

FUNCTIONS OF THE "OLFACTORY BRAIN"

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I. DEFINITION OF "RHINENCEPHALON"

Renewed interest in the "olfactory brain" or "rhinencephalon" has been provoked by the suggestion that in mammals this portion of the brain serves emotional rather than olfactory functions. Recent theoretical and experimental studies have examined various aspects of this suggestion. There has arisen a certain amount of confusion due to discrepancies in results. Furthermore, authors vary in their conceptions of what constitutes "emotion"; and they differ widely in their definitions of which morphological formations are to be subsumed under "rhinencephalon."

Some of the confusion may be traced to differences in results when different techniques are applied; a generalization from the data derived with one technique may not be substantiated by data derived with another technique. Discrepancies of fact may sometimes be resolved by considering the reliability of data (*i. e.*, the number of subjects used; the number of investigations reporting essentially similar results; and significance of the results if statistical techniques are applicable). At other times, the adequacy of the report must be taken into account (*e. g.*, comparing cerebral ablation studies without anatomical verification of lesions with those where such verification is reported). Usually, discrepancies can be resolved only by further experiments; ignoring them is least likely to encourage such experiments.

In this review, "emotion" is dealt with as an inference from behavioral data; speculations regarding emotions based solely on neuroanatomical data assume a greater knowledge of the biological variables determining emotion than we possess.

Choice of data is implicit in any survey of this scope and depends on the framework chosen for discussion. Whenever we are aware of them, such implicit choices will be made explicit. Thus, whether a neural formation might be subsumed under a definition of "rhinencephalon" depends in part on whether the reference is "olfactory function," or "emotional behavior," or both, as in this review. This first section deals, therefore, with our definition of the neural formations which are to be included in the "rhinencephalon."

The term "rhinencephalon" was first used by Kölliker⁸⁴ to denote a group of cerebral structures which, though apparently cortical, could be easily differentiated from the rest of the cerebral mantle. Meynert¹⁰⁰ had distinguished between cortex with gray surface and cortex with white surface: the latter constitutes Kölliker's "rhinencephalon" and is found in the "olfactory lobe," "hippocampus," and "septal region." The conception that

these structures are related to each other and to olfaction came from studies of comparative and ontogenetic morphology. In subreptilian vertebrates, the entire forebrain is interspersed with a large mass of fibers originating in the olfactory bulb or anterior olfactory nucleus.^{64, 70} In reptiles, although fibers originating in other systems become more prominent, the forebrain is still "dominated" by olfactory connections.⁶⁴ Those neural components of the forebrain which are recognizable in submammalian vertebrates can also be distinguished in mammals, although other, "newer" formations are added. In terms of the presumed order of their appearance, the divisions of the mammalian brain have been classified as "archipallium" ("hippocampus"), "paleopallium" ("olfactory lobe" and probably "septal region"), and "neopallium."⁶⁴ A body of evidence relating the size of structures subsumed under archi- and paleopallium to the size of peripheral olfactory structures has been summarized by Kappers *et al.*⁷⁹

Classification invariably runs into difficulty with junctional or transitional categories. Thus, in the case of pallial formations, it is often difficult to distinguish hilar cortex from subcortical masses, *viz.*, in the amygdaloid complex and in the septal region. Another difficulty in classification arises in distinguishing between neocortex and "older" cortex. At the turn of the century, the biological generalization that "ontogeny recapitulates phylogeny" became current.⁶¹ Brodmann²⁹ and the Vogts and their pupils¹⁵⁷ used Nissl's method for selectively staining cell bodies to make ontogenetic comparisons of cortical stratification in an attempt to resolve difficulties in classification. As can be seen from the recent review of these studies by Bailey and v. Bonin,¹⁵ they were only partially successful. However, their conclusions, in general, support the distinction between new and older cortical formations. The former, which pass through a developmental six-layered stage, were termed "isocortex"; the latter, "allocortex."

There remain, however, large areas of cortex which are not readily placed into one or another of these categories. One such area, the cingulate gyrus, does not pass through a six-layered developmental stage but approximates the appearance of isocortex in the adult. M. Rose¹³⁴ suggested the term "mesocortex" to designate this area. A still more useful suggestion is that made by Filimonoff⁴⁶ who finds a transitional zone of cortex (both in development and in the adult brain) to separate typical allo- and isocortex along the entire length of the junctional boundary. He designates this transitional cortex (including that of the cingulate gyrus) "juxtallocortex." This suggestion is congruent with the cytoarchitectonic descriptions of v. Economo⁴³ and has been adopted by Bailey and v. Bonin. We shall follow them in referring to this cortex as juxtallocortex.* In mammals, and especially primates, the increase in the size of isocortical relative to allocortical formations is shared by the increased development of the juxtallocortical transitional areas. Thus, allocortical and juxtallocortical structures form a ring around the hilus of the hemisphere. This ringlike formation was the basis upon which Broca²⁸ and others, reviewed by Elliot Smith,¹⁴² antici-

* However, we do not wish to follow Bailey and Bonin in classifying juxtallocortex as isocortex.

pating cytoarchitectural studies, grouped the hilar structures under the term limbic lobe. Support for this grouping has come not only from cytoarchitectural comparisons based on Nissl techniques, but also from the studies of Cajal³³ and Lorente de Nó^{94, 95} which, using silver staining methods, compared the minute fibro-architecture of these limbic portions of the cerebral mantle with some of those of the lateral cortex. Current interest in the relation of cortex to emotion has encompassed structures which can be discussed only if the definition of "rhinencephalon" includes juxtallocortex as well as allocortex. This review is concerned, therefore, with all cortical formations not typically isocortical: *i.e.*, those which do not definitely pass through a six-layer stage in ontogeny. A variety of structures make up the "rhinencephalon" when it is defined in this manner. On morphological grounds, the following units can be distinguished:

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 macrosmatic animals.

3. The *amygdaloid complex* lies caudomedial to the prepyriform cortex and may be subdivided into corticomедial and basolateral groups. The former is also referred to as the periamygdaloid cortex. These terms are preferred to pyriform or posterior pyriform which usually refer to the same structures because occasionally the latter are used to include the entorhinal cortex.

4. The *frontotemporal cortex* is a junctional band of cortex lying between prepyriform and periamygdaloid cortex and 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 medio-frontal isocortex on the other.*

8. *Ammon's formation* is composed of the hippocampus and adjacent structures, the subiculum and fascia dentata.¹²⁸ 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.

* Evidence regarding the histogenesis of the frontotemporal (unit 4) and subcallosal juxtallocortex (unit 7) is relatively scanty. These transitional areas are given status apart from isocortex for heuristic reasons. See below page 113 for further discussion.

9. The *entorhinal cortex* and adjacent *presubiculum* constitute a junctional band of cortex lying between Ammon's formation and temporal isocortex.

10. The *cingulate* and *retrosplenial areas* are a junctional band of cortex lying between the supracallosal hippocampal rudiment (synonym: induseum griseum) and 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.

II. CLASSIFICATION OF "RHINENCEPHALIC" SYSTEMS

A. Ontogenetic Histology

These heterogeneous morphological units which have been grouped together "by exclusion" (*i. e.*, by failing to meet the criterion defining isocortex) need not, *a priori*, serve homogeneous functions. It seems fruitful, therefore, to attempt some classification of these units into systems prior to a discussion of function.

TABLE I
M. ROSE'S HISTOGENETIC CLASSIFICATION (SIMPLIFIED)

I. Totocortex:
A. Holocortex: isocortex; cingulate and retrosplenial mesocortex; Ammon's formation.
B. Schizocortex: entorhinal cortex.
II. Semicortex: olfactory tubercle; area of the diagonal band; septal area; prepyriform cortex; periamygdaloid cortex.
III. Bicortex: insular cortex.

