Introduction

Perspectives on Cingulate Cortex in the Limbic System

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Because of the brain's extensive interconnections, it is sometimes said that it is impossible to establish limits on a system of structures and, therefore, makes no sense to speak of a "limbic" system. Based, however, on the comparative morphology of the mammalian brain and what is known about its functional neuroanatomy, one can, by the application of Occam-type rules of definition, arrive at an acceptable construct of what is meant by the term *limbic system*. The central unifying concept of the limbic system is that, in a modular sense, limbic cortex and its primary brainstem connections constitute a functionally integrated system.

This introduction seeks to establish the broad context and historical perspectives for the present volume. It begins with a short historical account of basic observations leading to the limbic system concept and then gives a summary of how views regarding limbic functions have developed over the past century. It helps to gain perspective of the diverse clinical and experimental findings if it is kept in mind that the evolution of the limbic system parallels the evolution in mammals of their family way of life. Throughout these considerations the particular place of cingulate cortex in the limbic system is stressed and, in the final part of this account, reasons are presented for focusing on cingulate cortex and "limbic" thalamus.

Basic Considerations

The Term Limbic

In regard to the term *limbic* and its use in describing the comparative morphology of the mammalian brain, the starting point must be the 1878 article by Paul Broca, French physician and pioneer anthropologist. It was Broca's special contribution to provide evidence that a large cerebral convolution, which he called "the great limbic lobe," exists as a common denominator in the brains of all mammals. Figure I.1 is a reproduction of Broca's first figure illustrating the medial aspect of the otter's brain. He used the word *limbic* because it is purely descriptive and indicated that the convolution occupies the border of the hemisphere surrounding the brainstem. He pointed out that 40 years earlier Gerdy referred to the same structure as the "annular convolution," whereas Foville described it has having the appearance of a "pull-string purse." Broca's own account is significant because it is based on a comparative study of a large variety of mammals. In the 34 figures in his article, Broca illustrated different views of the lobe in 17 mammalian species, including aquatic types represented by the otter, seal, and dolphin. In gyrencephalic animals, he pointed out that the rhinal and limbic fissure

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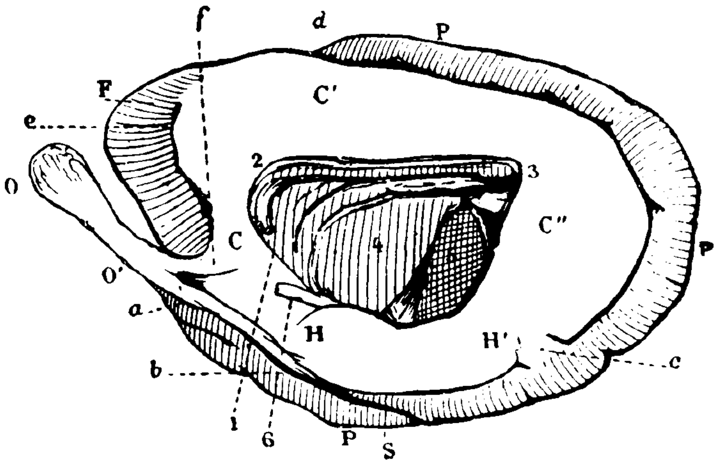

Fig. 1. *Schéma de la face inféro-interne de l'hémisphère droit de la loutre.*

FIGURE I.1 . In Broca's first figure in his article of 1878, he illustrates the location and configuration of the great limbic lobe in the otter's brain (unshaded area labeled with H's and C's). Olfactory bulb, O.

or "scissure" mark a boundary between the limbic lobe and the rest of the hemisphere. Elliot Smith (1902) should be consulted for further details regarding terms for variations in Broca's *"limbique scissure."*

Distinctive Features of Limbic Cortex

The next step in reaching a definition of the limbic system is to characterize the distinctive structural features of limbic cortex. By the year 1900 enough had been learned about the embryology and cytoarchitecture of cortex for E.A. Schäfer (1900) to state in his authoritative *Text-Book of Physiology* that limbic cortex "is phylogenetically and ontogenetically the oldest, and in many vertebrates remains throughout life the most important part of the cortex."

The phylogenetic judgment regarding the cortex could be made partially on the basis of comparative observations of reptiles and birds, but at the time no agreed-upon terms for different types of cortex existed. Names for different types of cortex developed somewhat accidentally. In a landmark article in 1901, Elliot Smith, using Reichert's term pallium, referred to cortex of the parahippocampal gyrus and the hippocampus as "old pallium" and designated cortex of the rest of the hemisphere as "neopallium." Much to Smith's disgust (1910), the German neurologist Edinger translated the expression old pallium as "archipallium," for which archicortex became a synonym. The neopallium became known as *neocortex.* Ariëns Kappers (1909) introduced the term *palaeo-cortex,* which implied "younger than archicortex" for cortex of the piriform area.

