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BIOPHYSICS OF INTRACRANIAL SELF-STIMULATION

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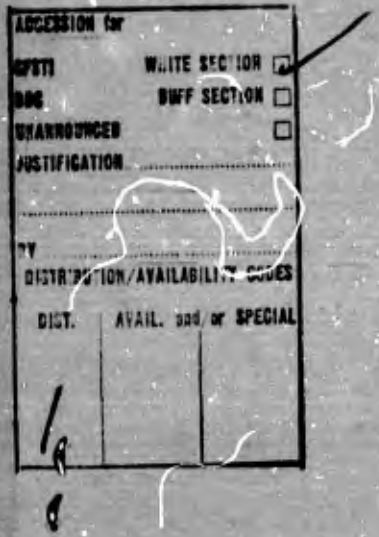
Air Force Systems Command
Holloman Air Force Base, New Mexico

The animals used in this study were handled in accordance with the "Guide for Laboratory Animal Facilities and Care" as promulgated by the National Academy of Sciences - National Research Council.



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FOREWORD

This experimentation, which began 1 November 1966 and was completed 31 July 1967, was performed by the Neuro-Sciences Laboratory at Florida Presbyterian College, St. Petersburg, Florida. The research was conducted under contract F296[illegible]-67-C-0011 with the 6571st Aeromedical Research Laboratory, Holloman AFB, New Mexico. The research was conducted under the monitorship of Lt Colonel Herbert H. Reynolds, whose generous advice and aid in technical and design matters is herewith gratefully acknowledged.

This technical report has been reviewed and approved for publication.

C.H. KRATOCHVIL, Colonel, USAF, MC
Commander

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ABSTRACT

A self-stimulation and E-controlled stimulation study was completed in one rat. The study supports the two-factor model of the self-stimulation mechanism which predicts (1) the shape of self-stimulation curves and changes in stimulation rate as a function of stimulation parameters, (2) dual autonomic effects of self-stimulation, (3) stimulus-bound feeding and self-stimulation at the same electrode site, (4) on-off behavior, and (5) changes in the above with changes in anatomical locus.

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LIST OF ABBREVIATIONS

A	anterior
ACTH	corticotropin
D	dorsal
E	experimenter
L	lateral
pps	pulses per second
Q	charge per train in microcoulombs
S	subject
SS	self-stimulation

INTRODUCTION

Since the discovery by Olds and Milner (Ref. 1) of the phenomenon of intracranial self-stimulation, many experiments have been performed, but few theories advanced. Olds explained the situation in terms of "pleasure centers" (Ref. 2) in the brain. One writer, however, (Gengerelli, et al., Ref. 3) has said that, "To invoke the stimulation of 'pleasure centers' in the brain to explain the phenomenon of cranial self-stimulation is a conceptual maneuver which is not acceptable in the context of a neurophysiological theory of learning."

Deutsch (Ref. 4); Deutsch and Howarth (Ref. 5); Gallistel (Ref. 6); and Stein (Ref. 7) have proposed the only major theories to account for self-stimulation. Deutsch uses the argument of simultaneous activation of "motivational" and "reinforcing" systems, the motivational pushing the animal to the bar and the reinforcing pulling the response to a terminus. Stein utilizes the idea of two distinct positively and negatively reinforcing substrates, with the phenomenon of rebound--at the termination of a positively reinforcing stimulation, the negative system rebounds, driving the animal to the bar for a positive reinforcement to quell the negative, and so on.

Problems with classical terminology have led Miller (Ref. 8) to propose an abandonment of the drive-reduction model of reward and the construction of a new model based on "stop" and "go" mechanisms. Lilly (Ref. 9) has suggested the same approach, refusing to use the conventional terminology. An interesting point is that both these changes were motivated by the same problem: the inability of traditional models of motivation to explain the phenomenon of intracranial reinforcement.

Reward has been defined as a reduction in "arousal level" (Hebb, Ref. 10). Attempts to treat electrical reinforcement in terms of arousal lowering quickly encounter difficulties. The autonomic correlates of arousal lowering should be parasympathetic in nature. Whereas septal stimulation has been shown to produce a consistent decline in both heart rate and blood pressure during both self-stimulation (Malmo, Ref. 11), and E-controlled stimulation (Covian, Ref. 12), hypothalamic self-stimulation raised heart rate (Meyers, et al., Ref. 13), and increased ACTH secretion (McHugh, et al., Ref. 14). E-controlled stimulation gave similar results (Slusher and Hyde, Ref. 15). DC cortical potential during self-stimulation also goes negative, indicating an increase in arousal (Wurtz, Ref. 16).

Furthermore, the same lateral hypothalamic electrode which produces self-stimulation also produces stimulus-bound feeding at the same intensities (Hoebel and Teitelbaum, Ref. 17) and (Margules and Olds, Ref. 18). If stimulus-bound feeding is a real motivational hunger and not motor activation, then the conclusion must be that the animal stimulates to make itself hungry, which directly opposes any drive-reduction hypothesis of intracranial reward.

The fact that stimulus-bound feeding occurs only in the "feeding center" lateral to the ventromedial nucleus of the hypothalamus indicates that a specific motivational drive is involved, fulfilling the criterion of specificity. However, the rewarding system as mapped by Olds, et al., (Ref. 19) is distributed throughout the entire lateral hypothalamic tube, with a negatively reinforcing system in the periventricular region. So any theory of self-stimulation must account for both specificity and non-specificity in reward.

Besides stimulus-bound feeding, any model of the self-stimulation mechanism must also account for so-called "on-off" behavior. In the para-medial nuclei into which both positive and negative systems project, a peculiar phenomenon has been found (Olds, Ref. 20). Numerous investigators (Bower and Miller, Ref. 21; Brown and Cohen, Ref. 22; Roberts, Ref. 23) have shown that if the animal is allowed to regulate the onset and offset of stimulating current, it will oscillate, turning the current on and off. Various suggestions have been made to explain the on-off phenomenon, ranging from overlap of current into negative areas (Bower and Miller, Ref. 21) and spread of neural excitation into negative areas (Stein, Ref. 24) to a simple decay of positive reinforcement (Keesey, Ref. 25).

Valenstein and Valenstein (Ref. 26) showed that on-off behavior occurs at all points where self-stimulation occurs, and does not occur at non-stimulation points, discrediting the idea of overlap into adjacent negative regions. Mogenson and Stevenson (Ref. 27) have found that stimulus-bound drinking increases as the duration of the stimulus train increases, while self-stimulation rate decreases, which may be interpreted as a progressive invasion of negative areas or an increase in "negativity" with a concurrent increase in "drive". Thus the parameter of train duration, which the investigators of stimulus-bound feeding and heart-rate change did not report, enters as a determinant. A similar finding was that of Reynolds (Ref. 28), who found that self-stimulation rate followed an inverted-U function as stimulus intensity increased.

McIntire and Wright (Ref. 29) have found a skewed inverted-U function of self-stimulation response rate and train duration, and Bower (Ref. 30), using an arrangement where the animal regulated train duration, found a decrease in duration with increasing intensity. The fact that both an increase in train duration at constant intensity and an increase in intensity at constant train decrease stimulation rate suggests a common denominator. All of the separate parameters of intensity, frequency, and train duration can be subsumed under the rubric of charge (Q) per train in microcoulombs, and Keesey (Ref. 31) found that curves of responding for CRF reinforcement as functions of intensity and duration become one curve when put in terms of Q per train. However, Ridgway, et al., (Ref. 32) reported that the microcoulomb as a predictor of reinforcement value measured by self-stimulation rate interacted with train duration, and Su, et al., (Ref. 33) have found interaction of charge needed and frequency; 60 pps needed a greater Q per train than 100 pps to achieve the same response rate.

Finally, Hodos and Valenstein (Ref. 34) have questioned the validity of self-stimulation rate as a measure of reward value of a given stimulus, noting that intertrial interval and reinforcement ratio may completely reverse response valency.

Any model of the self-stimulation mechanism must:

(1) predict changes in self-stimulation rate with changes in the stimulus parameters,
(2) account for observed autonomic effects,
(3) account for stimulus-bound feeding and drinking,
(4) account for on-off behavior, and
(5) predict changes in all of the above with changes in the anatomical locus of the stimulation.

The study presented here is an attempt to satisfy the requirements stated above.

METHOD

Subject

The subject was one Long-Evans hooded rat, approximately 120 days old at implantation, weighing 331 grams. S was fed ad lib. with standard lab chow and water.

S was implanted with a Fisher stainless steel bipolar electrode on a Johnson-Kreig (Stoelting) stereotaxic instrument while under phenobarbital and chloral hydrate anesthesia. Atropine sulfate was used to control salivation, and Aureomycin was topically applied postoperatively. The electrode coordinates (König and Klippel atlas, Ref. 35) were 6.4 A, 1.8 L, and 7.8 D, which is a locus in the medial forebrain bundle lateral to the ventromedial nucleus of the hypothalamus.

Apparatus

A Skinner box measuring 10" x 10" x 8 1/2", constructed of plexiglass on two sides and aluminum on the others, with a plexiglass top, was fitted with an adjustable metal operant response lever, the top of which was 1 1/2" above the floor and protruded 3/4 ".

A Grass S6 square wave stimulator was used, with variable pulse duration, frequency, voltage, and a biphasic output. Train duration was set with a Grason-Stadler electronic timer which was checked against calibrated equipment, and all response contingencies were programmed on automatic equipment. Response pattern was recorded graphically on a Bausch and Lomb VOM 5 recorder.

Procedure

Self-stimulation rate, average time per press, average reset time (time between presses), and response pattern were measured concomitantly in two separate test situations: set-train, where E set the train duration, and S-regulation, where S controlled the train duration.

Average time per press was calculated from:

$$\text{time/press} = \frac{\text{total response time}}{\text{number of responses}}$$

Average reset time was calculated from:

$$\text{reset time} = \frac{\text{total test time - response time}}{\text{number of responses - 1}}$$

Test sessions were 1 1/2 hours in length, once in the morning and once in the afternoon. To minimize the effects of "state" of the animal, as much data as possible was gathered in each session. For set-train performance, a 3-minute interval was used at each setting, and a 2-minute intertrial interval was used to negate sequential effects. During the intertrial interval, S was removed from the test situation and placed in the home cage. S-regulated performance used 2-minute test intervals and 2-minute intertrial intervals. The over-all design used parametric testing over the following schedule:

SUMMARY OF EXPERIMENTAL PROCEDURE

I. Effect of frequency at constant charge per train

frequency (pps)	train (sec)
40	.75
60	.50
100	.30
150	.20
200	.15

voltage: 5 volts
pulse: .20 msec
Q/train: 30 in all cases

II. Set-train performance

Frequencies: 40, 60, 100, 150, 200 pps
train durations: .2, .3, .5, .75 sec
voltage: 5 volts
pulse: .20 msec

To vary Q/train, each train was tested for one 1 1/2 hour session, holding train duration constant, and varying frequency twice over the 40-200 pps range, first ascending, then descending. Trains were counter-balanced.

III. S-regulated performance

frequencies: 40, 60, 80, 100, 120, 150, 170, 200 pps
pulse duration: .20, .40 msec
voltage: 5 volts
The animal determined the train duration.

Pulse and voltage were set and frequency varied over the range, first ascending, then descending.

Analysis

For the SS data, each point in the figures is the average of from 5 to 10 trials, to eliminate the effect of "state". For the S-regulation data, each point is the average of 2 or 3 trials. Of course, all average time/press and reset time is the average of 100 to 300 responses for each of 5 or 10 trials, so a large number of data are present for these measurements.

Charge per train was determined in arbitrary units. Constancy of resistance was checked with an oscilloscope. The waveform was found to be biphasic, and did not decay with trains up to one second in length, so resistance across the electrode could be considered constant. However, to facilitate calculations, a monophasic waveform was assumed, and Q, the charge per train, could be calculated from the formula:

Q/train = voltage X pulse duration X frequency X train

RESULTS

Set train analysis

Effect of "state" of the animal

Figure 1 shows the effect of the "state" of the animal upon response rate. Each set of points was taken at the same stimulus parameters, but one day separated the test sessions. The curve shape remained the same; the position of the curve moved by a constant due to the "state" of the animal. "State" includes such variables as hunger, fatigue, and various physiological cycles. The results demonstrated the necessity of acquiring a great deal of data for averaging, and the demand for gathering as many data as possible in one session. Furthermore, problems with using different animals in different states are indicated as hiding many data which can only be gained by the use of a single well-trained animal.

