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Operantly Conditioned Firing Patterns of Epileptic Neurons in the Monkey Motor Cortex

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In an awake rhesus monkey we operantly conditioned the activity of single precentral pyramidal tract cells near a chronic alumina-induced epileptic focus. Units chosen for conditioning fired predominantly in stereotyped high-frequency long-first-interval bursts. Most units also exhibited brief periods of tonic regular firing, typical of normal precentral cells. The proportion of spikes occurring as long-first-interval bursts was determined on the basis of interspike intervals and defined as the epileptic index. Operantly reinforcing transient increases in unit activity with applesauce produced increases in average rates in all nine cells, with no consistent change in the mean epileptic index. Reinforcing transient decreases in firing rate produced a clear decrease in average rate for two cells, no sustained rate changes in six, and an increase in one; the average epileptic index did not change consistently, although transient pauses in cell activity were invariably preceded and followed by long-first-interval bursts. Reinforcing decreases in the epileptic index produced a sustained drop in the number of long-first-interval bursts/min and a concomitant increase in both regular firing and total rate. Reinforcing an increase in epileptic index produced no consistent changes. These results suggest that firing patterns of epileptic cells may be synaptically modified in awake animals. Analysis of reinforced responses suggest that transient increases in synaptic drive generating higher rates may also decrease the proportion of long-first-interval bursts.

INTRODUCTION

Recent experiments have shown that normal monkeys can be operantly conditioned to control the firing patterns of most precentral motor cortex cells (5, 6). When the reinforced firing pattern was a transient

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increase of cell activity (operant burst), experienced monkeys readily learned to produce such bursts more often and with greater intensity, thereby raising the mean firing rates of these cells. When the reinforced pattern was a transient pause in cell activity, monkeys could also learn to reduce firing rates of the same cells over prolonged periods. The fact that rates of a given cell could be bidirectionally conditioned, and the fact that noncontingent reinforcement was generally ineffective in producing rate changes, indicate that correlation of reinforcement with a specific pattern was essential in producing changes in the rewarded direction. Operant bursts of unit activity have been the most thoroughly documented pattern. In normal monkeys operant bursts typically consist of an increase in firing rate to peak rates of 80–100/sec over 100–300 msec, followed by a drop in rate over 100–200 msec. Bursts were often accompanied by visually observed motor responses and were often correlated with bursts of EMG activity in contralateral limb muscles (6).

In monkeys rendered epileptic by subpial injection of alumina cream, spontaneous firing patterns of precentral cells are considerably different from those seen in normal cortex (2, 17, 18). Interictally, cells near the focus typically fire in brief high-frequency bursts. Often these bursts exhibit a stereotyped structured pattern in which the first interspike interval is consistently longer than the intervals in the rest of the burst (the afterburst), leading to the so-called long-first-interval burst pattern (2, 18). The object of this study was to determine whether firing patterns of such epileptic cells may also be modified by operant conditioning techniques.

It is useful to draw a clear distinction between operant bursts and long-first-interval bursts since both are involved in this study. Operant bursts are elicited from precentral cells in monkeys by operant reinforcement (food reward) and result from normal synaptic excitation of the cell, whereas long-first-interval bursts occur spontaneously in cells near an alumina focus and are presumably generated by some hyperexcitable portion of the cell (3, 18). During an operant burst the firing rate is continuously modulated over several hundred milliseconds; long-first-interval bursts consist of an abrupt high-frequency discharge lasting 10–30 msec. During operant bursts of precentral cells, peak rates rarely exceed 100/sec whereas the long-first-interval bursts exhibit rates of up to 500/sec in the afterburst. While operant bursts may vary in duration and intensity from one burst to the next, long-first-interval bursts are highly stereotyped.

In this study we tested the degree to which activity of cells exhibiting long-first-interval burst patterns could be operantly controlled. The same techniques previously used to condition normal cells (5, 6, 9) were employed to determine whether the monkey could increase or decrease the

average firing rates of long-first-interval cells. In addition, since most of these cells showed periods of regular firing as well as long-first-interval burst firing, we tested the degree to which the animal could modify the relative proportion of time the cell fired in a regular mode as opposed to epileptic long-first-interval bursting mode.

METHODS

We recorded activity of precentral units near an alumina focus in a *Macaca mulatta* monkey using techniques previously described (6, 18). The cells selected for conditioning were identified as pyramidal tract cells on the basis of an invariant short-latency response to stimulation of

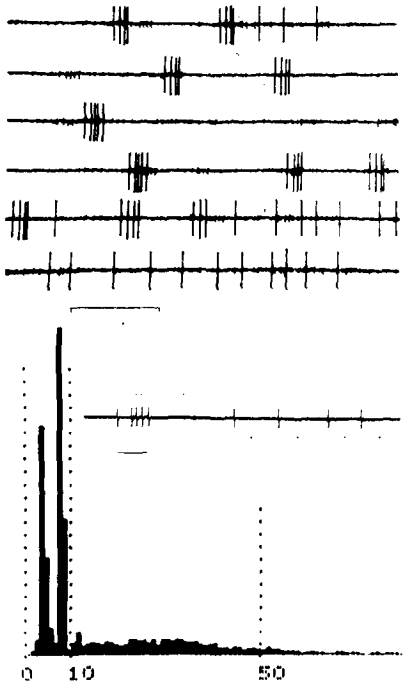

FIG. 1. Typical firing patterns of cells near alumina focus, showing bursting mode and regular activity. (A) Continuous record of cell activity from top to bottom. This unit (cell 5) fired predominantly in spontaneous long-first-interval bursts, but occasionally reverted to more tonic regular activity. (B) Interspike interval histogram of cell firing in both modes. Peak at 3–4 msec represents afterburst intervals, peak at 7–8 msec represents long first intervals, and shallow distribution above 10 msec represents intervals during regular firing. The height of the long-first-interval peak is comparable to the height of the afterburst interval peak because this cell (cell 6) fired in doublets during the sample (Fig. 2, Ref. 18). The inset illustrates on-line generation of separate pulse trains corresponding to spikes in bursts (dots above trace) and spikes in regular mode (dots below trace). Time bars represent 100 msec in A, 20 msec in inset.

