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The Effects of Non-Contingent Stimulation
on Brain Stimulation Reward

Selena Walker

Thesis presented to the
School of Graduate Studies and Research
at the University of Ottawa
in partial fulfillment of the requirements for a
Master of Arts degree.

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Dedication

To my mother Bernadette and my father Don,
without whose support this task
would have been impossible to accomplish.

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Introduction

With the discovery that rats would repeatedly perform an operant task which resulted in the electrical stimulation of their own brains (Olds & Milner, 1954) researchers began to speculate about the use of self-stimulation as a tool to study the neural circuitry underlying motivated behaviour. Although Olds and Milner's pioneering study postulated that there were no major differences between intracranial self-stimulation and operant responding for conventional rewards such as food and water, other researchers have demonstrated that self-stimulation extinguished more quickly (Culberton, Kling & Berkley, 1966; Deutsch & Howarth, 1963; Seward, Uyeda & Olds, 1959), could not be adequately maintained on low density reinforcement schedules (Brodie, Moreno, Malis & Brodie, 1960; Sidman, Brady, Boren, Conrad & Schulman, 1955), and did not satiate as did the more conventional reinforcers (Olds, 1958a; Valenstein & Beer, 1964). The idea that self-stimulation is mediated by brain circuits that ordinarily respond to conventional reinforcers could not be supported if these differences in quantity and temporal pattern were, in some way, fundamental.

Researchers have demonstrated that the method of reinforcement delivery can artificially produce differences in the acquisition of an operant response rewarded with food and water or rewarded with intracranial self-stimulation (Gibson, Reid, Sakai & Porter, 1965; McIntire & Wright, 1965; Pliskoff, Wright & Hawkins,

1965). Gibson et al. (1965) proposed that the major difference between biological reinforcers and rewarding brain stimulation was the delay associated with the reward. Associated with food and water reinforcers was a chain of behaviour in which the animal must perform the operant task before performing the consummatory response. The consummatory response refers to the point in the chain of behaviour when the subject obtains the reward and, in the case of food and water rewards, actually consumes the reward. According to Gibson et al. the consummatory response is associated with brain stimulation reward since the delivery of the reward coincides with the operant task. Thus with conventional rewards there is a delay imposed between the performance of the operant task and the consummatory reward whereas with brain stimulation reward there is little or no delay, the performance of the operant response and the consummatory response occur almost simultaneously.

To test their hypothesis that the delay associated with the reinforcer rather than the reinforcer itself artificially induced differences between the types of reinforcers, Gibson et al. (1965) equated the methods of reward delivery. One method of reward delivery, likened to the procedure commonly used with conventional rewards, required the subject to press a lever which activated a dipper located a small distance away. The dipper provided either brain stimulation reward or sugar-water. The second method, similar to that used with brain stimulation reward, required the subject to contact the dipper which delivered either rewarding

brain stimulation or sugar-water immediately. Gibson et al. noted that regardless of the reinforcer received there was no difference in the acquisition, rates, and extinction of responding when subjects were tested with the same method of reward delivery. Differences were found, however, between subjects which were tested with different methods of reward delivery. The extinction of an operant response was also found to be affected by the delay associated with the reinforcer; rats in which a delay was imposed between the performance of the operant task and the consummatory response were more resistant to extinction than rats in which the operant task coincided with the consummatory chain (McIntire and Wright, 1965).

Pliskoff, Wright & Hawkins (1965) modified the procedure involved in the delivery of the reinforcer to the rat in order to test for differences in responding for intermittent schedules of reinforcement for intracranial self-stimulation. Previous studies had indicated that rats would not maintain responding for low density reinforcement schedules (Brodie, Moreno, Malis & Brodie, 1960; Sidman, Brady, Boren, Conrad & Schulman, 1955). In order to equate the delivery of brain stimulation with the delivery of the more conventional rewards, Pliskoff et al. required the rat to respond in a two lever paradigm where responding on one lever controlled the schedule of reinforcement and lever-pressing on the other delivered the brain stimulation. Using that method of reward presentation Pliskoff et al. found that rats would maintain responding for schedules of reinforcement in the range of

parameter values consistent with those used for conventional food reinforcers.

Thus the apparent differences—rapid acquisition, quick extinction, and the inability to maintain responding on low-density schedules of reinforcement—between conventional biological reinforcers and brain stimulation reward disappeared when the methods of reinforcement delivery were made equivalent (Hogan & Roper, 1978; Mogenson & Cioe, 1977). Of course this in no way proves that self-stimulation and conventional reinforcers exploit the same neural circuits but it does reduce the apparent differences in responding to the status of artifact.

The delineation of the anatomical loci which support intracranial self-stimulation was of concern to researchers investigating the neural substrate for brain stimulation reward. In their study, Olds and Milner (1954) determined that a number of sites distributed throughout the brain would support self-stimulation. Olds (1958b) in a comprehensive study of self-stimulation structures also noted that a number of brain sites, from the midbrain through the hypothalamus and the thalamus into the cortical and subcortical regions of the rhinencephalon, mediated primary rewarding effects. In a subsequent study Olds and Olds (1963) tested a variety of electrode placements for their rewarding or punishing effects. The highest rates of self-stimulation with no evidence of escape behaviour in the rats were obtained from sites along the medial forebrain bundle, although the posterior and anterior extremes of the bundle seemed

to elicit escape tendencies as well as high rates of self-stimulation. To summarize, sites which produced positive reinforcement were widely distributed along the medial forebrain bundle.

The catecholamine theory of reward states that catecholaminergic neurons play a critical role in the mediation of brain stimulation reward. Evidence to support this theory has been derived from anatomical studies, indicating that there is a high degree of correlation between self-stimulation loci and structures located along the catecholamine pathways (German & Bowden, 1974; Wise, 1978), and from pharmacological studies which generally show that drugs which influence the action of catecholamines also influence intracranial self-stimulation in a like manner (Fibiger, 1978; German & Bowden, 1974; Wise, 1978). Studies which have investigated the effects of dopamine receptor blockers on self-stimulation have demonstrated that the antagonist pimozide interferes with the rewarding value of the stimulation rather than with the animals' ability to perform the task (Fouriezos & Wise, 1976; Franklin, 1978; Gallistel, Boytim, Gomita & Klebanoff, 1982; Fantie, 1984), suggesting that dopamine plays a significant role in mediating brain stimulation reward.

A number of studies, however, have demonstrated that the reward fibres along the medial forebrain bundle are small and myelinated with refractory periods ranging from 0.8 ms to 1.2 ms (Bielajew, Jordan, Ferme-Enright & Shizgal, 1981; Bielajew, Lapointe, Kiss & Shizgal, 1982; Yeomans, 1975; 1979), conduction

velocities between 1.0 m/s and 8.0 m/s (Bielajew & Shizgal, 1982; 1986; Shizgal, Bielajew, Corbett, Skelton & Yeomans, 1980), with the direction of conduction rostral-caudal or descending (Bielajew and Shizgal, 1986). Since dopamine fibres are unmyelinated, recovery from refractoriness is greater than 2.5 ms, generally conduction is generally less than 1 m/s, and are oriented in a caudo-rostral direction, these studies have led researchers to propose that although the neurons involved in the first stage of the reward process, the directly driven neurons, are non-catecholaminergic, the catecholaminergic neurons do play a critical role in the mediation of brain stimulation reward, probably at some point downstream of the medial forebrain bundle self-stimulation sites (Gallistel, Shizgal & Yeomans, 1981).

Studies investigating the effects of amphetamine, an indirect dopamine agonist, on intracranial self-stimulation have implicated a role for dopamine in the mediation of brain stimulation reward. The facilitation of self-stimulation by amphetamine has been well-documented (Domino & Olds, 1972; Olds, 1970; Stein, 1962; Stein & Ray, 1959). Amphetamine is thought to facilitate brain stimulation reward by inhibiting the reuptake of catecholamines from the synaptic cleft and by producing a leakage of dopamine from the presynaptic terminals (Von Voightlander & Moore, 1973). It is important to remember that indirect dopamine agonists such as amphetamine require that dopamine be present in the presynaptic terminals or in the synaptic cleft before amphetamine can enhance the release of or inhibit the reuptake of

dopamine. The increase in the level of dopamine at the synapse enhances the transmission of dopamine and is thought to result in the facilitation of brain stimulation reward.

Apomorphine, a direct dopamine agonist (Ernst, 1967; Ernst & Smelik, 1966), has also been studied in hope of elucidating the neurotransmitter involved in brain stimulation reward. Apomorphine differs from amphetamine in its mode of action. As a direct agonist apomorphine mimics the action of dopamine at the post-synaptic receptor site (Ernst, 1967; Ernst & Smelik, 1966) while amphetamine, an indirect agonist, enhances the release of dopamine and blocks the reuptake of dopamine from the synaptic cleft (Von Voightlander & Moore, 1973). Direct dopamine agonists do not require the presence of the neurotransmitter at the synapse since direct agonists, because of their biochemical similarities to dopamine, can stimulate the dopamine postsynaptic receptors directly.

Although a number of researchers have investigated the effects of apomorphine upon self-stimulation rates it is important to remember that a number of problems exist, most notably the inability to distinguish performance from reward effects using rate-dependent measures. . In 1973, Wauquier and Niemegeers tested the effects of doses of apomorphine injected subcutaneously upon self-stimulation in the rat. The authors discovered that low doses of apomorphine increased responding for rewarding brain stimulation while high doses of the drug caused responding to decrease in a dose-dependent manner. Broekkamp and van Rossum

(1974), in a similar experiment, determined that apomorphine increased rates of responding for brain stimulation in some subjects while inhibiting rates of responding in others. Broekkamp and van Rossum proposed that due to the take-over of the reinforcing effects of dopamine by the direct agonist apomorphine the rewarding value of the stimulation was diminished; therefore rats were reinforced by the behaviour they were performing at the time. Rats which were self-stimulating while apomorphine was exerting its effect increased responding for rewarding brain stimulation while rats performing alternative behaviours during apomorphine's effect increased these behaviours, and thus the rate of self-stimulation decreased.

Herberg, Stephens and Franklin (1976) also examined the effects of apomorphine upon brain stimulation reward. Apomorphine at low doses decreased self-stimulation while at the high doses self-stimulation was initially suppressed and then followed by an enhancement of self-stimulation rates. In a similar study Stephens and Herberg (1977) replicated the effects of apomorphine upon self-stimulation. The researchers reasoned that direct agonists would activate post-synaptic receptors independently of the animals' operant response perhaps causing a general arousal but disrupting operant responding such as self-stimulation.

A number of other direct dopamine agonists have been shown to disrupt intracranial self-stimulation. It is thought that the direct agonists do so by stimulating the dopamine receptors

independently of nerve-impulses and thus dissociate the reinforcing effect of the stimulation from the operant task. Herberg and Stephens (1975) tested the effects of amantadine upon rates of self-stimulation. Amantadine is a drug which acts as both a direct (Von Voigtlander & Moore, 1971) and an indirect (Von Voigtlander & Moore, 1973) dopamine agonist. Like amphetamine amantadine inhibits the reuptake of catecholamines from the synaptic cleft and enhances the release of dopamine. Unlike amphetamine the intraventricular administration of amantadine results in an impulse-independent release of dopamine. Herberg and Stephens found that intraperitoneally injected amantadine caused the rates for self-stimulation to initially decrease and then to increase. They concluded that the initial decrease in self-stimulation rates was due to the impulse-independent release of catecholamines which generated reward signals non-contingently and thereby disrupted lever-pressing for brain stimulation reward.

Franklin and Herberg (1977) tested the effects of intraventricular tyramine, a direct dopamine agonist, for its effects upon responding for brain stimulation reward. The authors found that low doses of tyramine caused a slight elevation in responding for brain stimulation reward but that increasing the dosage either had no effect or had strongly depressing effects upon rates of self-stimulation. Franklin and Herberg suggest that the depression of the self-stimulation rates was due to the dissociation of reward from the operant task by the non-contingent stimulation of the reward neurons.

The problems associated with the use of rate-dependent measures to determine the effects of pharmacological substances upon intracranial self-stimulation are well documented (Hodos & Valenstein, 1962; Valenstein, 1964). Performance and reward deficits cannot be dissociated. Performance deficits are effects which interfere with the ability of the animal to engage in the operant behaviour while reward effects are those which alter the rewarding value of the brain stimulation. Unfortunately each of the experiments described so far, designed to test the effects of apomorphine upon operant responding for rewarding brain stimulation, has employed rate as the dependent measure. This makes it difficult to interpret whether the effects of apomorphine were due to an alteration in the subjects' ability to perform the operant task or whether the effects were due to an alteration in the rewarding value of the stimulation.

A few studies, however, have used intensity thresholds to measure the effects of direct agonists. In 1982 Carey tested the effects of apomorphine upon self-stimulation rates obtained at three levels of intensity. He reported that apomorphine suppressed low rates of responding at low doses but that apomorphine was ineffective at high doses. Carey concluded that apomorphine produced a performance deficit but did not exert any effect upon the reinforcing value of the stimulation. Upon examination of the data presented, however, it appears that apomorphine did indeed affect the rewarding value of the stimulation; the intensity required to maintain half-maximal rates of responding seemed to

shift towards higher intensities as the dose of apomorphine increased. Nonetheless, since a full range of intensities was not tested and therefore the curve representing the reward summation function was incomplete, the conclusion that apomorphine interfered with the rewarding value of the stimulation remains tentative.

Strecker, Roberts and Koob (1982) also tested the effects of apomorphine on intensity thresholds for intracranial self-stimulation in rats with stimulating electrodes in the posterior hypothalamus. Half of the subjects tested were lesioned with 6-hydroxydopamine in the nucleus accumbens prior to treatment with apomorphine administered subcutaneously. The researchers noted that apomorphine resulted in suppressed rates of responding in unlesioned rats compared to unlesioned rats injected with saline whereas there was an increase in the rates of responding in the lesioned rats. Strecker et al. concluded that apomorphine facilitates brain stimulation reward. Nevertheless, if one examines the figure presented in the study in which current is plotted against rate, it appears that apomorphine suppressed maximal rates of responding for rewarding brain stimulation in sham lesioned rats but had no effect upon lesioned rats. Furthermore, the half-maximal threshold for the stimulation in sham lesioned rats was unaffected whereas it was decreased in lesioned rats. A possible explanation is that the lesion resulted in the supersensitivity of the denervated neurons to the administered apomorphine. In unlesioned rats a moderate dose of

apomorphine, such as the 0.1 mg/kg dose tested in this study, is thought to act on both the presynaptic and the postsynaptic receptors. Presynaptic activation inhibits the neurons involved in brain stimulation reward while postsynaptic activation directly stimulates the postsynaptic receptors (Skirboll, Grace, & Bunney, 1979). Thus in the sham lesioned rats the moderate dose of apomorphine, acting both to inhibit (presynaptic activation) and excite (postsynaptic activation) the reward neurons, did not effect frequency thresholds for brain stimulation reward. However, in the lesioned rats the denervated neurons may have become supersensitive causing the moderate dose of apomorphine to act like a high dose, thereby producing behavioural results similar to those obtained with high doses of apomorphine in controls; frequency thresholds were decreased.

Taken together, the results of the studies of direct agonists reported so far are inconclusive. Studies using the rate-dependent measures are unable to distinguish the performance from the rewarding effects of the drug upon self-stimulation. Carey (1982) reported the effects of apomorphine at three intensity levels and it appeared that apomorphine enhanced the rewarding value of the stimulation. The reward summation function, however, was incomplete rendering the results tentative. The results of the study by Strecker et. al. (1982) are also inconclusive; it appeared that apomorphine increased the rewarding value of the brain stimulation in lesioned rats but the shift was small and possibly non-significant.

In 1983 Francis tested the effects of five doses of apomorphine upon the frequency thresholds for brain stimulation reward. Francis determined that low doses of apomorphine produced shifts in the frequency thresholds toward higher pulse numbers, indicating that the rewarding value of the stimulation had decreased. Higher doses of the drug resulted in an initial shift toward greater pulse numbers followed by a shift toward lower pulse numbers and a subsequent shift toward higher pulse numbers, suggesting that the rewarding value of the stimulation had increased, then decreased, and once again increased over the time course of the drug. The researcher hypothesized that the increase in frequency thresholds at the low dose of apomorphine reflected the presynaptic inhibition of the reward process (Skirboll, Grace & Bunney, 1979). The initial decrease in frequency thresholds at the moderate doses of apomorphine also reflected the activation of the presynaptic receptors while the concentration of the drug was still low. As the concentration of the drug increased the post-synaptic receptors would be activated (Skirboll, Grace & Bunney, 1979). Thus at moderate doses of apomorphine both the presynaptic and the postsynaptic receptors would be activated. Activation of, predominantly, the post-synaptic receptors would occur at the high doses of apomorphine and would result in a facilitation of intracranial self-stimulation. As the concentration of the apomorphine increased maximum activation of the postsynaptic receptors would non-contingently reward the animal rendering it unable to distinguish between the rewarding

effects of the stimulation and the rewarding effects of the drug. The bombardment of the post-synaptic receptors would cause a decrease in the frequency thresholds for brain stimulation reward. Francis suggested that at high doses of apomorphine the stimulation of the post-synaptic receptors acted as a "free-reward" as Broekkamp and van Rossum (1974) postulated. To summarize Francis' findings, low doses of apomorphine are thought to activate the presynaptic receptors thereby inhibiting the reward process and causing an increase in the frequency threshold for self-stimulation. At the high doses of apomorphine the post-synaptic receptors were stimulated resulting in the enhancement of brain stimulation reward. Bombardment of the postsynaptic receptors, as is thought to occur with the highest concentrations of apomorphine, would render the self-stimulating animal unable to distinguish between the rewarding value of the drug and that of the brain stimulation.

In a similar study Leith (1983) tested the effects of three doses of apomorphine upon reward summation functions, from which the rewarding value of brain stimulation can be inferred by plotting the rate of responding for self-stimulation against the intensity of the stimulation required for brain stimulation reward. She found that at all doses of apomorphine the intensity threshold for self-stimulation increased indicating the rewarding value of the stimulation had decreased. There was no effect of apomorphine upon self-stimulation rates except at the higher doses which impaired responding for the brain stimulation. At the

highest dose the reward summation function flattened, indicating that the animals' behaviour was no longer influenced by the rewarding value of the stimulation. Leith proposed that the highest drug dose produced conditions comparable to those obtained when non-contingent stimulation was delivered to the rat. To test her hypothesis Leith delivered continuous, non-contingent stimulation with parameters which produced optimal responding and compared the patterns of responding to those obtained under the highest drug condition. She discovered that the patterns of responding were similar suggesting that the flattened reward summation curve obtained at the highest dose of apomorphine reflected the non-contingent stimulation of the neurons supporting brain stimulation reward. Leith qualifies her findings, noting that rats would not self-stimulate when administered the high doses of apomorphine if the rewarding brain stimulation was no longer available. She concluded that apomorphine mimicked the current but that the stimulation was necessary to motivate the animal to perform the operant task.

To summarize, we have seen that direct agonists have varied effects on rates of responding for intracranial self-stimulation. Low doses of the direct agonist apomorphine increased thresholds for self-stimulation. Higher doses of the apomorphine produced an initial increase in self-stimulation frequency thresholds, followed by a decrease and a subsequent increase, whereas intensity thresholds are increased by high doses of apomorphine. Various explanations have been proposed to account for the varied

findings of experiments attempting to determine the effects of direct agonists on intracranial self-stimulation. In one form or another, most of the explanations have employed the notion of free reward; apomorphine and other direct agonists are thought to influence self-stimulation because of their non-contingent bombardment of post-synaptic receptors normally driven by electrical stimulation (Franklin & Herberg, 1977; Herberg & Stephens, 1975; Herberg et. al., 1976; Stephens & Herberg, 1977). The idea is powerful in that it alone may explain both the enhancement and the disruption of self-stimulation. At doses of direct agonists that are just sufficient to stimulate post synaptic receptors, this activation would add to the electrically derived stimulation to increase rates of response or decrease thresholds. Dose related increases in rates or decreases in threshold should continue as long as the post-synaptic elements are not saturated by the combination of drug and electrically driven neurotransmitter. ~~At very high doses the agonists alone may saturate the system, such that the electrical activation adds nothing to the final result. This would effectively break the contingency between response (lever pressing) and reinforcement (electrical stimulation) and thereby might result in depressed responding.~~ (Note that the free reward explanation is restricted to concentrations of agonist that are sufficient to activate post-synaptic receptors; the inhibitory effects seen with the very low doses of apomorphine are thought to result from the activation of pre-synaptic receptors which down-regulate transmitter output

(Skirboll et. al., 1979).) Although the explanations that have been put forth to explain the action of direct receptor agonists make use of the concept of free or response-independent reward, no one has a clear idea of what free reward should be expected to do to self-stimulation.

