DISSOCIATION OF SELF-STIMULATION AND EPILEPTIFORM ACTIVITY[1]

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INTRODUCTION

The main focus of the self-stimulation phenomenon, as indicated by maximum rates for minimum stimulus levels and by lesion studies, lies in an olfactory midbrain pathway through septal area, lateral hypothalamus and ventrolateral tegmentum; over most of its course this pathway is called the medial forebrain bundle. The studies which indicated this "focus" also showed a gradient of self-stimulation along its course; the ordering of its subdivisions in terms of the rate and regularity of the self-stimulation behavior produced by stimulating them was (1) ventrolateral tegmentum which headed the list, (2) posterior lateral hypothalamus, (3) anterior lateral hypothalamus, and (4) septal area (Olds *et al.* 1960; Olds and Olds 1963; Olds and Olds 1964). These studies utilized rat, but the same regions were salient in studies with cat (Wilkinson and Peele 1963) and monkey (Bursten and Delgado 1958; Briese and Olds 1964). Minor areas of self-stimulation were found in parts of rhinencephalon and thalamus (Olds 1956).

Because of the suggestion that rhinencephalic and thalamic self-stimulation might be correlated with epileptiform activity (Porter *et al.* 1959; Newman and Feldman 1964), it seemed reasonable to find whether self-stimulation in the main focus would produce epileptiform activity and whether a correlation in threshold or intensity could be observed between after-discharges or seizures and self-stimulation. The present study was designed to answer these questions and to find whether self-stimulation activity might be itself part of a seizure, or whether after-discharges might be required as a part of the incentive for self-stimulation behavior, or alternatively, whether self-stimulation might be antagonized by some forms of after-discharge.

METHODS

Experiments were carried out on 10 male albino rats, each weighing about 350 g.

Nine 250 μ diameter stainless steel wires were chronically implanted in each rat. One probe was uninsulated and grounded, eight were enameled, with only the cross section of the tip uninsulated. These were aimed stereotaxically to lodge the exposed tip in (*1*) ventrolateral tegmentum (VLT) at stereotaxic coordinates −7/1/8, (*2*) posterior lateral hypothalamus (PLH) at −5/1.5/8, (*3*) anterior lateral hypothalamus (ALH) at 0/2/8, (*4*) septal area (S) at +2/1/5, (*5*) posterior lateral thalamus (PLTh) at −4.5/3/5, (*6*) epithalamus (ETh) at −3/0.5/5, (*7*) tectotegmental area (TT) at −8/1/5, and (*8*) visual cortex (VC) at −6/2/2. The three figures (coordinates) represent distances in mm from the primary skull marking bregma in the frontal, lateral, and horizontal directions respectively. In the frontal direction, plus numbers are anterior and minus numbers posterior in relation to the reference point bregma.

Electrical circuits and procedure

From the eight insulated electrodes, six were chosen for recording in a given experiment and one of these was also chosen for stimulation. The procedure and stimulus parameters are explained in the legend of Fig. 1.

The recording apparatus was a 6-channel

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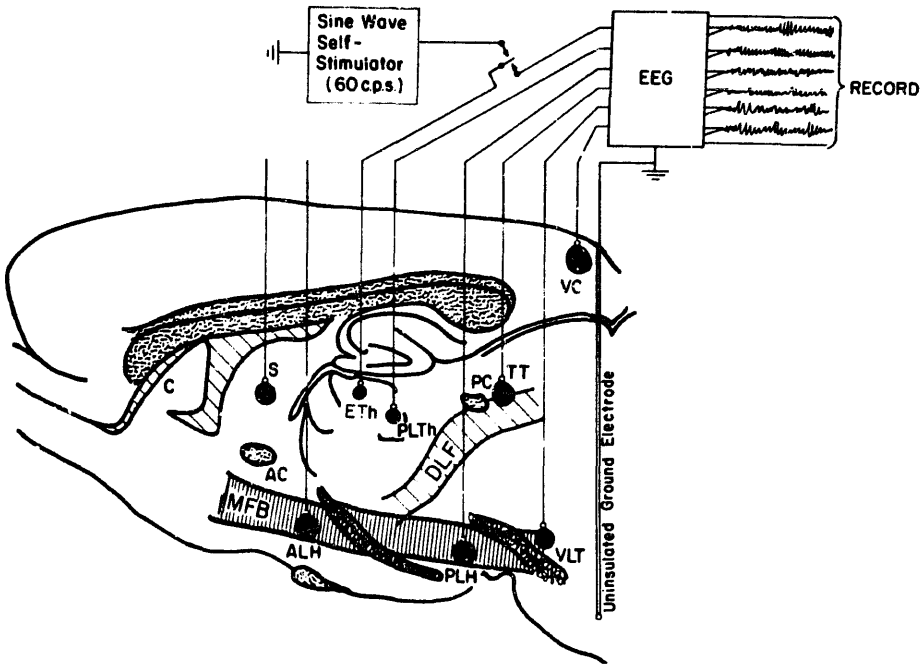


Fig. 1

Preparation and electric circuits. Electrodes were aimed at: (VLT) ventrolateral tegmentum; (PLH) posterior lateral hypothalamus, (ALH) anterior lateral hypothalamus, (S) septal region, (ETh) epithalamus, (PLTh) posterior lateral thalamus, (TT) tectotegmental boundary, and (VC) visual cortex. Also, a large uninsulated ground electrode was placed in the brain. Circuits were arranged so that any combination of six electrodes could be used to record from simultaneously and one of these six could also be chosen for self-stimulation. In self-stimulation, the animal's response caused a relay system to disconnect the self-stimulation electrode momentarily from the recording circuit, connect it to the stimulator, deliver the stimulus train, and return it to the start position. Stimulation and recording were monopolar. A sine wave stimulus of 60 c/sec was used; maximum train duration was 1/4 sec although this was shortened if the pedal depression was briefer. Currents ranged from 5 to 140 μA rms. Abbreviations not mentioned above are: AC = anterior commissure, C = caudate, DLF = dorsal longitudinal fasciculus, MFB = medial forebrain bundle, PC = posterior commissure.

type D Offner EEG machine. Because both stimulation and recordings were made through the same large indifferent electrode, considerable blocking occurred (2 sec locally and 1 sec for the other electrodes). Thus statements relating to after-discharges must be considered within these limitations.