the medullary pyramids. All cells were confirmed to be firing in long-first-interval bursts (the numbers used to identify these units refer to the numbers used in Table 1 of Ref. 18). These cells also exhibited periods of regular tonic firing (Fig. 1). In order to quantify the relative amount of bursting activity of these cells, we have defined an epileptic index as the ratio of the number of spikes appearing in the long-first-interval bursts to the total number of spikes over a given time period. Thus the epileptic index could range between the value of 1.0 for exclusively long-first-interval burst activity and the value of 0 for exclusively regular activity. The distinction between burst activity and regular activity was made on the basis of interspike intervals. During regular activity interspike intervals were almost always longer than even the long first interval of the long-first-interval burst. This is illustrated in Fig. 1 by a typical interspike interval histogram. The histogram shows three peaks: The first peak (at 3–4 msec) represents the shortest intervals, namely, the afterburst intervals; the peak at 7–8 msec represents the long first intervals and the very broad shallow distribution in the range between 10–60 msec represents intervals occurring during periods of regular firing. It was usually possible to set a criterion interval slightly larger than the long first interval (e.g., 10 msec in Fig. 1), which fell between the short intervals occurring during the long-first-interval bursts and the long intervals occurring during the regular activity. By counting the number of spikes associated with shorter intervals, we determined the number of spikes appearing in long-first-interval bursts. The ratio of this number to the total number of spikes in a given time period (typically 100 sec) determined the mean epileptic index for that period. For most of these cells the preconditioning epileptic index was between 0.60 and 0.99. The inset in Fig. 1 illustrates a sample of unit activity including one long-first-interval burst and three spikes in the regular mode. The dots above and below the spike train represent voltage pulses corresponding to burst and regular spikes, respectively, generated on-line by a logic circuit.[2]

Typical training sessions involved only a single unit. Unit firing rates were monitored for 10–15 min before any conditioning was attempted (preconditioning period). This was followed by a conditioning period in which reinforcement (1 ml of applesauce) was delivered for appropriate changes in firing patterns. During this time a meter in front of the monkey was illuminated and its needle deflection indicated the degree to which the monkey's response patterns met criterion for reinforcement. The

[2] Note that the dots on top equal the number of spikes in the long-first-interval burst; the first set of four dots occurs at the end of intervals shorter than criterion (10 msec); the last dot is added to count the initial spike as part of the burst. The dots below the spike train mark those spikes which were preceded and followed by an interval longer than the criterion interval.

conditioning period usually lasted 20–30 min and was followed by an extinction period in which reinforcement and feedback were removed. After the extinction period (5–15 min) another reinforcement period was introduced, presenting either the same schedule or, more often, a different schedule.

Firing patterns were reinforced using an electronic activity integrator consisting of a parallel RC integrator with a threshold level for triggering the feeder. The activity integrator could sum two inputs: Pulses in the positive input drove the activity integrator voltage toward feeder threshold and produced reinforcement; pulses in the negative input drove the activity integrator voltage away from the threshold and withheld reinforcement. The relative contribution of these pulses to the integrator voltage could be continuously varied so that for any schedule the activity integrator level fluctuated at some voltage below threshold and only transient fluctuations in the appropriate direction drove the level toward threshold. The deflections of the illuminated meter facing the monkey were always proportional to the integrator voltage; thus the extreme rightward position consistently corresponded to reinforcement level.

In this study, four types of schedules were used, two involving total firing rates and two involving the balance of bursting and regular activity, i.e., the epileptic index. Differential reinforcement of high rates (DRH) reinforced transient increases in total activity; a voltage pulse for every action potential was introduced into the positive input so that activity integrator voltage was proportional to total firing rate (Fig. 3). Differential reinforcement of zero activity (DRO) reinforced transient decreases in total activity; pulses from unit spikes were led to the negative input, while pulses generated by a multivibrator were led to the positive input. The relative gains were adjusted so that transient pauses in unit activity allowed the multivibrator pulses to drive the integrator to threshold (Fig. 3). In addition to total rate, we could also reinforce increases or decreases in the epileptic index by leading the pulses from bursting and regular activity to the two inputs separately. Differential reinforcement of regular activity (DRR) reinforced increases in regular activity and decreases in bursting activity. For this schedule we led pulses corresponding to regular firing into the positive input and pulses from long-first-interval bursts into the negative input (Fig. 3). The reverse schedule, called differential reinforcement of bursting activity (DRB), reinforced increases in long-first-interval bursting activity and decreases in regular activity; for this schedule we led the long-first-interval burst pulses into the positive input and the regular pulses into the negative input (Fig. 3). Again the relative gains were continually adjusted so that the activity integrator level fluctuated about some value below threshold and only transient changes of the epileptic index were reinforced.

Before operantly conditioning epileptic cells, we exposed the monkey to 15 training sessions involving normal precentral cells recorded several millimeters from the focus. At the end of these training sessions, the monkey demonstrated good increases in rates during differential reinforcement of high rates and moderate success in decreasing unit activity during differential reinforcement of zero activity.

During each session a Grass polygraph, run at 0.25 mm/sec, continuously recorded average firing rates, reinforcement events, and changes in schedules. On FM magnetic tape, we recorded action potentials of the unit, 1-msec voltage pulses triggered from each unit spike, activity integrator voltage, 1-sec voltage pulses initiated at each feeder discharge, and voice. The pulses triggered from the spikes were used to confirm that only one and the same unit was involved in the reinforcement schedules and were then further used in quantitative analysis of firing rates. The 1-sec feeder pulses were used to construct dot raster displays of unit activity during the reinforced response patterns; the tape was played backwards and these feeder pulses triggered a 2-sec raster sweep which then included the activity occurring around the feeder discharge. The same technique was used to compute response averages: by triggering a Nuclear Chicago data retrieval computer from the 1-sec feeder pulses, we compiled time histograms of unit activity over the 2-sec intervals straddling the reinforced response. Averages of total firing rates and epileptic index over 100-sec intervals throughout the session were computed off-line with an electronic counter.

RESULTS

We attempted to operantly condition activity of 24 precentral units. Fifteen of these were preliminary training sessions with normal cells recorded several millimeters from the alumina focus and showing no signs of interictal burst activity. During these training sessions the monkey was exposed to a total of 16.8 hr of differential reinforcement of high rates conditioning (15 cells) and a total of 5.5 hr of differential reinforcement of zero activity conditioning (seven cells). At the end of this time the monkey had demonstrated good proficiency at increasing rates under differential reinforcement of high rates (DRH) and moderate proficiency at decreasing rates under differential reinforcement of zero activity (DRO). The subsequent nine sessions involved epileptic cells recorded in the alumina focus. All nine units fired in the long-first-interval burst mode and responded antidromically to pyramidal tract stimulation. All units were conditioned under DRH and DRO schedules; some were also conditioned under differential reinforcement of regular activity (DRR) and differential reinforcement of bursting activity (DRB).

