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Behavioral Control of Firing Patterns of Normal and Abnormal Neurons in Chronic Epileptic Cortex

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One hundred ninety-eight cells in chronic alumina-induced foci of three monkeys were operantly conditioned for increased and decreased rates. One hundred seven cells exhibited entirely normal firing patterns. Of the abnormal cells, two groups were distinguished on the basis of the variability of their burst index (percentage of cell spikes occurring in bursts). Group I cells fired in structured bursts with high, invariant burst indices and could not be successfully bidirectionally conditioned; Group 2 cells had lower and more variable burst indices and were as easily conditioned as normal cells. These observations provide additional evidence that activity of the majority of epileptic cells may be modified synaptically and suggests therapeutic potentials for biofeedback conditioning in epileptic patients.

INTRODUCTION

Interictal firing patterns of single units in experimental models of epilepsy have been described by several investigators (3, 9, 15, 16, 27, 31) and the subject has been recently reviewed by Ward (27). The hallmark of epileptic activity in single cells is repetitive high-frequency (burst) firing, but the mechanism of such pathological bursting remains unresolved. Although many methods for the production of seizures (e.g., with topical convulsants) have been extensively studied (1, 15, 16, 20), the natural history and interictal behavior of these acute foci do not necessarily parallel human epilepsy. The chronic alumina gel focus is the closest experimental model of chronic human epilepsy (12, 27), since they show similar EEG correlates,

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seizure patterns, and single-cell burst structures (2, 27). But, unfortunately, intracellular studies using this model are not only technically difficult because of the intense gliotic scar the alumina induces (27, 30), but the drugs and experimental conditions necessary for acute recording provide neurons in a relatively unphysiological milieu. It is, therefore, difficult to extrapolate data from acute, intracellular studies to answer such questions as: (a) Are bursts generated intrinsically by the cell, or are they the result of a "pacemaker" cell's influence by either direct synaptic or ephaptic spread, or both (12); and (b) if the burst-generating mechanism is intrinsic to the neuron, is the normal action-potential-initiating mechanism(s) and region (i.e., axon hillock) responsible for burst production, or is there a pacemaker within a different region of the cell?

The firing rates of single cortical neurons can be brought under behavioral control by operant conditioning (8, 9). Applying such techniques to "epileptic" cells in animals chronically prepared allows observation of neuronal behavior during different extremes of firing patterns in the absence of drugs which might not only have direct cellular effects (11) but which might also alter afferent synaptic influences. Therefore, behavioral studies of neurons within chronically prepared epileptic cortex will provide more realistic data concerning possible burst-generating mechanisms and epileptic synchrony, and the degree to which such mechanisms can be voluntarily modified. A recent report (8) of our initial observations was limited to cells exhibiting only one type of epileptic burst pattern, the long-first-interval burst. The following communication concerns itself with comparisons between operant conditioning of normal and a broader range of epileptic neurons from alumina gel foci and does not include data previously reported.

METHODS

Terms used in this report are defined as follows:

(a) *Stereotyped bursts*: Recurrent high-frequency bursts of unit activity with interspike intervals less than 5 msec. If repeated bursts are aligned in a dot raster such that the first spike of each burst forms a column, the early portion of the burst is exceedingly invariant. The variance of the interspike intervals generally increases toward the end of the burst.

(b) *Structured bursts*: The commonest, and the only one relevant to this report, is the long-first-interval burst (3, 31), which is initiated by a single spike, followed by a relatively long interval which is often an integer multiple of the next interspike interval. The burst after the long first interval (i.e., the afterburst) is essentially a stereotyped burst.

(c) *Unstructured bursts*: Abnormally high frequency, randomly occurring bursts with variable interspike intervals.

(d) *Burst index*: The % ratio of the number of spikes occurring in bursts to total cell activity per unit time. (In this study, counts were compiled over 15-sec time intervals.) Thus, a cell showing only burst activity would have a burst index of 100, while a normal cell would have a burst index of 000.0. (In a previous report (8), we referred to this as the "epileptic index".)
(e) *DRH*: Differential reinforcement for high rates of activity.
(f) *DRO*: Differential reinforcement for zero rates of activity.
(g) S^{Δ}. An extinction period in which no reinforcement is given.

Production and Confirmation of Epilepsy. Six months prior to training, three male *Maccaca mulatta* monkeys (weight 2.5–4 kg) received subpial injection ot alumina gel in the hand region of left precentral and postcentral cortex following the protocol recently reviewed by Ward (27, 28). Preoperative EEGs were taken 1 day prior to surgery; postoperative EEGs were repeated at three-month intervals. By 3 months each monkey had developed EEG evidence of epileptiform activity. After 4 months, all monkeys underwent several 2-week periods of continuous 24-hr seizure monitoring using the methods described by Lockard (14). Each monkey had a minimum of two generalized seizures per week, as well as focal seizures. Training was not initiated until at least 6 months after the alumina had been injected and stable seizure frequencies had been documented.

