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UNILATERAL SENSORY-MOTOR-RHYTHM (SMR) TRAINING IN CATS: A BASIS FOR TESTING NEUROPHYSIOLOGICAL AND BEHAVIORAL EFFECTS OF MONOMETHYLHYDRAZINE (MMH)

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FOR THE COMMANDER

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Cats were trained to produce sensory-motor rhythm (SMR) in one brain hemisphere and to suppress it in the contralateral hemisphere. Rewarding brain stimulation was delivered automatically to the lateral hypothalamus when trains of SMR of specified duration and amplitude appeared only in the trained hemisphere. Evoked potentials induced bilaterally in the sensory-motor cortex by stimulation of radiations from the nucleus ventralis posteriolateralis of the thalamus were photographed and measured prior to, during, and following training. Unilateral SMR production could be achieved, but this training procedure had no systematic

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effect on thalamocortical evoked potentials; although changes unique to each of the three animals tested occurred more frequently in the trained hemisphere.

PREFACE

This research was initiated by the Toxicology Branch, Toxic Hazards Division, Aerospace Medical Research Laboratory, under Project 7163. Experiments were performed under Contract AF F33615-72-C-1855 by the Department of Anatomy and the Brain Research Institute, School of Medicine, University of California, Los Angeles, California 90024.

The experiments were conducted jointly by M. D. Fairchild, PhD, of the Veterans Administration Hospital, Long Beach, California, and M. B. Sterman, PhD, of the Veterans Administration Hospital, Sepulveda, California. Kenneth C. Back, PhD, was contract monitor for the Aerospace Medical Research Laboratory.

I N T R O D U C T I O N

The objective of our present research program is a continued evaluation of the central nervous system mechanisms which mediate the effects observed after exposure to monomethylhydrazine (MMH) and an exploration of potential therapies for such effects. In previous studies we observed that the bio-feed-back training of a specific sensorimotor EEG cortex pattern in cats led to a significant alteration in MMH-induced seizures as compared with control and alternately trained animals. Animals trained to produce this rhythm either showed a significant delay in the occurrence of seizures or, in several instances, showed no seizures at all. This was true although the normal sequence of preictal symptoms, including vomiting, panting and salivation, occurred with the same time delay as in untrained animals. We concluded that training of the sensorimotor cortex rhythm, or SMR, led to a significant increase in seizure thresholds. We have been particularly interested in exploiting this fact as a means of pursuing both of the above stated objectives. The present communication describes our initial efforts in this regard.

An attempt was made to train animals in the production of this rhythm on one side of the brain and then employ the evoked neuro-electric responses. We have previously studied the effects of MMH on these parameters in normal, untrained animals (Sterman et al., 1969; Sterman et al., 1972).

The SMR consists of a 12 - 16 cps EEG rhythm localized to sensori-motor cortex in the cat. It occurs exclusively during absence of spontaneous or trained motor activity. Neurophysiological studies have indicated that the SMR was generated by a thalamocortical circuit involving the nucleus ventralis posterolateralis and its projections

to somatosensory cortex (Howe and Sterman, 1972). Extracellular recordings from this thalamic nucleus identified one group of cells which became specifically active during the SMR and another larger group whose activity changed to a pattern of bursting followed by prolonged silence (Harper and Sterman, 1972). Cells in the red nucleus of the extrapyramidal motor pathway were clearly suppressed in activity during the SMR.

Evoked response studies have indicated a specific facilitation of sensory transmission in the first synapse of the somatosensory pathway (the dorsal column nuclei) during production of the SMR (Howe and Sterman, 1972). Functionally, this finding suggests that the animal is focusing attention upon somatosensory input during this state. In addition to these neuronal changes during the SMR, heart rate was found to be significantly decreased and respiration stabilized (Chase and Harper, 1969).

Behavioral studies showed that cats could learn to produce the SMR for a food or positive brain stimulation reward (Wyrwicka and Sterman, 1968; Sterman et al, 1972). This bio-feed-back technique provided a means of markedly increasing the occurrence of the SMR and of determining the effects of its increased production on other behavioral variables. Compared with untrained and oppositely trained control groups, animals given excessive training in SMR production showed altered sleep patterns (a significant reduction in motor disturbances during sleep and, correspondingly, less overall time spent in sleep during a 24-hour period) (Lucas and Sterman, 1973, in press).*

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*Lucas, E. A., and Sterman, M. B., An ultradian sleep-wake cycle in the cat: effects produced by a trained performance paradigm. Expl. Neurol., 1973, in press.

Similar bio-feed-back studies in man, utilizing lights and tones as rewards, have resulted in a significant reduction in the EEG and clinical manifestations of epilepsy. Assessment of the functional state of somatosensory cortex in SMR conditioned cats was approached in the present study by reference to somatosensory evoked potentials elicited by stimulation of thalamocortical afferent fibers. In this manner the excitability of cortical elements themselves could be assessed without the complication of changes at other synapses along the somatosensory pathway as, for example, would be the case if a peripheral stimulus were employed (Allison et al., 1966). The evoked response technique had the advantage also of sampling specific populations of neural elements whose properties are known in some detail.

