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Schedule Control of Behavior Reinforced by Electrical Stimulation of the Brain

Abstract. Electrical stimulation of the brain was used to train rats to respond on random interval schedules. Stimulation was either delayed for 0.5 second and preceded by a brief signal, delayed and unsigned, or presented contingently with the response. In every case, responding was maintained on schedules and showed resistance to extinction typical of food-reinforced responding. Priming was never necessary. These data cast doubt on the generality of beliefs about the behavioral effects of brain stimulation reinforcement.

It is part of the lore of experimental psychology that behavior established using response-contingent onset of reinforcing electrical stimulation of the brain (ESB) differs from behavior reinforced by conventional methods (such as food) (1). Thus, it is usually said that ESB-reinforced behaviors are difficult to bring under the control of schedules of intermittent reinforcement (2), show rapid extinction (3), and sometimes fail to occur after long periods without stimulation unless free (priming) stimulation is given (4). Conventionally reinforced behaviors, on the other hand, are said to show none of these characteristics (5). The three experiments described in this report indicate that these traditional beliefs are not true.

Cantor (6) demonstrated that ESB-reinforced behaviors could be brought under schedule control if ESB was signaled and delayed rather than being presented contingently with the response, as was usually done. He also showed that removal of the signal resulted in a decrease in response rate when the schedule made ESB available, on the average, once every 2 minutes. Experiment 1 was done as a partial replication of Cantor's work. Signaled, delayed ESB was used to train and maintain responding according to random interval (RI) schedules (7); removal of the signal, however, did not have the effect reported by Cantor.

Five male Long-Evans hooded rats were housed individually with food and water continuously available. Each was implanted, under Nembutal anesthesia, with one bipolar electrode aimed at the substantia nigra compacta (SN) (two rats) or the area tegmentalis ventralis Tsai (three rats) by conventional stereotaxic techniques.

The experimental environment consisted of a Plexiglas cubicle (approximately 22 cm) with a grid floor and one aluminum plate wall on which was located a lever (1.8 cm wide) with its surface at a height of 2.0 cm. The force requirement for the lever was 10.2 g. The cubicle was located in a ventilated, sound-attenuating box, lit by a small lamp and provided with constant masking noise.

Electrical stimulation was provided through leads attached to a mercury commutator, which permitted the rats freedom of movement. Electrical stimulation consisted of 0.5-second trains of squarewave, biphasic pulses 0.1 msec in duration presented at 100 hertz. The current varied from rat to rat, ranging from 200 to 400 µA, and was kept constant by placing a large resistance in series with the rat.

The lever-press response was shaped with reinforcement consisting of a train of ESB signaled with a click 0.5 second before its onset. The group consisted of the first five rats that could be trained to self-stimulate when given continuous reinforcement (CRF). All subsequent sessions were 30 minutes in duration. Each rat received a number of sessions with different reinforcement schedules in the following order: one session of CRF, one of RI reinforcement averaging 6 seconds (RI6), one of RI 12, two of RI 30, three of RI 45, two of extinction, two of RI 45, three of RI 45 with signal omitted, two of RI 45 with signal and delay omitted, and two of RI 45 with signal and delay reinstated. Four rats received two additional sessions of RI 45 after 67 days during which they remained in their home cages. Dependent variables were latency to the first response in each session and response rate (responses per minute).

In order to determine the operant levels of the dependent variables, three additional rats of the same strain, similarly implanted with electrodes aimed at the lateral hypothalamus (LH), were tested. These rats were connected to the stimulator and received seven 30-minute sessions of exposure to the chamber; ESB was never presented during these sessions.

The mean response rates for the first five sessions of experiment 1 are presented in Table 1 and the mean response rates for the last 15 sessions are shown in Fig. 1A. Response rates decreased during extinction (t = 4.06, df = 4, P < .01); however, all rats continued to respond during both extinction sessions and the mean rate for the two complete sessions was higher than the mean operant rate for the first two control sessions (shown as a dotted horizontal line in the extinction bar of Fig. 1A) (t = 3.63, df = 6, P < .01). This finding is clearly contradictory to the suggestion that ESB-maintained behaviors undergo unusually rapid extinction. When the signal was omitted, there was no change in mean response rate. When the delay was also removed, the mean response rate increased as compared to the preceding RI 45 sessions with signaled ESB (t = 3.12, df = 4, P < .05). The increase was seen in the individual data of each rat. This is opposite to the effect reported by Cantor (6) for one rat under similar conditions. Even after 67 days without ESB, when the rat was reintroduced to the experimental environment responding returned to its previous rate (Fig. 1A).

