Electroencephalography and Clinical Neurophysiology
Elsevier Publishing Company, Amsterdam – Printed in The Netherlands

MODIFICATION OF SEIZURE ACTIVITY BY ELECTRICAL STIMULATION: II. MOTOR SEIZURE[1]

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(Accepted for publication: August 23, 1971)

Repeated electrical stimulation of certain brain areas in the rat can decrease thresholds for epileptiform after-discharge (AD) in those areas (Racine 1972). Motor seizures, which cannot initially be evoked by electrical stimulation of subcortical nuclei in the rat, can also be developed by daily electrical stimulation via implanted electrodes (Goddard *et al.* 1969). Goddard *et al.*, however, recorded electrographic activity in very few rats and consequently presented little correlative data relating to AD thresholds and changes in the characteristics of the AD activity. Delgado and Sevillano (1961) found that AD durations increased in the hippocampus of the cat with repeated electrical stimulation. Goddard (unpublished data, cited in Morrell 1969) has recently found a similar increase in AD duration in the amygdala of the cat, and Straw and Mitchell (1966) found that stimulation of the cortex in acute preparations (cats) also increased AD durations.

The present paper seeks to extend these findings and to examine the relationship between the epileptiform after-discharge activity and the development of motor seizures.

GENERAL METHOD

The procedures for taming, surgery, stimulation and recording, and a description of the apparatus used were given in the previous paper (Racine 1972). The parameters of stimulation were also the same: 1 msec biphasic square wave pulses at 60 c/sec with a 1 sec duration of stimulation. The electrode placements cited here are illustrated in the previous paper.

[1] This work was supported by the National Research Council of Canada (APA 66 to Dr. Peter Milner), and by the National Institutes of Health, U.S.A. (Fellowship No. 1-F1-MH-34, 614-01 PS to Ronald Racine).

Experiment I

In previous experiments (Racine 1972) which dealt primarily with changes in AD thresholds, it was found that the subjects receiving suprathreshold stimulation developed motor seizures more rapidly than those receiving subthreshold stimulation. On the basis of the data from those experiments, it appeared that the number of ADs evoked might be the most important variable in the development of motor seizures. In the present experiment, the rate of seizure development is compared in subjects receiving several different intensities of electrical stimulation.

Method

Three groups of twelve subjects were implanted with electrodes in the anterior amygdala, and two groups of ten subjects were implanted with electrodes in the posterior hippocampus. One group of amygdala subjects and one group of hippocampal subjects were stimulated once each day for 6 weeks with subthreshold (for AD) stimulation.

Stimulation was begun in these groups at 80 μA. To keep the stimulation below AD threshold, the current was dropped after 4 days of stimulation to 60 μA, and then after an additional 10 days of stimulation was dropped again to 40 μA for the remaining 4 weeks. If ADs were evoked in any of these subjects during the 6 weeks' period, the current level was

immediately lowered by 20 μA for that subject.

When the 6 weeks of subthreshold stimulation were completed, the subjects were stimulated at 200 μA once each day until a full motor seizure was evoked.

The second group of twelve amygdala subjects and the remaining ten hippocampal subjects were stimulated from the beginning at 200 μA each day until a full motor seizure was evoked.

The third group of twelve amygdala subjects was stimulated from the beginning at 1,000 μA each day until a full motor seizure was evoked.

The motor seizures were rated on a five point scale with respect to strength. Initially, very little or no skeletal motor activity accompanies the AD. The subjects generally exhibit some exploratory behavior during part of the AD. Most subjects begin showing some immobility after several ADs have been evoked. The first clear signs of skeletal seizures are often rhythmic mouth movements (jaw-opening) and head nodding, which occurs in most subjects from 2 to 4 days before the appearance of full motor seizures. The next component of motor seizure to appear is usually forelimb contractions, followed by rearing and finally, during full motor seizures, rearing and falling. There is some variation in this progression, but 80% of amygdala subjects develop motor seizures as described. This development will be divided into 5 stages: (1) Mouth and facial movements. (2) Head nodding. (3) Forelimb clonus. (4) Rearing. (5) Rearing and falling. A full motor seizure, with loss of postural control, will be referred to as a Class 5 motor seizure.

Results

A few ADs were evoked during the 6 week period of subthreshold stimulation in the first amygdala and hippocampal groups, but these were kept to a minimum. Five subjects had one AD during this period, and one subject had two ADs. These ADs were included in the measure of the number of ADs evoked in a subject before the appearance of motor seizure. After the current was raised to 200 μA, all of these subjects showed ADs after each stimulation, and subjects that were stimulated at 200 μA from the beginning also never failed to show AD. Table I gives the range and mean number of ADs evoked in each group before Class 5 motor seizures were evoked.

TABLE I

The mean and range of the number of ADs evoked by 200 μA stimulation required to develop motor seizures in the amygdala and hippocampus following 6 weeks of subthreshold stimulation (subthreshold 200 μA), and without any previous subthreshold stimulation (suprathreshold 200 μA). Also shown are the mean and range of the number of ADs evoked by 1,000 μA stimulation required to develop motor seizures in the amygdala (suprathreshold 1,000 μA).

	After-discharges to seizure	
	mean	range
Amygdala		
Subthreshold (200 μA) (N = 12)	11.2	6–17
Suprathreshold (200 μA) (N = 12)	11.3	8–15
Suprathreshold (1000 μA) (N = 12)	10.3	5–14
Hippocampus		
Subthreshold (200 μA) (N = 10)	26	5–60
Suprathreshold (200 μA) (N = 10)	27.4	8–65

There were no significant differences among amygdala groups or among hippocampal groups. Subthreshold stimulation did not appear to contribute to the development of motor seizures or to changes in the characteristics of the AD (see below), and high intensity stimulation was no more effective than low intensity stimulation, providing ADs were evoked. The occurrence of AD is crucial for the development of motor seizures. There were differences between the structures tested, however, with amygdala groups requiring fewer ADs than hippocampal groups to develop motor seizures.

Modification of after-discharge

The data discussed here were gathered during the present experiment and during previous experiments (Racine 1972). ADs were frequently evoked in the subjects, and the changes in

the characteristics of their ADs over time will be reported. In all cases, the stimulus parameters were 1 msec biphasic square wave pulses, at 60 c/sec and a total stimulation duration of 1 sec each day. Current intensity varied, but providing it was suprathreshold for AD, the intensity rarely had any effect on the characteristics of the AD. All measurements were taken visually. The amplitude of AD spikes, for example, was measured peak to peak with reference to the 1 mm divisions on the EEG chart paper.