Recording Techniques. The monkeys underwent sterile craniectomy to affix the recording chamber and implant concentric, bipolar stimulating electrodes in the pyramidal tract ipsilateral to the focus as previously reported (6–9, 31). The scalp EEG was recorded on paper with a four-channel Grass polygraph, while local cortical EEG from the tungsten microelectrode was recorded on magnetic tape. To insure unequivocal action potential isolation for data analysis, the signal was filtered on-line (band pass of 350 Hz–10 kHz) to a separate oscilloscope and the computer. All action potentials were biphasic, negative–positive. An on-line polygraph recorded instantaneous firing rates and 10-sec integrated firing rates. Data were recorded on a six-channel FM Ampex tape recorder. An on-line PDP8 computer compiled and printed firing rates and burst indices over 15-sec periods. A Tektronix 5103N memory oscilloscope displayed unit activity on a slow raster, while a Tektronix 565 oscilloscope monitored action potential isolation on a fast sweep.

Analysis Criteria. Cells were identified as pyramidal tract neurons if they responded antidromically to three stimuli at rates of 500 pulses sec with an invariant latency.

Precentral cells were judged to be abnormal if they exhibited spontaneous bursts of high-frequency firing with interspike intervals less than 5 msec during alert wakefulness, and normal if they showed no intervals less than 5 msec. In fact, normal precentral cells rarely exhibited interspike intervals less than 10 msec, except during vigorous movements or sleep (6, 33).

The burst index was determined during an initial 5-min preconditioning period with the animal fully awake.

An exception to the above analysis criteria was made in the case of long-first-interval bursts, which may have the first interspike interval of each burst greater than 5 msec, as previously reported (31). To identify such bursts the computer required the second interval to be less than 5 msec and the sum of the first two intervals to be less than 17 msec. If these requirements were met, the computer counted all following intervals less than 5 msec as part of the long-first-interval burst. These were the only instances in which interspike intervals greater than 5 msec (the long first interval) was considered part of an epileptic burst.

High-frequency bursts due to cell injury by the microelectrodes sometimes closely resemble epileptic activity (34). Bursts of epileptic origin were distinguished from injury bursts by the following criteria: (a) During wakefulness, epileptic bursts usually showed a relatively consistent burst structure and duration, whereas injury bursts showed considerable variance in burst duration. (b) Duration and interburst intervals of injury bursts changed as a function of microelectrode position, whereas those of epileptic bursts did not. (c) Injury bursts were often preceded by a tonic crescendo train of action potentials characteristic of injury in normal cortex. (d) Injury bursts did not sustain repetitive burst firing for periods longer than 10–15 min. (e) Injury bursts showed interburst intervals well below 100 msec, whereas spontaneous epileptic bursts [with the exception of long-first-interval bursts (31)] did not demonstrate interburst intervals less than 100 msec. An example of injury bursts and spontaneous epileptic bursts are shown in Fig. 1.

Operant Conditioning. The monkey was considered fully trained if, with four consecutive cells, he could sustain an increase of cell activity of at least one standard deviation above the preceding time-out period for a minimum of 3 consecutive minutes on a DRH schedule, and could sustain a decrease in firing rate of at least one-half standard deviation below the preceding time-out period for 3 min on a DRO schedule. Thus, four successive cells were required to exhibit successful bidirectional control before the animal was considered trained. A cell was considered unconditionable if a minimum of 1 hr of attempted operant conditioning failed to produce consistent changes in the rewarded directions, and a normal pyramidal tract cell responding to passive movement of the contralateral arm was subsequently successfully bidirectionally conditioned on the same day. Thus, if control could not be obtained over the normal pyramidal tract cell, the previous cell was excluded from the data. This controlled for changes in motivation and other behavioral variables which might be responsible for the failure to condition cell activity.

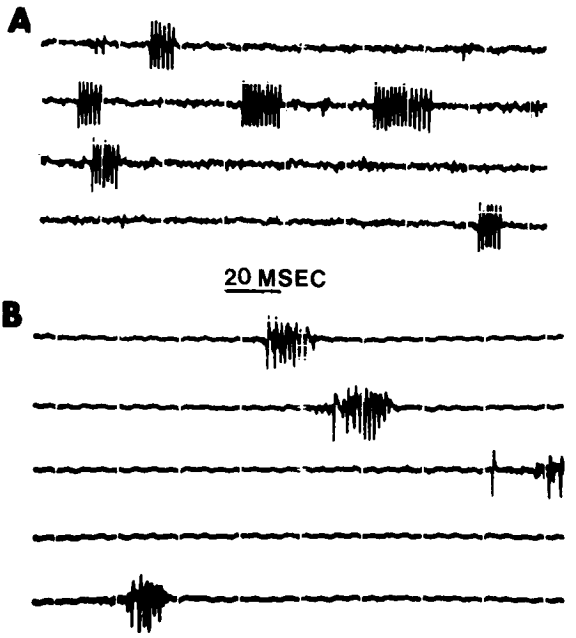

FIG. 1. Comparison of injury bursts produced by mechanical injury with the microelectrode (A) and spontaneous epileptic bursts typical of interictal activity in an alumina focus (B). Records show continuous samples of activity from two cells in the same monkey. Whereas duration of injury bursts were variable and showed an inverse relationship with interburst intervals, the duration of epileptic bursts was relatively constant and interburst intervals were rarely below 100 msec.

