Effects of varying reinforcement schedule, reward current, and pretrial priming stimulation on discrete-trial performance for brain stimulation reward

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The present study determined the effects of independently varying the reward current, the fixed ratio reinforcement schedule, and the amount of pretrial priming stimulation on reward summation functions collected in a discrete-trial self-stimulation paradigm. Rats were trained to respond eight times to receive a single train of brain-stimulation reward following the pretrial delivery of 10 trains of priming stimulation. The number of pulses in the reward train was decreased after every 12 trials, and reward summation functions were derived, relating response speed to reward strength. These reward summation functions were shifted laterally by varying the reward current or the fixed-ratio reinforcement schedule. In contrast, decreasing the priming yielded a transient decrease in the asymptotic response speeds and failed to produce enduring lateral shifts in the reward summation functions. Thus, the effects of changing the reinforcement schedule were not likely due to changes in priming. Rather, the schedule of reinforcement appeared to interact with the neural signal produced by the rewarding stimulation to determine the magnitude of the rewarding effect.

Analyses of the determinants of discrete-trial performance for brain stimulation reward (BSR) have distinguished two classes of controlling variables (Edmonds & Gallistel, 1974). Changes in the strength of the rewarding stimulation obtained on each trial displace the reward summation function (the function relating response vigour to the number of pulses in each reward train) laterally along the axis representing pulse number. Such changes may be produced by altering the current or the pulse duration (Edmonds & Gallistel, 1974; Edmonds, Stellar, & Gallistel, 1974; Matthews, 1977), or by pharmacological interventions that influence neural transmission at reward-relevant synapses (Franklin, 1978; Gallistel, Boytim, Gomita, & Klebanoff, 1982). In contrast, manipulations of the strength of noncontingent, pretrial priming stimulation, or of the effort required to perform the instrumental response, alter the asymptotic level of performance (Edmonds & Gallistel, 1974; Gallistel, Stellar, & Bubis, 1974). These changes in priming or task difficulty can be described as scaling the reward summation func-

tion vertically while producing little displacement of its position along the axis representing pulse number.

An additional manipulation that influences performance for BSR involves changes in the reinforcement schedule. Investigations of the dependence of free-operant performance on the schedule of reinforcement have shown that reward summation functions are displaced rightward as the reinforcement schedule becomes leaner (Fouriez & Emdin, 1988; Miliaressis, Rompré, Laviolette, Phillipe, & Coulombe, 1986). Given that the changes in reinforcement schedules do not represent direct manipulations of reward strength, and that variations in interval schedules do not constitute an increase in task difficulty, how might these effects be conceptualized within the constraints of the conventional distinction between reward and task variables? Miliaressis et al. (1986) and Fouriez and Emdin (1988) have suggested that the lateral displacements of the reward summation functions may be due to changes in the level of priming as a function of variations in the density of the reinforcement schedule. Thinning out the schedule of reinforcement in a free-operant paradigm increases the time between stimulations and therefore increases the amount of decay in the priming effects of each stimulus train. However, this interpretation is at variance with the view that changes in priming only scale reward summation functions vertically.

In the present experiment, we employed a discrete-trial paradigm to obtain separate measures of the effects of priming and reinforcement schedule on reward summation functions. This paradigm resembled that employed

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by Edmonds and Gallistel (1974), in that noncontingent priming stimulation was delivered at the start of each trial, and intertrial intervals were of sufficient length to minimize the carryover of priming effects from one trial to the next. However, instead of traversing a runway, rats in the present experiment were trained to press a lever eight times to receive the brain stimulation reward, and the speed with which they completed this fixed-ratio response requirement served as the dependent variable. The influence of reward strength, reinforcement schedule, and priming on the reward summation functions was then evaluated systematically by varying the reward current, the number of responses required for each reward train, and the level of pretrial stimulation, respectively.

METHOD

Subjects

Three male hooded rats (Charles River Breeding Farms, Long-Evans strain) weighing 350–450 g at the time of surgery were used as subjects. The rats were housed individually in plastic cages with food and water available ad lib. A 12:12-h reversed light:dark cycle was in effect in the animal colony, and behavioral testing occurred during the dark phase of the cycle.

Surgery and Histology

Surgery was performed under sodium pentobarbital anesthesia (Somnotol, 65 mg/kg, i.p.) with supplements administered as required. The skull was leveled so that bregma and lambda lay in the same horizontal plane, and stimulating electrodes (.25-mm-diam stainless steel wires, insulated with Formvar except for the tip) were implanted bilaterally in the lateral hypothalamus, using the following coordinates: 2.8 mm posterior to bregma, 1.7 mm lateral to the midsagittal suture, and 7.8 mm below the dura matter. Flexible wires, terminated with male Amphenol pins, extended from each electrode. Another uninsulated flexible wire (also terminated with a male Amphenol pin) was wrapped around five jeweler's screws placed in the skull to provide an anode for the stimulation circuit. The male Amphenol pins from the electrode and current return wires were then inserted into an externally threaded connector, and this assembly was cemented to the rat's head with dental acrylic. Morphine (5.0 mg/kg, i.p.) was administered following recovery from the anesthesia to reduce postsurgical pain. The rats were given at least 1 week to recover from surgery before testing began.