There have been two attempts to electrically model the effects of response-independent activation of the reward substrate by using brain stimulation not only as the response-contingent reward but also as the non-contingent or free reward. Herberg (1962) delivered non-contingent stimulation to a group of rats and discovered that they would not lever-press during the presentation unless non-responding resulted in the termination of the non-contingent stimulation. Herberg concluded that the non-contingent stimulation was rewarding but disrupted the animals' behaviour.

Leith (1983) also attempted to model the effects of direct agonists when she delivered suprathreshold, non-contingent stimulation to rats which had been trained to self-stimulate. She reported that the pattern of responding for the brain stimulation reward was similar to that obtained from self-stimulating rats which had been administered a high dose of apomorphine. The delivery of non-contingent stimulation which was already above threshold intensity caused the lever-pressing behavior of the rat to be disrupted. This disruption was reflected by a pattern of responding similar to that obtained when the rat was administered high doses of apomorphine. At high doses of apomorphine the reward

summation function was flattened—rates of responding at low intensities were increased while at high intensities the rates were decreased—indicating that the intensity of the stimulation no longer influenced and thereby disrupted the animal's behaviour. This disruption of the behavior makes it difficult to assess the non-contingent stimulation as an effective model for the effects of apomorphine.

In the present series of experiments we have attempted to model the effects of non-contingent stimulation or "free reward" by delivering subthreshold levels of non-contingent brain stimulation to self-stimulating rats. The presentation of subthreshold levels of "free reward" during brain stimulation reward allowed us to activate the reward substrate in a manner that resembles the low level of continuous, free reward that is thought to occur in pharmacological trials with receptor agonists. To measure the effect of the non-contingent stimulation upon frequency thresholds, the frequency thresholds for brain stimulation reward with and without the superposition of non-contingent stimulation were compared. It is important to note that although this work was initiated by a consideration of how apomorphine influences self-stimulation, the present set of experiments employed no drug; the non-contingent stimulation used throughout this thesis comprised electrical impulses identical to the ones that composed the trains of rewarding stimulation. The stimulation was deemed to model the direct receptor agonists in the conceptual sense that it could be used to administer

controlled, low levels of free reward.

The objective of the present set of experiments was to examine the effect of subthreshold levels of non-contingent stimulation upon frequency thresholds for brain stimulation reward. In Experiment 1 the effect of non-contingent stimulation upon rates of responding and frequency thresholds for self-stimulation was documented. In Experiment 2 we evaluated the relationship between the summation levels and the magnitude of the rewarding effect of the non-contingent stimulation. A significant correlation would indicate that the summation levels could be used to predict the magnitude of the non-contingent stimulation effect. An evaluation of the parametric robustness of the paradigm was conducted in Experiment 3 where the effect of the non-contingent stimulation was evaluated at different frequency thresholds for self-stimulation. In these three experiments we found that the delivery of the non-contingent stimulation resulted in a decrease in the frequency thresholds for brain stimulation reward. This decrease was equivalent to the frequency of the non-contingent stimulation indicating that the contingent and the non-contingent stimulation summated perfectly. In Experiment 4 we wished to determine if the summation was occurring solely during the self-stimulation trains or if the summation occurred outside the train of rewarding stimulation. Elimination of the non-contingent stimulation effect by the presentation of the non-contingent stimulation outside the train of rewarding stimulation would suggest that the summation occurred solely within the

self-stimulation train.

EXPERIMENT 1

In an attempt to study the effects of the administration of continuous low level brain stimulation we delivered non-contingent stimulation pulses to self-stimulating rats. To mimic a pharmacological bombardment as well as possible, a steady stream of low frequency pulses was continuously applied while the rats were pressing a lever to earn trains of response-contingent stimulation. The non-contingent pulses were uninterrupted; they were administered during response-contingent trains of stimulation, between trains, and even at times between trials when self-stimulation was prohibited. The non-contingent stimulation was subthreshold which was defined as stimulation for which subjects would not perform an operant task. The non-contingent stimulation was delivered at frequencies of 2, 5, 10, and 20 Hz, frequencies which never exceeded 75% of the animals' frequency thresholds. Rats were implanted with bilateral electrodes in the lateral hypothalamus.

In an effort to determine the effects of non-contingent stimulation contingent and non-contingent pulses were delivered to the same electrode. The parameters of the contingent and the non-contingent stimulation were identical with the exception of the frequencies at which they were presented. We compared frequency thresholds when response-contingent stimulation was delivered to the frequency thresholds obtained when both the background and the contingent stimulation were presented. This comparison allowed the determination of the effects of the

non-contingent stimulation upon the rewarding value of the response-contingent stimulation. Comparing the asymptotic rates of responding during the presentation of the contingent stimulation alone and during the presentation of the non-contingent stimulation would enable us to determine the existence of any performance-related effects of the non-contingent stimulation.

In order to fully document the effects of the background stimulation upon intracranial self-stimulation the contingent stimulation was delivered to one electrode while the background stimulation was delivered to the contralateral electrode. As in the unilateral case, described above, the background stimulation was subthreshold. The parameters of the contingent and the non-contingent stimulation were identical except for the frequencies at which each was presented. In addition to the main objective of Experiment 1 which was to document the extent to which non-contingent stimulation interacts with response-contingent stimulation, a secondary objective was to evaluate the degree to which the effects of non-contingent stimulation are related to the rewarding effect of this stimulation. As long as non-contingent stimulation is applied to the same electrode that receives the response-contingent stimulation, and as long as the remaining stimulation variables are held constant, any effect of non-contingent stimulation should be related to its pulse frequency. In the bilateral situation, however, stimulus pulses applied to one electrode may, and usually do, have rewarding effects that do not sum perfectly with those

obtained from the electrode's contralateral partner (Shizgal et. al., 1980). For example, two electrodes implanted in opposite hemispheres may each have frequency thresholds of 40 Hz but, when self-stimulation tests are conducted with pulses applied to both electrodes at roughly the same time, the frequency threshold of the combined stimulation is often greater than the predicted 20 Hz. This failure to perfectly transmit rewarding effects across the hemispheres is a common feature of bilateral implants and it is attributed to differences in the exact placement of the two electrodes. In testing the effects of non-contingent stimulation applied to the electrode contralateral to the one receiving the response-contingent stimulation, we anticipated that the non-contingent stimulation effect may transfer over imperfectly. To see if the transfer of the non-contingent stimulation effect was related to the transfer of the rewarding effect, a separate set of "summation" tests were also conducted to obtain estimates of reward summation.

Thus, there were three sets of sessions in this first experiment. First, each electrode was tested separately with response-contingent trains of stimulus pulses applied against a background of low frequency, continuous stimulation. Second, each electrode received the response-contingent trains while its contralateral mate received the non-contingent stimulation. Because of the inherent asymmetry of the preparation, each bilaterally implanted rat contributed two different sets of data. Third, each rat underwent a set of summation tests wherein the

reward summation between the two electrodes was estimated using response-contingent (only) trains of pairs of pulses with each member of the pairs administered to different electrodes.

Method

Subjects and Surgery

Subjects were four male, Long-Evans rats weighing between 300 and 500 g at the time of surgery. Rats were housed individually in clear plastic cages measuring 46 cm x 24 cm x 20 cm with wire tops. Maintained on a 12 hour light/dark cycle (7:00 am onset), rats were provided with continuous access to Purina Rat Chow and tap water.

In preparation for surgery rats were given a 65 mg/kg dose of somnotol intraperitoneally. Rats were also injected subcutaneously with 0.2 cc of 0.5 mg/ml atropine sulfate in saline to prevent mucus accumulation in the lungs. Furthermore, rats' ears, snouts, and upper palates were liberally anointed with xylocaine, a local anaesthetic, to prevent discomfort which could have arisen from the pressure of the ear bars, snout bar, and upper incisor bar.

Each rat was stereotaxically implanted, using a Stoelting stereotaxic instrument, with bilateral electrodes aimed at the lateral hypothalamus. Electrodes were made of stainless steel wire, 250 μ in diameter, soldered to gold-plated amphenol pins. Electrodes were insulated with Formvar to the tip and then were manually polished flat thus producing a tip exposure of 0.05 mm². The current return assembly consisted of a wire wrapped around

three skull screws and soldered to an indifferent connector. The electrodes and the current return assembly were affixed to the rat's skull with dental acrylic. The flat skull co-ordinates (Paxinos and Watson, 1982) used for the rats were as follows: 3.3 mm posterior (P) to bregma, 1.7 mm lateral (L) to the midline suture, and 8.5 mm ventral (V) to the surface of the skull for S16; 2.8 mm P, 1.7 mm L, and 8.0 mm V for SJ19; and 2.0 mm P, 1.7 mm L, and 8.0 mm V for S28. One rat SJ15 was implanted with DeGroot (1959) co-ordinates: 0.5 mm P, 1.7 mm L, and 8.0 mm below the dura.

Following surgery the wound was sutured and treated with neosporin, a topical antibiotic, in order to help prevent bacterial infection. Rats were allowed a recovery period of at least three days before screening for self-stimulation began.

Apparatus

Rats were tested in a wooden Skinner box with a clear Plexiglas front door and removeable wooden top. The box measured 46 cm x 28 cm x 50 cm. The Gerbrands lever was situated on the center of the right hand wall of the box and was 3 cm from the floor of the box. The floor of the Skinner box consisted of a removeable tray lined with shelf-liner and covered with fresh wood chips.

The stimulation pulses were derived from two sources, a response-contingent pulse generator and a non-contingent pulse generator. Triggered by a depression of the lever, the response-contingent pulse generator metered out 0.5 s trains of

rectangular pulses at frequencies that were varied as described below in the Procedure. During a test trial, each depression of the lever delivered a single train of pulses as long as the response was made while no train was being delivered. Responses made during trains were counted even though they triggered no stimulation. Non-contingent pulses were obtained from a second pulse generator which could be set to 0, 2, 5, 10, or 20 Hz of rectangular pulses. This stimulation could be delivered continuously, not only during but also between test trials.

Before being passed to the constant-current generators (Mundl, 1980), the two sources of pulses, the contingent and the non-contingent, were passed to a circuit interposed between the pulse generators and the constant-current generators. This circuit, first, allowed the two sources to be combined through OR gating, giving us the option to send both types to one electrode or to send each source to separate electrodes. Second, because the time bases for the response-contingent and the non-contingent pulses were asynchronous thus resulting in a flat distribution of phase relations between the two sources of pulses, this circuit imposed a 2 ms block, initiated by either pulse, which prohibited pulses from the other channel. That is, a non-contingent pulse falling within 2 ms of a response-contingent pulse would be blocked, as would a response-contingent pulse falling up to 2 ms after a non-contingent pulse. The value of 2 ms was selected to clear the refractory periods of lateral hypothalamic self-stimulation neurons (Bielajew, Jordan, Ferme-Enright &

Shizgal, 1981; Bielajew, Lapointe, Kiss & Shizgal, 1982; Yeomans, 1975; 1979).

Procedure

Screening and stabilization.

Following a minimum three day recovery period from surgery, rats underwent screening and training procedures. During screening rats were monitored for reactions to the delivered stimulation which consisted of monophasic, rectangular pulses with a pulse width of 0.1 ms and a train duration of 500 ms. The intensity was 200 uA and the frequency of the pulses was 100 Hz. If the rats appeared interested in the stimulation, as evidenced by exploration and sniffing, then the task of shaping the rats to the lever began. Rats were initially shaped to press the lever during a 30 s opportunity. When the rats were adept at this task they were presented with a series of five 30 s trials which were initiated by three experimenter-delivered trains of stimulation, termed primes, with the same parameters as the stimulation which the rats could self-administer. The 30 s count-down timer began with the first lever press or 12 s following the primes, whichever came first.

Once the rats were trained to self-stimulate they underwent the stabilization procedure. The pulse frequency was initially adjusted to a level that would support maximal or near-maximal rates of response and it was reduced by 0.05 log steps until the rat responded fewer than 10 times during the 30 s trial. Frequency thresholds were determined by plotting rate of responding against

the frequency of the stimulation (depicted in Figure 1). The resulting curve was cut at the half-maximal rate of responding and a line was dropped to the abscissa in order to interpolate the corresponding frequency which was termed the frequency threshold. Once the rats had stabilized, in other words once their frequency thresholds did not vary by more than 10% on three consecutive days, the experiment proper began.

Following stabilization, the intensity of the stimulation was held constant for each rat but varied across rats. For rats SJ15 and S16 the intensity for both electrodes was 250 μ A. The intensity of both electrodes for rats SJ19 and S28 was 320 μ A. The trial length was also held constant within animals but varied across rats. Rats SJ15, SJ19 and S16 had a trial length of 30 s, while S28 had 60 s trials.

Unilateral tests.

Two unilateral conditions, used to determine the effect of background stimulation upon frequency thresholds for contingent stimulation through the same electrode, were tested. Here, rats were presented with non-contingent stimulation and response-contingent stimulation to the same electrode. In the first condition, illustrated in Figure 2, the stimulation was delivered through the LEFT electrode. The frequency of the non-contingent stimulation was 2, 5, 10 or 20 Hz and was randomly varied across threshold determinations. A testing session consisted of two warm-up frequency-thresholds, which were not used when calculating the results of the experiment, followed by 16

frequency threshold determinations. Of the 16 frequency-threshold determinations, four (the first, the sixth, the eleventh and the last) were run when only the response-contingent stimulation was delivered to the rat, the other 12 thresholds were taken when both contingent and non-contingent stimulation were presented to the rat. Each frequency of non-contingent stimulation was randomly presented once during a series of four double-pulse, frequency threshold evaluations. Three such series were presented during each testing session; these test sessions were replicated five times for each rat. The second condition was as above except that the stimulation was presented through the right electrode. The left and right electrodes were tested using a randomized order.

Bilateral tests.

In the bilateral conditions the non-contingent stimulation was applied to the electrode contralateral to the one receiving the response-contingent stimulation. In the first of two bilateral conditions, depicted in Figure 3, non-contingent stimulation was delivered to the RIGHT electrode while the left electrode was presented with response-contingent stimulation. As above, the frequency of the non-contingent stimulation was 2, 5, 10, and 20 Hz and was randomly varied across frequency threshold determinations. As described earlier, a testing session consisted of two warm-ups followed by 16 frequency threshold determinations. Each background frequency was presented in random order during a series of four double-electrode frequency threshold determinations, each bounded by single-pulse frequency threshold

determinations. Three series of double-electrode threshold determinations were presented during a testing session. Each testing session was replicated five times. The second condition was the same as above except that the non-contingent stimulation was delivered to the left electrode and the contingent stimulation was delivered to the right electrode. These conditions were presented to the rat in random order.

Summation tests.

Summation tests were employed to determine the rewarding impact of self-administered pulses from the bilateral LH electrodes. In the summation tests the C or conditioning pulse was delivered to one of two electrodes and after a brief delay the T or test pulse was delivered to the other electrode. A graphic representation of the summation test is found in Figure 4. The C-T intervals, 0.5 ms, 1.0 ms, 2.0 ms, and 5.0 ms, were presented in random order.

The first summation condition involved the delivery of the C pulse to the left electrode and the T pulse to the right electrode. The C pulse was delivered to the right electrode and the T pulse to the left electrode; in the second summation condition. A summation session began with four single-pulse frequency threshold determinations, two for each electrode tested, which were considered warm-up trials and therefore were not used in the data analysis. The four warm-up trials were followed by six single-pulse and eight double-pulse threshold determinations. The six single-pulse determinations, three for the left electrode

alternated with three for the right electrode, occurred as the first, second, seventh, eighth, thirteenth, and fourteenth determinations. Each C-T interval was presented once during a series of four double-pulse threshold runs, these blocks in positions three through six and nine through twelve. The two summation conditions were tested in alternating order during the summation sessions. The summation session was replicated five times for each rat in the experiment. —

Summation levels across the bilateral LH electrodes were calculated for each rat. The formula used in the calculations was:

$$S = \frac{(F_C / F_{CN}) - 1}{F_C / F_N}$$

Where: S is the summation level; F_C is the single pulse frequency threshold obtained from the electrode delivering contingent pulses; F_{CN} is the double pulse frequency threshold obtained when contingent pulses are presented to one electrode and contingent pulses are delivered to the electrode which would have received the non-contingent stimulation; F_N is the single pulse frequency threshold obtained from the electrode which would have received the non-contingent stimulation. It should be noted that contingent stimulation, only, was delivered to the rat during summation sessions. The formula is a modification of Yeomans' (1979) effectiveness formula for pulses of unequal amplitude. The

numerator expresses the degree to which pulses added to the second electrode are integrated with the first while the denominator adjusts the value for inequality of frequency threshold between the two electrodes. A value of 1.0 indicates perfect summation whereas 0 indicates no functional summation between the two electrodes.

Histology.

Following completion of the experiment rats were sacrificed with a lethal dose of somnatol and were perfused through the heart with physiological saline followed by 10% formalin. The brains were removed and stored in 10% formalin for at least 24 hours. The brains were then sectioned in a cryostat with a microtome to 40 μ in thickness. Brain sections were immediately placed on gelatin-coated slides, dried, and stained with cresyl violet no less than 24 hours later.

Results and Discussion

Histology

The electrode tips for all the rats were located in the LH. The flat skull placements are depicted in Figure 5 and the deGroot placements are presented in Figure 6. Verification of the electrode placements for SJ15 was accomplished using the atlas of Pellegrino, Pellegrino and Cushman (1967). The right electrode tip for SJ15 was located in the lateral hypothalamus at the level of the dorsomedial hypothalamic nucleus, ventral to the zona incerta, medial to the internal capsule, and lateral and dorsal to the fornix. The tip of the left electrode was also located in the

lateral hypothalamus at the level of the dorsomedial hypothalamic nucleus but was midway between the internal capsule and the fornix.

The electrode tips for SJ19 and S28 were located in the lateral hypothalamus at the level of the dorsomedial hypothalamic nucleus. These placements were verified using the Paxinos and Watson (1982) atlas. The right electrode tip for SJ19 was located between the zona incerta and the internal capsule. SJ19's left electrode was located lateral to the perifornical hypothalamic nucleus and ventral to the internal capsule. The right electrode for S28 was equidistant from the fornix, the ventral tip of the optic tract and the base of the brain. ~~The~~ left electrode was located ventral to the zona incerta, medial to the internal capsule and lateral to the dorsal hypothalamic nucleus. The electrode tips for S16 could not be determined.

All electrodes supported vigorous self-stimulation with rates of responding between one and two responses per second. None of the animals displayed any motoric effects or seizure activity due to the response-contingent stimulation.

Rates of Responding.

In order to determine the effects of the non-contingent stimulation upon the maximal rates of responding, the maximal rates were plotted against the frequencies of the non-contingent stimulation. These graphs are portrayed in Figures 7-10. The correlation between the proportion of double-pulses, in comparison to the single-pulses required to sustain half-maximal rates of

responding, and the proportion of maximal rates, obtained during the double-pulse conditions in comparison to the maximal rates obtained during single-pulse conditions, was found to be significant ($r = -.21, p < .05$) indicating that as the frequency of the background stimulation increased the rats' maximal rates of responding decreased.

Additionally, we calculated these correlations separately for each electrode and each rat. The correlations, when the contingent and non-contingent stimulation were delivered to the left electrode, were as follows: .20 for SJ15; .07 for SJ19; -.09 for S16; and -.13 for S28. None of these correlations were significant indicating that there was no effect of non-contingent stimulation upon maximal rates of responding when the contingent and the non-contingent stimulation were delivered to the left electrode. When the contingent and the non-contingent stimulation were delivered to the right electrode the correlations were as follows: -.43 for SJ15; -.24 for SJ19; .22 for S16; and .24 for S28. All of these correlations were significant at the .05 level indicating that there was a significant effect of background stimulation upon the maximal rates of responding when the contingent and the non-contingent stimulation were delivered to the right electrode.

Thus the overall correlation between the non-contingent stimulation effect and the maximal rates of responding indicated that as the non-contingent stimulation effect increased so did the rats' maximal rates of responding but the individual correlations

revealed that sometimes the rates of responding increased, decreased or were unaffected by the non-contingent stimulation. Thus the rates, because they are affected by the non-contingent stimulation inconsistently, reveal little about the nature of the non-contingent stimulation.