By characterizing cingulate cortex of the limbic lobe as neopallium, Smith (1901) appears to have set a precedent for its subsequently being referred to by some authors as neocortex. Dart, for example, who had been one of Smith's students, published an influential study entitled "The Dual Structure of the Neopallium" (1935), in which he referred to the "parahippocampal neopallium" and the "parapyriform neopallium." Abbie (1942) adhered to the same characterization in elaborating on the proposition that the cerebral cortex evolved by "successive waves of circumferential differentiation." In an anatomicoevolutionary sense, however, most of cingulate cortex represents a transitional form of cortex.

Some anatomists of the Vogt school attempted to classify cortex on the basis of its fetal development. In this respect, Brodmann (1906) set the precedent by stating that a Nissl stain of the human fetal brain at 6 months shows that most of cortex has six alternating light and dark layers. He referred to this stratification as the tectogenetic basic type. The rest of cortex not showing the basic six layers was called *heterogenetic cortex.* The tectogenetic basic type is the isocortex of O. Vogt, while the heterogenetic is Vogt's allocortex (cf. Lorente de Nó, 1933).

Upon maturation, isocortex may show six layers more or less but regardless of that, it is usually defined as *neocortex,* whereas the allocortex would correspond to *archicortex* and *paleocortex.* It is evident that none of these terms describe what was referred to earlier as transitional cortex of the cingulate gyrus. Before enlarging on this matter, it should be noted, as Lorente de Nó (1933) forcefully contended, that the Nissl picture of cortical layering in the fetus may differ in significant detail from what is seen in corresponding Golgi preparations. Nevertheless, this same critic refers to Nissl descriptions of M. Rose (also of the Vogt school) as "a very remarkable piece of work" and agrees with the observations but not the interpretation (Lorente de Nó, 1933). Rose (1926, 1927) concluded that there were three main types of cortex that originate from a basic two-, five-, and seven-layer stage. He identified most of cingulate cortex as originating from the five-layered type (quinquestratificatus). Regarding it as transitional between archicortex and neocortex, he referred to it as "meocortex" (Rose, 1926). Since then some authors have borrowed other terms to apply to the same transitional cortex, such as Filiminoff's term *juxtallocortex* (Pribram and Kruger, 1954) and Vogt's term *proisocortex* (Sanides, 1969).

The next observation is so important and so germane to what has been described that it deserves to be set off in a paragraph by itself. In his comparative embryological study of 1926, Rose states that the five-layered cortex—*fünfschichtige Rinde*—(i.e., his *mesocortex*) found in the cingulate gyrus *appears for the first time in mammals* (p. 121).

System Definition

Given the evidence that the limbic convolution is a common denominator of the mammalian brain and that the enveloping cortex differs from that of neocortex, one can proceed to select criteria that would make it possible to decide whether or not limbic cortex and its connections comprise, in a modular sense, an integrated system. The first requisite for such a definition is to include only limbic-type cortex, the amygdala and septal portions of the telencephalon and their primary connections with the brainstem. The second requisite is to take into account the interconnectivity within the limbic lobe itself. The strength of such rules is illustrated by anatomical connection studies of cingulate cortex of the macaque monkey published in two articles by B.A. Vogt and coworkers (Vogt et al., 1987; Vogt and Pandya, 1987). It is unfortunate that computerization has not advanced to the stage where it is an easy and inexpensive matter to include both the text and figures together with halftones of these two articles on disks as an appendix to this volume.

Electrophysiological Evidence

At this point it should be interjected that nothing serves to illustrate more that limbic cortex and its primary brainstem connections constitute an anatomically and functionally integrated system than to map the propagation of neuronal afterdischarges included in limbic structures by electrical stimulation (Kaada, 1951; Creutzfeldt, 1956; MacLean, 1957). One consistently finds that the propagating nerve impulses stay within the confines of limbic circuitry. Similar observations have been made during therapeutic neurosurgical procedures (e.g., Feindel and Penfield, 1954; Pagni, 1963; Jasper, 1964).

