SOME EFFECTS OF BRAIN STIMULATION ON TIMING BEHAVIOR

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When reinforcement of a free operant is contingent upon a specified temporal delay between responses, an organism develops a pattern of "spaced responding" or "timing behavior" in accordance with the requirements of such a reward schedule (Anger, 1956; Conrad, Sidman, & Herrnstein, 1958; Sidman, 1956; Skinner, 1938; Wilson & Keller, 1953). The differential reinforcement of low rates (DRL) in this way generates a timing process which makes it possible for the organism to discriminate the duration of the interval elapsing since the last response. Since there is no exteroceptive discriminative stimulus in this situation, the event or events upon which reinforcement is contingent must be provided by the organism's own behavior. The specific aspects of the organism's interaction with its internal or external environment which mediate this timing process, however, are far from clear.

Recent reports of the rewarding properties of electrical brain stimulation (Olds & Milner, 1954; Brady, 1956; Brady, 1958) suggest an interesting approach to the exploration of central-nervous-system participation in such timing behavior. It has been demonstrated that stable lever pressing on several different schedules of reinforcement can be maintained in laboratory animals for an intracranial electrical stimulus in selected areas of the brain without any other reward (Sidman, Brady, Boren, Conrad, & Schulman, 1955). The purpose of the present study is to investigate the interaction between such rewarding brain stimulation and the timing process generated by the DRL schedule. Specifically, this report describes a preliminary comparative experimental analysis of DRL performance under conditions of intracranial electrical self-stimulation reward and food reinforcement in the rhesus monkey.

METHOD

General Procedure

Three mature, male, rhesus monkeys served as subjects. All animals were trained in lever pressing for both brain-shock reinforcement and food reward. Timing behavior was established on a DRL schedule requiring that lever responses be spaced at least 20 seconds apart to produce reinforcement. With stereotaxically implanted chronic electrodes in selected areas of the brain, DRL performance was compared under various conditions of electrical self-stimulation and/or food reinforcement. Upon completion of the behavioral observations, all animals were sacrificed and the electrode placements verified histologically.

Apparatus

The monkeys were housed, trained, and tested in a specially constructed primate chair previously described in some detail (Mason, 1958). This restraining device was equipped with an automatic pellet feeder (Davis) and mouth hopper (Foringer), a visual stimulus panel with five different-colored lights (Foringer), and a modified telegraph-key lever (Foringer). An electrical junction box and multiconductor cable attached to the chair provided for interconnections between the experimental space and the control, programming, and recording equipment in an adjoining room. Responses and reinforcements were recorded on electrical impulse counters, and a cumulative-response recorder (Gerbrands) pro-

vided continuous performance measures. A system of timers and counters automatically tabulated inter-response times in class intervals of 2 seconds and primed the reinforcement circuit at appropriate times. The output of a white-noise generator (Grason-Stadler) through a speaker in the experimental room masked sounds from the programming equipment which might have provided unwanted exteroceptive discriminative stimuli for the monkey.

The electrical brain stimulus used to reinforce lever pressing in the self-stimulation portions of these experiments was provided by a Tektronix stimulating unit modified to give a biphasic pulse similar to that described by Lilly, Hughes, Alvord, and Galkin (1955). The parameters of this intracranial electrical stimulus remained constant for each animal throughout the experiment. Each brain shock consisted of a 100-cycle-per-second, 0.2-millisecond pulse duration, 20-milliampere electrical stimulus applied for a train duration of 0.5 second. Tissue resistance values in the monkeys ranged between 1500 and 2000 ohms.

Operative Procedure

The electrode construction and implantation procedure involved the use of a stereotaxically placed multilead electrode array and common-socket pedestal rigidly fixed to the skull so that stimulating leads could be firmly attached according to a procedure recently described by Sheatz (1959). All surgery was performed aseptically under pentobarbital anesthesia, and the animals were permitted a postoperative recovery period of 1 to 2 weeks before behavioral procedures were introduced.

