

CHAPTER 21

Limbic System

KARL H. PRIBRAM

THE YEARS SINCE THE PUBLICATION of the now classical paper by Delgado and Livingston (1948) on the effects of orbital cortex stimulation have seen prodigious effort in this area of research. Outstanding are Kaada's monograph (1951); the theoretical challenges of Kubie (1948), Yakovlev (1948), and MacLean (1949); the amplification of our electrophysiological knowledge by Jasper (1949) and Gastaut (1952); the application to man of laboratory findings by Spiegel and Wycis (1949), Pool and Ransohoff (1949), Penfield (1952a), and Henry *et al.* (1950); and a synthesis by Fulton (1951) of these research endeavors. I shall review some of these experiments in an attempt to relate them to our increasing understanding of the organization of the central nervous system and to indicate some of the new areas of investigation that show promise.

My thesis is this: Significant advances in the study of the organization of the central nervous system during the past decade have been made by *vertical analysis*—that is, analysis “from inside out.” For example, Magoun and Lindsley's group (Moruzzi and Magoun, 1949; Lindsley *et al.*, 1950; Magoun, 1954) have centered their analysis on the differences in function between medial and lateral *mesencephalic* mechanisms; the group surrounding Jasper and Penfield (Jasper, 1949; Penfield and Jasper, 1954; Jasper, 1954), continuing the work initiated by Forbes (Forbes and Morison, 1939) and by the Morisons and Dempsey (Dempsey *et al.*, 1941; Dempsey and Morison, 1943; Morison and Dempsey, 1942), have centered on such differences at the *diencephalic* level; while the group surrounding Fulton (Livingston *et al.*, 1948a, b; Fulton, 1951) have studied the differences between the mediobasal “limbic” and the lateral *telencephalic* structures.

Though it is premature to attempt to systematize

in detail the results of this vertical analysis, one principle of organization has emerged beyond doubt: A gradient in function exists from the most lateral portions of the cerebrum and brain stem inward toward the ependymal lining of the central canal. This functional gradient is expressed, at any one moment in time, as the complexity of patterned neuronal activity within any one system. The nearer to the ependymal lining a system is located, the less complex are such patterns. That is, in these central systems the durational characteristics of neuronal activity predominate. My question therefore is, Do the neurophysiological correlates of limbic system stimulation support the concept that in the telencephalon, as in the diencephalon and mesencephalon, the organization of the mediobasal mechanisms is such that durational rather than complexly patterned momentary neural events dominate function?

I believe they do. Specifically, both in the afferent and the efferent connections of the limbic systems discrete topological correspondence between periphery and limbic structures is minimal. When the connections of these areas are served by long and relatively discretely organized tracts, the tracts are arranged in parallel in such a way that any two points are interconnected by two or more routes, each of which delays the signal to a slightly different extent. Thus the cumulative effect of temporal summation results in a flexibility of excitatory state rather than in an all-or-none type of discharge in the locations of convergence of the system. These locations, outside the telencephalon, are primarily the medial diencephalic and mesencephalic structures, which are characterized by diffusely organized short fiber systems containing a multitude of fine fibers and synapses—structures in which electrotonic, dendritic, and synaptic potentials, and

TABLE 6

SUMMARY SYSTEMATIZATION OF LIMBIC STRUCTURES

System	Definition	Morphological Formations Included
First: Rhinal	Direct connections with olfactory bulb	Olfactory tubercle; area of diagonal band; prepyriform cortex; corticomедial nuclei of the amygdaloid complex
Second: Paleol	Direct connections with first system but none with bulb	Subcallosal and frontotemporal justa-allocortex; septal nuclei of the amygdaloid complex; "olfactory" portions of corpus striatum
Third: Hippocampal-cingulate	Direct connections with second system but none with bulb or first system	Ammon's formation; entorhinal, retrosplenial, and cingulate justa-allocortex

1. The *olfactory tubercle* is synonymous with the anterior perforate substance in primates.
2. The *Prepyriform cortex* is the area surrounding the lateral olfactory tract. Because of current usage in primate literature, this term is preferred to "anterior pyriform," which is often used to describe the homologous cortex in macromammalian animals.
3. The *amygdaloid complex* lies caudomedial to the prepyriform cortex and may be subdivided into a corticomедial (also referred to as the periamygdaloid cortex) and a basolateral group. These terms are preferred to pyriform or posterior pyriform, which, though they usually designate the same structures, have occasionally been used to include the entorhinal cortex.
4. The *frontotemporal cortex* is a junctional band of cortex lying between the prepyriform and periamygdaloid cortex and the orbitofrontal and polar temporal isocortex. Synonymous with orbito-insulo-temporal cortex, "frontotemporal" is preferred because of brevity.
5. The *area of the diagonal band* is the cortex surrounding the medial olfactory stria.
6. The *septal region* has the same gross anatomical relationship to the area of the diagonal band as the amygdaloid complex has to the prepyriform cortex. The septal area

refers to the cortical portion; septal nuclei, to the subcortical portion of the region.

7. The *subcallosal area* is a junctional band of cortex lying between the area of the diagonal band and septal nuclei on the one hand, and the mediofrontal isocortex on the other.
8. *Ammon's formation* is composed of the hippocampus and adjacent structures, the subiculum, and the dentate gyrus. The term "Ammon's formation" is preferred to "hippocampal formation" because the latter has been used by some to include the hippocampal gyrus. Hippocampal gyrus has in turn been variously used. Some authors include only entorhinal cortex; others include isocortex and the amygdaloid complex as well.
9. The *entorhinal cortex* and adjacent *presubiculum* constitute a junctional band of cortex lying between Ammon's formation and the temporal isocortex.
10. The *cingulate* and *retrosplenial areas* are a junctional band of cortex lying between the supracallosal hippocampal rudiment (induseum griseum) and the medial frontoparietal isocortex. "Cingulate" is preferred to the term "limbic" because the latter is sometimes used to include the entorhinal cortex and Ammon's formation. (From Pribram and Kruger, 1954.)

neurochemical phenomena, are of greater total significance than the rapidly propagated signals manifested as action potentials.