In the tests for self-stimulation there were alternating periods of forced and free responding up to a total of 200 pedal responses, each response triggered a 1/4 sec stimulus train. Ten pedal responses at 1/sec were forced before each free response period. Free response periods were terminated whenever 40 sec elapsed without a response. Pre-tests showed that free responding either quickly rose to a level above 20 responses/min or it soon came to a stop altogether. Therefore a rate of 20 responses/min was taken as evidence for self-stimulation. On the other hand when 200 responses had occurred and free responding came to a stop, this was taken as evidence of failure.

Recording tests were divided into two types depending on whether self-stimulation (SS) developed with a given stimulus. If SS developed then a 60 response sequence was arranged as follows: (1) 10 SS responses, (2) 10 free but unreinforced (U) responses, (3) 10 SS responses, (4) 10 U responses, (5) 10 SS responses, (6) 10 U responses. EEG recordings were made during the U intervals commencing immediately after the blocking from SS intervals had ceased and lasting for periods of from 8 to 20 sec depending on the rate of responding. If SS failed to develop with a given stimulus then a similar sequence was arranged as follows: (1) 10 forced stimula-

tions (FS), (2) 12 sec, (3) 10 FS, (4) 12 sec, (5) 10 FS, (6) 12 sec. EEG recordings were made during the 12 sec intervals commencing immediately after blocking from FS had ceased.

The self-stimulation and recording tests were made repeatedly at successively higher current levels. The current was advanced from 0 to 140 μA (at 5 μA steps up to 50 and at 10 μA steps thereafter). Tests were made in all subjects with stimulation via VLT, PLH, ALH and S probes. In several animals tests were also made with stimulation via PLTh and/or ETh probes (see Table I).

RESULTS

The histological findings

The ventrolateral tegmental probes fell mainly in an area above and lateral to the interpeduncular nucleus and above the pyramidal tract (Fig. 2, *D*). They were often in a position to stimulate the mammillary peduncle and other nearby structures. The posterior lateral hypothalamic probes were placed in dorsolateral hypothalamus at a point which was often above the medial forebrain bundle and anterior to the mammilliary bodies (Fig. 2, *C*). The pr[illegible]

TABLE I

Threshold values (in μA RMS)

The absence of columns for AD and/or SP means that these forms of epileptiform activity could not be induced in the corresponding structure.
VLT: ventrolat. tegmentum; PLH: post. lat. hypothalamus; ALH: ant. lat. hypothalamus; S: septal area; PLTh: post. lat. thalamus; ETh: epithalamic area; SS: self-stimulation thresholds; SP: "spike" thresholds; AD: after-discharge thresholds.

Animal number	VLT	PLH			ALH		S		PLTh			ETh		
	SS	SS	SP	AD	SS	AD	SS	AD	SS	SP	AD	SS	SP	AD
9144	20	20	30	65	20	40+	20	45+	15	60*	—	25	—	35+
9145	--	15	35	65	15	80+	—	70*	—	25*	100*	—	60*	—
9146	15	—	45*	60*	15	70+	—	25*				20	70?	70?
9147	25	--	20*	25*	15	80+	15	45+				20	55	60+
9148	20	10	30	50	20	60+	20	—	20	25	30*	15	—	45*
9149	10	15	30*	50*	22	50?	35					—	60*	80*
9150	—	—	45*	50*	—	35*	—	10*	—	15*	30*			
9151	20	10	20	80	20	80*	—	—	—	40*	100*			
9152	15	5	20	—	20	30*	15	—	25	—	40*			
9143	25	15	100	—	—	45*	25	35+						

* No SS at this current level
\+ SS stopped by seizure
— Threshold not reached
Blank = No test
? Not clear whether SS stopped by seizure

Timetable and retest

The experiments were begun approximately 17 days after surgery and required about 2 weeks. To check the possible influence of the time factor a special retest similar to the series described above was made with some animals on the 60th day after surgery; this followed a period of about 4 weeks with no stimulation of any kind.

spoken of as anterior lateral hypothalamic occupied an area between the lateral preoptic and the anterior amygdaloid area, often affecting the anterior part of the medial forebrain bundle (Fig. 2, *B*). The so-called septal probes occupied a paraolfactory area in front of the septal area on a boundary between subcallosal cortex and the medial part of the head of caudate nucleus (Fig. 2, *A*). The epithalamic probe was often in