Behavioral Procedure

All animals were initially deprived of food for 24 hours and given a single 3-hour, "magazine-training" session during which sugar pellets (48 milligrams each) were automatically delivered into the food hopper on the chair on the average of once every 60 seconds. Then, they were trained in lever pressing on a continuous-reinforcement schedule (200 sugar pellets) followed by a series of 2-hour daily sessions on the DRL schedule. Reinforcement of the lever response with a sugar pellet occurred only if an interval of 20 seconds had elapsed since the last lever press. This differential reinforcement of low rates was continued with sugar pellets alone as reward until the average response rate per session and inter-response time distributions (IRT's) for each animal showed no consistent change from day to day.

Brain-stimulation Procedure

Following stabilization of the DRL performance, the brain stimulation was substituted for sugar pellets as reinforcement during a 2-hour experimental session. Responses spaced 20 seconds or more apart were reinforced during this session with a 20-milliampere electrical stimulus for 0.5 second at the electrode locations indicated in Fig. 1. All animals were then continued on an alternating-day procedure which provided a 2-hour DRL session for sugar pellets on one day followed the next day by a 2-hour DRL session for brain stimulation. This procedure was continued for 10 consecutive days, 5 days for sugar pellets and 5 days for brain stimulation, with comparison of the DRL performance under the two conditions. Then, with all three monkeys, several experimental sessions explored the effects of concurrent food and brain-shock reward upon the timing schedule. During these sessions, responses spaced 20 seconds or more apart were reinforced with both a sugar pellet and the electrical brain stimulus at the same time. Finally, one of the monkeys, M-12, was exposed

to a similar series of experimental sessions involving various combinations of food and brain stimulation alternatively and food and brain stimulation concurrently using the second electrode placement indicated in Fig. 1.

Histological Procedure

Histological verification of the electrode placements was obtained for all three monkeys upon completion of the experiment. The animals were perfused with physiological saline followed by 10% formalin in which the brains were then fixed for 1 to 4 weeks before embedding in paraffin. Serial sections were cut at 15μ and stained with thionin. The electrode placements were reconstructed after microscopic examination of all brains and photomicrographs of selected sections for each animal are shown in Fig. 1. Section M-197 is cut approximately through frontal level A-17 (Horsley-Clark coordinates), and shows the electrode track coursing through the caudate nucleus, internal capsule, and globus pallidus, with the stimulating tip in the area of the medial forebrain bundle. Section M-2 is cut approximately through frontal level A-16 (Horsley-Clark coordinates) and shows the electrode track leaving the caudate nucleus and internal capsule to terminate with the stimulating tip in the medial aspect of the globus pallidus. Section M-12 is cut approximately through frontal level A-11 (Horsley-Clark coordinates) and shows the two electrode placements used in this experiment. The rostral-medial aspects of the section on the left side show one electrode coursing through the cingulate gyrus, corpus callosum, and anterior ventral nucleus of the thalamus to terminate with the stimulating tip in the anterior medial nucleus of the thalamus. The more lateral aspects of the section on the right side show the other electrode leaving the internal capsule and terminating with the electrode tip in the most medial portion of the globus pallidus.

RESULTS, DISCUSSION, AND CONCLUSIONS

Following introduction of the 20-second DRL requirement for sugar-pellet reward, the lever-pressing rates for all three monkeys showed a gradual and orderly decline similar to that described by Wilson and Keller (1953) for the rat. Within 10 to 14 daily 2-hour sessions for sugar pellets alone, the animals developed a clear and relatively stable time discrimination as reflected in the distribution of inter-response times (IRT's) recorded for each monkey. With the exception of the previously reported (Sidman, 1956) high proportion of responses in the zero-to-2-second interval, the distribution of lever presses displayed the typically gradual rise to a peak around the 20-second interval, and then a gradual decline in the frequency of longer inter-response times. The characteristics of this base-line performance were common to all three monkeys prior to introduction of the brain stimulation.

The cumulative curves in Fig. 2 illustrate typical DRL performances for Monkey M-12 under conditions of sugar-pellet reinforcement (upper section) and brain-stimulation reward (lower section) through the electrode placement in the globus pallidus (lower right arrow, Section M-12, Fig. 1). The stable time discrimination generated by the "spaced-responding" contingency is clearly reflected in the low steady rate and high frequency of reinforcement (vertical pips indicate reinforcements) when sugar pellets alone reward the lever response. In contrast, the response rate for the brain-stimulus reward on the same DRL schedule shows a marked increase over the optimal "spaced-responding" performance with a consequent low frequency of reinforcement.

