A New Anatomical Framework for Neuropsychiatric Disorders and Drug Abuse

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Histotechnological breakthroughs in the late 1960s paved the way for anatomical discoveries that led to the concepts of the ventral striatal-pallidal system and the extended amygdala. These two macro-anatomical systems, together with the basal nucleus of Meynert, represent the main components of the new anatomy of the basal forebrain. The concept of the ventral striatal-pallidal system provided the first indication of the existence of parallel cortical-striatal-pallidal-thalamic-cortical circuits, which in turn led to the theory of segregated cortical-subcortical reentrant circuits as a conceptual framework for the study of neuropsychiatric disorders. The multifarious symptoms of neuropsychiatric disorders, however, cannot be understood unless the extended amygdala, the basal nucleus of Meynert, and the septal-diagonal band system are also included in such deliberations. All of these systems serve as output channels for activities in the greater limbic lobe, which usually is critically involved in neuropsychiatric disorders. Within the context of the new anatomy of the basal forebrain, structures such as the accumbens, the olfactory tubercle, and the amygdala have lost legitimacy as independent functional-anatomical units at the same time as the major components of the last uncharted territory of the human brain, the substantia innominata, have been identified.

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The suggestion that the limbic system (1) is of special importance for emotional function had a great impact in psychiatry. The limbic system, however, remains an enigma to many neuroscientists, some of whom have come to the same conclusion as the prominent Norwegian neuroanatomist Alf Brodal, who many years ago suggested (2) that the limbic system is conceptually too fuzzy and open-ended to serve as a vehicle for scientific progress and discourse. Perhaps more to the point, anatomical discoveries during the last quarter century have exposed one of the most pervasive misconceptions perpetuated regarding the limbic system, i.e., the limbic versus basal ganglia dichotomy, at the same time as they have given birth to a new anatomical framework for the study of neuropsychiatric disorders.

One of the most prominent reflections of the new anatomy of the basal forebrain has been popularized as the theory of parallel basal ganglia thalamic-cortical circuits (3), which is quickly becoming the dominant theory for explaining the phenomenology of neuropsychiatric disorders (4). This theory, especially as it relates to the field of neuropsychiatry, originated with the discovery of the ventral striatal-pallidal system (5) and the subsequent suggestion that its pallidal-thalamic link reaches the medial dorsal thalamic nucleus (6) rather than the ventral lateral thalamic nucleus. Since the terms ventral striatum and the ventral pallidum are becoming increasingly familiar in the field of neuropsychiatry, this may be an opportune time to ponder the origin and meaning of these terms.

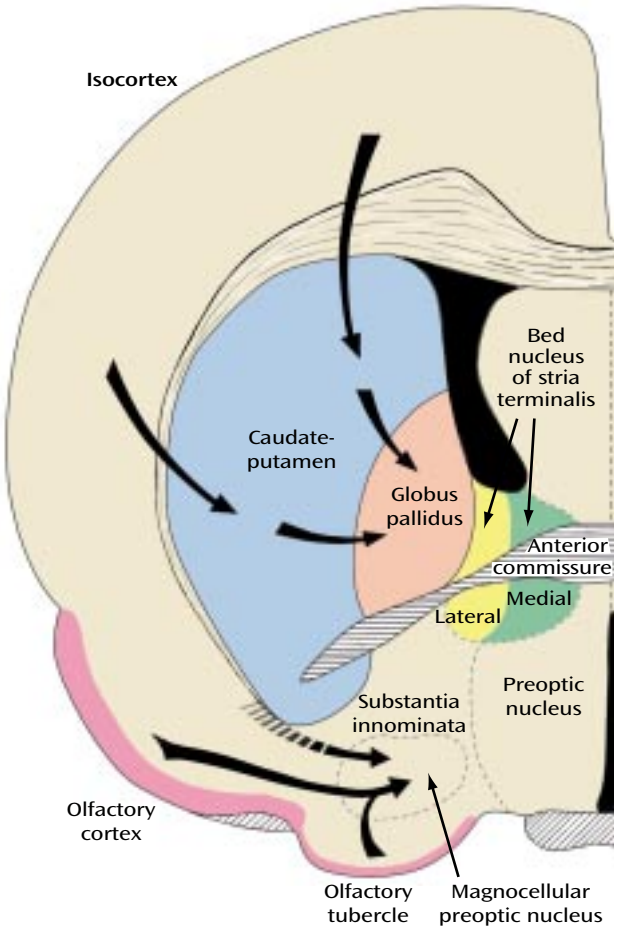
The extended amygdala (7) is another anatomical theory that is gaining in popularity, especially among researchers studying drug abuse. This system was first suggested on the basis of developmental studies by J.B. Johnston almost a century ago (8) but was soon forgotten, only to be rediscovered by de Olmos (9) and further developed, especially by de Olmos, Alheid, and their colleagues.

Scientists have struggled to explain the anatomy of the basal forebrain for the last 200 years, at the same time as they have nurtured the hope that a better understanding of this part of the brain will help explain the symptom profiles of neuropsychiatric disorders (10). As expected, the discoveries reviewed in this overview have indeed provided a new anatomical framework for functional and clinical studies of adaptive behaviors and neuropsychiatric disorders. Because of its complexity, it will take some patience to comprehend the new anatomy of the basal forebrain, but it may be a challenge well worth the effort.

The Golden Age of "the Silver Methods"

At the end of the 19th century, the Golgi (1875) and Marchi (1886) methods revolutionized the field of neuroanatomy. The Golgi method aided Ramón y Cajal in his monumental work on the nervous system (11). These achievements helped lay the foundation for modern neuroscience, and Cajal and Golgi shared the Nobel Prize in 1906. It was not until the middle of the last century, however, that the modern era of experimental tract tracing

FIGURE 1. General Understanding of the Organization of the Rat Forebrain in the 1960s, According to the Concept of the Limbic System[a]