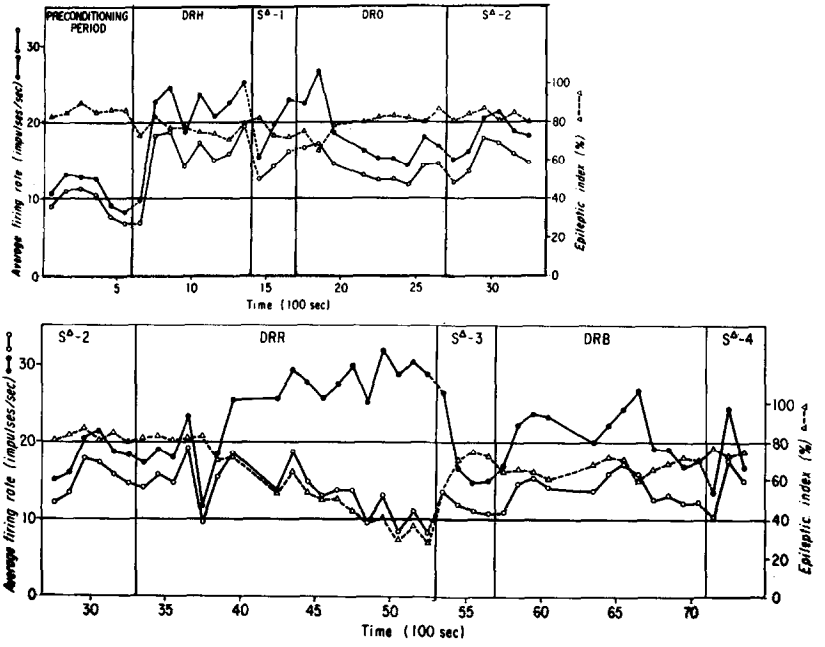

FIG. 2. Conditioning session with cell 5, showing responses during four different behavioral schedules. Each point represents an average over a 100-sec interval. Average firing rate is plotted with solid lines, both for total number of spikes per second (solid dots) and number of long-first-interval burst spikes per second (open circles). The mean epileptic index is plotted with dashed lines and scaled at right. Time axis is measured in multiples of 100-sec intervals. The bottom section is a continuation of top, with $S^{\Delta} - 2$ repeated for clarity.

A conditioning session in which the monkey was exposed to all four types of schedules is illustrated in Fig. 2. The graph plots average firing rates and epileptic index of this unit (cell 5) for successive 100-sec intervals during the session. The over-all mean firing rate and the mean epileptic index for each behavioral period is summarized in Table 1. During the 10-min preconditioning period the mean firing rate of this unit was 11.1 ± 1.9 (mean ± SD) impulses/sec. The epileptic index remained relatively steady over this period at 85.8% ± 2.1%, indicating that most activity was in the form of long-first-interval bursts. During differential reinforcement of high rates firing rates increased to a plateau level of 22.5 ± 2.1 inpulses/sec after the first 100-sec interval. The fact that the first 100-sec interval of the DRH period showed no increase in rate may be attributed to the fact that the monkey had to learn appro-

TABLE 1

FIRING RATES AND EPILEPTIC INDEX FOR CELL 5[a]

Period	Time	Mean rate	SD	Mean EI	SD
Precond. period	6	11.1	1.9	85.8	2.1
DRH	7*	22.5	2.1	76.6	3.5
S^{Δ}-1	3	19.4	3.1	75.7	4.5
DRO	6*	16.0	1.2	82.3	2.4
S^{Δ}-2	6	18.3	2.2	83.0	2.5
DRR	11*	28.3	2.1	45.2	10.6
S^{Δ}-3	4	18.3	4.8	68.3	8.3
DRB	12	21.0	3.0	67.1	3.8
S^{Δ}-4	3	18.3	4.5	75.0	1.6

[a] Averages of firing rates and epileptic index for different periods of session with cell 5 (Fig. 2). The time is given in multiples of 100-sec intervals; times marked * represent "terminal time," i.e., the time at the end of that period when reinforced responses had reached plateau levels. The mean rate indicates average of all activity during the designated times; the mean epileptic index gives ratio of burst spikes to total spikes during the same times. Standard deviations (SD) were computed for averages over the designated number of 100-sec time intervals.

priate response patterns to increase the firing rate.[3] Associated with the 100% increase in firing rate during differential reinforcement of high rates was a small drop in epileptic index, indicating a slight increase in the relative amount of regular activity. During the first extinction period ($S^{\Delta}1$), the total rates of this unit did not return to preconditioning levels although the rates did drop below the terminal DRH levels.

Subsequent to the extinction period, we presented a DRO period in which pauses in activity were reinforced. Initially the monkey generated high rates again, but after several minutes he began to reduce unit rates. While the monkey did not succeed in suppressing rates below preconditioning levels during the DRO period, the firing rates over the last 6 min of this period (16.0 ± 1.2) were lower than the average rate during all extinction periods (18.5 ± 3.6). Under differential reinforcement of zero activity the monkey did generate transient pauses in unit activity

[3] During this and subsequent conditioning periods the initial time during which the reinforced response pattern was acquired is designated as acquisition time and the remainder of the training periods is designated as terminal time. The mean values given in Table 1 for rates and epileptic index were compiled for terminal times of appropriate periods.

(Fig. 3); however, these pauses did not recur often enough to result in a reduction in total rates.

After a 10-min extinction period ($S^{\Delta} - 2$), we differentially reinforced regular activity, i.e., a drop in the epileptic index. After an initial 500-sec acquisition time the monkey consistently decreased the epileptic index. The graph in Fig. 2 shows that he decreased the epileptic index in two ways: by increasing the total amount of regular activity and by decreasing the total amount of burst activity. During the final 11 min of this period the epileptic index was clearly lower than the value during preceding and subsequent extinction periods (Table 1) with the value still dropping at the end (Fig. 2). During the subsequent extinction period ($S^{\Delta} - 3$) the epileptic index returned toward time-out levels.

During the final conditioning period we differentially reinforced bursting activity, i.e., increases in epileptic index. This schedule did not produce statistically significant changes in the over-all epileptic index in the rewarded direction. The values of the epileptic index and total number of long-first-interval bursts during this period were not significantly different from those occurring during the preceding and following extinction periods.

