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Effects of Operantly Conditioning Epileptic Unit Activity on Seizure Frequencies and Electrophysiology of Neocortical Experimental Foci

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Five Macaca mulatta monkeys were rendered chronically epileptic by subpial injection of aluminum hydroxide in sensorimotor cortex. After stable seizure frequencies were documented, a recording mount was placed surgically; this operation caused a dramatic, but transient, decrease in seizures in all monkeys. Subsequent periods of operant conditioning of interictal unit activity were associated with initially low levels of weekly seizure rates in three monkeys. Even more consistent than the decrease in clinically apparent seizures, was a steady decline in the number of abnormal neurons encountered. We conclude that single cell operant conditioning was associated with a decrease in the proportion of single units exhibiting interictal burst activity but not consistently associated with a reduction of seizure frequency.

INTRODUCTION

In recent years investigators have demonstrated that operant conditioning techniques can be used to modify gross central nervous system activity as well as firing rates of neocortical neurons (1, 3, 4, 5, 16). We have applied these techniques to study the degree to which epileptic neuronal behavior can be voluntarily modified in a chronic focus and to observe cell activity under more normal conditions than are obtained by acute neurophysiological experiments. During our initial study (5), we operantly conditioned interictal activity of single cells within the epileptic focus and found after

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several weeks that EEG abnormalities as well as pathologic single unit activity became progressively more difficult to document. We therefore undertook the present study specifically to investigate possible effects of repeated operant conditioning of single cells upon chronic alumina gel-induced focal cortical epilepsy. Our results suggest that some aspect of the procedure of recording and conditioning interictal single cell activity in a neocortical focus temporarily reduced seizure frequency and pathologic single-cell activity in three monkeys that learned the task; however, one monkey which was extremely epileptic was unable to learn the paradigm and experienced an increasing number of seizures.

METHODS

Production of Epilepsy. Five male Macaca mulatta monkeys (2.5–4 kg) with normal initial EEG were subjected to subpial alumina gel injection in left sensorimotor cortex using the method of Kopeloff (6). By three months all monkeys demonstrated EEG correlates of epilepsy. At four months the monkeys were placed in primate chairs, allowed to adapt to this restraint, and then underwent continuous 24-hr seizure monitoring using methods described by Lockard and Barensten (8). Chair oscillations were recorded by strain gauges whose output was continuously monitored on polygraphs. Seizures resulted in specific activity patterns on the polygraph record characteristic for individual monkeys. Therefore, polygraph records were initially correlated to videotape records until those patterns characteristic of each monkey's seizures could be clearly identified. This allowed quantification of motor seizures by parameters of magnitude, duration, and time of day. No anticonvulsant medication was administered to these monkeys.

Recordings. Techniques for chronic stereotaxically controlled tungsten microelectrode extracellular single unit recordings are described in earlier reports (4, 5, 15, 16). In addition to an implanted recording mount, bipolar pyramidal tract stimulating electrode and head stabilization screws, the monkeys had four epidural silver ball electrodes placed peripheral to the recording mount. Thus, sequential EEGs were recorded with a Grass polygraph (0.3 sec time constant and 30 mm/sec paper speed) utilizing invariant configurations. In two animals EEGs were taken immediately prior to and after the daily operant conditioning sessions, but the remaining animals' EEGs were monitored only three times per week prior to conditioning.

Daily microelectrode recordings were made from an area within 2 mm of the precentral alumina gel injection sites. All distinctly isolated neurons from each electrode pass were characterized as to their response to pyramidal tract stimulation, action potential amplitude, and burst index (defined as the ratio of high-frequency unit burst activity to total unit

activity per 15 sec). By previously described criteria (16) the burst index and its variability was used to characterize the cell as normal (negligible burst index), moderately epileptic (group 2; variable burst index, usually less than 60), or highly epileptic (group 1; invariant burst index, greater than 60). Epileptic neurons were characterized prior to conditioning, during periods in which the animal was at rest but awake by behavioral and EEG criteria.

Operant Conditioning. During operant conditioning sessions, monkeys were rewarded for increases or decreases in firing rates of single precentral neurons using the paradigm previously described (3, 4, 5, 16). After attaining criteria for successful control of normal units (16), the monkeys were subjected to daily conditioning sessions (lasting from one to several weeks) in which they attempted to control firing rates of epileptic neurons. Seizure activity of each monkey was then monitored for a postconditioning period of at least two weeks during which time the animal underwent no unit conditioning.

