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EFFECT OF EEG BIOFEEDBACK ON CONVULSIVE RESPONSE TO MONOMETHYLHYDRAZINE IN THE RHESUS MONKEY

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The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Information Office (OI) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

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FOR THE COMMANDER



ANTHONY A. THOMAS, MD
Director
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Toxic and convulsive responses to monomethylhydrazine (MMH) were compared in two groups of rhesus monkeys. One group received 12 weeks of feedback training with reinforcement provided for the production of rhythmic central cortical 12-14 Hz EEG activity (the sensorimotor rhythm or SMR) in the absence of movement and concurrent 8-11 Hz EEG activity. A second group was studied also but without feedback training. Three of the four trained animals demonstrated reliable acquisition of the rewarded response. Following training		

20. Abstract (continued).

a convulsive dose of MMH was administered to both groups. Trained animals showed a significantly prolonged latency to generalized seizures, fewer overall seizures, and a greater incidence of sustained quiescent behavior. Toxic responses, including emesis and episodes of agitated behavior, were comparable among the two groups. These findings indicate that threshold for MMH induced seizures can be modified in primates through EEG feedback training, as shown previously in the cat. A specific change in central motor control mechanisms is proposed as an explanation for this effect.

PREFACE

This research was initiated by the Toxicology Branch, Toxic Hazards Division, Aerospace Medical Research Laboratory, under Project 2312, Task 2312V1, Work Unit 2312V113. Experiments were performed under Contract AF F33615-76-C-5014 by the School of Medicine, University of California, Los Angeles, California 90024.

The experiments were conducted by M. B. Sterman, Ph.D., of the Veterans Administration Hospital, Sepulveda, California 91343, S. J. Goodman, M.D. of Harbor General Hospital, Torrance, California 90509, and M. F. Fairchild, Ph.D., of the Veterans Administration Hospital, Long Beach, California 90804. Kenneth C. Back, Ph.D., was contract monitor for the Aerospace Medical Research Laboratory.

EFFECT OF EEG BIOFEEDBACK ON CONVULSIVE RESPONSE
TO MONOMETHYLHYDRAZINE IN THE RHESUS MONKEY

INTRODUCTION

Neurobehavioral studies of the convulsive toxicity of hydrazine compounds have clearly established the protective influence of imposed or learned suppression of motor activity. In experiments using cats, immobilization produced by administration of a systematic neuromuscular blocking agent (Flaxedil[®]) significantly prolonged the latency to central nervous system seizures in response to unsymmetrical dimethylhydrazine (Goff et al., 1967), while restraint achieved by placing animals in an immobilizing bag produced a similar effect with exposure to monomethylhydrazine (MMH) at convulsive doses (Bowersox et al., 1978). In other studies, operant conditioning of EEG patterns associated with immobility and decreased motor excitability led also to a significant alteration in seizure latencies and thresholds (Sterman et al., 1969a; Sterman, 1976). Specifically, reward for a pattern of 12-15 c/sec rhythmic activity recorded over sensorimotor cortex (termed the sensorimotor rhythm or SMR) resulted in prolongation of seizure latency and elevation of seizure thresholds in cats exposed to MMH.

In more recent studies it was established that both restraint and EEG feedback training techniques were effective in facilitating the SMR pattern in the rhesus monkey as well (Sterman et al., 1977). The present study sought to evaluate seizure response to MMH following EEG feedback training directed toward an enhancement of SMR activity in this species. Besides the obvious advantages of an evaluation of this therapeutic route in primates, the greatly enriched behavioral repertoire of these animals could provide important information concerning the mechanism for observed effects.