M. Rose^{132,133} has presented thoroughly documented histogenetic studies in an attempt to make such a classification (see TABLE I). All cortex is derived from a migration of cells originating from centrally located nuclear masses of the forebrain. Rose pointed out that in some places practically all of the cells partake in this migration while in other places large nuclear masses remain behind. He labeled cortex formed from such "partial" migration as *semicortex*; it corresponds roughly to *paleocortex* (as defined phylogenetically). He labeled cortex formed when a "total" migration takes place as *totocortex*. This term subsumes a variety of structures including all of the *isocortex*, the *cingulate mesocortex*, the *entorhinal cortex*, and *Ammon's formation*. The *totocortex* was subdivided into "split" and "whole" types on the basis of relative contiguity of the migrated strata of cortical cells. *Schizocortex* (split), as in the entorhinal region, shows a split between the outer and inner layers; *holocortex* (whole) is found in *Ammon's formation*, the *cingulate region* and in *isocortex*. The various types of *holocortex* are distinguished on the basis of the number of cortical layers formed—respectively, two, five, and six. Rose, assuming the *claustrum*, an incompletely migrated formation, to be part of the overlying *insular cortex*, had to give special status to this formation ("*bicortex*"). Beck¹³⁴ has criticized the histogenetic findings upon which Rose's classification is based;

unfortunately he has so far failed to substitute a more tenable one. Filimonoff,⁴⁶ on the other hand, although similarly critical of Rose, places emphasis on the aforementioned transitional bands of cortex, and thus provides an alternative basis for classification. In agreement with other cytoarchitectonicists he distinguishes iso- from allocortex on the basis of the early development in the former of six recognizable layers. He places Ammon's formation in a separate allocortical category (archicortex) and suggests that the presubicular and entorhinal areas form a juxtallocortical (periarchicortical) formation which includes not only the usually recognized temporal portion but also supracallosal and retrosplenial portions (Rose's cingulate mesocortex). Thus, in spite of his criticisms of Rose's classification, Filimonoff, on independent grounds, comes to include in related classes (archicortex and periarchicortex) those allocortical structures which Rose had grouped as totocortex.* Filimonoff also agrees with other cytoarchitectonicists, including Rose, in grouping together, as semicortex, the olfactory tubercle, diagonal band, septal area, prepyriform cortex, and periamygdaloid cortex; however, here again he differs as to the basis of classification. Only with respect to the insular cortex does this difference result in a change. Because he disagrees with Rose regarding the cortical nature of the claustrum, Filimonoff is free to classify parts of insular cortex with parts of the remainder of the cerebral mantle. A band of transitional cortex abutting semicortical formations has been described repeatedly.^{24, 43, 45, 73} This delineation of a frontotemporal and subcallosal juxtallocortex (perisemicortex) appears useful in subsuming available anatomical and physiological data.

Summary. It is apparent that, although several authors use separate histogenetic criteria (and only Rose has stated his explicitly), similarities in final classification appear. Two major divisions of allo- and juxtallocortex may be distinguished. One includes the olfactory tubercle, area of the diagonal band, septal area, prepyriform and periamygdaloid cortex, and the surrounding subcallosal and frontotemporal transitional cortex. The other includes Ammon's formation and its surrounding transitional cortex: the entorhinal cortex of the temporal lobe, and the pericallosal cingulate and retrosplenial cortex. This classification supports the comparative anatomists' distinction between paleo- and archicortex, but suggests that the newer transitional formations be classified together with the adjacent older cortex rather than with the rest of the neocortex. Further evidence supporting the utility of this classification comes from a study of anatomical relationships *between* these several structures.

B. Axonographic Anatomy

A large body of evidence concerning the interrelationships between the several morphological units which are considered in this review has been accumulated by observation of stained "normal" brain sections. Therefore, before turning to the somewhat more reliable and often more specific in-

* The argument with respect to inclusion of the isocortex in this category does not concern this review.

formation derived from experimental material, an attempt will be made to cover the extensive literature based on observation of normal tissue.

Fibers are seen leaving the olfactory bulb (which receives the olfactory fila from the receptor), to course caudally, some terminating in the olfactory tubercle,^{40,75,79} and others crossing to comparable structures in the opposite cerebral hemisphere via the most rostral fibers of a large tract, the anterior commissure.²⁸ At the level of the olfactory tubercle, the fibers split into two major tracts, a medial and a lateral olfactory stria.

The medial stria can be followed into the subcallosal and septal regions. It appears, however, that these latter structures do not receive fibers directly from the bulb. Fox⁴⁶ found that, in the cat, major connections originate *only* from the olfactory tubercle. From the septal region, fibers can be traced to the area of the diagonal band and, perhaps partly through relay in this area, to the amygdaloid complex. Another major outflow of fibers from the septal region apparently reaches the habenular nuclei (of the epithalamus) via the stria medullaris, a conspicuous tract probably formed by fibers from other medial structures (especially amygdaloid complex and anterior hypothalamus). (See review by Brodal.²⁷)

The lateral olfactory tract can be traced to the prepyriform cortex and to the amygdaloid complex.^{60,66,74,115,165} From this complex a large outflow of fibers, the stria terminalis, apparently connects to the septal region and anterior hypothalamus. Connections between the amygdaloid complexes of the two sides have also been described to course in the stria terminalis as well as through the anterior commissure. Some of the fibers of the stria are also said to join the medial forebrain bundle to reach structures in the posterior hypothalamus.^{46,79,165}

The observations relating the other components of the limbic lobe (juxtallocortex and Ammon's formation) to the olfactory afferents are more tenuous. Fibers from the olfactory bulb and anterior olfactory nucleus, via the medial olfactory tract, have been described by a number of authors^{46,60,66,74,79,165} to reach the anterior end of the supracallosal hippocampal rudiment, a structure believed to be vestigial and distinct from the major portion of Ammon's formation, especially in mammals. Most reports are cautious in their descriptions. Thus, Fox states that fibers appear to "enter into relation" with the hippocampal rudiment. No direct connections between olfactory bulb and cingulate or entorhinal cortex have been claimed.

On the other hand, the interrelations between cingulate and entorhinal cortex and Ammon's formation are better established. Cajal³³ and Lorente de Nó^{94,95} described afferent fibers to Ammon's formation from the cingulate cortex via the cingulum and supracallosal stria and from the entorhinal cortex via "alvear" and "perforant" paths. From Ammon's formation emerges a large tract, the fornix. This tract apparently connects with the septal region and the mammillary body of the posterior hypothalamus.^{46,66,165} Other connections have been described, including the hippocampal commissure which relates the hippocampi of the two hemispheres. In addition,

fibers from the mammillary body can be traced via a conspicuous bundle, the tract of Vicq d'Azyr, to the anterior thalamic nuclei—the origin (*vide infra*) of the projections to the cingulate cortex.³⁶

Summary. From observation in normal stained material of the connections of the allocortical and juxtallocortical formations, three interconnected "systems" can be discerned. The first consists of primary olfactory structures apparently directly related to the olfactory bulb.* The second receives fibers from the first and consists primarily of the septal region and the amygdaloid complex. The third "system" consists of cingulate and entorhinal cortex and the structures of Ammon's formation. These appear to be remotely, if at all, related to olfactory afferents. (See excellent review by Brodal.²⁷) Both the second and third "systems" send efferents to the hypothalamus.