RESULTS

Figure 1 plots the number of seizures per seven-day epochs for periods preceding, during, and after conditioning. Surgery (S) refers to the five days following the operation in which the recording mount was implanted (not the subpial alumina injection, which occurred at least six months previously). The figure also indicates the total time devoted to operant conditioning sessions and whether or not they were successful. Since each monkey's record is unique, results will be discussed individually.

Monkey 215. The preconditioning seizure frequency was seven generalized seizures in 14 days, an average of 3.5 seizures a week. During the five days following surgery, no seizures occurred. During the first week of operant conditioning he had two seizures; during the second and third weeks he had one seizure per week, and during the fourth week he had none (total average 1.0/week). It is of considerable interest that the seizures which occurred during conditioning weeks, did so on weekend days when no conditioning sessions were run. The monkey then underwent a five-week period in which there were no conditioning sessions (NC1); during this time he maintained a stable seizure frequency of 1.6 seizures/week. During a second conditioning period of one week (C2) he had two weekend seizures. In a subsequent two-week nonconditioning period (NC2) he averaged two seizures per week. A third conditioning period of two weeks (C3) resulted in an average of six seizures per week, mostly on nonconditioning days; a final two-week nonconditioning period (NC3) resulted in an average of seven seizures per week.

Monkey 216. The preoperative seizure frequency was nine seizures per

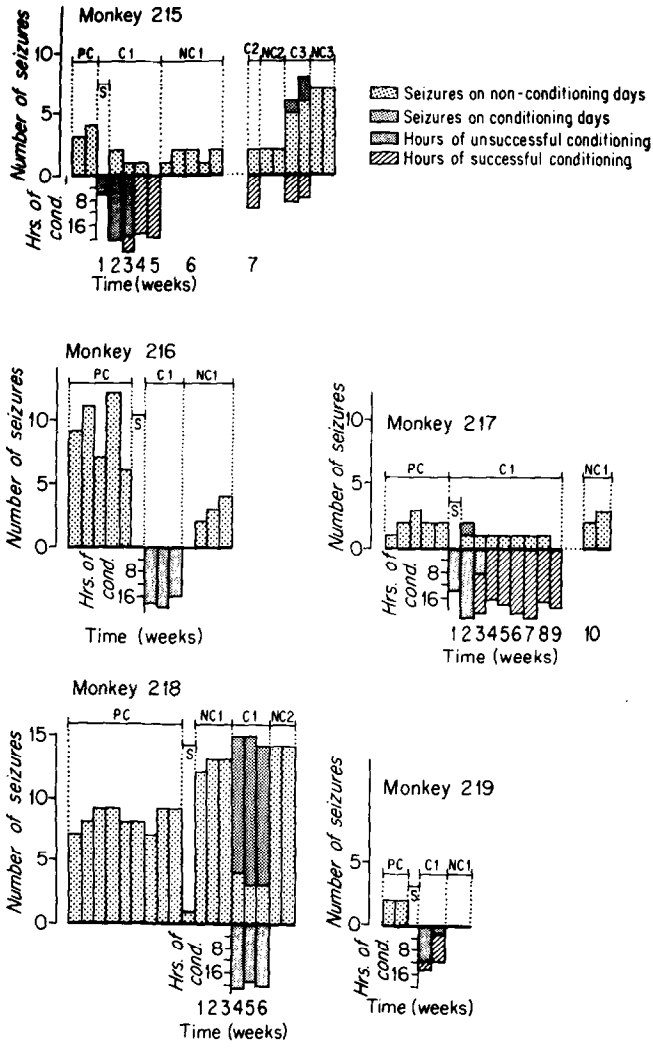

FIG. 1. Relation between frequency of seizures and operant conditioning sessions of five monkeys with alumina foci. Each bar represents 7 days (except for period "S" which represents 5 postoperative days) in which seizures were monitored for 24 hours. (Broken lines represent times in which seizure records were not obtained). Bar graph above baseline represents number of overt seizures and bar graph below baseline represents number of hours spent in unit conditioning sessions. The latter is further divided into sessions in which the monkey successfully controlled firing rates of cells (cross hatch) and session in which criteria for behavioral control was not obtained (stipple). Seizures which occurred during 24 hour periods in which no operant conditioning took place are represented by light stipple whereas seizures occurring on days of operant conditioning are shown by heavy stipple. Timing periods: PC = presurgery period, S = 5 day postoperative period, C = conditioning weeks, NC = nonconditioning weeks. For monkey 218 NC1 represents a control period for all variables

week for five weeks. During the immediate five-day postoperative period, as well as the next three consecutive conditioning weeks, this monkey had no seizures; but during the subsequent nonconditioning period, seizures returned with an average of three seizures per week. During the early nonconditioning period he was found to have developed a subdural empyemia and, in the subsequent nonconditioning period, he averaged three seizures per week. Because of the infection he was dropped from the experiment. Throughout the conditioning period this monkey did not show consistent proficiency at operant control of normal neurons.