Wave form of AD spike. When either the amygdala or the hippocampus is stimulated regularly, at current levels sufficient to produce AD, several characteristics of the AD undergo change. The AD spikes during the first discharge, for example, are generally of simple biphasic spike or spike and wave configuration. During the first few days of stimulation, however, these spikes become more complex. Notched or double spike configurations develop very early, and by the time motor seizures have developed, very complex waves are often seen (Fig. 1). No detailed analysis of the changes in wave form was made. It is assumed that the changes described are due, at least in part, to an increasing spread of the epileptiform discharge and subsequent feedback to the primary focus. No obvious relationship between change in wave form and motor seizure development was seen.

Frequency of AD spikes. Another change which was regularly observed in the amygdala AD was an increase in the frequency of the spikes. During the first AD, the dominant frequency was usually approximately 1/sec. The AD spike frequency increased regularly over the first five ADs until dominant frequencies of 3–5/sec were found (Fig. 1 and 2). A Friedman analysis of variance by ranks, performed on the frequency data from the first five ADs of thirty randomly selected subjects, shows a significant increase ($X^2=28$, df$=4$, $P<0.001$). After 5 days, no significant change in frequency was found, except for 14–16/sec bursts which usually began to appear some time after signs of motor seizure had developed (Fig. 1). These 14–16/sec bursts showed no apparent correlation with motor activity except that they generally occurred after the motor activity had developed.

Duration of AD. The changes which take place in the duration of AD are illustrated in Fig. 2 for the amygdala. Similar changes were found in the hippocampus. The mean duration of the first AD in the amygdala was 17.4 sec, with a range of 6–50 sec. There was a gradual increase in the duration of AD until about 3 ADs before the appearance of a Class 5, full strength, motor seizure, *i.e.*, when convulsive behavior began to appear in most subjects. The duration then began to change more rapidly until it reached a maximum shortly after the first appearance of Class 5 motor seizures. The mean duration of ADs in the amygdala following development of Class 5 motor seizures was 104 sec, and the range was from 50 to 350 sec.

The duration of the AD progressed in this manner for all subjects that were placed on an AD threshold reduction schedule (Racine 1972), which resulted in "spaced" ADs. Somewhat different effects were found for subjects that received predominantly suprathreshold stimulation. AD duration increased in the way

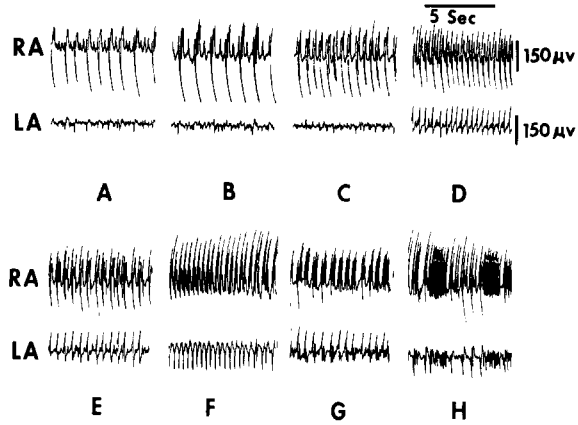


Fig. 1. Changes in wave form, frequency and amplitude of AD spikes in the amygdala as a result of electrical stimulation in the right amygdala: RA, right amygdala; LA, left amygdala. *A*: 1st AD, 400 μA stimulation, simple biphasic, 1/sec. *B*: 3rd AD, 300 μA, notched spikes, 1/sec. *C*: 5th AD, 200 μA, notched spikes, 2/sec. *D*: 6th AD, 200 μA, complex, 3/sec. *E*: 7th AD, 150 μA, complex, 2/sec. *F*: 10th AD, 150 μA, complex, 3–4/sec. *G*: 11th AD, 125 μA, complex, 2/sec. *H*: 14th AD, 100 μA, complex with 14–16/sec bursts. These samples represent the appearance of new spike forms. During the early discharges, only the simple wave forms are found. During later discharges, however, all previous wave forms may also be found in the same AD, along with the more complex forms. Induced changes in the left amygdala are also apparent in this figure, particularly increased spike amplitude.

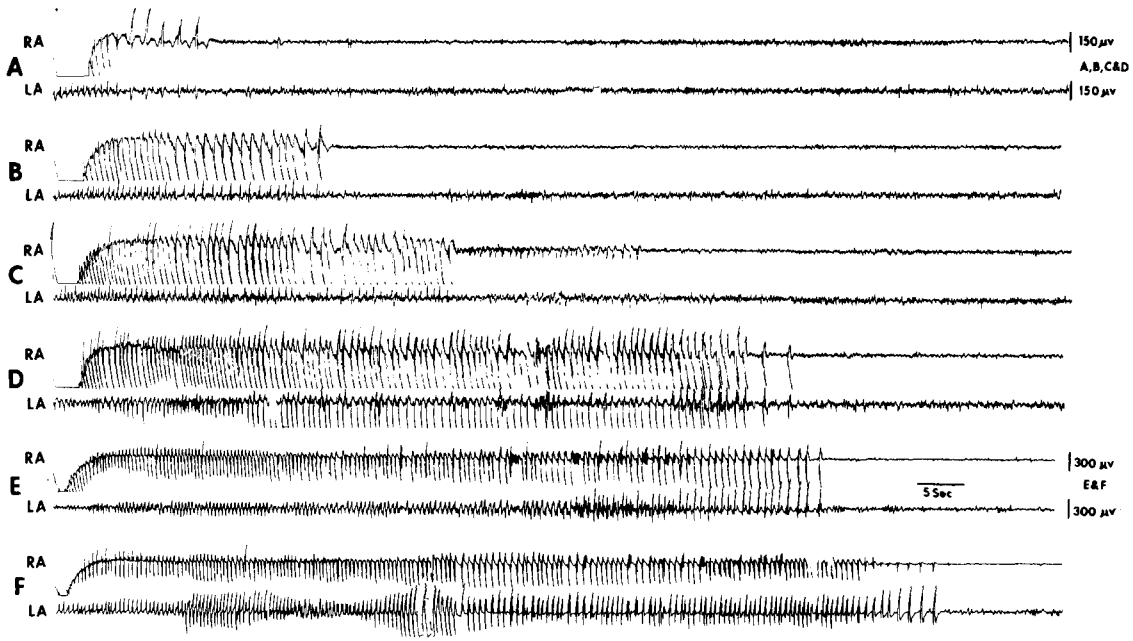


Fig. 2. Development of AD evoked by "spaced" suprathreshold electrical stimulation of the right amygdala. RA, right amygdala; LA, left amygdala. *A*: 2nd AD, 50 μA stimulation. *B*: 4th AD, 40 μA stimulation. *C*: 5th AD, 30 μA stimulation. *D*: 8th AD, 30 μA stimulation, Class 1 motor seizure. *E*: 10th AD, 25 μA stimulation, Class 3 motor seizure. *F*: 14th AD, 25 μA stimulation, Class 5 motor seizure. Note increased duration and spike amplitude, particularly in LA. Also, note change in amplifier sensitivity for records *E* and *F*.

described above for subjects receiving daily suprathreshold stimulation until motor seizures were evoked. Following the development of motor seizures, the AD duration often became progressively shorter with daily stimulation in these subjects (Fig. 3). This effect was presumably due to fatigue or temporary inhibition, because a rest of 48 h or more brought the AD duration back up to maximum levels.