The evoked potential in somatic cortex to stimulation of afferent fibers from the thalamic relay nucleus (VPL) and the basis for its measurement are shown in figure 1. It consists of five discrete components (Allison, 1965). Wave 1 is the thalamocortical afferent volley; measurement of this potential thus provides a control for the stability of the afferent input into somatic cortex. Wave 2 is probably of post-synaptic cortical origin. Waves 3 and 4 are agreed by all investigators to be of intracortical origin and to reflect activation of pyramidal cells (e.g., Schoolman and Evarts, 1959; Widen and Ajmone Marsan, 1960; Allison and Goff, 1968). Wave 5 is due to inactivity, in the most superficial cortical layers, of apical dendrites of pyramidal cells (Amassan et al., 1964; Bishop and Clare, 1953; Purpura, 1961; Towe, 1966).

This information was utilized to evaluate both the effects of SMR training on this potential and will be employed to examine the interactions of training and MMH administration.

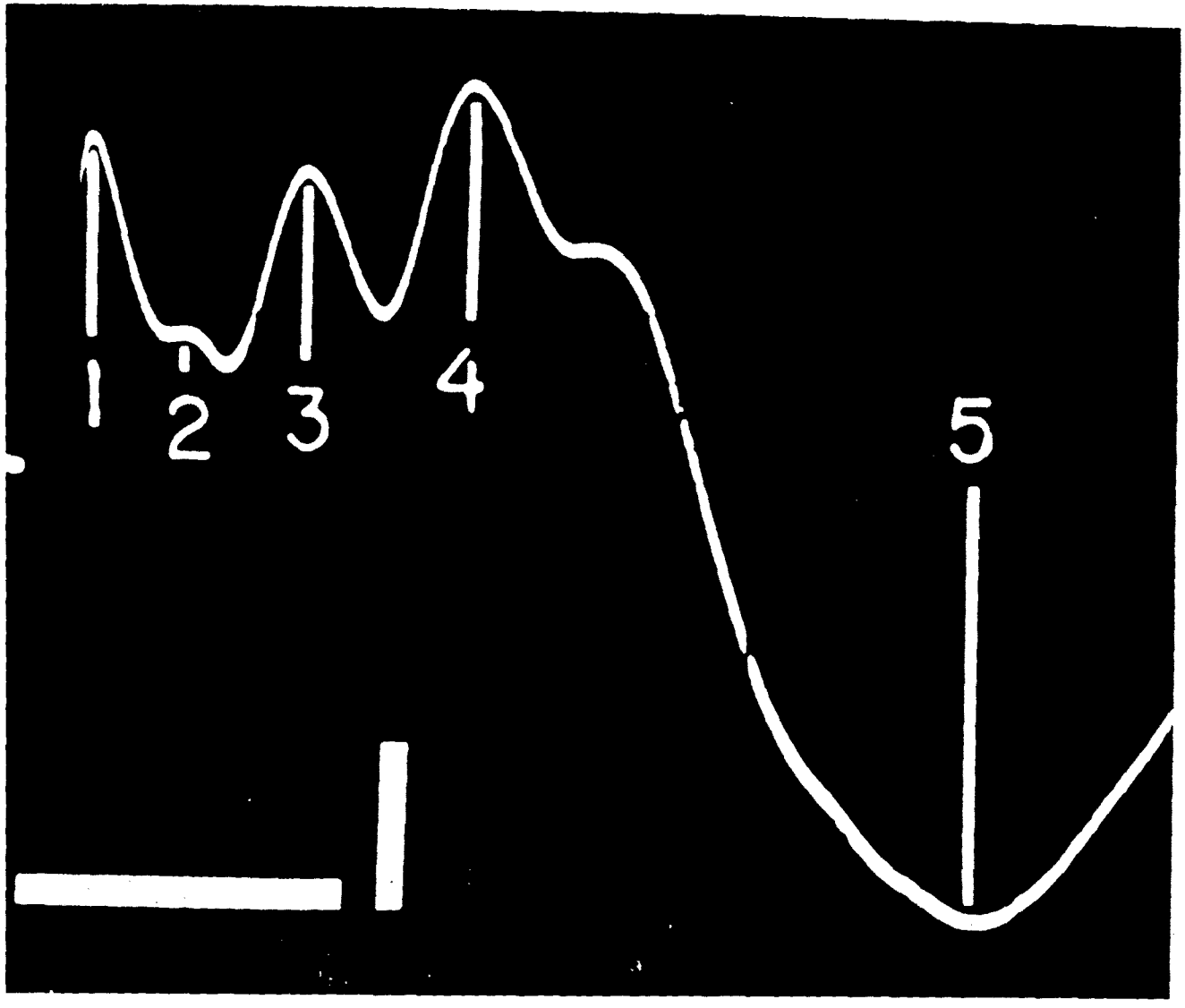

Figure 1: Somatosensory Cortex Evoked Response. Typical evoked potential recorded from the surface of the posterior sigmoid gyrus to the stimulation of thalamocortical afferents. Calibrations: 2 msec and 0.1 mV (Reproduced from Allison and Goff, 1968).