While the graph in Fig. 2 plots average rates and epileptic index throughout the session, examples of the reinforced patterns of cell firing during each period are illustrated in Figs. 3 and 4. Figure 3 illustrates dot rasters of successive responses which triggered the feeder and shows the trajectory of the activity integrator during a typical trial. Figure 4 shows the response averages, i.e., time histograms of mean firing rates compiled for 100 successive reinforced responses in each period.

The dot rasters of DRH responses indicate that transient increases in rates during differential reinforcement of high rates could be generated with either regular or bursting activity, although the bursts were more common, consistent with the high epileptic index. The DRH response average (Fig. 4) shows a brief peak in firing rate of 65 impulses/sec; the reason the firing rate during this peak is less than maximum rates occurring during the long-first-interval bursts is that the 20-msec time bins in the response average include interburst intervals.

During differential reinforcement of zero activity responses consisted of a complete pause in unit activity lasting 600 msec or longer (Fig. 3). Note that the first activity following the pause was invariably a long-first-interval burst; often the activity immediately preceding the pause was also in the bursting mode. The response average over 100 DRO responses confirms the complete cessation of unit activity during these reinforced pauses; it also reveals a slight peak caused by alignment of the last bursts preceding the pauses (Fig. 4).

During differential reinforcement of regular activity the reinforced responses consisted of tonic regular firing as illustrated by the dot rasters

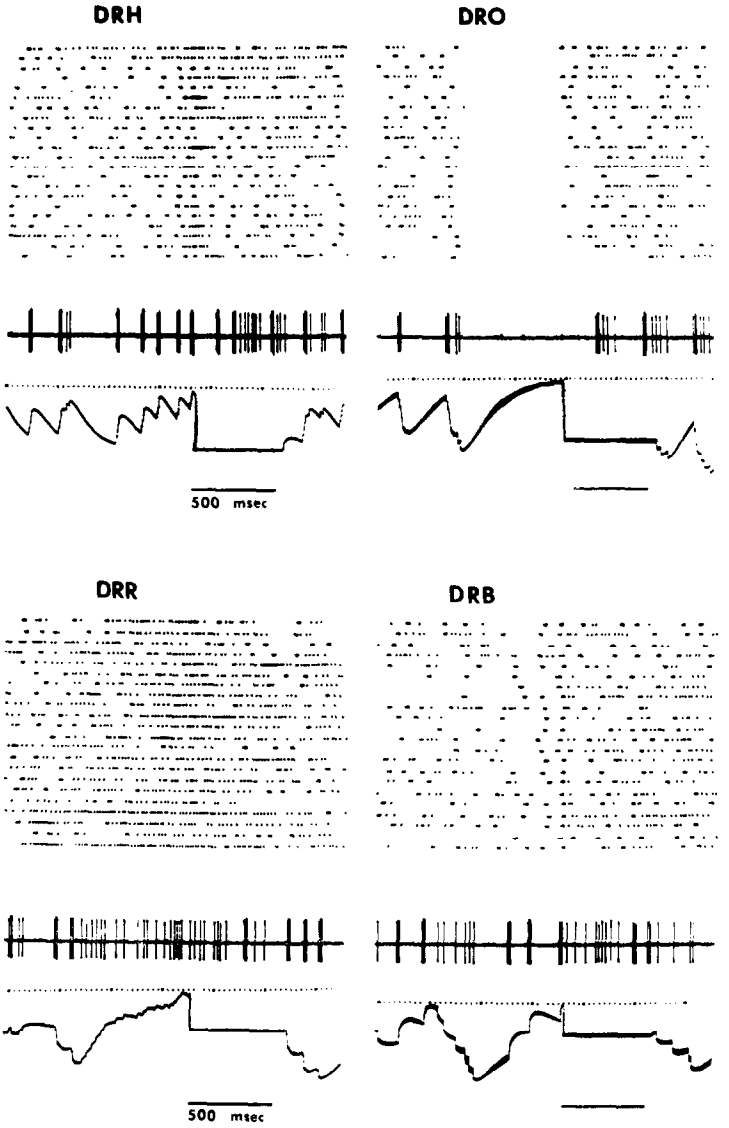

FIG. 3. Examples of reinforced firing patterns which triggered feeder on each behavioral schedule. At bottom of each section is a sample of unit activity, with corresponding trajectory of the activity integrator (AI) voltage below. After reaching reinforcement level (indicated by dotted lines), AI voltage was reset to zero for approximately 500 msec. Dot rasters show successive responses which triggered the feeder on each schedule. During differential reinforcement of high rates (DRH) all spikes drove the AI toward reinforcement level; during differential reinforcement of zero activity (DRO) pauses in cell activity allowed the AI to drift toward reinforcement level. During differentially reinforced regular activity (DRR), regular spikes drove the AI toward, and burst spikes drove AI away from reinforcement level; during differentially reinforced bursting activity (DRB), bursts were reinforced and regular activity prevented feeder discharge. (cell 5).

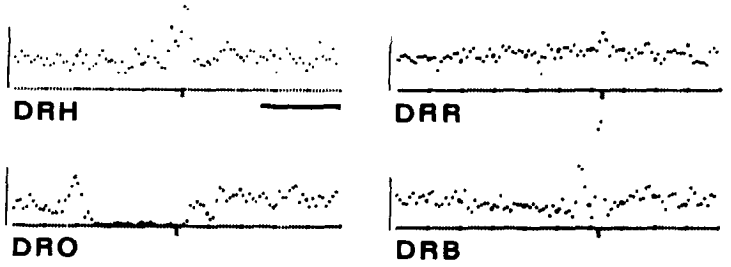

FIG. 4. Response averages of cell 5 showing time histograms of unit activity computed around feeder discharge (bar on baseline) for each behavioral schedule. Each record represents the average of 100 reinforced responses. Total horizontal sweep is 2 secs, divided into one hundred 20-msec time bins. Vertical bars calibrate firing rate of 50/sec; horizontal bar is 500 msec. Abbreviations as in Fig. 3.

of successive responses (Fig. 3). The DRR response average (Fig. 4) reveals a slight increase in over-all activity with a brief peak at the feeder discharge of about 48 impulses/sec. Thus, the total firing rate associated with DRR responses was relatively high, as previously noted. In contrast, the reinforced pattern during differential reinforcement of bursting activity consisted of a series of long-first-interval bursts (Fig. 3). The impression of lower over-all activity given by the dot rasters is confirmed by the response average in Fig. 4, showing a slight suppression in over-all rates preceding DRB responses; two peaks are evident: one for the long-first-interval bursts which triggered the feeder, and another occurring approximately 120 msec earlier.