The changes that took place in the hippocampal AD were similar but not so dramatic as those in the amygdala. The duration of AD changed from a mean of 28.9 to 68 sec.

Amplitude of AD spikes. The amplitude of AD spikes in the amygdala also increased with the number of ADs. In the stimulated amygdala the change was much more gradual and consistent than was the change in duration. The amplitude of AD spikes in the stimulated amygdala increased from a mean of 702 μV during the first AD to a mean of 986 μV following development of Class 5 motor seizures.

The most dramatic changes in amplitude of AD spikes took place in those structures that were "driven" by the primary focus. In the amygdala subjects, driving was initially very weak. The amplitude of the spikes from the contralateral amygdala increased gradually until about 3 days before the appearance of a Class 5 motor seizure. The amplitude of these spikes then increased very rapidly, and very extensively, until a Class 5 motor seizure was evoked, after which there was very little change. The spikes in the contralateral amygdala, then, start out at very small amplitudes and increase until they are equal to, or nearly equal to, those found in the "primary" site. A few subjects were found in which the spikes increased from 0 (or "noise") to amplitudes greater than those found in the primary site. (See Fig. 4 for a summary of the above data.)

The changes in amplitude of the hippocampal AD spikes were not so large, and there were no differences in spike amplitude between hippocampi. The mean amplitude of AD spikes in the primary focus increased from a mean of 1,050 μV to a mean of 1,520 μV. In the secondary focus, the AD spikes increased from 1,250 to 1,500 μV.

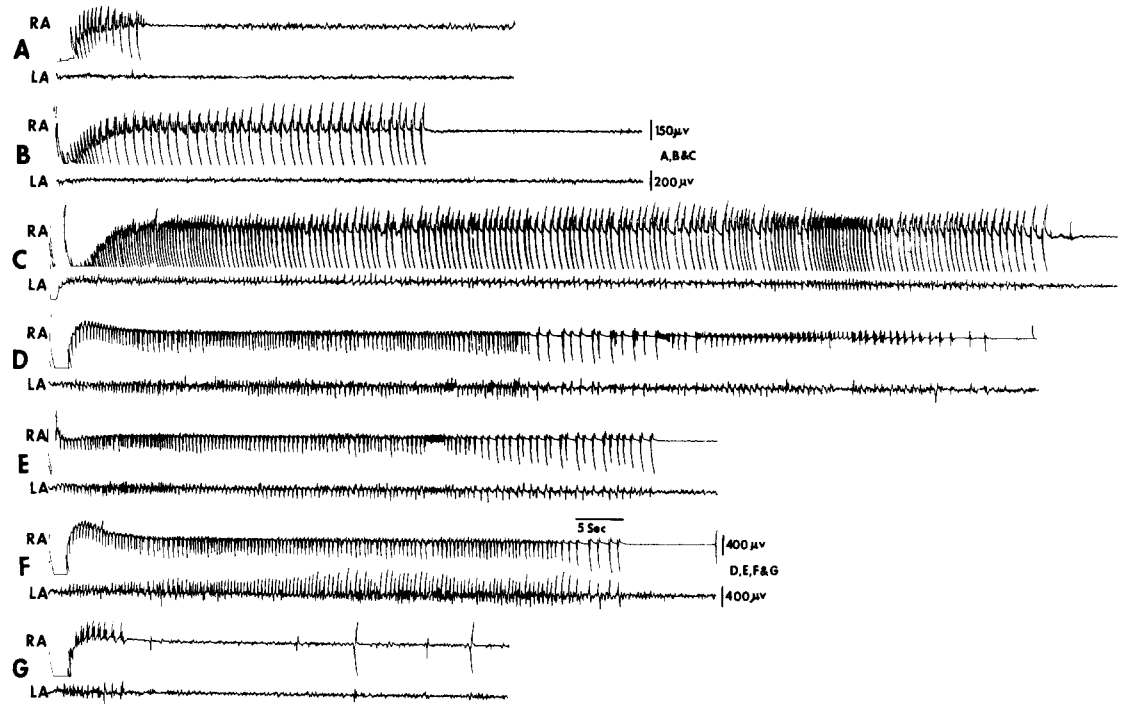
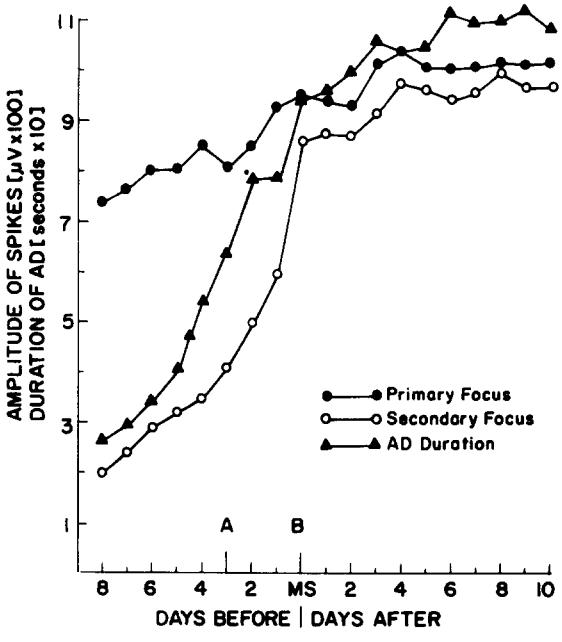


Fig. 3. Development of AD evoked by "massed" suprathreshold electrical stimulation of the right amygdala. RA, right amygdala; LA, left amygdala. *A*: 2nd AD, 150 μA stimulation. *B*: 4th AD, 150 μA. *C*: 8th AD, 150 μA. *D*: 12th AD, 150 μA, Class 2 motor seizure. *E*: 14th AD, 150 μA, Class 4 motor seizure. *F*: 16th AD, 150 μA, Class 5 motor seizure. *G*: 20th AD, 150 μA, "larval" discharge, Class 4 motor seizure.



There was an initial correlation between the onset of motor seizure activity and the amplitude of the AD spikes, particularly in the secondary focus. The appearance of motor activity was often associated with the appearance of large amplitude spikes in the secondary focus. As stimulation was continued, however, the latency of the motor seizure following stimulation decreased until there was practically no delay at all. The large amplitude spikes, although still present on the record, did not generally show the same decrease in latency. Consequently, during later stages of stimulation, there was no longer any close correlation between spike amplitude and the onset of motor seizure.