Monkey 217. Preoperative seizure frequency was two seizures per week (stable frequency for five weeks). Again, during the five-day postoperative period there were no seizures. Within the eight-week conditioning period seizures occurred at an average of one per week; with one exception, all seizures occurred on nonconditioning weekend days. The monkey then underwent a one-month nonconditioning period during which time seizure frequency was inadequately documented. During a subsequent two-week period of monitoring, seizures occurred at an average of 2.5 per week.

Monkey 218. Throughout the nine-week preoperative period he averaged 8.2 seizures per week, but within the five-day postoperative period, only one seizure occurred (on the fifth day). This monkey was intended as a control for the effects of variables other than conditioning, such as repeated cortical electrode penetration, pyramidal tract stimulation, etc. Therefore, for three immediate postoperative weeks no conditioning was administered; instead daily single unit recordings were made utilizing the same experimental environment as conditioning sessions. This monkey was also subjected to thalamic stimulation throughout this period. During this three-week control period the animal averaged 12.7 seizures per week. The subsequent three-week operant conditioning period resulted in a slight increase in seizures to 14.7 per week. It should be noted that within this time the monkey was never successful in appropriately modifying firing rates of either normal or epileptic cells. This monkey appeared agitated and stressed during his repeated failures in the training environment, a factor which may be relevant, as discussed later. Seizure frequency remained at 14 per week during the following two-week nonconditioning period.

Monkey 219. This animal averaged two seizures per week during the preoperative control period. From the day of surgery throughout the subsequent two-week conditioning and two-week nonconditioning periods, no further seizures were recorded.

Interictal EEG. Although sequential EEGs were recorded throughout

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except conditioning (see text). Numbers below bars refer to weeks illustrated in Fig. 2.

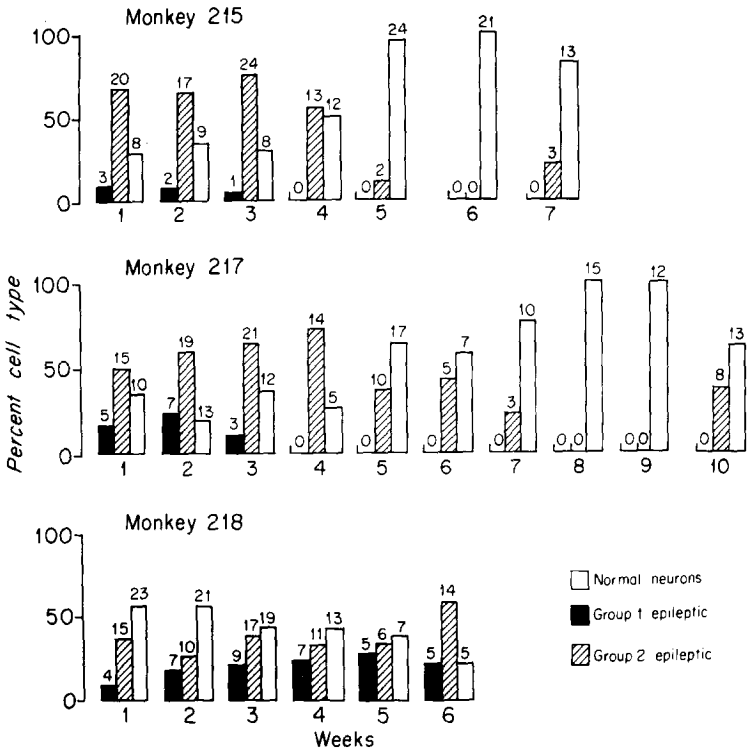

FIG. 2. Relative number of normal and abnormal group 1 and group 2 cells isolated in cortex during successive weeks of recording and conditioning in three monkeys. Each set of bars represents relative proportion of each type of cell encountered in five successive days of recording (absolute numbers are given above each bar) during the weeks numbered in Fig. 1. Scale for percent is given at left. As described in text, cells were characterized as highly epileptic (group 1, solid bar), moderately epileptic (group 2, stippled bar), or normal (clear bar).

the experiments, this parameter proved so highly influenced by uncontrolled variables that detailed analysis was not considered warranted.