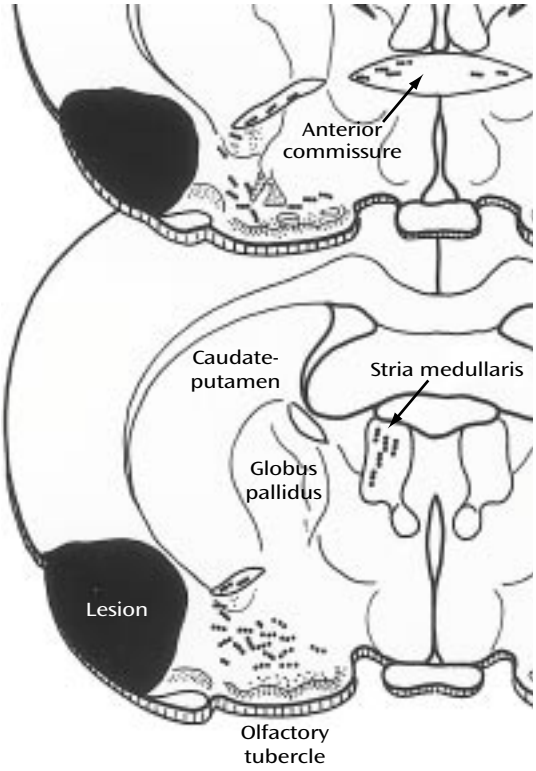


[a] Projections from limbic cortical areas, including the lateral-basal complex of the amygdala (broken arrow) were bellieved to terminate in the medial forebrain bundle area in the region of the magnocellular preoptic nucleus, whereas the isocortex was known to project to the basal ganglia (the caudate-putamen and the globus pallidus). (Graphic by Medical and Scientific Illustration, Crozet, Va.)

in the brain and the spinal cord began on a large scale with the aid of "the silver methods."

The most popular silver method in use during this time of rapid progress was the suppressive Nauta-Gygax method (12). After an experimental lesion in the place of origin of a pathway or after transection of a pathway, this method allowed for a more or less selective staining of degenerating axons in the midst of a large number of unstained or lightly stained normal fibers. Selectivity for the degenerating fibers, however, had been obtained at a cost (13), meaning that the finest axon ramifications and boutons were seldom stained. This problem was solved with the development of silver procedures, which selectively identify both degenerating fibers and boutons. Two of these methods, the Fink-Heimer method (14) and the cupric silver method of de Olmos (15), were critical to the discovery of the ventral striatal-pallidal system and the extended amygdala, respectively.

FIGURE 2. Degeneration in the Rat Basal Forebrain Following a Lesion in the Olfactory Cortex 2 Days Earlier[a]

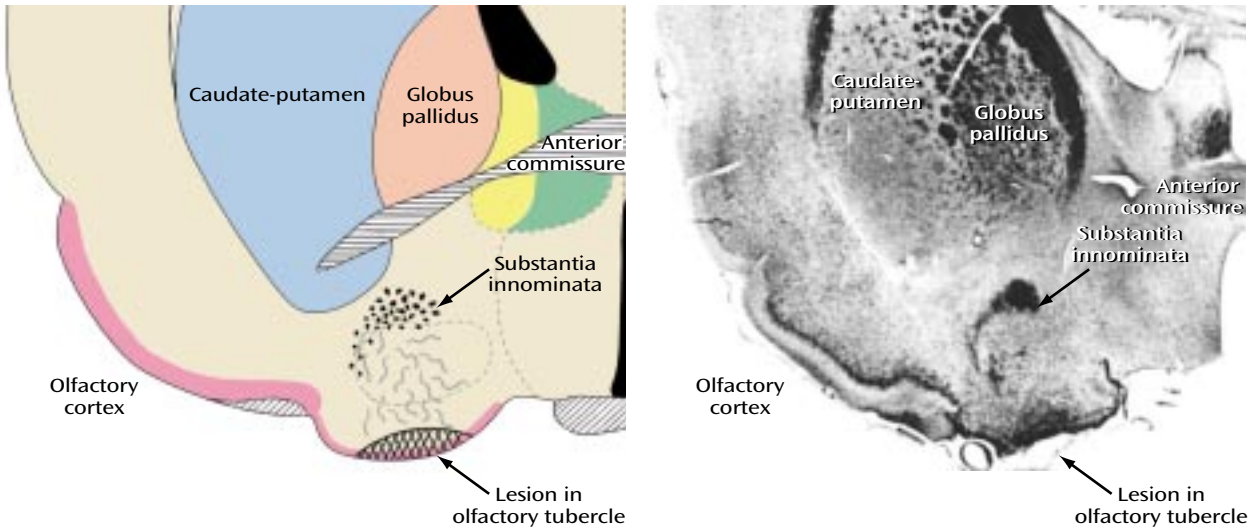


[a] The small dots indicate terminal degeneration; the large dots indicate degenerating fibers of passage; and the black areas indicate the lesion. The medium-sized cellular regions of the olfactory tubercle and the cellular bridges between the tubercle and the subcommissural striatal pocket are riddled with terminal degeneration, whereas the area of the magnocellular preoptic nucleus contains only fibers of passage. (Image modified from earlier work [20]. Copyright S. Karger Publishers, Basel, Switzerland.)

Since the silver methods made it possible to trace an entire pathway to its termination with the light microscopic, they can be termed the first modern methods for the experimental tracing of pathways; their introduction and the discovery of the Falck-Hillarp histofluorescence method for detection of monoamines heralded a second revolution in neuroanatomy, which continues today. Although the silver methods have been largely replaced by methods based on axoplasmic transport of various tracers, they have reemerged as major and indispensable tools in the fields of neuropsychology and neurotoxicology (16, 17).

Paradoxical as it may seem, the introduction of the electron microscope, which made it possible to identify the synaptic relationships of degenerating boutons, increased rather than alleviated the need for accuracy on the level of the light microscopic. The proper selection of tissue fragments for the identification of boutons and their postsynaptic elements by the electron microscope is impossible without prior visualization of the stained terminal end structures by the optic microscope (18). This point is especially well illustrated in studies that led to the discovery of the ventral striatal-pallidal system.

FIGURE 3. Characteristic Pattern of Degeneration in the General Region of the Medial Forebrain Bundle Following a Laminar Heat Lesion in a Rat Olfactory Tubercle 2 Days Earlier and a Matching Histological Section[a]



[a] The left-hand image shows that the degeneration is represented by terminal degeneration (arrow) in the region of the substantia innominata and by fibers of passage (wavy lines) in the area of the magnocellular preoptic nucleus. The matching histological section in the right-hand image is modified from work published elsewhere (5). (Copyright Raven Press, New York.) The terminal degeneration indicated by the arrow is shown in higher magnification in Figure 4. (Graphic by Medical and Scientific Illustration, Crozet, Va.)