Axonography of normal material thus supports the morphological distinction between those allo- and juxtallocortical areas related to the first and second system (semi- or paleocortical) and those related to third system (archicortical) formations. The distinction between first and second systems on the basis of direct connections with the olfactory bulb would prove useful if substantiated by more reliable techniques, since one of the referents of this review is "olfactory" function. We proceed, therefore, to an examination of experimental anatomical material.

C. Experimental Histology

In many instances, more specific information regarding the interrelationships of these several morphological units has been derived from experimental material. Four staining methods have been employed in tracing the course and termination of fibers originating at the site of an experimental lesion of the brain: the Weigert technique uses hematoxylin to trace neural pathways by their myelin content (interrupted pathways lose their myelin and fail to stain); the Marchi technique employs osmic acid to trace granules of degenerating myelin along interrupted pathways; the Bielshowsky silver method has recently been modified to demonstrate the dissolution of nerve fibers; and modifications of Nissl's thionin or methylene blue stain for cell bodies have been used to show gliosis along degenerating pathways or in related nuclei, and to determine the loss of cells in a structure due to retrograde degeneration when most of the fibers are severed from a parent cell. Each of these techniques has limitations; on the whole, however, those studies employing Nissl stain to study retrograde degeneration and those restricted to *terminal degeneration* when the silver stain is used, are the most reliable. The latter, however, may also demonstrate connections which are sparse.

Following lesions of the olfactory bulb (or, in monkey, of the tract emerg-

* In this review, the olfactory bulb is considered analogous to the thalamus. Both bulb and dorsal thalamus [see Rose and Woolsey¹² for review] contain structures which receive the final terminals of afferents from sense organs before relay to cerebral cortex. Thus, the numbering of our system proceeds from the bulb.

ing from the bulb), degenerating fibers may be traced in the rostral part of the anterior commissure to the bulb on the opposite side.^{32, 30, 49, 105, 124, 166} Such lesions also result in degenerating fibers reaching the olfactory tubercle and, via the medial olfactory tract, the anterior portion of the supracallosal hippocampal rudiment. In addition, degenerating fibers can be traced to the prepyriform area, and the periamygdaloid cortex.^{38, 105} Johnston⁷³ had divided this complex into corticomедial and basolateral groups on a comparative morphological basis. Only the corticomедial group receives direct fibers from the olfactory bulb.

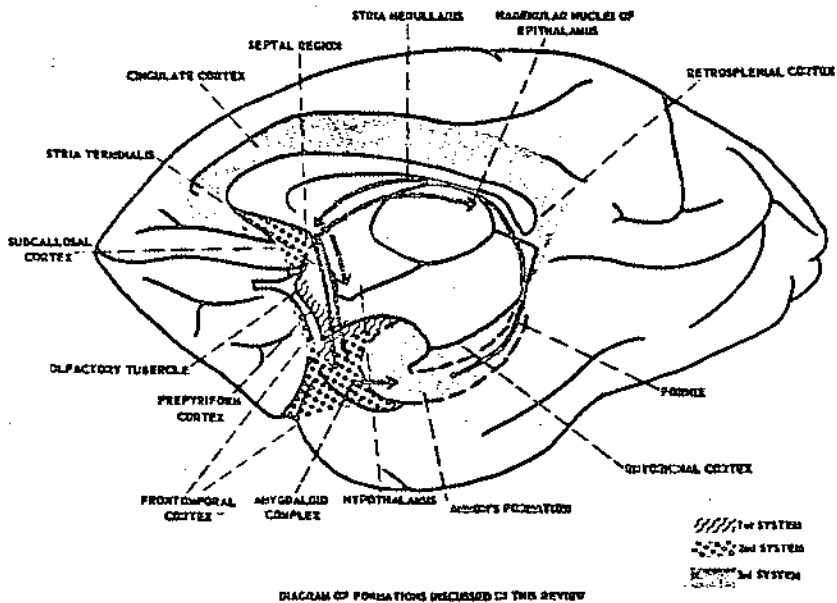


FIGURE 1. Diagrammatic representation of the mediobasal surface of a monkey brain outlining the formations discussed in this review and their relationships.

Discrete destructions separating those parts of the amygdaloid complex which receive olfactory afferents from those receiving none have not been accomplished. However, some information regarding connections can be gained from lesions limited to periamygdaloid cortex,¹⁵⁵ others including the entire amygdaloid complex,⁴⁷ and still others involving the stria terminalis.⁴⁹ Periamygdaloid cortex sends fibers to at least some portions of the frontotemporal juxtallocortex and to the basolateral amygdaloid nuclei,¹³ which, in turn, give rise to the major portion of the stria terminalis (the latter also includes fibers from the bed nucleus of the stria, a part of the corticomедial group). In these experiments the fibers of the stria terminalis can be traced to the septal region. Components of the anterior commissure are also found degenerated following amygdala lesions and can be traced to the amygdaloid complex of the opposite side.⁴⁷ Finally, fibers can be traced

from lesions of the amygdaloid complex (especially the basolateral group) to the ventromedial nucleus of the anterior hypothalamus.²

We turn to the interconnections of the third system as demonstrated by the methods of experimental anatomy. Whereas lesions of the amygdaloid complex do *not* result in degenerating fibers reaching the entorhinal cortex,¹³ those of entorhinal¹² and cingulate cortex^{1,3} give rise to degenerating fibers which can be traced to Ammon's formation. Experimental evidence confirms the findings based on normal material that the fornix serves as the major efferent from this formation to the rest of the nervous system.^{11, 57, 141, 147} Simpson's¹⁴¹ study divides the fornix into two divisions, a precommissural and a postcommissural. The former, and several times larger by fiber count, terminates in the septal region; the latter, in the mammillary body. Furthermore, when lesions are restricted to the anterior part of Ammon's formation, degenerating fibers can be traced only to the septal region^{52, 119} although an abnormal number of boutons terminaux appear in the mammillary nuclei;¹⁴¹ lesions involving the posterior portion of Ammon's formation result in fiber degeneration which extends to the mammillary body.^{109, 141} Degenerated fibers from lesions in the septal region have also been traced to the mammillary body.¹¹³ By means of the Marchi method, some fibers are reported to course back in the dorsal fornix to Ammon's formation.⁵⁷ It is, however, somewhat difficult to ascertain the directionality of the degenerating fibers with this method.

From lesions of the mammillary body, Le Gros Clark^{26, 33} traced fibers to the anterior nuclei of the thalamus. These, in turn, project to the cingulate cortex^{22, 120, 130, 160, 161} which, as we have already seen, is the origin of some of the fibers to Ammon's formation.

Another "circuit" has recently come to light. As mentioned above, the stria terminalis connects the amygdaloid complex and the septal nuclei with the anterior hypothalamus. This, in turn, sends fibers to the midline and intralaminar nuclei of the thalamus.^{37, 110} Silver techniques have shown these thalamic nuclei to project to the prepyriform, subcallosal, cingulate and entorhinal cortices which provide afferents to Ammon's formation.¹¹⁴ These findings were anticipated by the results of several studies utilizing the retrograde degeneration in the thalamus which follows cortical resections.^{14, 119, 131}

Recently still another experimental technique has been applied to the olfactory system by Bodian.²³ Extensive studies had shown that the spread of poliomyelitis virus within the nervous system conforms to known neural pathways. After inoculation of the olfactory mucosa, poliomyelitic lesions were found in the (1) bulb, (2) olfactory tubercle, (3) nucleus of the diagonal band, (4) prepyriform cortex, and (5) corticomedial group of the amygdaloid complex. In addition, some degeneration was found in the hypothalamus, the inferior claustrum, midline thalamic and habenular nuclei, and globus pallidus. No lesions were found in Ammon's formation, mammillary nuclei, putamen, caudate nucleus, or lateral thalamus. On the other hand, injection of the fornix causes extensive destruction in Ammon's

formation. Thus the relatively direct connection between olfactory receptor and the first system is again validated; the lack of such connections with the third system is again emphasized.