METHODS

Experiments were performed on three adult cats with electrodes chronically implanted bilaterally in radiations from the nucleus ventralis posterlateralis of the thalamus to the somatosensory cortex, the lateral hypothalamus, and over the somatosensory and occipital cortex. Subcortical electrodes consisted of two insulated 40 gauge stainless steel wires affixed to a 26 gauge stainless steel barrel with epoxylite electrode insulator. The wires extended 2 mm below the central shaft with 1.0 mm separating their exposed tips. Cortical electrodes consisted of 00-1/8 stainless steel machine screws placed bilaterally in arrays of three within the frontal sinus in bone overlying the pericruciate gyrus (Howe and Sterman, 1972) and posteriorly as single electrodes in the occipital area over the posterior marginal gyrus. An indifferent electrode was placed in the rostral aspects of the frontal sinus. All electrode leads were soldered to a minature connector premanently affixed to the skull with acrylic plastic.

Experiments were conducted in a sound-attenuated chamber equipped with a one-way mirror for observation. The animals were connected to the stimulating and recording equipment via low-noise cables through a counter-weighted slipping assembly (Lehigh Valley). Following recovery from surgery and a period for familiarization with the testing environment, the investigation of evoked potentials was begun. The thalamocortical radiations were stimulated once each second with a single monopolar pulse of 0.1 msec duration and 5 to 10 volts amplitude. Evoked potentials appearing in the somatosensory cortex were displayed on an oscilloscope and photographed. The latency and amplitude of the various components of the evoked potentials (see figure 1) were analyzed visually according to previously described criteria (Allison and Goff, 1968; Sterman et al., 1972).

Testing continued for a period of at least two weeks in order to establish optimal stimulus and recording parameters and to assess the range of variability occurring in the evoked potentials from both sides of the brain during the pre-training period. The cats were maintained in a state of relaxed wakefulness with low-voltage, fast-wave activity appearing in the EEG during all recordings of evoked potentials.

Sensory-motor rhythm (SMR) training was then initiated. As has been previously described (Howe and Sterman, 1972), the 12 - 14 Hz component of spontaneous brain electrical activity recorded from the somatosensory cortex was reinforced using electronic circuits designed to filter, rectify and integrate activity within the frequency range. These circuits were employed to operate devices for the delivery of positive reward, consisting either of small quantities of milk or electrical stimulation to the lateral hypothalamus, when the integrated voltage output reached a predetermined level. The threshold of the filtering circuits could be adjusted so that they responded to various SMR amplitudes and the operation of the reward devices could be made contingent on sustaining such activity over specified periods of time.

The animals were trained by gradually increasing the requirements for SMR duration and amplitude necessary for obtaining a reward. During the current experiments, two such analyzing circuits were employed, one for the right and the other for the left somatosensory cortex. Additional circuitry compared the SMR output from the two sides of the brain and made operation of the reward mechanisms contingent on its unilateral appearance. This, in effect, reinforced SMR in one hemisphere while simultaneously suppressing this rhythm in the opposite hemisphere. The

side of the brain exhibiting evoked potentials whose configuration most resembled the classical picture of thalamically induced activity in the somatosensory cortex (see figure 1) was selected to receive SMR reinforcement.

In two animals, differential SMR training was carried out initially using a food reward. This procedure proved unsatisfactory due to the relative difficulty of maintaining the animals at a constant level of reduced body weight for long periods of time. As a result, both cats were eventually switched to rewarding hypothalamic stimulation; the third animal received only the latter reinforcement.

Criteria for unilateral SMR training was defined as that point where 200 or more rewarding hypothalamic stimuli were received within a 1 hour period of testing. As each animal reached criteria, training was suspended and daily measurements of evoked potentials continued for at least two additional weeks. During the following two months evoked potentials were checked at various intervals.

R E S U L T S

Unilateral SMR Training

As can be seen upon inspection of figures 2, 3 and 4, a marked increase occurred in SMR output in all three cats as the result of training. This increase appeared in both the "trained" (SMR production necessary for reward) and the "untrained" (absence of SMR necessary for reward) hemispheres. In this sense, the training procedure failed to achieve a purely unilateral SMR effect. However, the trained side in each cat produced a greater abundance of SMR which can be appreciated from the appearance of the filtered records (LFT 12 - 14 CPS and RT 12 - 14 CPS), and particularly from the channels indicating when SMR amplitude and