Frequency Thresholds

Unilateral conditions.

Figures 11, 12, 13 and 14 represent the effect of the non-contingent stimulation upon frequency thresholds. In the figures frequency thresholds were plotted against the frequencies of the non-contingent stimulation. It was noted that as the frequency of the background stimulation increased, the frequency threshold decreased and it appeared that the decrease in frequency threshold was equal to the frequency of the non-contingent stimulation.

Statistical analysis of the data involved determining the slopes of the lines in Figures 11-14 representing the double-pulse frequency thresholds plotted against the frequencies of the background stimulation. It was expected, if the decrease in frequency threshold was equal to the frequency of the non-contingent stimulation, that the obtained slopes would be equal to -1.0. This was not the case and it was postulated that some of the pulses were lost as a result of the 2 ms block following each pulse. The proportion of pulses that were lost due to the 2 ms block were calculated and this correction was applied to the slope of -1.0, and this slope was termed the predicted

slope. The formula used to determine the proportion of pulses not eliminated by the 2 ms block was:

$$\text{proportion} = (500 - F_c) / 500$$

where F_c is the single pulse frequency threshold obtained from the electrode delivering contingent stimulation, and the constant 500 is the train duration in milliseconds.

To obtain this formula we determined the number of pulses, at threshold, in the 500 ms train of response-contingent pulses which is, simply, the frequency threshold of the contingent stimulation divided by two. Each of the pulses in the 500 ms train has a 2 ms block associated with it, therefore the time during which the block is in effect is the number of pulses in the response-contingent train multiplied by 2 ms. Since the original frequency threshold was divided by two to express the number of pulses in 500 ms and then multiplied by two because there were 2 ms per block, the total block is given directly by the value of the frequency threshold in ms. Thus a rat with a threshold of 42 Hz has the non-contingent pulses blocked for 42 of the 500ms in the train. The proportion of non-contingent pulses that would not be blocked is $(500\text{ms} - 42\text{ms}) / 500\text{ms}$ or 0.92. This proportion is then used to correct the slope of -1.0.

To determine whether the slope of -1.0 or the predicted slope was a better estimator of the obtained slope, difference scores were calculated. Difference scores involved the subtraction

of the value of the theoretical or the predicted slopes from the value of the obtained slopes. Difference scores were obtained for each condition and each rat. Then the average difference between the obtained slope and the slope of -1.0 ($.22 \pm .18$) and the average difference between the obtained slope and the predicted slope ($.12 \pm .18$) were compared. These results are shown in Table 1. A correlated t-test of the difference between the means was performed on the data. The average difference between the obtained and predicted slope was less than the difference between the obtained and the slope of -1.0 . The results of the t-test ($t = 7.17$, $df = 7$, $p = .01$), indicated that the decrease in the double-pulse frequency threshold was likely the result of the increase in the number of background pulses less the number of pulses removed by the 2 ms block.

Bilateral conditions.

To determine the effect of the background stimulation on the frequency thresholds for self-stimulation, the frequency thresholds obtained under the double-electrode conditions were plotted against the frequencies of the background stimulation. These results are depicted in Figures 11, 12, 13 and 14. Once again we found that as the frequency of the non-contingent stimulation increased the obtained frequency threshold decreased. The decreases in frequency threshold in the bilateral conditions were not as great as those obtained in the unilateral conditions, ranging from -0.16 to -0.90 . The summation levels, presented in Table 2, ranged from 0.20 to 0.60 , values that are in agreement

with the range of 0.25 to 0.80 observed by Shizgal et al. (1980).

Statistical analysis of these data, as in the unilateral condition, involved determining the slopes of the lines depicted in Figures 11-14. If the contingent and the non-contingent pulses were summing perfectly, the slope would be equal to -1.0, adjusted for the loss of pulses by the 2ms block. Taking summation into account, the predicted slopes were calculated by the following formula:

$$\text{predicted slope} = S(500 - F_c) / 500$$

Where: F_c is the single pulse frequency threshold obtained from the electrode delivering contingent stimulation; 500 is the train duration in milliseconds; S is the appropriate summation level for the bilateral condition of any particular subject.

The slope of -1.0 corrected by the summation level and the proportion of pulses lost by the 2 ms block was termed the predicted slope. In order to determine whether the predicted or the slope of -1.0 was a better predictor of the obtained slope, difference scores were calculated. The average difference between the observed slope and the slope of -1.0 ($.44 \pm .24$) was compared to the average difference between the observed slope and the predicted slope ($-.11 \pm .23$). These results are also contained in Table 1. A t-test of the difference between the means for correlated samples was used to analyze the data. The difference

between the observed slope and the predicted slope was less than the difference between the observed and the slope of -1.0 ($t = 5.92$, $df = 7$, $p = .01$), indicating that adding summation builds a better predictor of the non-contingent effect.

So far it has been seen that the non-contingent stimulation causes the frequency thresholds for brain stimulation reward to decrease. Furthermore, the non-contingent stimulation effect may be predicted by correcting the slope of -1.0 by the summation level and the loss of pulses by the 2ms block. In order to determine if the non-contingent stimulation causes a decrease in the thresholds for rewarding brain stimulation by adding to the rewarding effect of the contingent stimulation we correlated the obtained slopes of the non-contingent effect with the summation levels. Since the summation levels allow us to infer the rewarding impact of the administered non-contingent pulses, a negative correlation would indicate that the non-contingent stimulation contributes to the rewarding effect of the brain stimulation reward thereby causing the frequency thresholds for self-stimulation to decrease. We found that the correlation between the slopes of the non-contingent stimulation effect and the summation levels was $-.79$ ($p < .01$) leading to the conclusion that the non-contingent stimulation contributes to the rewarding impact of the contingent stimulation.

EXPERIMENT 2

The first experiment tested self-stimulation frequency thresholds under a background of low-frequency stimulation. It was determined that the delivery of non-contingent stimulation in conjunction with response-contingent stimulation resulted in decreased self-stimulation thresholds. In the unilateral case the decrease in the self-stimulation frequency thresholds was roughly equal to the frequency of the non-contingent stimulation. The decrease in frequency threshold was less than the frequency of the background stimulation in the bilateral conditions but, when the summation level was considered, it was discovered that the decrease in frequency threshold was well predicted by the background frequency corrected by the summation level.

In the present experiment the relationship between the summation levels and the magnitude of the rewarding effect of the non-contingent stimulation was further evaluated. We wanted to determine whether the non-contingent stimulation was reducing the frequency thresholds by contributing to the rewarding value of the contingent stimulation. If the rat receives the brain stimulation non-contingently we cannot determine, directly, if the stimulation is rewarding. However, it is possible that we may be able to determine indirectly if the non-contingent stimulation is rewarding. In order to accomplish this the summation level, which evaluates the rewarding impact of contingent stimulation from the second of a pair of electrodes, and the non-contingent effect will be correlated. Summation levels, obtained under a number of

intensity conditions where the intensity of the contingent stimulation delivered to one electrode is held constant and the intensity of the contingent stimulation to the other electrode is varied, were compared to the non-contingent effect, obtained when the intensity of the contingent stimulation presented to one electrode is held constant and the intensity of the non-contingent stimulation delivered to the contralateral electrode is varied. If the correlation is significant, indicating that the summation level can be used to predict the non-contingent effect, then it can be concluded that the non-contingent stimulation is rewarding. It can then be concluded that the rewarding effect of the non-contingent stimulation is summing to the rewarding effect of the contingent stimulation.

Method

Subjects and Surgery

Subjects were two male Long-Evans rats weighing 420 g and 450 g at the time of surgery. Rats were housed and maintained as previously described. Both rats were stereotaxically implanted with bilateral lateral hypothalamic electrodes as described in Experiment 1. The flat skull coordinates were: 2.0 mm P, 2.0 mm L, and 8.0 mm V.

Apparatus

The apparatus used in the experiment was described earlier in the previous experiment.

Procedure

Screening and stabilization.

Rats were screened and stabilized as described above in Experiment 1.

Frequency-intensity trade-off functions.

The frequency-intensity trade-off involved determining the frequency threshold at each of several intensities. A series of randomized intensities, ranging from 100 to 1000 uA and presented in 0.10 log steps, was presented to the rats. Frequency-intensity trade-off sessions, for each electrode, consisted of eleven frequency threshold determinations, each at a different intensity (100, 125, 160, 200, 250, 320, 400, 500, 630, 800 and 1000uA). The frequency-intensity trade-offs were replicated three times for each rat.

From these data five intensities for each electrode with stable frequency thresholds were chosen to be tested in the actual experiment. The frequency thresholds were deemed stable if they did not vary by more than 20% over two consecutive days. The intensities tested on the left and right electrodes of S32 were 200, 320, 400, 500, and 800 uA. The intensities tested on the left electrode of S33 were 250, 320, 400, 500, and 630 uA, while the intensities tested on the right electrode were 320, 400, 500, 630, and 800 uA. Each condition (described below) and each series of intensities were presented in random order.

Non-contingent stimulation tests.

In the first condition non-contingent stimulation was

delivered to the left electrode while the rat was presented with the opportunity to lever-press for stimulation of the right electrode. The intensity of the contingent stimulation remained constant, at the middle intensity of the five chosen for the test sessions, while the intensity of the non-contingent stimulation was varied. For rat S32 the intensity of the contingent stimulation was 400 uA, while the intensities for the non-contingent stimulation were 200, 320, 400, 500, and 800 uA. For rat S33 the intensity of the contingent stimulation was 500 uA while the intensities for the non-contingent stimulation were 320, 400, 500, 630, and 800 uA. The frequency of the background stimulation was held constant at 10 Hz.

The second condition was as above except the non-contingent stimulation was delivered to the right electrode while the contingent stimulation was presented to the left electrode. Thus, rat S32 received the mirror image currents while the intensities of the non-contingent stimulation for S33 were 250, 320, 400, 500, and 630 uA.

Beginning each test session was a warm-up trial, in which the frequency threshold for each electrode was determined. The warm-ups were not included in the data analysis. Following the warm-up trials two series of five double-electrode frequency threshold determinations, one series per electrode, bounded by the appropriate single-pulse frequency threshold determinations were presented. Each electrode was alternately tested first in the series. Each session was replicated ten times for S32 and six

times for S33.

Summation conditions.

Two summation conditions were tested. In the first condition the response-contingent C pulses were applied to the left electrode and following a brief delay response-contingent T pulses were applied to the right electrode. The intensity of the C pulse was held constant at 400 uA, while the intensity of the T pulse was 200, 320, 400, 500, or 800 uA for S32 and 250, 320, 400, 500, or 630 uA for S33. It may be noted that the intensities tested here, correspond to the intensities tested during the non-contingent stimulation test sessions. The delays between the pulses, 0.5, 1.0, 2.0, and 5.0 ms, were tested in random order.

The second condition was the same as the first with two exceptions. The first exception was that the fixed-current pulses were delivered to the right electrode while the varied-current pulses were presented to the left electrode. The second exception was that the intensity of the second pulse was randomly chosen from the following list: 320, 400, 500, 630, and 800 uA for S33. Testing sessions for the summation conditions were similar to those for non-contingent stimulation conditions: following two warm-up trials, which were not included in the data analysis, a series of five double-electrode frequency threshold determinations, for each electrode, bounded by the appropriate single-pulse frequency threshold determinations was presented. Each electrode was alternately tested first in the series. Each condition was replicated ten times for S32 and six times for S33.

Histology.

Rats were sacrificed and perfused as described earlier. The brains were sectioned and stained as described in the previous experiment.

Results and Discussion

Histology

The electrode placements for rats S32 and S33 were located in the lateral hypothalamus, as depicted in Figure 15, and were verified using the atlas of Paxinos and Watson (1982). The left electrode tip for S32 was located in the lateral hypothalamus at the level of the anterior hypothalamic area, ventral to the internal capsule, on the border between the lateral hypothalamus and the ventral pallidum. The right electrode tip for S32 was located in the lateral hypothalamus, also at the level of the anterior hypothalamic area, but midway between the internal capsule and the fornix. The right electrode tip for S33 was located just dorsal to the right electrode tip for S32. The left electrode tip was located in the lateral hypothalamus at the level of the ventral medial hypothalamic nucleus and was situated midway between the ventral tip of the internal capsule and the zona incerta, dorsal to the fornix.

All electrodes supported rapid self-stimulation with the rates of responding ranging from one to three responses per second. Two of the electrodes, the left electrode for S32 and the right electrode for S33, when stimulated, caused the rats to display seizure signs including facial twitching and chewing

movements. It should be noted that the convulsive activity never progressed beyond this level. Of these two electrodes the right electrode for S33 also produced a slight motoric effect whereby the rat's head lifted slightly and turned to the right. When stimulated the right electrode for S32 resulted in approach-avoidance behaviour in which the rat retreated to the back corner of the Skinner box after every two or three stimulations and then returned to the lever approximately two to five seconds later. The left electrode belonging to S33 produced no seizure activity or motor effects.

Non-contingent Stimulation and Summation Data

The ratio of the number of double-pulses (contingent and non-contingent) in comparison to the number of single-pulses (contingent) required to maintain half-maximal rates of responding (this proportion is termed the non-contingent stimulation effect) was calculated for each electrode and each intensity. These values are displayed in Table 4. The non-contingent effect is thought to measure the rewarding impact of pulses delivered to the second electrode in the same way that summation levels measure the rewarding impact of pulses delivered to a second electrode, that is, by comparing the frequency threshold obtained from a single electrode to the frequency threshold obtained when two electrodes are stimulated. The non-contingent stimulation effect ranged from 0.63 to 0.80 when contingent stimulation was delivered to S32's left electrode and the non-contingent stimulation was delivered to the right electrode. For this rat's right electrode, the

non-contingent stimulation effect ranged from 0.86 to 0.96. For S33, the non-contingent stimulation effect ranged from 0.77 to 0.90 when the contingent stimulation was presented to the left electrode and from 0.50 to 0.77 for the right. These data are also displayed in Table 4.

The summation levels were calculated using the formula described in Experiment 1. The summation levels, which are included in Table 4, ranged from 0.39 to 0.92 for S32 and from 0.24 to 0.60 for S33 when the contingent C pulse was delivered to the left electrode and the response-contingent T pulse was delivered to the right electrode. When the C pulse was delivered to the right and the T pulse to the left electrode the summation levels ranged from 0.18 to 0.83 for S32 and from 0.50 to 0.77 for S33.

A correlation was performed on the data to determine if the non-contingent stimulation effect and the summation levels were related. We expected a significant correlation if it was the rewarding property of the non-contingent stimulation that was adding to the response-contingent stimulation since the summation levels measure the rewarding impact of stimulation delivered to the second electrode. Furthermore, we expected that the correlation would be negative since the number of rewarding pulses required to maintain half-maximal rates of responding would decrease as the impact of the stimulation increases. The correlation coefficient, presented in Table 4, met our expectations. The correlation between the non-contingent

stimulation effect and the summation levels was $-.58$ ($p < .01$). Summation levels were altered by systematic variation of current, a manipulation that resulted in a coincident change in the non-contingent stimulation effect. Since measures of summation evaluate the degree of transfer of the rewarding effect of stimulation applied to a contralateral electrode, the significant correlation lends further support to the view that the non-contingent pulses decrease thresholds by virtue of their rewarding effect.

Experiment 3

Experiments 1 and 2 demonstrated that as the frequency of the non-contingent stimulation increased the frequency threshold for the contingent stimulation decreased. This decrease was equal to the frequency of the background stimulation corrected by the appropriate summation level and occurred whether the background stimulation was delivered to the ipsilateral or the contralateral electrode.

This experiment was designed to further evaluate the nature of the summation between the contingent and the non-contingent stimulation. It appeared on the basis of data from the previous experiments that the contingent and the non-contingent pulses added together to yield the original frequency threshold. For example, if the frequency threshold of regular stimulation were 50 Hz and one were to apply non-contingent stimulation of 10 Hz, the threshold would drop by 10 Hz to 40 Hz. We wondered if the relation was additive over a wide range of frequency thresholds.

In Experiment 3, the frequency threshold of the response-contingent stimulation was varied by changing the intensity of the stimulation. Decreasing the intensity caused the frequency thresholds to increase while increasing the intensity resulted in a drop in frequency thresholds. Rats were tested at three different intensities to force their frequency threshold to three different levels. It was expected that as the frequency of the non-contingent stimulation increased the frequency threshold for the contingent stimulation would decrease linearly regardless of the rat's frequency threshold for contingent stimulation.

Method

Subjects and Surgery

Subjects were three male, Long-Evans rats weighing 345, 370, and 460 g at the time of surgery. Rats were housed and maintained as described in Experiment 1.

Rats were stereotaxically implanted with either a single lateral hypothalamic electrode (S43) or with bilateral lateral hypothalamic electrodes (S35 and AC6). The flat skull coordinates were: 2.0 mm P, 2.0 mm L, and 8.0 mm V for all rats. The left electrode supported self-stimulation for rats S43 and AC6 while the right electrode for S35 supported self-stimulation.

Apparatus

The equipment was as described in Experiment 1.

Procedure

Screening and stabilization.

Screening and stabilization procedures were as previously

described.

Frequency-intensity trade-off functions.

A series of three frequency-intensity trade-offs was tested for each rat in order to determine the intensities to be used during the experiment. Frequency-intensity trade-off sessions were conducted as described in Experiment 2. Three intensities, with stable thresholds, resulting in frequency thresholds which were considered high (ranging from 65 to 73 Hz), medium (ranging from 37 to 46 Hz) and low (ranging from 23 to 35 Hz) were then chosen for each rat. The frequency thresholds for each intensity were considered stable if they did not vary by more than 20% over two consecutive days. Rat AC6 was tested with intensities of 160, 320, and 630 uA. S43 was tested with intensities of 200, 400, and 800 uA. The intensities used for S35 were 200, 320, and 500 uA. The intensities tested were the same for the contingent and the non-contingent stimulation.

Non-contingent stimulation tests.

The rats were presented simultaneously with non-contingent stimulation and the opportunity to lever-press for response-contingent brain stimulation. The stimulation was delivered through the left electrode with the exception of S35 in which the contingent and non-contingent stimulation were delivered to the right electrode. The frequency of the background stimulation was 2, 5, 10, or 20 Hz. Each intensity session consisted of two single-pulse warm-ups which were not included in the data analysis, followed by sixteen threshold determinations.

The first, sixth, eleventh and last were used to determine frequency thresholds for single pulses free of non-contingent stimulation. The single-pulse threshold determinations bounded three series of four double-pulse frequency thresholds during which each background frequency was presented only once. Intensities and background frequencies were presented in random order. Each test session was replicated three times.

Histology.

Histological procedures were described in Experiment 1.

Results and Discussion

Histology

The placements for the electrodes supporting self-stimulation are depicted in Figure 16. The left electrode for rat S43 was located in the lateral hypothalamus at the level of the dorsomedial hypothalamic nucleus. The tip was ventral to the zona incerta, medial to the internal capsule and dorsal to the ventral tip of the supraoptic decussation. The location of the left electrode for AC6 was the lateral hypothalamus at the level of the ventromedial hypothalamic nucleus, ventral to the zona incerta, medial to the internal capsule and lateral to the fornix. The right electrode for AC6, located on the border of the ventromedial thalamus and the zona incerta at the level of the ventromedial hypothalamic nucleus, did not support self-stimulation. The electrode tip for S35 could not be determined.

All self-stimulation electrodes supported vigorous

self-stimulation with rates of responding between one and two responses per second. Stimulation of the right electrode for S43 resulted in a motor effect in which the rat's head rotated downward to the right and also resulted in the display of seizure signs which were never more serious than facial and eye twitching. The right electrode for S35 supported both intracranial self-stimulation and seizure activity which caused facial and eye twitching.

Frequency Threshold Data

In Figures 17, 18, and 19 the frequency threshold data obtained under each intensity condition for each rat were plotted against the frequency of the non-contingent stimulation. Once again, as the frequency of the background stimulation increased the frequency thresholds decreased. This decrease in frequency threshold appeared to equal the frequency of the non-contingent stimulation. As was the case in Experiment 1, correcting the anticipated slopes of -1.0 for pulses lost to the 2 ms block partly accounted for the less than perfect summation of non-contingent stimulation (Table 5).

