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PRE- AND POSTTRIAL TEMPORAL LOBE SEIZURES IN MONKEYS AND MEMORY CONSOLIDATION[1]

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Stimulation applied to the inferotemporal cortex of monkeys produces an afterdischarge which temporarily disrupts visual discrimination learning, but only when this afterdischarge occurs during the appearance of the discriminanda. There is no impairment when it occurs just after the response. These results are based on a comparison of learning in unstimulated subjects with that in subjects receiving pre- or posttrial stimulation. The results conflict with the hypothesis that inferotemporal cortex is involved in consolidation of visual information, in mediating information transfer from a temporary to a more durable state, suggesting, instead, that this area is effective during reception of the stimuli, affecting the way in which the visual world is perceived and hence what is stored and can be recognized.

Electrical seizures induced in the inferotemporal cortex of monkeys produce a disruption of visual-discrimination learning as does surgical ablation of this area. Although chronically discharging epileptic foci made by placing aluminum hydroxide creme disks on the cortex can be used for this purpose (Stamm & Knight, 1963), it is also possible to produce seizures of a limited duration—afterdischarges which result from bursts of stimulation through implanted cortical electrodes (Chow, 1961). These afterdischarges, originally termed a kind of "reversible ablation," have been found to be disruptive both when the seizures occur during every trial of a successive discrimination (Chow, 1961) and when they are initiated at the start of short blocks of (successive) discrimination trials (Goldrich, 1966).

Chow (1961) suggested that "localized, electrographic after-discharges are incompatible with the normal patterning of neuronal circuits [p. 399]." Goldrich (1966) has suggested that the inferotemporal cortex may be involved in the fixation of visual memories, an hypothesis which is similar to that offered by Iversen and Weiskrantz (1964; but see more recent position in Weiskrantz, 1968). He has further proposed that stimulation-produced afterdischarges could be used to test this idea. Seizures occurring before or during the discrimination trials would be supposed to disturb normal neuronal activity in such a way that no permanent storage could take place. All of the studies to date have used this type of stimulation. If consolidation of visual information is the process which is disrupted by seizures and ablation as Goldrich proposed, introduction of the seizure immediately *after* each trial should also interfere with learning. This posttrial application of stimulation is obviously patterned after the use of posttrial ECS and other agents to study the "time course of consolidation" (McGaugh, 1965). The point in the sequence of events during a discrimination trial when normal operation of the inferotemporal cortex is essential has not yet been examined, although a similar investigation has been made with reference to the dorsolateral frontal cortex and its role in the performance of the delayed response task (Stamm, 1969; Stamm & Rosen, in press). The present study compares discrimination learning

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when the seizures are present during each trial with learning when the seizures occur posttrial, and also with normal learning, as a test of the hypothesis that the inferotemporal cortex is involved in posttrial processes leading to the storage of visual information.

Method

Subjects

The subjects were seven naive rhesus monkeys—four intact subjects and three which were implanted with electrodes for stimulation and recording. One monkey (344) had electrodes implanted specifically for this study; the other 2 monkeys had been prepared about 18 mos. prior to the start of the experiment and had been used in studies in which brain responses were simply evoked by flashes of light or clicks while it sat in a restraining chair. They had no previous formal training.

Implantation

The bipolar electrodes were made of enamel- and vinyl-coated Nichrome wire (300-μ diam.). Vertical tip separation was 1½ mm. The electrodes were implanted using aseptic techniques with the subject under Diabutal anaesthesia. Each electrode was inserted through a burr hole drilled in the skull and was held in place with dental acrylic. Cortical electrodes were either inserted perpendicular to the cortex so that the upper tip was just beneath the surface, or, in the case of the inferotemporal leads, so that they were oriented across the gyrus at an angle of about 45° from the vertical. Depth placements were made stereotaxically. The electrodes were attached to 25-pin Microdot connectors and the entire assembly secured with acrylic.

Each monkey had electrodes placed bilaterally in the striate cortex and in the inferotemporal cortex. The two temporal electrodes (three in Monkey 344) in each hemisphere were placed so that the most anterior and posterior leads were 1–1½ cm. apart along the gyrus with the most posterior located at approximately the level of the superior colliculus. In addition, Subject 344 had two hippocampal placements among its 12 electrodes. Subjects 28 and 29 had electrodes located in the lateral geniculate nucleus and in the cortex of the parietal lobe which were not used in this study (a total of 24 bipolar leads apiece).