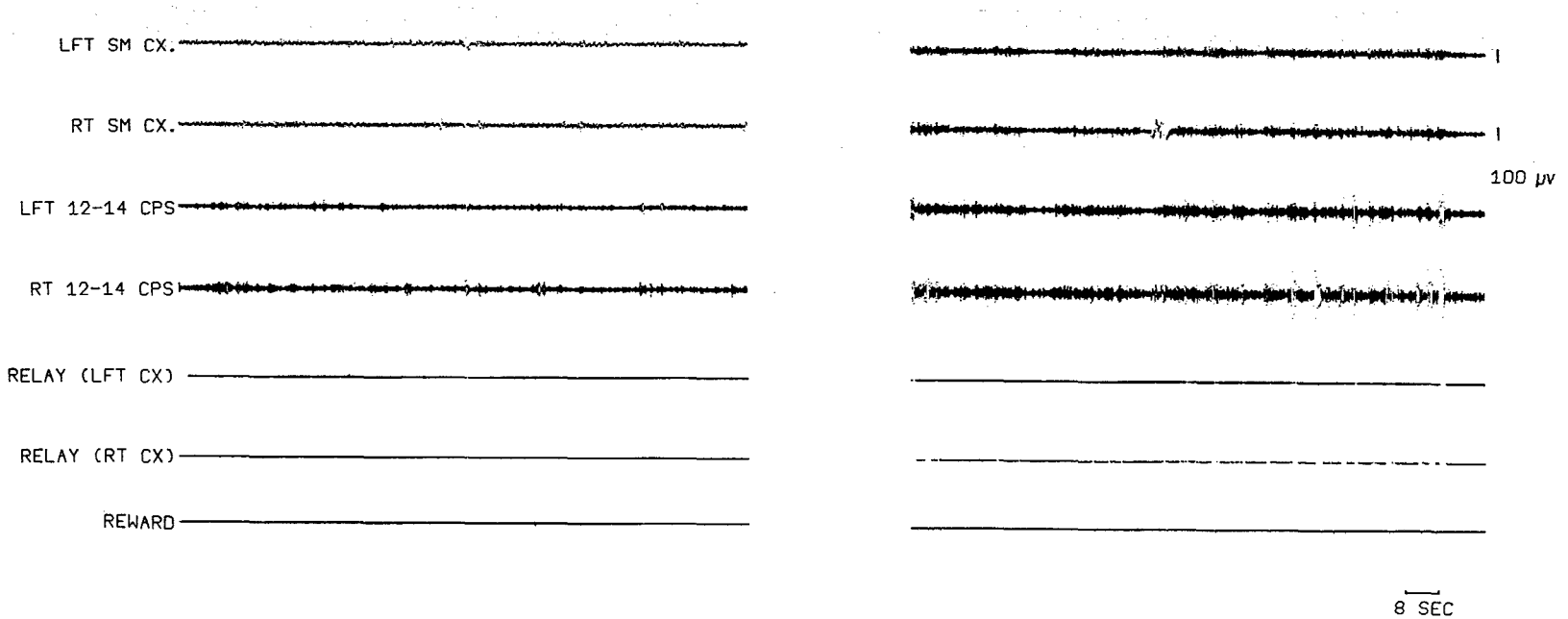

Figure 2. Cat SAA4. Effects of Unilateral SMR Training On The EEG. The right somatosensory cortex is the trained side. The recordings on the left side of the figure depict conditions during the pre-training period; those on the right were obtained after achieving criteria performance for unilateral SMR production. Abbreviation: LFT SM CX and RT SM CX, unfiltered EEG recordings from the left and right somatosensory cortex, respectively; LFT 12-14 CPS and RT 12-14 CPS, output of the SMR filters from the left and right cortices; RELAY (LFT CX) and RELAY (RT CX), indicates periods when SMR amplitude and duration were sufficient to activate the analyzer circuits; REWARD signifies periods when SMR activity appeared predominantly in the trained cortex and reward was delivered.