Biochemical Evidence

There also exist a number of chemical reasons for considering the limbic lobe itself as forming a system. Perhaps the earliest evidence in regard to the entire lobe was the autoradiographic finding in rats that, following the parenteral injection of ^{35}S-labeled L-methionine, there was a high uptake of this compound in the allocortical structures and cingulate mesocortex that distinguished limbic cortex from that of the rest of the hemisphere (Flanigan et al., 1957). With respect to this observation the findings of Levitt and coworkers are of particular interest (Levitt, 1984; Zacco et al., 1990). They identified a "limbic system-associated membrane protein" that is expressed throughout the limbic system. Localization of this protein leads one to question what relevance it has to the long-recognized predilection of certain viruses to invade limbic cortex in various forms of limbic encephalopathy, as, for example, the case described by Friedman and Allen (1969) in which the entire limbic lobe was involved. In this volume, one will find extensive reference to special receptor, chemical, and other distinctions of limbic structures, which new methods in molecular biology and immunohistochemistry have made possible.

History of Functional Concepts

As Broca explained in his 1878 article, *limbic* does not imply any theory in regard to function. For that same reason in an article appearing in 1952, the present author found it useful to introduce the expression *limbic system* as a designation for the limbic lobe and its primary connections with the brainstem. A descriptive word, rather than one implying function, is less conducive to a rigidity of thinking about how particular structures function. But this was not the fate with Broca's term, because it would be substituted for a functional name. Broca himself suggested that the characteristic presence of the limbic lobe in the mammalian brain indicated that it subserved animalistic functions, while the evolutionary expansion of the rest of the hemisphere indicated that it accounted for "intelligent" behavior. In the following year he formalized this suggestion by referring to the limbic lobe as the *"cerveau brutal"* and to the rest of the hemisphere as the *"cerveau intellectuel"* (Broca, 1879). In addition, Broca further elaborated that because of the robust connections of the rostral parts of the limbic lobe with the olfactory apparatus, the *entire* convolution was perhaps implicated in olfactory functions. In stating these suggestions, however, he did not propose any changes in his anatomical terminology.

Olfactory Functions

The rapidity with which Broca's suggestion of olfactory functions found popular appeal was illustrated by what E.A. Schäfer said in his well-known *Text-Book of Physiology.* In his words, "Broca was of the opinion that the whole limbic lobe is related to the sense of smell, although he fully admitted the probability of its having also another unknown function, as shown by its development in some anosmatics" (Schäfer, 1900, p. 765). Then he stated in a footnote that Broca's interpretation "has been followed by all subsequent writers," notably Schwalbe (1881), Zuckerkandl (1887), and Retzius (1897). Whereas Turner (1890) had appropriated the term *rhinencephalon* for use in a restricted sense, others extended the designation to apply to the entire limbic lobe. (See Smith, 1901, for further historical details.)

Because olfaction was regarded as an unimportant sense in human beings, the rhinencephalon received short shrift in the teaching of neuroanatomy. This is illustrated by what one anatomical authority stated in a 1957 book on the evolution of the brain

(Lassek). It stated that the rhinencephalon "probably has not contributed greatly to the evolution of the human brain and will . . . not be considered further" (Lassek, 1957).

In "Functions of the 'Olfactory Brain'," Pribram and Kruger (1954) included the entire limbic lobe in their definition of the rhinencephalon. They explained that their review was undertaken because "renewed interest in the 'olfactory brain' has been provoked by the suggestion that in mammals this portion of the brain serves emotional rather than olfactory functions." Starting with the olfactory bulb, which they "considered analogous to the thalamus," they divided the rhinencephalon into three systems on the basis of primary, secondary, and less direct connections with the olfactory bulb. In their words, "The first consists of primary olfactory structures apparently directly related to the . . . 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" and appears "to be remotely, if at all, related to olfactory afferents." In anticipation of the next topic to be discussed, the point of this listing is to call attention to their conclusions about the role of their designated second and third systems in emotional behavior. They concluded that the second system was implicated in diverse "olfactory-gustatory, metabolic, and socioemotional functions." In contrast, they said that experimental work on the third system had "contributed little to our understanding of its function" and that the hypothesis that it "forms the neural substrate of emotion has thus far failed to find much experimental support." It should be emphasized that their review focused mainly on experimental findings in animals and, as will be brought out subsequently, failed to take into account clinical developments providing the best evidence, and indeed the only subjective evidence, that the limbic system is basically involved in the experience and expression of emotional feelings.

Emotional Functions

Since behavioral manifestations provide our only means of evaluating the subjective state of another individual, Descartes's word *emotion* serves as a suitable term for what we identify as an expression of emotional experience. Subjectively speaking, emotional feelings are more properly denoted as *affects* (see later).

Despite the rhinencephalic designation given to the limbic lobe, a few authors singled out certain limbic structures as possibly having other than olfactory functions. For example, in his Croonian Lectures, Elliot Smith (1919) suggested that olfactory structures of the temporal lobe, unlike those of other sensory systems, might provide "an affective tone" that combines anticipation and consummation into one experience and thereby seed the germ of memory. Dart (1935), who had studied with Smith, suggested that parahippocampal cortex may play a role in controlling "reactions associated with the expression of emotion."