Changes in Interictal Burst Patterns of Units. To quantify our impression that epileptic cells became increasingly difficult to isolate, the number of normal and abnormal cells recorded was compiled for monkeys 215, 217, and 218; a total of 180, 224, and 198 neurons were included from monkeys 215, 217, and 218 respectively. As defined in the methods section, we distinguished two groups of epileptic neurons on the basis of their burst indices (16); group 1 neurons were highly epileptic, while group 2 were intermittently epileptic. In monkeys 215 and 217, all group 1 epileptic neurons were encountered during or shortly after success at operant conditioning sessions was achieved. Thereafter, a decreasing percentage of

group 2 neurons were found until only normal precentral EEG activity and neuronal firing patterns could be detected in what had previously been epileptic cortex. The relative number of normal, group 1, and group 2 epileptic cells encountered in successive weeks is illustrated in Fig. 2. In monkey 218, who showed no proficiency at operant control, the relative number of epileptic single cells and gross epileptiform EEG activity did not change significantly.

Immediately after the first two-week nonconditioning period, unit recordings in the original precentral foci did not yield epileptic single cell activity in monkeys 215 and 217 but a subsequent investigation of both animals one month following termination of operant conditioning failed to yield abnormal neuronal activity in the original precentral focus of 215 and showed a modest return of epileptic single cell activity in the original precentral focus of monkey 217 (Fig. 2). However, during both these periods, there was continuing epileptiform EEG spiking from the regions of the post-central alumina gel injection sites. More paradoxically, it was during these periods of decreased precentral single unit abnormalities that seizures returned.

DISCUSSION

Before considering any possible correlation between operant conditioning and seizure frequency, it is useful to review factors which are known to influence ictal activity associated with experimental alumina foci. Without intervention, alumina-gel foci have been reported to remain epileptogenic for up to seven years (6, 13, 14). Lockard (personal communication), studying a colony of chronic epileptic Macaca mulatta, reports that although there is no consistent relationship between the development of epileptiform EEG abnormalities and overt seizures, once generalized seizures occur at a rate of at least one per week, they are highly unlikely to cease spontaneously. Nevertheless, if alumina gel foci are to be used as models of chronic human epilepsy for the study of therapeutic procedures, more comprehensive longitudinal studies would certainly seem desirable to document the probability of spontaneous remissions of seizures. We reported that the monkey in our initial study was never observed to have a seizure (5); however, since he was not subjected to 24-hour monitoring, this statement was based on limited observations during the day, when seizures may be less probable than at night (7). We did not initially mention the observed disappearance of cortical epileptic abnormalities since we thought it might have represented a spontaneous regression of a weak epileptic focus rather than a direct result of recording or conditioning procedures.

However, the present subjects were all confirmed (by videotape) to have clinical seizures (often nocturnal); all demonstrated a reduction of those

seizures during the week following implant of the chamber and three showed lower seizure rates during the initial weeks of operant conditioning than during preconditioning weeks. It seems improbable that these all represent spontaneous reductions in seizures. Moreover, spontaneous remission is inconsistent with the subsequent return of seizures to preconditioning levels in three monkeys.

Lockard (7) has shown that stress may increase seizures in epileptic monkeys, and it may be suspected that initial seizure frequencies were artifactually elevated as a direct result of restricting the animals to the primate chairs. This was, in fact, observed with monkey 218; within two hours of being placed in the chair, he demonstrated repeated focal and generalized seizures approximately every 10 min for a period of over two hr, whereupon he was transferred to a cage and allowed to adapt to the monitoring chair more gradually. To eliminate this stress factor, we routinely began seizure monitoring after a week of chair adaptation for all monkeys. The seizure frequencies had clearly reached stable levels during the preconditioning weeks (see esp. 216, 217, 218).

A direct correlation between stress and seizures was also apparent with monkey 218 during conditioning sessions when he became behaviorally agitated. Within this three-week period he showed an increase in daily seizures, particularly associated with days of operant conditioning; in contrast monkeys 215, 217, and 219 learned the paradigm, received positive reinforcement and demonstrated a decrease in weekly seizure rates during conditioning. Upon learning the paradigm, the successful monkeys never objected to having their head restrained and often cooperated in preparing for the conditioning periods. Therefore, with the exception of monkey 218, the operant conditioning sessions appeared to be, in themselves, positively reinforcing.