METHODS

Eight young, adult female rhesus monkeys (*Macaca Mulatta*) participated in this study. All were healthy and within normal female weight range (4-6 kg). Each animal was prepared surgically with indwelling cortical electrodes placed bilaterally over sensorimotor cortex. This was accomplished using ketamine anesthesia and sterile surgical procedures. A bilateral frontal-parietal craniotomy was performed and the dura opened to identify cortical anatomy. The location of the central sulcus was translated to the bone flap, which was then wired back into place and small holes drilled for the placement of extradural silver-ball electrodes. A bilateral montage of electrodes was placed anterior and posterior to the central sulcus at 10 mm intervals from midline to 30 mm lateral to midline. Insulated leads from these electrodes were collected into a miniature female connector and secured to the skull with fixation screws and dental acrylic cement. The scalp was closed around this assemblage and the animals placed in their primate chairs for recovery. Animals had previously been adapted to these chairs and remained chaired throughout the subsequent investigation which began after a one-month recovery period.

All eight animals were housed in the same facility and maintained on identical care and feeding schedules. Four of these animals were provided with subsequent EEG operant conditioning. The other four animals were manipulated in a comparable manner during unrelated EEG studies.

Trained animals were initially adapted to a sound-attenuating isolation chamber. The entire chair was transferred into the chamber, and a food cup was clamped to the waist plate. A motorized food hopper outside the chamber was connected to the cup and each step advance of the hopper a single 50 mg food pellet was delivered to the food cup. The animals rapidly learned to remove pellets from the cup and feed themselves through an open porthole in the neck plate. The feeding schedule was adjusted so that each animal would promptly empty the cup and eat at least 100 pellets when brought into the chamber on a Monday-Wednesday-Friday schedule.

Training was begun after preliminary EEG studies indicated that the most easily detected sensorimotor rhythm (SMR) activity appeared at mid-lateral electrodes (i.e., leads at approximately 10 or 20 mm off midline). Reward was then provided for appropriate signals from a mid-lateral bipolar electrode pair over the left hemisphere. EEG activity from the specified electrodes was led to a logic circuit containing sharply tuned frequency filters set at 8-11 Hz and 12-15 Hz. The output of this logic circuit was a signal sufficient to trigger the release of one pellet from the feeder. Initial recordings were obtained from each animal for the purpose of adjusting the 8-11 Hz and 12-15 Hz amplitude criteria to comparable levels. Thereafter, all gains used for each animal were left unchanged for the several months of training. The criterion for a pellet reward was the presence of a 0.5 second burst of 12-15 Hz activity, the absence of 8-11 Hz, and the absence of short duration high voltage transients (movement artifacts). Criterion EEG voltage was variable among animals, but ranged consistently between 10-20 μ V. Training sessions were conducted on a fixed schedule, three times per week for 12 weeks. Each training session lasted for 60 min.

During two of the three sessions per week the following data were continuously recorded on a polygraph and on magnetic tape: unfiltered EEG activity from the "training" electrode pair, outputs from the 8-11 and 12-15 Hz filters, and a marker indicating each reinforcement. During one training session each week, polygraphic and magnetic tape recordings were obtained in all animals from multiple electrode sites over sensorimotor cortex in addition to activity recorded from the "training" electrodes.

After 36 training sessions (12 weeks) the response to a convulsive dose of MMH was tested in both trained and untrained animals. On the day preceding drug tests the animals were fed a light noon "meal" and then food deprived until after testing. Each animal was weighed on the morning of testing and then administered 15 mg/kg dose of MMH intramuscularly, between 9 and 11 AM. The MMH was obtained from Matheson, Coleman and Bell, Norwood, Ohio (MW = 46.07 gm/mole, sp.gr. = 0.852) and was diluted to 20 mg/cc in normal saline. Animals were tested on alternate days over a three week period. Drug tests were terminated after four hours with a therapeutic injection of barbiturate.

During MMH tests the primate chair was placed in a small, isolated room in front of a blank wall with a digital clock overhead. A video camera was placed in front of the chaired subject and recorded time and behavior from drug administration to termination of the test with barbiturate. A video monitor and recorder (Sony, model AV-3650) placed in an adjacent room provided for continuous observation of the animal and allowed for the permanent recording of significant events for future analysis.

Latency to generalized seizure was measured in minutes post-injection by reference both to behavior and concurrent EEG patterns (Figure 1). These data, together with the total incidence of interictal events, number of subsequent seizures and the incidence of certain specified behaviors, were tabulated from observational notes and video recordings for statistical comparison of group responses. Multiple t tests were performed for these comparisons.