Since Figs. 3 and 4 selected those 2-sec intervals around the reinforced responses, they illustrate examples of transient changes in pattern in the reinforced direction. In some periods, however, such changes did not recur often enough to affect the over-all rates. For example, although cell 5 did exhibit transient pauses in firing during differential reinforcement of zero activity and transient increases in bursts during differential reinforced bursting activity, it did not show convincing changes in the over-all average of these parameters during these specific periods. Another cell, for which the over-all rate was more convincingly suppressed during differential reinforcement of zero activity as well as increased during differential reinforcement of high rates (cell 6) is shown in Fig. 5. Average values for rates and epileptic index during extinction and reinforcement periods are summarized in Table 2. Again, during differenital reinforcement of high rates, over-all rates increased, with the terminal DRH rates being 70.7% higher than preconditioning rates. During the terminal DRH period the epileptic index dropped only slightly (6.3%). In this session the rates during extinction periods returned to levels comparable to those in the preconditioning period; the total mean extinction rate was

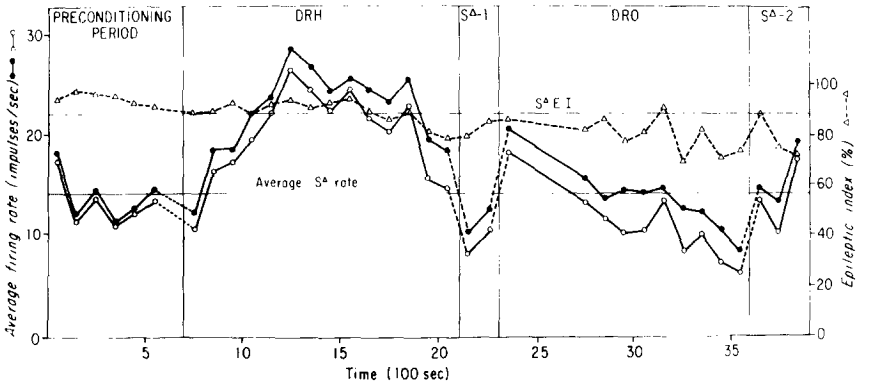

FIG. 5. Conditioning session showing suppression of total rate under DRO, as well as increased rate under DRH (cell 6). Same convention as graph in Fig. 3. Horizontal lines indicate average time-out values for epileptic index and total rate (i.e., average over preconditioning period and all S^{Δ} periods).

14.1 ± 3.2/sec compared to mean preconditioning period rate of 14.0 ± 2.2/sec. During differential reinforcement of zero activity rates dropped steadily and were still decreasing when the period was terminated. During the last 100-sec interval of the DRO period, the monkey suppressed firing rates to 8.6/sec (i.e., 61% of preconditioning rates). The fact that this suppression was sustained by reinforcement is confirmed by the fact that during the succeeding S^{Δ} period, rates again returned to higher levels. During this session the epilleptic index dropped gradually and continuously, but did not show any consistent fluctuation correlated with the behavioral conditions.

The preceding observations suggest that the monkey could modify the firing rates and patterns of these epileptic cells, presumably through

TABLE 2

FIRING RATES AND EPILEPTIC INDEX FOR CELL 6[a]

Period	Time	Mean rate	SD	Mean EI	SD
Precond. period	6	14.0	2.2	95.1	1.9
DRH	11*	23.9	2.8	89.1	4.7
S^{Δ}-1	2	11.5	1.3	82.4	2.7
DRO	4*	11.0	1.6	73.8	4.9
S^{Δ}-2	3	15.8	2.7	78.7	6.9

[a] Mean firing rates and epileptic index for session with cell 6 (Fig. 5). Definition of terms as in Table 1.

excitatory or inhibitory synaptic connections (or both) on the cells. In order to determine whether these synaptic influences modified the structure of the long-first-interval bursts, we compared long-first-interval bursts occurring during differential reinforcement of high rates and zero activity with those occurring during extinction. We found that long-first-interval bursts were altered in two ways as a consequence of the behavioral schedules. One change resulted from the fact that, as long-first-interval bursts recurred more frequently than about 10 bursts/sec, the number of spikes/burst decreased. This relation was illustrated in the previous study for pairs of antidromically evoked bursts and found to apply to spontaneous long-first-interval bursts as well (18). Under differential reinforcement of high rates and zero activity the extremes of total firing rates could be operantly elicited and this relationship was again observed. Figure 6 illustrates examples of long-first-interval bursts of cell 3 recorded immediately following reinforcement during the DRH and DRO periods i.e., during maximum and minimum total firing rates. It is clear that the long-first-interval bursts which recurred in rapid succession during the peak of activity in differential reinforcement of high rates were attenuated in comparison to bursts occurring after pauses in differential reinforcement of zero activity, which exhibited the full complement of afterburst spikes. This observation suggests that the increased excitatory synaptic drive during responses may generate more long-first-interval bursts but can result in a decrease in the total number of spikes per busts. A quantitative analysis of this phenomenon is presented in the discussion.

The second effect of the behavioral schedules on long-first-interval burst structure observed for some cells was a change in the modal distribution of the long first intervals. Figure 7 illustrates dot rasters and time histograms of long-first-interval bursts of cell 5 during different behavioral periods, all aligned on the second spike of the burst (2). In the preconditioning period, long first intervals exhibited a bimodal distribution: the first intervals tended to approximate either 7 or 10 msec, with roughly equal probability. Under differential reinforcement of high rates the first-interval distribution changed to prominent peak at 7 msec and a negligible peak at 10 msec. The 7 msec first interval continued to predominate through the first S^{Δ} period. However, under differential reinforcement of zero activity, the 10 msec first interval reappeared, making the distribution bimodal again. In another subsequent DRH period with this cell the distribution again became essentially unimodal at the shorter first interval. Cell 6 showed a similar shift from bimodal to unimodal distribution under differential reinforcement of high rates (Fig. 8). However, in this case the reversion to the bimodal distribution was seen during the S^{Δ} period as well as under differential reinforcement of zero activity.