Frequency thresholds for self-stimulation decreased as the frequency of the non-contingent stimulation increased (Figures 17-19). In order to determine if the addition of the rewarding effects occurred over a wide range of frequency thresholds for brain stimulation reward an analysis of variance (ANOVA, using the computer programme SPSSX) on the data collected from each rat was performed. We expected that if the non-contingent stimulation

continued to add to the rewarding effect of the contingent stimulation regardless of the rats' frequency thresholds, there would be a significant effect of intensity and of non-contingent stimulation frequency but that there should not be a significant interaction effect. For all three rats significant ($p < .01$) main effects of intensity (S35, $F = 699.38$, $df = 2$; S43, $F = 627.93$, $df = 2$; and AC6, $F = 786.07$, $df = 2$) and of background stimulation (S35, $F = 61.78$, $df = 3$; S43, $F = 59.10$, $df = 3$; and AC6, $F = 43.78$, $df = 3$) were found. The interaction effects were non-significant ($p > .05$) for all rats (S35, $F = 1.27$, $df = 6$; S43, $F = 1.37$, $df = 6$; and AC6, $F = 1.18$, $df = 6$). These data are presented in Table 6. These results suggested that the additive relationship between the contingent and the non-contingent stimulation occurred regardless of the rats' frequency threshold.

EXPERIMENT 4

In the three previous studies it was demonstrated that as the frequency of the non-contingent stimulation increased the frequency threshold for the contingent stimulation decreased. This decrease was equal to the frequency of the administered background stimulation. The non-contingent and the contingent stimulation summed together to defend a constant threshold. In other words, if we consider the events occurring during a self-stimulation train, adding the frequency of the background stimulation to the frequency of the response-contingent stimulation at threshold yields the original frequency threshold obtained without background pulses. We wondered if the critical addition was taking

place solely during the self-stimulation train or if it also occurred outside the train of contingent pulses.

In order to test whether any addition was occurring outside the self-stimulation train we presented the background stimulation before and after trains of intracranial self-stimulation but not during the trains. It was predicted that if the decrease in threshold were due to the combining of the rewarding effects of the non-contingent and the contingent stimulation solely during the stimulation train then there would be no effect upon the frequency thresholds. If the decrease in frequency threshold were at least partly due to the summing of contingent and non-contingent stimulation before and after the stimulation train then a decrease in the frequency threshold would still be observed during this experimental manipulation.

Method

Subjects and Surgery

Subjects were five male, Long-Evans rats weighing between 300 and 500 g at the time of surgery. Rats were housed and maintained as described in a previous experiment.

Each rat was stereotaxically implanted with a single LH electrode. The flat skull coordinates for rats S36, S38, S46, P96, and F457 were: 2.0 mm P, 2.0 mm L, and 8.0 mm V.

Apparatus

The equipment was as described previously.

Procedure

Screening and stabilization.

The screening and stabilization procedures were described in Experiment 1.

Non-contingent stimulation tests.

In the first of two conditions rats were simultaneously presented with experimenter-delivered stimulation and the opportunity to lever-press for brain stimulation reward. Both the experimenter-delivered and the contingent stimulation were delivered to the same electrode. Each pulse, contingent or non-contingent, was followed by a 2 ms block. The frequency of the background stimulation was randomly varied from 2, 5, 10, and 20 Hz. The intensity of both the contingent and the non-contingent stimulation was held constant at 320 uA for rats S38, S46, P96, and F457 and 400 uA for S36.

The second condition was the same as the first except that the first contingent pulse of each train was followed by a 500 ms block. The non-contingent pulses were followed by the usual 2 ms block. The 500 ms block prevented the non-contingent stimulation from being delivered during trains of response-contingent stimulation. Each condition was presented in a random order as were the background frequencies. Each condition was replicated three times.

Separate test sessions were conducted for each experimental condition. A session began with two warm-up trials. Following these trials the rat was presented with three (first, sixth and

last determinations) single-pulse threshold determinations and eight double-pulse threshold determinations. Two single-pulse threshold determinations bounded each of two series (with the exception of P96 whose single-pulse determinations bounded each of three series) of four double-pulse frequency threshold determinations. During a series a background frequency was presented only once and in random order. Test sessions were presented in random order and were replicated three times for each rat.

Histology.

Histological methods were as described in the first experiment.

Results and Discussion

Histology

All electrode placements, presented in Figure 20, were in the lateral hypothalamus. The electrode tips for S46, P96, and F457 were located in the lateral hypothalamus at the level of the anterior hypothalamic area, ventral to the internal capsule, medial to the central amygdaloid nucleus, lateral to the fornix and dorsal to the supraoptic hypothalamic nucleus. The electrode tip for S36 was also located in the lateral hypothalamus at the level of the anterior hypothalamic area but was ventral to the internal capsule, lateral to the anterior hypothalamic area and dorsal to the optic tract. The electrode tip for S38 was placed in the lateral hypothalamus at the level of the ventromedial hypothalamic nucleus, was medial to the internal capsule and

equidistant from the zona incerta and the fornix.

All electrode placements supported self-stimulation although the rates of responding were slower than in the previous experiments. The rates of responding in this experiment were less than one response per second. Stimulation through the electrodes for S36 and S38 also produced motor effects. The motor effect for S36 was a raising of the paws and a shifting of the upper body to the right, while for S38 the effect was a rotation of the head and paws to the left. Delivery of electrical stimulation through the electrode for S46 also produced approach-avoidance behaviour causing the rat to retreat to the back corner of the Skinner box after every two or three lever presses. The rat would always return to the lever after about two seconds at the back of the box.

Comparison of the 2 ms to the 500 ms Block

Figures 21-23 depict the frequency thresholds obtained under the 2 ms block condition for rats S36, S46 and F457 plotted against the frequency of the background stimulation. The frequency thresholds decreased as the frequency of the non-contingent stimulation increased and, as in the previous experiment and Experiment 1, it appeared that this decrease was equal to the frequency of the background stimulation. As in the previous experiments the expected slopes (of -1.0) adjusted to account for the pulses lost during the 2 ms block were better predictors of the obtained slopes than was the slope of -1.0 (Table 7) indicating good summation, less the pulses lost to the 2 ms block,

of the contingent and non-contingent stimulation.

In Figures 21-23 the frequency thresholds obtained under the 500 ms condition were plotted against the frequencies of the non-contingent stimulation. In contrast to our previous findings, it appeared that the frequency threshold did not decrease as a function of the increase in background frequency but that the frequency threshold remained fixed at the value obtained under the single-pulse condition. This indicated that the contingent and non-contingent stimulation summed together only during trains of self-stimulation but that the contingent did not summate with the non-contingent stimulation when it (the background stimulation) was presented before or after the self-stimulation train.

Although rats S38 and P96 began testing in this experiment accurate estimates of slopes representing their data were not possible since the data from the 20Hz condition were discarded due to the rats' lack of responding. As it was necessary to achieve accurate estimates of the slopes in order to demonstrate the effect of the 500 ms block condition the data from these rats were discarded.

Statistical analyses involved the determination of the slopes and their 95% confidence limits for the lines presented in Figures 21-23. These data are presented in Table 8. When the animals are presented with the 2 ms block the slopes obtained are negative indicating that the frequency thresholds for contingent stimulation decreases as the frequency of the non-contingent stimulation increases. These results are consistent with our

hypothesis that the contingent and the non-contingent stimulation summate during a self-stimulation train but do not summate when the background stimulation is presented before and after the train of self-stimulation.

In order to contrast the results obtained under the 2ms and the 500 ms block conditions two one-way ANOVAs, one for each of the two conditions, were performed on the data for each rat. These results are presented in Table 9. The 2 ms block condition for all rats yielded a significant effect of background stimulation upon frequency thresholds while there was no effect of background stimulation upon frequency thresholds under the 500 ms block condition. Thus the effect of the non-contingent stimulation, under the 2 ms block condition, was to produce a linear decrease in frequency threshold. Under the 500 ms block condition, during which the non-contingent stimulation was blocked, the non-contingent stimulation had no effect upon frequency thresholds for self-stimulation.

The previous experiments have demonstrated that the frequency thresholds for intracranial self-stimulation decrease as the frequency of the non-contingent stimulation increases. Furthermore, the decrease in the self-stimulation thresholds is equal to the frequency of the background stimulation, and that this relation is maintained over a wide range of frequency thresholds. This experiment was designed to determine whether the summation of the contingent and the non-contingent stimulation occurred solely within the stimulation train or if summation also

occurred outside the train of rewarding brain stimulation. We found that when the non-contingent pulses were blocked during the stimulation train no summation occurred. This indicated that the contingent and the non-contingent stimulation summate under the 2 ms block condition but do not summate at all during the 500 ms condition. We therefore suggest that the background stimulation summates only during a train of response-contingent stimulation and will not summate with the contingent stimulation when presented before and after the train.

General Discussion

The set of experiments presented in this thesis attempt to document the effects of subthreshold non-contingent stimulation upon intracranial self-stimulation. The effects of "free reward", the non-contingent activation of post-synaptic receptors as is thought to occur with high doses of direct agonists, were modelled by delivering non-contingent stimulation with a frequency of 2, 5, 10, and 20-Hz. In the past, researchers (Herberg, 1962; Leith, 1983) have attempted to model the effects of direct agonists by delivering non-contingent stimulation at threshold and suprathreshold intensities. Unfortunately, this likened the non-contingent stimulation to the highest doses of direct agonists and resulted in the disruption of behaviour. By delivering subthreshold levels of non-contingent stimulation we attempted to avoid the disruptive effects of the stimulation and were able to monitor the interaction between contingent and non-contingent stimulation.

In Experiment 1 it was determined that subthreshold levels of non-contingent stimulation did not disrupt self-stimulation. The existence of (self-stimulation) performance effects related to the delivery of non-contingent stimulation was determined by correlating the non-contingent stimulation effect with the proportion of maximal responses, in which the maximal number of response obtained during the double-pulse condition (contingent and non-contingent pulses were delivered) were compared to the maximal number of responses obtained when the response-contingent

stimulation was presented. No consistent effect of the background stimulation upon maximal rates of responding was found.

The most notable effect of the non-contingent stimulation, regardless of whether it was delivered to the same or to the contralateral electrode was the decrease in frequency thresholds for brain stimulation reward. The decrease in the frequency thresholds was equivalent to the frequency of the non-contingent stimulation, corrected by the number of pulses eliminated by the 2 ms block and by the appropriate summation level. The finding suggested that the background and the contingent stimulation summed perfectly.

In Experiment 2 we attempted to investigate the relationship between the summation levels and the magnitude of the rewarding effect of the non-contingent stimulation. Results from Experiment 1 showed that the effect of the non-contingent stimulation increased as the summation level increased leading us to postulate that non-contingent stimulation decreased the frequency thresholds for contingent stimulation by summing to the rewarding effect of the self-stimulation. By varying the intensity we produced alterations in the summation levels which resulted in corresponding changes in the non-contingent stimulation effect. This led to the conclusion that the non-contingent stimulation affected thresholds for brain stimulation reward by contributing to the rewarding effect of the contingent stimulation.

In Experiment 3 the effects of the non-contingent stimulation at three different intensities, which corresponded to

three different frequency thresholds, of brain stimulation were tested. The purpose of the experiment was to determine if the relationship between the response-contingent and the non-contingent was additive over a wide range of frequency thresholds. As in Experiment 1, the effect of the non-contingent stimulation, regardless of the frequency threshold for contingent stimulation, was to reduce the frequency thresholds for the response-contingent stimulation by the frequency of the background stimulation (less the number of pulses removed by the 2 ms block). This suggested that the relationship between the contingent and the non-contingent stimulation was indeed additive. Once again we concluded that the contingent and the non-contingent stimulation summated perfectly.

Finally, in Experiment 4 it was determined that the integration of the response-contingent and the non-contingent stimulation occurred during the self-stimulation train and not before and after the train. During the 2 ms block condition the frequency threshold for response-contingent stimulation decreased as the background frequency increased. The decrease in the frequency threshold for brain stimulation reward was equivalent to the frequency of the non-contingent stimulation. Under the 500 ms block condition, however, there was no effect of the background stimulation upon frequency thresholds for rewarding brain stimulation. These results suggested that the contingent and the background pulses summated only during the self-stimulation train and the pulses did not summate outside the train. Thus it was

concluded that the contingent and the non-contingent stimulation summated perfectly during trains of rewarding brain stimulation but did not summate at all outside the train of rewarding pulses.

Thus it has been shown that the administration of non-contingent pulses results in a decrease of the frequency thresholds for brain stimulation reward. This decrease is quantifiable and occurs in a lawful manner: Frequency thresholds for intracranial self-stimulation are decreased by an amount equal to the frequency of the non-contingent stimulation. The effects of electronic "free reward" are similar to those found when doses of direct post-synaptic receptor agonists are administered to self-stimulating rats—self-stimulation is enhanced. The similarity between the effects of the non-contingent stimulation and the effects of direct agonists renders it plausible that direct receptor agonism reduces thresholds by non-contingently stimulating the post-synaptic receptors of the reward system thereby acting as a "free reward".

An alternative explanation for our findings may exist. The non-contingent stimulation, which we delivered to our self-stimulating rats, is similar to priming pulses which are defined as bursts of stimulation which are not contingent upon any operant response. In the runway paradigm, in which subjects are trained to run the length of a runway to lever press for brain stimulation, priming pulses characteristically enhance performance (Edmonds & Gallistel, 1974; Gallistel, 1969; Reid, Hunsicker, Kent, Lindsay & Gallistel, 1973), are not blocked by

the dopamine-blocker pimozide (Wasserman, Gomita & Gallistel, 1982), and do not produce shifts in thresholds for rewarding brain stimulation (Edmonds & Gallistel, 1974). Gallistel (1967; 1969) has explained that primes do not act as reinforcers but rather, act as an incentive resulting in the enhancement of performance. Furthermore, Wasserman et. al. (1982) suggested that reinforcing pulses and priming pulses may be subserved by different substrates.

In the operant chamber, however, researchers have indicated that certain performance variables also affect the rewarding value of the stimulation (Pagotto, 1984; Wagner & Katz, 1984). It has been argued that in the operant chamber the effects of priming and reinforcing pulses are compounded thus performance variables may influence the animals' affinity for brain stimulation reward and may result in alterations in half-maximal thresholds for self-stimulation (Miliaressis, Rompre, Laviolette, Philippe & Coulombe, 1986). Although the possibility exists that the non-contingent stimulation resulted in shifts in the frequency thresholds in a manner similar to that reported by Miliaressis et al. (of the priming effect), it is unlikely. The results of Experiment 4, in which the delivery of the non-contingent stimulation was limited to exclude delivery during the train of rewarding brain stimulation, demonstrated that under this experimental condition (known as the 500 ms block condition) there was no effect of the non-contingent stimulation on frequency thresholds for brain stimulation reward. We suggest that if the

non-contingent stimulation effect was reducing frequency thresholds by combining reinforcing and priming effects such that the subjects' affinity for the rewarding brain stimulation was enhanced, then the presentation of the non-contingent stimulation should have affected thresholds for self-stimulation regardless of whether the non-contingent pulses were delivered during or outside the train of response-contingent pulses. Since the non-contingent effect was observed only when the non-contingent stimulation was presented during the train of rewarding pulses we concluded the non-contingent stimulation altered the frequency thresholds for brain stimulation reward solely by contributing to the rewarding effect of the response-contingent stimulation.

The delivery of subthreshold levels of non-contingent stimulation results in similar effects upon self-stimulation as does the delivery of direct agonists at doses which stimulate the post-synaptic receptors. Direct agonists have been shown to affect rates of responding for intracranial self-stimulation in a variety of ways: sometimes rates increase, sometimes they decrease and sometimes rates are unaffected. Similarly, non-contingent stimulation has been demonstrated to increase, to decrease or to have no effect upon rates of responding for brain stimulation reward. Low doses of direct agonists, such as apomorphine, are thought to inhibit the reward process by stimulating the pre-synaptic receptors thereby increasing thresholds for intracranial stimulation. According to the "free reward" hypothesis high doses of direct agonists facilitate

self-stimulation by stimulating the post-synaptic receptors while, increasing concentrations result in the maximum activation of the post-synaptic receptors which results in the inability of the animal to distinguish between the rewarding effects of the drug and the rewarding effects of the brain stimulation and thresholds for brain stimulation reward would increase. By administering subthreshold levels of non-contingent stimulation during brain stimulation reward we attempted to model the effects of "free reward". If the effects of the non-contingent stimulation upon self-stimulation were seen to resemble the effects of direct agonists upon brain stimulation reward then it could be concluded that the direct agonists (at doses which stimulate the post-synaptic receptors) act to enhance brain stimulation reward by non-contingently stimulating the reward substrate. It was determined that the non-contingent stimulation caused frequency thresholds for contingent stimulation to decrease, suggesting that the non-contingent stimulation enhanced intracranial self-stimulation. Thus, the effects of the non-contingent stimulation upon frequency thresholds for self-stimulation are equivalent to the effects of direct agonists at doses which stimulate the post-synaptic receptors. We therefore suggest that high doses of direct agonists enhance intracranial self-stimulation by non-contingently stimulating the post-synaptic receptors as proposed by the "free reward" hypothesis.

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Figure 1

The interpolation of frequency thresholds for brain stimulation reward when the non-contingent stimulation is presented (NCS 10Hz) and when only response-contingent stimulation is presented (NCS OFF).

Plotted on the abscissa is the frequency of the brain stimulation while the number of responses is plotted on the ordinate. The frequency threshold is interpolated by intercepting the curve at the half-maximal level of responding and dropping a line to the abscissa.

NUMBER OF RESPONSES IN 30 SECONDS

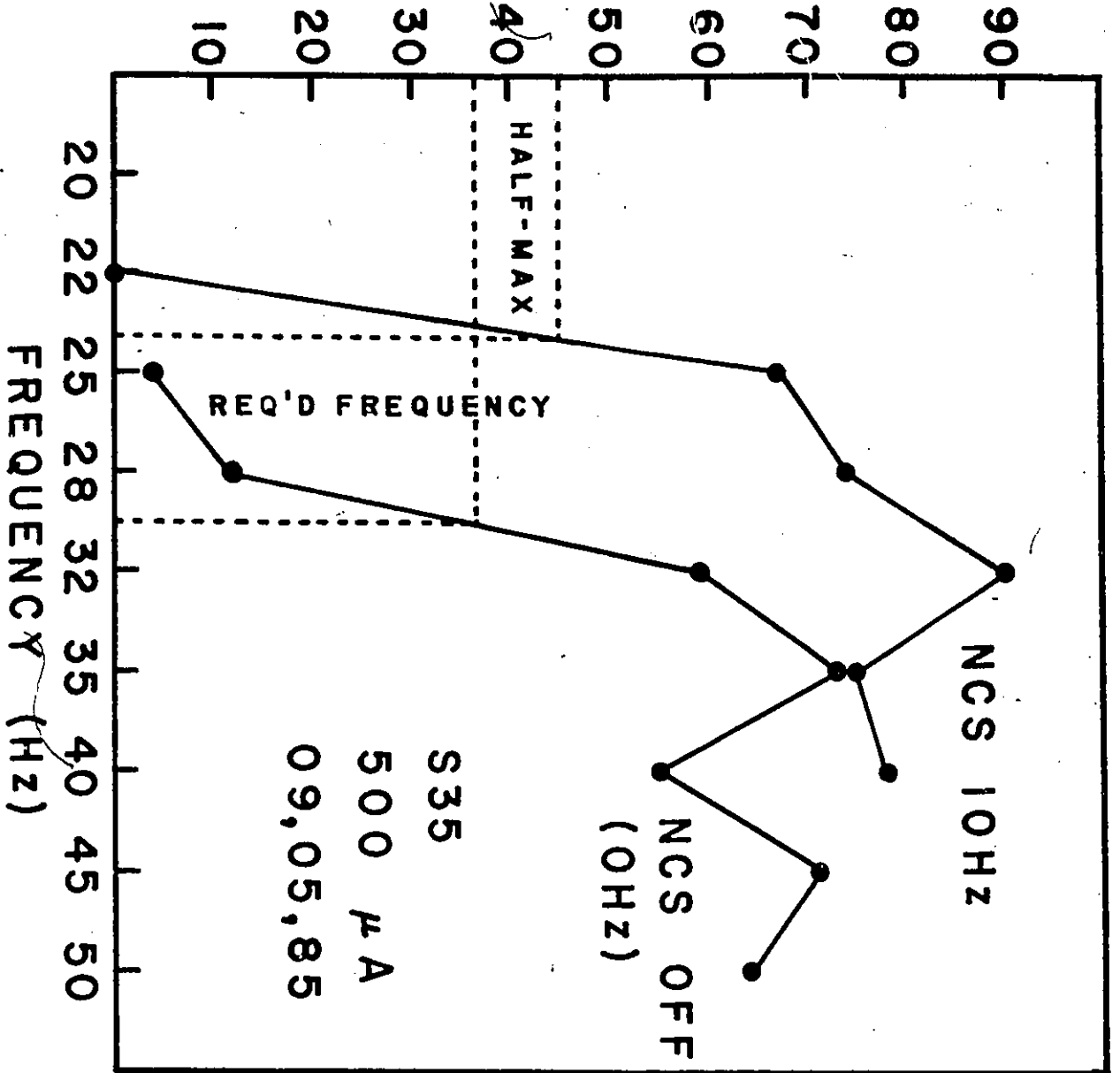


Figure 2

Schematic depicting the delivery of response-contingent and non-contingent stimulation to the left electrode (LEFT EL). The contingent stimulation is triggered by the lever press (LEVER). The right electrode (RIGHT EL) receives no brain stimulation.