RESULTS

I. RESPONSE ACQUISITION

With the initiation of EEG feedback training animals became alert and attentive and within a relatively short period began to produce sustained trains of 12-15 Hz rolandic EEG activity for food reward. These responses consisted of variable and brief bursts of rhythmic slower waves against an activated EEG baseline (Figure 2). The patterns observed became more regular, building to voltage levels clearly greater than background EEG activity.

Acquisition of this EEG response was measured as the number of criterion 12-15 Hz bursts (rewards) achieved during each successive 60 min training session. Response curves for the four animals provided with EEG training are shown in Figure 3. Indicated also are individual seizure latencies in minutes (brackets). All four animals demonstrated a sharp increase in responses after the first training session. One animal failed to show any further increase with subsequent training and, in fact, declined to baseline level by the sixth trial. The other three showed a variable increase to asymptotic levels by the fourth or fifth session and sustained relatively stable response rates during the first nine trials for which detailed data are presented. During subsequent training one of these animals demonstrated a sharp decline in responses, due in part to an increased criterion (one sec train) imposed upon this animal because of the very high response rates evident in earlier trials. Post-training seizure latencies were directly correlated with these acquisition data.

A more detailed analysis of response acquisition was provided by an evaluation of within-trial response distributions. Since the across-trial curves indicated a rapid increase in response rates this analysis focused upon trials 1, 3 and 5. The results are presented in Figure 4, in terms of the incidence and distribution of 0.5 sec bursts of 12-15 Hz EEG activity from sensorimotor cortex during the last 15 minutes of each of these trials. It can be seen that this pattern is rare and variably distributed in all animals

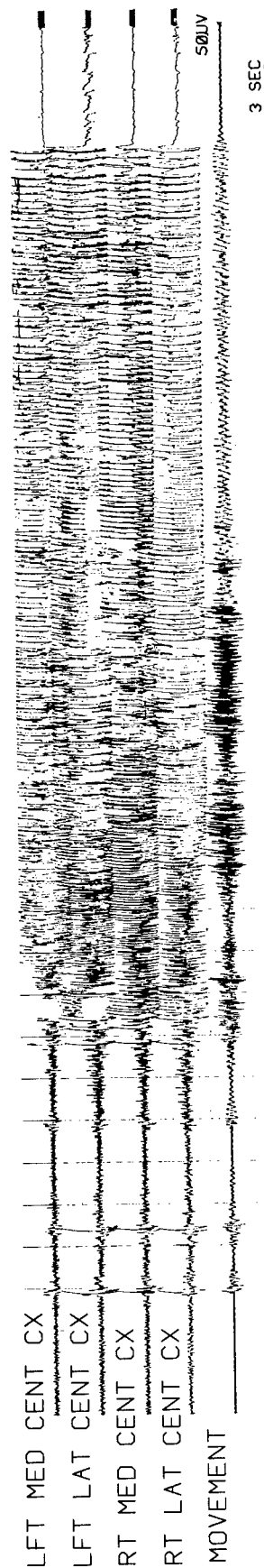


Figure 1. Onset of generalized EEG seizure following exposure to MMH administered intramuscularly in an adult rhesus monkey. This discrete EEG change together with corresponding behavioral seizure manifestations provided criterion for the timing of post-injection latency to generalized seizures.