SS rate versus Q per train

The results of the major fixed-train study are given in Figures 2, 3, 4, and 5. The data clearly showed a curvilinear relationship of SS rate to frequency (with Q/train increasing concomitantly), and the peak moving back as train duration was increased.

Self-stimulation rate versus train duration at different frequencies, the other plane of this three-dimensional design, showed a definite relationship to frequency, with the slope of the curve going positive, then negative, for the same value of train duration as frequency was increased.

When these curves were transformed into SS rate versus Q/train, where Q/train was determined by train duration and frequency separately, the transformed curves (Figs. 4 and 5) showed:

(1) a general similarity in shape for both SS rate over Q/train determined by train and Q/train determined by frequency, indicating that Q/train was most important in determining response rate, and

(2) a distinct effect of frequency upon SS rate at the same value of Q/train, where the same value of Q gave low SS rate at 40 pps, rose rapidly at 60 pps, and leveled at 100 pps.

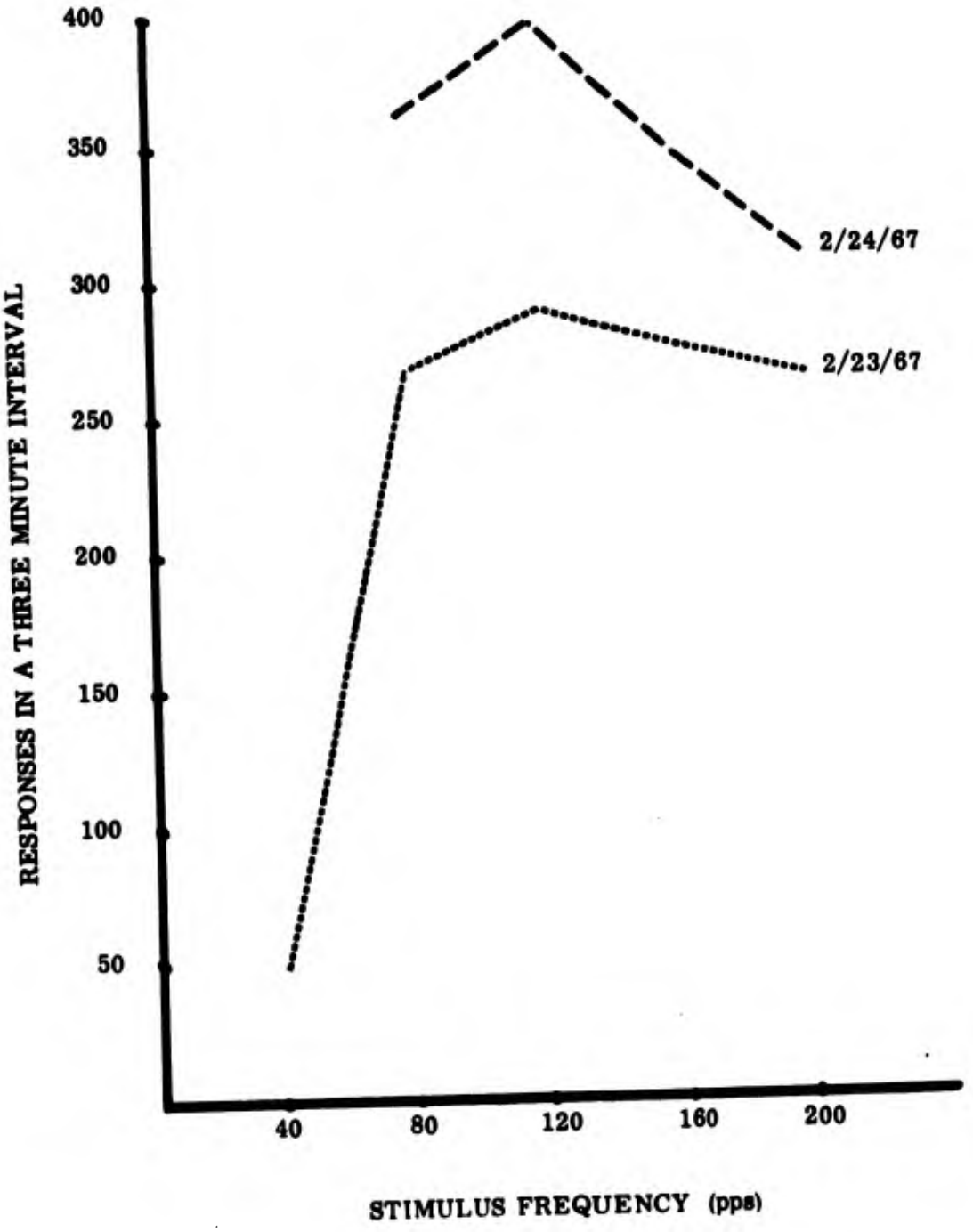

Figure 1. The effect of "state" of the animal upon response rate.

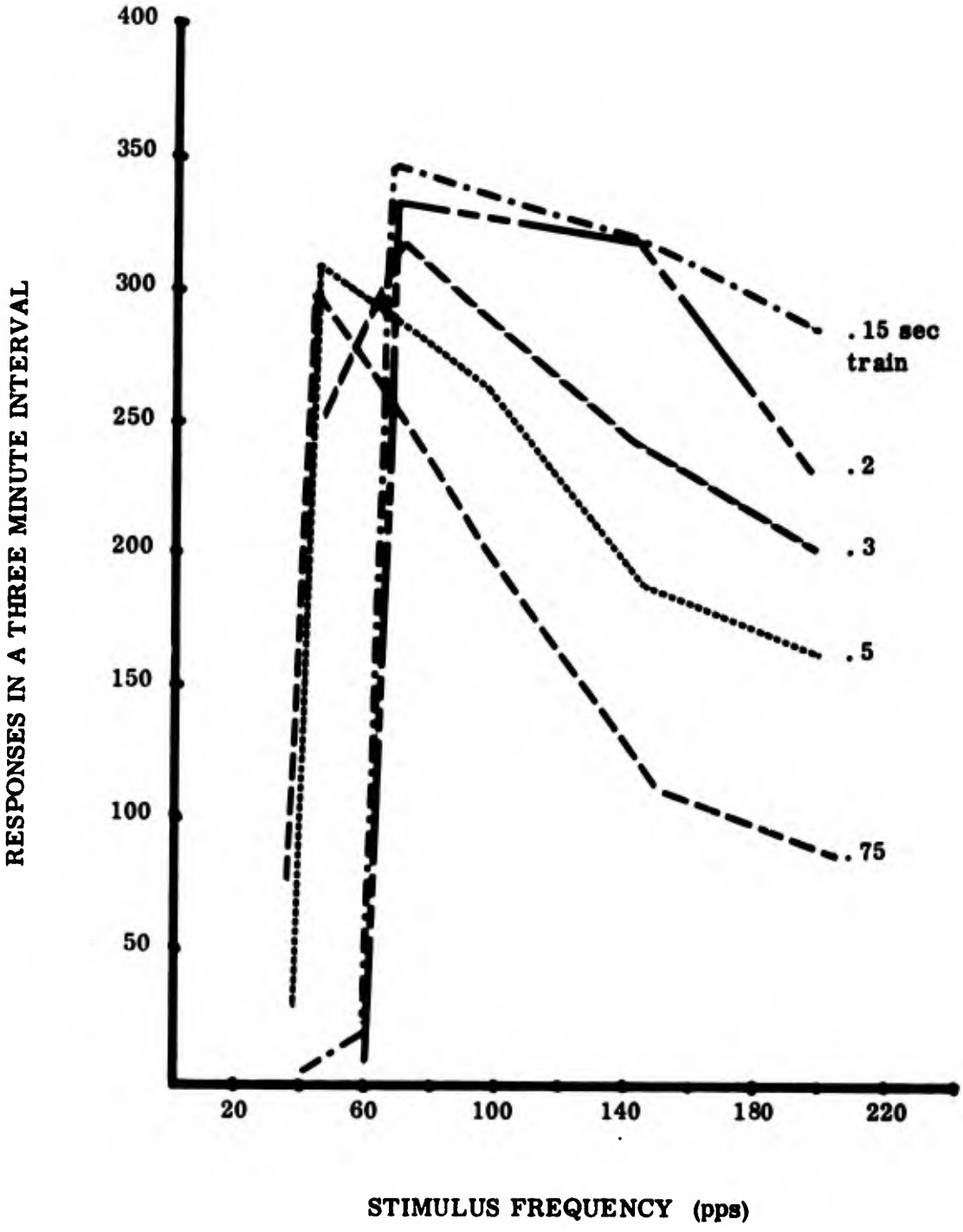

Figure 2. Self-stimulation rate versus frequency.

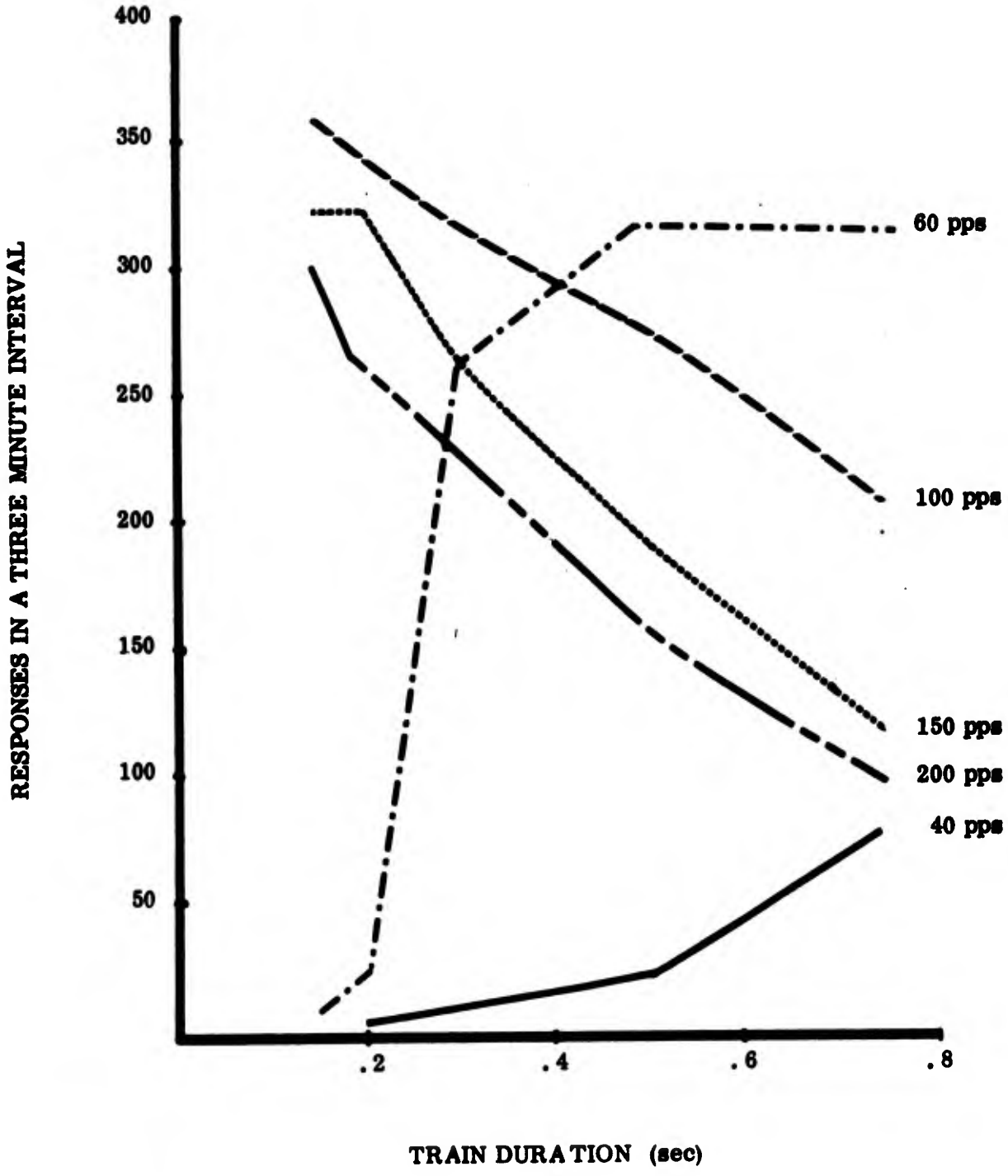

Figure 3. Self-stimulation rate versus train duration.