When all experiments were completed, a small lesioning current (.1 mA for 15 sec) was delivered through the stimulation electrodes, and the rats were then given an overdose of Somnotol before transcardial perfusion with physiological saline followed by 10% formalin. The brains were removed and soaked in Prussian blue for a few hours to produce blue deposits in the lesioned tissue surrounding the electrode tips. They were subsequently stored in 10% formalin, and transferred to a 10% sucrose formalin solution 24 h prior to slicing. Each brain was sliced in 30- μ m sections, mounted on gelatin-coated glass slides, and stained with formol thionine for verification of the electrode placements.

Apparatus

The subjects were tested in a wooden chamber (25 $\times$ 25 $\times$ 70 cm) with a Plexiglas front panel and wire mesh floor. A lever (Lehigh Valley) was mounted 5 cm above the floor at the center of one wall, and a yellow jewel light was located 5 cm above the lever. A 40-W light bulb was attached to the ceiling of the chamber. Electrical stimulation was delivered to the rats through a stimulation cable suspended from a slip-ring commutator fixed in the center of the

test cage ceiling. The stimulation was produced by dual constant-current amplifiers (Mundl, 1980) and controlled through an integrated circuit pulse generator. The stimulation current was monitored continuously on an oscilloscope by measuring the voltage drop across a 1-k Ω resistor placed in series with the rat. The accumulation of charge at the electrode tip was minimized by shorting the stimulator outputs through a 1-k Ω resistor when stimulation was not being delivered. A microcomputer was used to control the timing of events and record responses made by the rats.

Procedure

Training. The rats were trained first during four sessions to respond on the lever for single trains of BSR (500-msec trains consisting of fifty 0.1-msec duration cathodal pulses delivered at a current of 250 μ A) on a continuous reinforcement (CRF) schedule. Both electrodes were tested for their ability to support self-stimulation during these sessions. The rats were then given five sessions with the number of pulses in each reward train decreased by 0.1 log₁₀ every 60 sec. The resulting reward summation functions were examined to determine which of the two electrodes in each rat supported the higher asymptotic response rates and the lower pulse-number thresholds. The electrodes so designated were used exclusively in the discrete-trial procedure.

The discrete-trial sessions consisted of 72 trials spaced 25 sec apart. Each trial began with the illumination of the overhead house-light for 10 sec, during which the rats received ten 500-msec trains of experimenter-delivered priming stimulation (fifty 0.1-msec cathodal pulses at 250 μ A) presented at a rate of 1 Hz. The overhead light was then turned off and, after a delay of 5 sec, the lever light was illuminated to signal the availability of the rewarding stimulation. The rats could then respond on the lever to obtain a single 500-msec train of 0.1 msec, 250- μ A cathodal pulses. The number of pulses in each reward train was set at a high value at the start of each session and was decreased by 0.1 log₁₀ units after every 12th trial. During the experimental phases, the initial number of pulses tested differed by 0.05 log₁₀ units on alternate sessions so that the results of two such sessions could be combined to provide reward summation functions with 0.05 log₁₀ unit resolution.

At the beginning of discrete-trial training, the rats were required only to respond once on the lever to receive the train of BSR. This response requirement was subsequently increased after every fourth session from the initial fixed-ratio 1 (FR-1) through FR-2, FR-4, and FR-6 until an FR-8 schedule of reinforcement was in effect. If a rat failed to complete the required number of responses within 25 sec on any trial, the lever light was turned off and the trial was terminated (termination of the trial otherwise coincided with the delivery of BSR).

The time elapsed between the illumination of the lever light and the completion of the response requirement was recorded on all trials. The median of the latencies obtained from the last seven trials at each pulse-number value was then determined to provide a single measure of performance for each level of BSR. The latencies from the first five trials at each BSR level were discarded from the analysis to minimize variance caused by the gradual trial-by-trial adjustment to the change in pulse-number value. The median latency value thus derived was then inverted to obtain a dependent measure (response speed) that grew with the number of pulses per reward train.

Reward summation functions were constructed by plotting the logarithm of the median response speed against the logarithm of the pulse number. A broken line function consisting of a lower horizontal segment and an upper horizontal segment joined by a linearly ascending segment was fit by the least squares method to the points composing each reward summation function. The *x* coordinate of the intersection between the lower horizontal segment and the ascending segment was taken as the threshold.