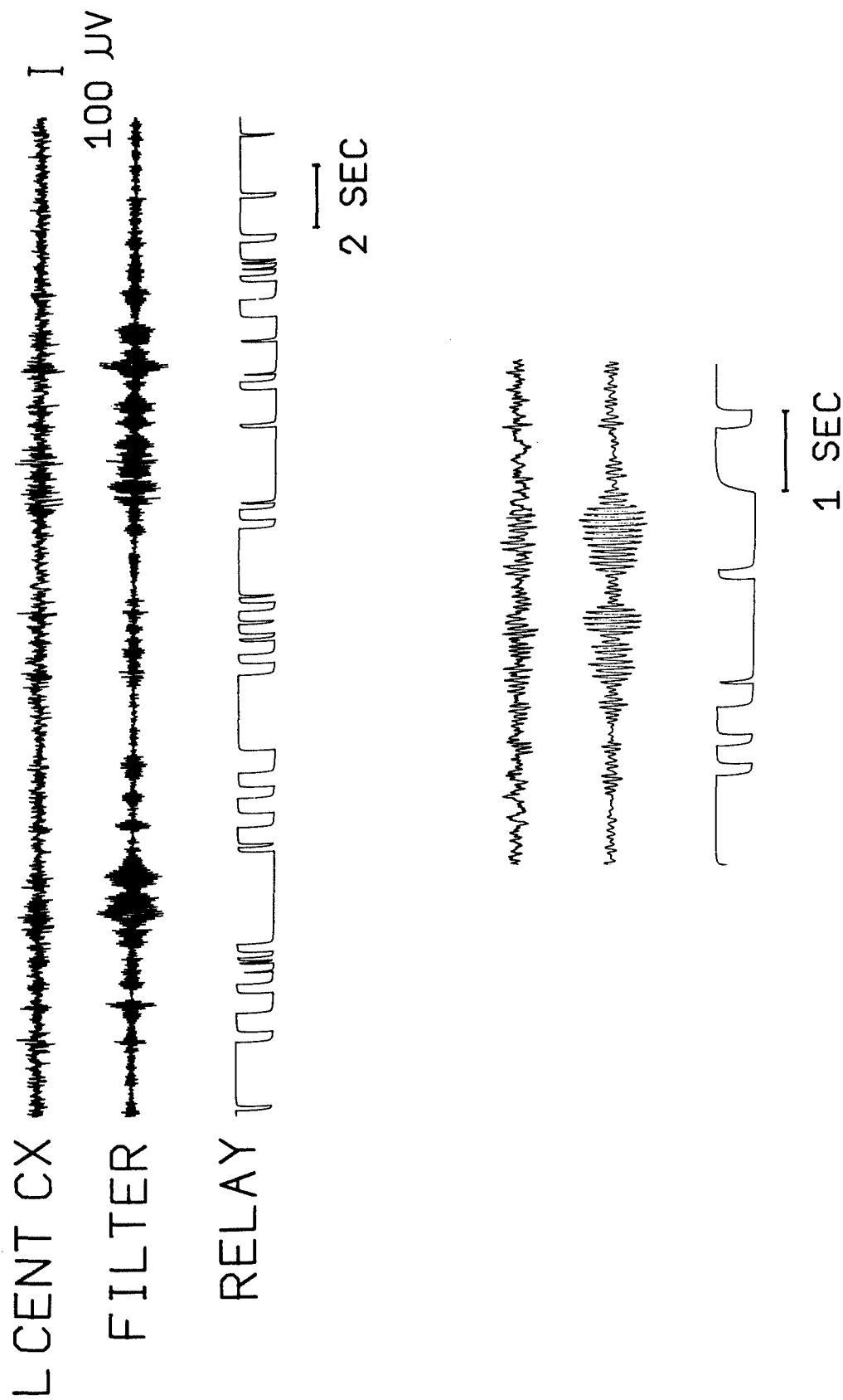


Figure 2. Sample tracing from left sensorimotor cortex in rhesus monkey trained to produce 12-15 Hz activity for food reward. Discharge of tuned 12-15 Hz filter is shown also, together with detection relay. Insert at bottom shows similar trained EEG response at faster paper speed.