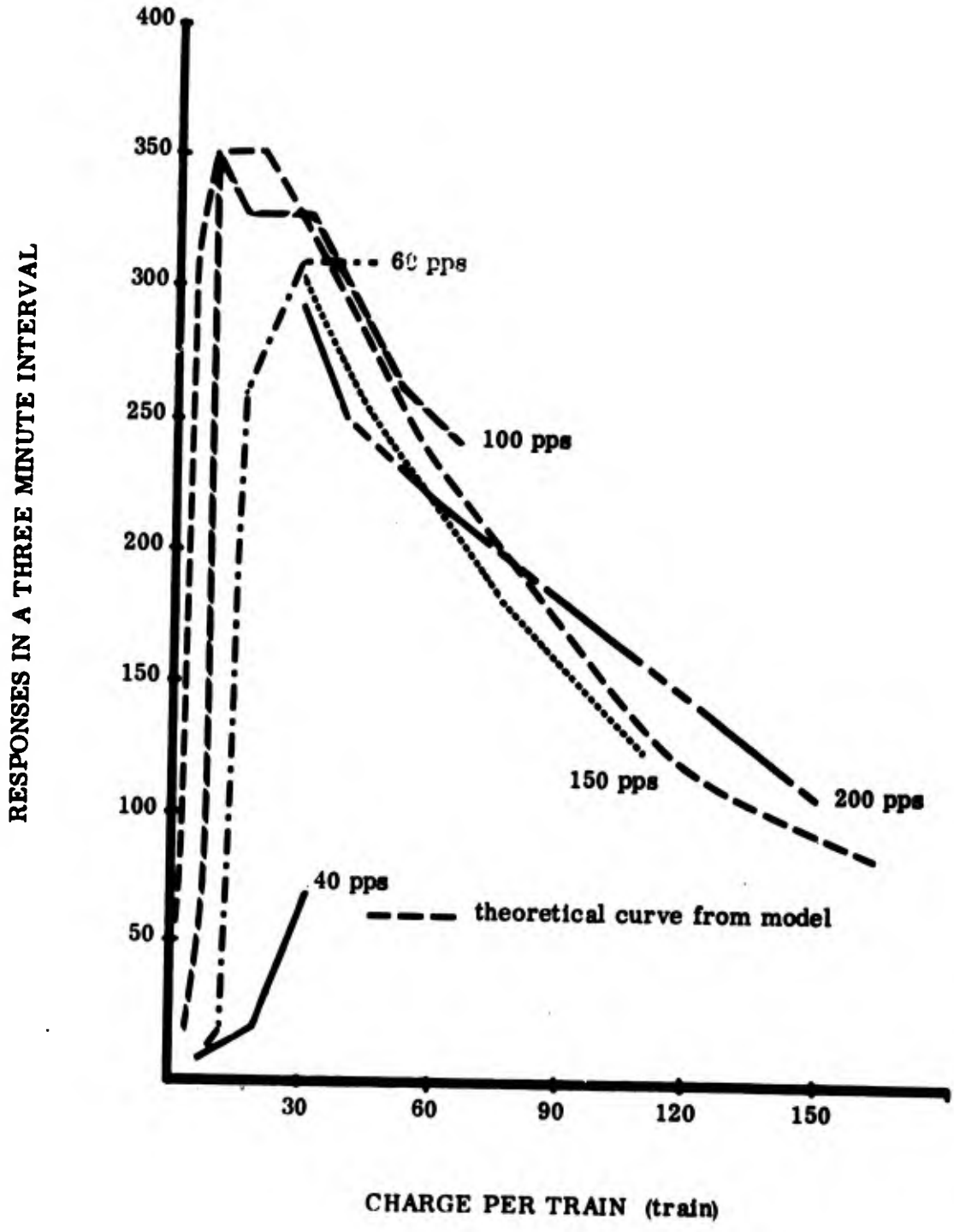

Figure 4. Self-stimulation rate versus Q/train determined by train.

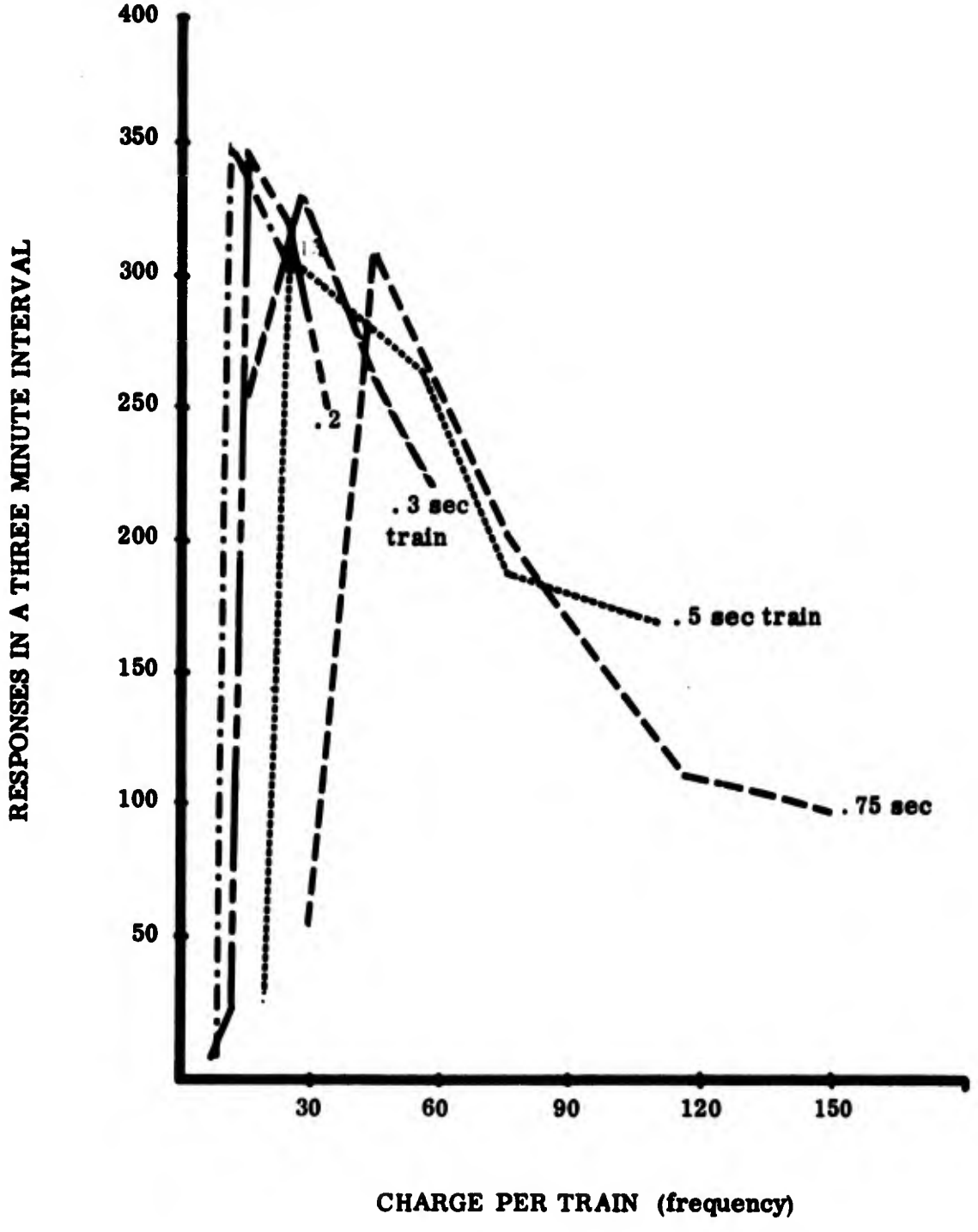

Figure 5. Self-stimulation rate versus Q/train determined by frequency.

It must be emphasized that SS rate is inaccurate at low values of Q; a score of 10 presses in a three minute interval does not mean a slower rate than a score of 200 presses--it simply means that the animal extinguished rapidly.

Time/press (Fig. 6) reached a minimum at a frequency which moved back at higher train durations due to excess Q/train. Reset time (time between responses) also reached a minimum at the same points, and the curves (Fig. 7) were very similar to those of time/press, implying that both depend upon the same variable. Both minimum time/press and minimum reset time combined to produce maximum SS rate at that point.

Analysis of the response pattern at increasing train duration, all else constant, showed a "burst" pattern (Fig. 8), with the inter-burst time increasing as Q/train increased past 80-100 pps.

The effect of frequency at constant Q/train

Figure 9 shows a definite curvilinear relationship of SS rate to frequency at constant Q/train, with a peak at 100 pps, implying that the available Q was most effective at 100 pps. Reset time reached a minimum at 60 pps (Fig. 10).

Qualitative observations

Dual autonomic and behavioral symptoms were observed in the same test session. Aversive (vocalization, active withdrawal from the bar, defecation), and pleasurable (ejaculation, approach to the bar) responses accompanied each other. At higher Q/train values increased withdrawal became apparent, with S attempting to escape the area of the bar.

S-regulation analysis

Time/press

Time per press decreased with increasing frequency. The curve appeared to be a constant-charge strength-duration curve, and the experimental points were fitted with theoretical constant-Q curves (Fig. 11). For a complete analysis, the

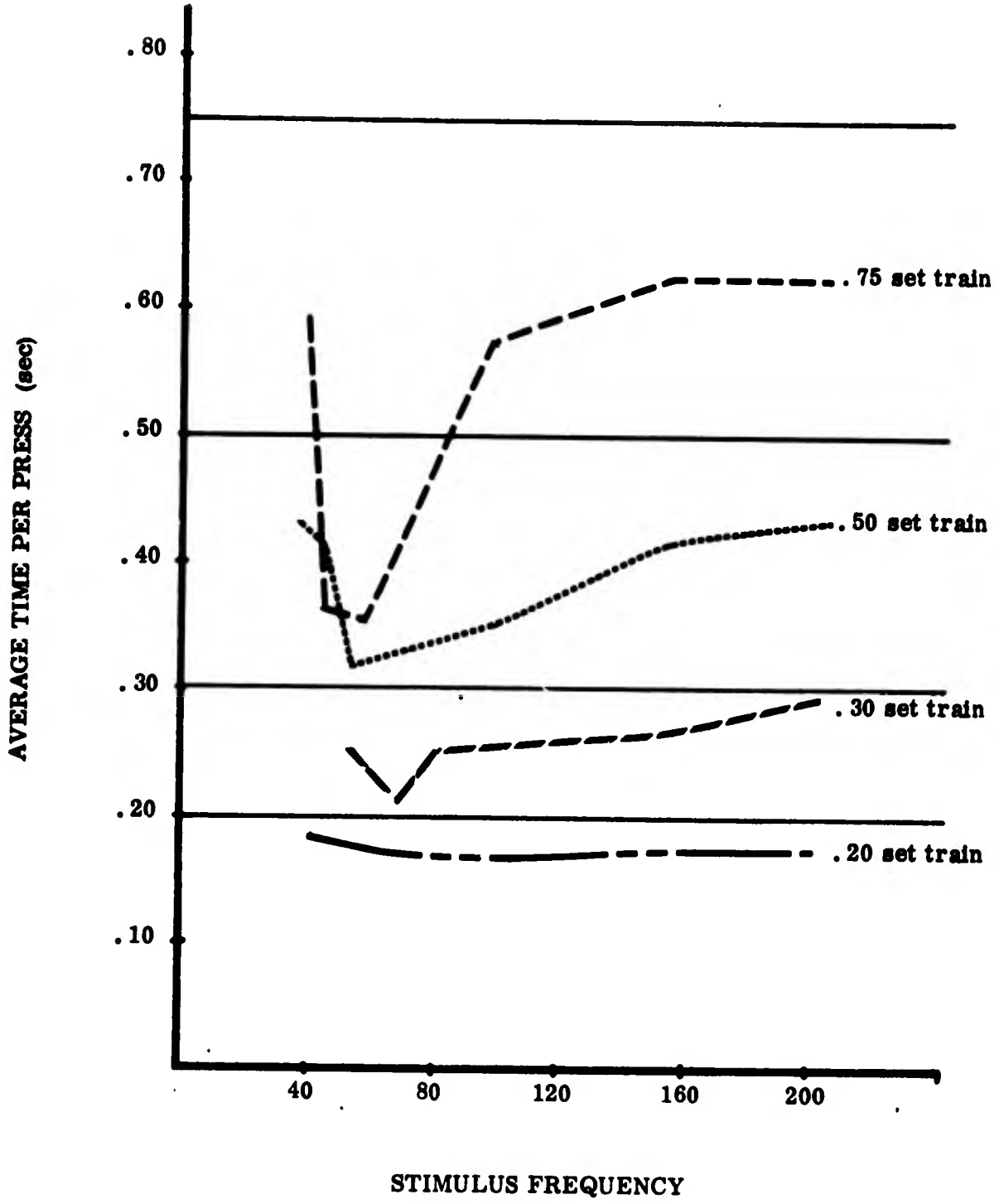

Figure 6. Time per press deviation from set train duration. Each point is the average of at least five test sessions.

