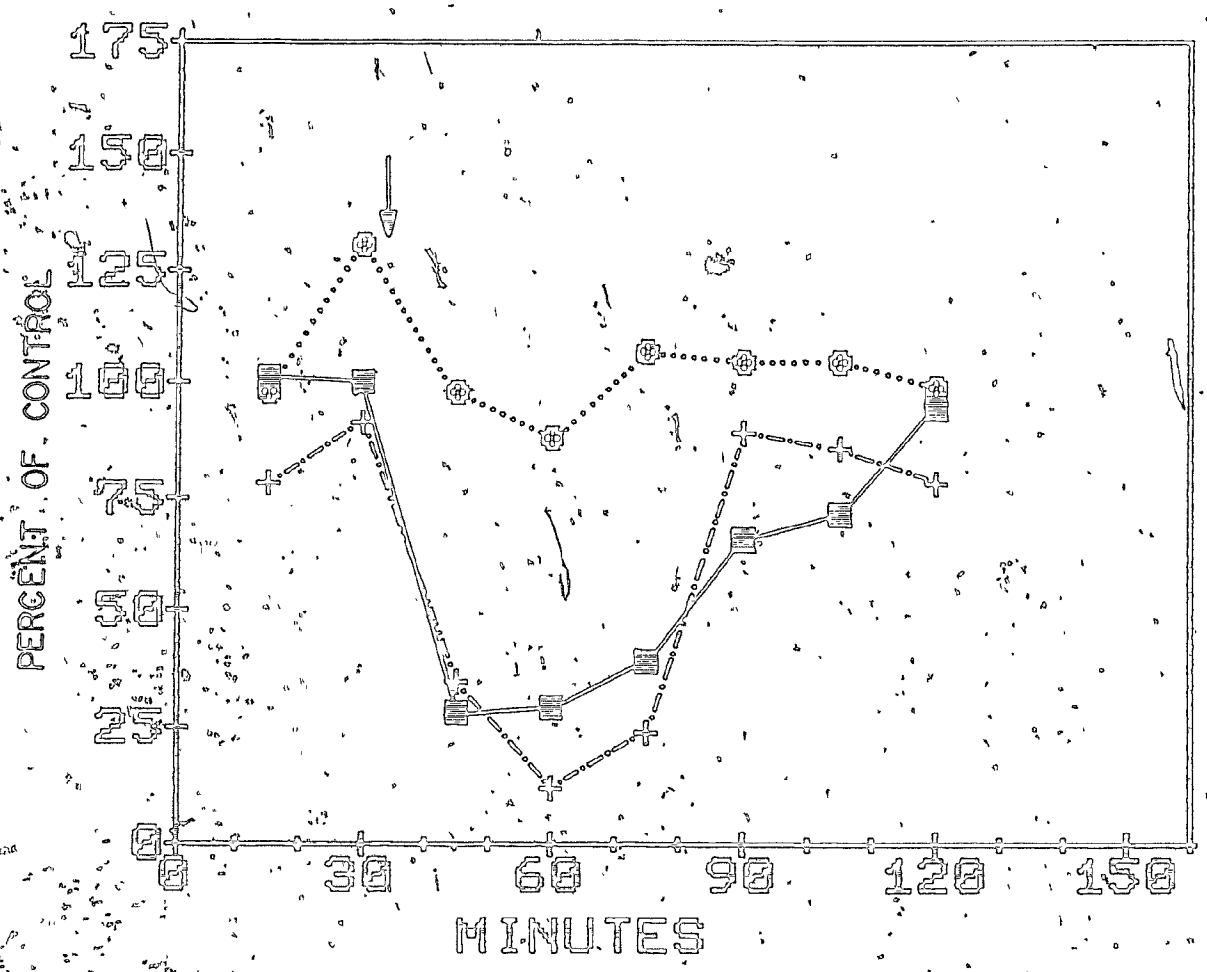
Mean number of bar-holding and theta responses before and after drug injection (indicated by arrow).

A. The effect of decamethonium bromide (0.2 mg/kg, i.p.) on 3 rats. Bar-pressing responses were obtained from an additional pair of rats.