Figure 3 shows the IRT's recorded for Monkey M-12 during the alternate-day 2-hour DRL sessions for sugar pellets and brain stimulation in the globus pallidus. The typical

“timing” performance during the sugar-pellet sessions shows a peak in the response distribution at or slightly above the 20-second interval required for reinforcement. The alternate-day IRT’s recorded during DRL performance for brain shock, however, show a

Figure 1. Low-power photomicrographs of brain sections for Monkeys M-2, M-197, and M-12. The location of the stimulating electrode tips are indicated by the arrows on each section.

Figure 2. Sample cumulative-response curves showing the differential effect of reinforcement with sugar pellets (upper section) and with brain stimulation in the globus pallidus (lower section) upon DRL performance for Monkey M-12. Pips on the record indicate reinforcements.

marked and consistent shift of the distribution toward the shorter intervals with the peak frequency occurring around the 10-second interval. The low relative frequency of inter-response times of 20 seconds or longer during these brain-shock sessions reduces sharply the number of reinforcements as indicated by the "reinforcement-per-response" ratio recorded above each IRT distribution in Fig. 3. This measure, which provides a rough index of "efficiency" under the two conditions, shows Monkey M-12 consistently obtaining approximately one reinforcement per two responses when working for sugar pellets (ratios around 0.50). The performance under conditions of brain stimulation, however, is characterized by a sharp drop in the "efficiency" ratio to values consistently around 0.03 and shows the animal obtaining only slightly better than one reinforcement per forty responses. A related effect is of course reflected in the markedly different response rates under the two reinforcement conditions. The rates in responses per minute are also recorded above the IRT distributions for each session and show the "brain-shock" rates to be consistently two to three times higher than the "sugar-pellet" rates. Clearly, however, the IRT's recorded during the brain-stimulation sessions continue to show a temporal discrimination as evidenced by the relatively sharp peaks around the 10-second interval. The animal continues to space responses but makes a rather consistent error in the duration of the delay interval required for brain-shock reinforcement.

Figure 4 shows a similar effect for Monkey M-2 with an electrode placement in a related portion of the globus pallidus (Section M-2, Fig. 1). The IRT's recorded during DRL sessions for sugar pellets show a peak frequency slightly below the required 20-second delay interval. The gradual decline in the relative frequency of longer inter-response times, how-

Figure 3. Inter-response time distributions for Monkey M-12 during the alternate-day, 2-hour DRL sessions. The upper distributions were recorded during sessions for sugar-pellet reinforcement, and the lower distributions were recorded during sessions for brain-shock reward through the electrodes in the globus pallidus. Additional numerical data recorded above each distribution are explained in the text.

Figure 4. Inter-response time distributions for Monkey M-2 during alternate-day, 2-hour DRL sessions. The upper distributions were recorded during sessions for sugar-pellet reinforcement, and the lower distributions were recorded during sessions for brain-shock reward through the electrodes in the globus pallidus. Additional numerical data recorded above each distribution are explained in the text.

ever, can be seen to extend well into the 30- and even 40-second delay interval compartments. In contrast, the DRL performance elicited with brain-shock reinforcement on alternate days is characterized by a shift in the IRT's to a peak frequency around the 10-second delay interval. The complete absence of inter-response times longer than 26 seconds under the brain-stimulation condition provides another striking similarity to the brain-shock performance of Monkey M-12 shown in Fig. 3. The relationships between the lever-pressing response rates and between the "reinforcement-per-response" ratios under the two different reinforcement conditions for Monkey M-2 are also reflected in the numerical recordings above the IRT's for each experimental session in Fig. 4. In general, these data show the same effects on response rate and reinforcement frequency described above for Monkey M-12.