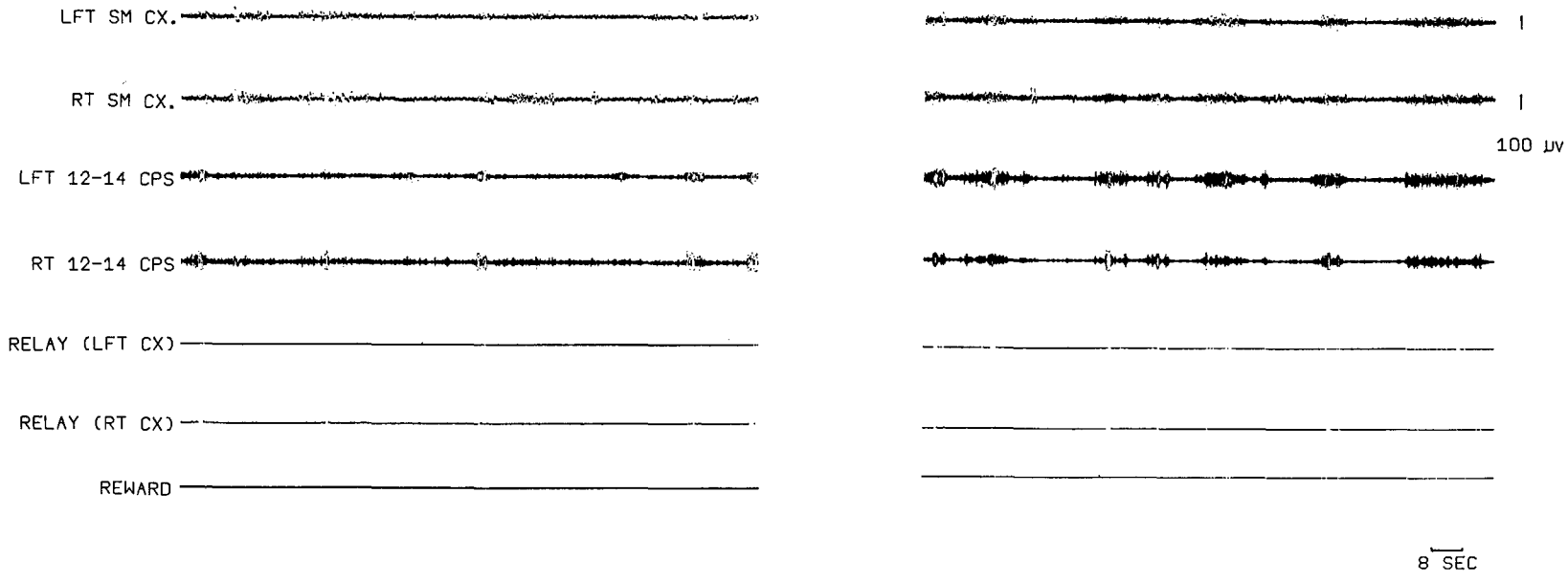

Figure 3. Cat SAA6. Effects Of Unilateral SMR Training On The EEG. The left somatosensory cortex is the trained side. For details see figure 2.

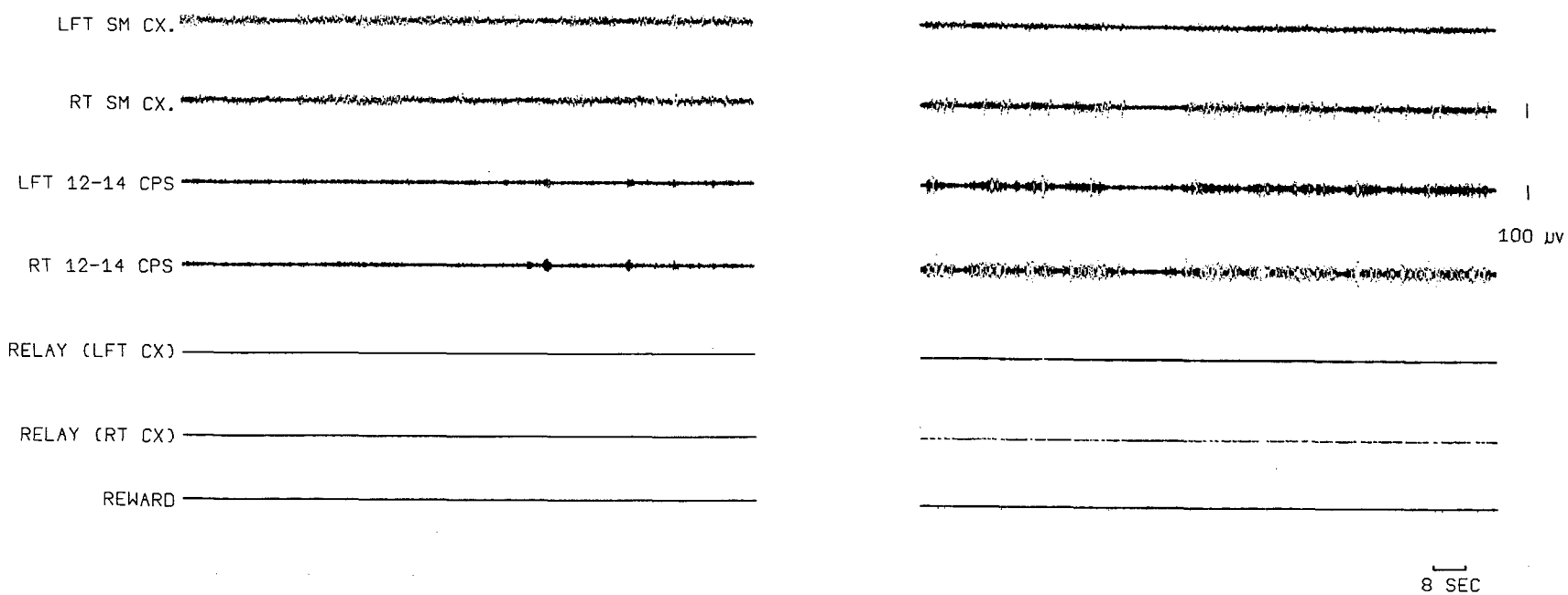

Figure 4: Cat SAA7. Effects of Unilateral SMR Training On The EEG. The right somatosensory cortex is the trained side. For details see figure 2.

duration were sufficient to activate the analyzing circuits [Relay (LFT CX) and relay (RT CX)]. The channels marked "reward" in figures 2, 3 and 4 signal delivery of positive reinforcement which occurred when SMR activity achieved threshold values only on the trained side. Apparently, reinforcement was obtained primarily during periods when SMR was out of phase in the two cortices or when burst duration in the trained side exceeded that in the untrained side.