Discovery of the Ventral Striatal-Pallidal System and the Notion of Parallel Cortical-Subcortical Reentrant Circuits

One of the basic tenets of the concept of the limbic system is that limbic forebrain structures project to the hypothalamus rather than the basal ganglia, whereas nonlimbic cortical areas, including most of the isocortex (neocortex), project to the basal ganglia. This dichotomy, reflected in countless renditions of the limbic system, is exemplified in Figure 1. Arrows demonstrate projections from isocortical areas to the basal ganglia, i.e., the striatum (caudate-putamen) and, hence, to the globus pallidus, whereas the olfactory cortex and olfactory tubercle were thought to project to the medial forebrain bundle area in the anterior lateral hypothalamus. This widely accepted view was reinforced by many silver impregnation studies, including an important article by Powell and his colleagues (19), and by the realization that the hypothalamus plays a vital role in emotional expression. "Limbic versus basal ganglia" and "limbic versus extrapyramidal" were common phrasings heard throughout the second half of the last century. A serious challenge to this limbic-system-inspired view of higher-order olfactory connections, however, was soon to come.

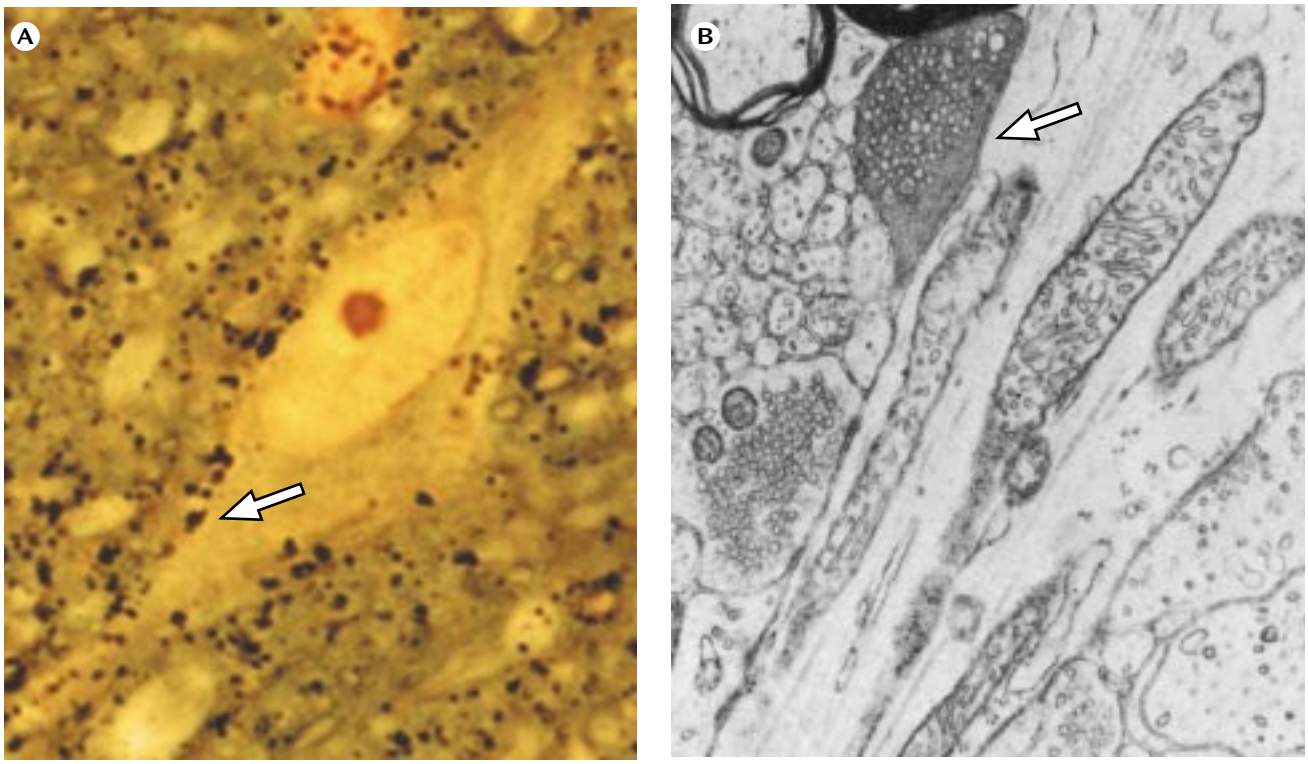
The Olfactory Tubercle: From a Cortical to a Basal Ganglia Structure

Aided by the Fink-Heimer method in combination with electron microscopy (20), I demonstrated that projections from the piriform cortex terminate prominently, not in the anterior lateral hypothalamus, but in surrounding extrahypothalamic regions (Figure 2). Data showing that the entire piriform-amygdaloid complex terminates massively in the ventral striatum rather than in the anterior lateral hypothalamus were also included.

Incidentally, projections from the olfactory cortex do terminate in the posterior lateral hypothalamus, but they are surprisingly modest, even in a macrosmatic mammal (21). After superficial laminar heat lesions of the olfactory tubercle, on the other hand, massive terminal degeneration did, as expected, appear in the general region of the medial forebrain bundle, which is also referred to as the substantia innominata (Figure 3), i.e., the neurological equivalent of the geographer's terra incognita, or die ungenannte Marksubstanz (22). A closer inspection (Figure 4), however, revealed that this area represents a ventral extension of the pallidal complex (5). To summarize, it turned out that the projection from the piriform cortex to the tubercle is a cortical-striatal projection rather than a cortical-cortical association pathway, which is consistent with the absence of a projection from the tubercle to the piriform cortex. The tubercle projection to the substantia innominata constitutes a striatal-pallidal pathway (Figure 5). This paradigm shift regarding higher-order olfactory connections was pivotal in the conceptualization of the ventral striatal-pallidal system.

This interpretation was further enhanced when the results of these studies were compared with the results from investigations of the accumbens projections, which were also aided by the Fink-Heimer method (e.g., reference 24). The continuity of the pallidal-like components related to the olfactory tubercle and accumbens was easily appreciated (see asterisk in Figure 5), as was their continuity with the main part of the pallidal complex, i.e., the globus pallidus, behind the temporal limb of the anterior commis-

FIGURE 4. High-Powered Light and Electron Micrographs Depicting Terminal Degeneration in Plastic-Embedded Sections of the Rat Brain[a]



[a] The section was stained with the Fink-Heimer technique. Image A shows terminal degeneration (in the region marked with an arrow in Figure 3). Electron microscopic studies of brain sections stained by this method have previously shown that many of the argyrophilic particles do represent degenerating boutons. The electron micrograph depicted in image B, which was compiled from samples taken from the general region shown in image A, confirmed that many argyrophilic black particles (a likely candidate is indicated by the arrow in image A) do represent degenerating boutons (e.g., the arrow in image B) in synaptic contact with pallidal neurons. (The images are slightly modified from an earlier article [23]. Copyright Scientific American, New York.)

sure. The accumbens' projection to the pallidal complex, however, was not a surprise since several previous authors had alluded to the striatal nature of the accumbens.

