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Both Response Effort and Current Intensity Affect Self-Stimulation Train Duration Thresholds

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FRANK, R. A. AND H. P. WILLIAMS. *Both response effort and current intensity affect self-stimulation train duration thresholds.* PHARMACOL BIOCHEM BEHAV 22(4) 527–530, 1985.—Self-stimulation thresholds obtained from rate/intensity functions have often been used to measure brain stimulation reward (BSR) under the assumption that these indices are not contaminated by performance factors. However, very few studies have explicitly examined the effect of performance variables on thresholds. The present experiment examined the joint effects of response effort and current intensity on train duration thresholds. Three levels of stimulation current and lever weightings were factorially combined and train duration thresholds (defined as 50% of maximum response rates) were determined for each condition. It was discovered that changes in both current intensity and response effort produced shifts in thresholds, and that these shifts were of approximately equal magnitude. It was concluded that caution must be exercised when interpreting self-stimulation threshold data since, at least under some conditions, both reward (i.e., train duration) and performance (i.e., effort) manipulations produced similar shifts in self-stimulation response functions.

Brain stimulation reward Self-stimulation thresholds Effort

SELF-STIMULATION thresholds have been used extensively to study the effects of drugs on brain stimulation reward (BSR) under the assumption that these measures are insensitive to the performance effects of pharmacological agents (see [11] for a review). However, few experiments have actually assessed the effect of performance manipulations on thresholds [2,17].

The present investigation assessed the combined effects of response effort and stimulation current on self-stimulation/train duration functions. Factorial combinations of current intensity levels and different lever weightings were used to compare the influence of a reward (current) and performance (weighting) variable on self-stimulation thresholds.

METHOD

Subjects

Twenty-four male Sprague-Dawley rats weighing between 300–400 g were implanted with bipolar stimulating electrodes (Plastic Products Co., electrode diameter=0.25 mm) under sodium pentobarbital anesthesia (50 mg/kg). The electrodes were aimed at the ventral tegmental area (VTA) using the stereotaxic coordinates 4.5 mm posterior from bregma, 1.5 mm lateral from the midline and 8.5 mm ventral from the skull's surface (with the skull flat between lambda and bregma).

The animals were individually housed and given continuous access to standard lab food and water except during testing. The illumination of the animal colony rooms followed a 12 hr light/dark cycle.

Apparatus

All training and testing was performed in six metal and Plexiglas chambers measuring 23×21×19 cm with a floor constructed of aluminum rods spaced 1.0 cm apart. Each chamber contained a metal lever mounted 5.0 cm above the floor. On the rear of each lever, outside the chamber, a hole was drilled so that a 10 or 13 g lead weight could be bolted to the lever, thus increasing the force required to lever press.

Brain stimulation was administered by constant current stimulators using 60 Hz sine waves. The stimulation train durations, data collection and all programming functions were controlled by an Ohio Scientific C1P microcomputer. Mercury swivel commutators and bipolar electrode leads allowed the animals to be connected to the stimulation circuit. A 5.0 V light bulb attached to each chamber was used to signal time-out periods during testing.

Procedure

Animals were screened for self-stimulation following a 10 day post-operative recovery period. The 12 rats that exhibited the most vigorous and reliable self-stimulation rates were retained for further testing. These animals were then trained to lever press for brain stimulation during eleven 3.0