Prior to 1937, it appears that no one had devoted an entire article contending that the whole limbic lobe accounted for other than olfactory functions. In that year Papez, neurologist and comparative neuroanatomist at Cornell University, published an article proposing that the entire limbic lobe was implicated in the experience and expression of emotion. Calling attention to findings that the hypothalamus was essential for the expression of emotion, he pointed out that the limbic lobe contained the only telencephalic cortex with strong hypothalamic connections. He then cited case material and other evidence indicating that the limbic lobe was involved in elaborating both the experience and expression of emotion. According to his proposal, "The central emotive process of cortical origin may be . . . conceived as being built up in the hippocampal formation and as being transferred to the mamillary body and thence through the anterior thalamic nulcei to the cortex of the gyrus cinguli. The cortex of the cingulate gyrus may be looked on as the receptive region for the experiencing of emotion as the result of impulses coming from the hypothalamic region, in the same way as the area striata is considered the receptive cortex for photic excitations coming from the retina" (p. 728).

At the time there was little indication that Papez's proposal attracted much attention. During the succeeding years, however, there was developing in the field of clinical electroencephalography the best evidence, and indeed the only subjective evidence, that structures in the temporal part of the limbic lobe were fundamentally involved in emotion. In 1938, the term *psychomotor epilepsy* was given to a condition that frequently occurred without convulsions but in which the onset was marked by a wide range of vivid emotional feelings, viscerosomatic manifestations, and other psychic experiences, followed by automatisms with obliteration of memory for anything that happened after their onset (F.A. Gibbs et al., 1938). Ten years later in a landmark article, E.L. Gibbs et al. (1948) reported their findings that in psychomotor epilepsy the epileptogenic focus appeared to be most often located in the anterior temporal region. The present author's research at that same time called for the use of improved nasopharyngeal electrodes for recording the electroencephalogram (EEG) at the base of the brain. Using leads from these electrodes, together with those from newly devised, soft tympanic electrodes, and from electrodes on the ear lobes, we recorded both the standard and basal EEG in a group of patients with psychomotor symptoms but with no previous localizing EEG signs (MacLean and Arellano, 1950). During light sleep, a majority of these patients showed spiking activity with maximum amplitude in the recording from one of the nasopharyngeal leads. Since the nasopharyngeal electrode is the one nearest the medial part of the temporal lobe, it was suggested that the epileptogenic focus might involve the hippocampal formation.

A Further Elaboration

Archicortex of the hippocampal formation was regarded as part of the olfactory apparatus. How, then, was one to explain not only the vivid emotional feelings experienced during the aura but also symptoms involving one or more of the sensory systems, particularly the visual, auditory, and somesthetic systems? In 1948 I discovered the article by Papez (1937) and asked him if he could suggest an anatomical explanation of involvement of the sensory systems in question (MacLean, 1978). With a specimen of the human brain, he exposed "association pathways" that could potentially connect visual, auditory, and somatic neocortical areas with the parahippocampal gyrus that in turn projects to the hippocampus. Later neuronographic studies in the monkey provided experimental support for such stepwise inputs to the parahippocampal gyrus (Pribram and MacLean, 1953), and neuroanatomical findings proved to be in essential agreement (e.g., Jones and Powell, 1970; Van Hoesen and Pandya, 1975). Of greater hodological interest, our microelectrode studies in which we recorded evoked unit activity in awake, sitting *Saimiri* monkeys furnished evidence of more direct connections to respective limbic areas via the brainstem, including inputs from interoceptive systems (see MacLean, 1990, pp. 469–498, for summary and significance).

Subsequent to visiting Papez, I wrote an article (1949) on new developments bearing on his proposed mechanism of emotion. In regard to the anatomy, emphasis was given to the possible connections of the visual, auditory, and somatic connections with the parahippocampal gyrus. It was also suggested that in the hippocampal formation "the possibility exists . . . for bringing into association not only oral (smell, taste, mouth) sensations, but also impressions from the sex organs, body wall, eye, and ear." Using the word *visceral* in its sixteenth-century meaning of "strong inward feelings," I referred to the rhinencephalon as the "visceral brain." The thrust of the just-mentioned anatomy and the article itself was that the visceral brain derives information in terms of feeling and "eludes the grasp of the intellect because its animalistic and primitive structure makes it impossible to communicate in verbal terms." "This situation," it was suggested, "provides a clue to understanding the difference between what we 'feel' and what we 'know'."