Further studies, reviewed elsewhere (25), strengthened the view that the medium-sized cell population of the olfactory tubercle is striatal in nature, and we (26) proposed that the pallidal complex extends ventrally into the deepest part of the olfactory tubercle. When pallidal markers became available, we confirmed that finger-like extensions of pallidal tissue extend all the way to the ventral surface to involve regions of the olfactory tubercle as well (26). The tubercle, therefore, is best characterized as a striatal-pallidal structure (Figure 5).

Definition of the Ventral Striatum and the Ventral Pallidum

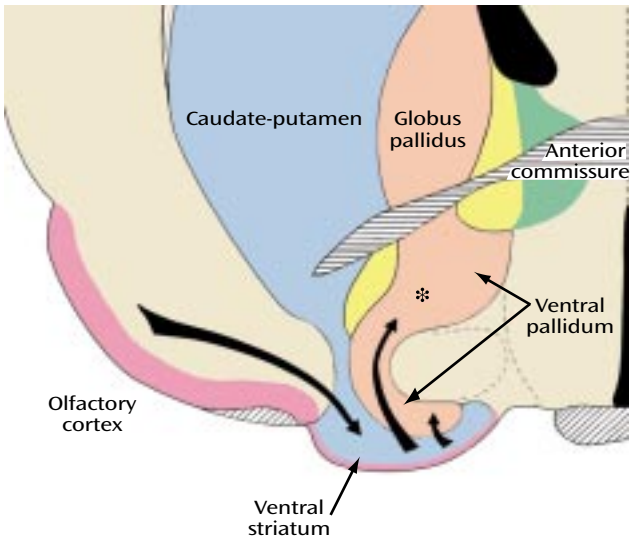
The accumbens and the striatal areas of the olfactory tubercle receive cortical projections, not only from the olfactory cortex and hippocampus (together referred to as the allocortex) but also from other parts of the greater limbic lobe (Figure 6). These parts include nonisocortical (mesocortical) areas, such as the entorhinal, insular, and cingulate cortex, as well as posterior orbital-medial cortices and the temporal pole.

The lateral basal cortical amygdala, which projects prominently to the ventral striatum, is also included in the greater limbic lobe, since it has many cortical-like features (27) and the same developmental genetic markers as the rest of the cortical mantle (28). Since the striatal and pallidal areas that receive allocortical and mesocortical input from the greater limbic lobe occupy several distinct areas that were not part of the classically defined basal ganglia, we referred to them as the ventral striatum and the ventral pallidum (5, 6).

The ventral striatum consists of an area usually referred to as the nucleus accumbens and of extensive, medium-sized cell populations in the olfactory tubercle as well as ventral medial parts of the caudate-putamen. The ventral pallidum occupies territories that were formerly included in the substantia innominata (30); as indicated, it also invades part of the olfactory tubercle. Since projections from isocortical and nonisocortical parts of the cerebral cortex do overlap to some extent in the striatum (caudate-putamen), the borders between ventral and dorsal regions of the striatum and pallidum are indistinct.

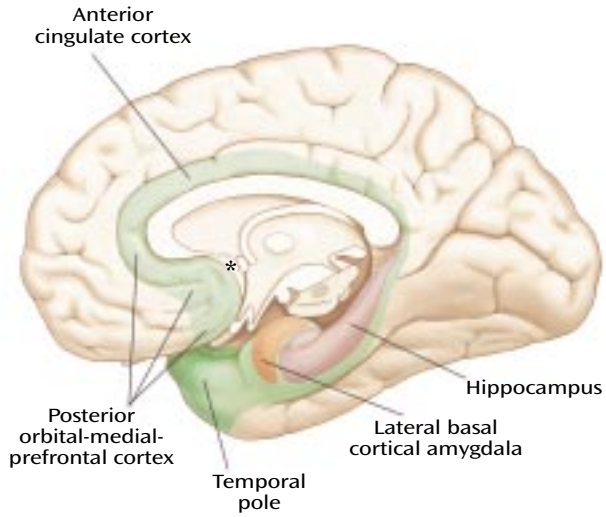
The importance of the ventral striatal-pallidal system is related not only to the topographic expansion of the basal ganglia but also to the realization that the entire cortical

FIGURE 5. Schematic Demonstration of the Paradigm Shift in the Early 1970s Regarding Higher-Order Olfactory Connections in the Rat Brain[a]



[a] The image reflects the olfactory tubercle as a ventral extension of the striatal complex, i.e., the ventral striatum, which in turn projects to a ventral extension of the globus pallidus, i.e., the ventral pallidum. The asterisk indicates the area of termination for the accumbens' projection at this level. (Graphic by Medical and Scientific Illustration, Crozet, Va.)

FIGURE 6. The Greater Limbic Lobe of the Human Brain[a]



[a] *Le grand lobe limbique* of Broca (1878) consists primarily of cingulate and parahippocampal gyri. Attempts to link Broca's definition of the limbic lobe with more recent cytoarchitectural studies have resulted in a number of different terms for various transitional-type cortices (e.g., mesocortex) that are interposed between an inner allocortical ring and the peripherally located six-layered isocortex. Based on current knowledge of cortical development and regional architecture, van Hoesen and I have included all nonisocortical regions in the concept of the greater limbic lobe. The term "limbic," according to this point of view, is restricted to cortical structures, including the cortical-like lateral basal cortical amygdala.

It is important to realize that large nonisocortical regions of the posterior orbital cortex and adjoining insula are also included in the greater limbic lobe, although they cannot be seen from the medial view. The lateral basal cortical amygdala and the hippocampus are projected onto the surface of the parahippocampal gyrus, a large part of which is represented by the entorhinal cortex. The green areas, including the entorhinal area, are sometimes referred to as paralimbic structures (29). The precommissural septum (represented by the asterisk, in front of the lamina terminalis) serves as an output channel for the hippocampus; it is not part of the greater limbic lobe. (Graphic by Medical and Scientific Illustration, Crozet, Va.; original artwork by van Hoesen and Heimer.)