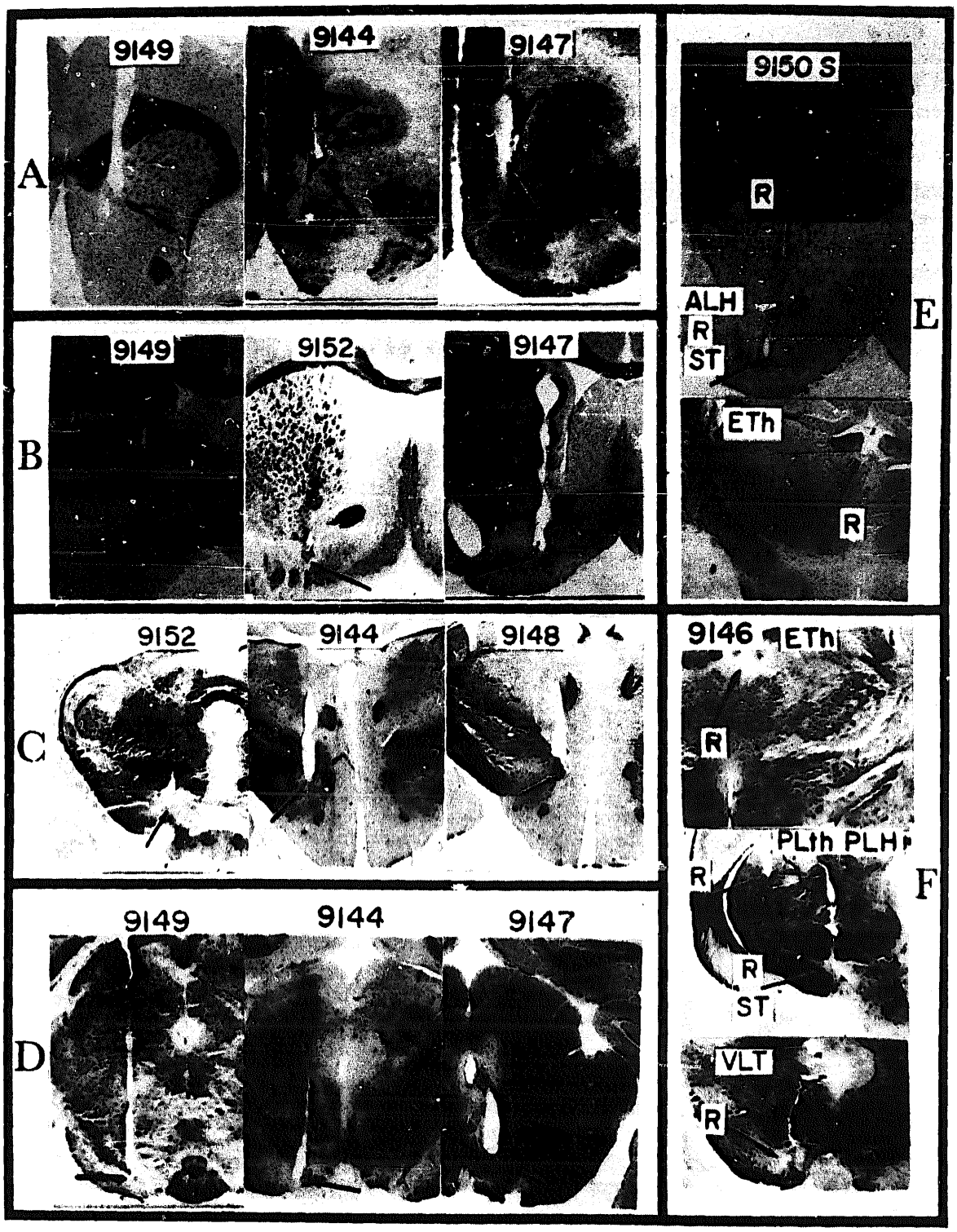


Fig. 2

Histological sections showing lower extremity of electrode tracks with probes aimed at: *A*: Septal area (lodged in the anterior paraolfactory area). *B*: ALH (lodged in lateral preoptic area and medial forebrain bundle). *C*: PLH (posterior lateral hypothalamus). *D*: VLT (ventrolateral tegmentum). *E*: Three tracks from 9150 showing points to which discharges spread after ALH stimulation (see Fig. 5, *G*). *F*: Four tracks from 9146 showing points to which spikes spread after PLH stimulation (see Fig. 5, *A*).

one of the habenular nuclei or nearby in the centrum medianum (Fig. 2, *E, F*). The tectotegmental probe was usually in the central gray just below and slightly lateral to the posterior commissure. The visual cortex probe was regularly in the occipital cortex.

Self-stimulation behavior

This was observed with stimulation via eight of ten VLT electrodes, seven of ten PLH electrodes, eigth of ten ALH electrodes, six of ten S electrodes, four of six ETh electrodes, and three of six PLTh electrodes (Table I). Irrespective of the stimulus location, there was no observation of epileptiform activity during self-stimulation tests at threshold levels (Fig. 3 *A, D*; 4, *A, C*).

Random spikes, after-discharges and seizures

VLT stimulation, even at the highest intensities, did not produce any spikes, after-discharges, or seizures (Fig. 3, *B, C*). PLH stimulation (with relatively high current), however, did produce random, local or generalized spikes without seizures in all ten cases (Fig. 3, *F*). ALH stimulation at similar strength levels produced rhythmic, local or generalized after-discharges in all cases and often these were accompanied by generalized motor seizures (Fig. 4, *B*). In six of ten cases, S (*i.e.*, subcallosal-caudate) stimulation of moderate intensity produced rhythmic, local or generalized after-discharges (Fig. 4 *D, E*), often accompanied by seizures. ETh stimulation of moderate strength caused either random, local spikes or rhythmic, local or generalized after-discharges and generalized seizures. PLTh stimulation produced random local spikes in five of six cases and generalized after-discharges accompanied by motor seizures in the other case. For all brain areas, epileptiform activity was produced equally by probes through which stimulation did or did not produce self-stimulation (Table I).

Random or rhythmic spikes, when they appeared during stimulation of PLH and PLTh, did not ordinarily cause self-stimulation behavior to cease. Rhythmic after-discharges, when they appeared during stimulation of the ALH, S, and ETh did cause self-stimulation to cease.

Thresholds of self-stimulation and epileptiform activity

For all the probes that clearly caused self-stimulation by our criterion, regardless of their placement, the thresholds for self-stimulation were below after-discharge thresholds. This was true for eight of ten VLT probes, seven of ten PLH probes, eight of ten ALH probes, six of ten S probes, four of six ETh probes and three of six PLTh probes. This is about seven cases out of every ten tested. Thus even if some of the so-called non-self-stimulation sites involved areas where thresholds for seizure were below self-stimulation thresholds, this would still hold for fewer than three cases out of ten. The various threshold values are shown in Table I.