Histology

At the termination of the experiment the three implanted monkeys were sacrificed and the brains perfused in situ with saline and Formalin. The brains were frozen and cut in 50-μ sections. Every second section in the region of an electrode tract was mounted and stained with cresyl violet. The intended placement of the inferotemporal, striate, and hippocampal leads was confirmed.

Stimulation Parameters and Seizures

Preliminary testing showed that bilateral seizures of between 5- and 40-sec. duration could be produced in every subject using a 5-sec. train of differentiated rectangular pulses, 1 msec. in duration, 2 mA. peak current, at a frequency of 30–35 Hz. Stimulation was always delivered bilaterally through the isolation transformer of an American Electronics Laboratories stimulator to the most posterior inferotemporal leads, and seizures were monitored from the most anterior electrodes, which were located at least 1 cm. further toward the temporal poles. The typical seizure pattern in all three monkeys consisted of a burst of rapid high voltage spiking (8–12/sec), followed by a period of "spike and dome" activity (2–4/sec), which then terminated abruptly in both hemispheres, giving way to an apparently normal EEG pattern. The behavioral signs produced by the stimulation were mild. The monkeys usually turned their heads and gazed up toward one side, turning forward again during the seizure. There was usually a slight twitching of the muscles around one eye during the stimulation. During the seizure itself, overt behavioral signs were not noticeable. The subject would respond to events in the environment and would accept and eat food.

Over the course of testing, the efficiency of the initial parameters given above decreased somewhat, so that a slightly greater voltage had to be applied in order to pass the same amount of current, and the current had to be increased to give seizures which would average over 5 sec. in duration. The initial current was 2 mA.; the maximum ever used was 4 mA. and it was generally below 3 mA. The other parameters were held constant for all subjects at 30 Hz. and 1 msec/pulse.

Procedure

During behavioral testing the monkey faced a 4 × 4 array of 16 plastic windows (1¼-in. diam.) on which two rear-projected patterns were displayed in locations which were varied from trial to trial. Depression of the correct panel produced a banana pellet in a cup located beneath the panels and terminated the trial; depression of the incorrect panel merely terminated the trial. In either case a response was necessary to end a trial and begin the intertrial interval (ITI). Presentation of the stimuli and recording of rewards and responses were controlled by a PDP-8 computer located in a separate room (Pribram, 1969). All seven monkeys were pretrained in portable cages to press any panel showing the numeral 1. The ITI between one response and the reappearance of the stimuli was initially 3 sec. It was gradually increased over a 1-wk. period to 3 min. When a subject was responding rapidly at the long ITI, it was continued on that schedule for another week

before discrimination training began. Early in pretraining the implanted monkeys were shifted from cages to restraining chairs, and for the final week of pretraining were tested with the stimulating-recording cable(s) attached. All of the subjects were returned to their home cages between testing sessions.

In the first discrimination training procedure, all subjects were required to choose between the numerals 3 and 8 (3 rewarded) for 15 trials per day at the 3-min. ITI. They were trained to a criterion of at least 13 correct responses out of 15 trials on each of 2 consecutive days (87%). A second discrimination problem was then introduced. The numerals 2 and 7 were used (2 rewarded) and the monkeys were trained for 15 trials per day with a 1½-min. ITI. The same criterion was used. After each trial of the 3 vs. 8 discrimination the implanted monkeys received 5 sec. of stimulation applied bilaterally to the posterior inferotemporal electrodes. Stimulation began approximately 3 sec. after the response on both correct and incorrect trials. In no case was it delivered more than 5 sec. after the response. On correct trials stimulation began only after the subject retrieved the pellet, which was generally within 3 sec. and always within 5 sec. of the response. On incorrect trials an imposed 3-sec. delay served to equate the time between response and stimulation on the two kinds of trials.