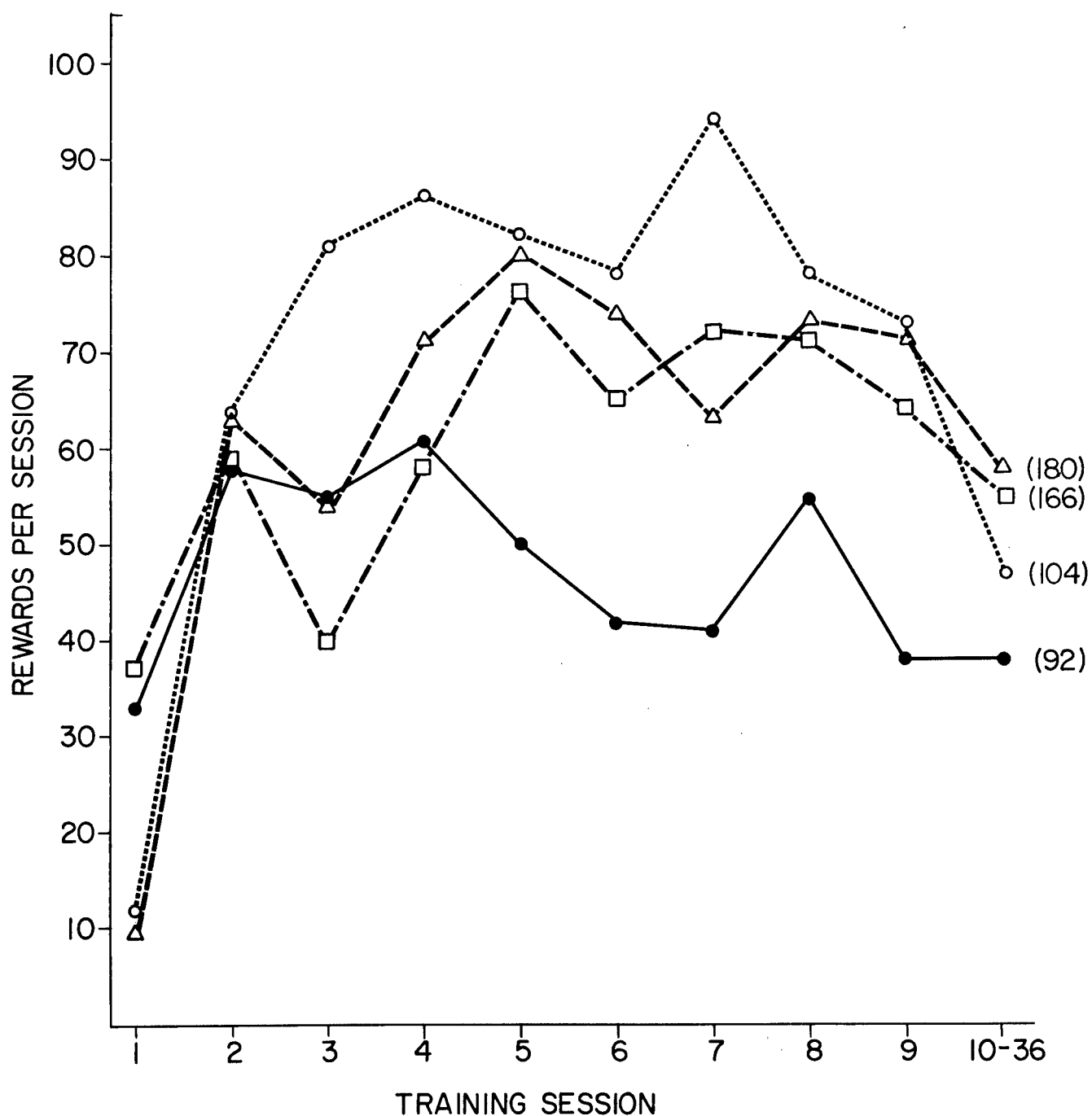


Figure 3. EEG response acquisition curves are shown here for the four animals provided with reward for central 12-15 Hz activity (0.5 sec train, 10 μ V or greater). Because of evidence for rapid acquisition first nine trials are shown together with mean values over subsequent trials. Shown also for each animal are seizure latencies, in minutes post-injection, as determined in tests carried out after training was completed.