Neurosurgical Observations

In the succeeding years the most crucial findings regarding emotional functions of limbic structures were derived in the course of neurosurgical procedures for the treatment of psychomotor epilepsy, which was also referred to as temporal lobe epilepsy or limbic epilepsy and, since 1970, as complex partial seizures. The most extensive and definitive observations were made by Penfield and Jasper (1954) and colleagues at the Montreal Neurological Institute. They frequently found a long-standing sclerosis (a yellowish, rubbery scarring) extending out from the hippocampal region with variable involvement of neighboring cortical areas. Electrical stimulation in the region of an ictal focus would often reproduce the usual symptoms of the aura which in one case or another involved a wide range of emotional feelings.

In the realm of subjective experience, a person's emotional feelings are referred to as *affects,* a term distinguishing them from emotion as it was behaviorally defined earlier. Affects may be qualified as agreeable to disagreeable feelings that "impart subjective information that is instrumental in guiding behavior required for self-preservation and preservation of the species" (MacLean, 1990, p. 425). Given such a definition, the phenomenology of psychomotor epilepsy indicates that limbic structures are implicated in generating three main forms of affects which may be designated as basic, specific, and general (MacLean, 1990, p. 426ff.). The basic affects apply to gradations of feelings associated with basic bodily needs such as feelings of hunger and thirst arising with the need for food and water and so on. The specific affects are agreeable or disagreeable feelings identified with specific sensory systems and include the so-called aesthetic or cultural affects. The general affects include what we commonly regard as emotional feelings. They are called *general* because they may pertain to individuals, situations, or things. Unlike the basic and specific affects, they do not depend on specific pathways to the sensorium and may occur and persist as the result of mentation. In case histories the words used by patients in describing their feelings during the aura represent a virtual thesaurus of basic, specific, and general affects.

Because of the regularity with which automatisms and the associated amnesia occurred with electrically induced afterdischarges in the medial temporal region, Feindel and Penfield (1954) were inclined to regard the amygdala and hippocampal formation as essential for the memory of ongoing experience. Both before and since then, case histories have accumulated showing that extensive bilateral damage of the hippocampus may result in a profound inability to retain the memory of ongoing experience. Elsewhere I have proposed that the amnesia for what occurs after the onset of automatisms in psychomotor epilepsy suggests insights into the underlying mechanisms. As noted earlier, both anatomical and electrophysiological evidence indicate that the diverse inputs to the hippocampal formation from the brainstem and certain limbic and neocortical areas provide special conditions for the integration of information from interoceptive and exteroceptive systems. It is premised that such an integration is essential for a sense of self without which self-referenced memory could not occur. It is therefore suggested that the propagation of a seizure discharge associated with the onset of the automatism interferes with the integration of internally and externally derived experience requisite for a sense of self and the valences for the memory of ongoing experience (MacLean, 1990, p. 512ff.).

Developments Relating to Cingulate Cortex and Limbic Thalamus

In turning, finally, to the purpose for focusing on cingulate cortex and limbic thalamus in this volume, it is especially relevant to keep in mind what was said initially about the evolution of the limbic system—namely, that it represents the history of the evolution of mammals and their family way of life.

Three Subdivisions of the Limbic System

If one uses the limbic lobe itself, rather than the olfactory bulb, as the starting point, one can, on the basis of anatomy and functions, arrive at quite a different parcellation of limbic structures than the one described by Pribram and Kruger. Here again three main subdivisions are apparent, but in this case each division consists of a sector of limbic cortex having connections predominantly with a particular group of nuclei (cf. MacLean, 1990). Since the focus here will be on the so-called thalamocingulate division, only brief mention will be made of the other two. The cortical sectors predominantly associated with the nuclei of the amygdala and septum, respectively, make up the so-called amygdalar and septal divisions. Experimental work indicates that the amygdalar division is primarily connected with self-preservation as it pertains to the search for food and feeding, as well as the fighting and defense that may be required in obtaining food. On the contrary, there is evidence that the septal division is involved in the elicitation of elemental sexual functions and behavior conducive to sociability and procreation.

The thalamocingulate division has become of special interest because it has been found to be involved in three forms of family-related behavior, that distinguish the evolutionary transition from reptiles to mammals—namely, nursing in conjunction with maternal care, audiovocal communication for maintaining maternal-offspring contact, and play. This division consists chiefly of the mesocortex of the cingulate gyrus and its associated nuclei of the thalamus, hence the designation thalamocingulate division. Significantly, there is no definite represention of any part of this division in the reptilian brain (Clark and Meyer, 1950).