BACKGROUND TO SAME ELECTRODE

LEVER



LEFT EL



CONDITION

RIGHT EL



LL

Figure 3

Schematic depicting the delivery of response-contingent stimulation to the left electrode (LEFT EL) and non-contingent stimulation to the right electrode (RIGHT EL). The response-contingent stimulation is triggered by the lever press (LEVER).

BACKGROUND TO

CONTRALATERAL ELECTRODE

LEVER

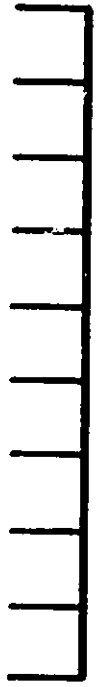


LEFT EL



CONDITION

RIGHT EL



LR

Figure 4

Graphic representation of the summation condition in which contingent stimulation is delivered to both electrodes.

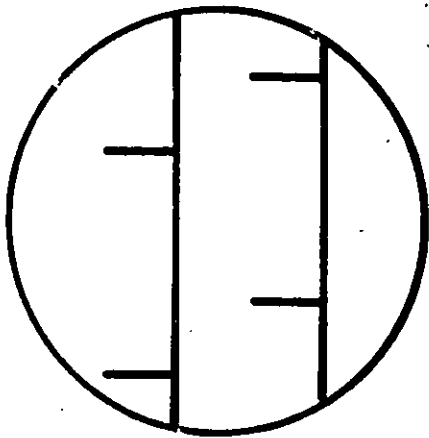
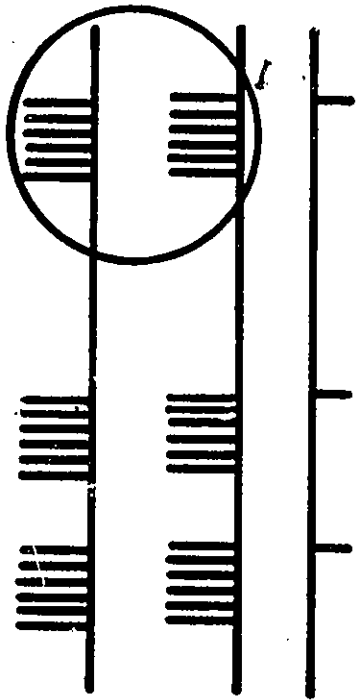
The inset shows that the C or conditioning pulse, delivered to the left electrode, precedes the T or test pulse, delivered to the right electrode.

SUMMATION

LEVER

LEFT EL

RIGHT EL



6



Figure 5

Placements of electrodes implanted with flat skull co-ordinates for subjects in Experiment 1.

The numerical value represents the anterior-posterior co-ordinate, referenced to bregma, while the alpha-numeric values designate the subjects. The filled circles represent the placements of the electrode tips.

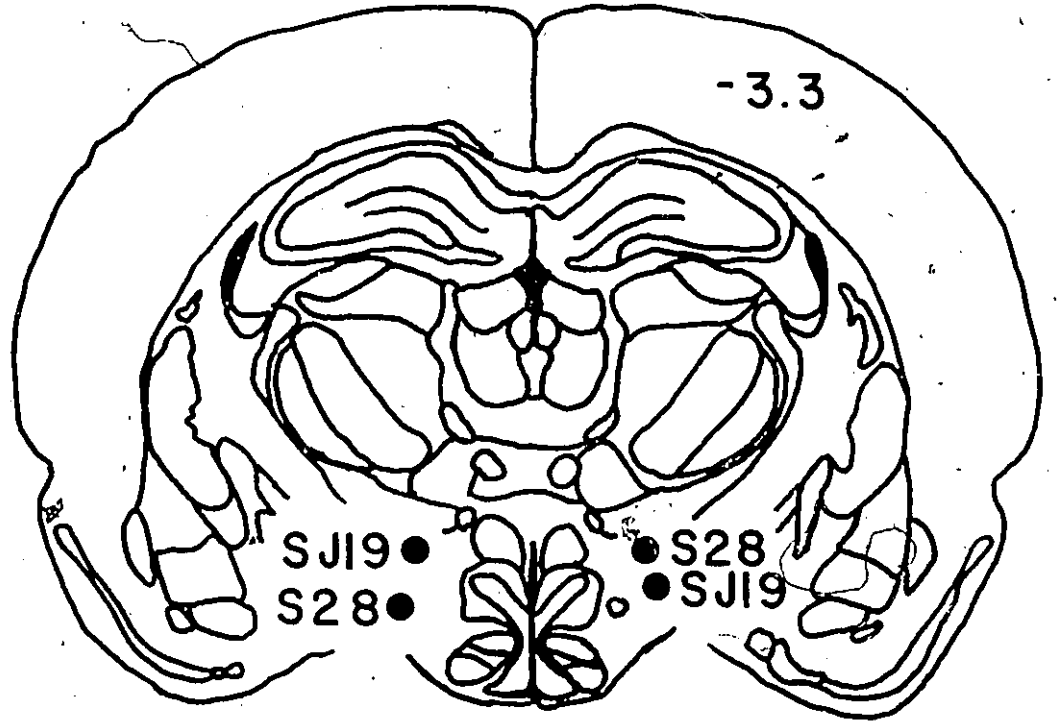


Figure 6

Placements of electrodes implanted with deGroot co-ordinates for one subject (SJ15) in Experiment 1.

The numerical value represents the anterior-posterior co-ordinate, referenced to bregma, while the alpha-numeric values designate the subjects. The filled circles represent the placements of the electrode tips.

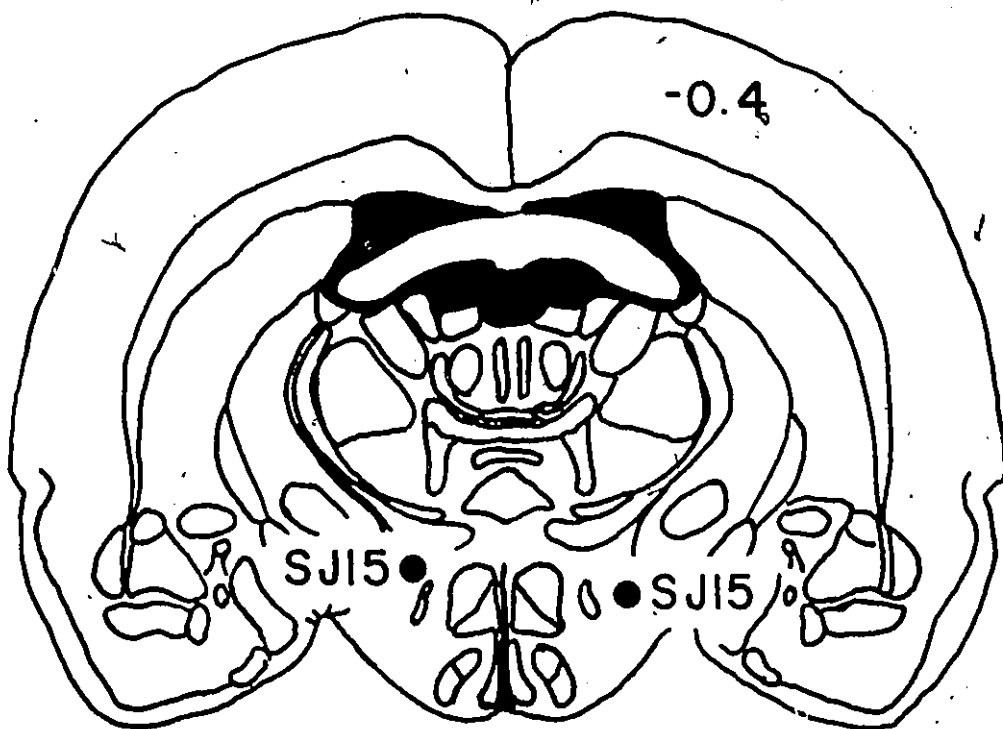


Figure 7

The effect of the non-contingent stimulation (NCS) upon the maximal rate of responding for brain stimulation reward in subject SJ15.

LL refers to the experimental condition in which contingent and non-contingent stimulation are presented to the left electrode while RR represents the condition in which both types of stimulation are delivered to the right electrode.

LR refers to the experimental condition in which the contingent stimulation is presented to the left electrode and the non-contingent stimulation is presented to the right electrode, RL, in which the contingent stimulation is presented to the right electrode and the non-contingent to the left electrode.

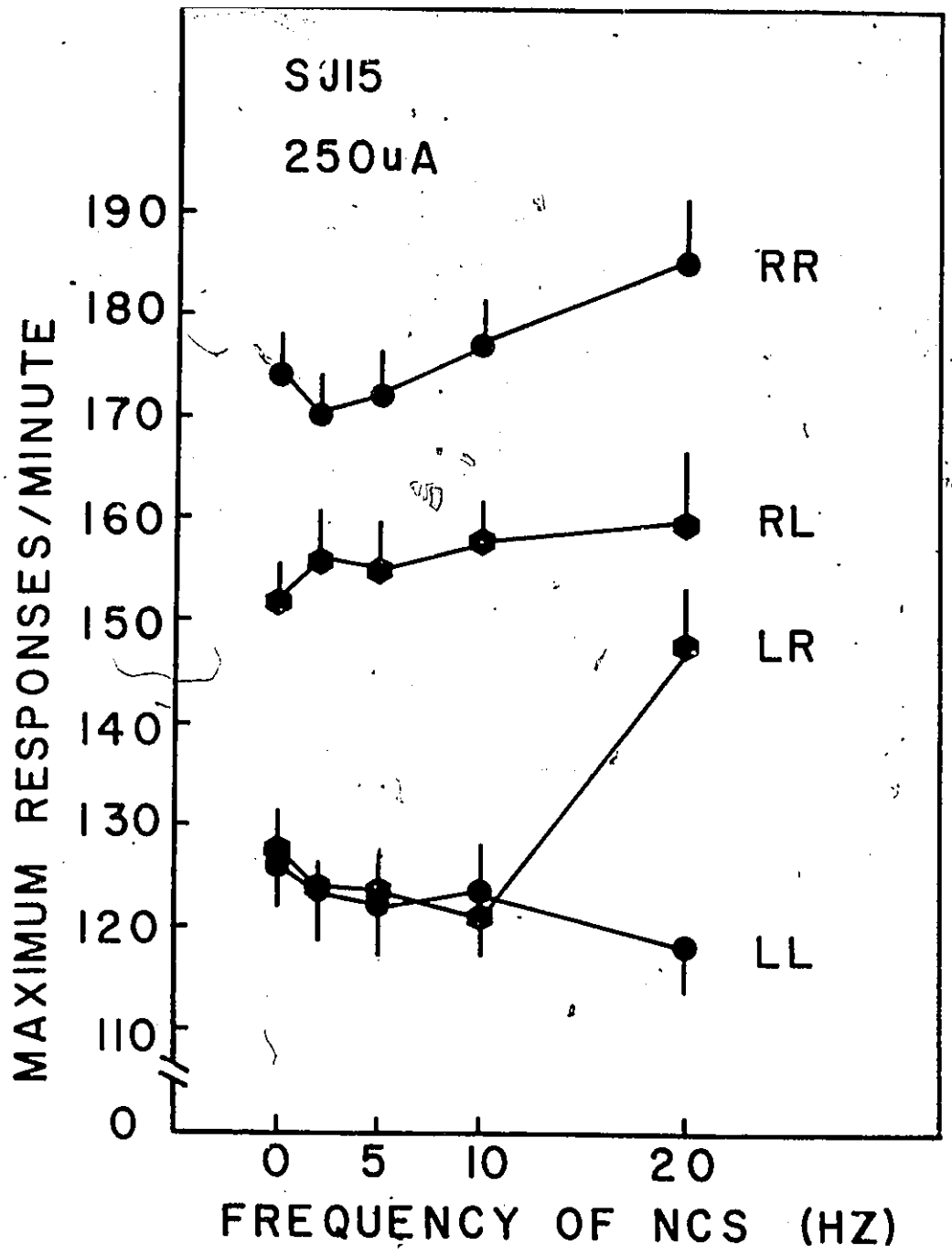


Figure 8

The effect of non-contingent stimulation upon the maximal rate of responding for brain stimulation reward for SJ19.

LL refers to the experimental condition in which contingent and non-contingent stimulation are presented to the left electrode while RR represents the condition in both types of stimulation are delivered to the right electrode.

LR refers to the experimental condition in which the contingent stimulation is presented to the left electrode and the non-contingent stimulation is presented to the right electrode, RL, in which the contingent stimulation is presented to the right electrode and the non-contingent to the left electrode.

MAXIMUM RESPONSES / MINUTE

SJ19

320uA

150
140
130
120
110
100
90
0

FREQUENCY OF NCS (HZ)

RL
LL
LR
RR

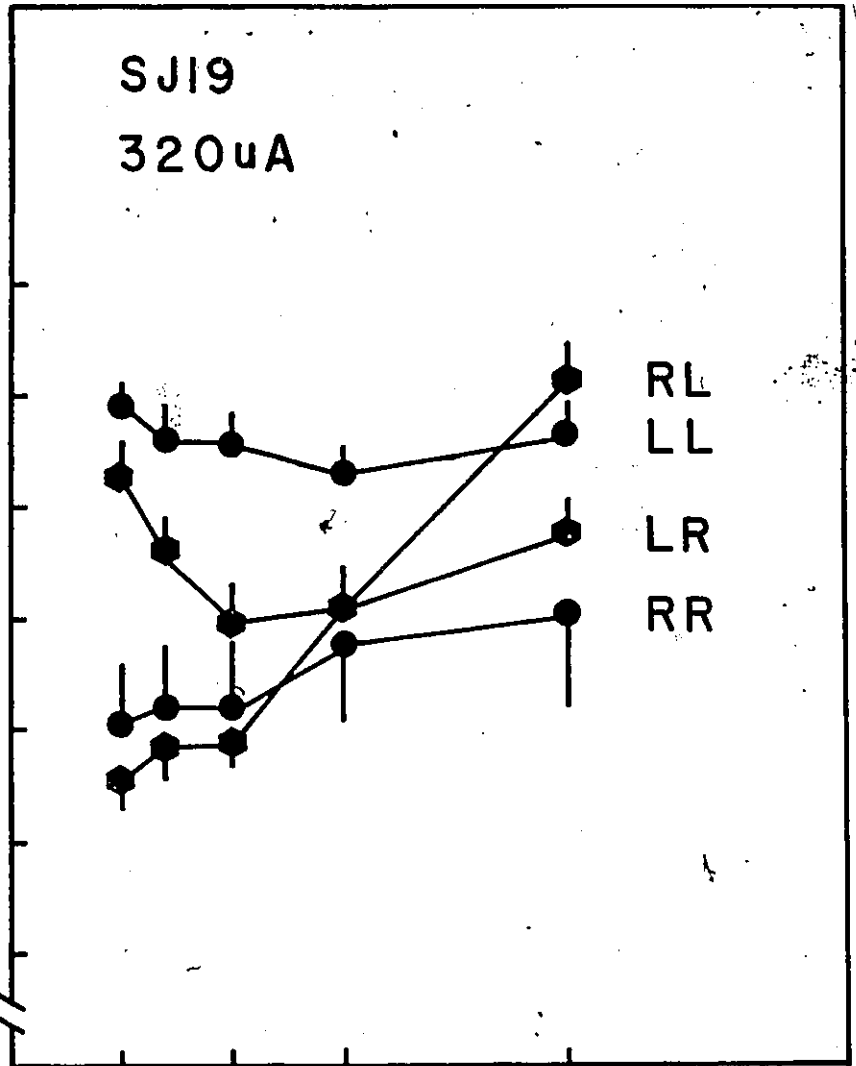


Figure 9

The effect of non-contingent stimulation upon the maximal rate of responding for brain stimulation reward for S16.

LL refers to the experimental condition in which contingent and non-contingent stimulation are presented to the left electrode while RR represents the condition in which the both types of stimulation are delivered to the right electrode.

LR refers to the experimental condition in which the contingent stimulation is presented to the left electrode and the non-contingent stimulation is presented to the right electrode, RL, in which the contingent stimulation is presented to the right electrode and the non-contingent to the left electrode.

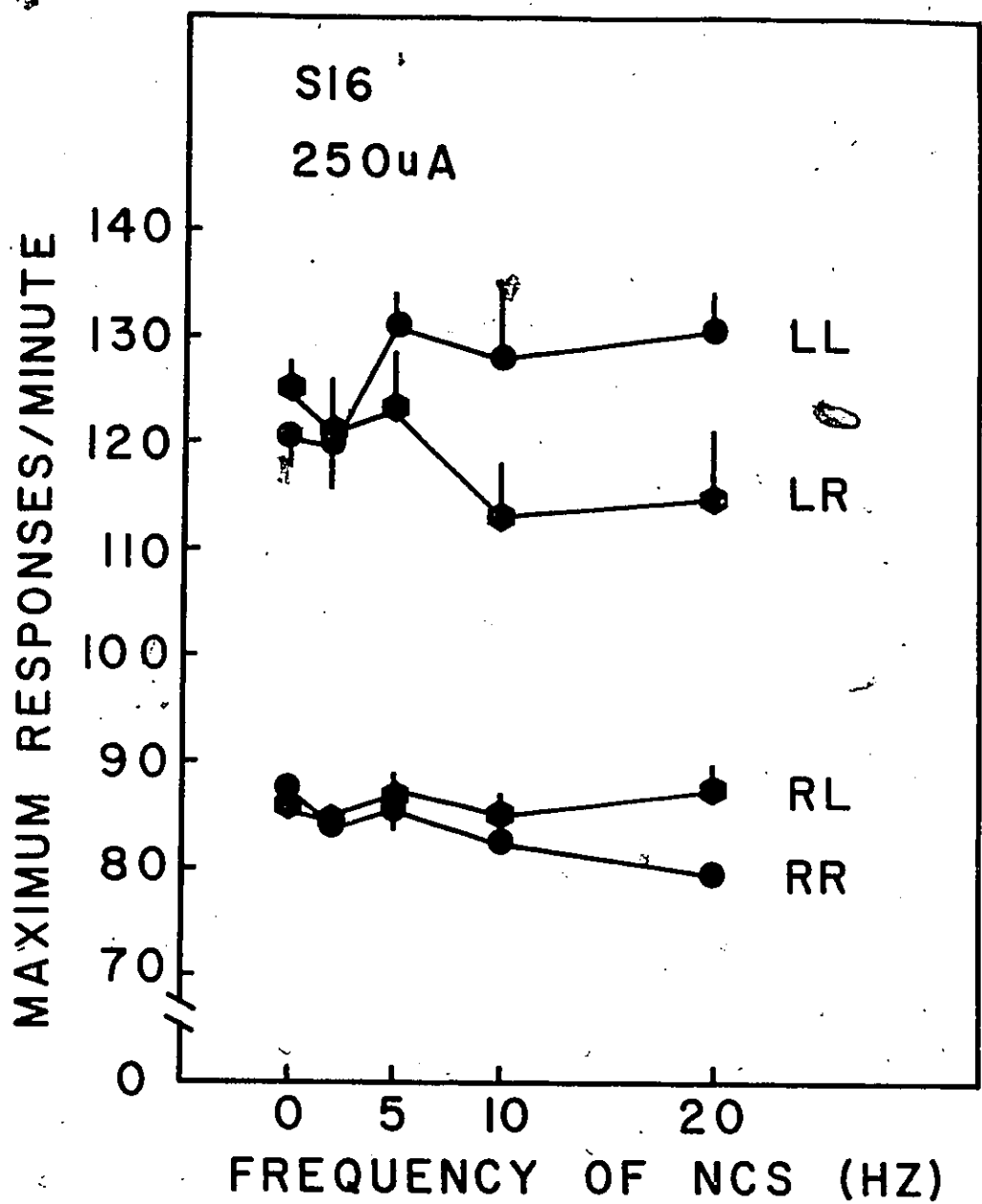


Figure 10

The effect of non-contingent stimulation upon the maximal rate of responding for brain stimulation reward for S28.