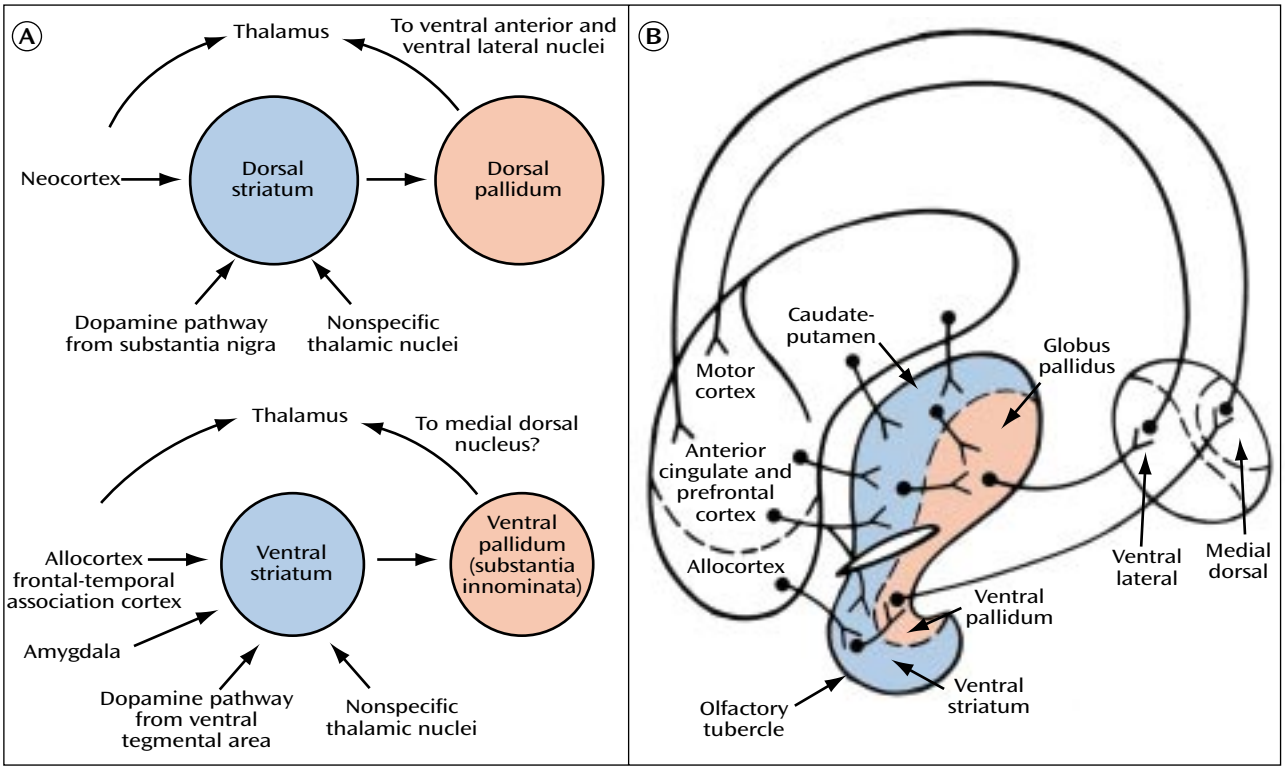
mantle projects to the basal ganglia. That this principle was discovered in studies of higher-order olfactory pathways in the rat, in which the olfactory cortex has a relatively much greater effect on basal ganglia mechanisms than in the primate brain, does not diminish its relevance for overall organization of the mammalian brain, including that of the human. In fact, studies of a macrosmatic mammal with a well-developed olfactory cortex, such as the rat, may well have been the only realistic way to discover this fundamental principle of forebrain organization. The realization that the whole cortical mantle is related to the basal ganglia has provided a new blueprint of forebrain organization, and the ventral striatum and ventral pallidum are integral parts of what is now promoted as a new theoretical framework for adaptive responding and neuropsychiatric disorders (31–33).

The Notion of Parallel Cortical-Subcortical Reentrant Circuits

We conceived of the ventral cortical-striatal-pallidal system as separate from the classic dorsal motor-related cortical-striatal-pallidal system (5) and suggested a few years later (6, 34) that the medial dorsal nucleus is the thalamic relay for the ventral striatal-pallidal system (Figure 7, image A). Since the medial-dorsal nucleus is reciprocally related to the prefrontal cortex rather than the motor and supplementary motor cortical areas, this discovery, which has been amply confirmed, provided the first indication of segregated cortical-subcortical reentrant circuits through the basal ganglia to the motor cortex and prefrontal cortex, respectively (Figure 7, image B). A similar notion of segregated cortical-subcortical reentrant circuits, as they relate to the influence of sensorimotor areas and dorsal lateral frontal association areas in the monkey, was suggested by DeLong and Georgopoulos (35) based on physiological experiments and published reports regarding basal ganglia connectivity.

As a way of summarizing and expanding on these discoveries in the rat and monkey, Alexander et al. (3) suggested the existence of five parallel or segregated cortical-subcortical reentrant circuits, one each for motor, oculomotor, and executive lateral prefrontal function, and two circuits (anterior cingulate and orbital frontal) for emotional-motivational functions. A few additional circuits have subsequently been proposed (36, 37). The terms "parallel" and "segregated" should be used lightly considering the multiplicity of connections in the brain and the tendency for overlap of the various cortical-fugal projections, especially in the ventral striatum.

FIGURE 7. Dorsal and Ventral Cortical-Subcortical Circuits Through the Basal Ganglia and Thalamus[a]



[a] The images show basic similarities between the classic dorsal and ventral cortical-striatal-pallidal-thalamic reentrant circuits. After the discovery of the ventral striatal-pallidal system in 1975 (5), I suggested in 1978 (image A) that the medial-dorsal nucleus, rather than the ventral lateral thalamic motor nucleus, is the likely thalamic target for the ventral striatal-pallidal system (6). (Copyright Plenus Press, New York.) Image B emphasizes the parallel character of the cortical-subcortical reentrant circuits throughout the dorsal and ventral regions of the basal ganglia in the rat (34) (Copyright Elsevier, Amsterdam.) (The images were modified for clarity only and not for content.)

Resistance to the Concept of a Ventral Striatal-Pallidal System

In spite of the fact that the discovery of the ventral striatal-pallidal system paved the way for the popular theory of parallel cortical-subcortical reentrant circuits through the basal ganglia, the concept of the ventral striatal-pallidal system met with considerable resistance for many years. Some basal ganglia experts were reluctant to introduce the concept of the ventral striatal-pallidal system in their discussions of the basal ganglia in the primate (38–40), in all likelihood because of the popularity of the limbic system and because the conceptualization of the ventral striatal-pallidal system was based on studies of olfactory connections in the rat, in which the olfactory system is much more prominent than in the primate. That limbic structures such as the olfactory cortex and the olfactory tubercle project to the basal ganglia or, in the case of the tubercle, are part of the basal ganglia ran counter to the notion of a limbic-basal-ganglia dichotomy, which is a salient feature in countless descriptions and figures of the concept of the limbic system (see, e.g., MacLean [41], p. 296). As mentioned earlier, however, the definition of the ventral striatum is based not only on projections from the allocortex (the olfactory cortex and the hippocampus) and other parts of the greater limbic lobe (the colored areas in Figure 6) but also on the fact that its pallidal counterpart projects to the medial dorsal thalamus rather than to the ventral lateral motor nucleus of the thalamus. Therefore, it is unjustified to shun the concept of the ventral striatal-pallidal system in the microsmatic primate and the human if one accepts it in the macrosmatic rat.