CLASSIFICATION

The mediobasal forebrain structures have been classified into three systems: the first, or rhinal; the second, or paleol; and the third, or hippocampal-cingulate system (Pribram and Kruger, 1954). Details and definitions are given in Table 6 (see also Fig. 21.1). The present chapter concerns those forebrain structures included in the second (paleol) and third (hippocampal-cingulate) systems.

One classificatory point warrants special mention because of its increasing significance. Electrical stimulation of the anesthetized preparation suggests that a distinction can be made between the anterior and posterior portions of the limbic systems. Stimu-

lation of the anterior portion results in peripheral effects: gross movements, oral phenomena, pupillary and oculomotor effects, and changes in blood pressure, respiration, and gastrointestinal motility. No such effects are obtained from the posterior portions of these systems.

Roughly, the peripheral effects of stimulation are obtained from areas classified as the second system, though they have also been occasionally reported from the anteriormost portions of the third system (the rostral extremity of Ammon's formation and of the cingulate cortex). Thus the anterior limbic structures may be conceived as forming a "mediobasal motor cortex" (see Fig. 21.2) analogous to the precentral cortex, which has been labeled the classical motor cortex. Electrical excitation of the classical motor cortex under deep anesthesia results in *discrete* movements; excision of this cortex results

LIMBIC SYSTEM

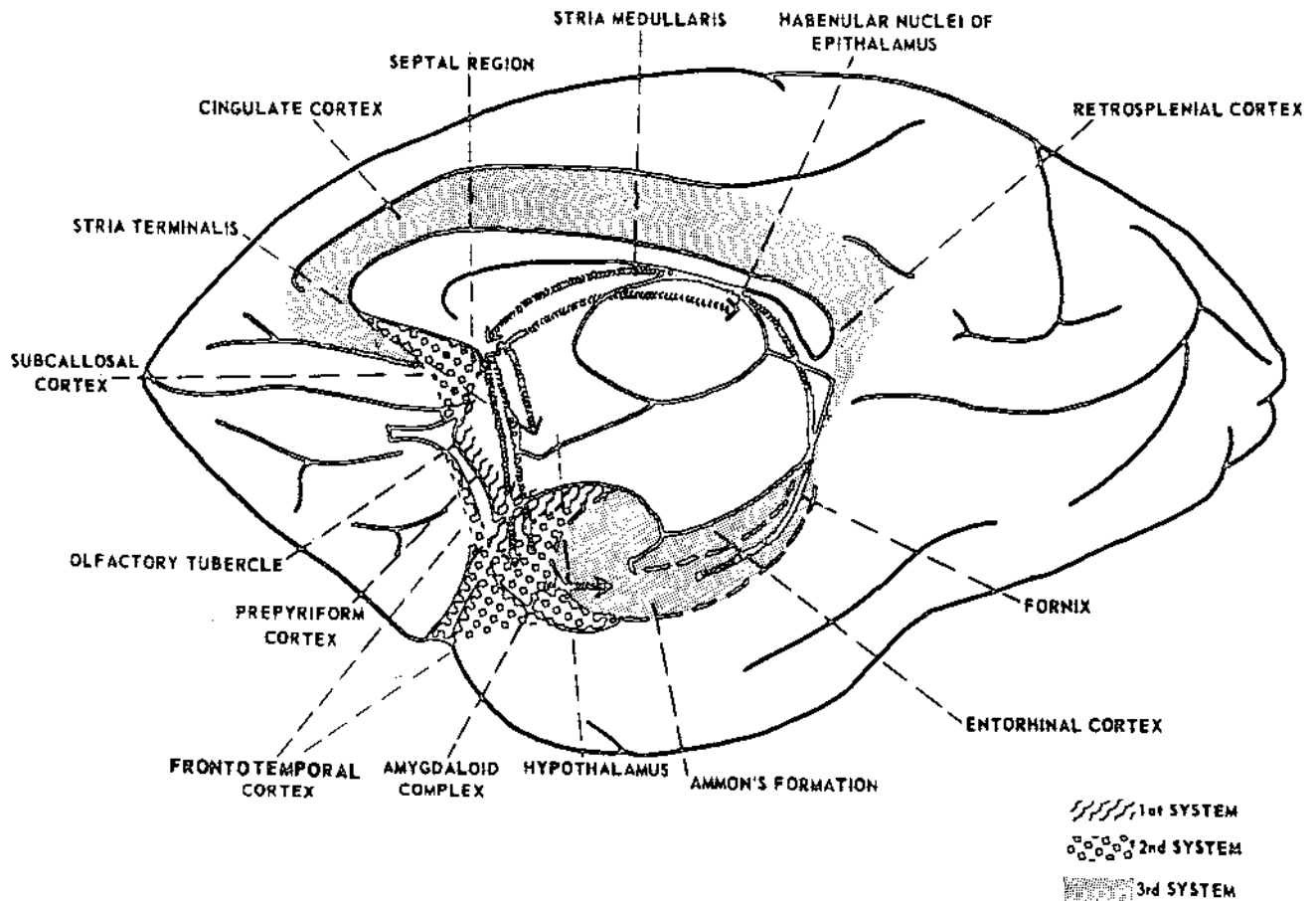


FIG. 21.1. The limbic systems of the monkey represented on a mediobasal view of the cerebral hemisphere. The classification into three systems is summarized in Table 6. (From Pribram and Kruger, 1954.)

in scotomata of action (Pribram *et al.*, 1955–56). Electrical excitation of the mediobasal motor cortex results in *diffuse* movements; excision impairs hoarding (Stamm, 1955a) and other aspects of feeding behavior (Pribram and Bagshaw, 1953), fighting and fleeing behavior (Brady and Nauta, 1953; Rosvold *et al.*, 1954), and mating and maternal behavior (Klüver and Bucy, 1937; Walker *et al.*, 1953; Schreiner and Kling, 1953; Stamm, 1955b).