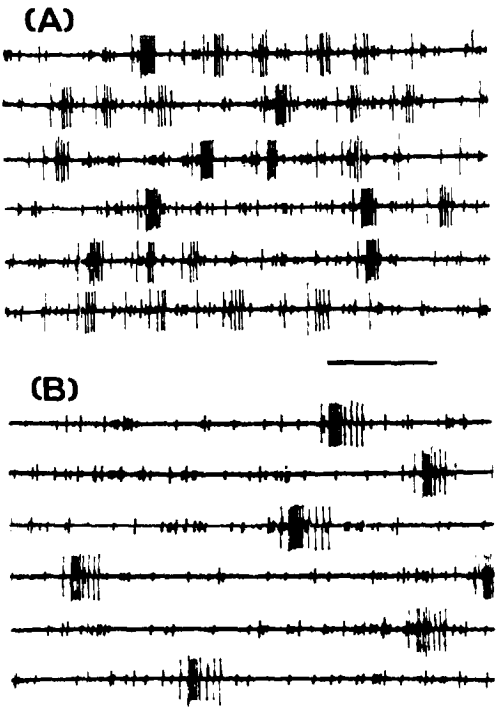

FIG. 6. Difference in long-first-interval bursts of cell 3 occurring during increased firing under differential reinforcement of high rates (A) and after prolonged inactivity under differential reinforcement of zero activity (B). Each sweep was initiated by feeder discharge. During DRH responses, long-first-interval bursts recurred in rapid succession and were proportionately attenuated. The bursts from DRO shown in B were preceded by 1–2 sec of inactivity, and were among the longest recorded for this cell. Time calibration: 100 msec.

The possibility that these changes might be attributable to computer sampling errors was eliminated by close inspection of the originally recorded spike trains. Examination of the recorded data confirms that under differential reinforcement of high rates the long-first-interval bursts did consistently occur with shorter first intervals.

DISCUSSION

This study represents the first attempt to directly operantly condition firing rates and firing patterns of epileptic cells in precentral cortex of awake monkeys. The predominant firing pattern of these cells during interictal periods consisted of high-frequency long-first-interval bursts, suggesting a pathological burst-generating mechanism within the cell (2, 3, 18). The degree to which such interictal firing patterns might be modified by voluntary effort is of considerable clinical relevance in the

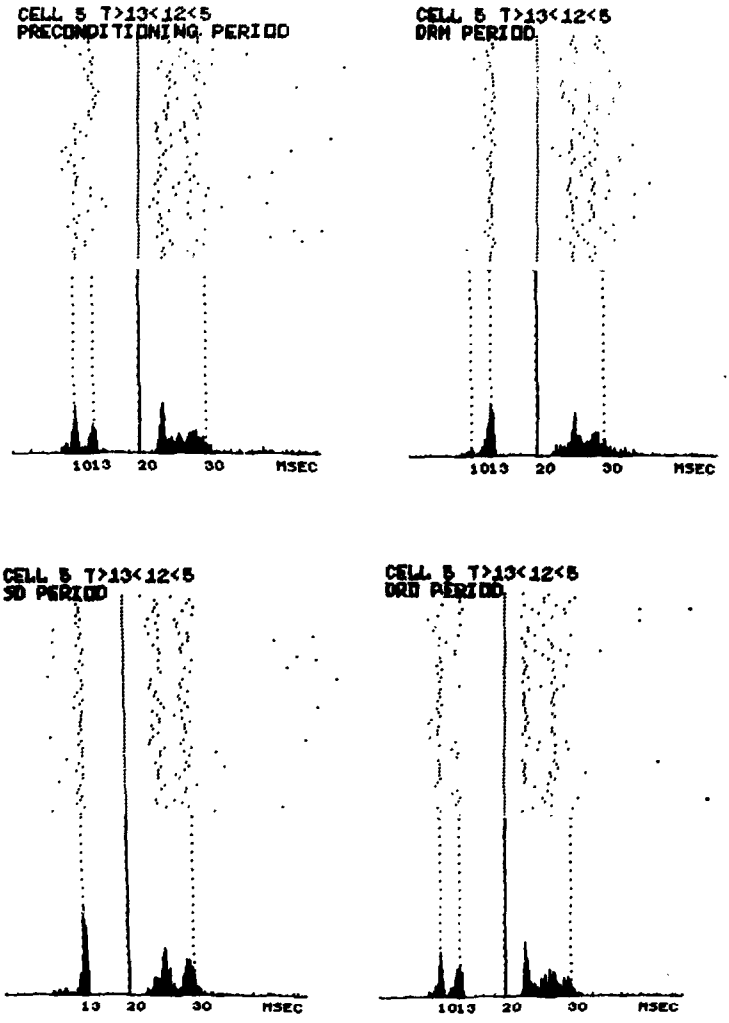

FIG. 7. Change in long-first-interval burst structure under different behavioral conditions for cell 5. Each record shows dot rasters (top) and time histograms of long-first-interval bursts (below) occurring during designated periods and aligned on second spike. Numbers below histogram abscissa mark locations of vertical columns of dots relative to origin; all second spikes were arbitrarily aligned at 20. During preconditioning period (top left), long-first-interval distribution was bimodal with peaks at 7 and 10 msec. Under DRH conditions (top right), long-first-interval distribution became essentially unimodal at 7 msec and mean first afterburst interval lengthened. This change continued through the subsequent extinction period (bottom left). During the DRO period (bottom right), long-first-interval distribution again resembled preconditioning distribution.

control of epilepsy. Since normal monkeys can readily be trained to control firing rates of precentral cells, presumably via synaptic connections on these cells, the object of this study was to determine whether such syn-