Modifications of electrical after-discharge thresholds over time

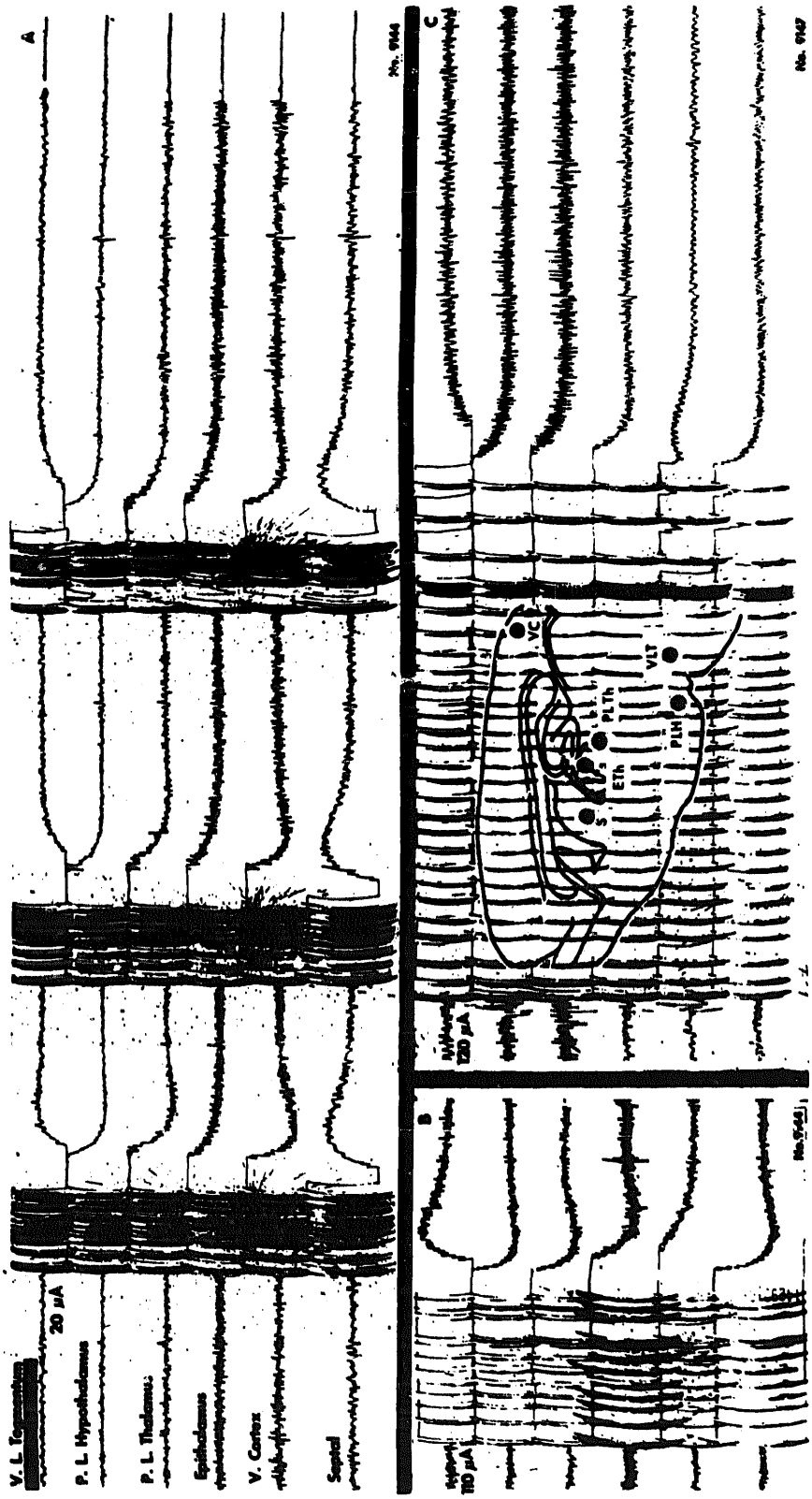
The experiments were performed between the 17th and the 35th day after implantation of brain probes and retests were made, in 6 rats, on the 60th day after implantation. Modifications in self-stimulation and after-discharge thresholds became readily apparent. During retest it was still impossible to generate abnormal electrical activity by stimulating the VLT probes; the PLH probes still had self-stimulation thresholds which were below the thresholds for experimental epileptiform activity. However, with probes at points in ALH and S, seizure thresholds had declined to such an extent that self-stimulation thresholds were often at or above seizure thresholds; and self-stimulation behavior seemed to be more likely to commence at very low current levels if the electrical stimulus caused some after-discharges.

Patterns of spread of electrical after-discharges

These patterns were the same whether the stimulation or recording probes were in "self-stimulation" or "non-self-stimulation" subdivisions of a gross anatomical region.

The isolated spikes induced by PLH tended to propagate to ventrolateral and dorsomedial tegmentum and to the epithalamic region; they were not propagated to anterior lateral hypothalamus or to septal region (Fig. 3, *F*; 5, *A, B*). Ordinarily, the spikes appeared first and largest in amplitude at the stimulated PLH probes.