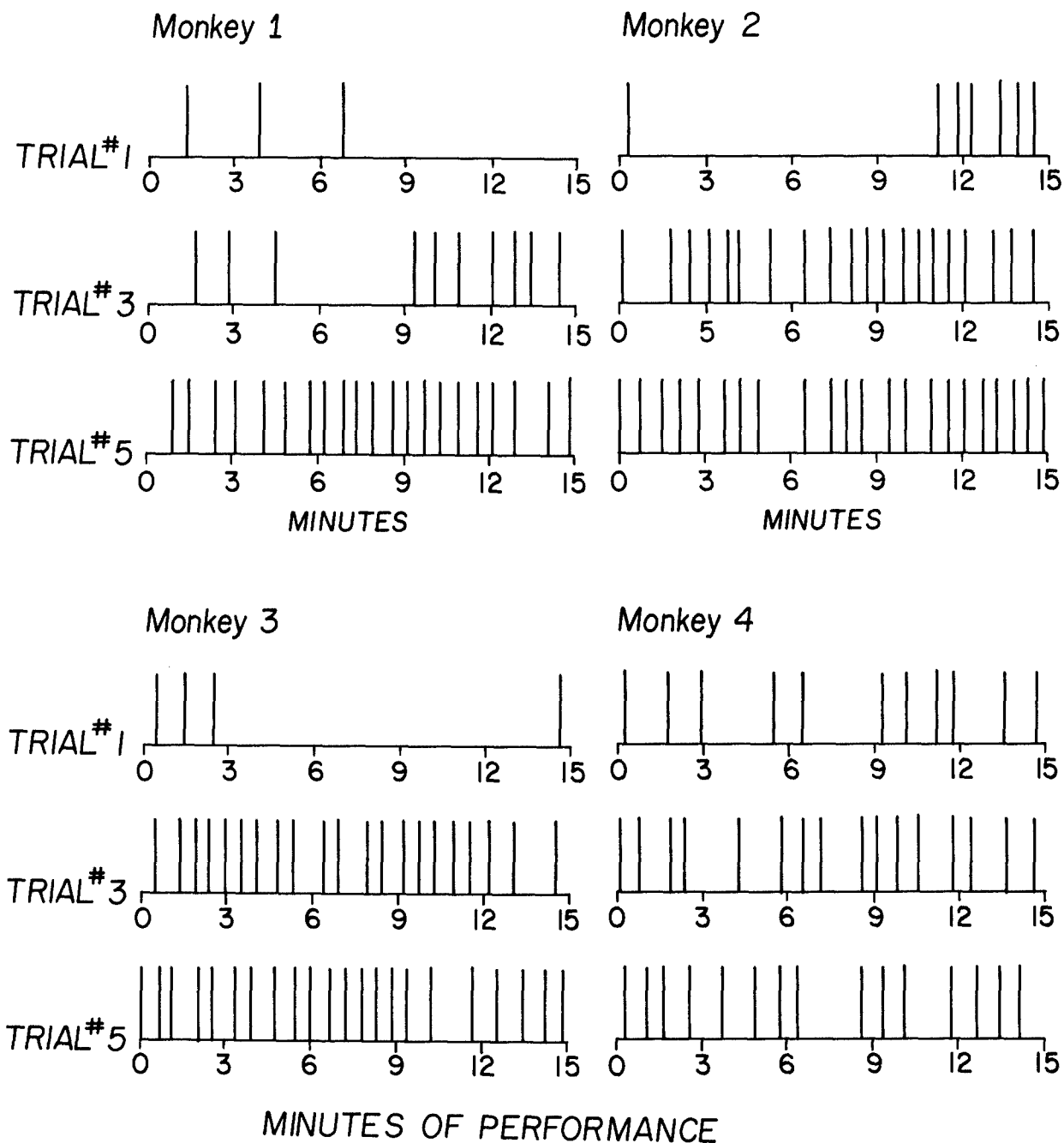


Figure 4. Analysis of EEG response acquisition as reflected by within-trial distribution of criterion response in the four animals given EEG feedback training. Evaluation focused on first five trials due to evidence of rapid acquisition from data in Figure 3. Monkey #4 showed no sustained response acquisition.

during trial 1. By the third trial all animals demonstrated an increased rate and more regular distribution of this activity, and by the fifth trial three of the animals (numbers 1, 2 and 3) were producing repeated bursts more or less systematically across time. Monkey number 4 failed to learn the required response, as indicated also in Figure 2 by her acquisition curve (solid line). This evaluation suggested that acquisition of the required EEG response was achieved rapidly and was reflected both by an increase in the rate and regularity of response.