A clear decrease in seizures was associated with the surgical procedure for implanting the adapter which held the microdrive. All monkeys showed paucity of ictal events during the first four postoperative days. Monkey 218 had one generalized seizure on the fifth postoperative day, and monkeys 215 and 217 had seizures on the sixth postoperative day. The surgery consisted of a craniectomy (but only in monkey 216 was the dura violated) and particular care was taken to not traumatize the underlying cortex (epileptic focus). Premedication was standardized to Atropine and Surital in doses proportional to body weight and anesthesia (Halothane) was administered through an endotracheal tube. To our knowledge, neither anoxia nor circulatory insufficiency occured during the 4–5 hour surgery. What aspect of the surgery is responsible for the acute postoperative cessation of seizures remains unresolved, although the effect was clear.

Since cortical cooling may decrease seizure activity it may be questioned whether the recording mount provided sufficient heat dissipation to cool

the focus. Any cooling would be minimized by the fact that the extracranial metal ring was insulated from cortex by the skull. In any case, the observed return of seizures would argue against this explanation.

All the monkeys were male, and therefore the effects of estrus upon seizures is not a consideration in this study.

Changes in sleep, especially lack of REM sleep may have profound activating influences upon seizures. Inspection of the polygraph activity patterns did not show differences between preoperative and postoperative periods of inactivity (indicative of sleep), and therefore there appeared to be no effect upon sleep cycles during the study. (This cannot be assured since actual EEG verification of sleep periods was not obtained).

Studies of supersensitivity in undercut cortex (12), showed that daily cortical electrical stimulation of isolated cortical slabs reduced the development of afterdischarge when compared to nonstimulated controls. It may be suggested that the pyramidal tract stimuli (used to characterize each newly encountered unit) might parallel electrical stimulation of undercut cortex. Monkey 218 was subjected to three weeks of daily 4–5 hr sessions which simulated the actual operant conditioning periods but nothing more was done than isolate neurons, stimulate the pyramidal tract and thalamus and map their peripheral sensory fields. This control period, which provided more electrical stimulation than would have occurred had the animal undergone operant conditioning, did not decrease the seizure frequency.

Monkey 218 was unique insofar as a bipolar stimulating electrode was implanted in the ipsilateral thalamic nucleus, centre median. During the three-week control period each unit was tested for response to single, paired, and repetitive thalamic stimulation. With repetitive stimuli, epileptic and normal units synchronized at "critical frequencies" (below those optimal for eliciting recruiting responses) and produced epileptiform EEG spiking (18). These critical frequencies were associated with an increase in the magnitude of this monkey's *epilepsia partialis continuans* (which involved the contralateral arm). Although a generalized seizure was never provoked by this stimulation, it did significantly enhance neuronal synchronization within the focus and could possibly have contributed to the elevated seizure frequency during the control and conditioning weeks. The effect of this variable cannot be fully evaluated since other monkeys similarly prepared (not subjects of this report) have not undergone extensive seizure monitoring.

Recently Sterman, *et al.* (11) have reported that reinforcement of sensory-motor-rhythms in cats increased the threshold to monomethylhydrazine-induced seizures. Extrapolating this finding, he reinforced the occurrence of sensory-motor-rhythm in a group of epileptics and found that the frequency of their seizures diminished (9, 10), but several months after terminating conditioning, seizures returned. We find this data extremely

interesting; however, along with Sterman, we would be hesitant to ascribe such a relationship specifically to reinforcement of sensory-motor-rhythm. The sensory-motor-rhythm is similar to sleep spindles in gross appearance but is not necessarily generated by the same neuronal mechanism. We have shown that during sleep-associated spindles, augmented single cell epileptic bursts are produced to which surrounding normal cells are synchronized (17). Moreover, Sterman (10) reported a change in sleep patterns associated with conditioning of sensory-motor-rhythm, and manipulation of sleep cycles has potent effects upon ictal occurrences. Therefore, both studies involve other variables than conditioning of sensory-motor-rhythm which preclude specific correlations between the occurrence of reinforced behaviors and a subsequent decrease in ictal events. In contrast to Sterman's human subjects, our monkeys were neither on anticonvulsants nor subject to placebo effect.