Evoked Potentials

Neither food reward nor positively reinforcing hypothalamic stimulation produced any consistent effect on the thalamocortical evoked potentials recorded from the trained and untrained somatosensory cortices. Hand measurements of the five major peaks of these potentials were carried out on a daily basis, both as changes from baseline (voltage level just prior to stimulation) and on a peak-to-peak basis. The most reproducible portions of these data are presented in figures 5, 6 and 7 in which the median values of change from baseline for peaks 2, 4 and 5 are plotted for each week during the various phases of the experiments. An inspection of these figures gives the general impression that alterations in the shape of the thalamocortical evoked potential tended to occur most frequently on the trained side of the brain (upper diagram in each figure) but there was no consistency of effect and a clear recovery to pre-training voltage levels was not realized upon cessation of SMR training. Also, in cat SAA4 (figure 5) the largest evoked potential change appeared in peak 2 from the untrained hemisphere.

In addition to considering the values for the individual measurements, certain ratios of change were constructed among the five peaks in an attempt to minimize possible daily variations in the overall amplitude

of the evoked potentials, a parameter which is critically dependent on the amount of stimulating current. While certain interesting relationships appeared in portions of these data, again no consistent effects were revealed which could be definitely attributed to unilateral SMR training.

D I S C U S S I O N

The increase in SMR as the result of positive reinforcement was substantial and confirms previous studies (Wyrwicka and Sterman, 1968). While the techniques employed failed to completely suppress SMR on the untrained side of the brain, there was clearly a more pronounced effect in the trained hemisphere and all three cats eventually reached criteria for production of unilateral SMR activity. Although alterations in the thalamocortical evoked potentials apparently had no systematic relationship to the training procedures employed in these studies, certain changes unique to each animal did occur as criteria for unilaterial SMR production was approached and these changes tended to occur more frequently in the somatosensory cortex being conditioned for the generation of the rhythm. The failure of the thalamocortical evoked potentials to return to their pre-training configuration during the extinction phase of the experiments could be interpreted as indicating SMR training was not the causative agent for this change. However, such a result could also signify that relatively permanent alterations in the underlying neuronal circuits were produced; such an implication is not inconsistent with the fact that SMR training has been demonstrated to produce long-lasting alterations in the sleep patterns of cats (Lucas and Sterman, 1973, in press).*

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*See footnote on page 1.