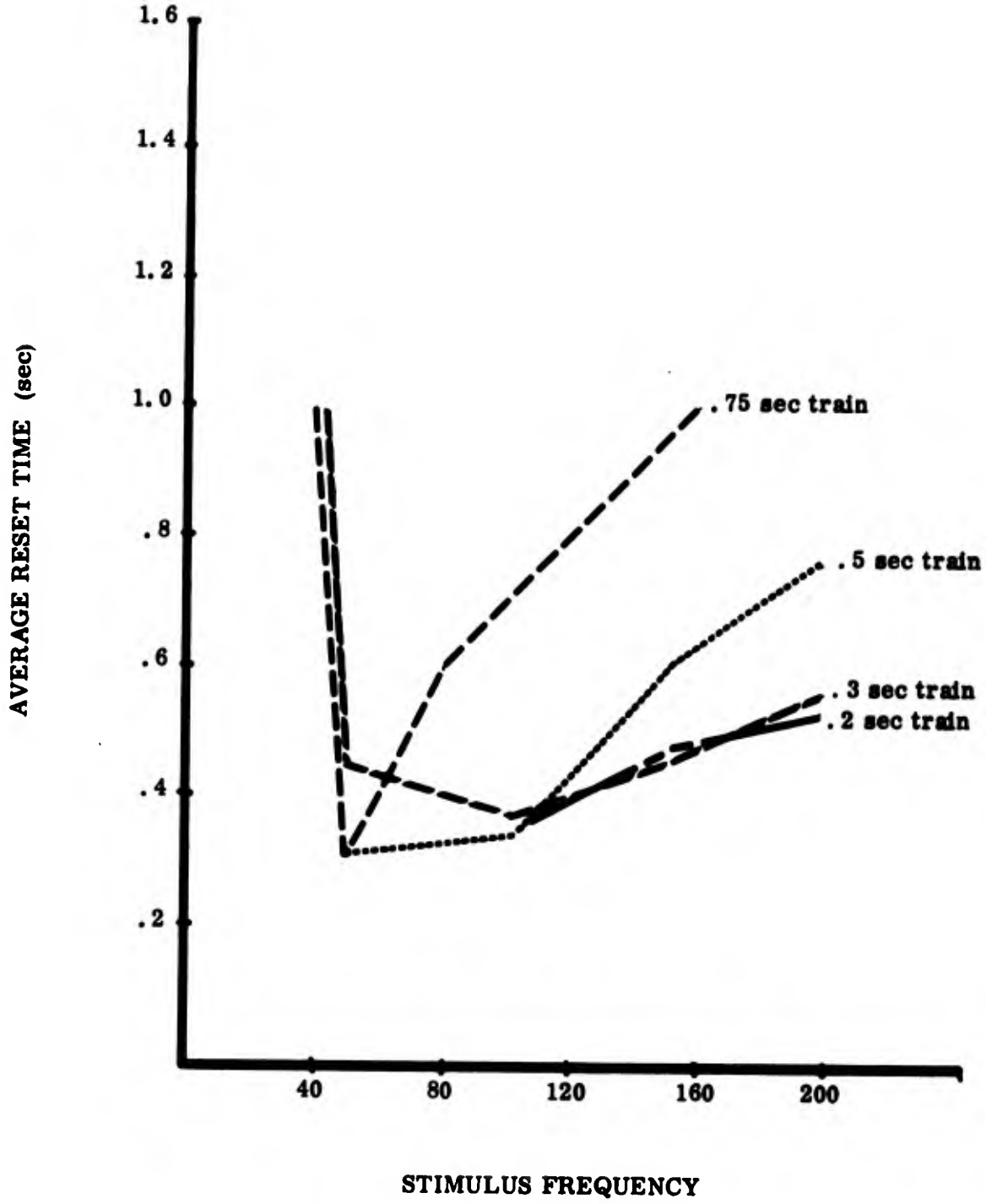

Figure 7. Reset time versus frequency for various fixed train values.

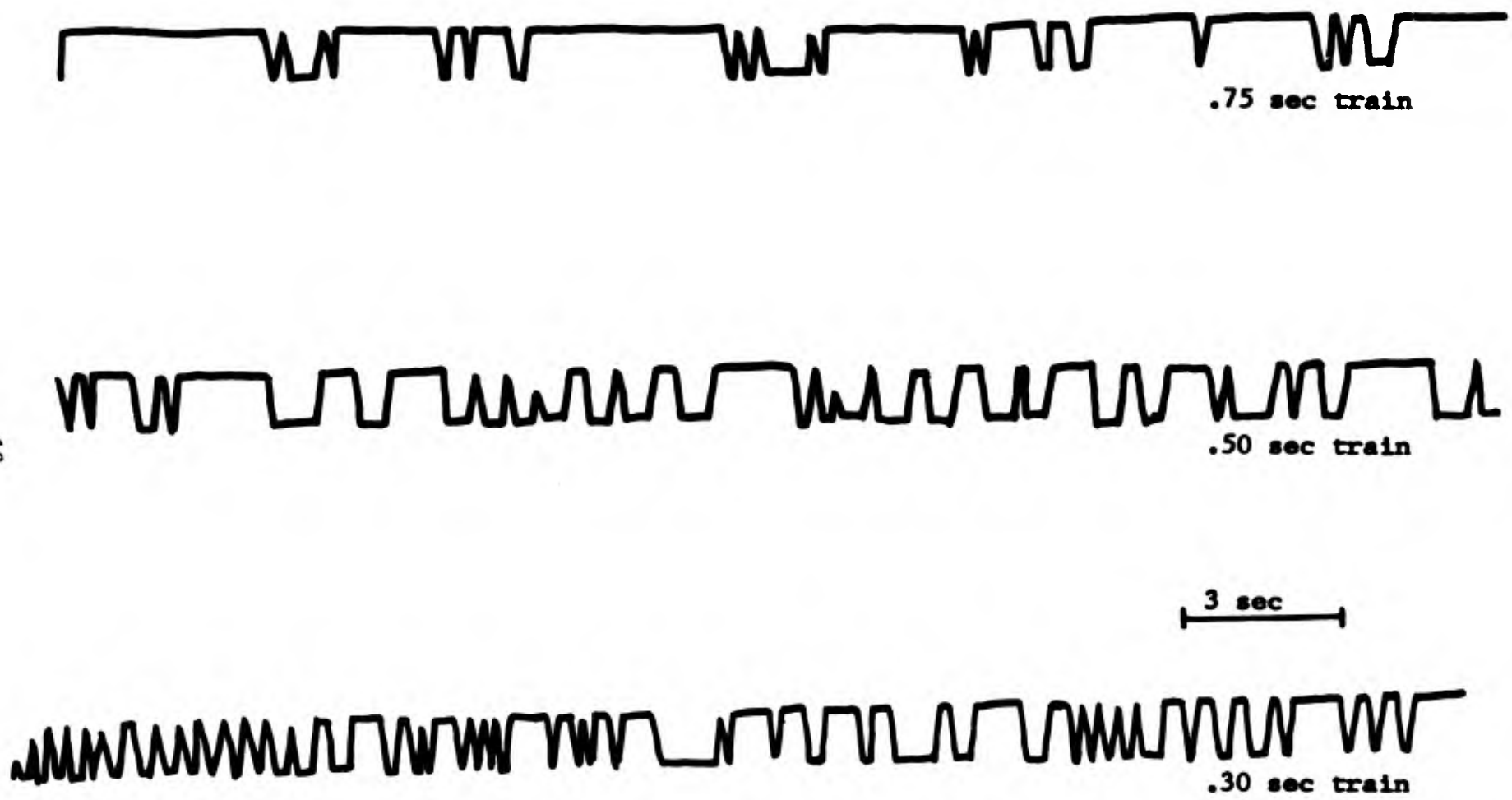

Figure 8. Response pattern for various fixed-train durations.

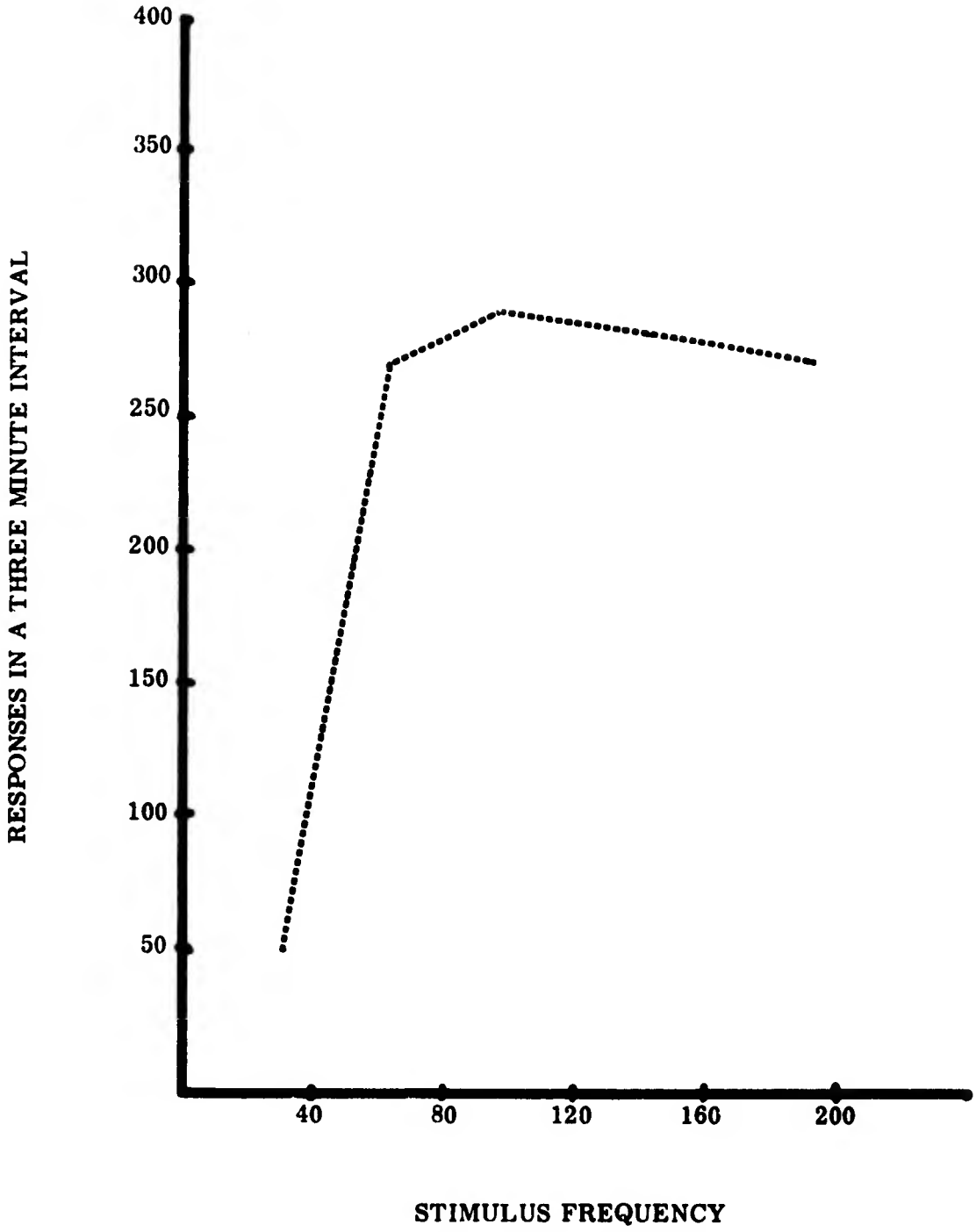

Figure 9. Self-stimulation rate versus frequency at constant charge per train.