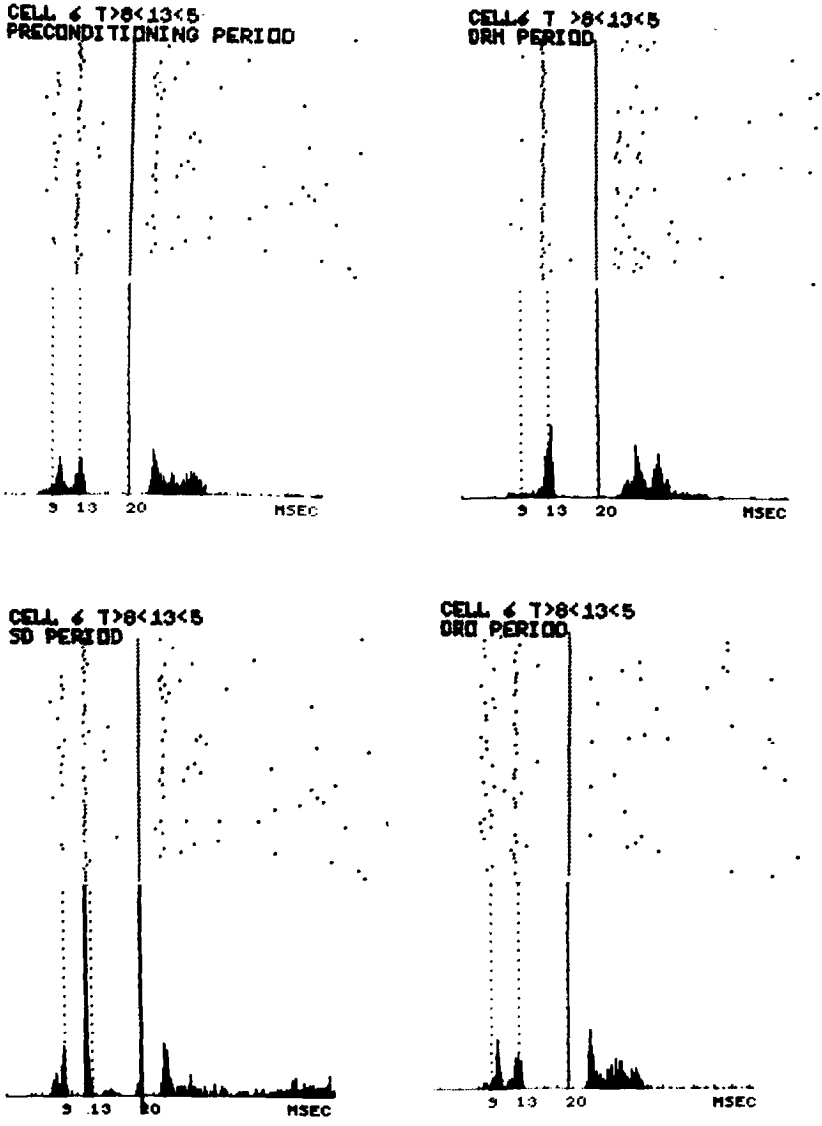

FIG. 8. Change in long-first-interval burst structure under different behavioral conditions for cell 6. Same convention as Fig. 7. Here the bimodal long-first-interval distribution changed to unimodal only during the DRH period. This cell also tended to fire more often in a doublet pattern (Fig. 2, Ref. 18).

aptic connections remain sufficiently potent on epileptic cells to permit control of their interictal firing patterns.

The two parameters of cell firing which were operantly conditioned were the over-all firing rate and the relative amount of bursting activity (epileptic index). Both parameters were bidirectionally conditioned, to

control for effects of reinforcement and discriminative stimuli (1). During differential reinforcement of high rates and zero activity schedules, operant reinforcement was contingent on transient increases and decreases in firing rates, respectively. In all nine sessions differential reinforcement of high rates produced an increase in average firing rates. Such increases were not simply the result of feeding activity because reinforcement delivered at comparable rates, but contingent on pauses in cell activity (differential reinforcements of zero activity) did not produce increased rates in eight sessions. (In one session, both differential reinforcement of high rates and zero activity produced increases in average rates; this cell was found to fire after each feeder discharge, and was apparently involved in feeding behavior.) In two sessions, average activity during differential reinforcement of zero activity decreased below time-out levels. The fact that relatively few DRO periods were successful in decreasing overall firing rates may be related to the fact that this monkey had three times as much exposure to DRH conditioning as to DRO conditioning and, consequently, often attempted to increase rates during conditioning periods. Skinner (11) has also argued that differential conditioning of decreased responses is inherently more difficult than increased responses. We suspect that with further training the monkey could have exhibited greater proficiency at decreasing rates under differential reinforcement of zero activity.

Differential conditioning of regular and bursting activity was also attempted in several sessions. During DRB and DRR periods, operant reinforcement was contingent on transient increases and decreases in the epileptic index respectively. The three sessions in which DRB conditioning was attempted showed no consistent changes in the epileptic index; the session in which the DRR schedule was presented produced a rather dramatic decrease in the epileptic index, associated with an increase in total rate (Fig. 2).

Even when the differential schedules did not produce sustained changes in the reinforced parameter, the activity integrator identified those times when unit activity fluctuated in the appropriate direction. Thus, samples of transient shifts in the direction of the reinforced parameter could be examined, whether or not they recurred sufficiently often to change the average value of that parameter. Thus, for cell 5, even though the DRO period produced no convincing drop in average rates, the reinforced pauses in unit activity were identified and could be displayed in the form of dot rasters (Fig. 3) or response averages (Fig. 4). Such displays often revealed interesting features of these responses; for example, the fact that long-first-interval bursts tended to occur before and after pauses in firing.

Various lines of evidence suggest that the average firing rate and the epileptic index are not entirely independent parameters. In many cases,

there seemed to be some tendency for increased firing rates to be associated with decreased epileptic index; conversely, suppression of average firing was often associated with greater proportion of bursts. This tendency toward an inverse relationship between firing rates and epileptic index can be seen in the average values of these parameters plotted in Fig. 2 and in the responses shown in Fig. 3. The relationship was illustrated most dramatically during the DRR period: as the epileptic index dropped the average firing rate increased dramatically (Fig. 2). During the DRH period, increased rates were also associated with slightly decreased epileptic index. On the other hand, pauses in firing rates under DRO conditions were preceded and followed by long-first-interval burst activity. This suggests that increased excitatory synaptic drive on these cells was associated with an increased probability of firing in a regular mode, as opposed to the long-first-interval burst mode. Conversely, when synaptic drive was sufficiently reduced, cell activity occurred predominantly in long-first-interval bursts.

This result is more readily understood if we recall that some of these cells exhibited two types of action potentials: simple action potentials, occurring during regular firing and as initial spikes of the long-first-interval bursts, and compound action potentials occurring during the afterburst. On the basis of this and related evidence, we concluded that the simple spikes probably represent normal synaptic activation of the cell, whereas the compound afterburst spikes may represent the pathological activation by a burst-generating mechanism within the cell (18). Thus, the long-first-interval burst might be considered to consist of a synaptically generated initial spike which triggers an internal pacemaker mechanism generating the afterburst spikes. According to this interpretation, the initial spike is the event which is synaptically controlled, while the afterburst is a dependent phenomenon which appears under appropriate conditions. We have noted that the length of the afterbursts was found to be a function of the interburst interval. For cell 3, when initial spikes occurred at rates less than about 10/sec, the full complement of afterburst spikes appeared; at rates exceeding 10/sec, the afterburst was proportionately attenuated until it finally disappeared. Thus, as synaptic drive increases, producing initial spikes at higher rates, the long-first-interval bursts become shorter, producing less total activity per initial spike. The relative effect of these two opposing trends on overall rate can be assessed by considering a specific parametric model based on the observations of cell 3 (cf. Fig. 4 in Ref. 18). This model will also allow us to derive a quantitative expression for total firing rates, F (F = number of initial + afterburst spikes/unit time) as a function of initial spike rate, f.