Summary. (See Figure 1.) On the basis of experimental anatomical studies, a more definitive description of the primary olfactory system may be given: from the olfactory bulb (either directly or via the anterior olfactory nuclei), olfactory afferents reach medially to the olfactory tubercle, the anterior extremity of the supracallosal hippocampal rudiment, and laterally to the prepyriform and periamygdaloid cortex. Direct connections from the bulb could *not* be traced to any other structures discussed heretofore: specifically, *no* olfactory afferents reached the septal nuclei, the basolateral group of the amygdaloid complex, the entorhinal and cingulate cortex or Ammon's formation. Thus a clearer picture of the *second* system emerges from the experimental studies as compared with that obtained from normal material: the frontotemporal (and possibly the subcallosal) juxtallocortex, the basolateral group of the amygdaloid complex, and septal nuclei are now included. In keeping with the semicortical classification of this system, parts of it are cortical, parts form subcortical nuclei.

The impressions concerning the organization of the third system derived from normal anatomy are verified and considerably amplified by experimental studies. This system centers around Ammon's formation, which receives fibers from the entorhinal and cingulate cortex. The main efferent path of Ammon's formation, the fornix, projects to the septal nuclei and to the mammillary body of the posterior hypothalamus. The septal nuclei also send fibers to the mammillary body, and both septal and amygdaloid complexes project to the anterior hypothalamus via the stria terminalis. From anterior and posterior hypothalamus, pathways have been traced via anterior and midline thalamus to prepyriform, entorhinal, and cingulate cortex. Thus, multiple closed loops characterize the connections of the third system; these involve the structures of the second system and those of the hypothalamus as well as those of the anterior and midline dorsal thalamus.

D. Electrographic Anatomy

The histological techniques discussed so far are applied to the study of the brain *in vitro*. Since the development of electrical stimulation, amplification, and recording devices, pathways may also be traced in the living animal. Another method for checking the relationships of neural structures is thus available.

When the olfactory apparatus is exposed to stimulants (*e.g.*, guaiacol, cloves, asafetida, indol, chinolin, or smoke), changes can be observed in the electrical activity in the region of the olfactory bulb and tract, olfactory tubercle, septal region, prepyriform and periamygdaloid cortex, and the Ammon's formation.^{4, 10, 63, 100} Because of technical difficulties, stimulus control has been crude; in addition, systematic mapping of responsive and nonresponsive points has not yet been done. Thus the results are tentative, but they indicate that many of the structures included in each of the three

systems may be excited by stimulation of the olfactory apparatus. Precise data are more easily obtained from experiments utilizing electrical stimulation of neural structures. As the olfactory fila are difficult to explore in most mammals, the olfactory bulb has been the choice of most investigators using this technique.

TABLE 2
SUMMARY OF ELECTROGRAPHIC RESPONSES TO OLFACTORY BULB STIMULATION

Neural formation	Rose & Woolsey (12)	Fox, et al. (13)	Kaada (17)	Berry, et al. (14)
Olfactory tract	+	+	+	+
Olfactory tubercle	0	+	+	+
Diagonal band	0	0	—	+
Septal region	—	0	0*	+
Prepyriform cortex	+	+	+	+
Periamygdaloid cortex	+	+	+	+
Basolateral amygdaloid nuclei	—	0	+	+
Frontotemporal cortex	—	—	+	—
Anterior entorhinal area	+	—	+	+
Retrosplenial area	0	—	—	+
Cingulate cortex	—	—	0	+
Ammon's formation	0	0	0*	+
Caudate (head)	—	—	—	+
Putamen	—	+	—	+
Globus pallidus	—	+	—	+
Clastrum	—	—	—	+

*Present under chloralose anesthesia

**In posterior portion; only under chloralose anesthesia

+ = Response

0 = No Response

— = Not Reported

Electrical stimulation of the olfactory bulb results in abrupt changes in the electrical potential recorded from presumably related structures. Using the conventional techniques of recording with a large exploring electrode, all of the structures which have been classified on an experimental anatomical basis as belonging to the first system have been shown to be activated by bulb stimulation in at least two independent studies, although discrepancies exist (see TABLE 2). All of these structures respond with sufficiently short latency to preclude the probability of multisynaptic connection and can, therefore, be designated as "primary."

With regard to the second and third systems as defined on the basis of anatomical data, the results of electrical studies are less clear. All of the investigations using a conventional electrode have produced negative results, except for some scanty observations using chloralose anesthesia.¹⁷ However, Berry *et al.*,¹⁴ using small (50 micra) bipolar electrodes, which by virtue of their size might be expected to record potentials from only a few elements, have been able to record potentials from some of the structures which have been designated as second and third systems on histological grounds. Differences in latencies distinguish the response in different systems: structures in the first system respond within 4 msec.; in the second system, within 10 msec.; and, in the third, at widely varying intervals longer than 10 msec. For example, the prepyriform cortex yields a response

1.2-3.0 msec. after bulb stimulation, the response from the periamygdaloid cortex is obtained at 2.5-4 msec., whereas the responses from Ammon's formation were found after latencies of 10-32 msec. and those near the mammillothalamic tract after 25-34 msec. Responses also appeared in the frontotemporal juxtalloccortex and parts of the striatum, supporting prior findings of comparative anatomists.^{64, 75}

Electrical stimuli have also been applied to structures included in the third system, and the resultant electrical activity in other neural structures have been investigated. Essentially, these experiments confirm the previously outlined interrelationships within this system. Thus, Renshaw *et al.*¹²³ showed that the hippocampus is activated by entorhinal stimulation; both an afferent and efferent relationship between Ammon's formation and the septal region via the fornix has been found;⁵² and the posterior cingulate cortex was activated by stimulation of the mammillary body.¹⁶⁴

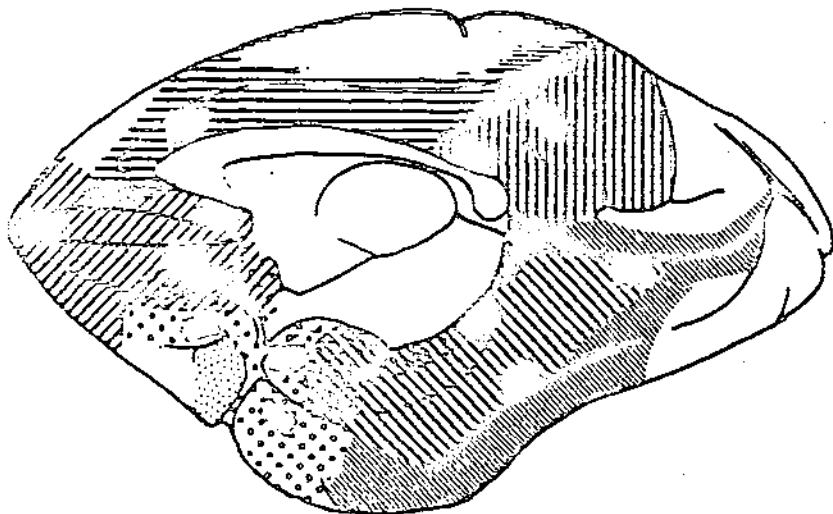


FIGURE 2. Diagrammatic representation of the mediobasal surface of a monkey brain showing the distribution of neuronographically determined subdivisions. Black rectangles indicate representative sites of strychninizations: hilar sites of allo- and juxtalloccortex, more peripheral ones of isocortex. Coarse stippling or striations indicate regional parcellations based on reciprocally related cortical points. Finer stippling or striations represent maximum additional cortex unidirectionally activated from within a region. Taken from Pribram and MacLean.¹²²

A further check of these relationships comes from the changes in electrical potentials induced by chemical stimulation of neural structures, usually by the local application of strychnine. Such "neuronographic" studies (FIGURE 2), in addition to confirming most of the findings discussed above, substantiate the relation, proposed on the basis of anatomy, of much of the mediobasal cortex with Ammon's formation.^{101, 121, 122, 152} These studies support the conception that, in spite of the increased development which the juxtalloccortex shares with isocortex in primates, juxtalloccortical areas are better classified with the particular allocortical formations to which they are related.