B. The effect of atropine sulphate (50 mg/kg, i.p.) on 2 rats.

Fantie
64

A


175
150
125
100
75
50
25
0
PERCENT OF CONTROL
0
30
60
90
120
150
MINUTES
BAR-HOLDING
REWARDED THETA
BAR-PRESSING

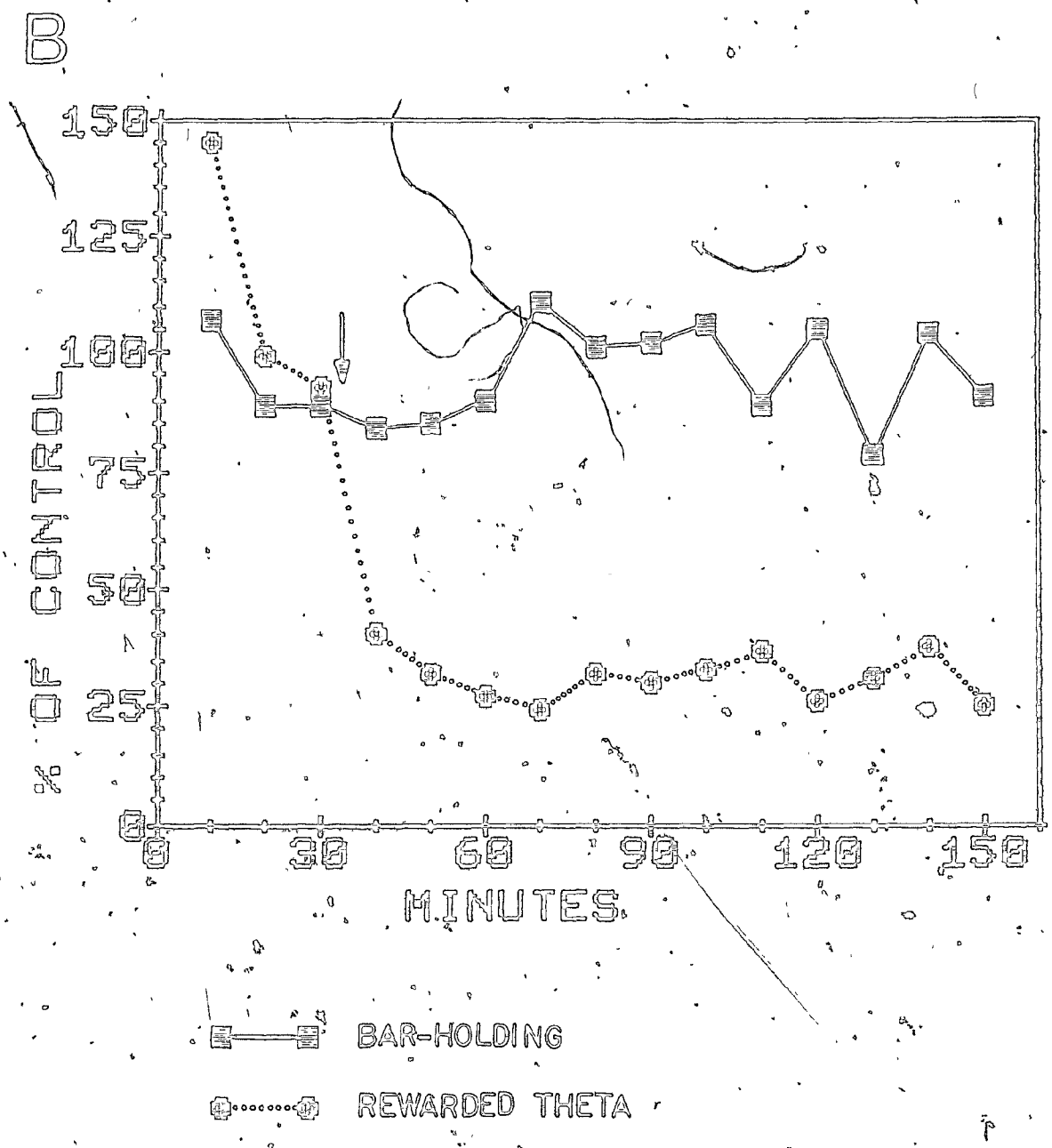

B
150
125
100
75
50
25
0
CONTROL
0
30
60
90
120
150
MINUTES
BAR-HOLDING
REWARDED THETA

Figure 8.

The effect of pimozide (0.5 mg/kg, i.p.), on bar-holding and the theta response for two rats. The drug was injected 4 hours before the start of the session.