Figure 2 shows the mean log latencies to the first response for each session. No rat during any session had to be primed except for one rat in the first session. The mean log latency was never greater than 2.0 (latency of 100 seconds) after the first session and continued to show a declining trend over the first 19 sessions (F = 7.124, df = 17, 68, P < .001). Response
initiation was not due simply to accidental lever depression during movement since control latencies never showed a decrease. Even after 67 days without ESB, all rats initiated responding in 15 seconds or less (mean log latency of 0.54 on session 20). These data show that priming is not necessary to initiate responding for ESB.

Experiment 1 confirms that ESB-reinforced behaviors can be brought under RI schedule control when the ESB is signaled and that the schedule control is not lost when the signal or both the signal and delay are removed (although there may be rate changes). It may be that only the delay is needed to establish schedule control; this factor was confounded with the signal in both Cantor’s experiment and experiment 1. Experiment 2 was done to test this possibility.

Five male Long-Evans hooded rats, housed and implanted as described above, had electrodes aimed at SN (three rats) or LH (two rats). The experimental environment and brain stimulation parameters were as described above. Training followed the same sequence of schedules used in experiment 1 except that initially reinforcement consisted of one train of ESB that was delayed by 0.5 second, but not signaled, and the rats were not retested after 67 days.

The results (Table 1, Fig. 1B) revealed that simply delaying the onset of ESB was a sufficient condition for establishing RI schedule control. Rates decreased during extinction ($t = 2.67, \ d.f. = 4, \ P < .05$) although responding did continue throughout two extinction sessions at an average rate of 2.3 response/min, which was greater than the operant rate of the control group ($t = 2.15, \ d.f. = 6, \ P < .05$). Neither addition of the signal nor removal of the delay affected responding ($P > .05$ in both cases) (Fig. 1B). As in experiment 1, no rat had to be primed; the mean log latencies (Fig. 2) were almost always well under control latencies but failed to show any change over sessions ($F = 1.46, \ d.f. = 17.68, \ P > .05$) as they did in experiment 1.

Experiment 3 was done to confirm earlier reports of failure to establish responding on schedules of intermittent reinforcement with response-continguous onset of ESB as the reinforcer, a control not performed by Cantor. Six male Long-Evans rats, housed and implanted as described above, had electrodes aimed at SN (one rat) or LH (five rats).

Training was carried out in the apparatus described above with reinforcement consisting of a 0.5-second train of ESB, the onset of which was contiguous with lever depression. As in experiments 1 and 2, shaping was followed by a series of sessions: one of CRF, one of RI 6, one of RI 12, two of RI 30, three of RI 45, two of extinction, two of RI 45, two of RI 45 with signal and delay, and two of RI 45 without signal and delay.

The results were unexpected. All six rats continued to respond throughout the series of schedules (Table 1, Fig. 1C). Response rates decreased during extinction ($t = 4.18, \ d.f. = 5, \ P < .005$) but continued throughout both extinction sessions at an average rate of 1.5 response/min, which exceeded the operant rate (Fig. 1C) ($t = 5.10, \ d.f. = 7, \ P < .005$). Addition of the signal had no effect on responding. Average log latencies (Fig. 2) were usually much shorter than control latencies, and no rat ever needed priming. Log latencies did not change systematically across sessions ($F = 1.47, \ d.f. = 15.75, \ P > .05$).

From the results of these experiments it is concluded that (i) rats will respond regularly for ESB on an interval schedule and therefore ESB can be used to establish at least RI schedule control; (ii) animals are resistant to extinction of ESB, a phenomenon often reported for conventional reinforcers; (iii) priming is not necessary to initiate responding for ESB; and (iv) the same observations are made when ESB is neither signaled nor delayed.

What led to the earlier conclusions about the behavioral effects of ESB? Part of the answer may concern priming. We have found no data concerning response latency for ESB in the lever-press paradigm. Some early reports (4) mentioned giving free ESB to initiate responding but in none was latency to a first response explicitly timed. We have observed that once a rat becomes “accustomed” to being primed, the likelihood of its initiating responding without priming is reduced. This may explain in part the difficulty, reported by some, in training rats to respond on schedules of intermittent reinforcement as well as reports of unusually rapid extinction.

Animals initiated responding for ESB, even after months without exposure to it, with latencies very much shorter than those of control rats. Even if reinforcement occurred for the first response, this rapid initiation of responding raises some theoretical questions about the physiological processes necessary for appetitive behavior and positive reinforcement. Behavior is usually studied in deprived organisms working for substances which reduce the level of deprivation. Behavior in nondeprived animals working for brain stimulation may be analogous to human behaviors directed towards the attainment of substances not necessary for survival but apparently rewarding. It may be possible to use laboratory studies of ESB to discover environmental factors controlling such behaviors.

Table 1. Mean response rate during the first five sessions of experiments 1, 2, and 3.