ABSENCE OF TOPOGRAPHIC SPECIFICITY

The pattern of responses (whether neural, smooth or striped muscular or humoral) obtained from stimulation of any one locus within the mediobasal motor cortex is very similar to that obtained from most other parts (Spencer, 1894; Hoff and Green, 1936; Tower, 1936; W. K. Smith, 1938; Bailey and Sweet, 1940; Hodes and Magoun, 1942a, b; K. U. Smith, 1945; Kremer, 1947; Sugar *et al.*, 1948; Ward, 1948; Delgado and Livingston, 1948; Livingston *et al.*, 1948a, b; Kaada *et al.*, 1949, 1953, 1954; Pool

and Ransohoff, 1949; Sachs *et al.*, 1949; Speakman and Babkin, 1949; Babkin and Kite, 1950; Lennox *et al.*, 1950; Akert *et al.*, 1951; Fulton, 1951; Kaada, 1951; Gastaut, 1952; Koikegami and Fuse, 1952a; Koikegami *et al.*, 1953; MacLean and Delgado, 1953; Pribram and Kruger, 1954; Gloor, 1955a, b).

With regard to the diffuse autonomic and somatomotor responses, differences in the effects of stimulation of two loci cannot be characterized as either sympathetic or parasympathetic. For example, pressor or depressor reactions are obtained from any one locus depending on other variables such as rate of respiration or level of anesthesia. The somatic motor responses obtained from limbic stimulation differ from the topographically discrete motor responses obtained from precentral stimulation and resemble responses from medial diencephalic and mesencephalic stimulation. Masticatory and facial movements, gross aversive and vermiform somatic movements, and the facilitation and inhibition of ongoing movements of the extremities result from

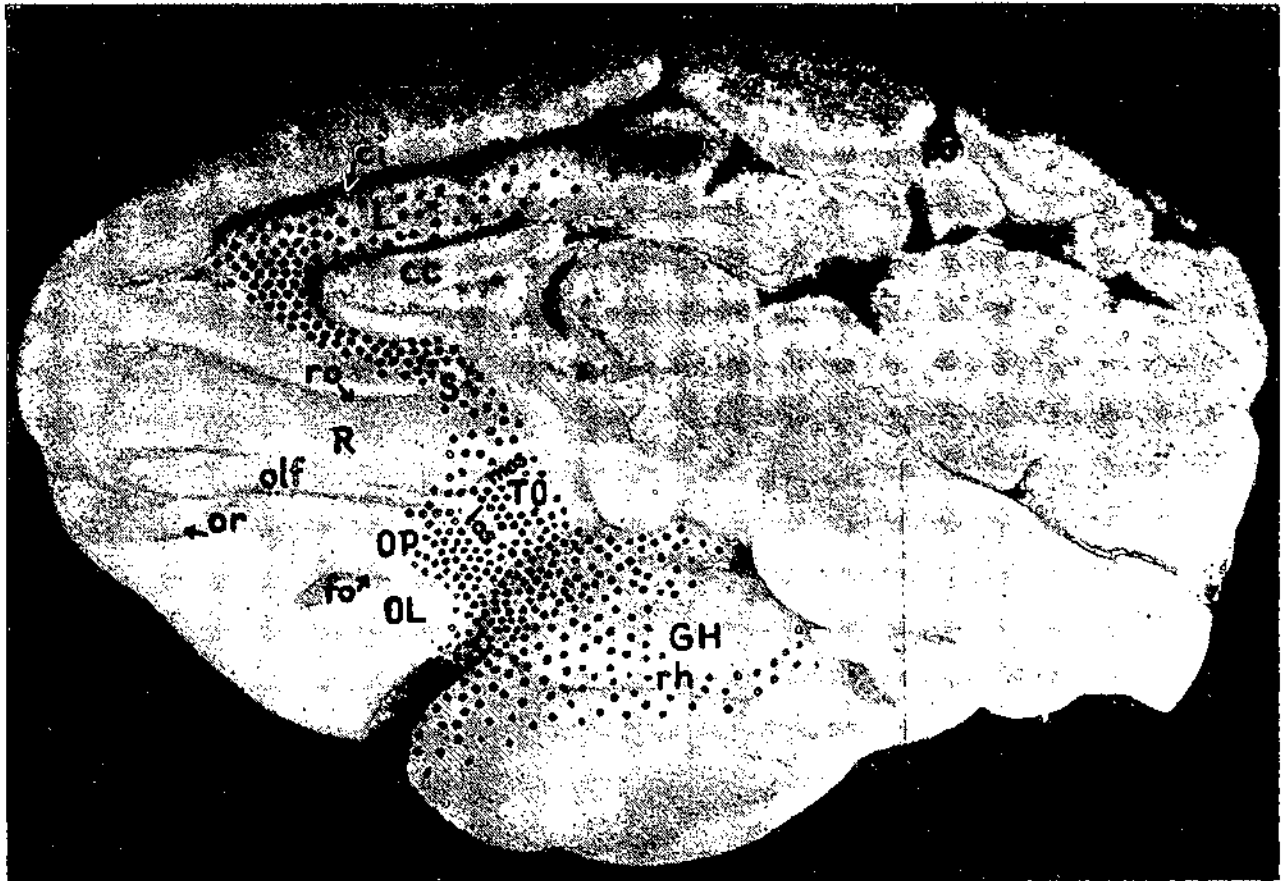


FIG. 21.2. View of the mediobasal motor cortex (indicated by stippling) in monkey. Abbreviations: *cc*, corpus callosum; *ci*, cingulate sulcus; *fc*, fronto-orbital sulcus; *GH*, hippocampal gyrus; *IN*, insula; *L*, cingulate gyrus; *los*, lateral olfactory stria; *mos*, medial olfactory stria; *OL*, lateral orbital gyrus; *olf*, olfactory tract; *OP*, posterior orbital gyrus; *or*, orbital sulcus; *po*, parieto-occipital fissure; *R*, gyrus rectus; *rh*, rhinal fissure; *ro*, rostral sulcus; *S*, subcallosal gyrus; *TO*, olfactory tubercle. (From Kaada, 1951.)