LL refers to the experimental condition in which contingent and non-contingent stimulation are presented to the left electrode while RR represents the condition in which the both types of stimulation are delivered to the right electrode.

LR refers to the experimental condition in which the contingent stimulation is presented to the left electrode and the non-contingent stimulation is presented to the right electrode, RL, in which the contingent stimulation is presented to the right electrode and the non-contingent to the left electrode.

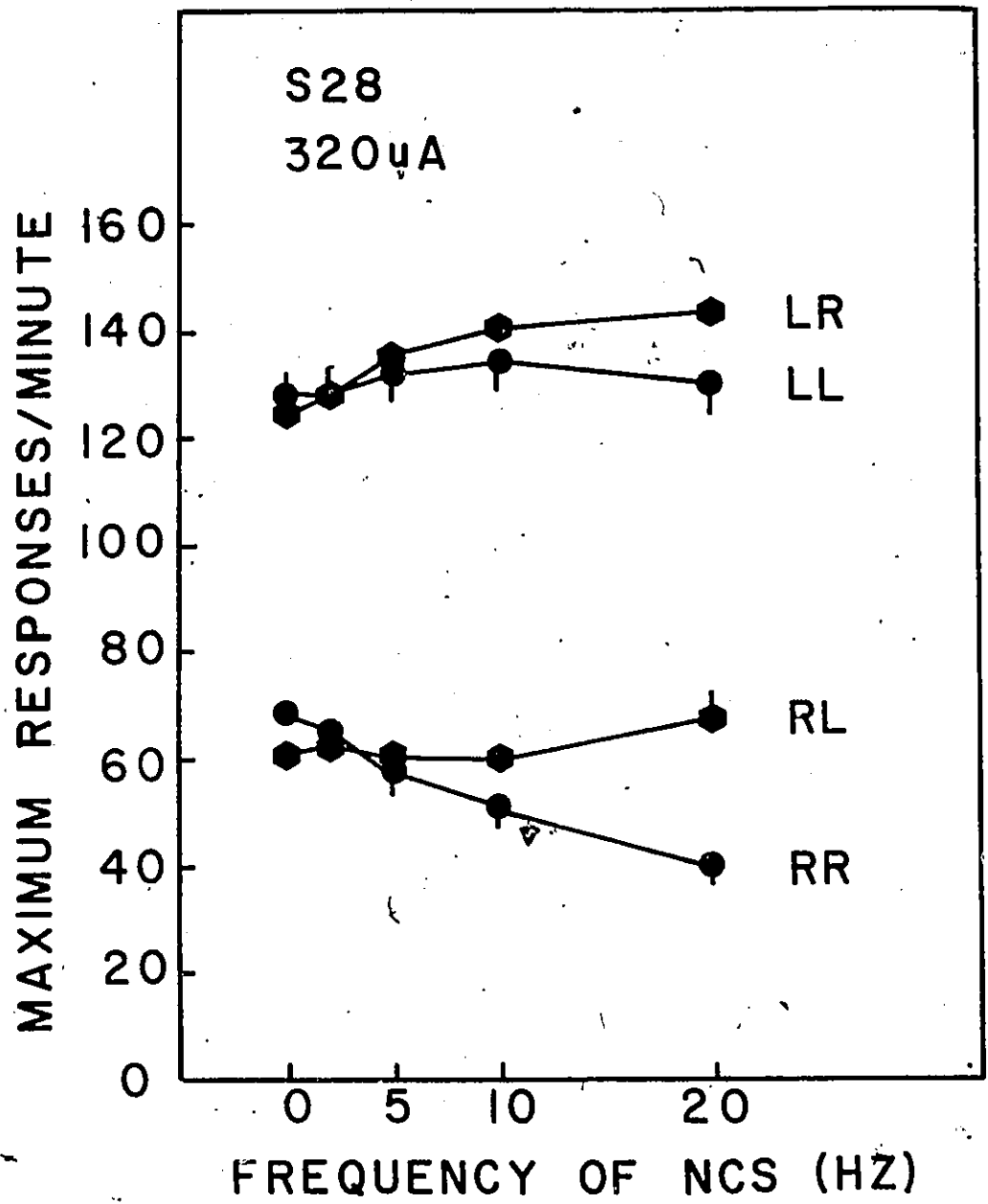


Figure 11

The effect of the non-contingent stimulation (NCS) upon frequency thresholds for brain stimulation reward in subject SJ15.

LL refers to the experimental condition in which contingent and non-contingent stimulation are presented to the left electrode while RR represents the condition in which both types of stimulation are delivered to the right electrode.

LR refers to the experimental condition in which the contingent stimulation is presented to the left electrode and the non-contingent stimulation is presented to the right electrode, RL, in which the contingent stimulation is presented to the right electrode and the non-contingent to the left electrode.

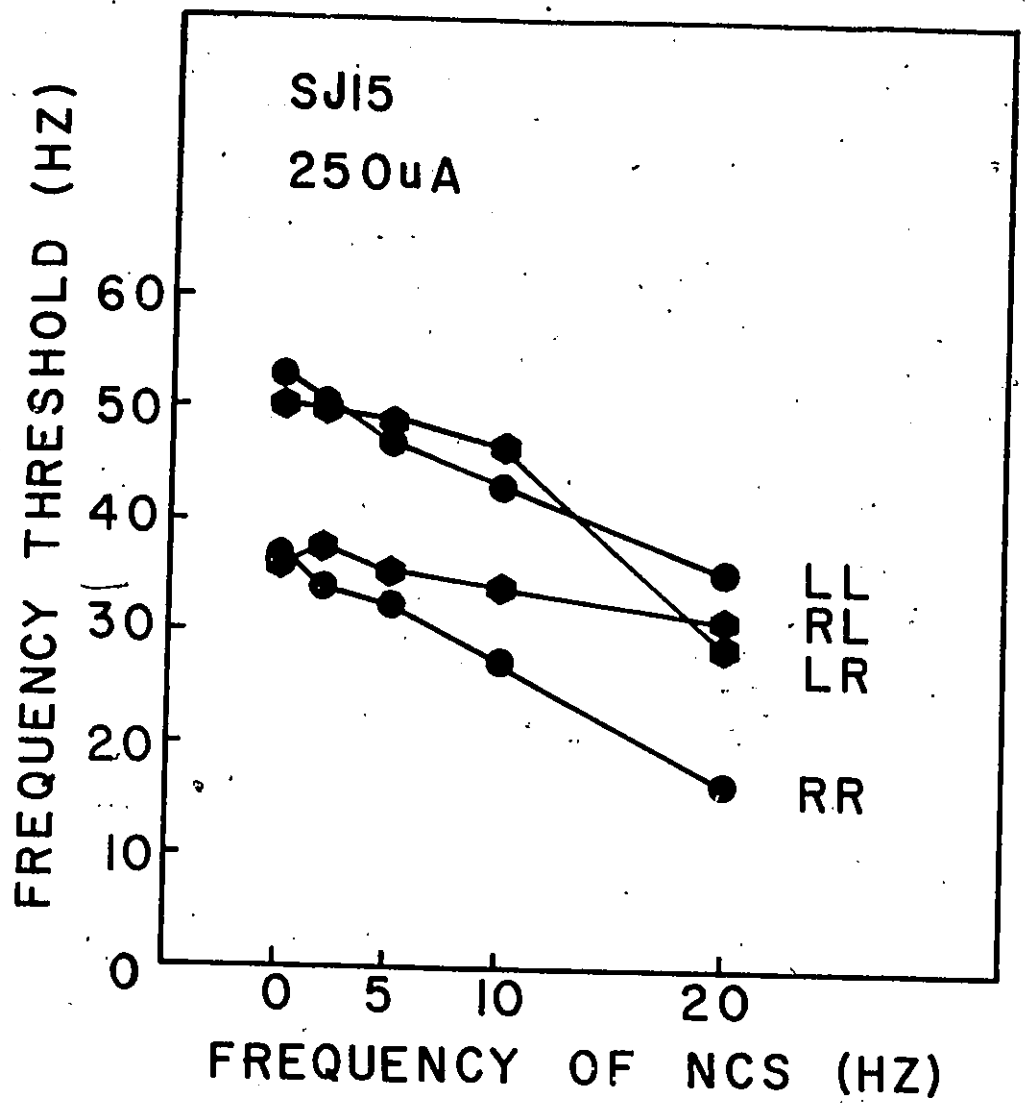


Figure 12

The effect of the non-contingent stimulation upon frequency thresholds for brain stimulation reward in SJ19.

LL refers to the experimental condition in which contingent and non-contingent stimulation are presented to the left electrode while RR represents the condition in which both types of stimulation are delivered to the right electrode.

LR refers to the experimental condition in which the contingent stimulation is presented to the left electrode and the non-contingent stimulation is presented to the right electrode, RL, in which the contingent stimulation is presented to the right electrode and the non-contingent to the left electrode.

FREQUENCY THRESHOLD (HZ)

SJ19

320uA

40
30
20
10
0

FREQUENCY OF NCS (HZ)

LR
RL
LL
RR

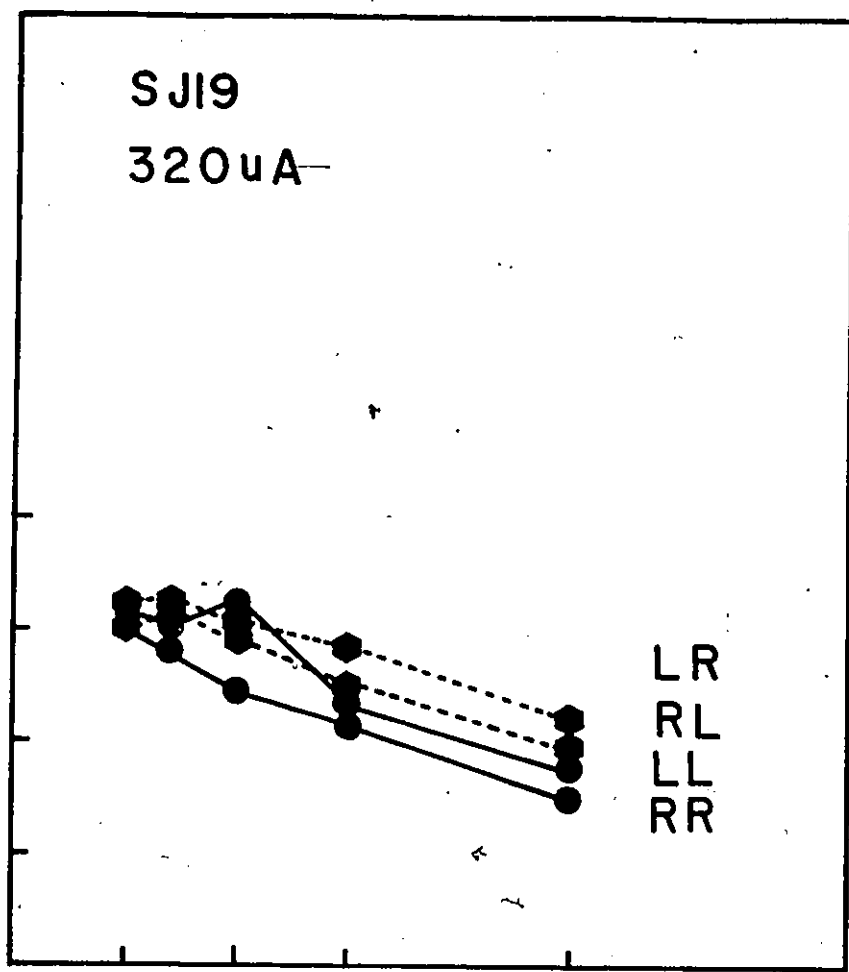


Figure 13

The effect of the non-contingent stimulation upon frequency thresholds for brain stimulation reward in S16.

LL refers to the experimental condition in which contingent and non-contingent stimulation are presented to the left electrode while RR represents the condition in which both types of stimulation are delivered to the right electrode.

LR refers to the experimental condition in which the contingent stimulation is presented to the left electrode and the non-contingent stimulation is presented to the right electrode, RL, in which the contingent stimulation is presented to the right electrode and the non-contingent to the left electrode.

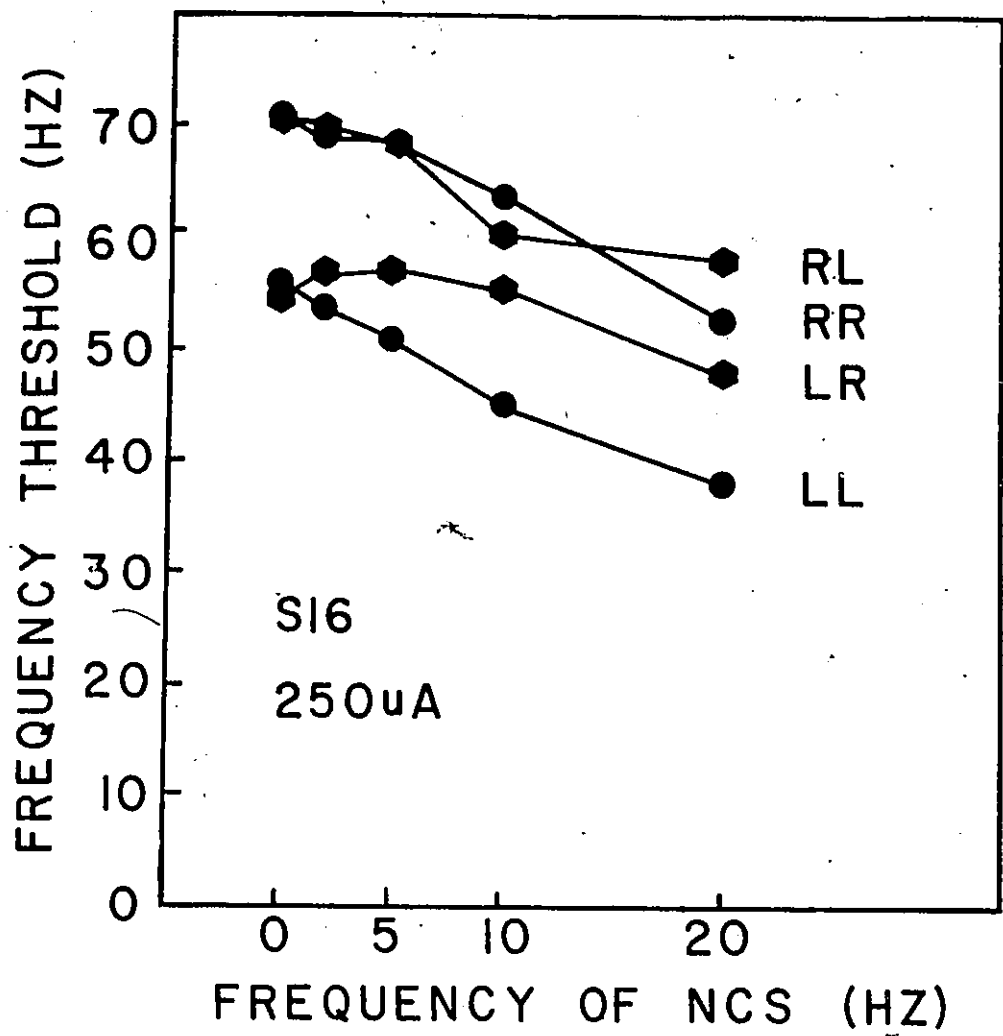


Figure 14

The effect of the non-contingent stimulation upon frequency thresholds for brain stimulation reward in S28.

LL refers to the experimental condition in which contingent and non-contingent stimulation are presented to the left electrode while RR represents the condition in both types of stimulation are delivered to the right electrode.

LR refers to the experimental condition in which the contingent stimulation is presented to the left electrode and the non-contingent stimulation is presented to the right electrode, RL, in which the contingent stimulation is presented to the right electrode and the non-contingent to the left electrode.

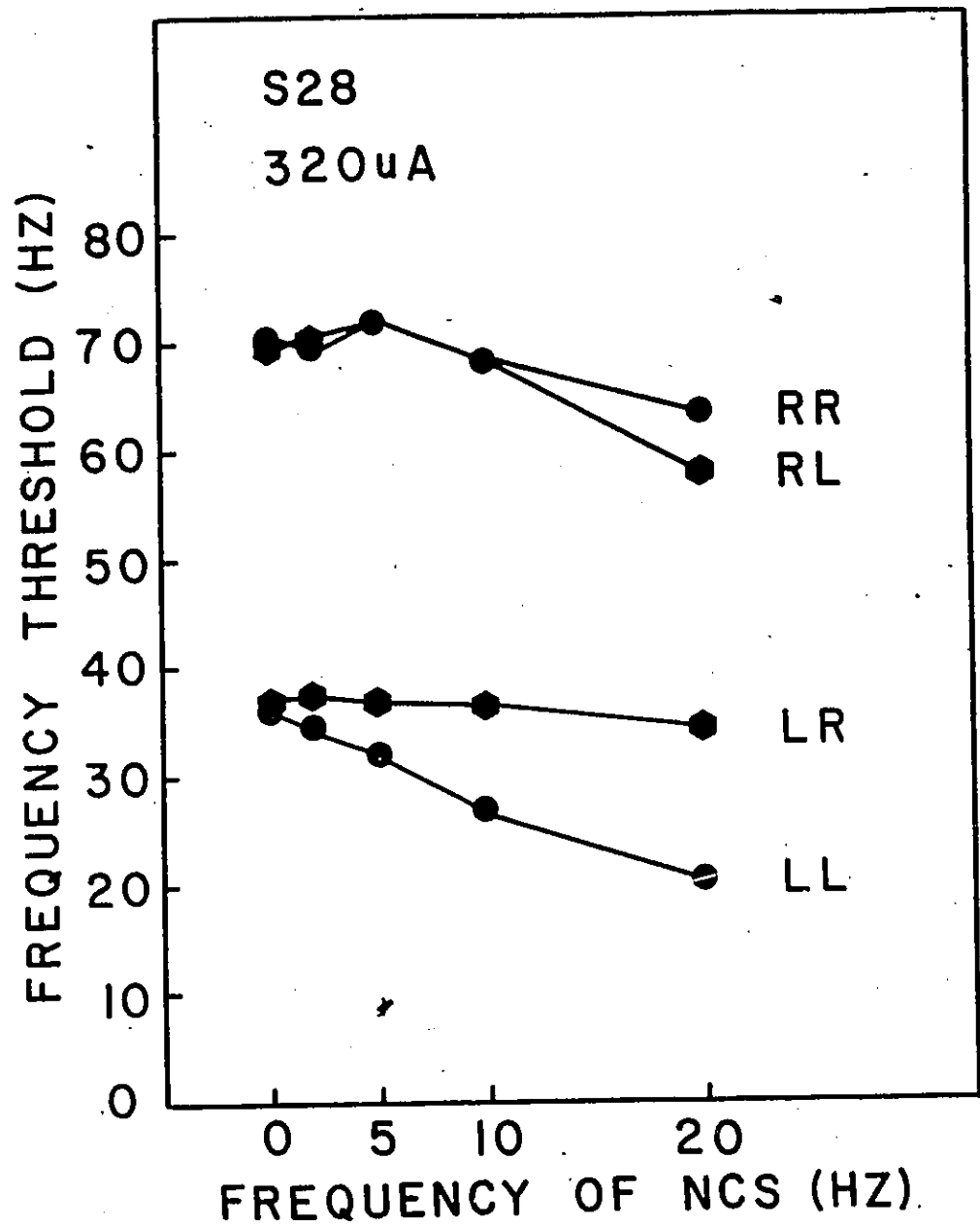


Figure 15

Placements of the electrodes implanted with flat skull co-ordinates for subjects in Experiment 2.

The alphanumeric values represent the identities of the subjects while the numeric values represent the anterior-posterior coordinates referenced to bregma. The filled circles locate the placements of the electrode tips.