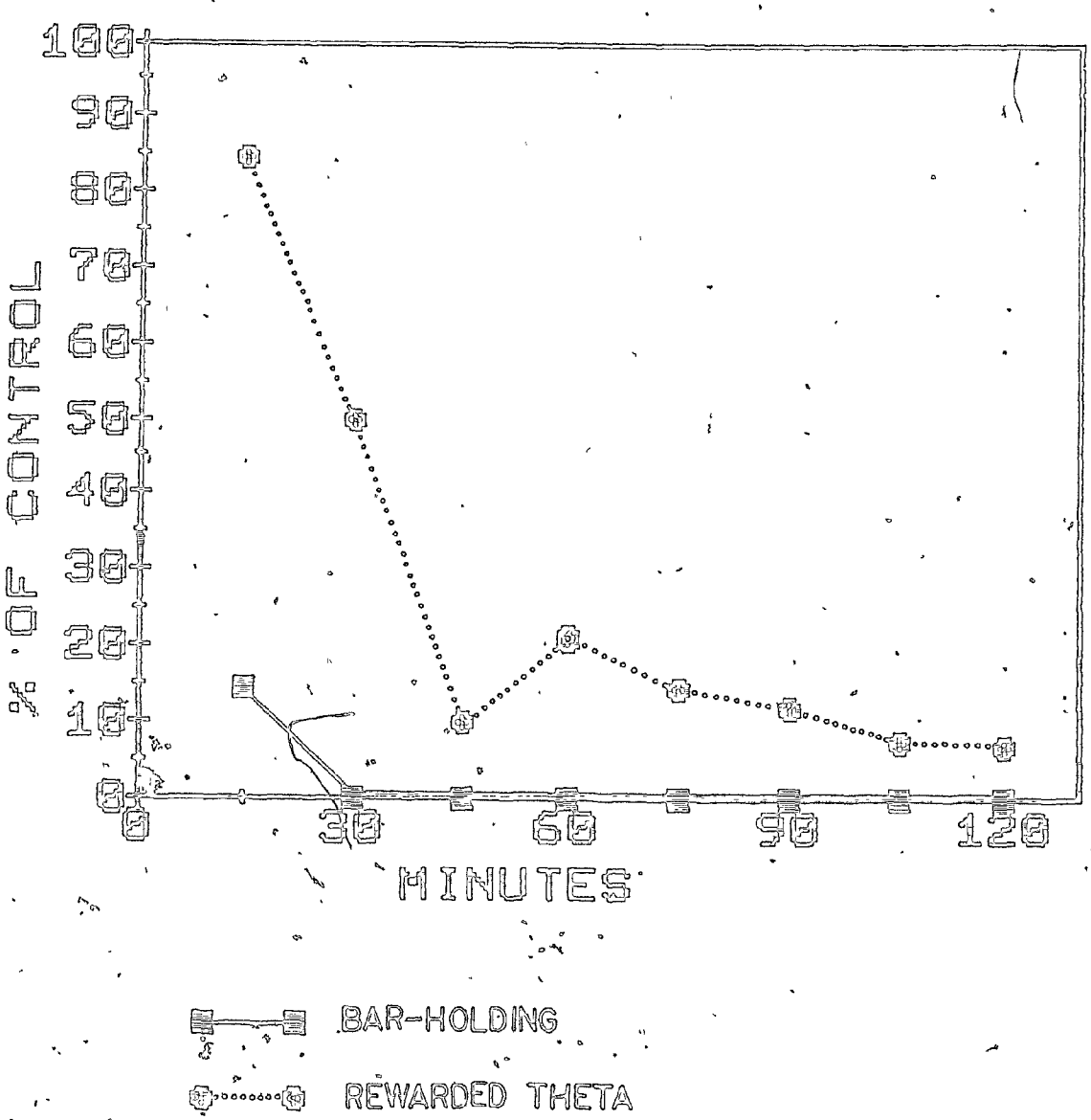
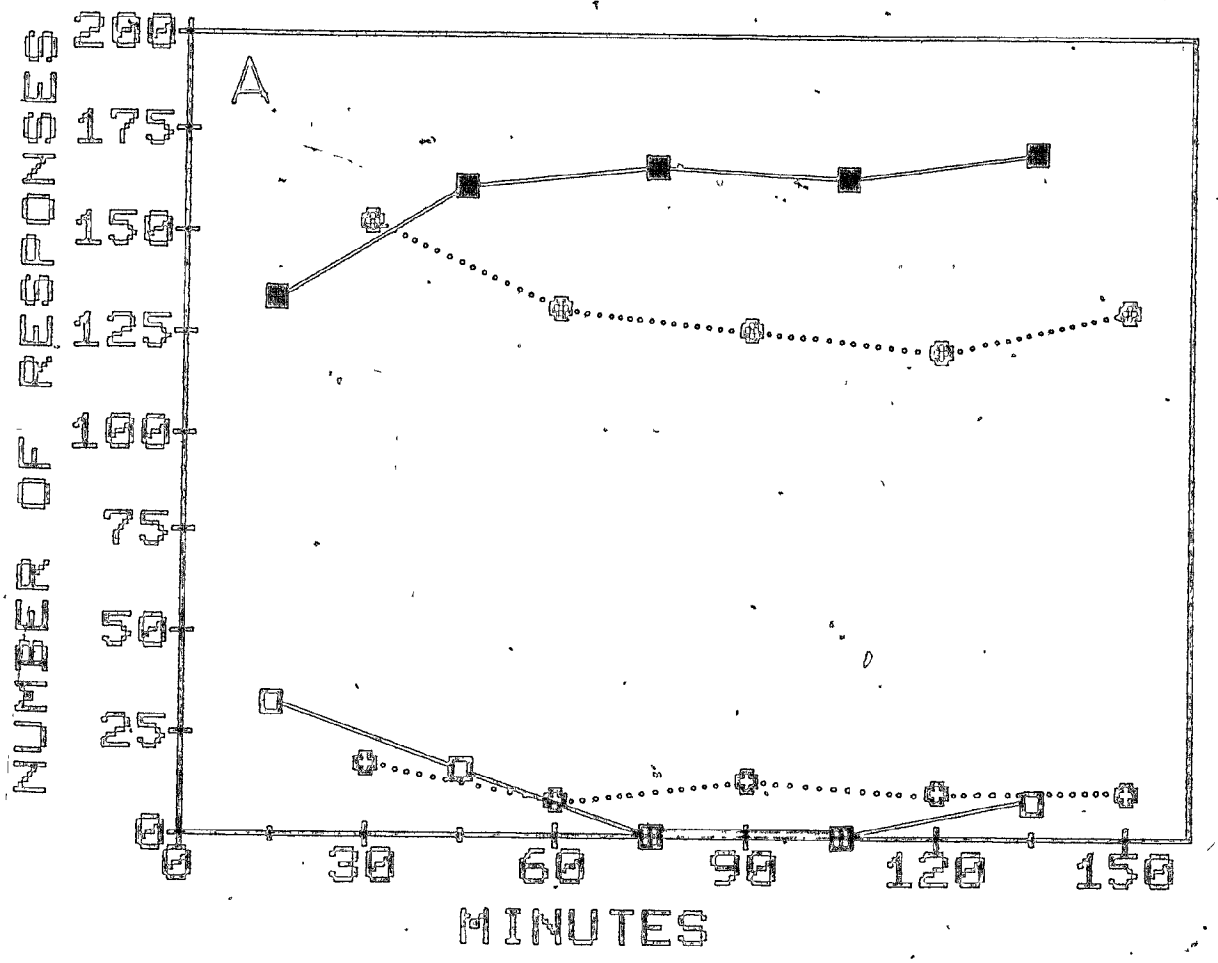