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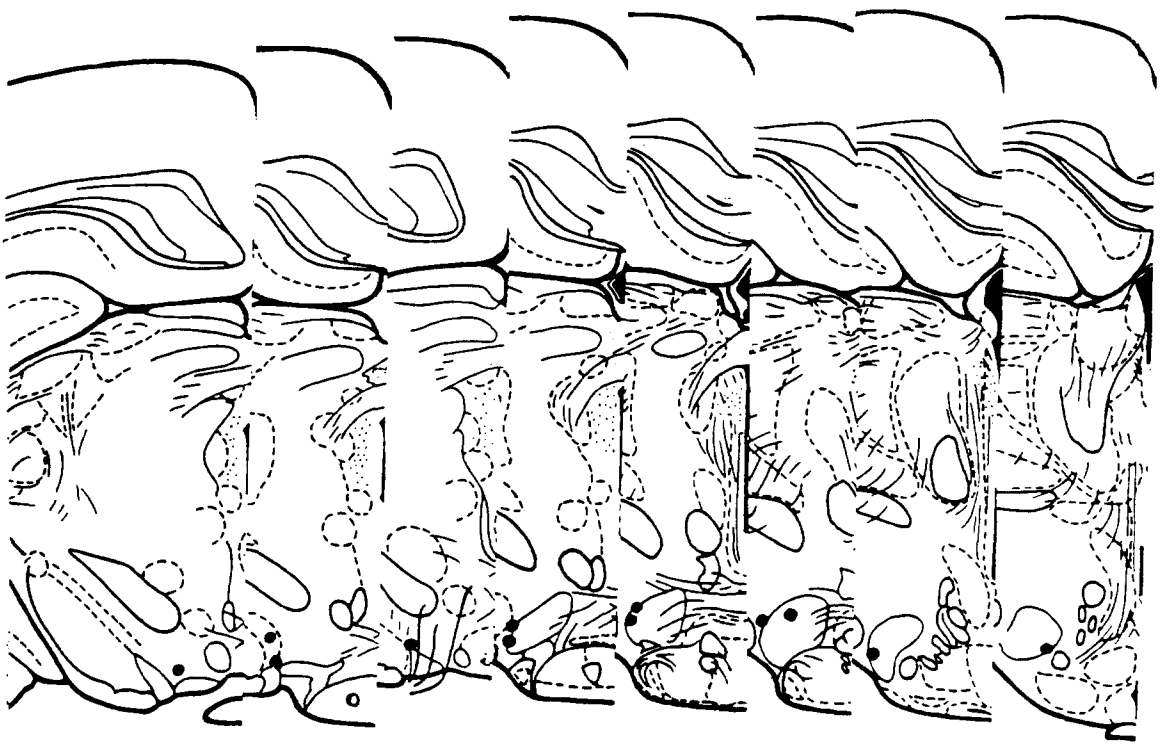

FIG. 1. Locations of the electrode tips for the animals used in the study. The plates are from [9].

min stimulation periods separated by 1.0 min time-outs. Therefore, each session lasted 44.0 min. Both the number of reinforcers delivered and lever presses for stimulation were recorded for these periods. The time-out periods were signalled by the illumination of a small light bulb attached to each chamber. Responses during time-out periods were counted but not reinforced.

During training sessions, the brain stimulation current intensity was set at 40 μa and train durations were maintained at 100 msec. One session per day was run. After a week of training, an assessment of train duration thresholds began. The train duration available during the 3.0 min stimulation periods was varied from 20 to 100 msec in 10 msec steps. In addition to these nine train durations, a 0 msec and additional 100 msec were added to make a total of eleven 3.0 min periods. The 0 msec trial was included to provide an estimate of operant rates when no stimulation was available and the additional 100 msec train duration always occurred on the sixth trial and was used to insure good response maintenance and train duration sampling throughout the testing session. As in the training phase, the 3.0 min stimulation periods were followed by 1.0 min time-outs. The train durations were presented in a random order (except the 100 msec sixth trial) and one session/day was run. It should be noted that for the range of train durations that were used, train duration and current intensity trade off perfectly (holding other parameters constant) and no adaptation of the rewarding effects occurs [1,7].

In the next phase of the experiment, baseline thresholds were established and the current intensities to be used for the final testing phase were determined for each subject. These intensities were chosen to center each animal's train duration threshold between 40 and 70 msec. After 19 test days, stimulation currents were set at either 40 or 50 μa for each rat and the final phase of the experiment commenced. During this phase, three brain stimulation current levels (5 μa above baseline testing current, baseline current and 5 μa below baseline current) and three lever weighting levels (a lever weighted with 10 or 13 g more than the lever weight of baseline testing or a lever of the same weight as baseline tests) were factorially combined to produce nine test conditions. Each test condition was run three times and the sequence of conditions was randomized across the 27 days required to complete this phase of the experiment. Data collected during the testing phase were recorded on a minute by minute basis for both the stimulation and time-out periods.

Histology

At the completion of testing, the rats were sacrificed with an overdose of sodium pentobarbital and then perfused through the heart with a 10% formal-saline solution. The brains were subsequently sectioned at 40 μm using the frozen method, and then microscopically examined to determine the location of the electrode tips. The results of the histological analyses are shown in Fig. 1.