Summary. In reviewing the electrographic data, therefore, one finds an independent method which supports the conceptions derived from ontogenetic, normal, and experimental anatomy. Allo- and juxtallocortical formations may be grouped into three systems. The first system consists of olfactory tubercle, area of the diagonal band, prepyriform cortex, and the cortico-medial nuclei of the amygdala. This system has direct connections with the olfactory bulb. A second system has only secondary connections with the olfactory bulb. It consists of the basolateral nuclei of the amygdala, the septal nuclei, the frontotemporal (and possibly the subcallosal) juxtallocortex, and probably includes basal parts of the striatum. On histogenetic grounds, the structures grouped as first and second system (semicortex and perisemicortex) were distinguished from Ammon's formation and related cortex (archicortex and periarthicortex). This distinction is supported by axonography. The third allo- and juxtallocortical system composed of Ammon's formation and cingulate and entorhinal cortex has abundantly demonstrated electrographic as well as histological intracconnections and is only remotely related by any technique to the olfactory bulb.

Discussion

Because of recent interest in the possible role in emotional behavior of parts of the forebrain which previously had been thought to serve olfaction, we have reviewed observations and experiments concerning the anatomy of the "olfactory brain" or "rhinencephalon." We have chosen to include all morphological formations not typically isocortical; *i.e.*, those which do not definitely pass through a six-layered stage in ontogeny. This choice has been determined by two considerations. Speculation has included transitional (juxtallocortical) formations as well as allocortical ones in the neural substrate of emotion; data can be more simply organized when both allo- and juxtallocortical formations are included. In mammals, and especially primates, the increase in isocortical relative to allocortical formations is shared by the increased development of the juxtallocortical ones. Thus the classical distinction between neocortical and older formations is modified in favor of the distinction between isocortex on the one hand and allo- and juxtallocortex on the other. In addition, the classical distinction between paleo- and archicortex is broadened to include the transitional formations related to each type of allocortex (semi- and perisemicortex on the one hand; archi- and periarthicortex, on the other). The histogenetic evidence upon which these distinctions are based has been reviewed.

Lorente de Nó⁹⁶ has pointed out the limitation of all cytoarchitectonic classifications based on Nissl preparations. Essentially, his criticism is that differences which appear between cortical areas in Nissl preparations do not appear when other staining methods are used. Such criticism implies that the cerebral cortex may be subdivided in only one way which can be specified by the application of a variety of anatomical techniques. An alternative conception would consider that different methods of subdivision are possible, each delineated by one of several techniques and each correlating with

different functions. One cortical area might thus be part of two differently organized cerebral systems. In this frame of reference, different anatomical techniques might be expected to uncover different principles of cerebral organization. The relevance of *each* principle to function would have to be established separately. A static conception of "the" function of a cerebral area is replaced by a dynamic conception which considers the different functions of an area under different conditions. The conditions examined in this review are those leading to olfactory and emotional behavior; the relevance to such behavior of the morphological distinctions outlined rather than their *anatomical* generality is in question. Nevertheless, support for the acceptance of the classification based on histogenetic data has come from a review of the interrelationships between the several morphological units included under allo- and juxtallocortex. An additional distinction could be made between those structures receiving axons from the olfactory bulb and those which do not. Thus, on the basis of connections, three systems were described; the distinction between the second and third supporting a similar distinction based on histogenesis.* The three systems are defined as follows: the first, or primary system, receives afferents from the olfactory bulb; the second and third do not. The second system is defined in terms of direct connections with the primary; the third system has no such connections, but is connected with the second. As primary system we have included the olfactory tubercle, area of the diagonal band, prepyriform cortex, and the corticomедial nuclei of the amygdaloid complex. The main components of the second system are not all cortical; they include the subcallosal and frontotemporal juxtallocortex, the basolateral nuclei of the amygdaloid complex, and the septal nuclei; in addition, there is evidence that at least portions of the striatum ("olfactory" striatum) should be included, evidence which is in congruence with the semicortical ontogeny of this system. The third system centers around Ammon's formation; it includes also the entorhinal, cingulate, and retrosplenial juxtallocortical areas.

The major interrelationships between the three systems may be described as follows: beginning at the olfactory bulb, fibers can be traced to a *primary* olfactory system consisting of olfactory tubercle, olfactory trigone, the prepyriform cortex, and the corticomедial nucleus of the amygdaloid complex. The primary system of each hemisphere is connected to that of the opposite hemisphere by the rostral fibers of the anterior commissure. This system is connected with the subcallosal and frontotemporal cortex and through the medial and lateral striae with the septal nuclei, nuclei of the diagonal band, and the basolateral part of the amygdaloid complex. These structures make up the second system interconnected through the anterior commissure and stria terminalis. As noted, some comparative studies and electrophysiological data suggest that parts of the striatum might profitably be in-

* Actually, the distinction between first and second system can also be made on a histogenetic basis: the first system is semicortical; the second, perisemicortical and subcortical. However, a similar distinction between archi- and periarhincortical formations was not made on the basis of axonography. (It could have been, if a more complex definition had been invoked.) Thus, whether allo- and juxtallocortical formations are grouped into three or four systems is arbitrary.

cluded in this system. Efferents from the septal nuclei and amygdaloid complex reach the epithalamus and anterior hypothalamus; in turn, the latter connects with the midline and intralaminar nuclei of the dorsal thalamus. These nuclei apparently project to the juxtallocortex. Ammon's formation receives fibers from the cingulate, retrosplenial, and entorhinal part of this cortex, thus making up the third system. This system, in addition to the circuit involving *anterior* hypothalamus via the fornix and the septal nuclei, is also related to the *posterior* hypothalamus (mammillary bodies) via the fornix. The mamillothalamic tract, and the projections from the anterior thalamic nuclei to the cingulate juxtallocortex, and the fibers to Ammon's formation from the cingulate cortex complete the circuit.

TABLE 3
SUMMARY SYSTEMATIZATION OF RHINENCEPHALIC FORMATIONS

System	Definition	Morphological Formations Included
First	Direct connections with olfactory bulb	Olfactory tubercle; area of diagonal band; pyriform cortex; corticomедial nuclei of the amygdaloid complex
Second	Direct connections with first system but none with bulb	Subcallosal and frontotemporal juxtallocortex; septal nuclei and basolateral nuclei of the amygdaloid complex
Third	Direct connections with second system but none with bulb or first system	Ammon's formation; entorhinal, retrosplenial, and cingulate juxtallocortex

Summary. A definition of "rhinencephalon" which includes juxtallocortical as well as allocortical formations was chosen because of recent interest in the possible functions of these portions of the brain in emotional as well as olfactory behavior. This choice has proved useful in subsuming a large body of data derived from the application of phylogenetic, ontogenetic, axonographic, and electrographic data. This definition of "rhinencephalon" modifies the classical distinction between neocortical and older formations in favor of a distinction between isocortex on the one hand and allo- and juxtallocortex on the other. Findings have been reviewed which support the classification of "rhinencephalic" structures as thus defined into three systems (see TABLE 3). The distinction between the first and second systems on the one hand and the third system on the other are extensions of the phylogenetic distinction between paleo- and archicortical formations. This distinction is supported by histogenetic, axonographic, and electrographic data. The distinction between the first and second systems is most reliably rooted in experimental histological studies. The inclusion of subcortical as well as cortical formations in the second system is derived as well from phylogenetic, ontogenetic, axonographic, or electrographic techniques. Each system is abundantly intraconnected. Both second and third systems are efferently related to the hypothalamus and afferently re-

lated to the anterior and midline thalamus. These intra- and interconnections provide the anatomical base for a consideration of the functions of these systems which follows.