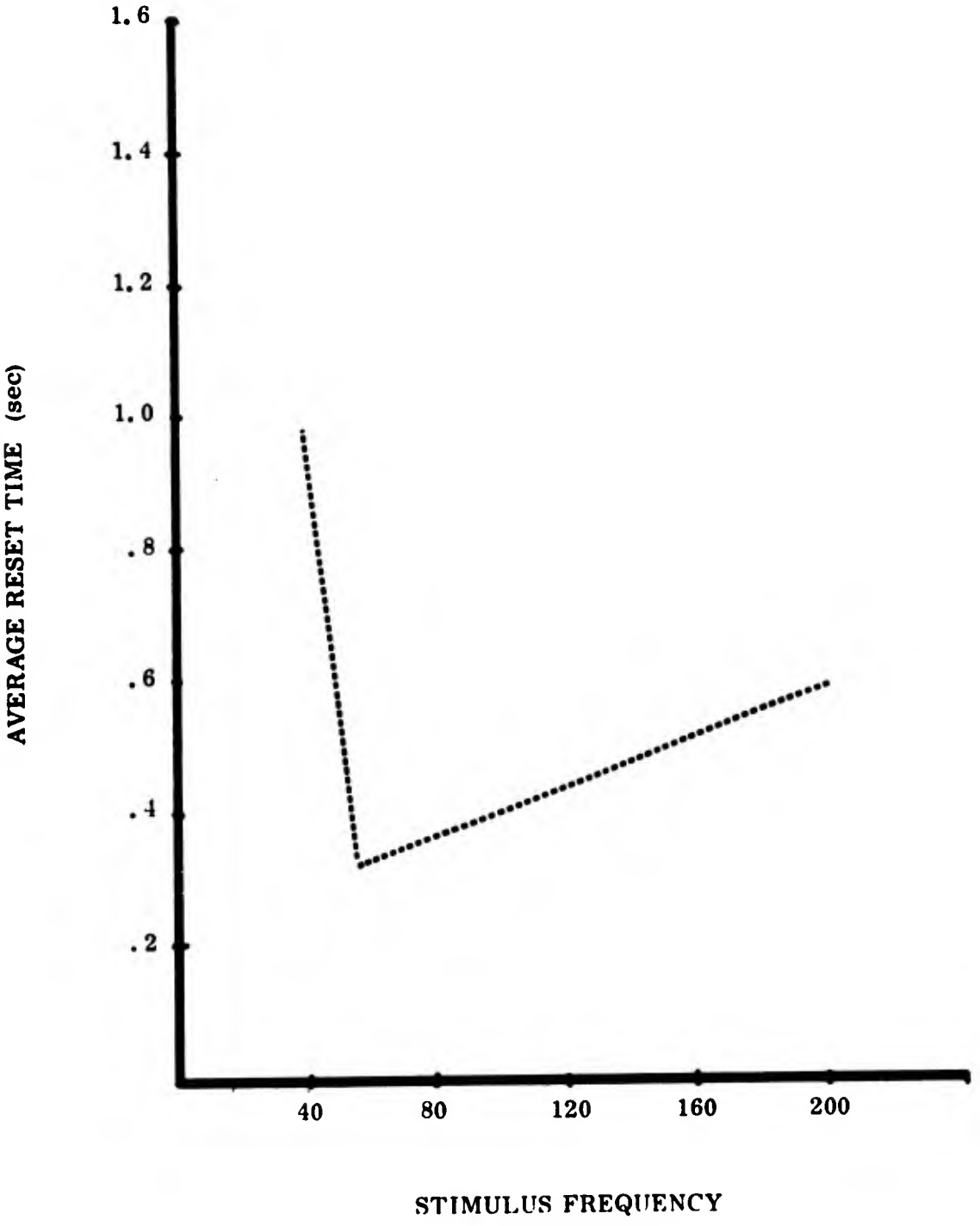

Figure 10. Reset time at constant charge per train as a function of frequency.

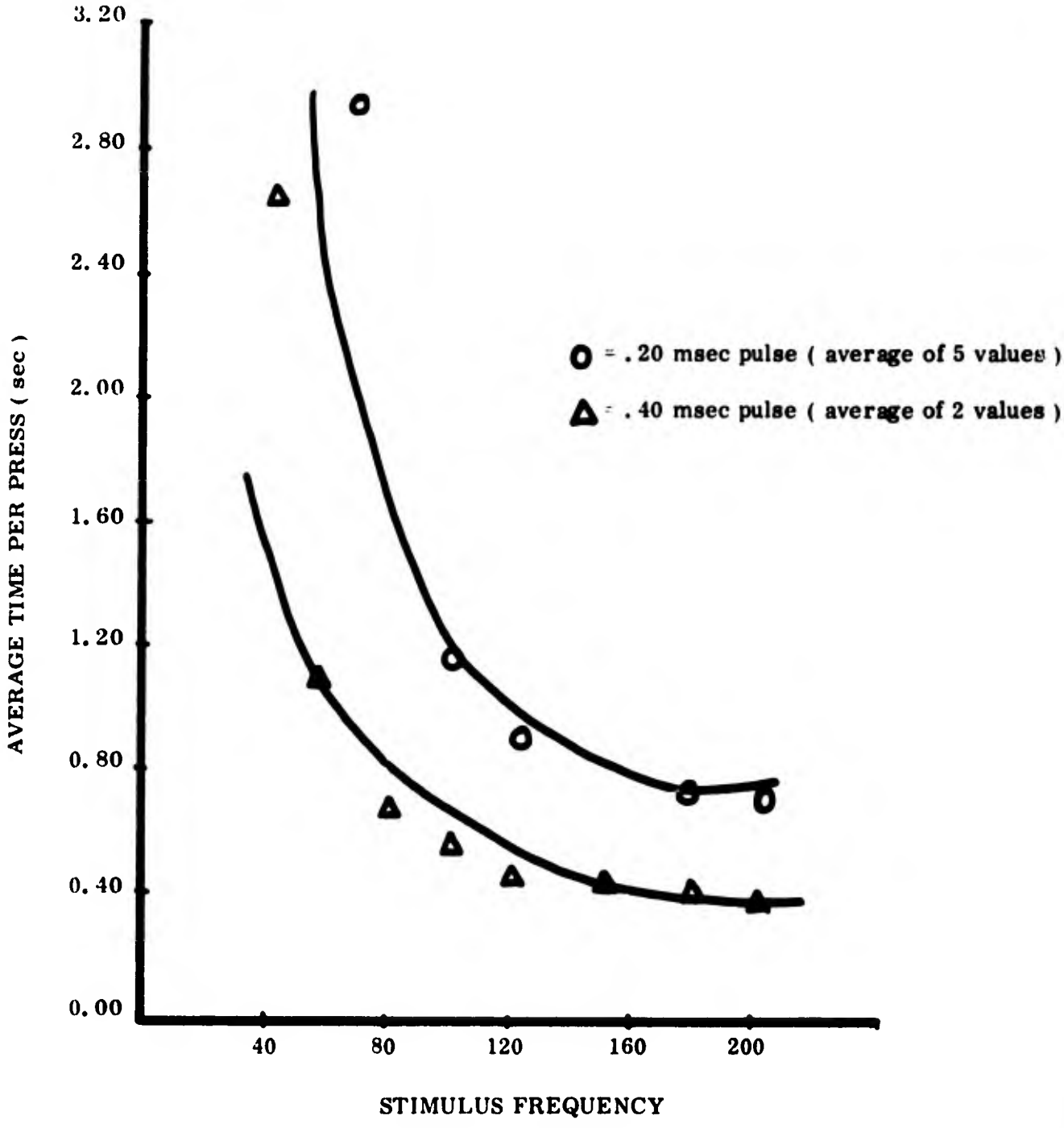

Figure 11. S-determined time per press.

results of a representative session are analyzed to show all the information which can be derived, beginning with a strength-duration curve (Fig. 12).

Effect of frequency upon Q value chosen

Closer analysis of Q/press showed a minimum Q needed to attain aversive threshold in the 80-100 pps range (Fig. 13).

Reset time

Reset time appeared to reach a minimum in the 80-100 pps range (Fig. 14), similar to the Q/press curve of Figure 13.

Response rate

SS rate attained a peak at 80-100 pps (Fig. 15) due to the minimum reset time, even though time/press was continually decreasing.

Effect of pulse duration

Increased pulse duration (from .20 to .40 msec) lowered the time/press as expected, but surprisingly increased the Q needed for aversive threshold (Fig. 13).

Response pattern

Analysis of response pattern (Fig. 16) showed a "bursting" similar to that of set-train performance, but not as marked. Such data implied that bursting was due to something other than simple negative overdriving in the set-train situation.

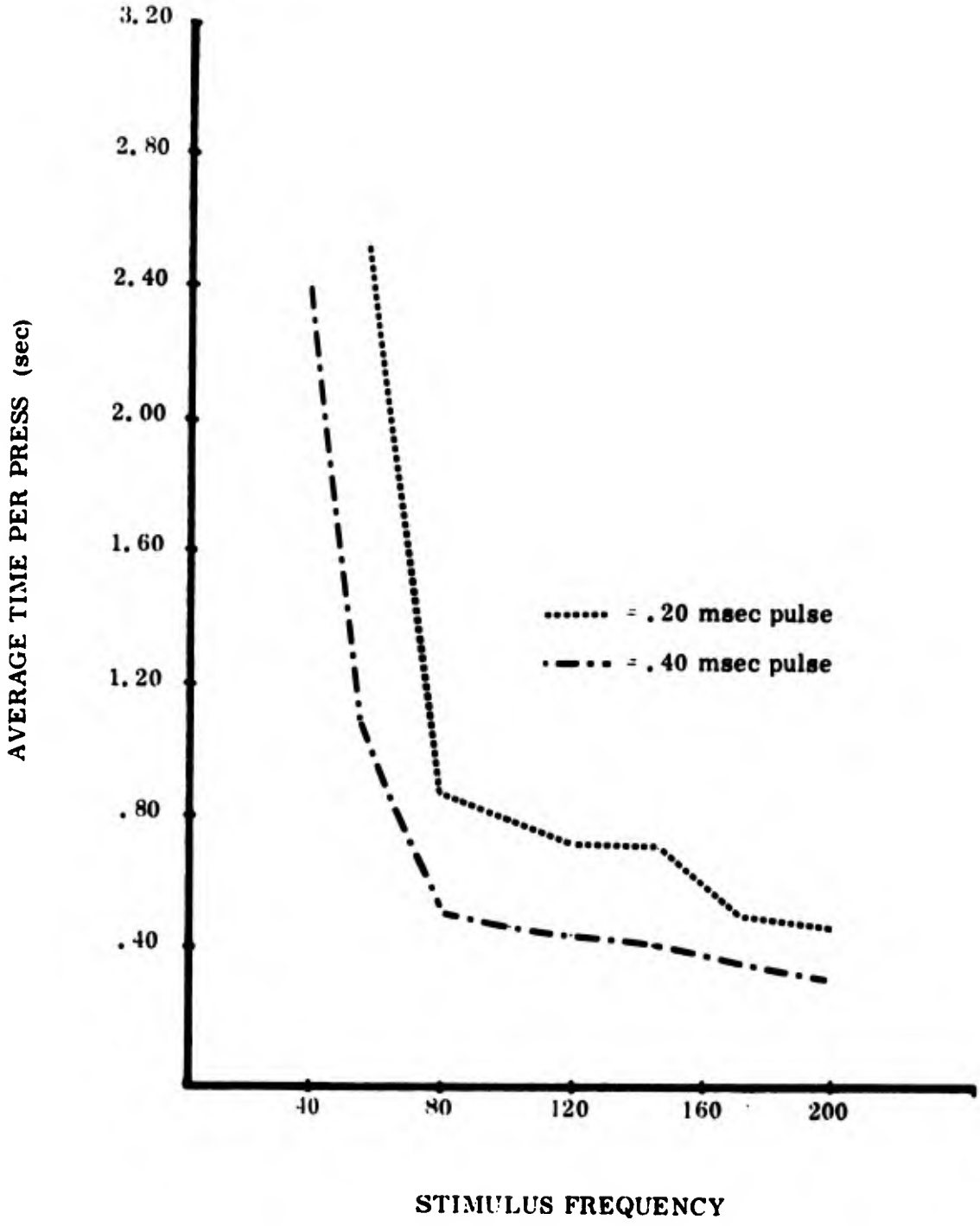

Figure 12. Representative S-determined time/press curve.