limbic stimulations (Smith, 1945; Kaada *et al.*, 1949; Kaada, 1951; Akert *et al.*, 1951; Castaut, 1952; Sloan and Kaada, 1953; MacLean and Delgado, 1953). Characteristically, these somatomotor responses show no topographical specificity; the stimulation of one locus may produce inhibition, or facilitation, or any one of the effects just mentioned (see Fig. 21.3). This does not mean that stimulation of any one point invariably produces the whole gamut of responses. Rather, stimulation of adjacent points in one animal may produce somewhat varying effects in that particular animal. However, under different conditions and in different animals, and certainly in reports made by different investigators, there is a minimal amount of "localization" of responses.

Just as the peripheral effects of limbic stimulation are relatively diffuse, so the electrographic effects produced in the limbic systems by peripheral stimulation are also diffuse. Although the usual type of

abrupt potential change evoked after a relatively brief latency in anesthetized animals and recorded from the lateral "projection" areas has been reported to occur in the limbic structures (Gerard *et al.*, 1936; Robinson and Lennox, 1951; Liberson and Akert, 1952; Cadilhac, 1955), the possibility that these abrupt potential changes are artifactitious has not been ruled out. Such abrupt potential changes may also be occasionally evoked in the orbito-insulo-temporal regions by vagal stimulation (MacLean and Pribram in Fulton, 1951; Dell, 1952). However, this happens infrequently, and the conditions under which these changes are obtained remain obscure.¹

¹ In the anesthetized preparation, a report by Machne and Segundo (1956) confirms that the rate of discharge of single units in the amygdaloid complex is affected by sciatic, vagal, olfactory, auditory, and mesencephalic reticular stimulation. They reported: "A common and striking finding was the convergence of different sensory modalities upon single units."

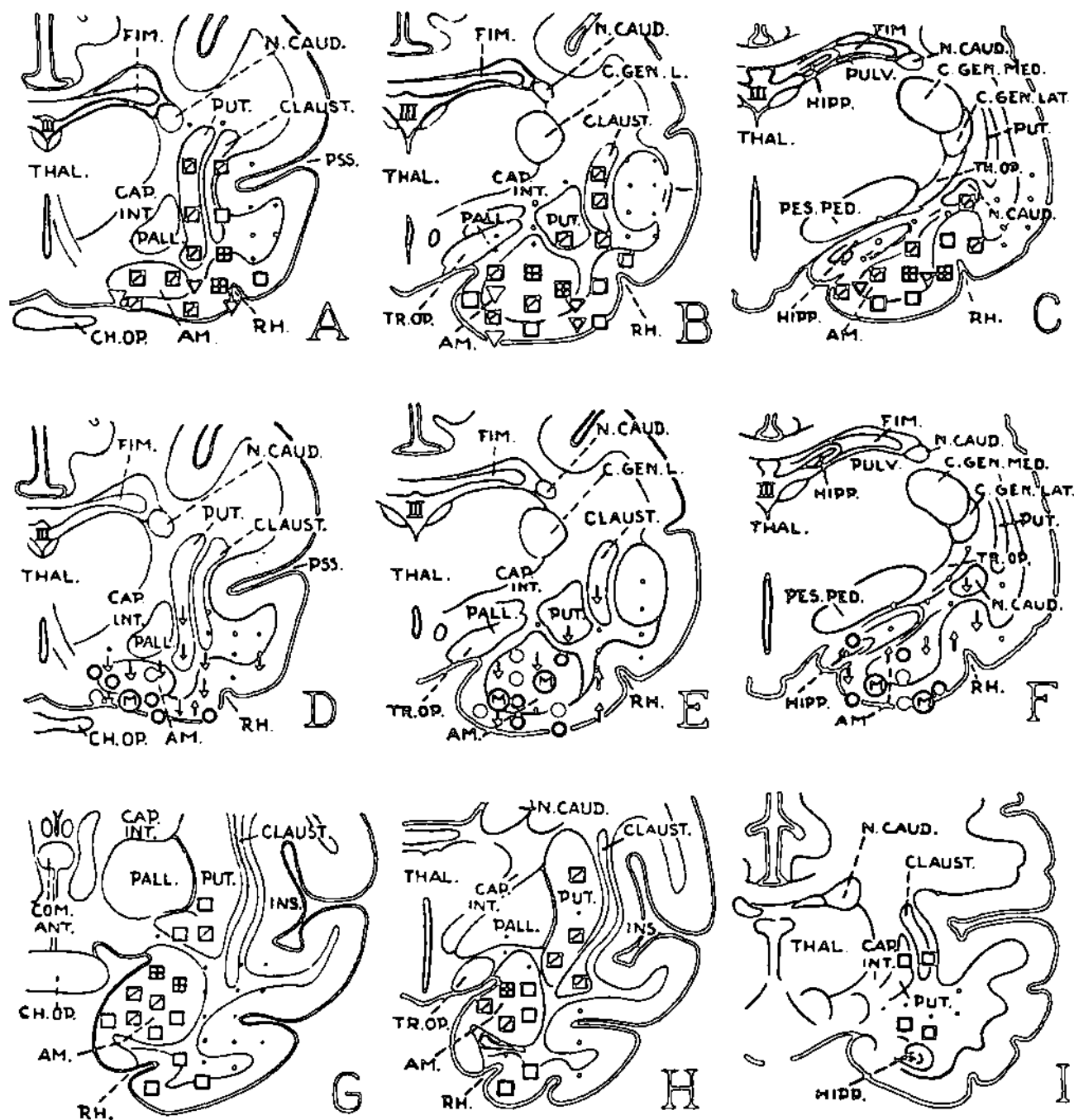


FIG. 21.3. Various somatomotor, autonomic, and electrocorticographic responses produced with electrical stimulation of points in the amygdaloid complex. Transverse sections through the amygdala (AM) in the cat (A to C and D to F) and the *Macaca mulatta* (G to I).