Therapsid-Mammalian Transition

At this point it is worth a reminder that the mammal-like reptiles (therapsids) are considered to be the antecedents of mammals. There were several lines of therapsids that were showing physical changes approaching the mammalian condition in what is termed *directional evolution*. In some of the advanced therapsids, the resemblance was so close to mammals that the most reliable distinction has proved to be the presence in the therapsid jaw joint of two small bones that become the malleus and incus of the mammalian middle ear. It is to be emphasized, however, that cranial endocasts reveal that the therapsid brain was reptilian in its morphology. This last observation must be considered in the light of maternal behavior. Most lizards, for example, which have an auditory apparatus and postcranial skeleton resembling therapsids, lay their eggs and leave them to hatch on their own, and the young must fend for themselves. The young of some species must hide in deep underbrush or, like those of the giant Komodo dragon, retreat to the trees so as to avoid being cannibalized by their parents or other adult lizards.

This behavior is to be contrasted with the condition of young mammals for which any prolonged separation from the mother is fatal. Granted an ignorance of evolutionary mechanisms, the drastic nature of this situation may have been a factor in contributing to the "separation cry" that appears to be characteristic of most mammals. The earliest mammals are inferred to have been tiny, nocturnal animals living in the dark floor of the forest, and it is apparent that the separation cry would have helped to ensure the contact of mother and young. For that reason, it has been suggested that the separation cry may represent the earliest and most basic of mammalian vocalizations.

Since the mammal-like reptiles had an auditory apparatus like that of lizards, it is probable that they, too, were hard of hearing and may not have vocalized. If they were also cannibalistic, it would have promoted survival of the young if, unlike baby mammals, they did not call attention to themselves by making a separation cry. It should be noted here, however, that there exists one fossil find in South Africa in which the skull of an immature therapsid was next to another of adult size, suggesting to the discoverer the possibility of parenting (Brink, 1955).

Maternal Behavior

Stamm in 1955 appears to have been the first to report that ablations of cingulate cortex disrupted maternal behavior. In view of the importance of this revelation in regard to the evolution of mammals, it is curious that since then it has attracted so little interest. He made observations on three groups of impregnated rats, one group of which served as controls, one group that had ablation of cingulate cortex, and one group with neocortical ablations of equal size along the border of cingulate cortex. All groups delivered litters with an average of about nine pups. In contrast to the control group and those animals with neocortical lesions, the animals with cingulate lesions failed to construct a preparatory nest and were deficient in performing the five expected postpartum forms of maternal behavior. Only 12% of the pups survived. In 1967, Slotnick reported a confirmation and extension of Stamm's observations.

We obtained confirmation in another kind of experiment in which cortical ablations were made in hamsters on the second neonatal day. Both male and female animals deprived of neocortex grew and developed normally, manifesting every form of hamster-typical behavior. But if, in addition, cingulate cortex was ablated the females showed the same kind of deficits in maternal behavior as already noted (Murphy et al., 1981).

Playful Behavior

In the experiments on hamsters described earlier, unexpected and particularly notable findings pertained to one of the three forms of behavior that distinguish the evolutionary transition from reptiles to mammals—namely, playful behavior. In rodents, play behavior is commonly characterized as "play fighting." In hamsters, play fighting in the nest may be expected to occur as early as the thirteenth day. In both female and male hamsters with the additional ablation of cingulate cortex, play behavior failed to develop.

Separation Cry

The third form of behavior of the family-related triad that characterizes the evolutionary transition from reptiles to mammals is audiovocal communication for maintaining maternal-offspring contact. As already described earlier, it is typically manifest in mammals by the separation cry. As illustrated by *Saimiri* monkeys (see later), the cry also becomes used for maintaining contact among members of an affiliated group. It appears that as yet the only experimental work focusing specifically on the cortical representation of the cry has been performed on monkeys. As originally described by W. K. Smith (1945), it is well established that anterior cingulate cortex is one of the two cortical areas in the monkey where electrical stimulation elicits vocalization. Consequently, in a study dealing specifically with the cortical localization of the separation cry, Newman and I focused on the rostral limbic cortex, comparing also the effects of ablations of midline frontal neocortex on the pre- and postoperative production of the cry by *adult Saimiri* monkeys. Since the testing is done while the subjects are isolated in a soundproof chamber, the cry under these conditions is referred to as the "isolation call." Somewhat like a fingerprint, the sound spectrogram is characteristic for each individual monkey and is typified by a somewhat sustained tone in a frequency range of 10 kHz. In experiments with 10 monkeys, the process of elimination showed that a continuous strip of paragenual and subcallosal cingulate cortex is requisite for the spontaneous production of the isolation call (MacLean and Newman, 1988).