Fig. 4. Changes in AD spike amplitude and AD duration in the amygdala during the 8 ADs before and the 10 ADs after the first appearance of a Class 5 motor seizure (MS). *A* indicates day on which first signs of motor seizure activity generally appear. *B* indicates first day of Class 5 motor seizure. The right amygdala is the primary (stimulated) focus, and the left amygdala is the secondary (driven) focus.

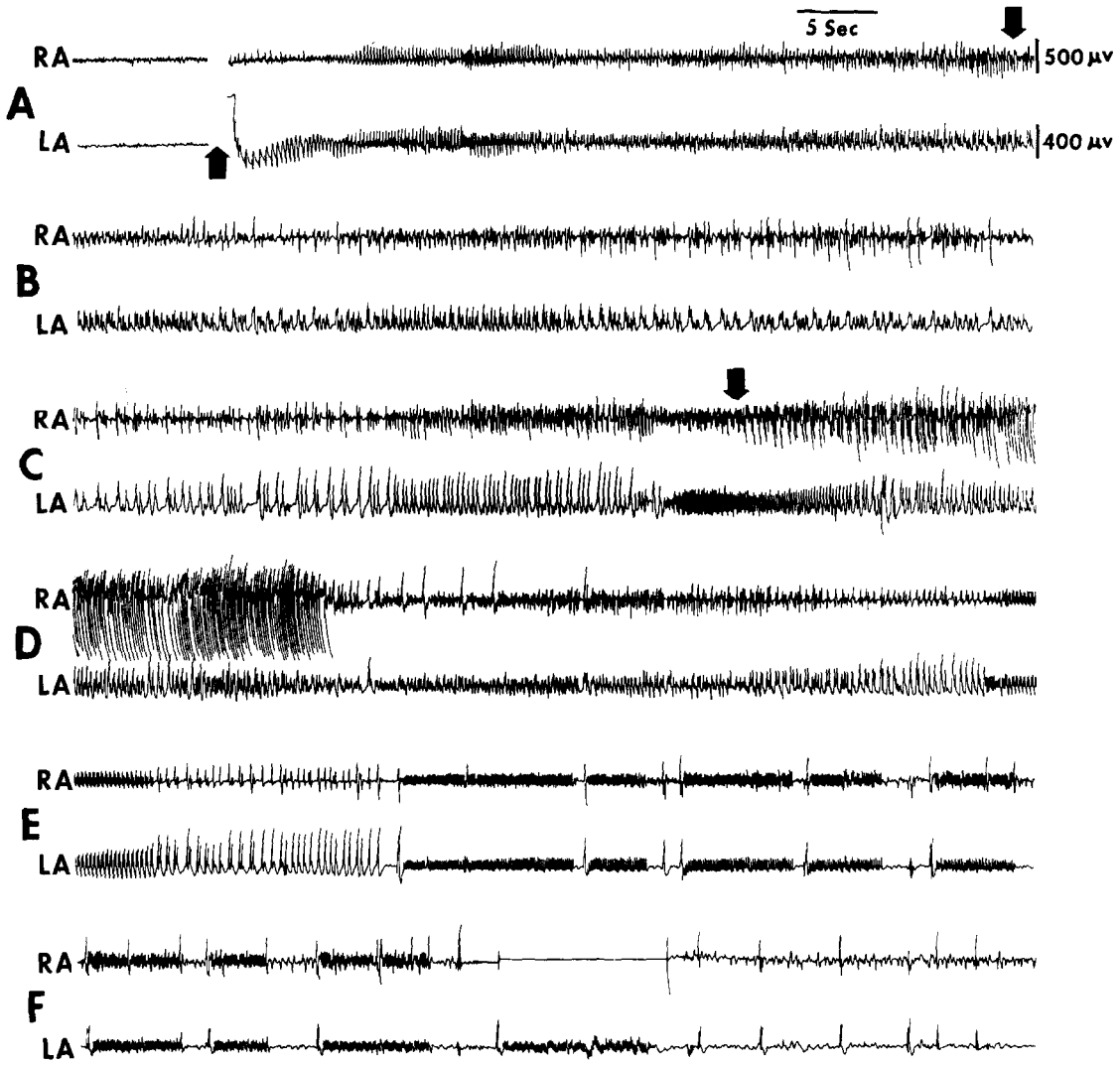


Fig. 5. Six min AD in the amygdala, after motor seizures have been developed, showing the numerous changes in amplitude, frequency and wave form which occur during a single AD. Stimulation was applied to the left amygdala (upward arrow). Two separate Class 5 motor seizures occurred during this discharge (downward arrows). RA, right amygdala; LA, left amygdala. *A–F*: Continuous record of AD.

In the hippocampus, the motor seizure very often appeared during the silent period (a 20–60 sec flattening of the EEG) following the AD. Occasionally, a 4–6/sec oscillation (theta) replaced the portion of the silent period during which seizure occurred. During this portion of the hippocampal silent period, epileptiform spikes in the reticular formation and amygdala often shift from small or medium amplitude to very large amplitude rather suddenly. The seizure evoked by hippocampal stimulation is clearly not being driven by hippocampal discharge, at least not from that portion of the hippocampus near the electrode.

Other effects that were regularly found in the AD records for both amygdala and hippocampus were changes in the amplitude, polarity, complexity of wave form and frequency of AD spikes during a single AD after seizures were well developed (Fig. 5). These effects are assumed to be due, at least in part, to a shifting of the epileptogenic focus or foci within the structure stimulated, and to other structures. Independent AD activity can clearly be evoked in structures