The ALH or S stimulation provoked rhythmic after-discharges with largest amplitude at the stimulated electrodes. The ALH after-discharges


A
C
B
20 μA
V. L. Tegmentum
P. L. Hypothalamus
P. L. Thalamus
Epithalamus
V. Cortex
Septal
VC
VLT
PL Th
PLH
ETh
S
120 μA

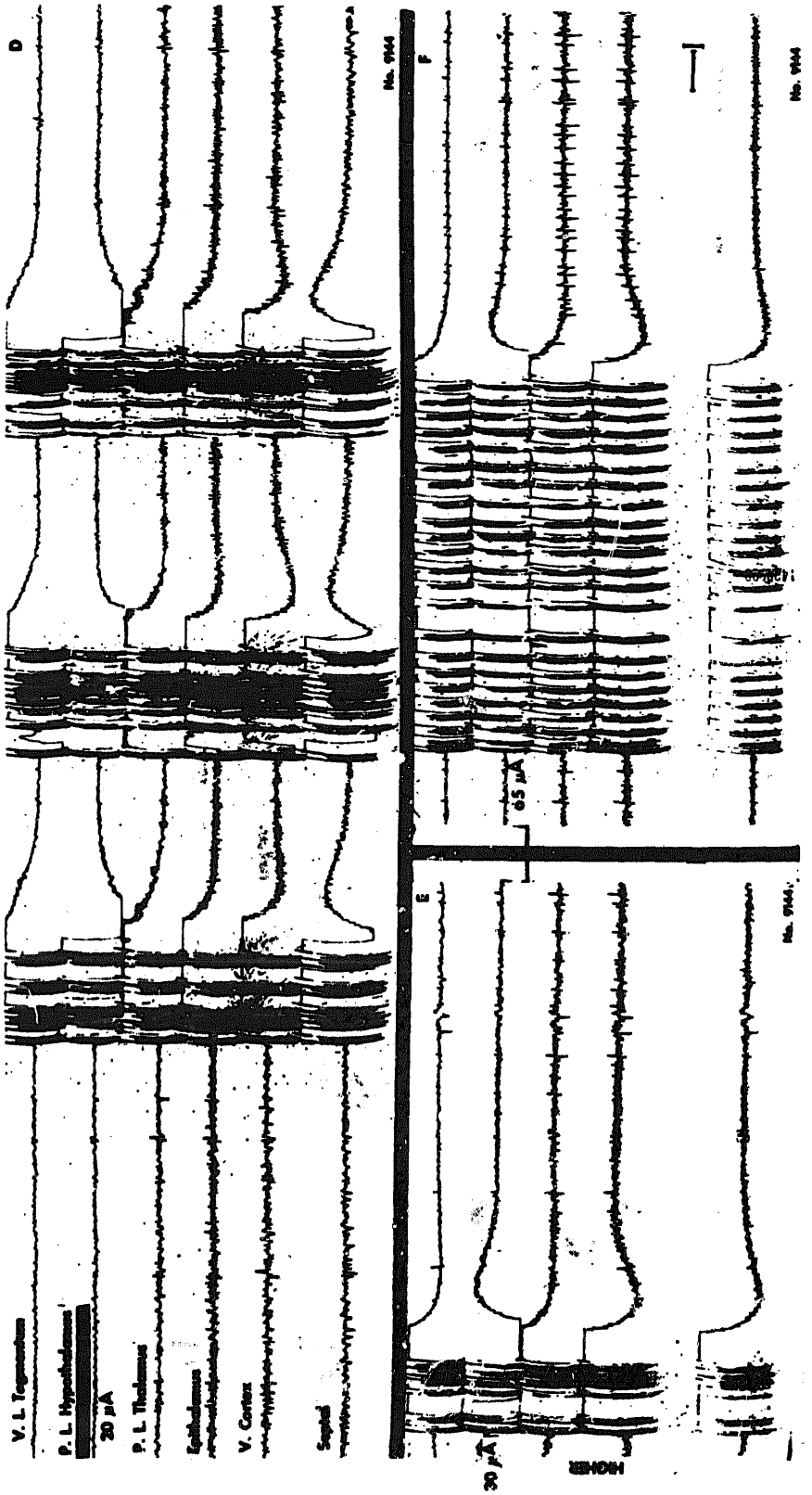
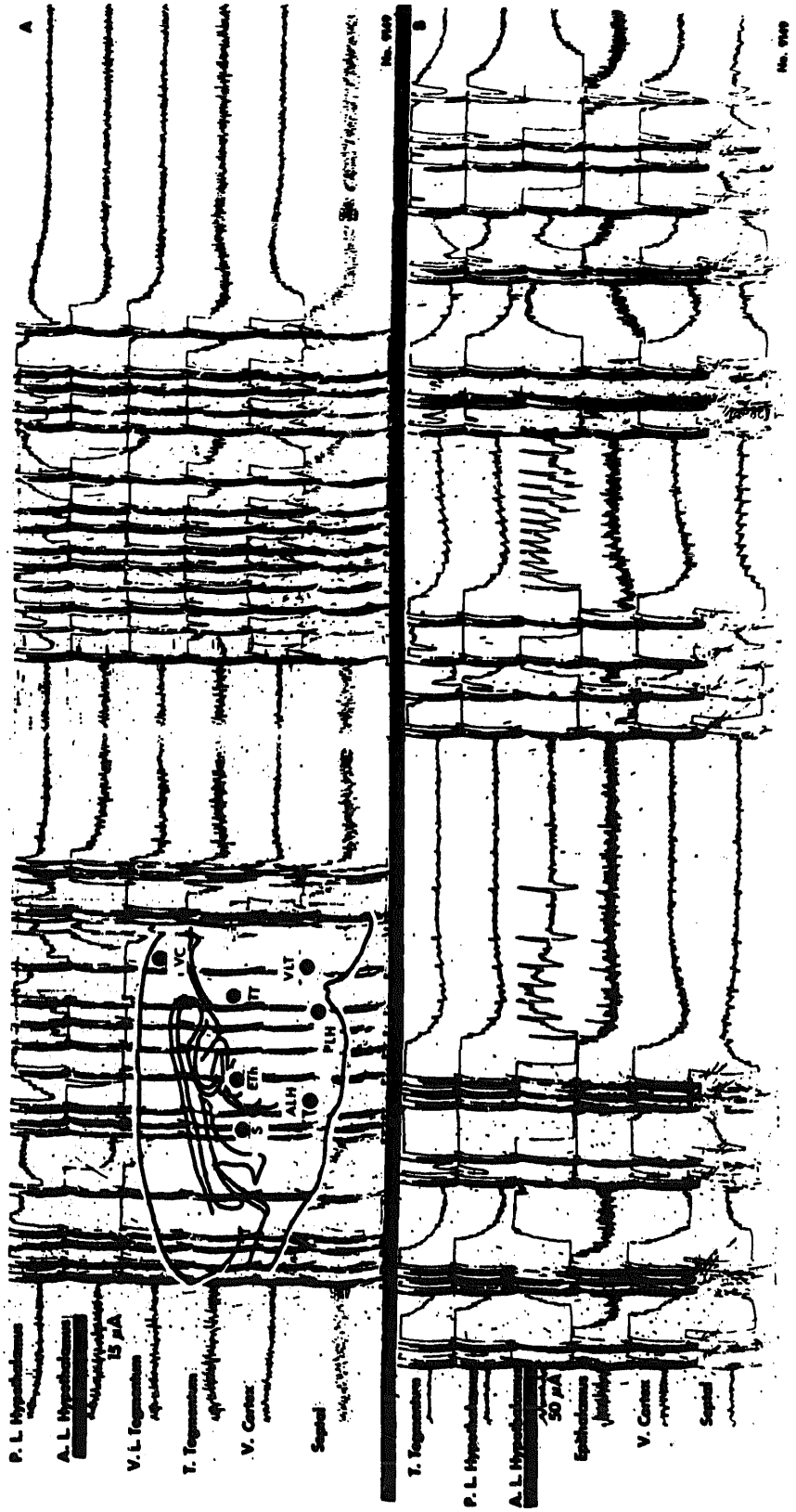