II. SEIZURE CHARACTERISTICS

Videotape records of post-injection behaviors, the initial generalized seizure and subsequent seizures during a standard four hour measurement period provided comparative data for EEG trained and untrained animals (Table 1). Included among significant behaviors tabulated were sustained periods of behavioral quiescence one minute or longer (SQ), similarly sustained periods of behavioral agitation (SA) and episodes of emesis as indicated by vomiting (Vom.). Statistical comparison of group data (t-tests) established a number of differences between these groups. The EEG trained group showed a significantly longer mean latency to seizures, fewer total seizures, and more periods of sustained quiescence than the control group. No significant differences were obtained in the incidence of agitated behavior or emesis. It is interesting to note that the one animal in the trained group that failed to demonstrate response acquisition (animal #4) registered values in these measures corresponding to those of the control group. Indeed, inspection of the data presented in Table 1 suggests a consistent negative correlation between initial seizure latencies and both the number of quiescent periods and subsequent seizures.

In the interest of comparison, seizure latency data from the two groups of rhesus monkeys studied here are presented in graphic expression (Figure 5) together with similar data reported in a previous study using larger groups of cats (Stermann, 1976). In both studies animals provided with sensorimotor EEG operant conditioning showed longer latencies to seizures and greater variability in this measure than similarly prepared, untrained control animals.

DISCUSSION

The findings reported here support previous conclusions suggesting therapeutic, anticonvulsant effects in relation to MMH exposure with learned facilitation of rhythmic 12-15 Hz activity in rolandic cortex (Stermann et al., 1969a; Stermann, 1976). While toxic response to this compound, as indicated by emesis and behavioral agitation, was not affected by EEG training, behavioral control, initial seizure latency, and total number of seizures all showed significant alteration in relation to this experience. Moreover, the magnitude of protection afforded appeared to be directly associated with the degree of learning demonstrated.

TABLE 1

Comparison of behavioral and seizure responses to MMH exposure (15 mg/kg) in two groups of rhesus monkeys. Data were tabulated over a standard four hour period beginning with drug administration. Abbreviations: S.Q. = periods of sustained quiescence 60 sec or longer; S.A. = periods of sustained agitation 60 sec or longer; Vom. = emesis.

CONTROLS					
Monkey No.	S.Q.	S.A.	Vom.	Init. Seiz. Latency	Total Number of Seizures
1.	4	8	1	59	4
2.	0	3	5	81	6
3.	9	4	13	102	2
4.	4	17	5	98	4
$\bar{X}$	4.25	8.0	6.0	85.0	4.0

EEG TRAINED					
Monkey No.	S.Q.	S.A.	Vom.	Init. Seiz. Latency	Total Number of Seizures
1.	20	20	7	166	1
2.	15	9	10	104	2
3.	26	4	10	180	1
4.	2	17	2	92	3
$\bar{X}$	15.75	12.5	7.25	135.5	1.75