A dramatically different picture emerged with Monkey M-197 under the same general experimental conditions, but with the self-stimulation electrode placement in the area of the medial forebrain bundle (Section M-197, Fig. 1). Figure 5 shows the IRT's for Monkey M-197 throughout the 10-day alternating sugar pellet and brain-shock reinforcement period and indicates that this animal maintained a remarkably stable and accurate time discrimination under both conditions. For all 10 experimental sessions, the IRT's show a sharp peak at the 20-second delay interval required for reinforcement, and neither the lever-pressing response rates nor the "reinforcement-per-response" ratios appear to differ significantly under the two conditions. Clearly, an effect on timing behavior does not appear to be a necessary consequence either of electrical stimulation of brain tissue *per se* or of the reinforcing properties of such brain stimulation. Indeed, these findings suggest that the particular tissue regions involved in the electrical stimulation play a critical role in the determination of the timing performance.

Additional data relevant to the neural "localization" of timing processes were obtained from further experiments with Monkey M-12 involving the second electrode placement in the anterior thalamus (upper left arrow, Section M-12, Fig. 1). Although electrical stimulation in this region did reinforce lever pressing, the effect on DRL performance was quite different from that observed with the same animal working for brain shock in the globus pallidus (lower right arrow, Section M-12, Fig. 1). Performance on DRL 20 for the anterior thalamus brain-shock reward did not produce the clear shift in IRT's to the 10-second peak seen in Fig. 3 with stimulation of the globus pallidus as reinforcement. The data obtained with Monkey M-12 under conditions of concurrent brain shock and sugar-pellet reinforcement shows further that this differential effect on the timing process is specifically related to the neural tissue regions affected by the electrical stimulus *per se*. Figure 6 shows the effect on the lever-pressing rate of superimposing electrical stimulation of the globus pallidus and the anterior thalamus upon the sugar-pellet reinforcement during the DRL performance. When both sugar pellets and brain shock in the globus pallidus are delivered concurrently to reward the 20-second spaced responding, a marked elevation in the lever-pressing rate and a relatively low frequency of reinforcements (pips on the cumulative curve) are the result (upper portion of Fig. 6). In contrast, however, the DRL performance under conditions of concurrent sugar-pellet and anterior-thalamus-stimulation reinforcement (lower portion of Fig. 6) is quite similar to the performance recorded when sugar pellets alone reinforce spaced responding in this same animal (upper portion of Fig. 2). Superimposing electrical stimulation of the anterior thalamus upon sugar-pellet reward in this monkey neither elevates the lever-pressing rate nor reduces the reinforcement frequency.

MONKEY M-197
(MEDIAL FOREBRAIN BUNDLE)
DRL 20 SECONDS

Figure 5. Inter-response time distributions for Monkey M-197 during alternate-day, 2-hour DRL sessions. The upper distributions were recorded during sessions for sugar-pellet reinforcement, and the lower distributions were recorded during sessions for brain-shock reward through the electrodes in the area of the median forebrain bundle. Additional numerical data recorded above each distribution are explained in the text.

Figure 6. Sample cumulative-response curves showing the differential effect of brain stimulation in the globus pallidus (upper section) and brain stimulation in the anterior thalamus (lower section) superimposed upon DRL performance for sugar-pellet reinforcement with Monkey M-12. Pips on the record indicate reinforcements.

Figure 7 summarizes the differential effect of brain stimulation in the anterior thalamus and brain stimulation in the globus pallidus in the same monkey (M-12) upon the IRT's for several experimental sessions under the two conditions. The upper two compartments of Fig. 7 show the two base-line IRT's, each representing the percentage of total responses in the indicated inter-response intervals for four 2-hour sessions with sugar pellets alone as reinforcement. The lower-left compartment of Fig. 7 shows the combined IRT's for four 2-hour sessions with sugar pellets plus brain shock in the anterior thalamus as reinforcement. The IRT's, the lever-pressing response rate, and the "reinforcement-per-response" ratio under this anterior-thalamus-stimulation condition are virtually indistinguishable from the two base-line distributions shown in the upper compartments. In contrast, the combined IRT's for the four sessions with concurrent sugar-pellet and globus-pallidus stimulation as reinforcement shown in the lower-right compartment of Fig. 7 reflect a rather marked change from both the base-line performances illustrated in the upper two compartments and the performance under conditions of thalamic stimulation shown in the lower-left compartment. The superimposition of brain stimulation in the globus pallidus upon the DRL performance for sugar-pellet reinforcement can be seen to produce a marked shift in the IRT's toward the shorter intervals resulting in better than a 100% lever-pressing rate increase and a sharp drop in the reinforcement frequency.