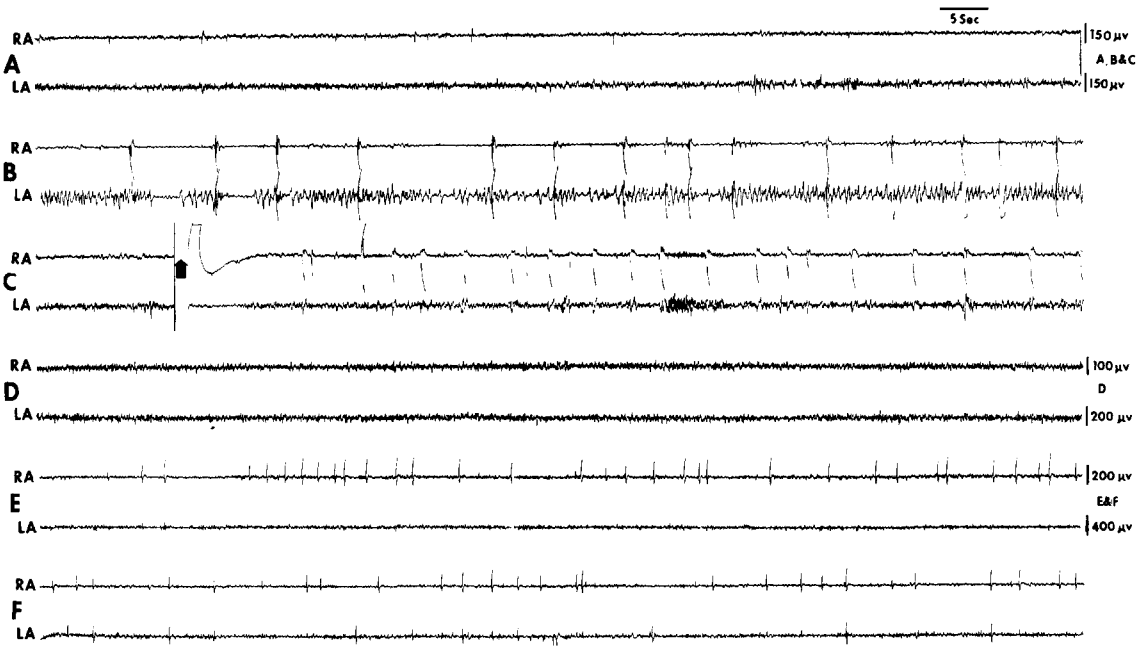


Fig. 6. Spike patterns, other than AD, in the amygdala. RA, right amygdala; LA, left amygdala. First subject: *A*: 60–170 sec after the occurrence of the 1st AD evoked by stimulation of the right amygdala. *B*: 60–170 sec after the occurrence of the 15th AD, and development of motor seizures, evoked by stimulation of the right amygdala. Note sharp spiking in both amygdalae and slower waves in left amygdala. *C*: Spiking pattern which occurs after subthreshold stimulation of the right amygdala (arrow) in subjects that have developed motor seizures. Second subject: *D*: Spontaneous activity before any ADs had been evoked. *E*: Spontaneous activity after 15 ADs had been evoked, note that spiking is still unilateral. *F*: Spontaneous activity after 32 ADs had been evoked; spiking is now bilateral and appears to be independent on both sides.

outside the area stimulated, particularly after the development of motor seizures. Many examples were found of AD activity which lasted longer in the secondary foci than in the primary focus.

The increased "driving" effect found in contralateral homologous areas resulting from repeated stimulation was also found in other structures, *i.e.*, from amygdala to hippocampus, from amygdala to septal area, and from hippocampus to amygdala.

Other electrographic developments. As can be seen from Fig. 6, *A* the amygdala AD is initially followed by a rapid return to normal activity. As stimulation progresses, however, the AD is followed by progressively longer and longer periods of isolated spiking at frequencies of 3–12/min (Fig. 6, *B*). After motor seizures develop, these spikes can persist for up to an hour or more following the AD. Large amplitude slow waves also begin to appear at this stage. Myoclonic jerks often accompany these spikes. When the subjects have sustained a number of ADs, particularly if motor seizures have developed, isolated spike activity similar to that just described often follows subthreshold stimulation (Fig. 6, *C*).

An interesting effect found in approximately 20% of the subjects that received regular suprathreshold stimulation was a spontaneous spiking pattern which occurred even in the absence of stimulation (Fig. 6, *D–F*). It is not clear whether this is due to the creation of an epileptic focus or whether the activity is somehow conditioned to the testing situation. Records were taken for up to an hour in several of these subjects, without stimulation, and there was no reduction in frequency or amplitude of the spikes. When these subjects were returned to the testing situation after a rest of several weeks, however, the spikes were absent in all but one subject.

The triggering of ADs was found to be necessary to effect any of the changes described

above. Subthreshold stimulation had no effect on the characteristics of subsequently evoked ADs.

Experiment II

Previous experiments (Racine 1972) provided no evidence for reductions in AD threshold extending beyond the area stimulated. Goddard *et al.* (1969) describe an experiment which suggests that repeated electrical stimulation in the amygdala of rats does produce changes in other brain areas. After the development of motor seizures from stimulation of the amygdala, there was a significant reduction in the number of stimulations required in the contralateral amygdala and the ipsilateral septal area for the development of a motor seizure. Unfortunately, the appropriate lesion controls were not made, so it is not possible to say whether these results demonstrate a real change in the sensitivity of the secondary structures, or whether their increased reactivity is simply a reflection of their being strongly connected to the original, now sensitized, focus.

The present experiment was designed to determine whether or not the motor seizure triggering potential, which develops in a structure as a result of electrical stimulation, transfers to other structures.

Method

Forty subjects used in a previous experiment (Racine 1972) were submitted to further testing and will again be referred to in this experiment. In addition, twenty-eight amygdala subjects and ten hippocampal subjects, with bilateral electrodes, were tested.

Amygdala to amygdala. This group consists of thirty subjects from a previous experiment (Racine 1972) in which AD thresholds were lowered (and motor seizures elicited) in the right amygdala, followed by AD threshold reduction (and motor seizure development) in the left amygdala. It was shown in Experiment I, above, that the development of motor seizures depends upon the number of ADs evoked and not on the stimulation *per se*. So for the purposes of this experiment, the number of ADs evoked by stimulation of the left amygdala, before the occurrence of a full motor seizure, is of importance. This provides a measure of the number of ADs required in the amygdaloid region of the left hemisphere to elicit motor seizure, after motor seizures had been developed by stimulation in the homologous area in the right hemisphere. All ADs were counted, including any evoked during initial threshold testing.

Amygdala to septal. This experiment is based on data obtained from five subjects implanted with electrodes in both amygdalae and in the septal area. These subjects had undergone AD threshold reduction (and development of motor seizure) in the right amygdala following which thresholds were again measured in the left amygdala and septal area (Racine 1972). These subjects were then stimulated at 200 μA in the septal area until full Class 5 seizures were evoked.

Amygdala to hippocampus. The five subjects used in this experiment were implanted with electrodes in the amygdalae and hippocampus. These subjects had undergone AD threshold reduction (and development of motor seizures) in the right amygdala, following which thresholds were remeasured in the left amygdala and hippocampus (Racine 1972). They were then stimulated at 200 μA in the hippocampus until full seizures were evoked.

Amygdala to amygdala with lesion control. Eighteen subjects, not previously cited, were used in this experiment. Electrodes were implanted bilaterally into the amygdala. All subjects were then stimulated at 200 μA in the right amygdala until full motor seizures were evoked, after which four additional daily stimulations were given. Eight subjects were stimulated at 200 μA in the left amygdala, with the right amygdala intact, until a full motor seizure was evoked. In the remaining ten subjects, a large lesion was produced in the right amygdala using 10 mA of DC current for 60 sec. These subjects were then allowed 2 weeks for post-operative recovery, after which the left amygdala was stimulated at 200 μA daily until a full motor seizure was triggered.