To dispel any doubt about the authenticity of the striatal-pallidal-thalamic circuit(s) through the ventral areas of the basal ganglia, several studies have focused on multisynaptic tracing of the striatal-pallidal-thalamic circuits through the ventral pallidum and on boundaries of the tubercle- and accumbens-related areas of the ventral pallidum (reviewed in reference 25). The identification of the ventral striatum and the ventral pallidum provided the necessary conceptual framework for explaining much of the basal forebrain previously known as the substantia innominata.

In 1980, a popular idea, according to which the accumbens was a specialized limbic-motor interface (42), attracted interest at the same time that it put the concept of the ventral striatal-pallidal system on hold. This notion was based on the belief that the accumbens, which receives input from the hippocampus and the amygdala,

projects to the globus pallidus (and, hence, to the motor system). The popularity of this hypothesis was so pervasive that even today the accumbens is often conceived of as a well-defined anatomical nucleus that is specialized to transfer limbic activities to the motor system. Neuroanatomical discoveries during the last quarter century, however, have shown that practically all major brain regions involved in emotional and motivational functions have a more or less direct relation to motor structures in the brainstem. Activity through much of the greater limbic lobe, for instance, is channeled through both the ventral striatal-pallidal system and the extended amygdala to the brainstem. This has led to the notion of an emotional motor system, as distinct from the rest of the motor system (43). The emotional motor system, however, may eventually suffer the same fate as the limbic system, if it has not already done so. There are many different possibilities, both on the cortical and subcortical level, in which structures in the emotional-motivational domain can interface not only with the general motor system but also with prefrontal cognitive-executive circuits. As if to emphasize this point, a couple of intriguing interfaces have been suggested for the potential integration of emotional, cognitive, and motor functions. Both are characterized by spiraling pathways, either between limbic lobe and prefrontal-cortical regions and the motor cortex by means of ventral areas of the basal ganglia (44) or between the ventral striatum and the rest of the striatal complex, with the mesotelencephalic dopamine system acting as an intermediary (45, 46).

Anatomy of the Human Basal Forebrain

The Ventral Striatal-Pallidal System and Its Cortical-Subcortical Reentrant Circuits

The broad striatal continuum (in blue) beneath the anterior section of the internal capsule (Figure 8, image A) includes the accumbens' region of the ventral striatum, also referred to as the fundus striati, which is directly continuous with significant ventral striatal areas in what was previously referred to as the substantia innominata (Figure 8, image B).

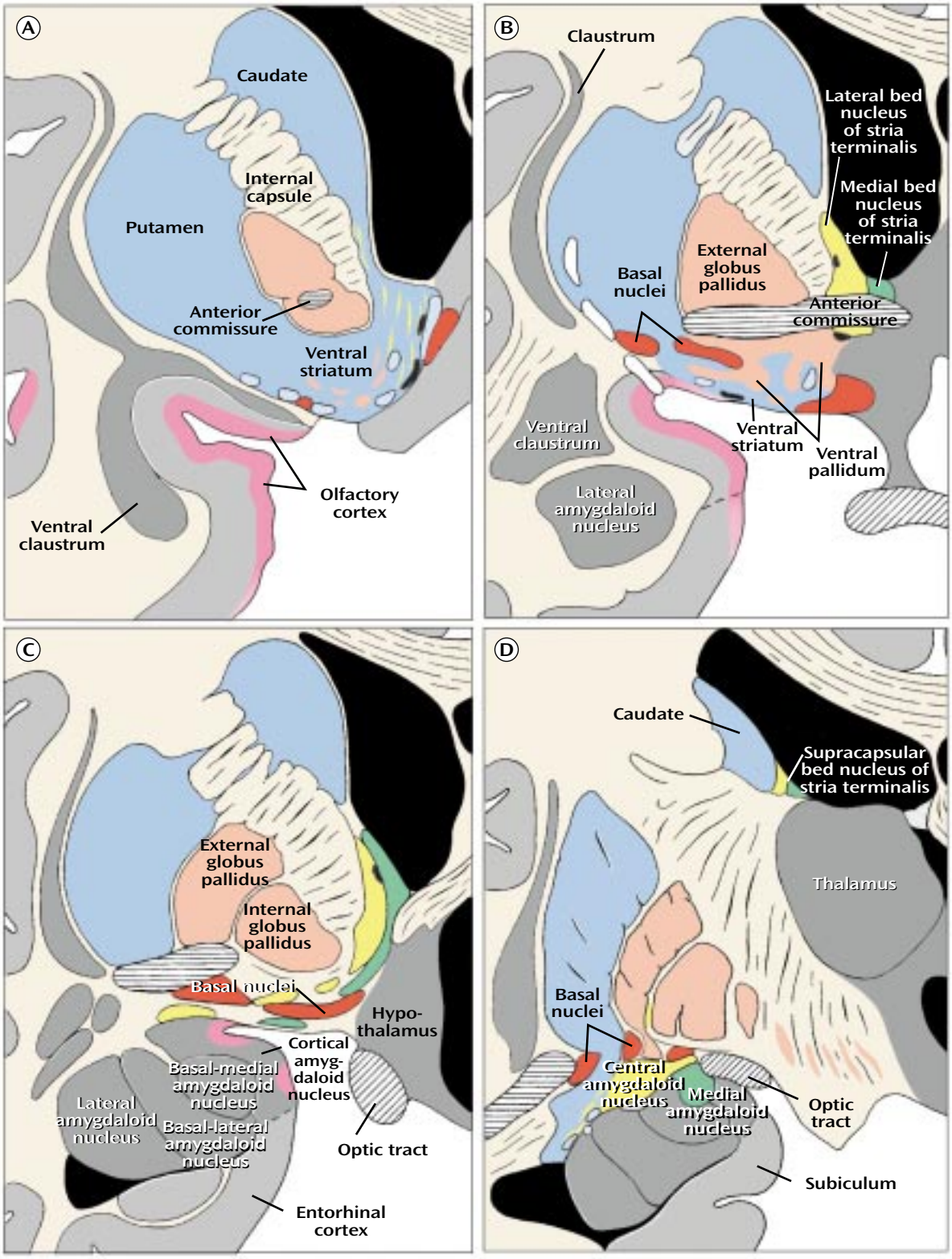
The subdivision of the striatal complex into ventral (orange), central (yellow), and dorsal (blue) territories (Figure 9), which is based on the distribution of isocortical lobe and nonisocortical frontal limbic lobe projections to the striatum, serves as a good starting point for any discussion of cortical-subcortical reentrant circuits. Three circuits—the anterior cingulate, the lateral orbital-frontal, and the medial orbital-frontal—are related to the ventral emotional-motivational striatal domain (in orange). These circuits are closed in the sense that they supposedly originate and terminate in the same area of the frontal lobe. There is ample reason for uncertainty, however, since there seem to be a number of ways in which nearby cortical-subcortical reentrant circuits can interact. One intriguing scenario, mentioned earlier as a potential interface between the emotional-motivational domain and the motor system, is the spiraling of frontal-subcortical circuits from prefrontal areas related to the limbic lobe into the motor cortex (44). The potential for translocation of information from one circuit to a nearby circuit is an important issue when one considers the current unwavering promotion of segregated frontal-subcortical circuits in the context of neuropsychiatric disorders.