This shift in the IRT's toward the shorter delay intervals produced by electrical stimulation of the globus pallidus suggested a comparison with the effects of amphetamine upon timing behavior reported by Sidman (1955) using a similar DRL procedure with rats. Figure 8 makes this comparison directly for Monkey M-12 under three conditions as reflected in both the cumulative-response curves and the corresponding IRT distributions. The top sec-

MONKEY M-12
DRL 20 SECONDS

Figure 7. Inter-response time distributions for Monkey M-12 under conditions of sugar-pellet reinforcement alone (upper distributions), sugar pellets plus brain shock in the anterior thalamus as reinforcement (lower-left distribution), and sugar pellets plus brain shock in the globus pallidus as reinforcement (lower-right distribution). Each distribution represents the combined percentage of total responses in the indicated inter-response intervals for four separate sessions. Additional numerical data recorded above each distribution are explained in the text.

tion of Fig. 8 shows a typically stable DRL performance for sugar pellets alone as reinforcement: the lever-pressing rate is appropriately low, the reinforcement frequency is relatively high, and the IRT's show a peak around the 20-second delay interval. In contrast, the DRL performance for sugar pellets plus electrical stimulation of the globus pallidus as reinforcement shown in the middle section of Fig. 8 reflects the now familiar lever-pressing-rate increase, drop in reinforcement frequency, and shift in IRT's to the shorter delay intervals. Similarly, the lowest section of Fig. 8 shows the DRL performance for this same

DRL-20 SECONDS

MONKEY M-12

Figure 8. Sample cumulative-response curves and inter-response time distributions recorded under conditions of sugar-pellet reinforcement alone (top section), sugar pellets plus brain shock in the globus pallidus as reinforcement (middle section), and sugar-pellet reinforcement plus amphetamine (bottom section). Pips on the record indicate reinforcements. Additional numerical data recorded above each distribution are explained in the text.

monkey recorded during a 2-hour experimental session for sugar pellets alone following intraperitoneal administration of 2 milligrams per kilogram of amphetamine sulfate. A comparison between the two lower sections of Fig. 8 reveals the striking similarity in lever-pressing rates, reinforcement frequencies, and IRT distributions recorded under the two conditions of "sugar pellets plus brain shock" and "sugar pellets plus amphetamine." These two operations, electrical stimulation of the globus pallidus and administration of amphetamine, clearly produce similar effects upon timing behavior under the conditions of this experiment. However, only further experimental analysis can determine whether or not these effects are produced in the same way by these two independent operations.

One further comparison between the effects of brain stimulation and of food reinforcement was provided by an experiment with Monkey M-197 performing on a variable-interval

schedule. Figure 9 shows the cumulative curves recorded for this animal during the two 1-hour experimental sessions on the same VI schedule (average 60 seconds). The top section of Fig. 9 shows the VI performance with sugar pellets alone as reinforcement, and the bottom section shows the VI performance for brain-shock reinforcement alone in the area of

Figure 9. Sample cumulative-response curves showing the differential effect of reinforcement with sugar pellets (upper section) and with brain stimulation in the area of the median forebrain bundle (lower section) upon VI performance for Monkey M-197. Pips on the record indicate reinforcements.

the medial forebrain bundle. The sharp rate increase illustrated in the lower section of Fig. 9 is similar to that observed with Monkeys M-2 and M-12, and indicates that the effects of brain stimulation upon the response rate are not specific to the DRL schedule. It is also clear, however, that these effects of brain stimulation upon the response rate do not necessarily reflect the same process under the two different reinforcement-schedule conditions. Monkey M-197 showed little or no change in the base-line DRL performance (Fig. 5) with the same electrical stimulation reinforcement in the area of the median forebrain bundle which produced the rate increase during the VI performance shown in Fig. 9. Unfortunately, Monkeys M-2 and M-12 were not available for similar experiments on the effects of brain stimulation upon VI performance. Comparison of the effects upon both VI and DRL performance with an electrical brain stimulus producing temporal effects on the DRL might well provide valuable additional data on the neural-behavioral relationships under experimental analysis.

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