Pre-stimulation lesion control. In order to be certain that a lesion in one amygdala does not in itself increase the sensitivity of the contralateral structure, a group of ten subjects was

tested in which unilateral amygdaloid lesions were produced before stimulation of the contralateral structure. The first electrical stimulation these subjects received, then, was 200 μA in the contralateral structure 2 weeks after the amygdaloid lesions were produced. This was continued each day until the subjects showed Class 5 motor seizures.

Hippocampus to hippocampus. This experiment was performed on ten subjects implanted with bilateral electrodes into the posterior hippocampus. The right hippocampus was stimulated with suprathreshold stimulation (200 μA) until Class 5 motor seizures were evoked. Four additional days of stimulation were given. These subjects were then stimulated in the left hippocampus, at 200 μA, until a Class 5 motor seizure was evoked.

Results

Amygdala to amygdala. The data are summarized in Table II. Fifteen subjects had a full, Class 5, motor seizure on the first stimulation in the left amygdala, following seizure development in the right amygdala. At least one AD had already been evoked in the left amygdala

TABLE II

The first section shows the mean and range of the numbers of ADs required in the right amygdala to develop motor seizures and the number of ADs required to develop motor seizures in the left amygdala, septal area, and hippocampus after seizures had been developed in the right amygdala. Significantly fewer ADs were required in the left amygdala ($U=3$, $P<0.0005$) and in the septal area ($U=1$, $P<0.001$) but not in the hippocampus ($U=20$, $P>0.46$) when compared with control subjects.

The second section shows the mean and range of the number of ADs required in the right amygdala to develop motor seizures and the number of ADs required in the left amygdala after seizures had been developed by right amygdala stimulation (rt. amyg. intact), and the number of ADs required in the left amygdala after seizures had been developed by right amygdala stimulation followed by lesion of the right amygdala (rt. amyg. lesion). In both left amygdala groups the number of ADs to seizure differed significantly from the number of ADs to seizure in the right amygdala (amygdala intact: $U=4.5$, $P<0.002$; amygdala lesioned: $U=3$, $P<0.001$). When these two groups were compared with each other, however, no difference was found ($U=24$, $P>0.24$, two-tailed). The section labelled "Pre-stimulation control" shows the number of ADs required in the left amygdala to develop motor seizures after a lesion had been produced in, but no stimulation had been applied to, the right amygdala. When compared with control subjects, no significant difference was found ($U=40$, $P>0.46$).

The last section shows the number of ADs to seizure in the right hippocampus and the number of ADs to seizure required subsequently in the left hippocampus. The difference between the left hippocampus and the hippocampal control group is significant ($U=1.5$, $P<0.0002$). Also shown in this section are the amygdala and hippocampal control groups.

	After-discharges to seizure	
	mean	range
Amygdala to secondary foci		
Right amygdala (Primary focus) (N = 40)	12	5–23
Left amygdala (Secondary focus) (N = 30)	4	2–10
Septal area (Secondary focus) (N = 5)	4	2–6
Hippocampus (Secondary focus) (N = 5)	21	12–32
Amygdala to amygdala with lesion control		
Right amygdala (Primary focus) (N = 18)	11.8	5–19
Left amygdala (Right amygdala intact) (N = 8)	5.5	4– 7
Left amygdala (Right amygdala lesion) (N = 10)	4.6	1–10
Pre-stimulation lesion control		
Left amygdala (Right amygdala lesion) (N = 10)	13	4–27
Hippocampus to hippocampus		
Right hippocampus (Primary focus) (N = 10)	24.6	5–43
Left hippocampus (Secondary focus) (N = 10)	3	1– 8
Amygdala		
Control (N = 10)	11.8	6–15
Hippocampus		
Control (N = 10)	26.3	5–47

during the original threshold testing before seizure development in the primary focus (right amygdala). These ADs were included in the tally. The difference between the right and left amygdalae in the total number of ADs elicited before Class 5 seizures is highly significant ($P < 0.0005$).

Amygdala to septal area. The data for the five subjects in this group are summarized in Table II. These subjects were selected randomly from a larger group (20 subjects) used in a previous experiment (Racine 1972). In that experiment, AD thresholds were being examined, but during the threshold tests, data pertinent to the present experiment were collected. After lowering of AD threshold and seizure development in the amygdala, AD thresholds were tested in the septal area. Although only a few ADs were evoked in the septal area during this testing, the results provide some useful information with regard to the transfer of motor seizure. Ten of these subjects had Class 5 motor seizures during the first AD evoked in the septal area. This compares to the nine subjects of the same group that had Class 5 motor seizures during the first AD of the second threshold test of the left amygdala.

The five subjects used in the present experiment were then selected randomly to undergo further septal stimulation, and those data are summarized in Table II. The difference between the amygdala and septal area in the total number of ADs required to develop Class 5 seizures is significant ($P < 0.001$). Although the appropriate control group, *i.e.*, one which has undergone seizure development in the septal area without prior treatment in the amygdala, has not been tested, the work of Burnham (unpublished thesis) on the same strain of rats indicates that the lateral septal nucleus normally requires *more* ADs than the amygdala before Class 5 motor seizures can be evoked. The results of this experiment, then, indicate that the transfer of motor seizure effects from the amygdala to the septal area is comparable to the transfer from the amygdala to the contralateral amygdala.

Amygdala to hippocampus. The results of this experiment stand in contrast to those of the preceding one. Referring again to the previous experiment (Racine 1972) of which these subjects were a part, none of the hippocampal subjects showed any signs of seizure activity during threshold test, even though Class 5 seizures had already been generated in the right amygdala. The five subjects that had been selected for further testing showed no significant reduction in the number of ADs required to develop motor seizures when compared with ten control subjects, without prior amygdala stimulation. These results would seem to indicate that there is little or no transfer of motor seizure effects from the anterior amygdaloid region to the posterior hippocampus.

Amygdala to amygdala with lesion control. The left amygdala required significantly fewer ADs to develop motor seizures, following seizure development in the right amygdala, in both the lesioned and non-lesioned groups. There was no difference, on the other hand, between the intact and lesioned groups with respect to the number of ADs to seizure in the left amygdala. Thus, the neural changes underlying the development of motor seizures from amygdala stimulation take place outside the area stimulated, and probably outside the amygdala itself. (See Fig. 7 for illustration of the maximum and minimum extent of these lesions.)

Pre-stimulation lesion control. These subjects required the same number of ADs in the amygdala contralateral to the lesion to develop motor seizures as subjects with both amygdalae intact. These results indicate that unilateral lesions of the amygdala do not make the contralateral structure more susceptible to the development of motor seizure.