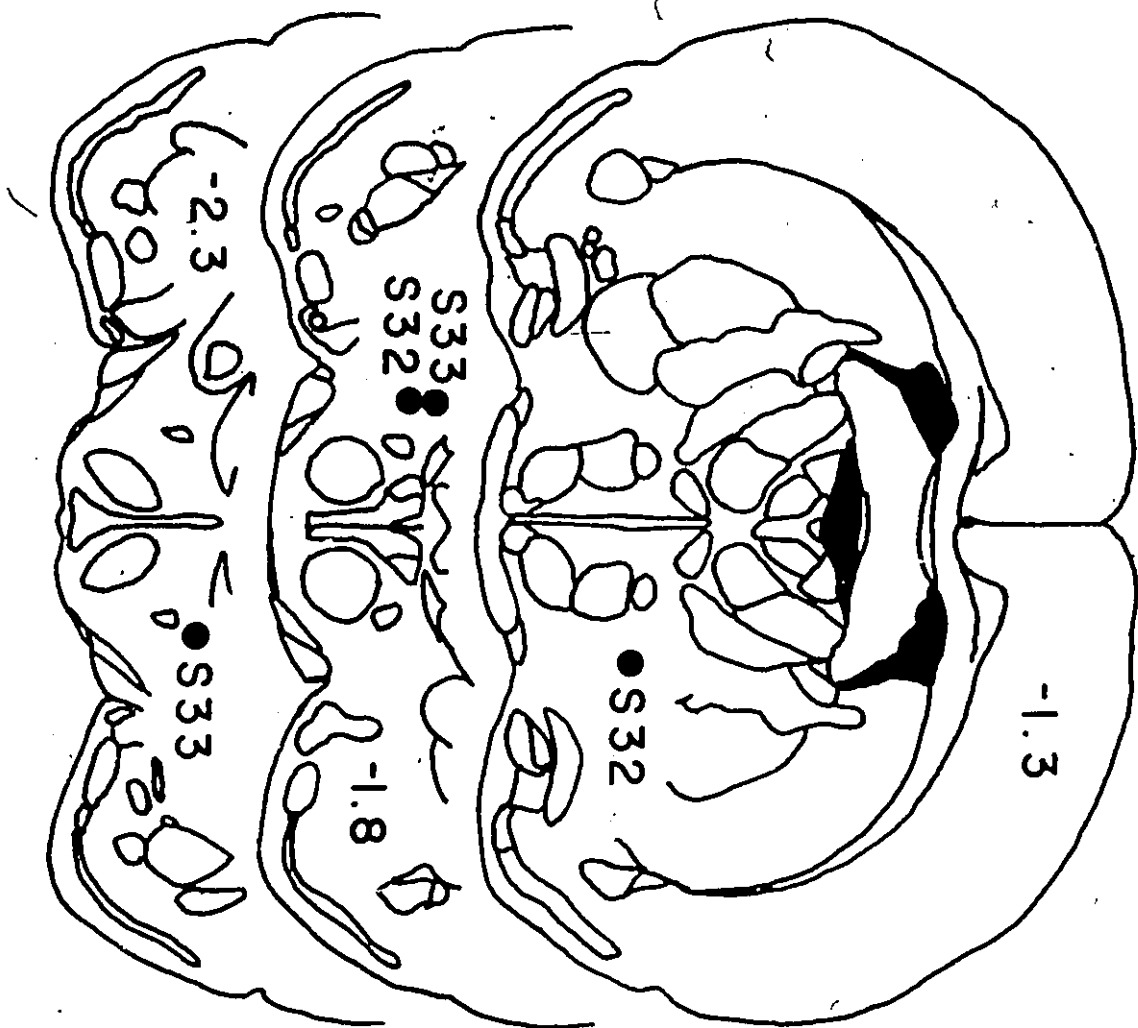


Figure 16

Placements of the electrodes implanted with flat skull co-ordinates for subjects in Experiment 3.

The alphanumeric values represent the identities of the subjects while the numeric values represent the anterior-posterior coordinates referenced to bregma. The filled circles locate the placements of the electrode tips.

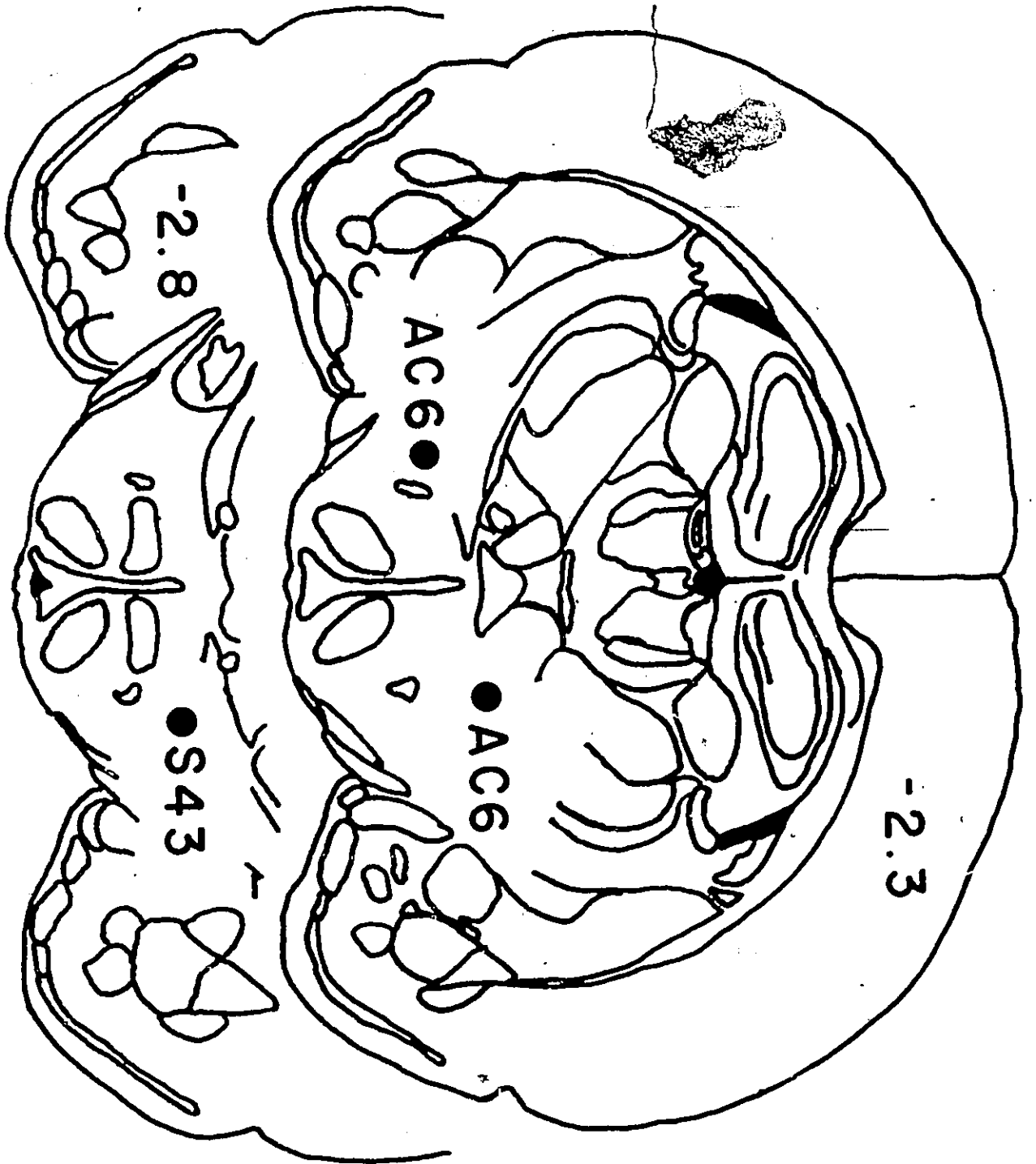


Figure 17

The effect of non-contingent stimulation upon the frequency thresholds for brain stimulation reward in subject S35.

The effect was calculated at three different intensities. Low intensities are represented by filled circles, medium intensities by filled hexagons, and high intensities by filled triangles. The actual value of the intensity in microamperes is found adjacent to the corresponding curve.

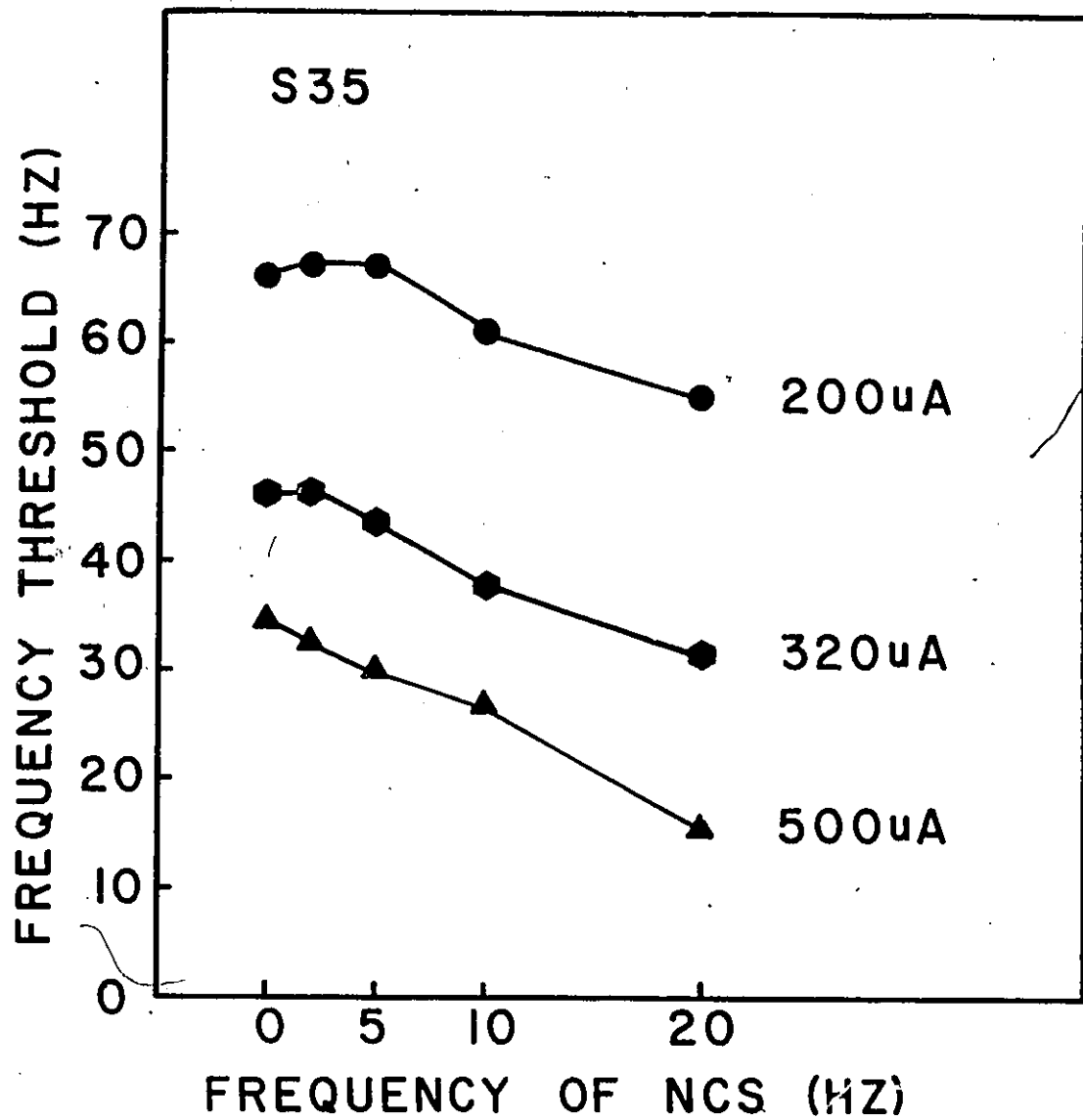
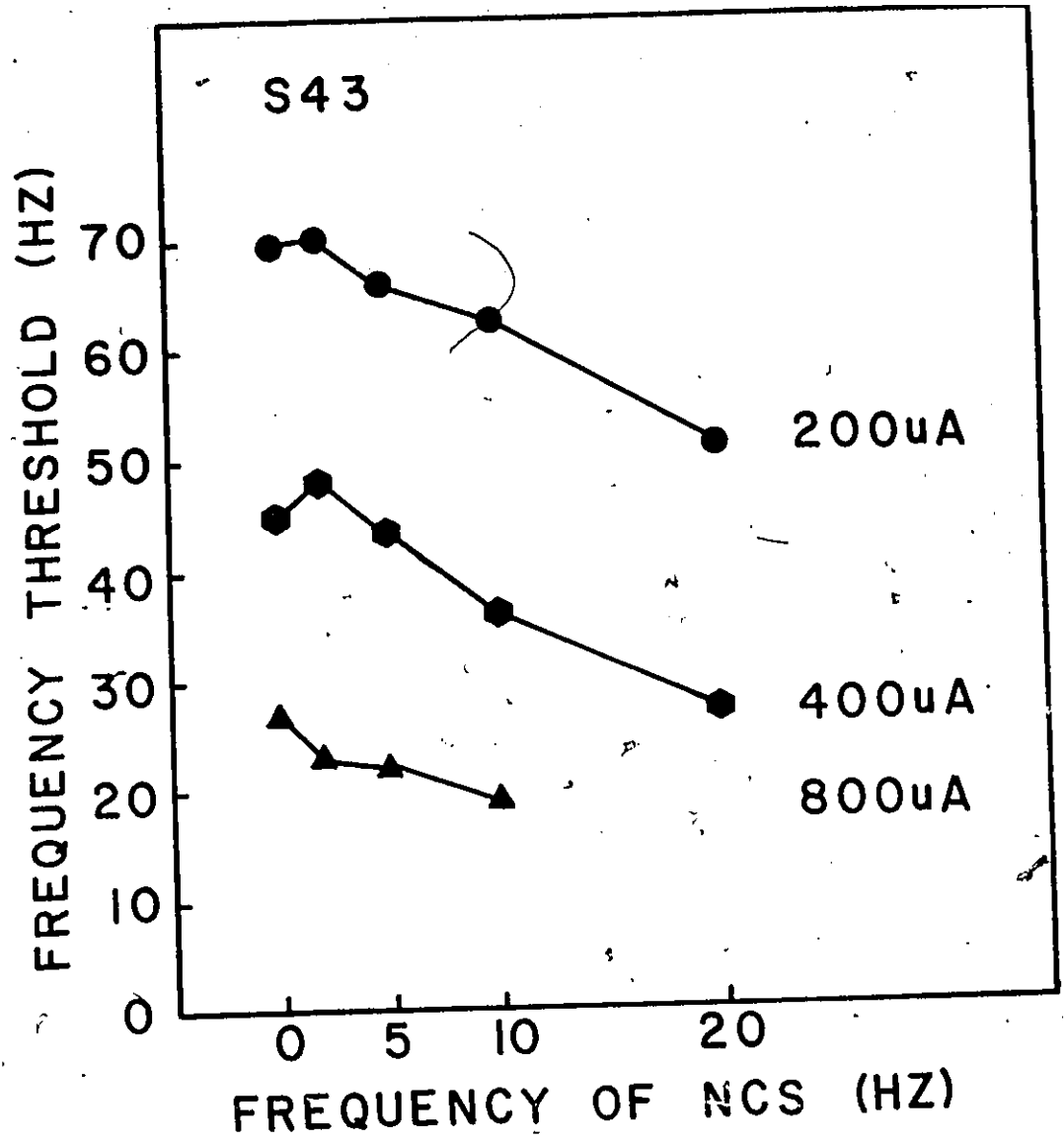


Figure 18

The effect of non-contingent stimulation upon the frequency thresholds for brain stimulation reward in subject S43.

The effect was calculated at three different intensities. Low intensities are represented by filled circles, medium intensities by filled hexagons, and high intensities by filled triangles. The actual value of the intensity in microamperes is found adjacent to the corresponding curve.



U

Figure 19

The effect of non-contingent stimulation upon the frequency thresholds for brain stimulation reward in subject AC6.

The effect was calculated at three different intensities. Low intensities are represented by filled circles, medium intensities by filled hexagons, and high intensities by filled triangles. The actual value of the intensity in microamperes is found adjacent to the corresponding curve.

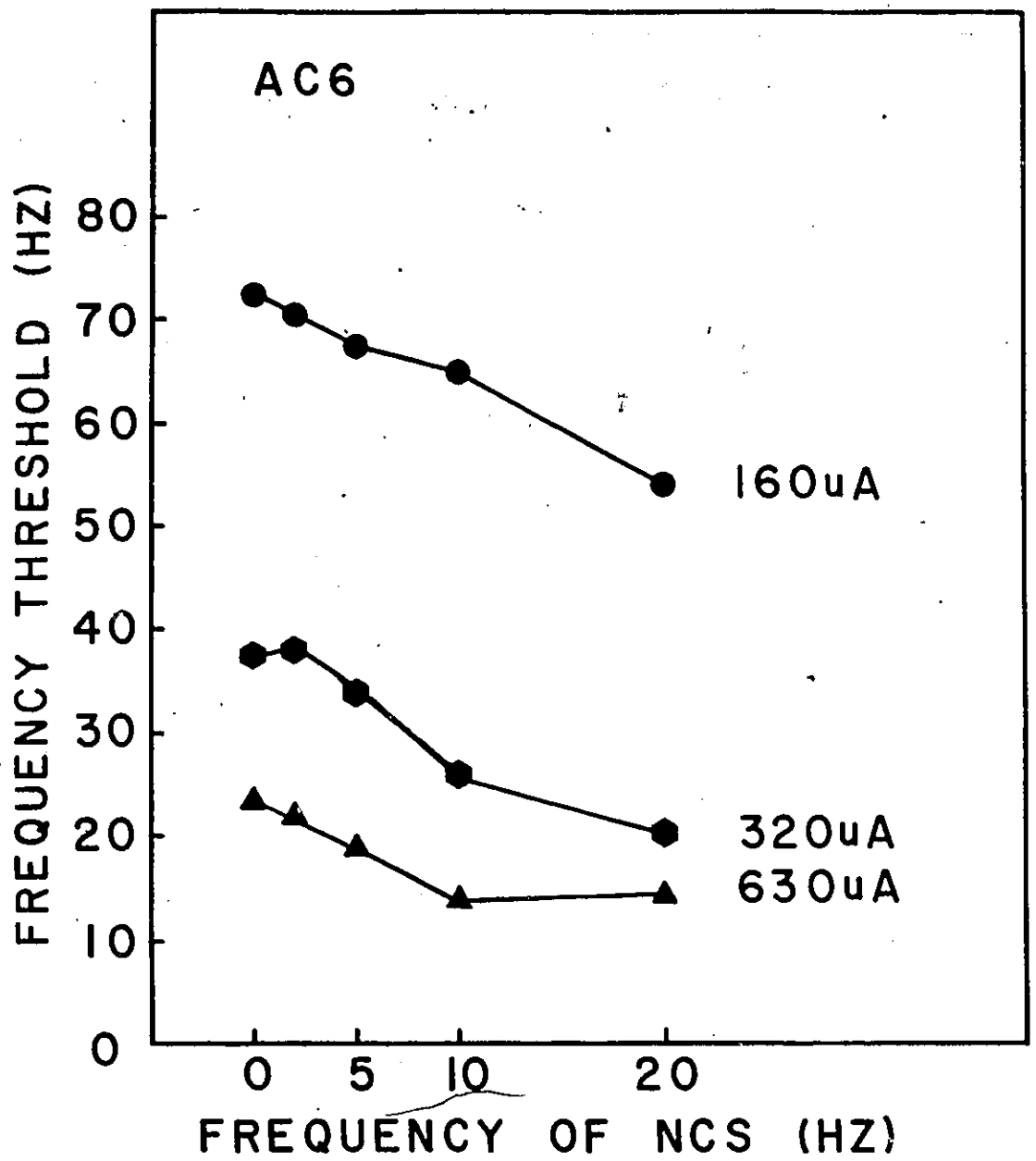


Figure 20

Placements of the electrodes implanted with flat skull co-ordinates for subjects in Experiment 4.

The numerical values represent the anterior-posterior coordinates referenced to bregma while the alphanumeric values refers to the subjects' identities. The filled circles locate the placements of the electrode tips.