RESULTS

Approximately 46 hr (daily sessions for 2 weeks) were devoted to training each monkey prior to adequate demonstration of behavioral proficiency. Sixty percent of all training time was spent on DRO, and 40% on DRH; nevertheless, monkeys reached proficiency with DRH before DRO.

Cell Characteristics. Of 198 precentral cells included in this study, 110 (56%) were pyramidal tract cells. Neurons with spontaneous firing frequencies below 3/sec were not conditioned. Action potentials ranged between 200 μv and 4 mv, with a median of 800 μv. Sixty-three per cent of all cells were responsive to one or more of the following: light touch, pressure, or percussion over joints and tendons, and passive movement of joints (two cells responded to movements in the visual field). One hundred seven cells were judged normal, and 91 abnormal on the basis of burst indices between 10 and 100. Normal and abnormal cells did not differ significantly with respect to responsiveness to peripheral and pyramidal tract stimula-

tion: 58% of normal cells were pyramidal tract neurons, while 53% of abnormal cells were pyramidal tract neurons; 62% of abnormal and 65% of normal cells were driven by peripheral stimuli.

Although many cells occasionally fired with long-first-interval bursts,

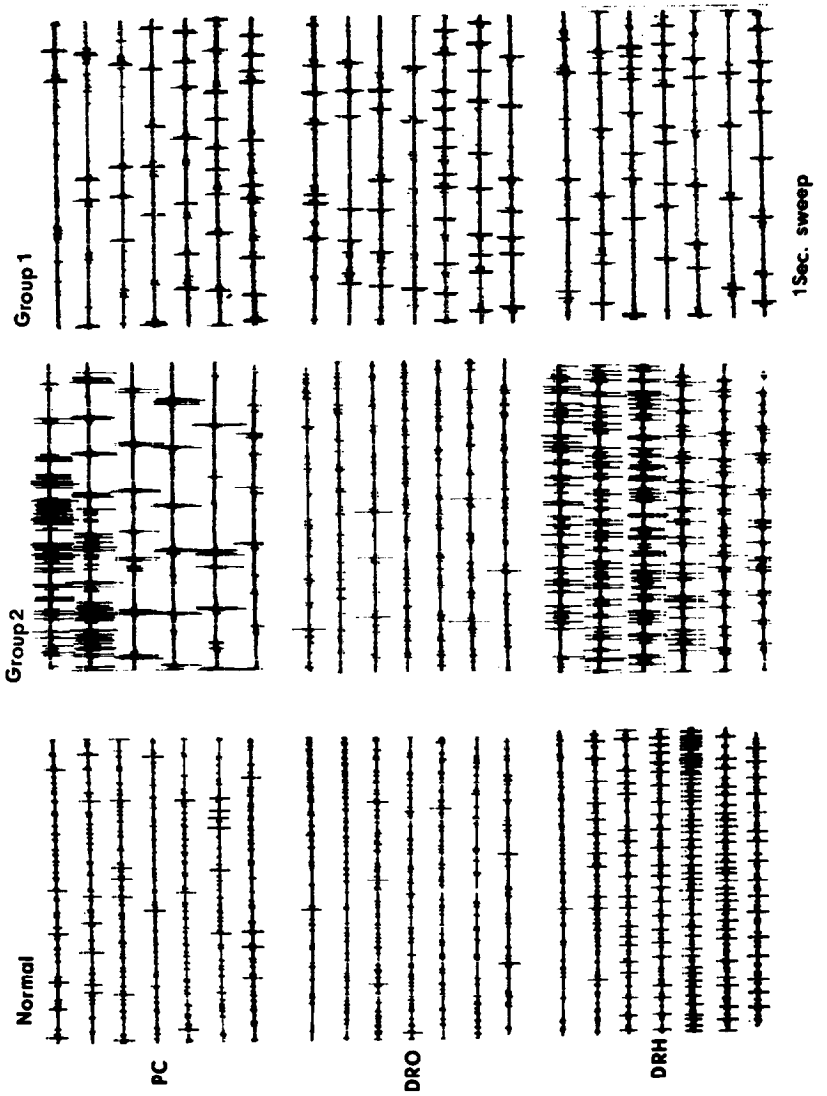

FIG. 2. Samples of unit activity typical of cells characterized as normal, Group 1, and Group 2. Continuous 1-sec sweeps show samples of firing patterns from preconditioning periods, DRO, and DRH periods of sessions plotted in Figs. 5–7. These three cells were recorded in alumina focus of the same monkey.