Hippocampus to hippocampus. Significantly fewer ADs were required in the left hippocampus to develop seizure than were required in the right hippocampus ($P < 0.0002$). These results compare with those of the amygdala-to-amygdala transfer described above. Two pilot subjects showed Class 5 motor seizure in the left hippocampus on the first day following seizure development and subsequent lesion of the right hippocampus. No additional controls have been tested for the hippocampus.

In all of the above experiments, the subjects were finally tested for motor seizure again in the primary focus following the initial transfer

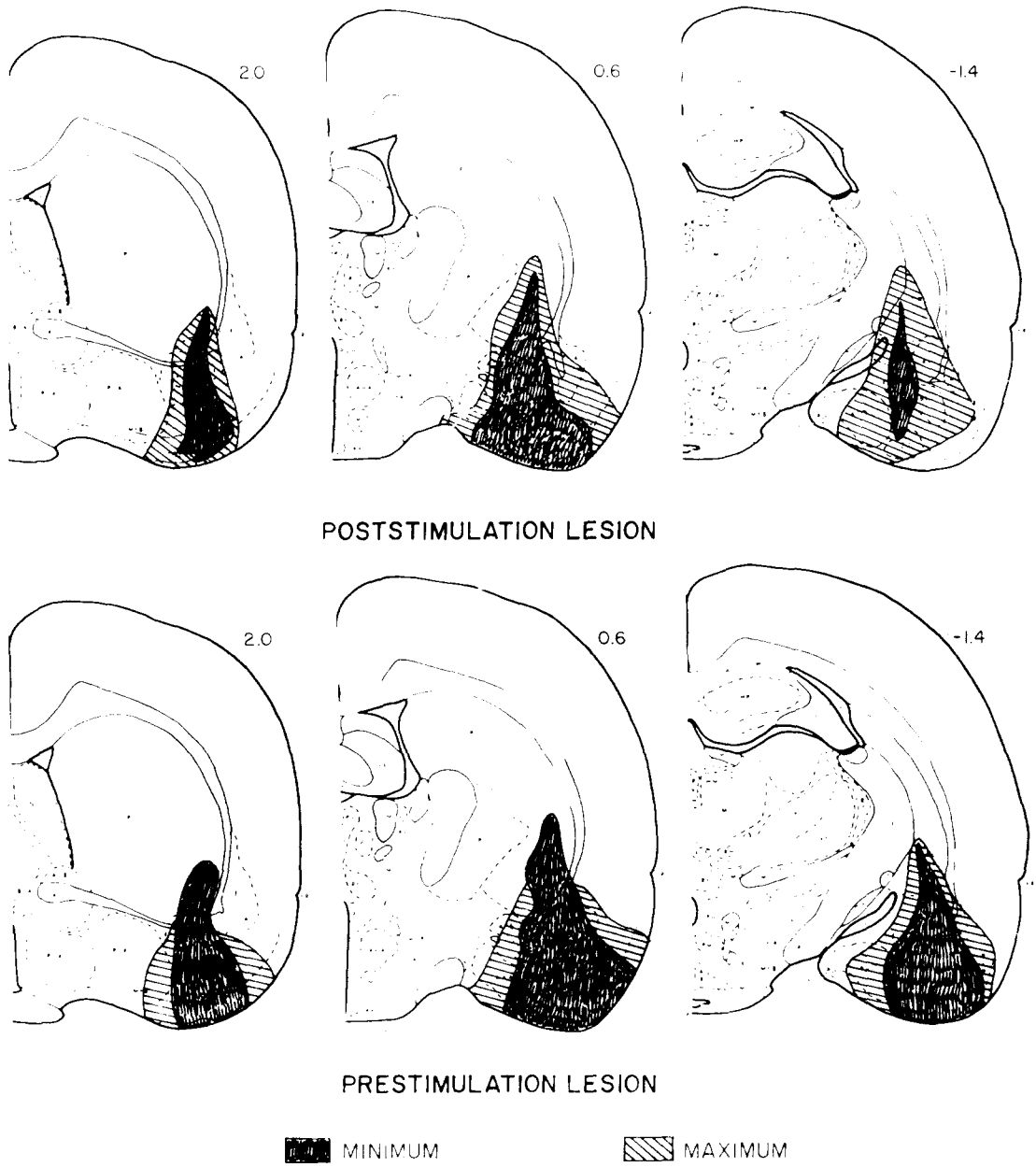


Fig. 7. Minimal and maximal extent of lesions produced in the right amygdala of the "post-stimulation" control subjects, and the "pre-stimulation" control subjects described in the text.

tests. Motor seizures were evoked in most subjects during the first AD. Goddard *et al.* (1969) on the other hand, found that a number of stimulations were required when returning to the primary focus to evoke motor seizures. They suggested that this was a demonstration of "retroactive inhibition" or competition for seizure circuits. No evidence in support of this hypothesis was found in the present study.

DISCUSSION

The experiments reported above indicate some of the relationships between electrographic seizure development and behavioral seizure development. They show, for example, that motor

seizure development requires the repetitive triggering of ADs. The mapping by Goddard *et al.* (1969) of the sensitivity of brain areas with respect to motor seizure development was based on the use of only one stimulus intensity (50 μA), and electrographic responses were not recorded. It is now clear that this would not provide the measure of "relative sensitivity" claimed by Goddard *et al.* That claim is based on the assumption that the relative disposition of different structures to the development of motor seizure triggering potential will remain the same when higher or lower current levels are used. It is not, however, the stimulation *per se* but the AD that causes the development of motor seizures, and the AD thresholds vary between structures.

Many of the permanent changes in the characteristics of subcortical ADs that are produced by repeated electrical stimulation also require the triggering of ADs; subthreshold stimulation has no effect on these characteristics. These changes in AD characteristics lead to some conclusions about the mechanisms underlying the development of motor seizures. The development of motor seizures cannot be a result of increases in duration of the AD. The duration of AD builds up to 30 sec or more within the first few days of stimulation. When the motor seizure appears, the AD has become much longer, but the convulsive activity still begins approximately 30 sec after the AD begins. When the motor seizures are well developed, latency decreases until the seizures begin *during* the stimulation with a delay of a few milliseconds. Also, some subjects developed seizures while maintaining relatively short ADs. Finally, in approximately 30% of amygdala and hippocampal subjects, "larval" discharges with short duration were occasionally evoked after motor seizures had been developed (Fig. 3). If motor seizures were well developed, convulsive responses almost always accompanied the short amygdala discharges, even though they were only a few seconds in duration. (The short hippocampal discharges appeared to be truly "larval" in the sense that they remained localized with no propagation. Convulsive activity did not usually accompany these short hippocampal discharges.)

The only electrographic event that does seem to be closely related to the development of motor seizures is the growth in amplitude of secondary foci spikes. Even when the amygdala AD duration reverts to a "larval" stage after seizure development (as described above), the amplitude of the secondary foci spikes remains much larger than during the early stages of stimulation (Fig. 3).