Sections A to C and G to I: Inhibition of respiration and other spontaneous movements \square , associated with inhibition \boxminus , or facilitation \boxplus , of the knee jerk and cortically induced movements. Spasmodic expirations ∇ , and spasmodic inspirations ∇ . No effects are indicated by dots.

Sections D to F: Rises \uparrow , and falls \downarrow , of blood pressure. Masticatory movements \otimes . Generalized \circ , or partial \circ , activation of the electrocorticogram. No blood pressure responses are indicated by dots. (From Kaada, 1951.)

Experiments by Galambos *et al.* (1956) suggest that the relevant variable for reliably producing a relatively abrupt potential change in the medio-basal structures of unanesthetized animals may be the conditioning of the animal. When an auditory signal is followed by a shock, the animal gradually acquires some conditioned (instrumental) response to the onset of the auditory signal. An abrupt potential change of variable latency is evoked by the auditory signal and recorded from a great number of cerebral structures, including the limbic areas, during the period in which the animal shows the conditioned response.

The effects of peripheral stimulation on the ongoing electrical activity have been repeatedly and reliably reported to result in recordings made from practically all of the limbic structures (Bailey and Sweet, 1940; Liberson and Akert, 1952; MacLean *et al.*, 1952; Cadilhac, 1955). Here again no topographical specificity has been found.

Thus the effects of both limbic system stimulation on peripheral structures and peripheral stimulation on the electrical activity of the limbic system demonstrate an absence of topographical specificity in the relationship between periphery and the medio-basal telencephalon.

INTERCONNECTIONS

Electrical stimulation of any part of the limbic system also produces diffuse electrocorticographic effects (see Fig. 21.4). These are best described as an activation pattern characterized by low-voltage fast activity, although other effects, such as "suppression" of spontaneous activity, may also result (Lennox *et al.*, 1950; Sloan and Jasper, 1950; Kaada, 1951; Feindel and Gloor, 1954). The activation pattern shows considerable similarity to that produced by stimulation of the reticular formation in the medial mesencephalon and in the posterior hypothalamic area of the diencephalon (Moruzzi and Magoun, 1949). These changes in electrocortical activity invariably spread to other limbic areas, and the anterofrontal cortex is also easily involved in the spread of the electrographic pattern. However, the remainder of the isocortex is very rarely involved.

Subcortical telencephalic structures which have most frequently been reported to show change in electrical activity are the amygdaloid and septal complexes and portions of the corpus striatum (Stoll *et al.*, 1951; Jasper and Ajmone-Marsan, 1952; Jasper *et al.*, 1952; Gloor, 1955a, b). All in all, these

data on electrographic effects of limbic stimulation suggest that the various areas within the limbic system are heavily interconnected; and that these areas are, in turn, related to basal nuclear forebrain structures and probably to the anterior frontal isocortex as well.

The effects of limbic system stimulation on the electrical activity of the diencephalon have been studied by Jasper and his colleagues (Sloan and Jasper, 1950; Stoll *et al.*, 1951; Ajmone-Marsan and Stoll, 1951; Jasper *et al.*, 1952; Gloor, 1955a, b). Stimulation of the temporal pole and the amygdaloid (see Fig. 21.5) results in changes in the electrical activity recorded from the anteromedial and posterolateral hypothalamic regions and from the anterior and central (centre median, intralaminar) nuclei of the thalamus. Some changes are also recorded from the lateral portion (parvocellular) of the medial thalamic nucleus (cat) and from the medial portion of the posterior group (monkey: lateral posterior nucleus and pulvinar). Stimulation of the cingulate cortex results in changes in the electrical activity recorded from the posterior hypothalamus and the central group of thalamic nuclei (centre median, intralaminar). Such changes have also been recorded from the medial thalamic nucleus, and on occasion from the anterior.²

Posterior to the diencephalon, limbic system stimulation affects the electrical activity recorded from the region of the subthalamus, the red nucleus, and the substantia nigra (Ajmone-Marsan and Stoll, 1951; Jasper *et al.*, 1952; French *et al.*, 1955; Gloor, 1955a). The caudal extremity of the effects of limbic stimulation, as reported by French *et al.* (1955) and Gloor (1955a), is in the periaqueductal gray (central gray) and in the mesencephalic reticular substance.

Thus the effects of limbic system stimulation on the electroneural activity of the diencephalon and mesencephalon can be recorded from the anterior and central thalamic nuclei, and in some instances from the medial and posterior nuclei. The anteromedial and posterior hypothalamus are regularly involved, as are the regions of the subthalamus, red

² Records of the electrical activity of the ventromedial portion of the ventral anterior nucleus often show a change when limbic structures are stimulated. Since this region of the ventral nuclear group contains a large fiber tract (which may be considered a contribution to the medial forebrain bundle), a special difficulty is encountered in the interpretation of this particular result. Should the effect be attributed to changes in the activity of the ventral anterior nucleus or to the activity of the fibers in passage?