RESULTS

An examination of individual subject data revealed several interesting characteristics of the response patterns of the rats that were important to consider when analyzing the results. For example, the animals would sample the stimulation at the beginning of each trial regardless of whether or not the train duration presented on that trial subsequently maintained suprathreshold levels of responding. An exam-

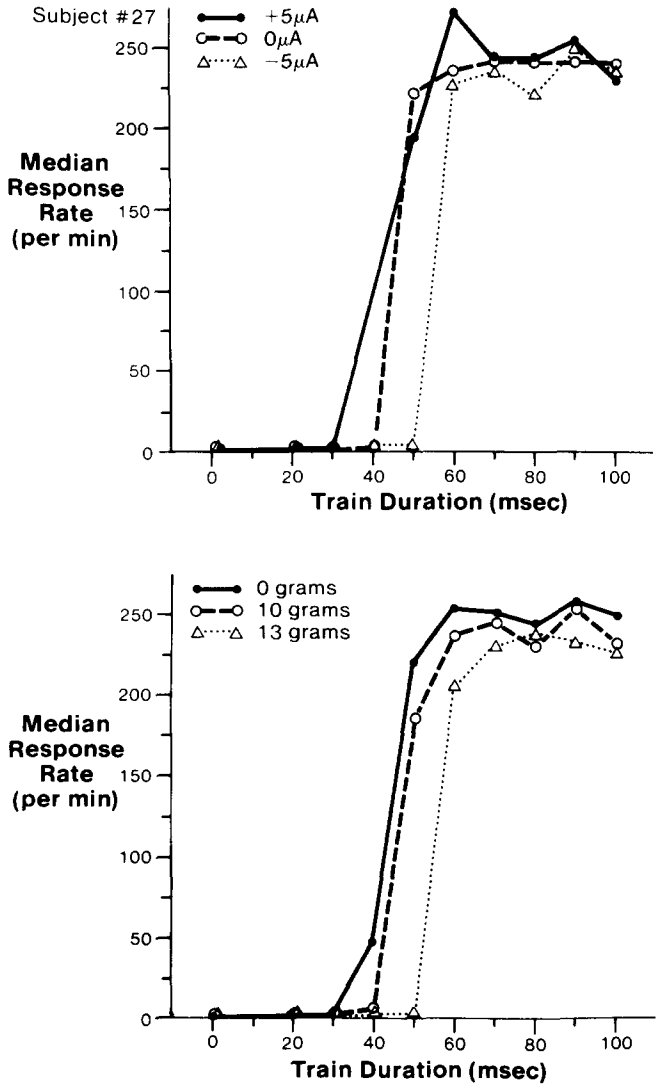

FIG. 2. Median response rates for each train duration for the current and weight manipulations for subject 27. Notice that the points from the current conditions were obtained by summing across the weight levels and vice versa.

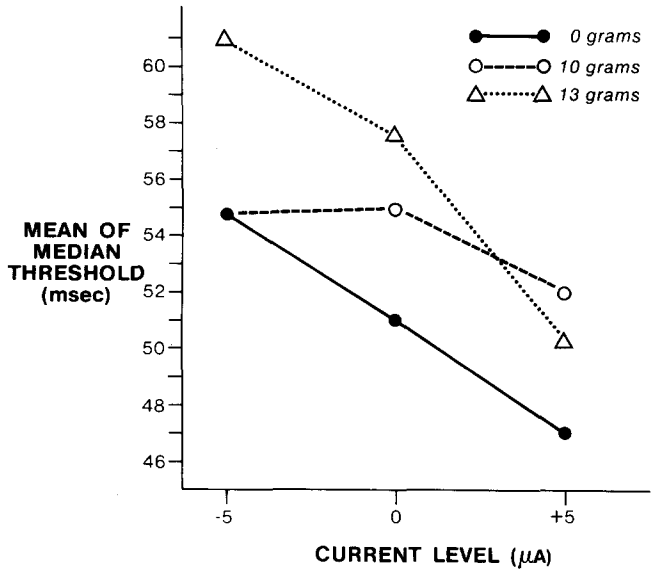

FIG. 3. The joint effects of stimulation current and lever weighting on 50% of maximal response thresholds. The current levels are expressed as deviations from a baseline level.