% OF CONTROL
100
90
80
70
60
50
40
30
20
10
0
30
60
90
120
MINUTES
BAR-HOLDING
REWARDED THETA

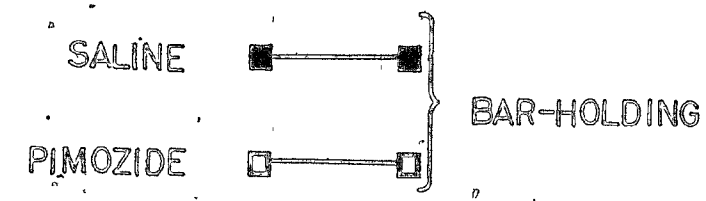
Figure 9.

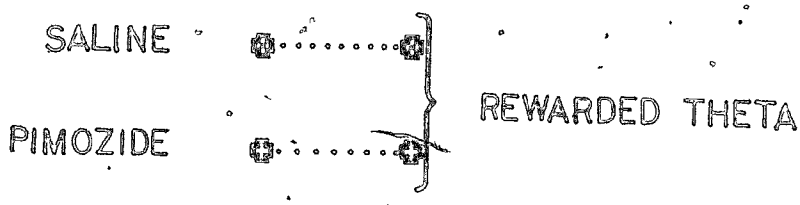
The effect of pimozide on alternating responses.

A. Every 15 min, during the first 2 1/2 hr of the session, the task that earned ESB alternated between bar-holding and theta production. Pimozide (0.5 mg/kg, i.p.), injected 4 hr before the session began, suppressed both responses.

B. Theta trains, produced while the bar was available, were not rewarded and appeared at a relatively constant rate after the saline injection. In contrast to its effect on bar-holding and rewarded theta production, pimozide did not suppress unrewarded theta production. Therefore, pimozide did not affect the rat's ability to produce hippocampal theta.