It is convenient to consider separately three ranges of initial spike

firing rates. In the low-frequency range the interval between initial spikes (I) is greater than 100 msec; in this range the full complement of afterburst spikes is generated. If we let N = the average number of spikes in the long-first-interval bursts in this range, the total firing rate $F = Nf = N/I$. In the intermediate range (e.g., 20 msec $\leq I \leq$ 100 msec), the number of afterburst spikes is reduced as an inverse function of the interburst interval. If $n(I)$ = average number of spikes in the long-first-interval burst,

$$n(I) = 1 + (N - 1)\frac{(I - 20)}{80} \qquad 20 \leq I \leq 100$$

and

$$F = n(I)f = n(I)/I.$$

Finally, in the high-frequency range ($I \leq 20$ msec.) the afterburst is totally eliminated, firing is in the regular mode, and $F = f$. Plotting $F(f)$ shows that the total firing rate F is always a monotonically increasing function of the initial spike firing rate f. Thus, as excitatory drive increases, the afterburst never shortens sufficiently rapidly that an increase in f produces a decrease in F. While this model yields formulae for average values of these parameters, as if synaptic drive were steady, the actual situation deviates from the model mainly due to transient fluctuations about these average values.

Operant reinforcement was contingent on firing patterns of only one cortical cell. The degree to which other cortical units may also have changed their activity was not documented. Previous studies of operant conditioning of cortical units in normal monkeys indicated that adjacent cells may also undergo correlated changes in firing rate. One would expect at least those cells controlling the firing pattern of the conditioned cell to show some correlated activity; in addition, other cells involved in a wider response pattern probably also fire in some relation to the reinforced unit. Calvin (3) has calculated that a relatively modest number of interconnections in a population of neurons are sufficient to sustain and spread bursting patterns of activity. Thus, modification of the bursting activity of one element would suggest a correlated modification of burst patterns in connected neural elements. More recently we have observed that unit bursts were often correlated with typical interictal sharp waves in the EEG, and that regular firing was accompanied by disappearance of the sharp waves (Fetz and Smith, unpublished observations). Such a correlation, not directly documented in this study, would suggest that interictal EEG sharp waves might also be operantly modified.

Most previous studies on conditioning of epileptiform activity have employed classical conditioning paradigms. In the case of reflex epilepsies, or sensory precipitated seizures, specific stimuli may reliably

trigger paroxysmal EEG and motor discharges (10); in such cases, the triggering stimulus may be treated as an unconditioned stimulus eliciting the epileptic activity as the unconditioned response. Attempts to classically condition such epileptiform EEG responses to a previously neutral conditioned stimulus by repeated conditioned stimulus–unconditioned stimulus pairing have been reported to be successful in the abstract of Morrell and Naquit (8); however, Stevens (13, 14, 16) reported negative results in classically conditioning spike-wave discharges elicited by photic stimulation to follow a neutral tone stimulus. In these papers, Stevens also briefly mentioned paradigms which might operantly modify the reflex spike-wave discharges triggered by light flashes. When a rewarding or aversive stimulus was paired with such spike-wave discharges, there was apparently no change in the probability of eliciting such discharges with photic stimuli.

Classical conditioning techniques have also been used to suppress epileptic activity. Efron reported a patient who could stop the progression of a psychomotor seizure of uncinate origin by a strong olfactory stimulus (4). This inhibition of seizure activity (unconditioned response) was classically transferred from the olfactory stimulus (unconditioned stimulus) to a visual stimulus (conditioned stimulus) by repeated pairing of the olfactory stimulus and the sight of a silver bracelet. After several days of conditioned stimulus–unconditioned stimulus pairing the patient could inhibit the seizure progression by looking at the bracelet; later she averted seizures by just thinking about the bracelet.

By appropriate conditioning procedures, Forster (7) desensitized patients to a variety of stimuli which reliably triggered seizures. He repeatedly presented similar but innocuous stimuli, and gradually modified the parameters of the innocuous stimuli until they became identical to the previously noxious stimuli; at this point the latter had become ineffective for precipitating seizures. This conditioning procedure proved effective for treating patients sensitive to stroboscopic flashes, startle stimuli, visual patterns and musical stimuli (for review, 7).

More recently, Stevens, Milstein and Dodds (15) investigated the possibility of using spontaneous EEG spikes as the conditioned stimulus; with such EEG spikes (conditioned stimulus) they paired a painful skin shock (unconditioned stimulus) which elicited characteristic autonomic responses (unconditioned response). After repeated pairings, they found no evidence to suggest that epileptiform EEG spikes could serve as a conditioned stimulus for eliciting autonomic responses. Of more relevance to the present study is the fact that the same situation also represents an operant conditioning paradigm in which the spontaneous EEG spikes could represent an operant punished by the aversive shocks. Stevens and associates (15) did not report any evidence that EEG spikes recurred

less frequently under these conditions; however, the maximum number of reinforced spikes in a given subject was only 140.

Recently, Sterman and Friar (12) have reported evidence that operant conditioning of a regular EEG slow-wave activity over sensorimotor cortex—the sensorimotor rhythm—may reduce susceptibility to seizures. In cats with prolonged sensorimotor rhythm training, the resistance to drug-induced seizures went up; in such animals, convulsive doses of monomethyl-hydrazene produced typical preictal symptoms, but overt seizure activity was significantly delayed or entirely abolished. In a human patient, sensorimotor rhythm training sessions (approximately two/week) reduced the frequency of nocturnal generalized motor seizures over a period of several months. Sterman's studies represent instances in which effects of biofeedback training transferred to other physiological phenomena (1).

Direct operant conditioning of epileptic activity has been suggested, but to our knowledge not reported until now. In this study the conditioned activity was the interictal firing patterns of single precentral cortex cells near an alumina focus. Evidence that burst discharges in units correlate with interictal EEG sharp waves suggests that desynchronization of the latter could also be conditioned. It has been known that volitional maneuvers can sometimes modify interictal and preictal epileptic activity. Thus, it should prove possible to elicit such responses by making operant reinforcement directly contingent on modification of interictal EEG patterns.

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