A significant observation is that seizures decreased before the monkeys demonstrated consistent bidirectional control of neuronal firing rates. This observation indicates that operant conditioning per se was not initially the most relevant variable in decreasing seizures. It is a long-known clinical observation that many epileptics demonstrate better seizure control when placed in a productive, protective, enriched environment. This seems particularly relevant since the monkeys were idle and semi-isolated during nonconditioning periods. During days of operant conditioning, they had more opportunities to interact with their environment. Although such circumstances are difficult to quantify, it seems reasonable that on those days in which the animals were undergoing conditioning experiments, they may have spent a larger percentage of waking hours with desynchronized EEGs and this may be the final common denominator associated with decreased seizures. It should be reiterated that two monkeys (215, 217) which continued to have seizures during the weeks of operant conditioning did so mainly on weekend days in which no operant conditioning was undertaken.

When epileptic neurons produce an ictal event, they must presumably recruit surrounding neuronal activity into synchronous firing until a "critical mass" is reached, at which point clinical manifestations and/or propagation of the pathologic cellular activity is apparent. Recently we have proposed that there is a spectrum of epileptic neurons, based on the individual interictal neuronal activity during a variety of behavioral situations (16, 17). We have postulated that group 2 epileptic neurons (16), because of their inherent lability of burst firing and because of the proclivity for bursts to be synchronized by massive synaptic influences, might represent the potential "critical mass" available for rapid enlargement of a focus. It is precisely this group of neurons that may have its pathologic activity diminished during operant conditioning (16). In some sessions in

which group 2 neurons were successfully bidirectionally conditioned, the cell's burst index steadily decreased as the conditioning continued and remained low for up to one hour following the end of the conditioning. Unfortunately, we did not maintain isolation of such neurons for more than one hour after termination of the experiments. It may be that such neurons continued to maintain decreased amounts of burst firing, possibly accounting for the finding that as the experiments progressed, monkeys 215, 217, and 219 showed a decreasing number of epileptic neurons.

Although our data provides some preliminary evidence that single unit operant conditioning within the region of the focus may be associated with a temporary decrease in seizures for those animals which learned the paradigm, the number of subjects is too small to generate statistically significant results; rather the data does little more than confirm the lability of detectable ictal activity to environmental manipulations. The data also tentatively suggests an inverse relationship between the frequency of overt seizures and rate at which the monkeys were able to learn the operant conditioning task.

The observation of particular interest is that in those monkeys in which successful bidirectional operant control was demonstrable, epileptic single neurons within a confined region of precentral cortex became increasingly difficult to record, whereas normal units became predominant. The progressive decrease in the proportion of single epileptic units is unlikely to be due to experimenter bias, since epileptic units were specifically sought during conditioning experiments. Paradoxically seizures recurred in monkeys 215 and 217 even though the precentral focus remained populated by normally behaving units. Two obvious factors may help explain this observation. In preparing these monkeys, alumina gel was injected in both precentral and postcentral gyrus and no systematic evaluation of postcentral single cell activity was undertaken although this region continued to show epileptiform EEG patterns during periods of epileptic quiescence of the precentral focus. It is possible that the postcentral foci could have been responsible for the continued seizure activity. Secondly, we are aware of no systematic control for the cumulative cortical damage incurred by repeated electrode penetrations of the region of the focus and this may help account for the eventual seizure increase in all monkeys except 219 (who was not monitored for a prolonged period of time following conditioning). Dr. George Sypert (personal communication) reports that with four monkeys prepared in exactly the same manner, repeated microelectrode recordings for periods in excess of two weeks was correlated with increasing single unit epileptic activity. Dr. Frank Glötzner (personal communication) confirmed this observation. It therefore seems unlikely that any cortical damage induced by the microelectrode penetrations could account for the reduction in single unit abnormalities in this study.

In retrospect, two flaws in our experimental design become obvious: first, since it is now apparent that the operation to implant the chamber dramatically reduces postoperative seizure frequencies, the monkeys should have undergone postoperative seizure monitoring until stable seizure frequencies were reestablished. Even though immediate postoperative EEG and single unit recordings demonstrated active epileptic abnormalities, we do not know if the potency of the surgical effect is related to the magnitude of the preoperative seizure frequency and, if so, it would be advantageous to know the time course of seizure recovery before initating therapeutic intervention. Secondly, injecting alumina gel into both precentral and postcentral cortex confounded any correlation between single precentral unit conditioning and ictal events, since the seizures returned during subsequent conditioning epochs, although there was no demonstrable single unit epileptic activity within the previously abnormal precentral foci.

Clearly, before any definitive conclusions may be drawn from our observations, further studies are necessary to document the effects of different variables on seizure frequency. We nevertheless present these observations to indicate which variables may be relevant and should be controlled in future experiments.

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