The EEG activity from the anterior inferotemporal electrodes was amplified 15,000× through Tektronix preamplifiers (8–250 Hz.) and capacity-coupled Philbrick P65 amplifiers, then monitored on an oscilloscope. Hippocampal as well as selected striate electrodes were also monitored. A record was kept of the duration of each seizure, and periodically, the EEG from an entire session was recorded on Ampex tape and later written out on a Grass penwriter. The electrical recording and stimulation were controlled by an experimenter located in the area outside and adjacent to the testing chamber.

On each trial of the 2 vs. 7 discrimination, stimulation was applied for the 5 sec. immediately *preceding* the appearance of the stimuli. The seizure thus occurred while the stimuli were present. Seizure duration was again recorded, as well as whether the monkey responded during or just after the seizure discharge.

Results

The data shown in Table 1 reveal no significant difference between the monkeys receiving posttrial stimulation and the control subjects on the first (3 vs. 8) discrimination problem. (All statistical results refer to the Mann-Whitney *U* test, one-tailed.) This is reflected in both trials and errors prior to criterion. On the subsequent 2 vs. 7 discrimination, the control subjects learned in an average of 34 trials (11 errors), whereas the monkeys now receiving pretrial stimulation averaged 233 trials (87 errors). One monkey failed to reach criterion in 390 trials and stimulation was discontinued. Quite clearly, subjects stimulated before each trial do significantly worse than the controls ($p \leq .03$). This is also borne out by the "savings" ratios between scores on the 2 vs. 7 and the 3 vs. 8 discriminations, which show that all of the experimental subjects require more than 1½ times as many trials to learn the problem with pretrial stimula-

TABLE 1

Trials and Errors Prior to Criterion on Three Versus Eight and Two Versus Seven Discriminations

Discrimination	Stimulation				No stimulation				
	Subject 28	Subject 29	Subject 344	*M*	Subject 338	Subject 339	Subject 340	Subject 342	*M*
Three vs. eight (post-trial)									
Trials	151	75	115	114	263	45	240	254	200
Errors	52	26	56	45	127	16	91	104	84
Two vs. seven (pre-trial)									
Trials	*390*	121	187	233	15	15	30	75	34
Errors	*166*	52	42	87	5	5	12	23	11
Savings									
Trials	*2.54*	1.61	1.63	2.04	0.06	0.33	0.12	0.29	0.17
Errors	*3.20*	2.00	0.75	1.93	0.04	0.31	0.13	0.22	0.13

Note.—Italics indicate failure to reach criterion.

TABLE 2
DURATION OF SEIZURE DISCHARGES (IN SEC.)

Monkey	Three vs. eight (posttrial)			Two vs. seven (pretrial)		
	M	*SD*	*Mdn*	*M*	*SD*	*Mdn*
Subject 28	8.3	3.5	7.1	6.8	4.1	5.4
Subject 29	14.7	7.3	11.9	11.1	6.9	8.7
Subject 344	6.9	3.8	5.7	6.6	4.5	5.4
M	10.8		8.2	8.2		6.5

tion as they had taken to learn the problem presented under the posttrial condition. They differ significantly ($p \leq .03$) from the normal subjects who take less than ⅓ as many trials to learn their second problem.

Table 2 gives the means, standard deviations, and medians of the distributions of seizure durations for each subject. The average seizure duration is somewhat less on the second pretrial stimulation problem, where the disruption of performance was observed. In the pretrial stimulation condition the monkeys do not always respond *during* the seizure, but are free to respond after it has terminated. Subject 28 responded during the seizure on 13% of the trials, Subject 29 on 96%, and Subject 344 on 62%; on the remaining trials they responded directly following the seizure. There is, however, no obvious relationship between the magnitude of the deficit which resulted and either the duration of the seizures or the percentage of the total responses which occurred during the seizure. Within two of the monkeys there was no relationship between the occurrence of a correct response or an error and whether the response was made during the seizure or immediately after it. In Subject 28, those responses occurring after the seizure tended to be correct and those during the seizure to be incorrect ($\chi^2 = 7.98$, $df = 1$, $p \leq .01$, two-tailed).