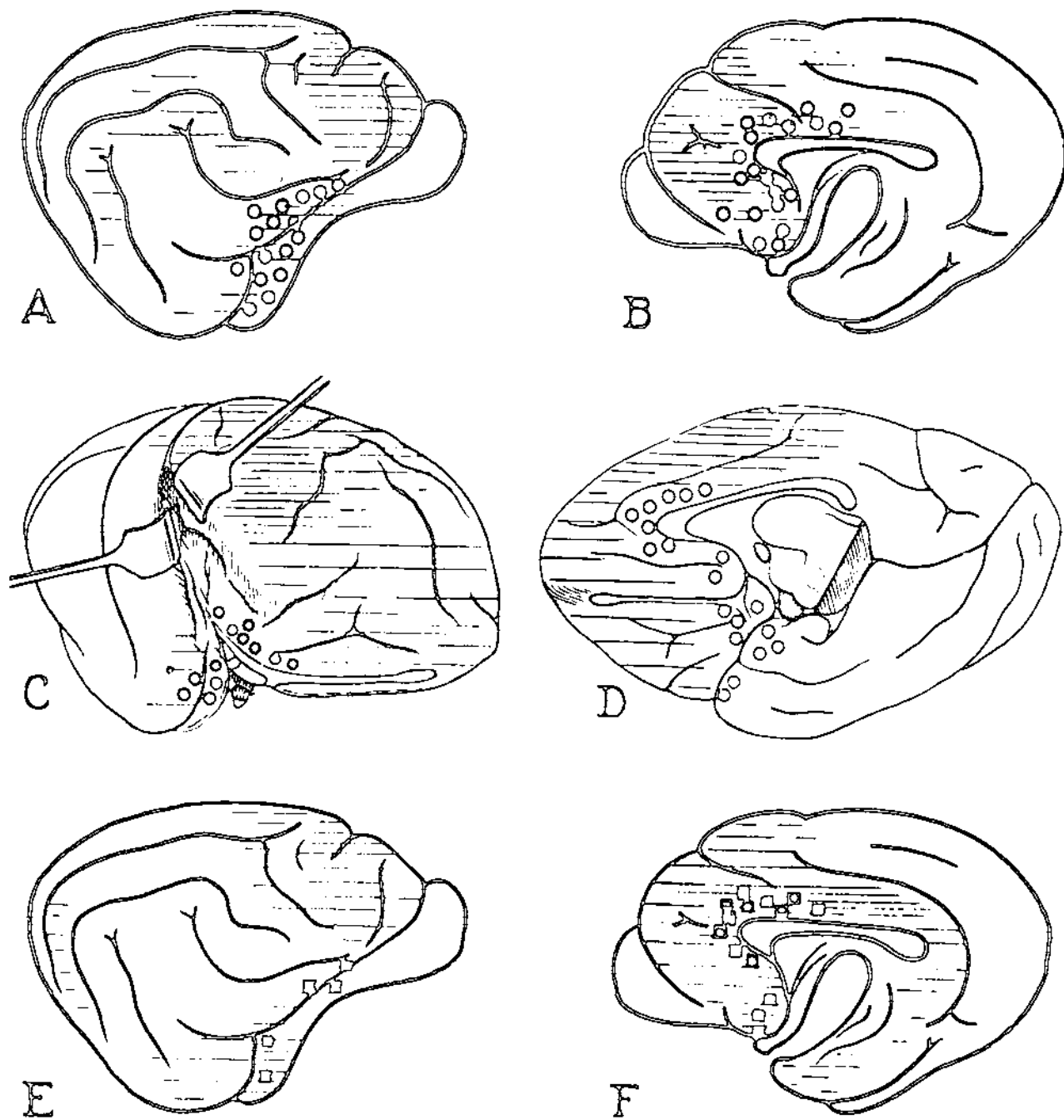


FIG. 21.4. Electrographic effects evoked upon electrical stimulation of the limbic region. Lateral and medial views of the cat's brain (A-B and E-F) and the monkey's brain (C-D).

Sections A to D: Points from which generalized activation of the ECG was obtained upon electrical stimulation indicated by ●. Activation of the ECG mainly in the shaded areas, usually on both hemispheres, obtained upon stimulation of points indicated by ○.

Sections E-F: Points from which generalized depression of the ECG was obtained upon electrical stimulation indicated by □. Electrical afterdischarges in the shaded areas were occasionally produced by stimulation of points in the anterior limbic region indicated by □. At other times depression of the ECG was obtained in the same shaded areas as a result of anterior limbic stimulation. (From Kaada, 1951.)