III. FUNCTIONS OF "RHINENCEPHALIC" SYSTEMS

A. Experimental Physiology

We now turn from investigations concerning the organization of the "olfactory brain" to investigations of function. As already noted, changes in electrical potential can be recorded in many of the formations considered in this review when the olfactory apparatus is exposed to stimulants. The initiation of such changes is not limited to "olfactory" stimulation, however. MacLean *et al.* have shown that, in the prepyriform, periamygdaloid, and entorhinal cortex, in the basolateral amygdaloid nuclei, and in Ammon's formation, such changes may also be produced by placing salt on the animal's tongue or pinching its tail and extremities.¹⁰⁰ There is some additional though scanty evidence^{50, 127} that tactile, auditory, and visual stimuli affect the electrical activity of the third system (specifically Ammon's formation and the cingulate gyrus); it is thus likely that, while the several morphological formations included in this review have been shown to be influenced by olfactory stimuli, they are influenced, as well, by "nonolfactory" stimuli.

Such experiments delineating the afferent physiological control of the structures reviewed have been few. On the other hand, recent observations of the efferent control this system exerts on effectors have been many. Numerous investigators have electrically and chemically stimulated the various morphological formations under consideration.^{54, 86, 93, 128, 144} Some of the effects of such stimulation might have been predicted on the basis of the respiratory and vascular responses which follow inhalation of various odoriferous gases.^{5, 6, 20, 85} In addition, gross movements apparently not somatotopically localized have been described repeatedly and have been reviewed by Kaada⁷⁷ and Gastaut.⁵⁵ Such effects have been systematically studied. Stimulation of every structure included in the first and second systems as well as the anterior portions of the third (bulb, tract, tubercle, diagonal band, septal region, prepyriform cortex, amygdaloid complex, and frontotemporal, subcallosal, and anterior cingulate regions) has resulted in respiratory, vascular, and gross motor changes.⁷⁸ In addition, respiratory and vascular responses have been found on electrical stimulation of the habenula and anterior and midline thalamic nuclei, but not elsewhere in the thalamus.¹³⁸ Similar effects from Ammon's formation are more readily demonstrated by chemical (sodium citrate) stimulation.⁷ The characteristics of these responses have recently been reviewed by Kaada⁷⁷ and Gastaut.⁵⁵ In this presentation it is sufficient to point out that in view of other efferent as well as afferent relationships most allo- and juxtallo-cortical formations cannot be solely designated as olfactory. Recently the control of visceral function (through the autonomic nervous system) by

these formations has been promulgated and other relationships neglected. In the light of the efferent control of somatic movement exerted by allo-cortex and juxtallocortex and, conversely, the control of the autonomic nervous system exerted by the lateral isocortex,^{65, 80, 118, 137, 155} it seems preferable to emphasize the massive and diffuse nature of the allo- and juxtallocortical control of both smooth and striped muscle (as contrasted with the more discrete control exerted by the lateral isocortex).

With respect to delineation of a specific function for allocortical and related systems, another electrophysiological finding is of interest: electrical stimulation of many of these formations results in a spread of altered electrical activity to the other related formations (prolonged after-discharge, activation and depression of spontaneous rhythms, and abolition of strychnine spikes and burst potentials) and, under certain conditions, to the rest of the cerebrum as well.^{76, 77, 89, 90, 125} These phenomena could possibly be mediated via the midline and intralaminar nuclei from which "recruiting" responses are obtained.^{91, 91, 69, 70, 71, 111, 151} It is more likely that interaction between midline-intralaminar and anterior thalamic nuclei, the cortex to which they project (prepyriform, subcallosal, frontotemporal, cingulate, and entorhinal), and Ammon's formation provides the basis for such generalized changes in cerebral electrical activity. Another related finding of great interest is that peripheral stimulation which "arouses" the animal and "activates" the electrical activity of the isocortex^{50, 51, 52, 69, 70, 71, 91, 92, 102, 103, 112, 117, 148, 149, 150} apparently results in electrical hypersynchrony in Ammon's formation.⁵⁹

Summary. Physiological experiments support the conception that the allo- and juxtallocortical formations have different functions from typically isocortical formations. These experiments emphasize the diffuse nature of the relationships between allo- and juxtallocortical formations and peripheral structures, confirming Herrick's earlier findings utilizing phylogenetic material.⁸⁴ There appears to be no basis for the substitution of "visceral" for "rhinal" in designating the functions of most of these formations: both terms suggest a particular selective function common to all formations included in this part of the brain which is not supported by evidence. (See discussion of MacLean by Pribram.⁹⁸) On the other hand, the diffuseness of the relationships of these formations with peripheral structures contrasts sharply with the discreteness of the organization of afferent and efferent projection systems to parts of the isocortex. This difference may prove to be fundamental.

B. *Experimental Psychology*

There remains to be considered another type of evidence regarding the functions of the "rhinencephalon": studies of the behavior of the animal following excision or stimulation of neural structures. Can the three systems delineated by anatomical and physiological techniques be distinguished on the basis of their relation to olfactory or emotional behavior? Is such a relationship, if demonstrated, a selective one? These questions cannot yet

be answered fully because of the paucity of available data. However, a beginning has been made, and these experiments are reviewed.

Extensive and clearcut experiments on olfactory discriminations were performed by Swann.^{133,134} Using 130 rats trained in a T maze in which odorous wood shavings were placed on one side, he found that olfactory bulb excision and section of the intermediate olfactory stria impaired discrimination. Sections of the (1) medial and (2) lateral olfactory stria, and (3) lesions of the septal region, (4) prepyriform cortex, (5) amygdaloid complex, and (6) Ammon's formation failed to interfere with performance. Neither small isocortical lesions nor extensive ones involving as much as 85 per cent of the total cortex interfered with performance. Additional experiments by Brown and Ghiselli³⁰ failed to confirm Swann on the effects of sections of the intermediate olfactory stria and, in addition, showed that extensive lesions of many subcortical masses also failed to interfere with such discriminations. The only structures classified as "olfactory brain" by anatomists which were not involved in these experiments were studied by Lashley and Sperry.³⁸ In these experiments, the radiations from the anterior nuclei of the thalamus to the cingulate cortex were interrupted, and time for retrograde degeneration was allowed to elapse. Again, no alteration in discrimination performance resulted. It seems, therefore, that, with respect to the most elementary behavior determined by olfactory cues, only the olfactory bulb has been shown to be significant.