In the wake of the great popularity of the theory of frontal subcortical circuits (48), it may be tempting to overestimate their closed and segregated character, but their open character is equally impressive (49). In other words, at every level of circuitry—cortical, striatal, pallidal, or thalamic—a variety of inputs from different parts of the brain have the potential to modify activity in the circuits. This point is particularly relevant regarding the ventral striatum, which receives a multitude of cortical projections from various regions of the greater limbic lobe (50–53). How the ventral striatum integrates these various cortical and subcortical inputs to adapt our behavior to changing environmental stimuli has been the focus of a large number of behavioral and pharmacological experiments. In a broad sense of functional subdivision, a consensus has gradually emerged that the prefrontal-subcortical reentrant circuit (with its various subcircuits) through the ventral striatal-pallidal system (the "motive" circuit of Kalivas et al. [54]) is critical for the initiation and mobilization of appropriate adaptive behavior (the "reward-guided choice behavior" of Schultz et al. [55]) in response to environmental stimuli similar to the way in which the motor loop through the dorsal parts of the basal ganglia is regarded as important for movement control.

Core-Shell Dichotomy. With a number of different techniques, the peripheral, ventrally located shell of the ventral striatum (Figure 10) can be distinguished from the central core, which merges imperceptibly with the rest of the striatum (56). Although the shell, like the core, is part of the ventral striatum, it also has features that are reminiscent of the extended amygdala (Figure 8, image A, indicated by the yellow areas) that translate into a number of anatomical and functional distinctions between the shell and the core (57, 58). The shell is characterized by moderate to high opiate and dopamine D_1 and D_3 receptor binding, and the shell, rather than the core, seems to be an especially significant target for the action of antipsychotic drugs (59). I mentioned earlier that the view of the accumbens as a specialized limbic-motor interface is deceptive. To refer to the nucleus accumbens in the sense of an anatomical entity is equally fallacious.

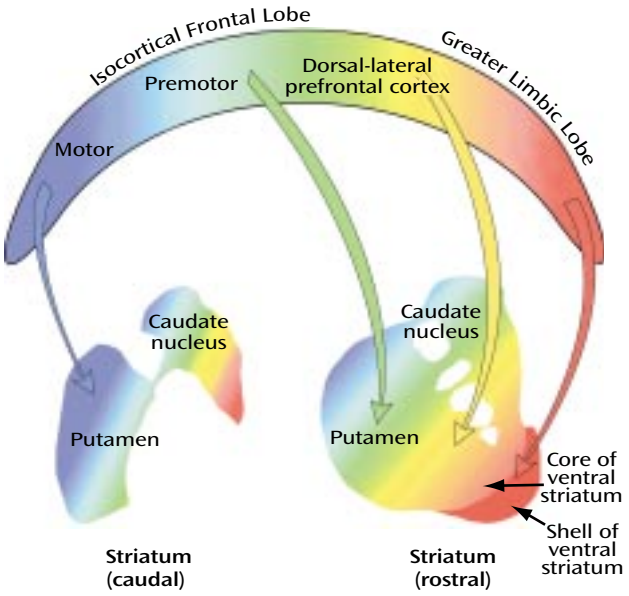
Small-Celled Islands. One of the most characteristic features of the ventral striatum is its small-celled islands (60), which are especially prominent in the shell (Figure 8, image A) but are present in other parts of the ventral striatum

FIGURE 8. Schematic Drawings Showing the Human Basal Forebrain in a Series of Four Coronal Images[a]



[a] Image A (the rostral view) depicts the level in which the caudate nucleus and the putamen are continuous underneath the anterior limb of the internal capsule to form the rostral part of the ventral striatum (also known as accumbens or fundus striate), and the caudal image (D) represents the caudal amygdala. The blue and salmon-colored regions represent the basal ganglia; yellow and green, the extended amygdala; and pink, the projection areas of the olfactory bulb. Each area circumscribed in blue and black in the ventral striatum and the extended amygdala indicates the presence of several small-celled islands. (Modified from earlier work [47], copyright Elsevier, Amsterdam); graphics by Medical and Scientific Illustration, Crozet, Va.)

FIGURE 9. Diagram of Cortical-Fugal Projections From the Isocortical Frontal Lobe and the Greater Limbic Lobe of the Human Brain[a]

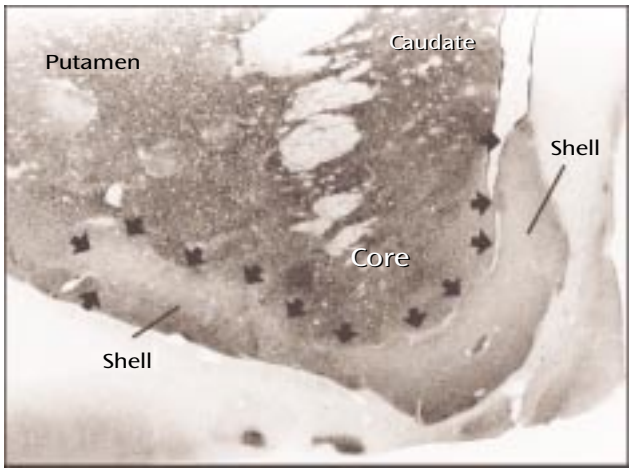


[a] The gradual change in color indicates overlapping projections. Although the crescent-shaped figure represents the isocortical frontal lobe and the nonisocortical greater limbic lobe only, it should be emphasized that cortical-striatal projections do come from the entire cerebral cortex. The greater limbic lobe regions include all nonisocortical parts of the cerebral cortex, including the basal cortical-like lateral basal cortical amygdala (see Figure 6). (Original artwork courtesy of Suzanne Haber.)

and also in the extended amygdala. Their neurons contain an abundance of opioid and dopamine receptors (61) in addition to the Bcl-2 protein (62), a marker of neuronal immaturity. When one considers the potential for development of these neurons, it is not difficult to envision the ventral striatum as especially prone to remodeling in response to changing circumstances. However, its greater reservoir of immature neurons may come with a price in the sense that the ventral striatum and extended amygdala may also be especially vulnerable to a number of damaging extrinsic and intrinsic factors throughout life, particularly during puberty (63, 64).