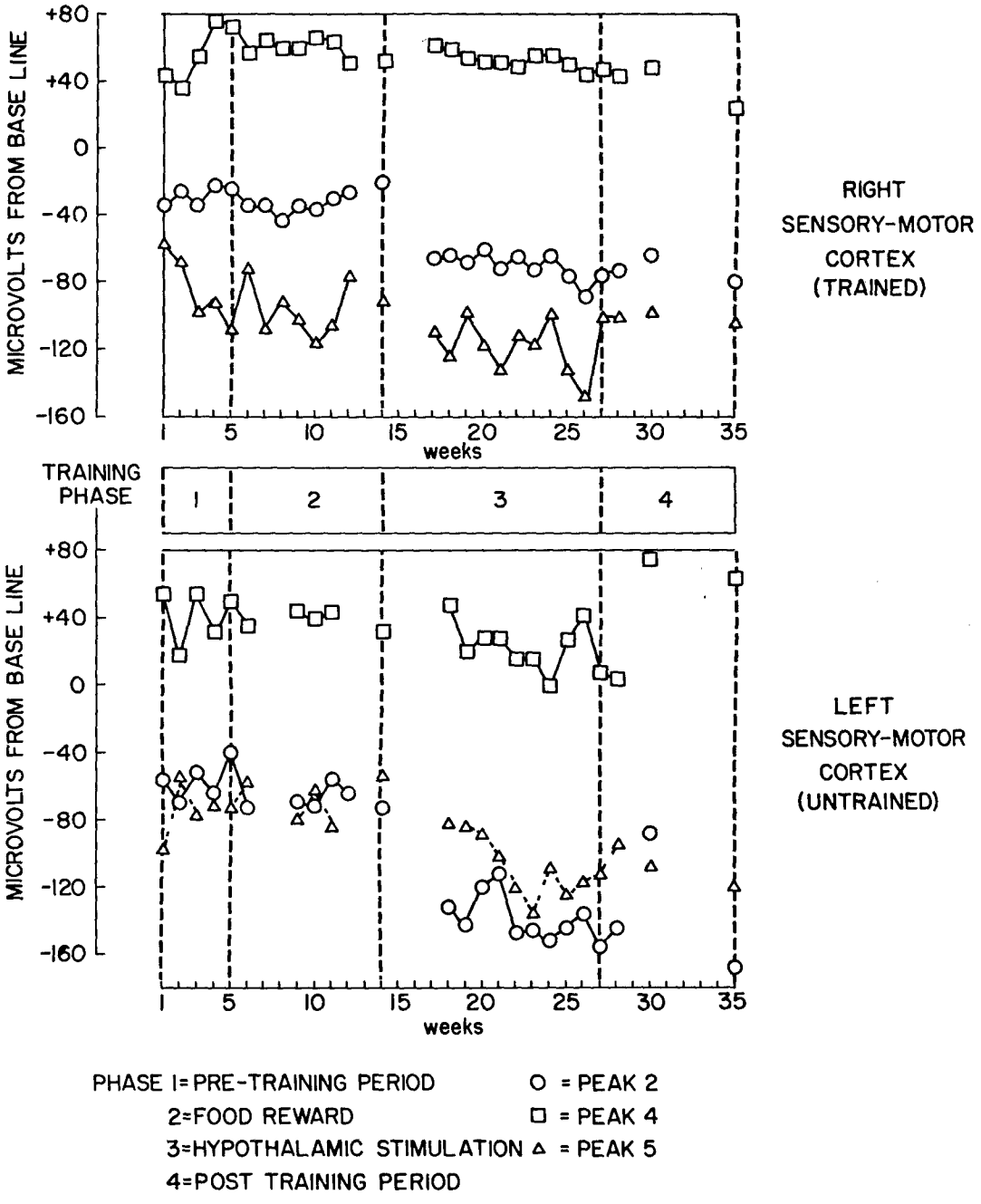

Figure 5: Cat SAA4. Somatosensory Evoked Response Amplitudes. Each point in the figure represents the median voltage from baseline obtained for the indicated peaks of the somatosensory evoked response during 5 consecutive days of measurement (1 week) in the various phases of training.