A somewhat more complicated olfactory discrimination utilizing the conditioned foreleg response of dogs was used by Allen.^{9,9} He found that lesions of pyriform cortex and amygdaloid complex and the associated frontotemporal cortex resulted in the loss of a "negative" conditioned habit (though the "positive" was retained). In other words, animals which had been trained (using aversive stimulation) to raise the foreleg whenever cloves were presented and to refrain from raising the leg when asafetida was used as stimulus, after surgery, raised the foreleg to both cues. Ablation of Ammon's formation failed to alter preoperative performance. None of these lesions affected the ability of a blindfolded dog to pick out a bag containing meat from others containing sawdust. These results essentially confirm those of Swann; the loss of the "negative" conditioned response may be due either to a *selective* loss of ability to discriminate between several olfactory cues or to a more *general* change affecting either the reaction to aversive stimulation or a whole range of complex discriminations.

Because of the difficulties in separating introspectively the sensations of smell and taste, and the occurrence of "uncinate" seizures in man which sometimes include both, it has been suggested that the amygdaloid complex and Ammon's formation are concerned in gustatory as well as olfactory functions. We have already seen that gustatory stimulation will alter the electrical activity of these structures. Quantitative tests of monkeys' preference for water over a bitter quinine solution show, however, that the insular-opercular cortex rather than the amygdaloid complex or Ammon's formation are implicated in "primary" gustatory functions.^{14,21} On the other hand, a

change in dietary habits is observed following ablations of the amygdaloid complex and surrounding cortex,¹¹⁰ an effect *not* obtained from lesions elsewhere (either in the insular-opercular, Ammon's, or lateral isocortical formations). These changes in gustatory behavior following amygdala resections, may be explained, as in the case of olfaction, in one of two ways: (1) the animal may be unable to *select* between several cues whether these are olfactory or gustatory and the change is limited to these modalities, or (2) the animal may be more *generally* impaired with respect to any complex discrimination. The latter interpretation is untenable in the light of a considerable body of experimental evidence. Resections limited to the second system fail to interfere with learned visual discriminations¹¹⁹ or with performance of such tasks as delayed response and delayed alternation.¹²⁰ These findings take on added significance from the fact that isocortical ablations adjacent to the second allo- and juxtalloccortical system markedly impair an animal's performance of these tasks.^{108, 109, 123}

However, disturbance is not limited to olfactory and gustatory behavior when the second system is stimulated or extirpated. Changes in temperature regulation, in quantity of food intake, and in sleep-activity cycles have been reported.¹¹⁹ While one is tempted to look for some phrase which subsumes all of these categories of behavior, it is probably best to wait for additional evidence before making the attempt. The advisability of waiting is emphasized by yet another series of disturbances in behavior which follow lesions of allo- and juxtalloccortex; *i.e.*, disturbances of "emotional" behavior.

Following the almost simultaneous publication of the effects of resection of the entire temporal lobe of monkeys (including the amygdaloid and Ammon's formations) by Klüver and Bucy^{81, 82, 83} and the theoretical inferences derived from anatomy about "emotional behavior" by Papez,¹¹⁶ a number of investigators have become interested in this problem. Klüver and Bucy, confirming an older report by Brown and Schäfer,⁸¹ found, amongst other effects, that temporal lobectomy resulted in marked tanning of monkeys. Papez suggested that the circuit nature of Ammon's formation, fornix, mammillary body, anterior thalamic nucleus, cingulate cortex, Ammon's formation, constitutes an anatomical base for emotional behavior. Experiments by Smith¹⁴³ and Ward,¹⁶² in which the anterior cingulate gyrus was resected with effects on general behavior similar to those described by Klüver and Bucy, tended to support the Papez hypothesis.

Another series of experiments, motivated by considerations other than those described above, have implicated the anterior rhinencephalic structures (especially of carnivores) in "emotional" behavior. Spiegel *et al.*¹⁴⁶ in acute preparations showed that the "rage reactions" observed previously in decorticated cats¹⁷ and after prechiasmatal incisions³⁴ could be obtained from lesions in the region of the olfactory tubercle and amygdaloid complex. In an extensive series of chronically observed cats, Bard and Mountcastle¹⁶ showed that ablation of the entire isocortical mantle failed to produce such symptoms; in fact, such cats became refractory to most stimuli.

lation. If additional damage was inflicted on either the midline (cingulate) cortex or to the region of the amygdaloid complex, the animal's threshold of excitation dropped markedly and "rage reactions" were displayed. When isocortex was uninjured, such reactions resulted only from ablations of the region of the amygdaloid complex—though, in many instances, only after a delay of several weeks. Removal of Ammon's formation resulted in a more "placid" animal. More recently Schreiner *et al.*¹³⁰ reported another series of carnivores in which extirpations in the region of the amygdaloid complex had been made. Contrary to Bard and Mountcastle, these authors found a marked diminution of "aggressive" behavior following such lesions. These latter results are in consonance with those obtained in primates; however, until adequate comparison of the precise locus of lesions is possible and until the postoperative environmental variables are controlled, no definitive statement resolving this discrepancy is possible. Nevertheless, irrespective of the direction of change, all studies agree that the dimension of change is "emotional" behavior.

Corroboration for some of the alterations observed to follow ablations of these structures comes from electrical and chemical stimulation. "Arrest," "avoidance," and "attack" may be provoked by such stimulation of the amygdaloid complex in the unanesthetized animal.^{55,99} In addition, ablation experiments in the immediate past have supported the findings that the structures classified as the second system (frontotemporal juxtalloccortex, amygdaloid complex, and septal region) are implicated in "emotional" behavior.^{25, 34, 113, 145, 163}

In some of these experiments, social¹³⁵ and other^{25, 163} environmental conditions have been rigorously controlled and the anatomical effect of surgery carefully specified. One series of such experiments demonstrated that behavior based on "fear" as measured by a conditioned avoidance response is especially disturbed by lesions of the frontotemporal cortex and amygdaloid complex. This finding, taken together with previously reviewed evidence, confirms the impression obtained from studies involving olfactory and gustatory behavior as well as those involving energy relationships (food intake, sleep, activity, and temperature regulation) that the second system serves a variety of functions which, thus far at least, cannot be easily subsumed under any "primary" category.

The major portion of the hypothesis of Papez has not fared as well in gaining adequate experimental support. Although promulgated and amplified in an excellent review by MacLean,⁹⁷ exploration of the effects of stimulation and resection of the supposed anatomical substrate of emotion have thus far been few and crude. The experiments of Smith and Ward concerning the effects of cingulate ablations have not been confirmed. Since neither Smith nor Ward presented anatomical verification of their lesions, or explored behavior by any systematic techniques, subsequent findings^{58, 120} must be considered. In addition, as already mentioned, systematic analysis^{21, 34, 35, 108, 109, 110, 135, 163} of the syndrome reported by Klüver and Bucy has thus far related the "emotional" and "social" changes in behavior fol-

lowing temporal lobectomy to involvement of the region of the amygdaloid complex. Studies from other laboratories^{25, 156, 158} confirm these findings and extend them to include the effects of lesions of the septal nuclei.¹¹³ Thus, at present, an abundance of evidence implicates the second rather than the third system in emotional and social behavior whereas evidence with respect to the functions of the third system remains sparse. A few stimulation studies^{67, 90} indicate that arrest of ongoing behavior sometimes results. These observations, however, are still fragmentary. Often seizure discharges can be recorded from Ammon's formation in the absence of any observable changes in an animal's behavior. We must face the fact that up to now there have been no reliable clues from behavioral studies as to the function of the third system.

Summary. The results of experiments utilizing behavioral techniques may be summarized as follows: Only the olfactory bulb has been implicated in simple olfactory discriminations. It is possible that resections of the primary system were not complete enough to result in olfactory discrimination deficits, since it has been found that, in vision,^{62, 140} somesthesia,^{135, 167, 168, 169} audition,^{42, 44, 73, 104} and gustation,¹⁴ removals of primary projection cortex must include practically the entire system before any discrimination deficit results.