Implications of Findings on Family-Related Behavior

As a preface to a brief discussion of the implications of the earlier research on family-related behavior, it is to be noted that the findings are relevant to the questions raised earlier about the justification of referring to limbic structures as a system and the role of the thalamocingulate division in emotional functions. The continued surfacing of such questions is illustrated by an article which made these three comments:

> There are no . . . accepted criteria for deciding which brain areas belong to the limbic system.
>
> There is little evidence that limbic areas . . . function together as an integrated system in the mediation of emotion.
>
> Most limbic areas tend to be more involved with cognitive processes such as . . . declarative memory, than with emotional processes (LeDoux, 1991).

The last statement would seem to imply that cognition and memory were incompatible with any system that arrived at decisions on the basis of affective feelings rather than abstract thought. The following comments need not linger on that matter, but will deal first with some of the implications of the observations on the separation cry and play and conclude with pointing out the significance of research on maternal behavior to family and social attachments in general.

Pain of Separation

It has been said that a condition that makes being a mammal so painful is separation. In an evolutionary sense, one might speculate that the roots of the painful aspects of separation are traceable to the drastic consequences of separation of mother and offspring when nursing became a mammalian way of life. In this connection it is of interest that the implicated cingulate area for the separation call is innervated by nuclei involved in the perception of pain (see MacLean, 1990, p. 541). It is also pertinent that there is a high concentration of opioid receptors in cingulate cortex (see, e.g., Hiller et al., 1973; Kuhar et al., 1973; Wise and Herkenham, 1982; Chapter 10 of the present volume). It has been recognized for many years that the administration of opiate drugs to dogs and other animals greatly reduces the number of cries resulting from the distress of separation (Panksepp et al., 1978). Apropos of this negating effect of cingulate ablations on the separation cry of adult squirrel monkeys, Newman and coworkers (1982) observed that small doses of morphine sulfate suppressed their cries, whereas the antagonist naloxone reinstated the cries. It is said that morphine relieves human feelings of separation (e.g., Panksepp et al., 1978), leading to the suggestion that more than the sought-after state of euphoria, those suffering from opiate addiction seek relief from feelings of social isolation and alienation.

Clinical Findings on Crying and Laughing: Relevance to Emotion and Limbic Integration

The question as to brain mechanisms of crying and laughing has been one of the unresolved problems of clinical neurology. Physiologically, the autonomic and somatic manifestations of crying and laughing are the type that rids the body of something noxious. With crying the affect is one of dejection, whereas with laughing it is one of relief. Although chimpanzees and gorillas display faciovocal and gesticulating manifestations of crying and laughing, human beings are the only creatures known to shed tears during either condition. Consequently, comparative neurobehavioral studies of the kind described in regard to crying would give only an incomplete picture of the nature of the underlying neural mechanisms in human beings. The outlook is only slightly less hopeless in investigating the fragile behavior of play in primates, in which, the "squeals" of *Saimiri* monkeys associated with play might be considered the equivalent of laughter.

The finding that rostral cingulate cortex is implicated in the spontaneous production of the separation cry made it desirable to review clinical case material with respect to the localization of epileptogenic foci and lesions associated with crying and laughing, as well as places where electrical stimulation elicited these manifestations during neurosurgical intervention. The outcome of the review involves too much detail to be described here, but the substance of it may be summarized by saying that implicated structures, both with respect to tearing and the somatic manifestations, were located in structures of the "Papez circuit," namely, the rostral hippocampal formation and contiguous amygdala, mamillary bodies, anterior thalamus, and midline frontocingulate cortex (MacLean, 1990, pp. 534-538).

Since laughter is identified with affective feelings opposite and reciprocal to those of separation, the clinical findings in regard to both phenomena suggest their reciprocal innervation not only within the thalamocingulate division but also with other parts of the limbic system. In view of the common association of feeding or feasting with successful or triumphant occasions, it evinces no surprise that ictal discharges or electrical stimulation in certain parts of the amygdalar division may be associated with eruptions of laughter. But the frequently observed association of grief with hunger and eating has seemed paradoxical. The existence of a neural substrate for these manifestations in the frontotemporal region of the amygdalar division is suggested by the case study of psychomotor epilepsy. For example, a patient with an epileptogenic focus in this region described his aura to me as a feeling of sadness and wanting to cry followed by a feeling of hunger and a welling up of tears.

Granted the perplexity in regard to motor mechanisms of crying and laughing, an analysis of clinical and anatomical data suggests links of the frontal lobe with striopallidonigral, pallidothalamic, and cerebellar circuits (MacLean, 1990, pp. 539–541). A case described by Rubens (1975) indicates that the supplementary motor area may play an adjuvant role. Following a vascular lesion involving that area, the patient is said to have been aphonic for 10 days, with "weeping and hearty laughter not accompanied by any sounds." In view of the "cingulate motor areas" (Chapter 14 of this volume), it will be important to be mindful of these same areas in the analysis of cases involving crying and laughing.