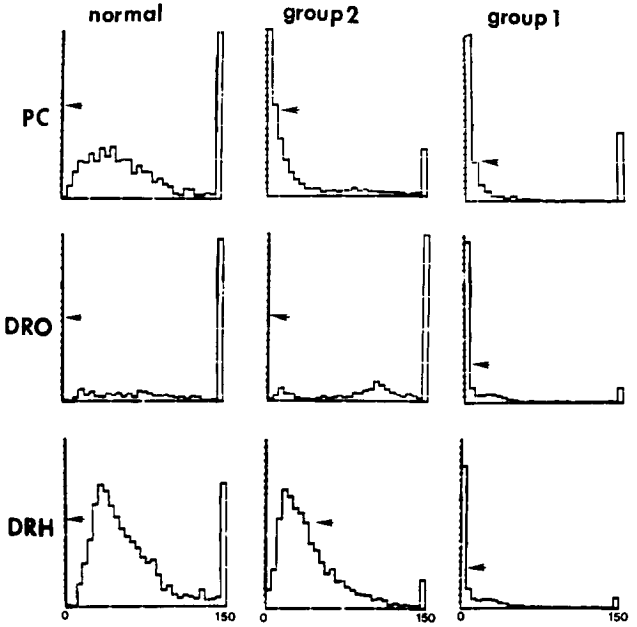

FIG. 3. Interspike interval histograms of three neurons characterized as normal, Group 1, and Group 2. Histograms were compiled with 5-msec bin widths; the last bin includes all intervals greater than 145 msec. Arrows mark the height of a count of 1,000 intervals. Histograms were compiled for equal number of intervals during the time periods indicated by horizontal bars in Figs. 5, 6, and 7.

only two cells consistently showed this structured burst pattern. Based on the variability of the initial burst index observed over 5 min, two groups of cells were distinguished. Group 1 (eight cells) had a preconditioning burst index with a variability of less than $\pm$ 10 while Group 2 (83 cells) had a variability much greater than $\pm$ 10. Differences in firing patterns of normal, Group 1 and Group 2 cells is illustrated in Fig. 2, showing samples of activity, and Fig. 3, showing representative interspike interval histograms. Normal precentral cells, typically, showed greater than 90% of all interspike intervals longer than 10 msec, and rarely less than 5 msec during wakefulness. Group 1 cells usually showed over 60% interspike intervals less than 5 msec, and Group 2 cells showed greater than 10% interspike intervals less than 5 msec. The criterion for deciding between Group 1 and 2 abnormal neurons was the *variability* of the burst index, and *not* its magnitude. But in a fully awake animal, the average value of the burst index was often inversely related to its variance. Therefore, Group 2 cells generally had lower mean burst index than Group 1 cells. Among the many uncontrolled variables affecting the burst index, the most obvious were the level of consciousness, the motor activity of the monkey, and "periodic variance," as discussed below.

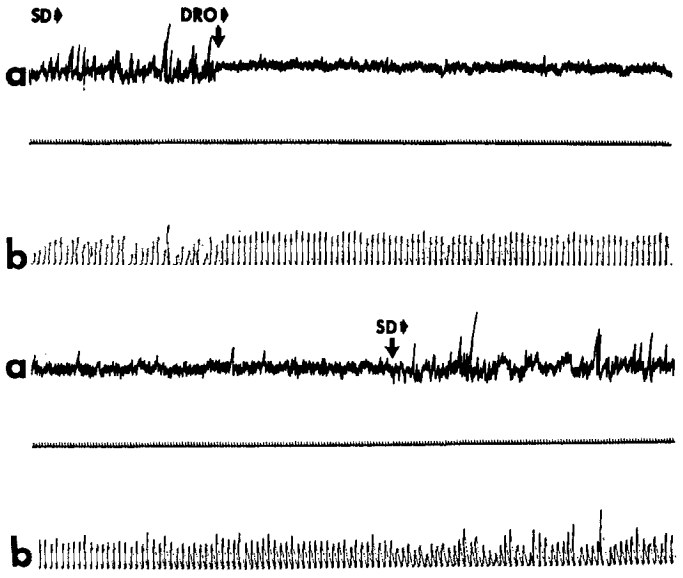

FIG. 4. Continuous polygraph record of unit activity of a Group 1 neuron. Lines *a* show actual firing rates, whereas lines *b* show firing rates integrated over 10-sec epochs. Note that during the extinction periods (SD) the firing rate showed much more variance than during the period on DRO with a concomitant increase in mean firing rate on DRO (although burst index did not change).