ination of the response patterns for the 0 msec and other low train durations revealed that the sampling always ceased by the third minute of testing. To eliminate the influence of these sampling responses only data from the third test minute were used to calculate thresholds. It was also noted that self-stimulation tended to be "all or none." The animals either responded to the stimulation with very high response rates, or not at all. Thus, the transition from responding to no responding at threshold produced step-like response/train duration functions. These response patterns produced bimodal rather than normally distributed response frequency distributions, especially near threshold train durations. In fact, across all animals, 45.5% of the response rates were between 0 and 10 responses/min, 2.8% ranged from 11 to 99/min, and 51.7% were over 100 responses/min. This distribution of rates lead to the choice of medians to summarize the data of individual animals. A final point that should be mentioned is that the asymptotic response rates observed in the present study probably do not indicate an asymptote of the stimulation reward value but rather reflect an attempt to maintain continuous stimulation at low train durations [1].

The median response rates for the current and weight manipulations for one subject are shown in Fig. 2. This particular animal demonstrated differential sensitivity to each manipulation level. It is particularly interesting to note the shift in the response function to the left as one campares the 13 g and 0 g conditions. This pattern of results, which was produced by a performance manipulation, is often taken as evidence for a reward effect [6,8]. As can be seen in Fig. 2, changes in either weighting or current produced shifts of the entire response/train duration function.

To assess the joint effect of current level and lever weighting on thresholds across animals, the mean of the median threshold values was obtained for each of the nine experimental conditions. These thresholds were determined by calculating (usually by interpolation) the train duration value at which a subject was responding at 50% of the median, maximum rate. The resulting values are presented in Fig. 3.

A two factor, repeated measures ANOVA was used to analyze the data and it was discovered that both the current and weight manipulations produced significant changes in threshold (both $p<0.01$). In addition, the current × weight interaction was significant ($p<0.05$). This interaction appeared to be due to the relative insensitivity of the 10 g condition to changes in current as compared to the 0 and 13 g conditions.

DISCUSSION

The shifts in train duration thresholds induced by changes in response effort make it clear that changes in self-stimulation thresholds cannot always be attributed to variations in reward. Although the shifts in threshold induced by the current manipulations were somewhat greater than those

found with changes in weight, the two effects were of approximately the same magnitude. In addition, in a recent study it was found that 5 and 10 mg/kg morphine (SC) produced threshold shifts of from 5 to 10 msec, a range that is consistent with the present findings [5]. This is an important point to consider in light of previous research demonstrating a small and apparently insignificant effect of performance manipulation on self-stimulation thresholds using other procedures [2]. In a recent, as yet unpublished, experiment a "small but reliable" effect of response effort was found for 50% of maximal response rates calculated from brain stimulation frequency/response functions (Fouriezos, personal communication). It therefore does not appear that the issue is whether or not these performance effects exist. Rather, the issue is whether they are of sufficient magnitude to complicate the interpretation of self-stimulation data.

Perhaps it would be wise to remember the fate of the threshold concept in psychophysics. Signal detection theory [14, 15, 16] has all but eliminated the notion of a sensory threshold from the perception literature by recognizing that subjects are both sensors and decision makers. Detection of a stimulus is only one of the events that is important in determining if a response will occur. By the same token, it is probably naive to believe that self-stimulation thresholds are immune to biasing factors. In fact, many of the variables that have been shown to influence sensory thresholds also affect self-stimulation rates and thresholds, e.g., stimulus spacing, ascending vs. descending trials, contrast and context effects [2, 3, 4, 10, 12, 13].

Some of the techniques that are presently used to measure response thresholds may avoid contamination by performance factors. For example, White [17] found that the rheobase and chronoxie values for stimulation current/pulse duration trade-off functions were not altered by an increase of 30 g in lever weight. The methods used by Edmonds and Gallistel [2] also seemed to be relatively insensitive to changes in performance factors. A comparison of the procedures used by Edmonds and Gallistel and in the present study suggests that brain stimulation priming effects, which were assiduously avoided by Edmonds and Gallistel, may have interacted with the performance manipulations used in the present study to produce the observed pattern of results. We recently began to examine this possibility by running subjects on fixed interval schedules that insure decay of priming between self-administered stimulation trains. This experiment should provide the data needed to delineate the role of priming effects in the present study.

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