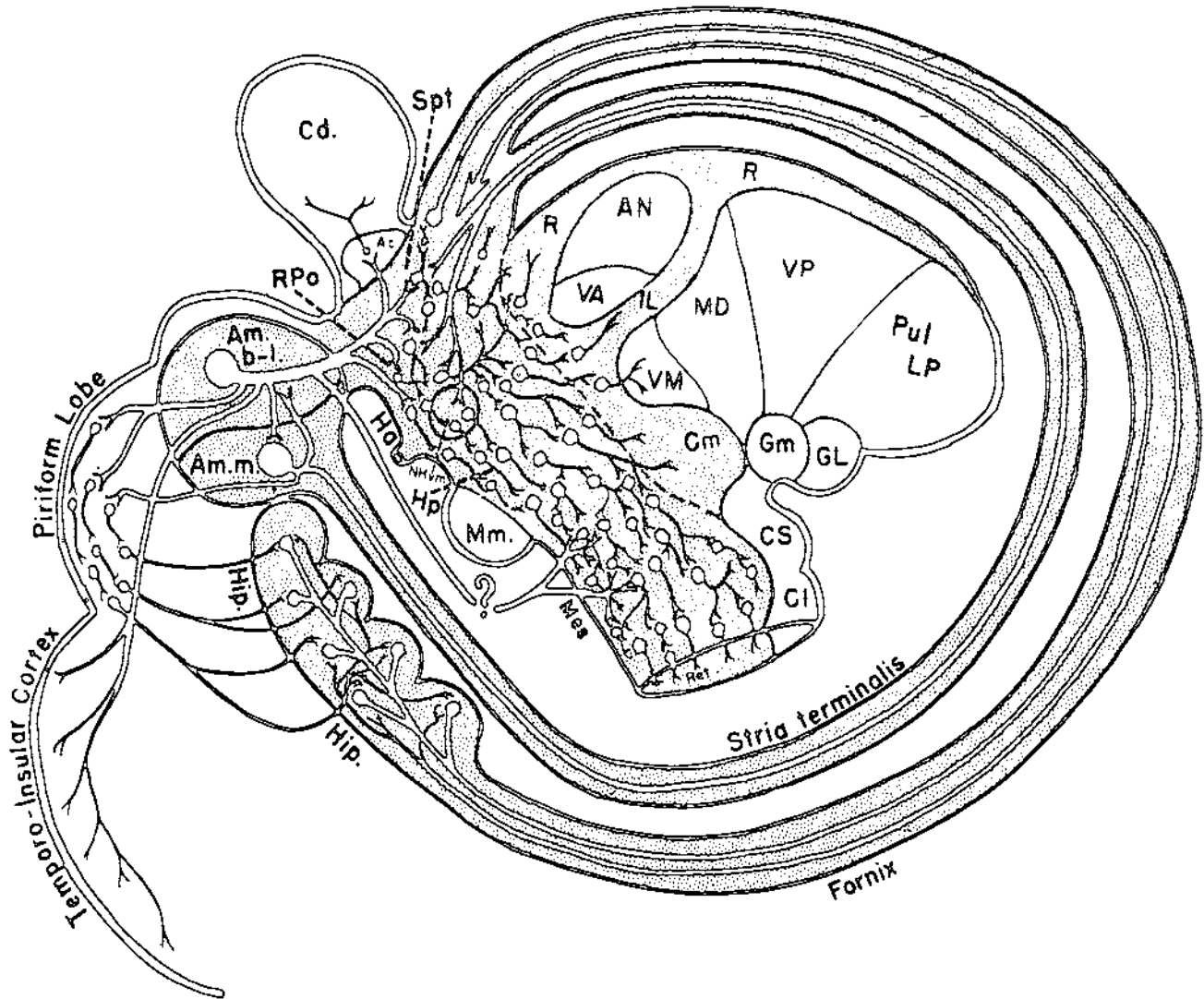


FIG. 21.5. Schematic representation of the neuronal organization of the amygdaloid projection system as revealed by electrophysiological studies. The stippled area indicates subcortical integrative structures regulating "global" somato-autonomic responses, diffuse projection mechanisms, and limbic structures projecting into this subcortical system. Key: *Ac*, anterior commissure; *Am. b-l*, basolateral subdivision of the amygdala; *Am. m.*, corticomedial subdivision of the amygdala; *AN*, anterior thalamic nuclei; *Cd*, caudate nucleus; *CI*, inferior colliculus; *Cm*, centre median thalamic nucleus; *CS*, superior colliculus; *GL*, lateral geniculate body; *Gm*, medial geniculate body; *Hu.*, anterior hypothalamus; *Hip.*, hippocampus; *Hp*, posterior hypothalamus; *IL*, intralaminar thalamic nuclei; *LP*, lateral posterior thalamic nucleus; *MD*, medial dorsal thalamic nucleus; *Mes*, mesencephalon; *Mm*, mammillary body; *NH vm*, ventromedial hypothalamic nucleus; *Pul*, pulvinar; *R*, reticular thalamic nucleus; *Ret*, reticular formation; *Rpo*, preoptic area; *Spt*, septal region; *VA*, ventral anterior thalamic nucleus; *VM*, ventral medial thalamic nucleus; *VP*, ventral posterior thalamic nucleus. (From Gloor, 1955a.)

nucleus, and substantia nigra. The affected portions of the neuraxis extend caudally into the central gray and the mesencephalic reticular substance. These data amply support the notion that both the medial diencephalon and the medial mesencephalon have an intimate relationship with the mediobasal fore-brain (see Fig. 21.6). What can the stimulation

experiments tell us of the mechanisms involved in this relationship?

NEURAL MECHANISMS

The effects of limbic stimulation are mediated via both short, fine fiber systems and long, large fiber tracts. The latter include such prominent structures