The burst index varied as a function of the animal's level of consciousness in several situations. During time-out periods, when the animal could become inattentive with concomitant EEG synchronization (but no behavioral or EEG correlates of sleep), Group 2 cells' burst indices often increased by 15–100%, whereas Group 1 cells' burst indices did not increase more than 10%. Presenting a discriminative stimulus for reinforcement (regardless of whether the contingencies were for high or low firing rates), would cause EEG desynchronization and usually marked drops in the burst indices of most Group 2 cells, but changes of less than 10% in the burst indices of Group 1 cells. (The EEG desynchronized equally during DRO and DRH periods.) Curiosly, in four Group 1 and several Group 2 neurons, desynchronization of the EEG correlated with a marked decrease in the variance of firing rates, but only slight increase in mean firing rates, (and no change in the burst index of Group 1 cells). An example is shown in Fig. 4.

Many of the cells undergoing conditioning were associated with movement of the contralateral arm. After the monkeys learned this, for each newly encountered cell they often proceeded through a repertoire of movements that had been associated with reinforcement in previous sessions. Usually, once the monkey obtained control over the cell, he could drive it

bidirectionally without observable movements. Change in neuronal firing rate with coinciding movement, especially forceful ones, always tended to lower the burst index by increasing regular activity, as previously documented with "long-first-interval cells" (8). (This observation was most consistent for pyramidal tract neurons.) The higher and less variant the burst index, the less strongly this relationship held.

Finally, cells could exhibit periodic variance in bursting not attributable to the above factors. Group 2 neurons exhibited intermittent periods of bursting lasting several seconds. These also tended to occur, but much less frequently, during successful reinforcement periods and were not suppressed by the monkey. These were apparently not related to changes in levels of consciousness, although this could not always be confirmed. These episodes of periodic bursting were most obvious during DRO periods, and their occurrence appeared to be more commonly associated with cells exhibiting higher burst indices.

Many abnormal cells increased their firing rates with onset of reinforcement schedules (Fig. 4), and successful suppression under DRO contingencies was especially difficult to obtain. Of the eight Group 1 neurons, none reached bidirectional operant criteria, but the two cells firing in long-first-interval bursts were successfully conditioned on DRH. All of the eight remaining Group 1 cells showed transient changes in firing rates in the reinforced direction, but failed to sustain these changes sufficiently to reach criteria.

One hundred five of 107 normal cells (98%) were successfully conditioned. The proportion of conditionable neurons in Group 2 was not significantly different from the normal group; however, the proportion of

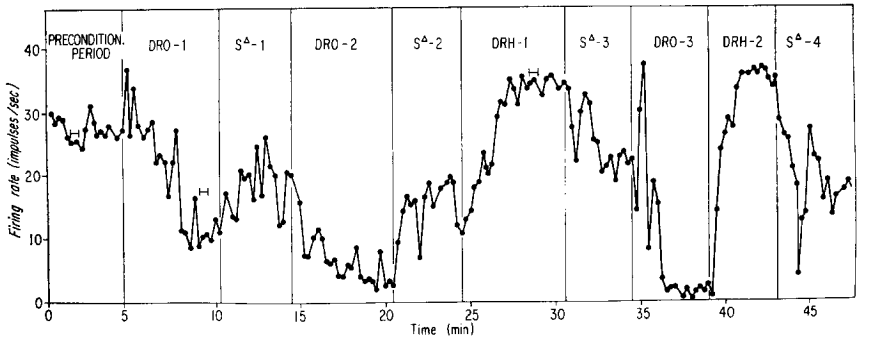

FIG. 5. Conditioning session of a "normal" precentral cell recorded in the alumina focus. Graph plots successive 15-sec counts of unit firing rate during different behavioral periods. After two DRO and one DRH period, the monkey demonstrated convincing bidirectional control at ends of DRO-3 and DRH-2. Samples of firing patterns are shown in Fig. 2 and interspike interval histograms in Fig. 3.

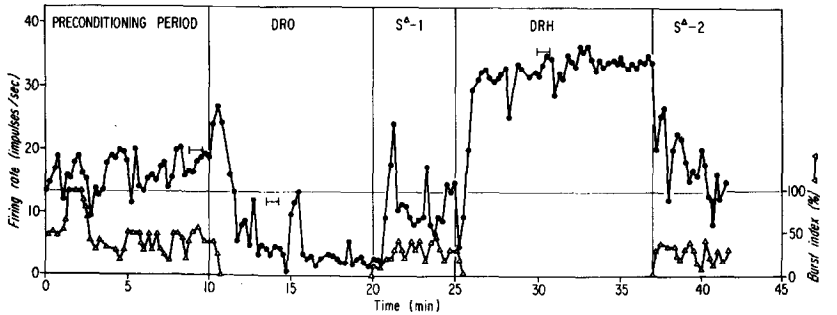

FIG. 6. Conditioning session with a Group 2 neuron which was bidirectionally conditioned. Firing rates and burst indices are plotted for successive 15-sec intervals. During both operant periods the burst index fell to zero, but returned during time-out periods. Horizontal line marks burst index of 100% (scale at right).

conditionable cells in Group 1 was significantly less than either normal or Group 2 cells (chi square test with 0.05 level of confidence). Further comparison between Group 1 and Group 2 cells shows marked differences in cell types: Group 1 consisted of six non-pyramidal tract cells, and two pyramidal tract cells (both of which fired in long-first-interval bursts). Combining this with previous data (31), 100% of the studied long-first-interval cells have been pyramidal tract neurons, whereas all stereotyped bursting cells have been non-pyramidal tract neurons).