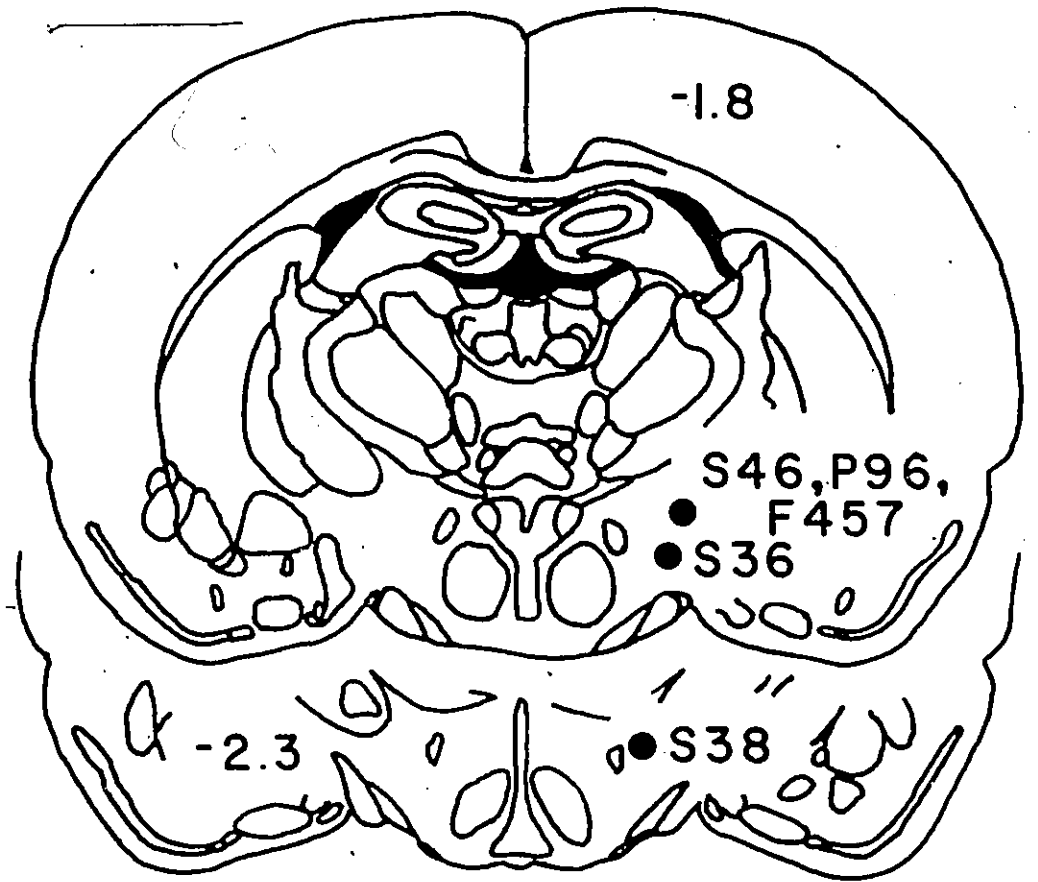


Figure 21

The effect of non-contingent stimulation during the 2 ms block condition and during the 500 ms block condition on frequency thresholds for brain stimulation reward for subject S36.

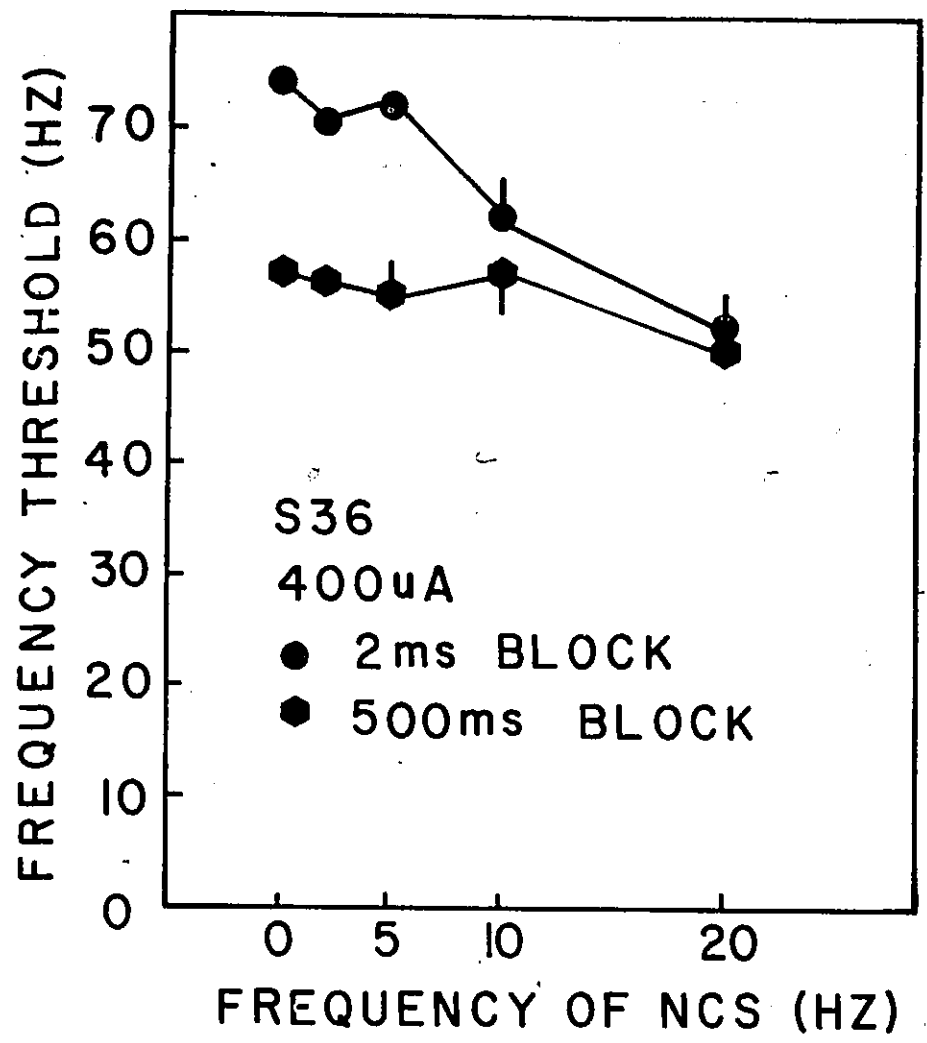
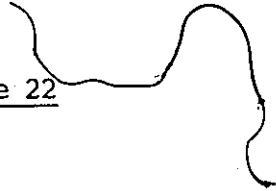


Figure 22



The effect of non-contingent stimulation during the 2 ms block condition and during the 500 ms block condition on frequency thresholds for brain stimulation reward for subject S46.

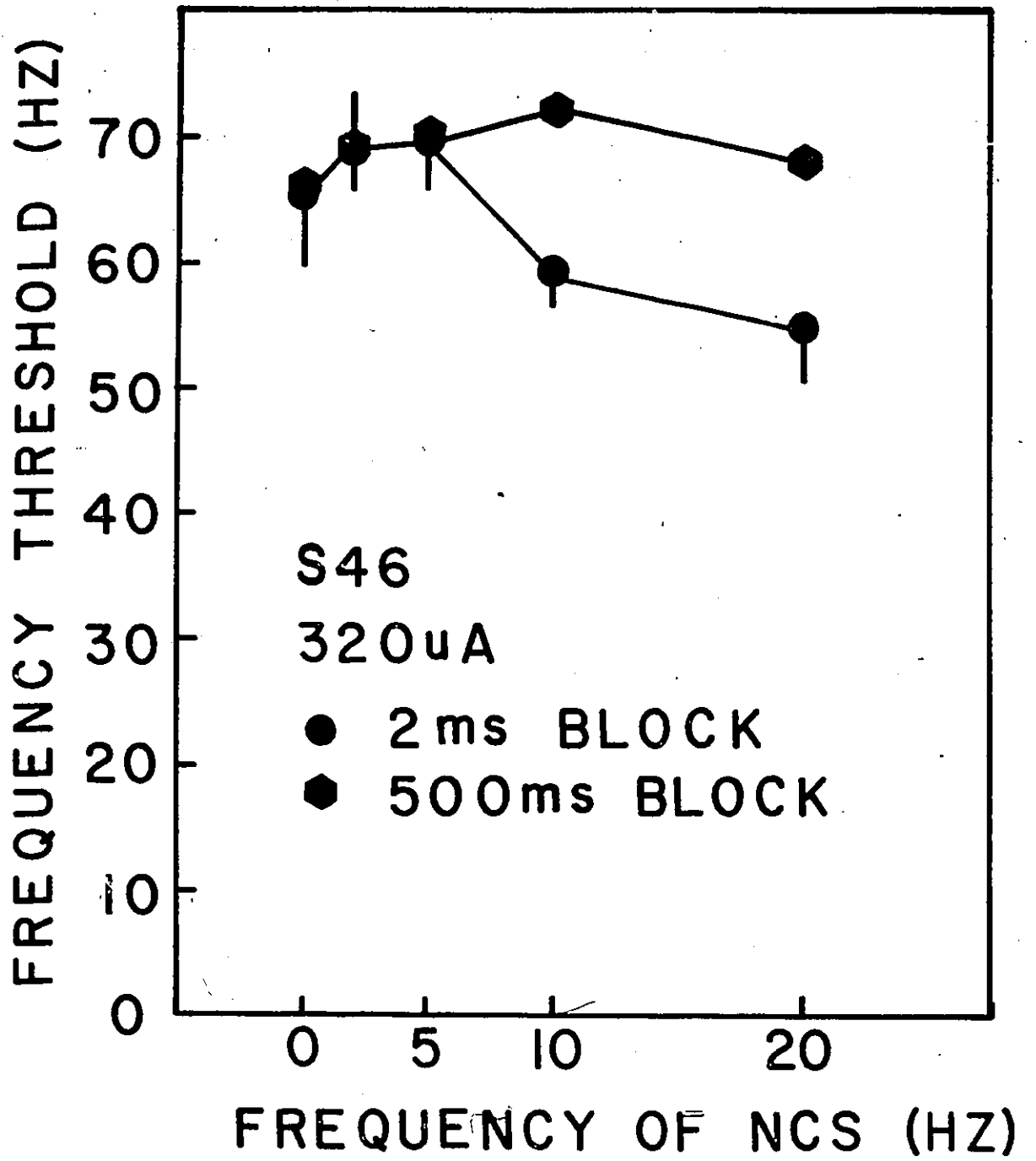


Figure 23

The effect of non-contingent stimulation during the 2 ms block condition and during the 500 ms block condition on frequency thresholds for brain stimulation reward for subject F457.

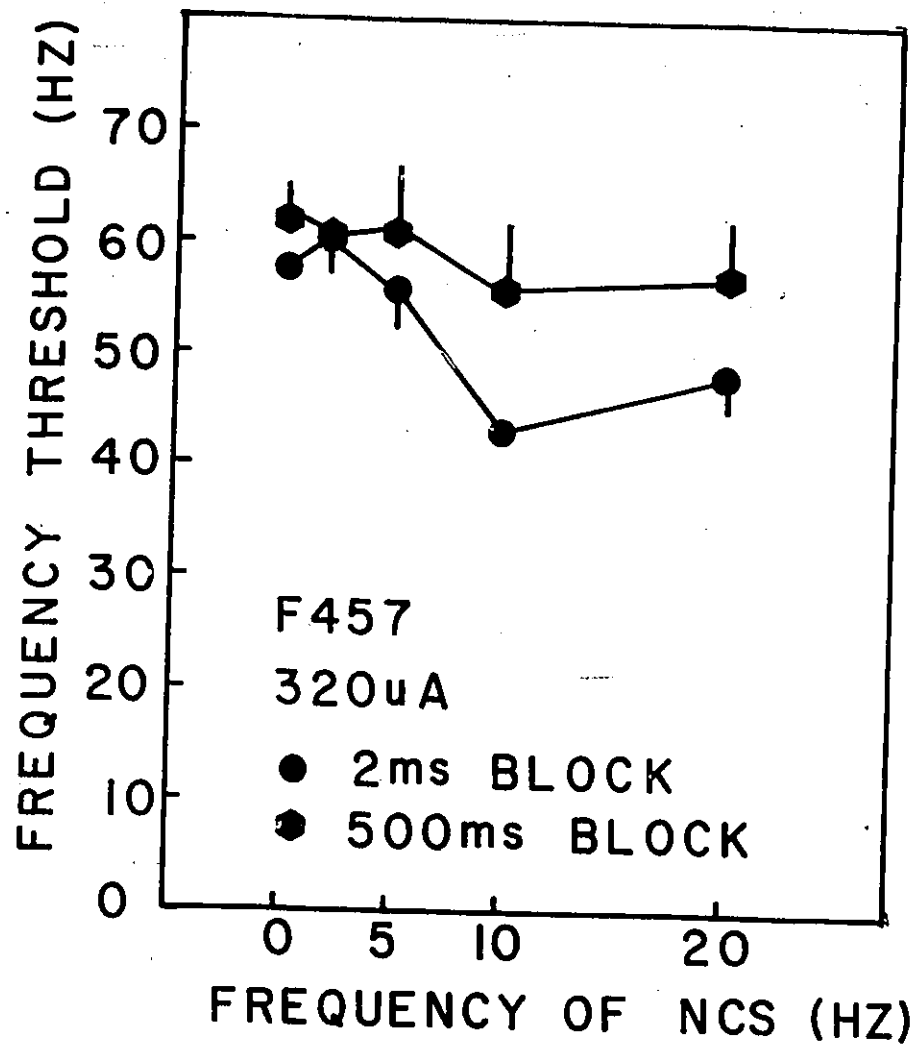


Table 1

Difference Scores obtained from subjects in Experiment 1Where: O refers to the obtained slope, and P to the predicted slope

Subject	Experimental Condition	Slope		Difference Scores	
		O	P	O-P	O-1.0
SJ15	LL	-.83	-.89	.06	.17
	RR	-1.0	-.93	-.07	.00
	LR	-.90	-.44	-.46	.10
	RL	-.32	-.26	-.06	.68
SJ19	LL	-.68	-.94	.26	.32
	RR	-.71	-.94	.23	.29
	LR	-.58	-.41	-.17	.42
	RL	-.64	-.32	-.32	.36
S16	LL	-.86	-.89	.03	.14
	RR	-.97	-.86	-.11	.03
	LR	-.50	-.43	-.07	.50
	RL	-.67	-.52	-.15	.33
S28	LL	-.79	-.93	.14	.21
	RR	-.42	-.86	.44	.58
	LR	-.16	-.19	.03	.85
	RL	-.75	-.45	.30	.25
Overall Mean				.005	.33
S.E.M				.06	.06

Table 2

Summation Levels obtained from subjects in Experiment 1

Subject	Experimental Condition	Summation Level
SJ15	LR	0.49
	RL	0.28
SJ19	LR	0.44
	RL	0.34
S16	LR	0.48
	RL	0.60
S28	LR	0.20
	RL	0.52

Table 3

Correlation of summation levels and obtained slopes
for Experiment 1

Subject	Experimental Condition	Summation	Slopes
SJ15	LR	0.49	-.90
	RL	0.28	-.32
SJ19	LR	0.44	-.58
	RL	0.34	-.64
S16	LR	0.48	-.50
	RL	0.60	-.67
S28	LR	0.20	-.16
	RL	0.53	-.75
Correlation		-.79	
p<.01			

Table 4

Summation Levels and the Non-Contingent Stimulation Effect
(NCS Effect) for the subjects in Experiment 2

	Intensity (uA)						
	Left Fixed		Right Varied				
Subject S32	400uA	200	320	400	500	800	r(p<.05)
Summation Level		.39	.51	.60	.60	.92	-0.48
NCS Effect		.80	.79	.74	.68	.63	
Subject S33	400uA	250	320	400	500	630	r(p<.05)
Summation Level		.24	.31	.42	.60	.53	-0.31
NCS Effect		.85	.90	.81	.79	.77	
	Intensity (uA)						
	Right Fixed		Left Varied				
Subject S32	400uA	200	320	400	500	800	r(p<.05)
Summation Level		.18	.33	.43	.49	.83	-0.27
NCS Effect		.96	.92	.87	.86	.88	
Subject S33	500uA	320	400	500	630	800	r(p<.05)
Summation Level		.43	.53	.86	.92	1.29	-0.60
NCS Effect		.77	.69	.67	.58	.50	
Overall Correlation						r(p<.05)	
							-0.58

Table 5

Difference Scores obtained from subjects in Experiment 3Where: O refers to the obtained slope, and P to the predicted slope

Subject	Experimental Condition	Slope		Difference Scores	
		O	P	O-P	O-1.0
S35	200uA	-.72	-.87	.15	.28
	320uA	-.81	-.91	.10	.19
	500uA	-.93	-.93	.00	.07
S43	200uA	-1.03	-.86	-.17	-.03
	400uA	-1.14	-.91	-.23	-.14
	800uA	-.55	-.95	.40	.45
AC6	160uA	-.92	-.85	-.07	.08
	320uA	-.97	-.93	-.04	.03
	630uA	-1.04	-.95	-.09	-.04
Overall Mean				.006	.10
S.E.M				.19	.19

Table 6

Analysis of Variance determining whether Non-Contingent
Stimulation and Intensity affect Frequency thresholds for
Self-stimulation

Subject	Source	SS	df	MS	F	P
S35	Main Effects	27579	5	5515.8	320.37	<.01
	Intensity	24082.5	2	12041.2	699.38	<.01
	Frequency	3191.3	3	1063.8	61.78	<.01
	Interaction	132.13	6	22.02	1.27	.27
S43	Main Effects	24850	5	4970	260.98	<.01
	Intensity	23916.1	2	11958.1	627.93	<.01
	Frequency	3376.4	3	1125.5	59.10	<.01
	Interaction	131.16	6	26.23	1.37	.24
AC6	Main Effects	40949.9	5	8190	324.25	<.01
	Intensity	39709	2	19854.5	786.07	<.01
	Frequency	3317.7	3	1105.9	43.78	<.01
	Interaction	149.96	5	29.99	1.18	.32

Table 7

Difference Scores obtained from subjects

during the 2ms Block condition in Experiment 4

Where: O refers to the obtained slope, and P to the predicted slope

Subject	Slope		Difference Scores	
	O	P	O-P	O-1.0
S36	-1.15	-.85	-.30	-.15
S46	-.89	-.88	-.01	.11
F457	-.66	-.89	.23	.34
Overall Mean			.20	.31
S.E.M.			.36	.34

Table 8

Slopes and the 95% Confidence Limits for the 500ms Block condition

Subject	Slope	95% Confidence Limits
S36	-.34	-.72 to .04
S46	-.06	-.45 to .33
F457	-.24	-1.55 to 1.07

Table 9

Analysis of Variance determining whether Non-contingent stimulation presented under the 2 ms and the 500 ms conditions affects Frequency thresholds for Brain Stimulation Reward

Condition	Source	SS	df	MS	F	P
RAT S36						
2 ms	Between	2009.8	4	502.4	13.4	<.05
	Within	937.22	25	37.5		
500 ms	Between	202.7	4	50.7	1.19	.34
	Within	1064.97	25	42.6		
RAT S46						
2 ms	Between	1012.7	4	253.2	3.20	<.05
	Within	1979.1	25	79.2		
500 ms	Between	131.14	4	32.8	.77	.55
	Within	1058.2	25	42.3		
RAT F457						
2 ms	Between	1224.79	4	306.20	6.32	<.05
	Within	1211.47	25	48.46		
500 ms	Between	153.30	4	38.32	.29	.88
	Within	3193.89	24	133.08		

ABSTRACT

In an attempt to model the effects of "free reward", such as is thought to occur when direct dopamine receptor agonists are evaluated in self-stimulation, subthreshold levels of non-contingent stimulation were delivered. The continuous delivery of low levels of stimulation during decreased frequency thresholds for brain stimulation reward by a value equal to the frequency of non-contingent pulses. The reduction occurred whether the non-contingent stimulation was delivered to the same electrode or to the electrode contralateral to the one receiving the response-contingent stimulation. In the contralateral case, the decrease was predicted by the contralateral electrode's relative effectiveness. Changes in current which did shift self-stimulation frequency thresholds, did not influence the non-contingent effect, suggesting that simple addition was taking place between the non-contingent and the response contingent pulses. These results led to the conclusion that the response-contingent and the non-contingent stimulation summated perfectly. The threshold reducing effect of the non-contingent stimulation was eliminated when it was delivered before and after, but not during the train of contingent pulses. These findings concerning the integration of "free reward" may generalize to pharmacological "free reward".