df = 6	t = -2.11	-.92	-.39	2.09	2.37
	p = <.05	NS	NS	<.05	<.05

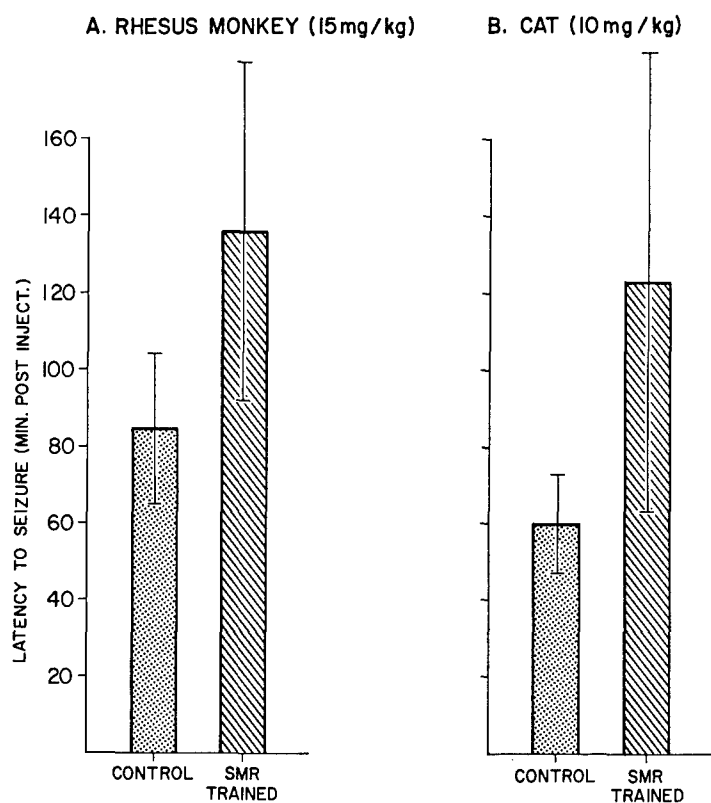


Figure 5. Comparison of mean seizure latency data from previous study of cats (Sterman, 1976) with 10 animals in each group and present findings in rhesus monkey. Increased variability of seizure latencies following EEG training in cats was attributed to variable response acquisition, a fact well established in the monkey data presented here.

A number of theoretical issues arising from this field of investigation can be addressed through the data presented here. First, it is clear that the rhesus monkey is capable of expressing an EEG pattern of rhythmic 12-15 Hz (sigma) activity during alert, waking behavior. A number of investigators have questioned the existence of this pattern in the waking EEG of man (Kaplan, 1975; Wyler et al., 1976; Kuhlman, 1978), while its presence in the cat has been abundantly documented (Brazier, 1963; Roth et al., 1967; Sterman and Wyrwicka, 1967; Sterman et al., 1969b; Rougeul et al., 1972; Kaplan, 1977). The established presence of this pattern in the waking EEG of primates, an observation supported also by the studies of Bouyer (1974), Cazard and Da Costa (1977) and Rougeul et al. (1978) greatly reinforces the proposed existence of this pattern in man as well (Sterman et al., 1974). It should be remembered also that recording studies in cats and monkeys have used electrodes placed either directly on cortex or threaded into the calvarium, an approach which has not yet been carefully explored in the few human studies where such recordings would be possible.

Secondly, it is apparent that EEG feedback training procedures can modify the expression of this intrinsic EEG pattern in primates, a fact confirmed also by the findings of Cazard and Da Costa (1977). Given this fact, one can then question whether the raised seizure thresholds observed were due specifically to CNS changes resulting from sustained enhancement of central cortical 12-15 Hz activity or some more general process associated with attendant immobility. It is interesting to note, in this regard, that trained animals displayed significantly increased episodes of sustained motor quiescence despite the fact that activity levels were the same as untrained animals. Again, in a previous study with cats it was found that similar operant conditioning in the waking animal resulted in a decrease in movements during sleep and an increase in the duration of sustained, motionless sleep (Sterman et al., 1970). Collectively, these findings suggest that therapeutic effects are related to an increased capacity for sustaining quiescent states. Since this effect has been documented during both wakefulness and sleep, it is reasonable to assume that its basis resides in some alteration in central organization rather than a learned suppression of movement. Similarly, while restraint alone can alter the seizure response to MMH (Bowersox et al., 1978), this condition is also associated with a similar central reorganization, as indicated by the increase in central cortical 12-15 Hz activity which parallels restraint (Sterman et al., 1977). A more permanent protective mechanism is suggested also by the fact that the recurrence of seizures following the initial seizure experience was attenuated in trained animals as compared to controls. The trauma, confusion, and CNS depression resulting from the initial seizure would certainly undermine any learned behavioral coping mechanisms.

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