Since the percentage change in rate during any operant period depends upon numerous variables, the relative degrees of success between normal

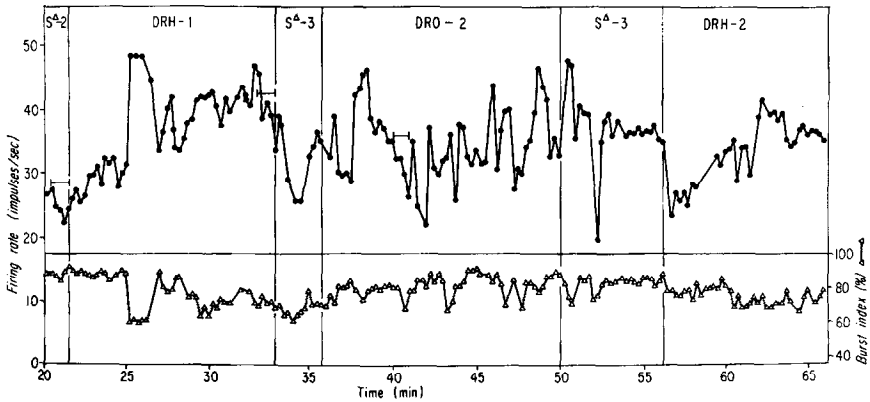

FIG. 7. Attempted conditioning session with a Group 1 neuron. Graph shows three operant periods after an initial DRO period (not shown) in which unit rates were not considered successfully modified in the reinforced direction (although a subsequent session on the same day with a normal cell showed bidirectional success). Burst index was high and relatively stable (note scale at right does not begin at zero).

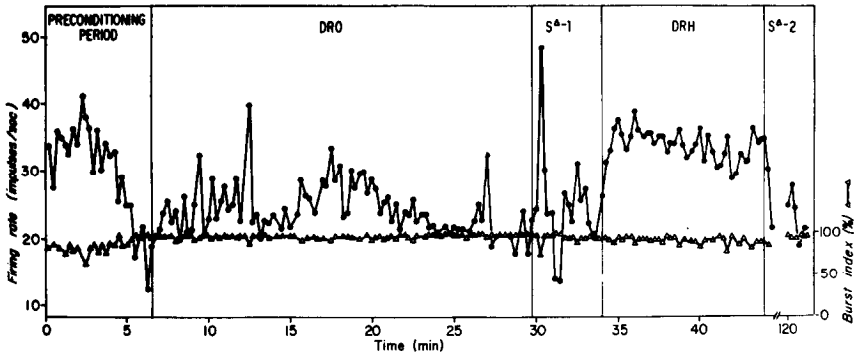

FIG. 8. Attempted conditioning session with a Group 1 cell firing in long-first-interval bursts. Rates during DRO and DRH never exceeded lowest and highest rates reached during time-out periods, although overall mean DRH rate was higher than mean time-out rate. Note high and invariant burst index.

and abnormal cells cannot be quantified. Figures 5–8 show representative graphs of operant conditioning sessions for each type of cell. Figure 5 shows a normal cell that was bidirectionally conditioned. Figure 6 shows a conditioning session of a Group 2 neuron, which could also be bidirectionally controlled; during conditioning periods the burst index went to zero. Figure 7 shows an unsuccessful session with a Group 1 cell; note that the burst index remains relatively stable, independent of fluctuations of firing rate. Figure 8 shows the operant conditioning of a long-first-interval cell (Group 1 cell) which demonstrates success at DRH, but inconsistent success at DRO. Figure 9 shows continuous samples of unit activity from another Group 1 neuron with a lower burst index. Note that there are only minimal differences in interburst single spike activity during the different operant periods.

During operant periods, Group 1 neurons showed no consistent change in duration of bursts, although interburst intervals sometimes underwent some changes; interburst intervals were slightly longer on DRO than during extinction periods and, conversely, interburst intervals were slightly shorter on DRH than during extinction periods. For all Group 2 cells, bursts occurred less frequently during both DRO and DRH periods, but when they did occur, they had the same duration as during extinction periods. The long-first-interval cell of Fig. 8 showed prolonged periods during DRO in which interburst single spike activity was completely suppressed and the burst index reached 100. At no time during any of the extinction periods was a burst index of such magnitude demonstrated for this cell. In this example, control of the burst-generating mechanism apparently was more difficult to regulate than single-spike activity. The corollary is that the higher (and less variant) the burst index, the less the animal appears able to control the neuronal firing rate.