The data obtained from the transfer experiment (Experiment II) together with data from additional pilot studies, suggest that if more seizures are evoked in the primary structure, then fewer ADs will have to be evoked in the secondary structure to develop seizures. Initially, there is little or no propagation from the primary to the secondary structures. Eventually, however, the propagation not only increases, but independent, self-sustaining discharges appear in the secondary structure following stimulation of the primary structure. Delgado and Sevillano (1961) refer to these as "reactive" discharges.

The data so far obtained suggest that these "reactive" ADs may produce effects that are similar to those evoked directly by electrical stimulation. That is, the number of "reactive" ADs required in the secondary structure before motor seizures can be produced by direct stimulation of that structure may be the same as the number of directly evoked ADs required in a primary structure. If 12 ADs are required in the primary structure to produce a full seizure, for example, and if the last 4 of those 12 ADs produced "reactive" ADs, then only 8 stimulations would be required in the contralateral amygdala to produce seizures. If 20 ADs are produced in the primary site, then transfer would be immediate to the secondary site. The data so far obtained support this hypothesis, but exact quantitative data are difficult to collect because it is not always clear when the ADs in the secondary site become "reactive". In the pilot analyses discussed here, a mean spike amplitude in the secondary focus discharge which was at least 80% of that in the primary focus was considered to be a sign of "reactive" discharge. Work is now under way with unit recording in rats to find out when the unit discharges in the secondary focus shift from simple low frequency (driven) bursts to high frequency bursts superimposed upon large amplitude depolarization

shifts. This shift should be expected when the region becomes actively "epileptic" (Matsumoto and Ajmone Marsan 1964; Sawa *et al.* 1965; Dichter and Spencer 1969; Okujava 1969).

Whatever process caused the development of the secondary focus discharge did not seem to develop a reciprocal effect. A common observation, when testing a secondary site after seizure development in the primary site, was that the first transfer AD evoked in the secondary site showed no increased driving effects in the primary site. The AD in the secondary site may, however, evoke a fully reactive discharge on the *second* transfer trial or occasionally, after a long delay, during the first transfer trial.

The reduction of AD thresholds by electrical stimulation was reported in a previous paper (Racine 1972) and does not appear to be related to the development of motor seizures. The triggering of ADs was not necessary for the reduction of AD thresholds but was shown in this paper to be crucial for the development of motor seizures. AD threshold reduction and the development of motor seizures follow separate time courses with AD thresholds changing most rapidly during the first few days of stimulation and motor seizures developing later. There is no correlation between AD threshold change and the development of motor seizures in individual animals, *i.e.*, some subjects show little or no threshold change yet may develop motor seizures rapidly. Other subjects show rapid and extensive changes in AD threshold yet may require many ADs before the appearance of a motor seizure. Also, the AD threshold reduction is a gradual process, whereas the development of motor seizures can be a very sudden, all or none, type of phenomenon. Seizures are occasionally seen at full strength without any previous sign of convulsive behavior, and once seizure activity is evoked, it can be evoked at any current level that produces AD. Finally, AD threshold reduction is a local event, whereas the development of motor seizures involves changes that occur beyond the structure stimulated.

Racine (1972) argued against tissue damage being the cause of AD threshold reduction. It seems even more evident that tissue damage cannot account for motor seizure development.

Goddard (personal communication) found no tissue damage around the stimulated focus using both light and electron microscopy. Goddard *et al.* (1969) found that histologically undetectable lesions produced by a brief low-intensity direct current results in a very large increase in the stimulation current required to develop motor seizures but no change in the number of days of stimulation required. Platinum, nichrome, stainless steel and constantin electrodes and local injections of carbachol all produce seizure development at a similar rate, indicating that metallic ion deposits cannot be responsible.

The transfer data also support the conclusion that motor seizure development is not a result of tissue damage by showing that changes occur outside of the area of stimulation.

SUMMARY

Daily electrical stimulations of the amygdala and hippocampus at intensities sufficient to evoke after-discharges (ADs) resulted in the development of motor seizures, which could not initially be evoked by these stimulations. The triggering of ADs was critical for this development, as well as for the development of permanent changes in the characteristics of the AD. The wave form of the AD "spikes" became more complex. The frequency of these spikes and the duration of AD increased. The amplitude of the AD spikes increased in the structure stimulated as well as in secondary structures to which the AD was "projected". This increase in amplitude of "projected" spikes often correlated with the appearance of motor seizures. Other electrographic developments are discussed including the appearance of spontaneous "inter-ictal" spiking in the amygdala. It was found that the development of motor seizures by stimulation of the amygdala resulted in an increased ability of the contralateral amygdala, and the septal area, but not of the hippocampus, to drive motor seizures when stimulated ("transfer"). Motor seizure development in the hippocampus transferred to the contralateral hippocampus. These developments were shown, by means of control subjects, with lesions in the primary focus to involve changes outside the primary focus.

The implications of these developments with respect to seizure development are discussed.

RESUME

MODIFICATION DE L'ACTIVITE CRITIQUE PAR STIMULATION ELECTRIQUE: II. CRISE MOTRICE

Des stimulations électriques quotidiennes de l'amygdale et de l'hippocampe à des intensités suffisantes pour provoquer des post-décharges aboutissent à l'apparition de crises motrices qui ne pouvaient pas être provoquées initialement par ces stimulations. Le déclenchement des post-décharges est déterminant pour ce développement, de même que pour le développement de modifications permanentes des caractéristiques de la post-décharge. La morphologie des pointes des post-décharges devient plus complexe. La fréquence de ces pointes et la durée de la post-décharge augmentent. L'amplitude des pointes de post-décharges augmente dans la structure stimulée, de même que dans des structures secondaires auxquelles les post-décharges sont "projetées". Cette augmentation d'amplitude des pointes "projetées" correspond souvent à l'apparition des crises motrices. D'autres conséquences électrographiques comportant l'apparition de pointes spontanées "inter-critiques" dans l'amygdale sont discutées. L'auteur observe que le développement des crises motrices par stimulation de l'amygdale provoque une augmentation de la capacité de l'amygdale controlatérale, de l'aire septale, mais non de l'hippocampe d'entraîner des crises motrices lorsqu'elles sont stimulées ("transfert"). Le développement de crises motrices dans l'hippocampe se transfère à l'hippocampe controlatéral. Au moyen d'animaux de contrôle porteurs de lésions dans le foyer primaire il est possible de voir que ces développements impliquent l'existence de modifications en dehors de ce foyer primaire.

L'auteur discute les implications de ces modifications par rapport à la genèse des crises.

I wish to thank Dr. Peter Milner for his interest and support during the course of this research.

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