DISCUSSION

The finding that posttrial stimulation has no effect on learning while pretrial stimulation is clearly disruptive argues strongly against the hypothesis that electrical seizures in the inferotemporal cortex produce their effect by disrupting the transfer of visual information into long-term storage. Consolidation processes (of a measurable duration) are not disrupted. Seizures produced by the techniques used here do disrupt learning, but only when they occur *during* the presentation of the stimuli. The duration of the seizure is not a critical variable here (see Table 2 and Results).

Since the problem on which a deficit appeared was the last one tested, it would be possible that this deficit was simply due to cumulative damage to the cortex as a result of the repeated seizures. However, when Subject 28 failed to learn in almost 400 trials with pretrial stimulation, testing was continued without any stimulation, and this monkey then reached criterion in only 45 additional trials (16 errors). If one were to assume that little or no learning had taken place during the stimulation (performance in fact averaged 51% over the last 45 stimulation trials), this would give a "savings" ratio of .03, which is clearly within normal limits. Also, histological examination of the brains of all three monkeys revealed only a small amount of damage around the stimulating electrodes. This amount of damage is negligible when compared with the amount of tissue which must be removed surgically to produce a deficit.[4]

Both Chow (1961) and Goldrich (1966) found that unilateral seizures, like unilateral ablations, do not give rise to a deficit in learning. We made an observation on Subject 344 which may be related to this phenomenon. Midway through the third day of testing on the second discrimination it was discovered that stimulation was only being

[4] The magnitude of the effect of pretrial stimulation may have been enhanced here by the use of a 1½-min. ITI for the two vs. seven discrimination, as compared with a 3-min. ITI for the three vs. eight discrimination. Preliminary experimentation with the stimulation showed that no discernible EEG abnormality existed even 1 min. after stimulation, and hence 1½ min. was deemed to be sufficient to avoid intertrial effects. However, when the stimulation was being delivered *after* each trial the authors wished to be even more certain that no effect of the previous seizure was present when the stimuli reappeared. There is no reason to expect the absence of a posttrial effect to be peculiar to the 3-min. ITI.

delivered to one hemisphere. The difficulty was corrected and bilateral seizures reinstated, but performance had begun to rise above 50%-correct responses, and it remained above that level for 10 more days before criterion was attained. The fact that bilateral seizures could keep performance below criterion is also compatible with the observation made by Chow that performance of a previously learned discrimination could be disrupted by such (bilateral) seizures. Goldrich found only a slight disruption in performance, but since he reports that, on the average, bilateral seizures occurred on only 45% of the trials during the acquisition phase, and presumably, although the data are not given, also during the retention tests, the discrepancy is perhaps understandable. Chow only presented the stimuli to the subject when a bilateral seizure occurred. Generally, it does appear that afterdischarge and aluminum hydroxide creme techniques have less effect on performance than does ablation, and this may also be true of their effect on acquisition.

While recording the afterdischarges from the inferotemporal cortex, electrodes in other areas were simultaneously monitored. During the seizure the striate leads often showed spikes which were time-locked to the inferotemporal spikes. However, since neither aluminum hydroxide creme induced discharges (Kraft, Obrist, & Pribram, 1960) nor direct seizure-producing stimulation of occipital cortex (Goldrich, 1966) impair visual discrimination, the results we have observed would not seem to be due to seizures occurring in the primary cortex. Similarly, seizures set up directly in the hippocampus do not affect discrimination performance (Chow, 1961). Unlike Chow, we did not observe any seizure-like activity in the hippocampus due to the inferotemporal seizures.

The results of this study extend the knowledge of inferotemporal cortex function obtained through the use of disruptive electrical stimulation by pointing to the events occurring *during* the subject's perception of the stimuli and/or choice between them as being significantly affected by the activity of this cortical area. This implication—that the relevant events are intratrial rather than posttrial ones—embraces many current views on the function of the inferotemporal cortex (Wilson, 1968), but it is not consistent with others, as we have indicated. Our own theoretical preference is to view the inferotemporal cortex as exerting an efferent control over events in the primary visual pathway (Pribram, 1958). According to this view, the inferotemporal cortex becomes related to "memory processes" in the sense that what is stored depends on what was perceived. What can subsequently be recognized is conceived to be dependent both on what was previously stored and on the organization of current input in the visual system, which is again under the influence of the inferotemporal cortex.

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