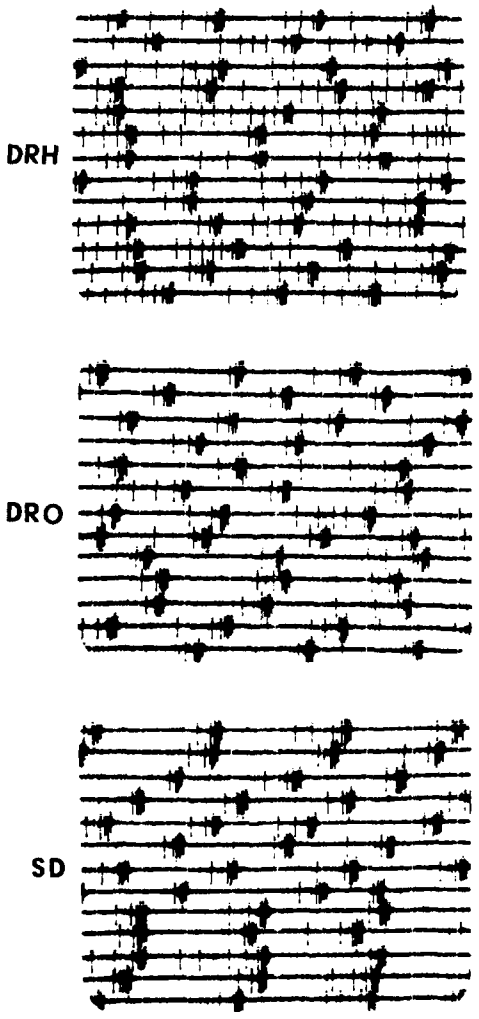

FIG. 9. One-second sweeps of continuous unit activity of an unsuccessfully conditioned Group 1 neuron. Note that during DRH there is more single-unit activity between bursts than during the DRO or time-out periods, although there is no significant change in burst frequency.

DISCUSSION

Previous investigations of interictal behavior of neurons in chronic foci have described, primarily, grossly abnormal cells displaying repetitive high-frequency bursts. In this study over half the cells isolated within alumina gel-induced epileptogenic cortex were normal; of the remaining abnormal cells, the majority were only variably "bursty" in the waking state. It may be suggested that since the actual epileptogenic focus is only poorly defined by electroencephalography, our results may be due to recording at the

periphery of the focus; however, the cells we considered normal were isolated in the same electrode tracks in which bursting neurons were also encountered. Of the cells considered abnormal, only a minority showed high frequency bursts as their predominant firing pattern, the others having various proportions of bursts and normal activity. We believe that these variably epileptic cells are vitally important in the natural history of the focus, since such cells are likely to be responsible for the rapid enlargement of the focus during the onset of a seizure. We have evidence that Group 2 cells dramatically increase their burst indices and synchronize with surrounding cells during transitions into early sleep (33)—a period in which seizure susceptibility is relatively high.

Our separation of the abnormal cells into Group 1 and Group 2 is only to draw distinctions between the degree with which different variables affect the observed cells; this grouping merely separates two ends of a continuous spectrum of abnormal neurons; the point at which a Group 2 epileptic neuron becomes a Group 1 neuron is not precisely defined. The spectrum begins at the normal end with Group 2 cells whose burst index is low and becomes zero during operant periods (Fig. 6); the spectrum continues through cells in which the burst-generating mechanism becomes more potent and the monkey is able to control only normal, single-spike activity. It, therefore, appears that under periods of sustained behavioral control, the the burst index and its variance reflects the degree of pathology of the neuron. At the end of the spectrum are Group 1 neurons with burst indices of 99–100; these appear to be autonomously firing cells which comprise less than 1% of the neuronal population of the focus.

A feasible explanation for a spectrum of epileptic neurons could be based on theories of denervation hypersensitivity and the abnormalities observed in alumina cortex (30). Thus, for any one cell, the amount of dendritic deafferentation and the degree to which the dendritic neuropil affects that cell's activity, may be reflected in the amount of pathologic activity demonstrable. The wide variations between the amount of dendritic damage and the ratio of dendrite to soma for cells within the focus is one obvious correlate of the spectrum of cells we have observed.

Calvin (4) has speculated that it takes only 2% of a normal neuron's synapses to provide enough spatial summation to recruit a normal cell into a high-frequency, bursting neuron. Applying Calvin's theory to Group 2 cells, keeping in mind their proclivity to burst, there is now a large proportion of neurons within the focus that are potentially more susceptible to burst recruitment than normal cells. This wide spectrum of Group 2 cells may, therefore, provide the "critical mass" required to initiate and propagate an ictal episode. That the Group 2 cells are responsible for generating their own bursts, and are not merely following pacemaker cells, is supported by the observation that specific antidromic and orthodromic activation of these

cells will produce pathologic bursts (31, 32), an event not observed in normal precentral neurons.