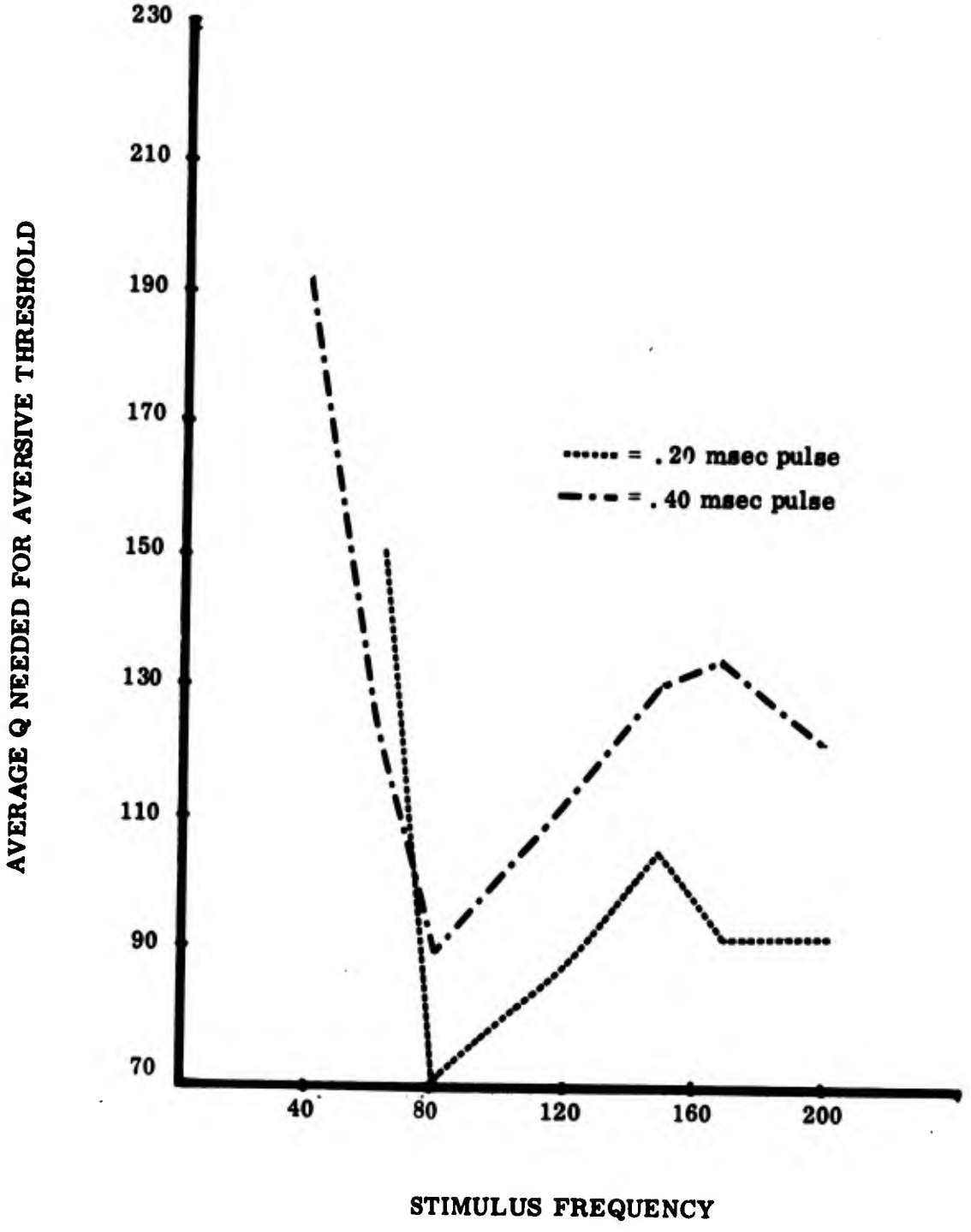

Figure 13. Q needed for aversive threshold as a function of frequency.

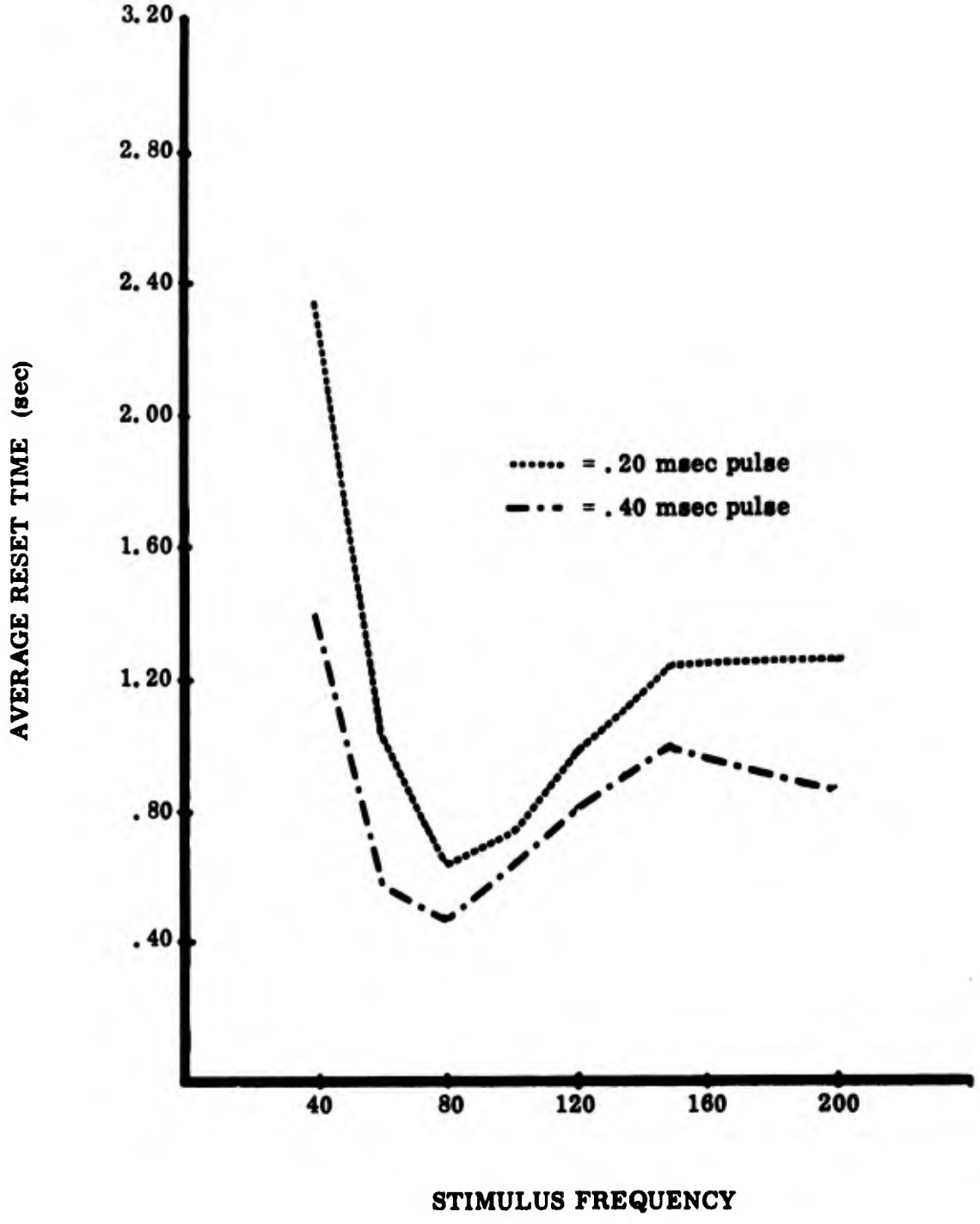

Figure 14. Reset time as a function of frequency and pulse duration.

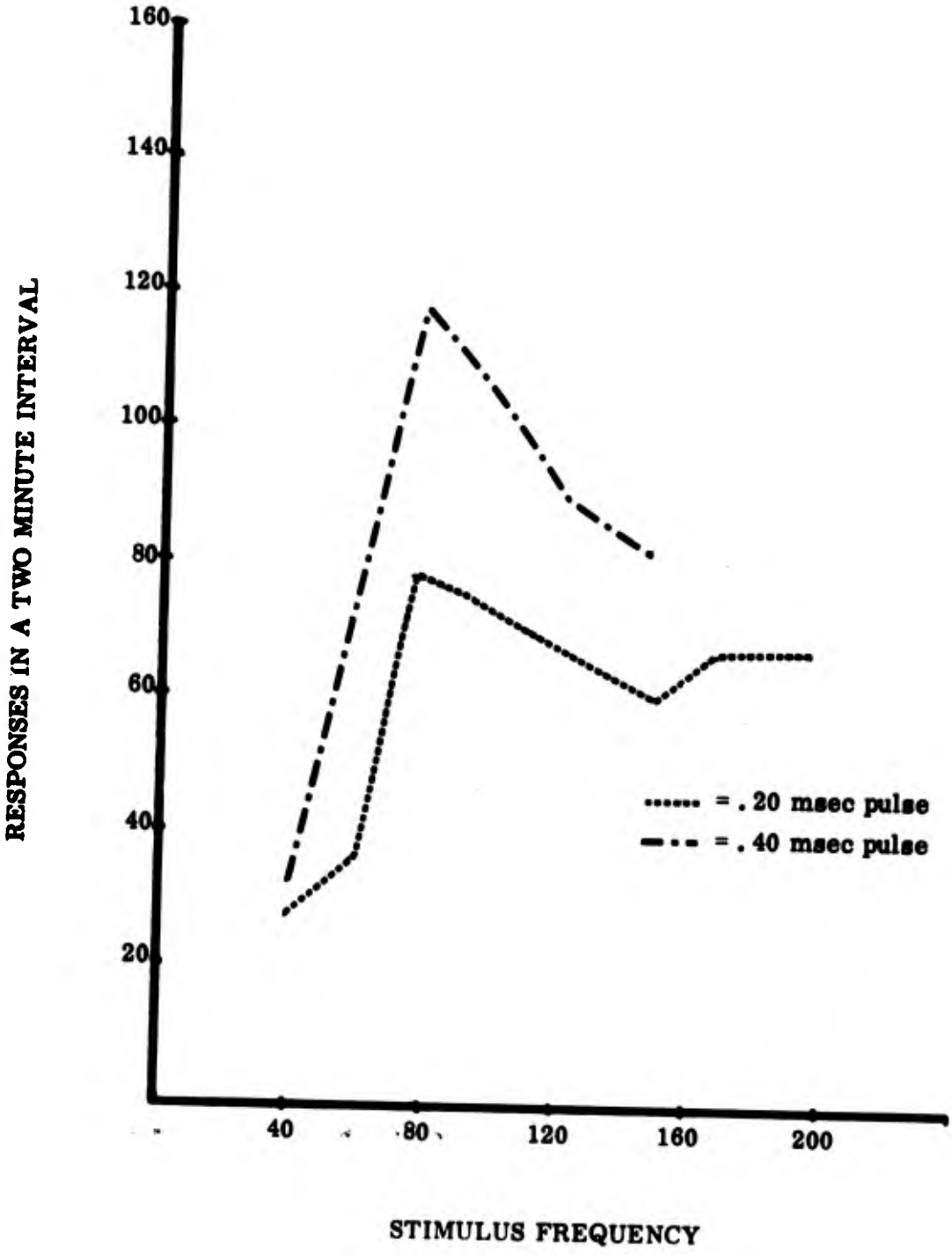

Figure 15. Response rate as a function of frequency on S-determined train schedule.