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Number of sessions</th>
<th>Mean responses per minute</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exp. 1</td>
<td>Exp. 2</td>
</tr>
<tr>
<td>CRF</td>
<td>1</td>
<td>30.1</td>
</tr>
<tr>
<td>R16</td>
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<td>24.2</td>
</tr>
<tr>
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<td>1</td>
<td>21.2</td>
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<tr>
<td>RI30</td>
<td>2</td>
<td>9.9</td>
</tr>
</tbody>
</table>

**Fig. 1B**

Mean log latencies for each session of experiments 1, 2, and 3, and for seven control sessions. All points for experiments 1 represent the mean data for five rats except those marked by an asterisk, which represent the mean for four rats.

**Fig. 1C**

Mean log latencies for each session of experiments 1, 2, and 3, and for seven control sessions. All points for experiments 1 represent the mean data for five rats except those marked by an asterisk, which represent the mean for four rats.

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Levodopa, Fertility, and Longevity

Abstract. High concentrations of the dopaminergic drug levodopa (1-dopa, 1-3,4-dihydroxyphenylalanine) administered to mice in their diet affected fertility to a moderate degree and prolonged the mean life-span by a maximum of 50 percent.

Because of its effects on Parkinsonism and other motor disturbances, the dopaminergic drug levodopa is being consumed by many persons (1) most, but not all, of whom are beyond the childbearing age (2). Preliminary observations suggested that large concentrations of levodopa in the diets of male mice enhance fertility and longevity (3). Our study continues these observations. It extends these observations to both sexes, in which the maximal tolerated concentrations of dietary levodopa were determined and were given either during breeding or over the entire life-span of these mice.

Approximately 1100 male and 1500 female Swiss Albino mice were reared on Purina chow, which remained as the diet of all control animals. All experimental mice were shifted at 4 to 5 weeks of age to diets containing increasing amounts of 1-3,4-dihydroxyphenylalanine (l-dopa, levodopa) given in 5-mg increments ranging from 1 to 100 mg per gram of Purina chow (hereafter referred to as mg/g).

The maximum concentration that caused no deaths for 22 days was 40 mg/g for males and, notably, 80 mg/g for females.

During mating experiments, the maximum levodopa concentration in the diet was 40 mg/g to protect the males. Concentrations of 0, 10, 20, and 40 mg/g were each continuously fed to groups of mating partners as follows: females only, males only, and both. Matings were started in week 10 of life by keeping two females in a cage with one male for 4 days. All young were examined during day 1 of life. Their numbers per litter and their weights were recorded at birth and checked weekly for 3 weeks. This procedure was followed for five matings at 8-week intervals, the total number of females being 1152 and the total number of offspring 6669.

Levodopa did not affect significantly the number of pregnancies (50 to 68 percent of females), the numbers of young (6 to 8 per litter), or the weights of the young (1.5 to 1.8 g per mouse) except when 40 mg/g was fed to the females, in which case significant decreases emerged in each of these items (P < .01). The effects were less when levodopa was fed only to the males and were not additive when it was fed to both partners. The young appeared normal on inspection, and cannibalism was not noted. These results demonstrate the feasibility of rearing sequential generations of mice on levodopa. Experiments of this type have been used to enhance nutritional effects in the past (4) and might prove useful in testing for effects on longevity.

In the beginning of our longevity experiments, we assigned 4- to 5-week-old males to groups of 100 in such a way that the body weights were not significantly different from group to group. This was done in view of the increased longevity induced by undernutrition (5-7). The animals on levodopa, however, in time developed differences in weight, shown in Table 1 as percentages of the weights of the corresponding controls. An impressive diminution in weight emerged during the first month on 40 mg/g. The other differences, even when statistically significant, were small by comparison to those induced during experiments on undernutrition (5, 6). The grams of food consumed per mouse per day were estimated on 15 occasions after the first month on levodopa. The controls consumed 5.4 ± 0.7 g/day, and the food consumption by the other groups showed no significant differences.

Survival curves for the four groups of males receiving 0, 1, 20, and 40 mg/g are shown in Fig. 1. The distributions of the survival times were found to be normal for the 1 mg/g, 20 mg/g, and control groups, while the 40 mg/g group appeared to be a mixture of two normal distributions with 13 percent having a life-span of 130 days and 86 percent having a much longer life-span.

A summary of the data is given in Table 2 both for the entire group and for the censored group, using only those that lived more than 130 days. The median life, the mean life, the standard deviation (S.D.), and the range for the treatment increased with dosage, although the

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Fig. 1 (left). Survival curves comparing control male Swiss Albino mice with similar mice consuming levodopa in their diets. Fig. 2 (right). Survival curves of control male and control female Swiss Albino mice and of those consuming levodopa (40 mg per gram of chow). See text.