Fig. 3 (see part on preceding page)

Subcortical and cortical recordings during: *A–C*: VLT self-stimulation at successively higher current levels; *D–F*: PLH self-stimulation at the indicated current levels. All records except *C* were from the same animal (9144). In all cases, pedal responding at rates higher than 0.5 sec continued for the first 5 sec after cessation of the stimulus artifact. Calibrations in this and Fig. 4 and 5: 2 sec and 100 μV. In each group of stimulations there are at least ten trains (less than 250 msec each, see artifacts). Unmarked tracings match their predecessors except that the V. cortex tracing is missing in *E* and *F*.


A
B
No. 940
No. 940
VC
VLT
E
PLH
Eth
ALH
TO
S
15 μA
50 μA
P. L. Hypothalamus
A. L. Hypothalamus
V. L. Tegmentum
T. Tegmentum
V. Cortex
Septal
Epithalamus

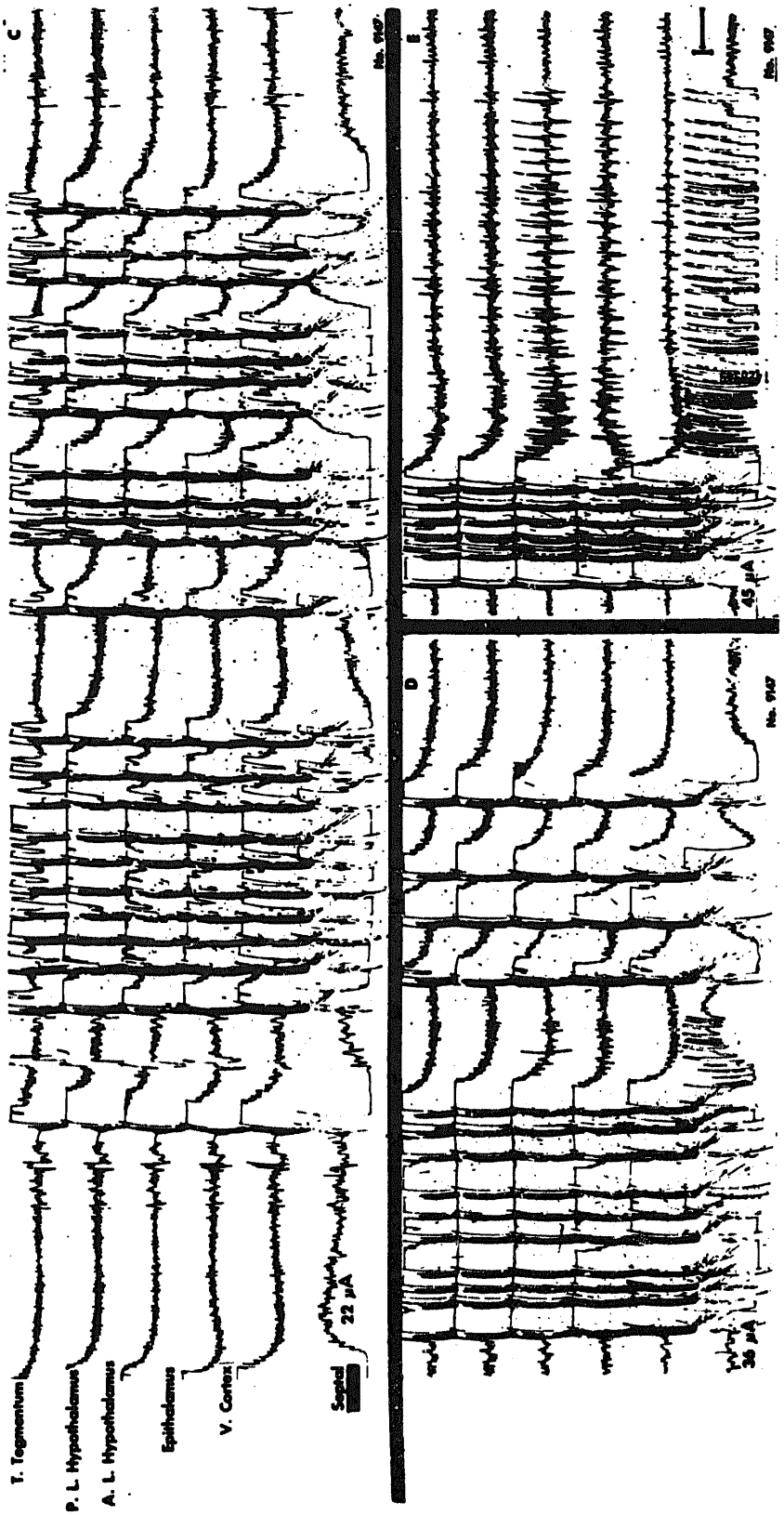


Fig. 4 (see part on preceding page)
Same as Fig. 3 except that *A–B* = ALH self-stimulation (animal 9149), *C–E* = S self-stimulation (animal 9147).