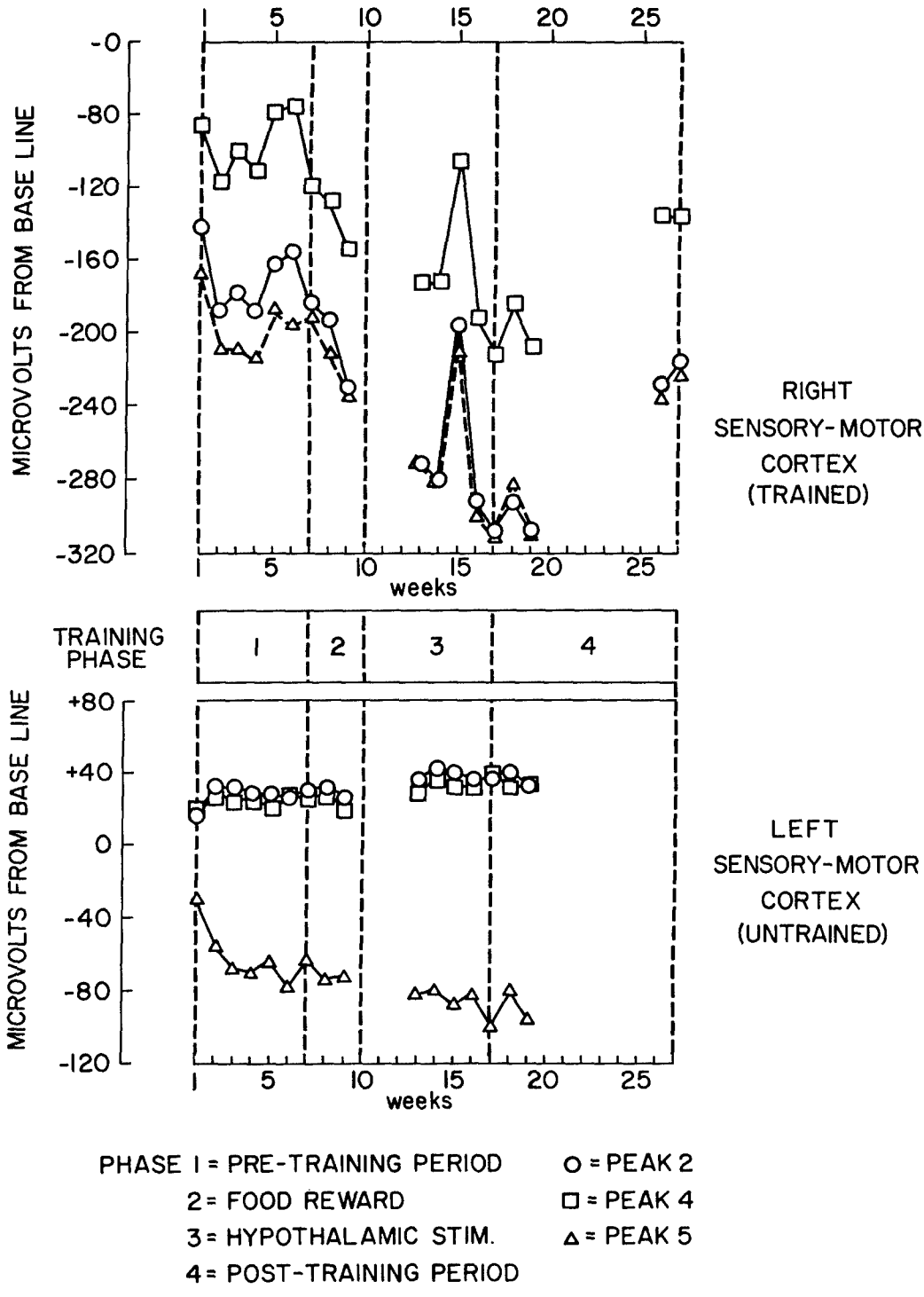

Figure 6: Cat SAA6. Somatosensory Evoked Response Amplitudes. For details see figure 5.

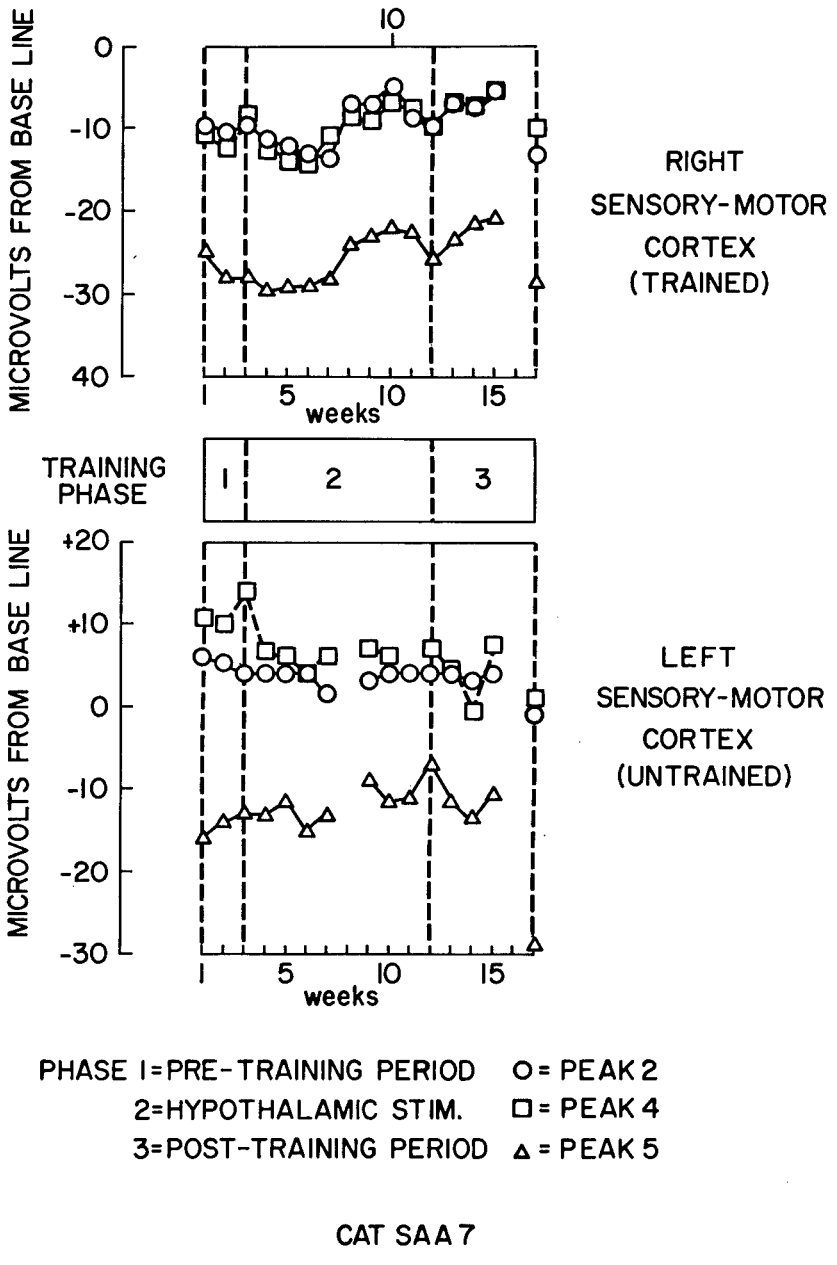

Figure 7: Cat SAA7. Somatosensory Evoked Response Amplitudes. For details see figure 5.

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