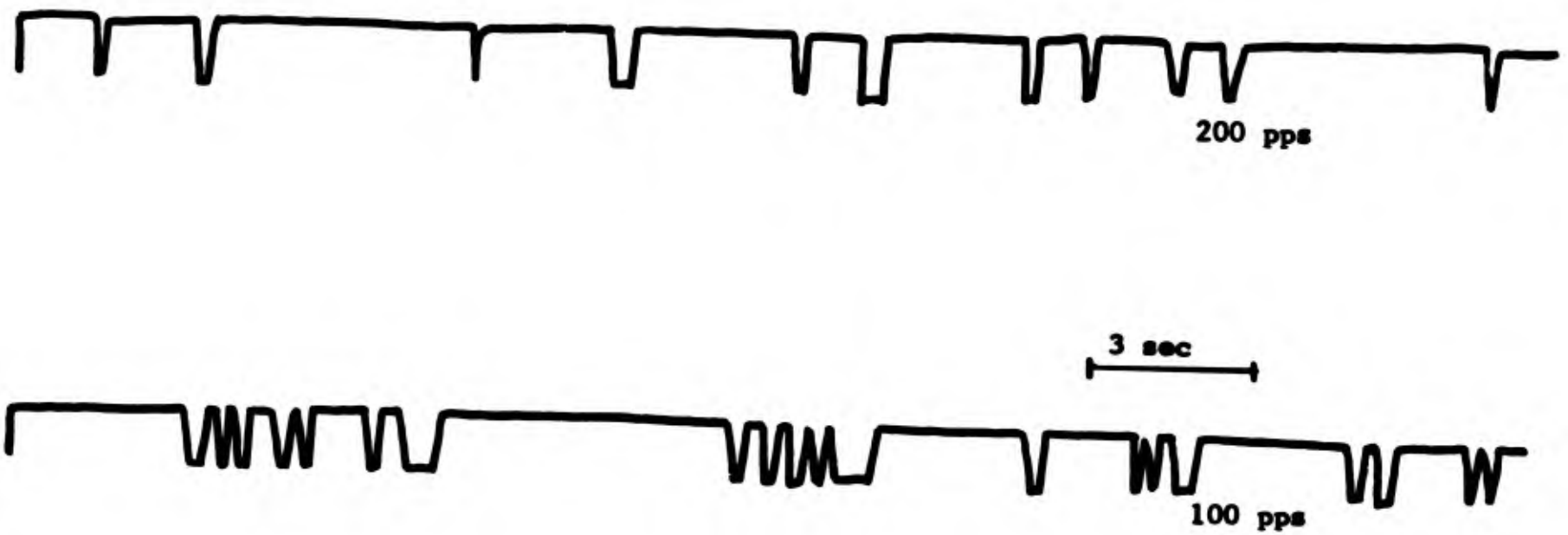

Figure 16. Response pattern for S-regulated schedule at different frequencies.

DISCUSSION

Self-stimulation rate is clearly a function of at least three variables: frequency, charge per train, and train duration. A number of general theories have been proposed to account for various aspects of the phenomenon:

I. Single factor theory

   A. Stimulus decay
   B. The channel capacity model

      1. Activation-arousal model
      2. Interference model

II. Two factor theory

   A. Deutsch's simultaneous activation model
   B. Stein's "rebound" model

Each of these models shall now be considered using the data of this study.

SINGLE FACTOR THEORIES

Stimulus decay

Keesey (Ref. 25) has argued that the decrement in CRF response rate as train duration is increased is due to a decay of excitation. The aversive behavior observed at longer durations could be due to frustrative non-reward (Amsel, Ref. 36). Mickle (Ref. 37) has discussed the exponential decay of current over time through stimulating electrodes when monophasic rectangular pulses are used. Such decay is due to polarization at the electrode tip, and can be eliminated by the use of biphasic stimulation. The waveform used in these experiments was monitored on a CRT during some tests, and found to be a biphasic square wave which did not decay. Thus current decay was excluded in this case.

Activation-arousal model

Single factor theory postulates a single substrate, the degree of activation of which determines the reward value. An inverted-U function describes the general curve, and the peak of the curve represents the optimal excitation. Duffy (Ref. 38) has been the main proponent of this activation theory, with Hebb's (Ref. 10) "level of arousal function" furnishing the neurophysiological correlate. Studies on sensory restriction (Schultz, Ref. 39) and novelty as reward (Berlyne, Ref. 40) emphasize such a curve.

Now we may assume that self-stimulation represents an increase or decrease in arousal. The general U-shaped function of the Q curves (Fig. 4) and the tendency to keep Q at a constant value in self-stimulation (Fig. 11) support the idea of an optimal level of arousal.

Autonomic measures of ACTH secretion (McHugh, et al., Ref. 14), some heart rate (Meyers, et al., Ref. 13), and DC potential (Wurtz, Ref. 16) studies support the view that self-stimulation is rewarding because it increases arousal level. Such a view could account for the on-off effect as an indication that an optimal level of Q exists, and readily explain self-stimulation and stimulus-bound feeding at the same electrode as increase of rewarding arousal.

The activation model is negated by the finding that the optimal Q for S-regulation (Fig. 11) was over four times greater than the peak Q for the self-stimulation curves (Fig. 4). If an optimal Q was present, the two values should coincide, and they do not.

Interference model

Alternatively, electrical stimulation may block local nervous activity, as shown by Cattell and Gerard (Ref. 41) for some high frequencies. Besides the fact that the highest frequency used in the present study was 200 pps, the same argument used for the activation-arousal model negates this approach.

TWO-FACTOR THEORIES

The two-factor theories are more prevalent. Their basic postulate is the existence of two antagonistic elements, either structural or functional, in the dynamics. Approach, pull, or "go" mechanisms and avoidance, push, or "stop" mechanisms as determinants of animal behavior have a long history (Schneirla, Ref. 42). The existence of antagonistic systems in the brain was found by Hess (Ref. 43), who termed them "ergotropic" (avoidance-sympathetic), and "trophotropic" (approach-parasympathetic), and delineated their anatomy. Olds and Milner (Ref. 44) discovered positive reinforcement and Delgado, et al., (Ref. 45) negative reinforcement by intracranial stimulation.

Gellhorn (Ref. 46) has done extensive work on the anatomy and dynamics of these antagonistic systems. The anatomical congruency (Olds, Ref. 47) of Hess' ergotropic and trophotropic with Olds' (Olds, et al., Ref. 19) negative and positive systems respectively, supports the idea that rewarding stimulation is calming and parasympathetic in action.

But the curvilinear nature of the curves suggests "too much calming" for high values of Q, and the problem becomes one of single factor theory, which has been dismissed.

Stein's rebound model

Stein's (Ref. 7) consideration of "rebound" is another option. The rebound phenomenon, known since the spinal reflex studies of Sherrington (Ref. 48), is that after activation of one member of an antagonistic pair, whether in muscle reciprocal innervation or central antagonistic systems, the second member will "rebound" with supernormal activity. Grastýan, et al., (Ref. 49) have shown that rebound occurs in recordings of hippocampal activity during stimulation of rewarding hypothalamic sites.

Rebound accounts for the "push" to the bar after a press as a need to alleviate a punishing rebound from the preceding stimulation, and the rapid extinction; with no rebound, the chain is broken. It also explains why SS rises quickly to a peak and then declines; enough Q for rebound is required to maintain SS, and higher Q simply increases rebound, decreasing self-stimulation.

A behavioral problem is found with the rebound concept: at high SS rates, the animal presses at a rate faster than once a train. Figure 6 demonstrates that time per press decreases to a minimum at maximum SS rate. Rebound accounts only for rebound at offset of the train, and hence no pressing at a time per press below the limit set by the train duration. However, the data show that time per press becomes proportionately smaller, and deviation from the set train actually increases with increasing duration. Obviously, if negatively reinforcing excitation drives the animal to the bar before offset, negative excitation must have been developing all along and has not suddenly appeared at offset.

Deutsch's two-factor model

Deutsch (Deutsch and Howarth, Ref. 5) notes (1) the inability to attain satiation, and (2) the rapid extinction of self-stimulation, and attempts to fit SS into his behavior system. Citing the findings of Sidman, et al., (Ref. 50) that high ratios of rewarded to non-rewarded trials were necessary to maintain self-stimulation, he comes to the same conclusion as Stein about self-stimulation being a vicious circle situation. Utilizing simultaneous activation of "motivational" and "reinforcement" pathways, he predicts increased feeding, for instance, at rewarding sites. But he cannot account for other drive effects such as hunger upon SS rate, nor can he account for on-off behavior, claiming that his system is not anatomical. Yet the findings of Valenstein and Valenstein (Ref. 26) showed on-off behavior to be present at all self-stimulating sites. Deutsch appears to have no place in his system for a negatively reinforcing system.

A proposed model

We propose a two factor model which we feel satisfactorily explains much, if not all, of self-stimulation behavior. In its general structure, it is most similar to that of Deutsch. Noting the problem with single-factor theory, i.e., the differences in peak Q for SS and S-regulation, which seem to indicate a developing negativity, an hypothesis may be stated: negativity increases with Q until a value of Q is reached which elicits pure avoidance.

Observing the S-regulation curve (Fig. 11), we note that nearly constant Q was maintained. Such strength-duration curves for the threshold of single nerve fibers follow a similar function (Scott, Ref. 51). These data are understood as indicating the aversive threshold for that electrode location.

Since the SS curve Q-peak is over four times smaller than the aversive threshold, we must conclude that "negativity" steadily increases with Q. Because of the shape of the SS curve, however, negativity must not increase as rapidly as positivity does with Q.

Choosing the single factor theory of the nerve impulse (Blair, Ref. 52), a simple first order differential equation describes the increase of an "excitability level" with Q:

$$\frac{dE}{dQ} = K\ (E_o - E) \tag{1}$$

where E_o = maximum excitability possible. Integrating,

$$E = E_o\ (1 - e^{-KQ}) \tag{2}$$

for the general equation. Applying the general equation to two separate positive and negative systems:

$$P = P_o\ (1 - e^{-KpQ}) \tag{3}$$

$$N = N_o\ (1 - e^{-KnQ}) \tag{4}$$

Making the assumption that effective positivity is the difference between positive and negative excitability levels, and self-stimulation rate is directly proportional to it,

$$\text{effective positivity} = P - N = \text{SS rate}$$

and substituting the quations for P and N,

$$\text{SS rate} = P_o\ (1 - e^{-KpQ}) - N_o\ (1 - e^{-KnQ}) \tag{5}$$

From the evidence that positivity increases more rapidly than negativity over Q, and assuming for the sake of convenience that their final excitability level is equal,

$$K_p > K_n;\quad P_o = N_o$$

which graphically is solved for (5) in Figure 17.

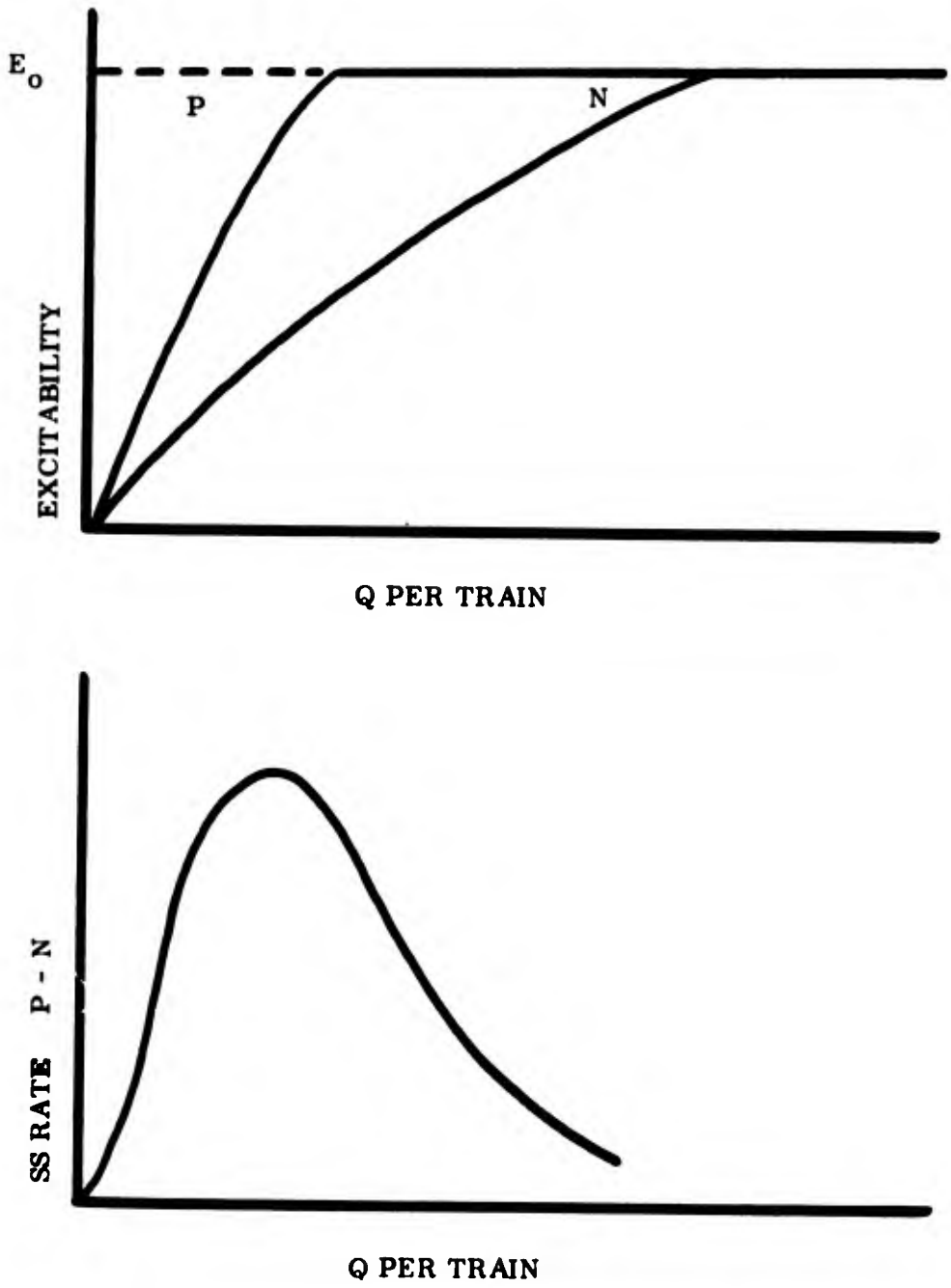

Figure 17. Excitability and self-stimulation rate.