A
NUMBER OF RESPONSES
200
175
150
125
100
75
50
25
0
0
30
60
90
120
150
MINUTES


SALINE
PIMOZIDE
BAR-HOLDING


SALINE
PIMOZIDE
REWARDED THETA

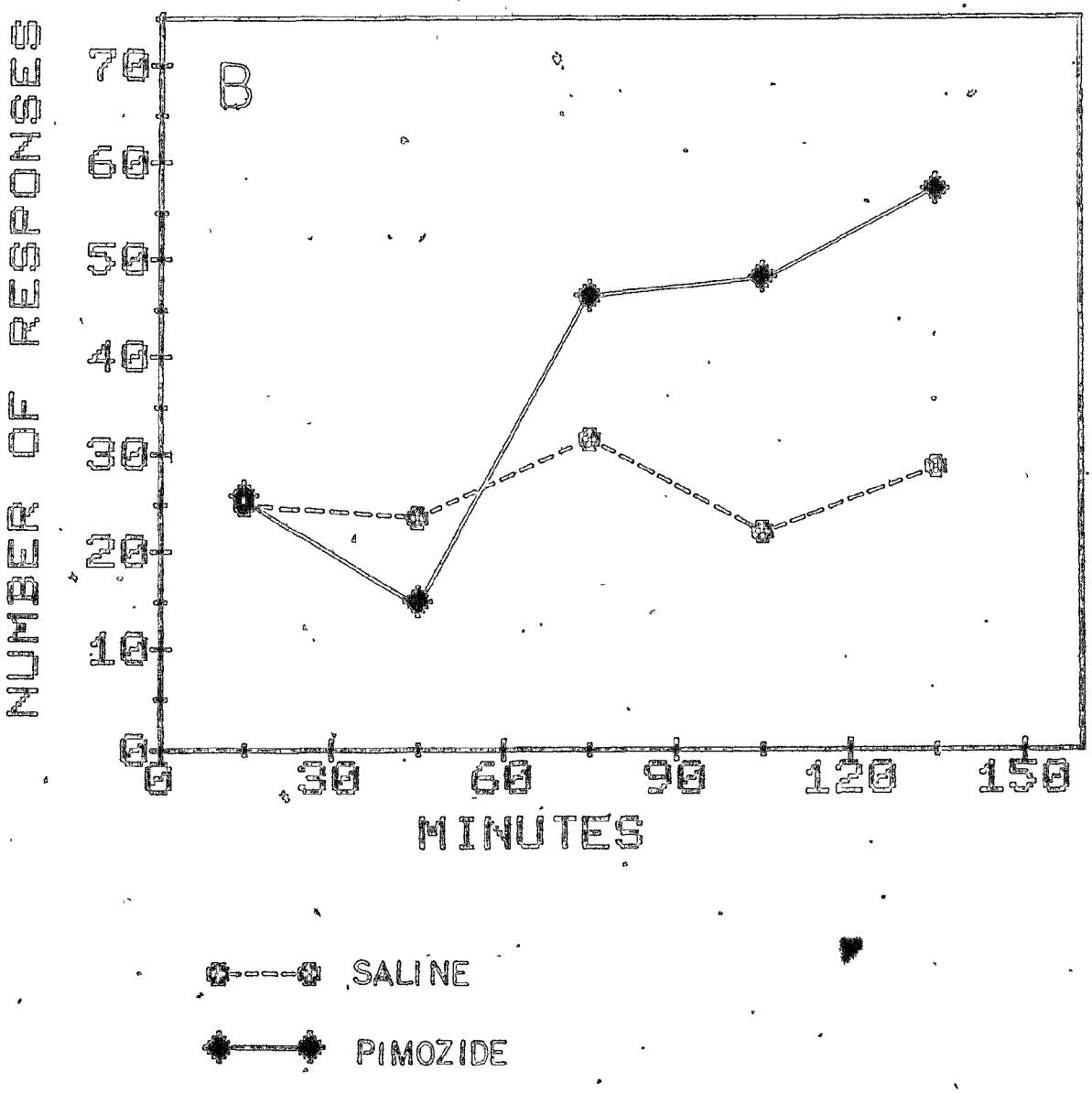
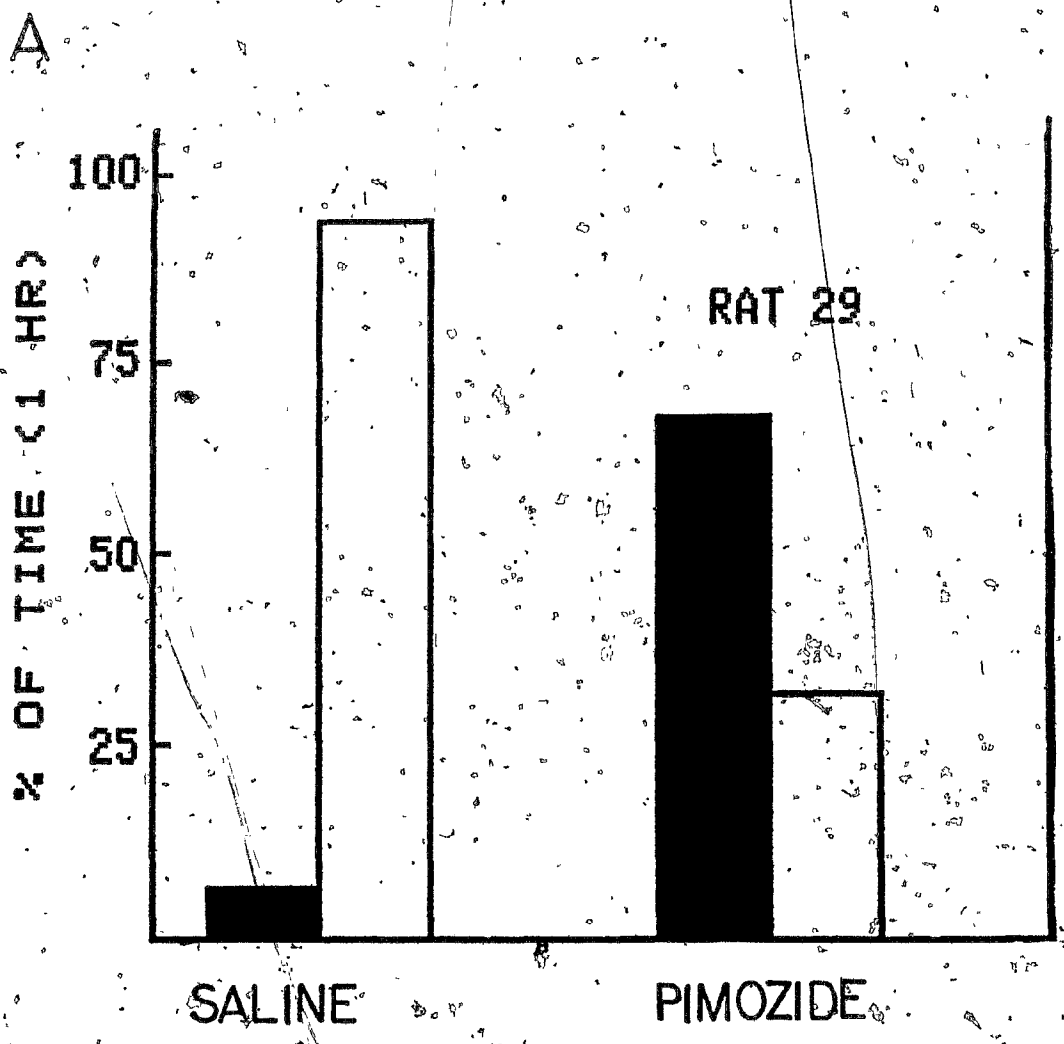

NUMBER OF RESPONSES
B
70
60
50
40
30
20
10
0
30
60
90
120
150
MINUTES
SALINE
PIMOZIDE

Figure 10.