Deficits in olfactory discriminations utilizing "negative" responses have, however, been reported to follow ablations in the region of the amygdaloid complex. Similar changes with respect to gustatory discriminations follows such lesions. These changes are not *generalized* to visual behavior nor do they extend to such tasks as delayed response. However, the effect of amygdala lesions is not *restricted* to olfactory-gustatory behavior. Changes in regulation of quantity of food intake, temperature regulation, and sleep-activity cycles occur. Furthermore, lesions anywhere in the second system (amygdaloid complex, septal region, and frontotemporal and subcallosal juxtallocortex) affect emotional behavior (*e.g.*, as measured by conditioned avoidance responses). It seems, therefore, premature to speculate regarding the "essential" function of the second system.

The third system has remained recalcitrant to date. Behavioral investigations have thus far been too crude and sparse to support Papez' much publicized speculations regarding the neural substrate of emotion.

Discussion

Studies of function have so far implicated only the olfactory bulb in simple olfactory discriminations. This may be due in part to difficulty in making total removals of the primary system, which is spread out along the length of the olfactory striae. A working hypothesis (based on anatomical knowledge of the connections of the primary olfactory system and the neuropsychological data obtained for the primary projection systems in vision, gustation, and somesthesia) would predict olfactory discrimination deficits to follow only when the greater portion of cortex which receives direct afferents from the olfactory bulb is removed. This hypothesis is testable with available surgi-

cal-anatomical and behavioral techniques provided a macrosomatic species is used.

A profusion of changes in an organism's behavior follows resections or stimulations of the second system. The following three formulations of these effects are possible:

(1) A simple hypothesis may be suggested to account for the variety of changes. It is possible that the second system as defined in this review must be further subdivided and that a separate function may ultimately be ascribed to each subdivision. If this is the case, the syndrome which follows lesions of the second system could be analyzed into components by selective ablations.

(2) On the other hand, the observed changes in olfactory-gustatory behavior (not simple preference threshold changes) *might* be related to changes in quantitative food intake, sleep-activity cycles, and basal temperature. These, in turn, *might* be related to the changes in "emotional" behavior as measured by the change in social reactions and in conditioned avoidance responses. At present, data are insufficient to formulate such a relationship in precise terms. Imprecisely, this hypothesis would consider one basic change in the organism's reaction to its environment to underlie the various manifestations. The changes in behavior following lesions of the second system are reminiscent of those following hypothalamic lesions; however, they are less drastic. Whereas an animal with hypothalamic damage will be either unreactive or become abruptly and vigorously hyperreactive to environmental change, the animal with lesions in the second allo- and juxtallocortical system will be hypo- or hyperactive within the limits of apparently adaptive and thus less "abnormal" behavior. It has often been stated that the key to understanding the cerebral isocortex lies in the dorsal thalamus; in a similar manner, the key to understanding the second allo- and juxtallocortical system may be found in the hypothalamus. As was pointed out, these changes in behavior cannot be ascribed solely to the relationship of hypothalamus and second system with autonomic and visceral mechanisms. There is no evidence of a *selective* afferent or efferent relationship between the autonomic nervous system and allo- and juxtallocortical formations. As is the case with stimulation of the hypothalamus, the massive autonomic discharge which follows excitation of many of the structures of the second system has obscured the equally massive mobilization of the somatic motor system which frequently occurs, especially in unanesthetized animals. The current obfuscation derives in part from the effects on emotional behavior produced by such stimulation; the acceptance of "visceral" theories of emotion, such as those of James⁶⁸ and Lange;⁶⁷ and the still older conceptualization of the basis of "feeling" which are carried in our everyday language.

(3) A third hypothesis concerning the variety of effects which follow resections and stimulations of the second system must be considered. It is possible that the second system (as well as the hypothalamus) serves several functions, not because it is composed of several subdivisions, each of which

is related to some separate function, but because the second system may, in the living organism, become a part of several larger systems. For example, it is possible that the olfactory-gustatory functions of the second system depend on the relationship between it and the primary olfactory and primary gustatory projections. The metabolic functions of the system may, on the other hand, depend on the relationship of the second system to the hypothalamus. Finally, the changes in socio-emotional behavior may be the result of interference with the interrelationship between the second system and the frontal isocortex. This hypothesis is based on a principle of cerebral organization other than the classical static one derived exclusively from the organization of the peripheral nervous system. Such a principle, that of "dynamic" organization, was proposed earlier in this review in a discussion of the criticisms of histogenetic data.

It seems fruitful to pursue investigations designed to test any of the hypotheses concerning the functions of the second system. At present there seems to be no basis for choosing one hypothesis rather than another except by personal preference which depends, in part, on the investigator's relative facility with anatomical, electrophysiological, surgical, or behavioral techniques.

In spite of the wealth of anatomical knowledge concerning the third system, experiments have contributed little to our understanding of its function. The hypothesis that this portion of the brain forms the neural substrate of emotion has thus far failed to find much experimental support. This may be due, at least in part, to the lack of careful behavioral investigation of the effects of stimulation or resection of portions of this system; investigations which are long overdue. The finding that stimuli which result in an animal's "arousal" and in "activation" of the electrical activity of the isocortex produce electrical hypersynchrony in Ammon's formation provides another avenue of approach to the problem. Part of the difficulty has been the surgical inaccessibility of these structures, a difficulty which has recently been overcome. Thus, relevant data may be expected to become available in the immediate future.

Summary. We have examined the basis for the current interest in the "olfactory brain." Of two acceptable definitions of "rhinencephalon," the broader, including both allo- and juxtallocortex, has been chosen because it subsumes available data parsimoniously. On anatomical grounds, three allo- and juxtallocortical systems have been distinguished. The first (made up of olfactory tubercle, area of the diagonal band, prepyriform cortex, and the corticomедial nuclei of the amygdala) is considered a "primary" olfactory system on the basis of its direct connections with the olfactory bulb. A second system (made up of subcallosal and frontotemporal juxtallocortex and the septal and basolateral amygdaloid nuclei) is connected with the primary system but not with the olfactory bulb and is characterized by subcortical as well as cortical components. The lack of anatomical differentiation between cortex and subcortex in this system is found whether phylogenetic, histogenetic, axonographic, physiological, or behavioral data are

considered. This system has been implicated in diverse functions: olfactory-gustatory, metabolic, and socio-emotional. Future investigation must determine whether some unitary function underlies the others, whether the multiplicity of functions reflects a multiplicity of subdivisions within the second system, or whether this system is, under different conditions, part of one or another larger system. Finally, a third allo- and juxtallocortical system (made up of Ammon's formation, entorhinal, and retrosplenial and cingulate cortex) can be distinguished from the others on a histogenetic, axonographic, and electrographic basis. The hypothesis that this system is the neural base of emotion has so far failed to receive conclusive experimental confirmation. This may be due in part to the lack of quantitative behavioral studies of the effects of stimulation or ablation of portions of this system and to their surgical inaccessibility. These shortcomings are being overcome and relevant data should be forthcoming.

We must end this review with the thought that the "olfactory brain," as defined, is not primarily olfactory though parts of it serve olfactory functions. Nor is the current conception of a "visceral brain" more tenable though visceromotoric functions are also served. It is clear that the formations in this portion of the brain, though they share several characteristics, are not, at this time, usefully thought of as a brain serving any *one* function. Since at least three distinct systems can be delineated, each might profitably be investigated separately before an attempt is made to define what functions they have in common. Current speculation has provided impetus to the systematic accumulation of data; however, if this accumulation is to continue, the formation of hypotheses must become more specific and remain sufficiently flexible to incorporate its product.

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