Experiment 1: Alteration of Reward Strength. After responding had stabilized on the FR-8 reinforcement schedule, the rats were tested with the priming held constant and the reward current varied. Initially, a baseline reward summation function was collected at the usual reward current (250 μ A) by decreasing the number of pulses per train within each of two alternate sessions as described above. Reward summation functions were then collected in this manner with the current halved to 125 μ A and the numbers of pulses per train increased to a range appropriate for that current. Following these tests with the low current, another baseline function was obtained with the usual reward current (250 μ A). The rats were then tested with the current doubled to 500 μ A and the pulse numbers decreased to a range appropriate for that current. This cycle of baseline, low current, baseline, and then high current was repeated once to obtain two reward summation functions at each of the novel currents.

Experiment 2: Alteration of Reinforcement Schedule. For this experiment, the schedule of reinforcement was varied by changing the number of responses required to obtain rewarding stimulation on each trial. The rats were first given 1 week of baseline testing with the usual FR-8 reinforcement schedule. The response requirement was then increased to FR-16 (either directly or after some training with FR-12), and four reward summation functions were collected with this schedule. Subsequently, the fixed ratio was halved after every fourth summation function so that reward summation functions were collected at FR-16, 8, 4, 2, and 1.

Experiment 3: Alteration of Priming Strength. After baseline performance was reestablished with the FR-8 schedule, eight reward summation functions were collected in alternating sequence, with the priming stimulation either present or absent on all trials. During the tests without priming, trials began with the usual illumination of the overhead houselight for 10 sec. However, this signal was not accompanied by the delivery of priming stimulation. All other aspects of these no-priming tests were identical to the conditions in effect during the baseline sessions.

RESULTS

Preliminary rate-number tests were conducted in a free-operant paradigm under a CRF schedule, and the results were used to select one electrode for each rat to be used in subsequent testing. Each of the selected electrodes supported asymptotic CRF self-stimulation levels of between 80 and 100 presses per minute; number thresholds ranged from 15 to 25 pulses. Histological analyses indicated that the tips of these electrodes were located in the mediodorsal region of the lateral hypothalamus, within the perforal region.

The discrete-trial self-stimulation task was readily acquired by all rats within the first session after transfer from the free-operant procedure. However, the reward summation functions obtained from the initial session with the FR-1 response requirement were relatively shallow. The rats often emitted the single response required to receive the BSR even when the number of pulses in the reward train was very low. The reward summation functions became somewhat steeper with continued training on the FR-1 schedule, and they steepened sharply when the response requirement was increased to an FR-2 schedule.

Figure 1. Reward summation functions obtained with reward currents of 125, 250, and 500 μ A for each of the three rats. Each plot indicates the inverse latency (left y-axis) or latency (right y-axis) to complete the FR-8 response requirement as a function of the number of pulses per train of rewarding stimulation. The data points represent the median of the last 7 of the 12 trials at each pulse number, with the results of the first, second, and third determinations represented by filled circles, squares, and triangles, respectively. As in previous experiments, lowering the reward current produced rightward lateral shifts in the reward summation functions toward higher pulse numbers, whereas increasing the reward current shifted the functions leftward toward lower pulse numbers.

Figure 2. Reward summation functions obtained with the response requirement for each reinforcement set at FR-1, FR-2, FR-4, FR-8, and FR-16. As the fixed ratio was decreased from FR-16 to FR-1, the reward summation functions shifted progressively leftward toward lower pulse numbers. The decreases in asymptotic levels of responding associated with the increases in the fixed ratio resulted primarily from increases in the time required to satisfy the greater response requirements.

The reward summation functions did not steepen further with subsequent increases in the FR response requirement, but the functions were shifted laterally along the pulse-number axis toward higher values.

Experiment 1 Alteration of Reward Strength

Figure 1 shows reward summation functions collected with the intensity of the rewarding stimulation set at three different values. The functions collected at $250 \mu\text{A}$ reflect the responses measured under the usual baseline conditions. As may be seen in the figure, halving the current to $125 \mu\text{A}$ (a $0.30 \log_{10}$ unit change) shifted the thresholds of the reward summation functions for each rat laterally toward higher pulse numbers (by 0.32 to $0.57 \log_{10}$ units). Doubling the current to $500 \mu\text{A}$ (a $0.30 \log_{10}$ unit increase) shifted the reward summation functions toward lower pulse numbers (by 0.26 to $0.36 \log_{10}$ units). Thus, the position of the reward summation functions along the number axis was greatly influenced by changes in the intensity of the rewarding stimulation, but it was consistent across repeated tests at the same current.