The more variable the burst index, the more potent different factors were in suppressing it. That the level of consciousness clearly influenced bursting was demonstrated by the observation that most Group 2 cells lowered their burst index when placed on operant schedules, even before the animal demonstrated appropriate control of the neurons. Once cell activity was under operant control, the burst index was usually further suppressed, often decreasing to zero (Fig. 6). The burst index was also lowered if the animal was alerted by novel stimuli. During behavioral and EEG correlates of drowsiness, the burst index universally increased dramatically for Group 2 cells (33). Although Evarts (6) and Steriade (25, 26) have reported that normal units restructure firing patterns into bursts during transitions into sleep, interspike intervals were rarely less than 5 msec. We have confirmed this observation with a group of normal cells in epileptic cortex (33). Therefore, Group 2 cells have a proclivity to fire in pathologic bursts during EEG synchronization, and the occurrence of such bursts is diminished with EEG desynchronization.

The drop in burst index with "weakly epileptic" cells might be explained by the following observations. Calvin (5) has proposed delayed depolarization as one mechanism for production of repetitive firing in epileptic neurons. Whitlock, Arduini and Moruzzi (29), Evarts (6), and Steriade (26) have documented decreases in firing rates of pyramidal tract neurons with either midbrain reticular stimulation or more physiologic arousal; moreover, Klee (13) reported a loss of delayed depolarization in cat pyramidal tract neurons during midbrain reticular stimulation concomitant with a polarization of the cell's membrane of $3 \rightarrow 13$ mv. In the communication of Whitlock *et al.* (29), EEG spiking (with correlated pyramidal tract discharges) induced by cortical application of 0.2% concentration of strychnine could be blocked by reticular stimulation, whereas spikes resulting from more concentrated solutions (1%) could not be blocked by the same stimulation. These observations are consistent with Calvin's suggestions and our data. The observation that the mean firing rates of Group 1 non-pyramidal tract cells increase during alerting may coincide with Steriade's proposal (25, 26) that cortical (Golgi type 2) interneurons are "disinhibited" by arousal. It is noteworthy that non-pyramidal tract Group 1 cells had smaller than median action potentials, suggestive of smaller cells—perhaps interneurons.

Since bursts have a propensity to occur after cell inactivity, the initial neuronal activity after reinforcement during successful DRO was specifically inspected. In cells that continued to burst during terminal periods of successful DRO, reinforced pauses of activity were usually followed by burst activity, as previously reported (9).

Cells with high and invariant burst indices, but having some single-spike activity during interburst periods, showed increases and decreases in the single-spike activity during the appropriate operant periods, but since bursts accounted for a high percentage of total activity, mean firing rates did not reach criteria for successful conditioning. This relationship was best illustrated for the long-first-interval cell in Fig. 8. The above data, added to previous observations (9, 32) with long-first-interval cells, shows that during initial DRH periods, burst frequency increases until a critical interburst interval of 100 msec is reached, at which point the burst becomes attenuated until only regular activity is responsible for further increases in rate. This indirectly supports the thesis that, at least for pyramidal tract neurons, the burst appears to originate or be modulated by a different region of the cell than normal spikes (31). The smaller cells (non-pyramidal tract), because of different spatial morphology, may be more dominantly influenced by the pacemaker and, therefore, are unable to achieve the unidirectional success of long-first-interval cells.

When the monkey rested quietly, and the EEG was stable, many Group 2 cells demonstrated periodic episodes in which bursting waxed and waned. Each cell had its own period, which tended to be between 10 and 20 sec in duration. This phenomenon may relate to studies by Prince (17–19) in which he found the excitability for eliciting EEG spikes in optic cortex to be periodical, each cycle being sensitive to changes in stimulation frequency and intensity. The basis for this variance in production of bursts appears independent of direct subcortical and interhemispheral influences since Prince demonstrated this phenomenon with isolated cortical slabs.

Synaptic modulation of epileptic cells may account for the observation that concentration and forced movements may abolish EEG spiking over sensorimotor cortex (10, 21). Moreover, the observation that cells involved in specific movements may revert to normal activity during participation in such movements (9, 31), could possibly explain the long-standing clinical observation that many Jacksonian seizures may be aborted by sensory and proprioceptive stimulation of the affected limb.

It is, therefore, apparent that the majority of the abnormal cells within the epileptic focus have varying degrees of effective synaptic modulation, and this ability to control epileptic cells may have important therapeutic implications. Sterman, Lopresti, and Fairchild (22) reported that by reinforcing gross EEG sensorimotor rhythms, seizure thresholds in cats challenged with monomethylhydrazine were raised. Moreover, in a group of epileptic patients trained to produce sensori-motor rhythms, a decrease in seizures (23) and a decrease in EEG slow-wave abnormalities resulted (Sterman, personal communication). Perhaps, by reinforcing desynchronized patterns of EEG activity, one could not only lower the frequency of seizures, but make more efficient use of epileptic cortex by

decreasing abnormal bursting in a large number of neurons. We have observed that, with repeated single cell conditioning within the focus, there is a progressive decrease over weeks, not only in the number of epileptic neurons encountered, but in the frequency of overt seizures. We are presently investigating which of several possible variables might be responsible for these changes.

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