Preferences for the side of the shuttlebox associated with each type of response in a choice situation. Pimozide injections abolished the preferences previously demonstrated for each response.

A. Rat 29 preferred the side where theta earned ESB in the control condition. After pimozide, this rat spent more time on the side where the bar was available but did earn ESB.

B. Rat 6 preferred the side where the bar was available in the control condition. After pimozide, this rat spent about the same amount of time on each side although it did not continue to respond.


A
100
75
50
25
% OF TIME (1 HR)
RAT 29
SALINE
PIMOZIDE
BAR
THETA
SIDE ASSOCIATED WITH

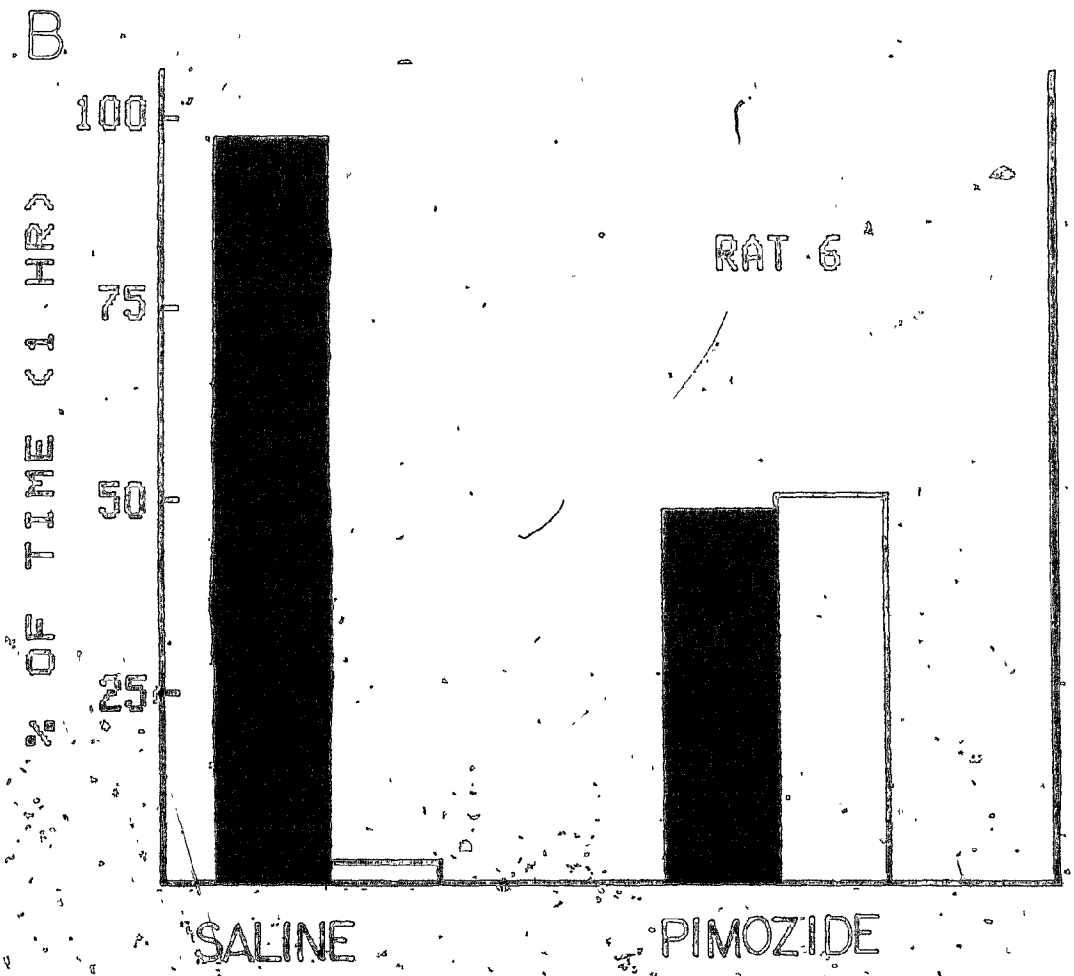
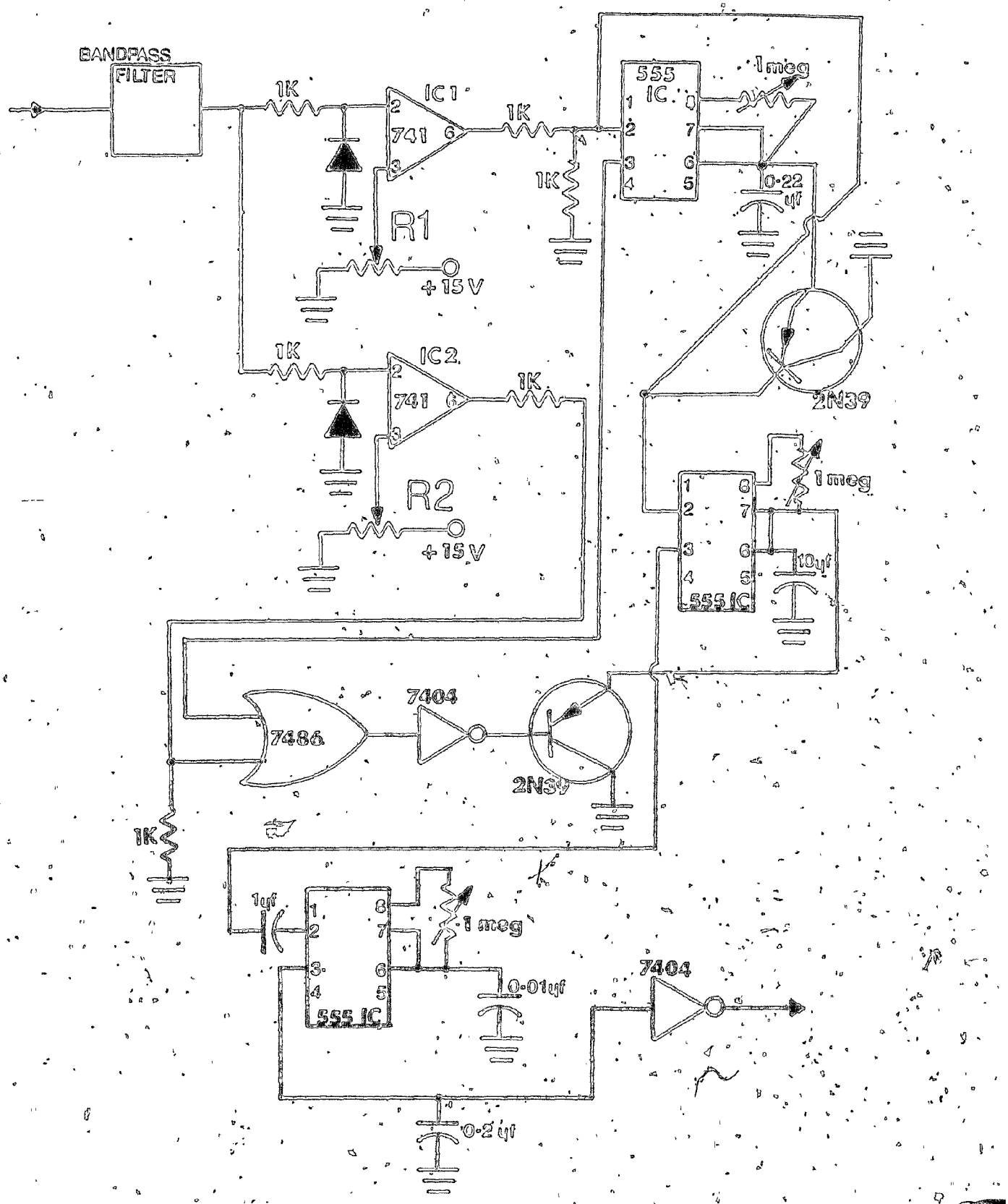

B.
100
75
50
25
% OF TIME SPENT IN
RAT 6
SALINE
PIMOZIDE
BAR
SIDE ASSOCIATED WITH
THETA

Figure 11.

Schematic diagram of theta trigger.

R1 sets the minimum voltage requirement while R2 sets the upper limit.


BANDPASS
FILTER
1K
IC 1
741
1K
1K
R1
+15V
555
IC
1meg
0·22
μf
2N39
1K
IC 2.
741
1K
R2
+15V
1meg
10μf
555 IC
7404
7486
2N39
1K
1μf
1meg
0·01μf
555 IC
7404
0·2μf