Experiment 2 Alteration of Reinforcement Schedule

The panels in Figure 2 show reward summation functions obtained with the response requirement for each BSR train set at FR-1, FR-2, FR-4, FR-8, and FR-16. As the fixed ratio was decreased from FR-16 to FR-1, the thresholds of the reward summation functions for each rat were shifted leftward toward lower pulse numbers (by 0.24 to $0.41 \log_{10}$ units). Thus, changing the number of responses required to obtain each reward train strongly affected the positions of the reward summation functions along the number axis. Decreasing the fixed ratio requirement also increased the asymptotic response speed (inverse latency) in each animal. These changes in asymptotic speeds were primarily due to decreases in the time required to complete the response requirements of the lower fixed ratios.

Experiment 3 Alteration of Priming Strength

Figure 3 shows reward summation functions obtained both with and without pretrial priming stimulation. On the left-hand side of each panel, the first of four reward summation functions obtained in the absence of priming is compared with a baseline reward summation function collected on the preceding day in the presence of priming stimulation. Initial removal of the priming decreased asymptotic levels of responding in all rats. This manipulation also produced a rightward shift of the reward summation function ($0.19 \log_{10}$ units) in at least 1 rat. However, as may be seen on the right-hand side of each panel, the effects of removing the priming stimulation were transient and had all but disappeared by the fourth test.

Figure 3. Comparison of reward summation functions obtained in the presence (open circles) and absence (filled circles) of pretrial priming stimulation. The left-hand panel for each rat shows the first of four functions obtained without priming, along with a baseline function collected in the presence of pretrial priming stimulation on the previous day. The right-hand panels compare the fourth function obtained without priming to the associated baseline curves. Initial removal of priming decreased asymptotic levels of responding in all rats, and also produced a rightward shift in the function of Rat 3. However, these effects of removing the priming were greatly diminished by the fourth test.

DISCUSSION

The present study confirms that the location of reward summation functions along the pulse-number axis can be altered by changes in the reinforcement schedule. Specifically, these functions were displaced progressively to the left as the number of responses required for each BSR train (the fixed-ratio) was decreased from FR-16 to FR-1. The magnitude of the displacement was similar to that produced by a 50% increase in the reward current. These results indicate that rewarding efficacy depends both on the strength of the rewarding stimulation *and* on the reinforcement schedule.

The shifts in the reward summation functions observed in Experiment 2 cannot be explained by changes in the level of priming associated with the different reinforcement schedules. Differences in priming across trials were minimized by the imposition of a fixed interval between self-stimulation trials and by the delivery of a constant level of priming at the start of each trial. Moreover, as Gallistel and co-workers had previously observed (Edmonds & Gallistel, 1974), altering the level of priming did not result in enduring lateral displacements of the reward summation functions.

An unexpected result was the transience of the effects produced by removal of the pretrial stimulation in Experiment 3. Although initial elimination of the priming stimulation produced a decrement of asymptotic response speeds in all rats (Figure 3, Test 1), the magnitude of this decrement was reduced on subsequent tests, and the effect was all but absent by the fourth test without pretrial priming. This recovery of the asymptotic response decrement as a consequence of experience suggests that learning factors may have played a role in the expression of the priming effects measured in this experiment. It is important to note that the rats in the present study were trained to respond for BSR always after delivery of pretrial stimulation (this is common in studies of brain-stimulation priming effects). The sudden removal of this stimulation would have altered the stimulus conditions that normally cue the rats to respond for BSR, and this effect may have been responsible for the observed delays in responding. Accordingly, the recovery of asymptotic response levels with repeated testing may have reflected learning to respond for BSR in the absence of the pretrial brain-stimulation cues. These results indicate that the measurement of priming effects may be confounded by learning factors when barpressing measures are employed to evaluate performance for BSR in rats trained with consistent pretrial stimulation. It remains to be determined whether priming effects measured with the runway procedure may also be confounded by such factors.

The conclusion that the rewarding efficacy of electrical brain stimulation depends on the schedule of reinforcement is consistent with evidence from numerous sources that the net value of a rewarding stimulus is a function

of both the magnitude and the rate of occurrence of the stimulus. The contribution of these two factors in determining behavioral responses to natural reinforcers has been characterized extensively both in terms of foraging theory (Harper, 1982) and within the context of the matching law (Herrnstein, 1970). From these theoretical perspectives, animals are seen to allocate time and energy between sources of reinforcement according to the relative abundance and rate of availability of the reinforcer.

Recently, Gallistel and Leon (1991) demonstrated matching in rats performing for rewarding brain stimulation. These investigators found that changes in preference produced by increasing the stimulation frequency or current could be offset by decreasing the average interval at which stimulation was made available. Taken together, their results and those of the present study show that the schedule of reinforcement is not merely a task variable controlling the asymptotic rate of performance but rather that it is fundamental to determining the affinity of the rat for the rewarding stimulation.

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