Maternal and Other Forms of Affiliation

Based on some writings, one would get the impression that the limbic system functioned as a whole in generating diffuse emotional feelings. This may be owing in part to the recognition that electrical stimulation of respective parts of the limbic lobe elicited a wide variety of autonomic-related responses. In his classic 1951 monograph on the comparative physiology of "rhinencephalic structures," Kaada reviewed the prior work that had been performed. The only autonomic-related manifestation not known about at that time was the representation of elemental genital functions in the forebrain and, in particular, the septal and thalamocingulate divisions of the limbic system (MacLean, 1990, pp. 348–350, 356–372). The idea of limbic generation of diffuse emotional feelings seems to have accounted for some of the psychosurgical procedures once employed in the treatment of mental illness. On the contrary, the picture emerging from the studies reviewed here would indicate that different divisions of the limbic system may be implicated in forms of emotional feeling and expression germane to their respective functions. Since in the case of the cingulate gyrus there existed no experimental background in regard to family-related functions, there were no clues as to what alterations to look for in patients with various spontaneous or surgical lesions involving the cingulate gyrus and neighboring structures. It would have been helpful, for example, to have had in mind the kind of questions raised by Benes in Chapter 20 of this volume. When considering the symptomatology of schizophrenia in relation to changes seen in the cingulate cortex, she observes, "It is rare for a schizophrenic [patient] to marry and have children. When female schizophrenics do conceive, they are generally unable to care for and nurture their child."

Although the neural substract is incompletely known, it is recognized that reproductive hormones play an important part in the initiation and continuation of maternal affiliation. In regard to cingulate mechanisms it is to be noted that electrical stimulation of paragenual cortex in the cat elicits milk ejection dependent on the paraventricular release of oxytocin (Beyer et al., 1961). In view of the side-by-side midline cortical representation of the nipple and genital (Penfield and Rasmussen, 1952), it is possibly of some correlative interest that stimulation of the paragenual region elicits penile erection (MacLean, 1959, 1990) and that injection of oxytocin into the paraventricular nucleus results in priapism (Melis et al., 1986). The release of oxytocin leading to contraction of the myoepithelial cells of the mammary glands is known to result from nipple stimulation, and it is possible that one pathway for the reflex arc might be via the vagal nucleus to rostral cingulate cortex (cf. Chapter 6 of this volume). How, one might ask, does the feedback from the mammary glands affect the disposition and calling of a mother separated from her young? This question might also extend to forms of depression seen clinically in women, resulting, as it were, from separation reactions in vacuo.

The relevance of oxytocin to affiliation has presented itself from another perspective. In rodents, autoradiography has shown that oxytocin receptors have different concentrations in certain brainstem and cortical structures of different species. Although of unknown significance, it is of interest to point out in the present context that Insel and Shapiro (1992) found that the oxytocin binding in rostral cingulate cortex of the monogamous vole is considerably greater than that of the polygamous vole. Taking into account what has already been learned about the role of oxytocin in affiliation, the authors propose that the results of their study may be a reflection of the different social organization of these two species of voles.

It is impossible here to give proper emphasis to the important role of play in mammalian evolution and in human creativity in the arts and sciences. In regard to affiliation, one must take into account its inferred role in promoting harmony in the nest and its more obvious contribution later on to group and larger social affiliations. During temporary or longer interruptions in affiliations, various equivalents of the separation cry serve to prolong the spirit of adhesiveness among individuals.

Finally, in contemplating the nature and direction of future research, it is to be remembered that the thalamocingulate division, as it has been defined here, reaches its greatest proportions in the human brain. If further investigation involving the diagnosis and treatment of disease of the cingulate mesocortex and limbic thalamus should support and give additional information regarding a role in the family-related functions considered above, it would have momentous implications not only about the evolution of the human cerebrum but also about the cultural evolution taking place before our very eyes. The respective struggle for self-preservation and the survival of the species may be regarded as two basic life principles. Both can be promoted by long-range anticipation and planning for the future. Parental concern for the survival of human progeny is now involving activities and calculations for colonizing other worlds. The question arises that were it not for the great development of the limbic thalamus and cingulate cortex, would there have been the large growth of the connecting granulofrontal neocortex requisite for foresight and planning? Without the limbic thalamocingulate division with its parental concern underlying empathy and altruism, would we be witnessing for the first time in the known history of biology the evolution of beings with concern not only for the future of their own kind but also for the suffering and dying of all living things?

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