It was found that the experimental data could be fitted using such assumptions of $K_p > K_n$ and $N_o = P_o$, setting an arbitrary value of 500 for N_o and P_o by the equation:

$$\text{SS rate} = 500 \quad (1 - e^{-.13Q}) - 500 \quad (1 - e^{-.013Q})$$

showing that $K_p = .13$ was ten times as large as $K_n = .013$.

Such a curve assumes that frequency and train duration are not independent variables, only Q. However, the data clearly show an increase in slope of SS versus Q (train) due to frequency, particularly below 100 pps. In the S-regulated curves, frequency was a definite factor in determining the aversive threshold. Figure 13 shows that Q needed to attain aversive threshold was an inverted-U function of frequency, showing a minimum at 80-100 pps and increasing on each side of that range.

Similar frequency effects have been found for thresholds of cortical stimulation in motor areas (Cure and Rasmussen, Ref. 53; Lilly, et al., Ref. 54; Mihailovic and Delgado, Ref. 55). Gengerelli, et al., (Ref. 3) found peak SS rate at 100 pps when Q per train was constant, as did we (Fig. 9). Coppée (Ref. 56) found that the Q needed to fire single fibers was an inverted-U function of frequency, and Hill (Ref. 57) has treated this resonance phenomenon theoretically.

A further variable remains. As seen in Figure 13, Q needed for aversive threshold increases with pulse duration. The phenomenon is known as accommodation, and has been found in single nerve, threshold for septal self-stimulation (Ward, Ref. 58), and treated theoretically (Hill, Ref. 57). Q needed is increased due to electrolytic injury to the tissue at longer pulse durations (Lilly, Ref. 59).

This effect of frequency upon aversive threshold explains the previously confusing increase in time/press above and below 80-100 pps at every train duration (Fig. 6); without the negative component being as large, the animal holds the bar down longer and thus the stimulation rate is lower at frequencies above and below 80-100 pps.

Self-stimulation rate at constant train over Q (freq) (Fig. 5) shows the SS curve expected but at different levels. This effect could be due to: (1) the fact that the animal just cannot stimulate as fast as train increases because of motor limitations, or (2) some effect of train duration analogous to pulse duration is present.

It is to be understood that equations (3 and 4) at a constant frequency are really functions of time as well as Q:

$$\frac{dE}{dt} = k\ (E_o - E) \qquad \begin{array}{l} k = \text{time constant} \\ K = \text{"charge constant"} \end{array}$$

$$N = N_o\ (1 - e^{-knt}) \tag{7}$$

$$P = P_o\ (1 - e^{-kpt}) \tag{8}$$

where $k_p > k_n$. Rashevsky (Ref. 60) has developed a similar two factor theory extensively for his "neuroelements."

S-regulation analysis

Analyzing S-regulated performance, we found a minimum in reset time (time between presses) and a maximum in self-stimulation rate at 80-100 pps. Comparing 100 pps and 150 pps graphically in terms of our mechanism, we can readily see that time/press for 150 pps should be much less than for 100 pps because of the higher rate of input. But to explain the increase in reset time above 100 pps without invoking an effect of frequency upon decay constant is more difficult. At offset, the two decay curves for 100 pps and 150 pps should be identical. Such a mechanism could not account for the increase in reset time above 100 pps.

Two factors play against each other in determining response rate. First, negativity up to a certain point drives the animal to the bar for the positivity which will alleviate the negativity. Secondly, negativity above a certain point results in active withdrawal from the bar because the negativity overwhelms any positivity that otherwise might alleviate it. Our equation (5) simply expresses this limiting factor of negativity; it does not assume the facilitatory effect of negativity upon response rate below and at the peak SS point, but bases response rate upon the amount of positivity available. As such, the equation represents a general limiting function, and this limitation must be recognized.

The increase in reset time can be explained by an increase in negativity which is too great and is accompanied by active withdrawal. Since no effect of offset decay can be held, we must conclude that the increase in reset time is not

on the level of each individual press, but on the averaged level. Using such a rationale, we predicted a change in response pattern. Figure 16 shows that such a change in response pattern was found, and a phenomenon of "bursting" was identified.

Bursting cannot be explained by an analysis of offset decay. It must be due to some sort of aftereffect. Two options are open: (1) rebound, and (2) summation. Rebound must be discarded due to the finding on set train analysis that the animal released the bar before the train was over. Summation in the negative system is much more likely.

Summation would explain all of the experimental results found by Stein (Ref. 7) which led to his postulation of rebound as the basis for self-stimulation, and also the electrophysiological results of Grastyán, et al., (Ref. 49). Apparent rebound is not true rebound, it is a continuing excitation of the negative system. This increase in reset time is the most important determinant of self-stimulation rate; even while time/press decreased from 100 to 150 pps, the increase in reset time was enough to lower the 150 pps response rate.

Finally, S-regulated performance showed that self-stimulation is not due to stimulation of a "pleasure center", but of two antagonistic systems, one pleasurable, the other avoidance-eliciting. If pleasure only were involved, the animal would hold the bar down and leave it down, and it certainly did not.

Set-train analysis

Analyzing set train data, we found that reset time reached a minimum at 100 pps and constant Q/train (Fig. 10), that increasing Q/train could move the peak frequency back to 60 pps due to the overriding influence of Q (Fig. 2), and that both time/press (Fig. 6) and reset time (Fig. 7) reached minima at the same point.

Similar to the model developed for S-regulation, the decrease in self-stimulation at higher Q was due to the increase in reset time (see Fig. 7). The increasing time/press helped this decrease in SS rate, and both effects combined to produce a drop in SS rate. Since the animal could not control the train duration, the train and therefore Q/train rather than the resonant effect played the major role. Figure 8 shows the change in pattern with increasing Q/train.

Increasing negativity first increased SS rate by decreasing time/press and reset time, then lowered it by continuing to decrease time/press while increasing reset time. Again, the increase in reset time is explained by summation in the negative system.

Anatomy

Although this study treated the self-stimulation mechanism as a black box, the parameters of the model tell us something about the anatomy. First, the relative concentrations of the positive and negative systems are known from the autonomic mappings of Hess (Ref. 43) and the self-stimulation mappings of Olds, et al. (Ref. 19). Areas of high positive density should show a slow increase of SS rate with Q, long S-regulation time/press with poor regulation, nearly pure parasympathetic autonomic effects, and a tendency toward seizures due to overdriving of the positive system. All of these are characteristic of the anterior hypothalamus and septal regions. Areas of high negative density should show a rapid increase of SS rate with Q, short S-regulation time/press with excellent regulation, largely sympathetic autonomic effects, and little chance of seizures since the excellent regulation prevents overdriving of the positive system. All of these are characteristic of the posterior hypothalamus. The model predicts epileptiform spiking in the high positive regions due to overdriving; it is to be noted that spikes are not necessary for self-stimulation, as has been shown by Bogacz and Olds (Ref. 61).

Finally, the greater time constant of the negative system reveals a greater latency of transmission in the negative system. Since the main source of latency in neural systems is synaptic delay, we conclude that the negative system is polysynaptic. Moruzzi and Magoun (Ref. 62) identified such polysynaptic systems as reticular. Amphetamine, known to affect the reticular formation above all other structures, raises self-stimulation rate (Stein, Ref. 7). For our model, this represents an increase in k_n. However, the increase in SS rate should be dependent upon the anatomical concentration of the negative system at the stimulation point, for further increase in k_n in a highly negative area means a decline in SS rate.

Self-stimulation as a measure of reward

It has been argued (Hodos and Valenstein, Ref. 34) that bar-pressing performance is not a valid measure of the reinforcing value of an intercranial stimulation, and our study supports the argument. Self-stimulation is an artifact, playing two systems against each other, and only reveals the existence of the two systems. Chemical stimulation is necessary to separate the pure reward system from the pure aversion system.

Once the animal is given one pulse, it must have another to alleviate the negativity of the first, and a chain is developed, from which the animal escapes only by seizure or exhaustion. With this model in mind, the peculiar facts of the necessity of priming, rapid extinction, and performance to exhaustion all fall into place. Results using VI schedules (Keesey, Ref. 25; Pliskoff, et al., Ref. 63; Sidman, et al., Ref. 50) and runways (Wetzel, Ref. 64) have shown how the intertrial interval is all important in maintaining self-stimulation. Our model also explains why Roberts (Ref. 23) found both self-stimulation and escape at the same electrode, same intensity. If the animal had no escape, it self-stimulated; if it could escape, it ran furiously and was reluctant to return.

Stimulus-bound feeding and drinking can be understood on the basis of the two time constants. If the electrode tip is in the lateral hypothalamic "feeding center", then the increasing negativity can be equated with increased hunger or thirst drive. Accordingly, there should be a delay between onset of stimulation and the elicited feeding. Also, self-stimulation rate and stimulus-bound feeding and drinking should be inverse functions of charge, which they are (Mogenson and Stevenson, Ref. 27).

Such a relationship of the specific drive of hunger and self-stimulation explains the problem of the "state" of the animal for an electrode located in that region. An increase in hunger means an increase in the neural activity of the negative component of the hunger "monitor", or for our model an increase in k_n. As described for drug effects, such an increase in k_n raises SS rate, and such a facilitatory effect of hunger upon SS rate has been observed (Brady, et al., Ref. 65; Olds, Ref. 66).

On-off behavior should occur for the model at all self-stimulation sites, and not just in "mixed" areas, because both systems must be stimulated simultaneously for self-stimulation to be maintained. Additionally, the model's

antagonistic systems explain why self-stimulation cannot be described as purely sympathetic or parasympathetic in autonomic effect. This study observed indices of aversion (vocalization, active avoidance, defecation) and of approach (active approach, ejaculation) in the same test session. Such dual effects are explainable with our two factor model.

A further characteristic of self-stimulation was noted: the S continually gnashed its teeth, an indication of anxiety in the rat. Gellhorn (Ref. 67) has hypothesized that anxiety is observed when both activating (negative) and synchronizing (positive) systems are activated simultaneously. In behavioral terms, anxiety contains both approach and avoidance.

In conclusion, this study supports a two-factor model of the self-stimulation mechanism which predicts (1) the shape of self-stimulation curves and changes in stimulation rate as a function of stimulus parameters, (2) dual autonomic effects of self-stimulation, (3) stimulus-bound feeding and self-stimulation at the same electrode, same intensity, (4) on-off behavior at all self-stimulation sites, and (5) changes in all of the above with changes in anatomical locus.

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13. ABSTRACT

A self-stimulation and E-controlled stimulation study was completed in one rat. The study supports the two-factor model of the self-stimulation mechanism which predicts (1) the shape of self-stimulation curves and changes in stimulation rate as a function of stimulation parameters, (2) dual autonomic effects of self-stimulation, (3) stimulus-bound feeding and self-stimulation at the same electrode site, (4) on-off behavior, and (5) changes in the above with changes in anatomical locus.

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