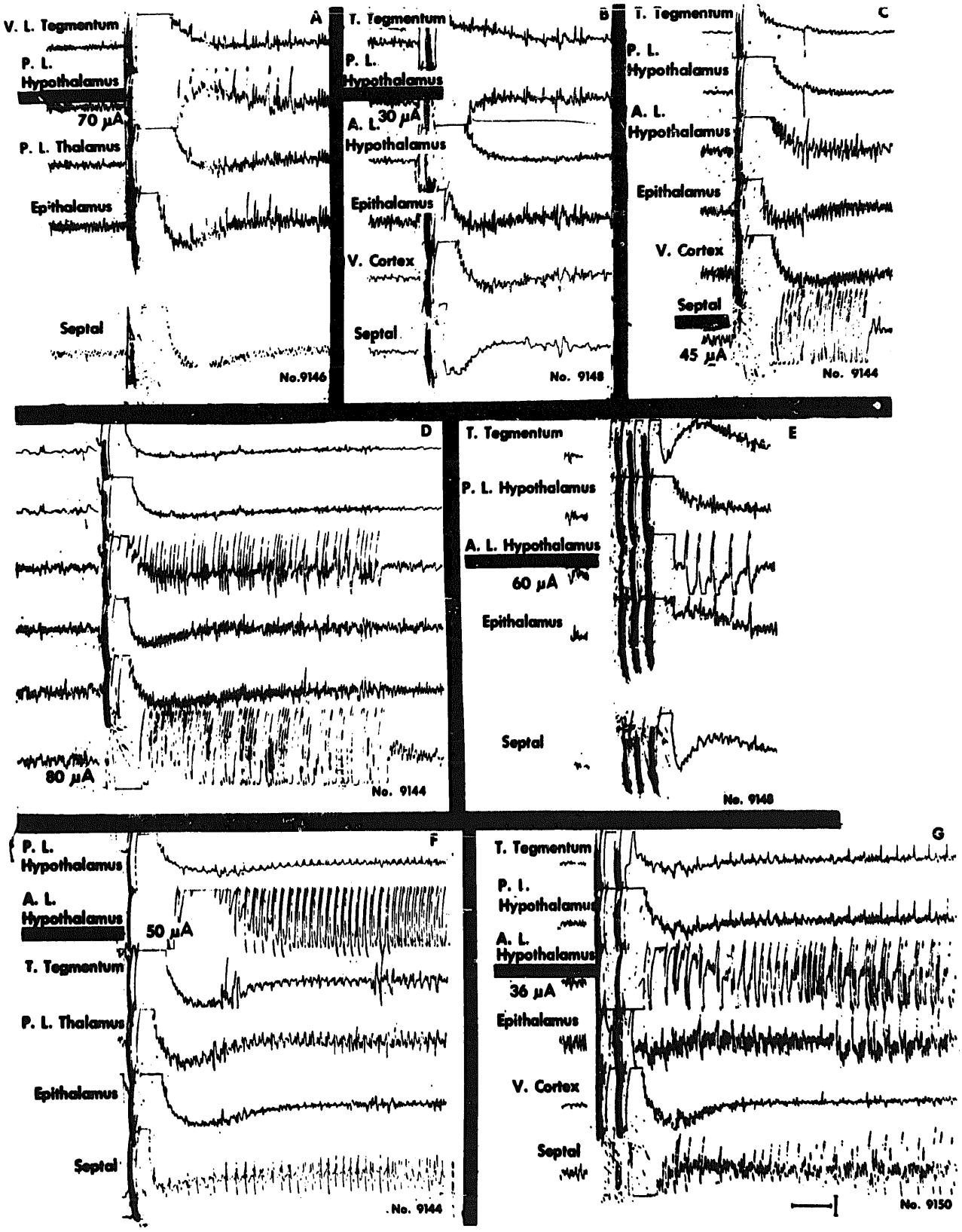


Fig. 5

Epileptiform activity provoked by: *A–B*: PLH stimulation; *C–D*: S stimulation; *E–G*: ALH stimulation. Histological correlates for *A* and *G* are portrayed in Fig. 2, *F* and *E* respectively.

spread to the septal and epithalamic regions. The S after-discharges spread to ALH or to the epithalamic regions and, often, simultaneously to both (Fig. 4, 5).

The ETh stimulation provoked a more complex pattern. The after-discharges spread either to S and ALH probes or to the posterior group of electrodes (*i.e.*, VLT, TT, PLH). In these cases, the pattern of the after-discharge was similar to one of the two patterns described. When the after-discharges were generalized, both groups of electrodes appeared to be involved.

When the PLTh was stimulated, only random or rhythmic local spikes were usually observed.

Changes in background activity

Ordinarily, the series of stimulus trains delivered during a period of self-stimulation behavior did not alter the background EEG to an extent which could be determined by visual analysis. However, with local stimulation the epithalamic and thalamic 8–10/sec activity showed an amplitude increase and a tendency toward improved regularization.