LIMBIC SYSTEM

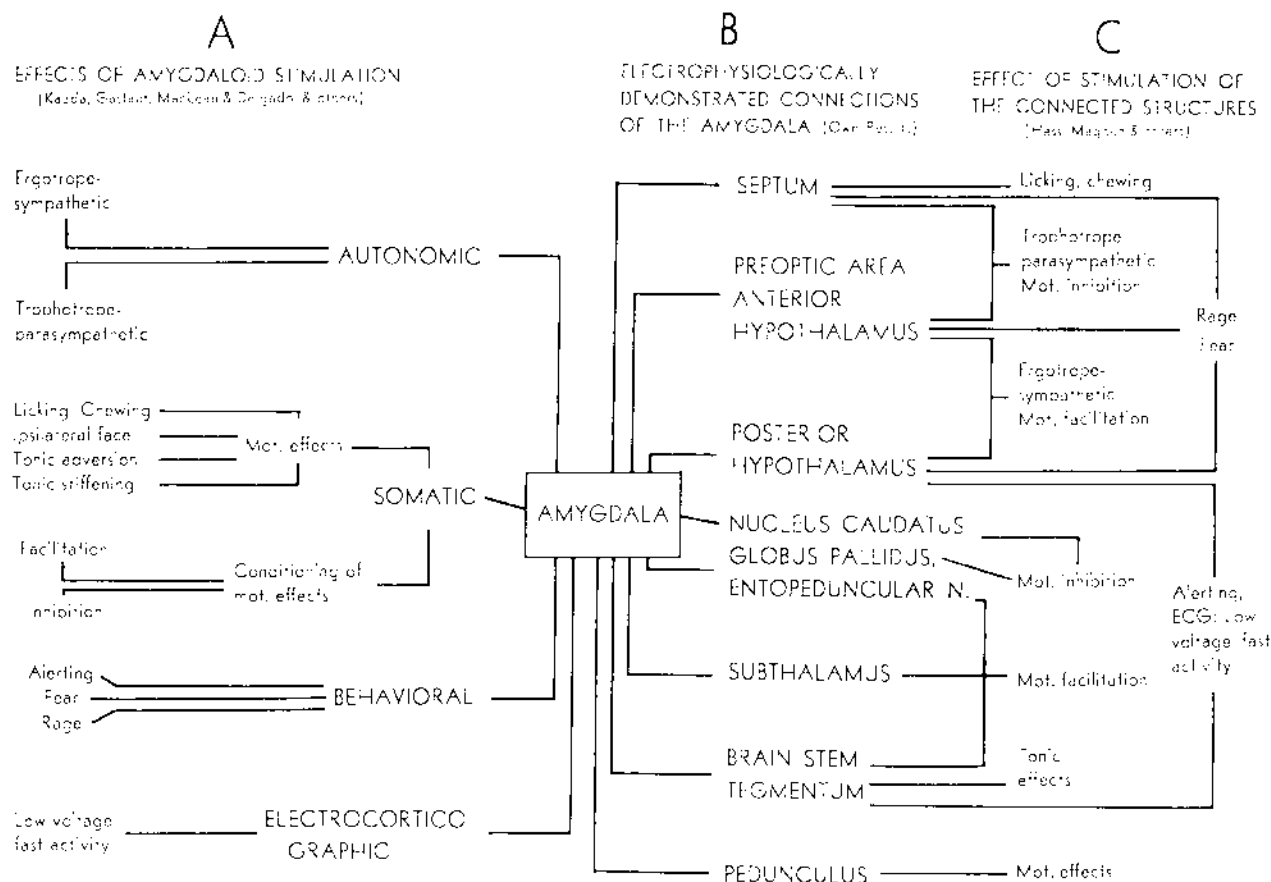


FIG. 21.6. Diagram illustrating the functional significance of the pattern of projection of the amygdala to subcortical structures. The relationship between physiological mechanisms as activated by amygdaloid and subcortical stimulation is indicated in the three columns: *A*, the different responses elicited by amygdaloid stimulation; *B*, the subcortical structures which are activated in a direct or indirect way from the amygdala as revealed by electrophysiological studies; *C*, the different responses elicited by stimulation of the subcortical structures. The responses obtained with amygdaloid stimulation are also obtained from one or a number of the subcortical structures to which the amygdala projects. There is a topographical organization of these effects in the subcortical structures, but such an organization is absent at the amygdaloid level. (From Gloor, 1955a.)

as the fornix, the terminal stria, the medullary stria, the mammillothalamic tract, and the projection systems to the limbic structures from the anterior and central nuclear groups of the thalamus. The functional characteristics of the connections served by these long fiber tracts are of special interest. In an extensive study of the effects of stimulation of the amygdaloid complex, Gloor (1955a, b) has uncovered mechanisms which are probably representative of those serving other structures of the limbic system (see French *et al.*, 1955). The following changes were observed to follow repetitive stimulation: recruitment, obliteration, and changes in latency (either decrease or increase).

On the basis of these data, it appears likely that the portion of the diencephalon and mesencephalon

which is connected with the amygdaloid structures by long fiber systems is also connected with them by a rather complex system of multisynaptic relays. Important, too, is the anatomical fact that connections between any two points are served by more than one of the long fiber tracts. For example, the basolateral amygdaloid and the septal nuclei are reciprocally connected not only by the medullary stria but also by the terminal stria (via the cortico-medial amygdala) and by the fornix (via Ammon's formation). Characteristically, these fiber tracts are so arranged that they produce different amounts of synaptic delay—an arrangement in parallel best suited to result in temporal summation. Thus changes in the excitability of the central nervous system, rather than changes in the momentary

patterns of activity, result from limbic system stimulation.

DISCUSSION

The data resulting from the vertical analysis of the central nervous system amply support the thesis that the telencephalon, as well as the diencephalon and mesencephalon, shows a gradient of organization from the ependymal lining outward. This gradient is expressed as the complexity of possible neuronal patterning within a system at any one moment in time. Not only are the mediobasal limbic systems of the telencephalon heavily interconnected with the medial diencephalon and mesencephalon, but they also show functional similarities to these latter systems. Diffuseness rather than spatial or modality specificity characterizes the relationships of the limbic systems and peripheral structure. Activity in the limbic systems affects other central neural mechanisms through parallel connections so arranged that different amounts of synaptic delay are interposed in each of the connecting tracts. The result is an accumulation of neuronal activity effecting changes in excitability of neural tissue, not changes in momentary patterns of activity.

If the effects of the activity of the limbic system are accurately designated as changes in excitability

of the medial diencephalon and mesencephalon, these changes are much more akin to the electrotonic, synaptic, and dendritic potential changes of neural activity than to the propagated nerve impulse. Thus studies such as those of Clare and Bishop (1955*a, b*) on dendritic potentials, and neuropharmacological experiments such as those of Feldberg and Sherwood (1954) on injections of drugs into the ventricular system, Marazzi (Michaelis *et al.*, 1954) on "central transmitting" agents, and M. Vogt (1954) on the adrenergic properties of the medial diencephalic and mesencephalic reticular substance, become of utmost importance to our understanding of the effects of limbic system stimulation. These neural properties show a slow time course and provide mechanisms for the cumulation of neuronal activity which are considerably different from those which permit the complex spatial and temporal patterning of rapidly propagated impulses—mechanisms which characterize the lateral "projection" systems. Exploration of these cumulative or "durational" mechanisms might profitably be the next step in furthering our understanding of those aspects of behavior which are related to the mediobasal limbic telencephalon—behaviors which are categorized as feeding, fighting, mating, and maternal.