DISCUSSION

No significant relation could be demonstrated between self-stimulation and epileptiform activity, at least judging from the threshold values for the latter or from its duration and generalization which did not seem to be enhanced when induced in optimal sites for self-stimulation.

It was also quite clear that mapping with respect to epileptiform activity yielded quite a different picture from that of self-stimulation, as epileptiform activity was minimal when probes in the midbrain were stimulated and maximal with probes nearer to the cortex.

The effects of epileptiform activity upon self-stimulation were related to both the form and origin of the discharges. The relatively unrhythmical discharges produced by stimulation of PLH and PLTh points usually failed to become generalized even after they were propagated to other caudal structures. They were not accompanied by seizures, and they usually failed to interrupt self-stimulation. The rhythmical discharges which were produced by ALH or S probes caused immediate cessation of self-stimulation behavior, regardless of whether they were localized or generalized. Behavior usually was resumed shortly after the end of these discharges.

The ventrolateral tegmentum would appear to be refractory to epileptiform activity since its stimulation from zero to the threshold of self-stimulation and up to a level 10 or 20 times such threshold yielded negative results.

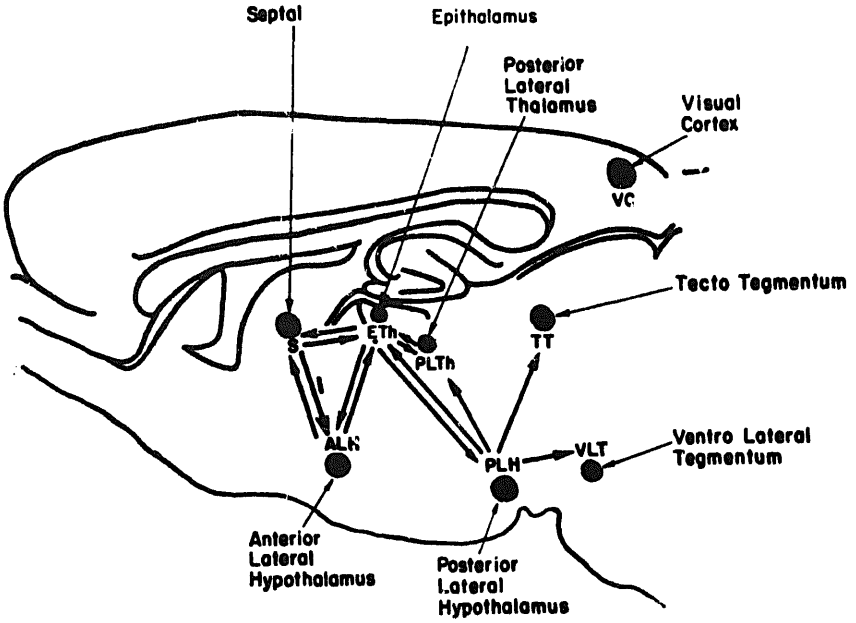


Fig. 6
Patterns of propagation of epileptiform activity.

The patterns of the spread of after-discharges differed according to the stimulation points and are summarized in Fig. 6. The specific spread between anterior lateral hypothalamus and septal area suggests that the septal component of the medial forebrain bundle (Ariëns Kappers *et al.* 1936) is possibly most important at the level of the ALH. The spread to epithalamus must follow the stria medularis which connects this habenular region to both septal area and ALH. Owing to the general dissociation of after-discharges and self-stimulation, it was difficult to guess whether the functional relation indicated by the spread of the after-discharges played any role in the mechanisms of self-stimulation. Furthermore, it should be noted that the patterns of after-discharge spread were not determined by the involvement of the probe in the reinforcement process.

It was difficult to understand why with time seizure thresholds declined to a greater extent than self-stimulation thresholds. It is possible that the decline in seizure thresholds derives from a failure of negative feedback rather than from a decline in the threshold of excitability. If this were so, then a single stimulus would have resulted in a relatively more enduring train of discharges. If some of the cells involved were those that mediated septal self-stimulation, then this longer duration of the train, by itself, would explain both the decline in self-stimulation thresholds and the association of self-stimulation with after-discharges which sometimes appeared in the 60th day retests.

The facts reported here were compatible with those reported by Porter *et al.* (1959) and by Newman and Feldman (1964). However, since our study suggests that after-discharges were not necessary to self-stimulation, it would also indirectly support the conclusions of Reid *et al.* (1964), who based them on the finding that anti-epileptic drugs augmented the rate of self-stimulation behavior.

SUMMARY

1. Ventrolateral tegmental stimulation caused self-stimulation behavior at very high rates but no epileptiform discharges even with much higher current levels.

2. Posterior lateral hypothalamic stimulation caused self-stimulation and (at higher current levels) random spikes which were unrelated to self-stimulation; that is, (a) they did not stop self-stimulation and (b) they appeared even in cases where self-stimulation did not.

3. Anterior lateral hypothalamic stimulation and septal region stimulation caused self-stimulation and (at higher intensity levels) organized epileptiform after-discharges which usually caused self-stimulation behavior to cease for a period during, and a few seconds after the abnormal electrical discharges.

4. Epithalamic and posterior lateral thalamic stimulation sometimes caused self-stimulation; stimulation of these areas also often caused one or the other of the epileptiform patterns described above.

5. For all probes clearly yielding both effects, thresholds for self-stimulation were lower than those for epileptiform discharges during the period of initial tests. However, at a later date (about two months after surgery) epileptiform thresholds were below self-stimulation thresholds in some cases with probes in the anterior lateral hypothalamus or septal area.

6. The random spikes provoked by stimulation in the posterior lateral hypothalamus spread preferentially to tegmental and thalamic probes and much less, if at all, to septal or anterior lateral hypothalamic probes. The organized discharges provoked by stimulation of anterior lateral hypothalamus, septal area, and epithalamus spread preferentially to other members of this triadic group.

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