Clinical Correlations. Ever since Swerdlow and Koob (65) and Modell et al. (66) used the cortical-subcortical reentrant circuit(s) through the ventral striatal-pallidal system in their discussions of depression, schizophrenia, and obsessive-compulsive disorders, an increasing number of authors have focused their attention on the functional and clinical correlates of the cortical-subcortical reentrant circuits through the ventral striatal-pallidal system. Not surprisingly, imaging studies of mood and affective disorders (67, 68), obsessive-compulsive disorders (69), and substance abuse (70, 71) have consistently shown changes in cortical areas of the greater limbic lobe, which is the source of most of the cortical input to the ventral striatal-pallidal system.

FIGURE 10. Photomicrograph of a Calbindin-Immunoreacted Coronal Section Through the Ventral Striatum, or Accumbens, of the Rhesus Monkey[a]



[a] The border between the core and shell is marked with arrows. (Modified from work by Meredith et al. [56], courtesy of Gloria Meredith, copyright John Wiley, New York.)

Although the dorsal-lateral prefrontal cortex has received much attention in schizophrenia, the greater limbic lobe areas and/or their circuits through the ventral striatal-pallidal system are likely to be of particular importance in the study of schizophrenia (63, 72–74). Nevertheless, it is important to realize that the ventral striatal-pallidal system is only one of several prominent output channels of special significance for the phenomenology of schizophrenia and other neuropsychiatric disorders. The extended amygdala and the basal nucleus of Meynert, as well as the precommissural septum (see Figure 6), are particularly important in this context since they, like the ventral striatal-pallidal system, receive cortical input primarily from the greater limbic lobe.

The Extended Amygdala

The notion that the bed nucleus of stria terminalis and the central medial amygdala form a continuous structure in human embryos and that remnants of this continuum can still be found in the form of interrupted cell columns within the stria terminalis as it makes a semicircular detour above and behind the internal capsule and thalamus to connect the bed nucleus (Figure 8, image B) with the central-medial amygdala (Figure 8, image D) was first suggested by Johnston in 1923 (8). Half a century later, José de Olmos (9) identified a histochemically distinct subpallidal neuronal continuum between the central amygdaloid nucleus and the bed nucleus of stria terminalis in the adult rat. Although it is difficult, if not impossible, to illustrate the subpallidal part of the human extended amygdala as a continuum in sections that show only neuronal cell bodies (Figure 8, image C), continuity is indicated by stains for peptidergic fibers and terminals that are typical for the bed nucleus of stria terminalis and the central-medial

amygdala (7, 47, 75, 76). In addition, far-reaching parallels between the two major components of the extended amygdala, i.e., the central-medial amygdala and the bed nucleus of stria terminalis, have been described, in regard to cytoarchitecture, histochemistry, and connectivity (76, 77).

The extended amygdala (Figure 11), which, as indicated earlier, does not include the lateral basal cortical amygdala, consists of central (yellow) and medial (green) divisions defined by their relations to central and medial amygdaloid nuclei, respectively. The extended amygdala is characterized by long and strikingly abundant associative connections and has prominent projections to autonomic and somatomotor centers in the lateral hypothalamus and brainstem (central division) and to the endocrine-related medial hypothalamus (medial division). The extended amygdala, like the ventral striatum, receives input primarily from nonisocortical regions of the greater limbic lobe, including the lateral basal cortical amygdala. Thus, it represents a strategically placed ring formation capable of coordinating activities in regions of the multiple limbic lobe forebrain for the development of coherent behavioral responses through the referenced output channels.

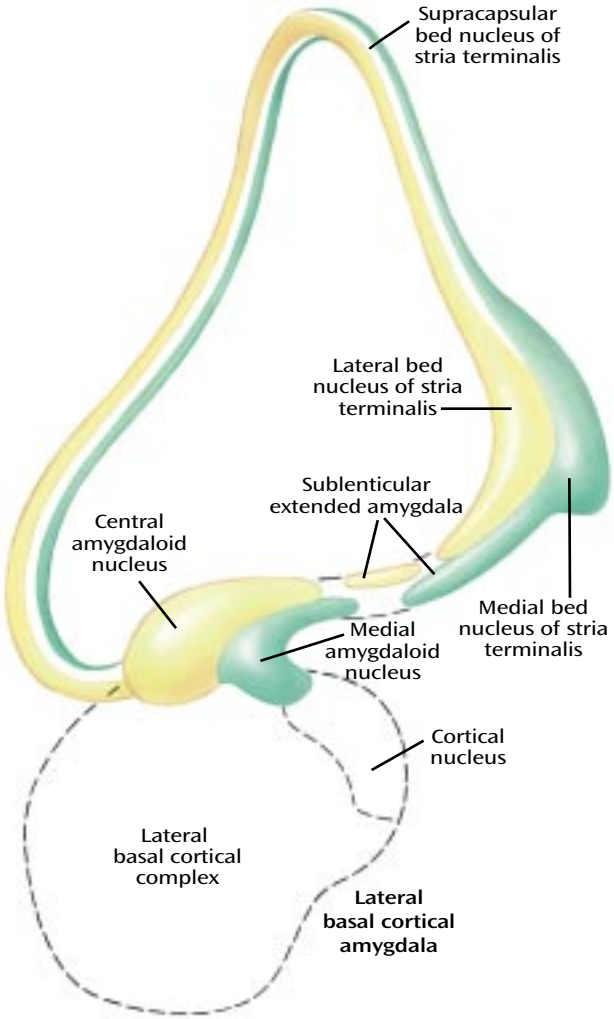
The prevailing view in the past has been that the bed nucleus of stria terminalis is ultimately a relay in a downstream projection from the central and medial amygdaloid nuclei. The concept of the extended amygdala, in which the bed nucleus and the central and medial amygdaloid nuclei are parts of the same macrostructure, represents a significantly different way of looking at this part of the brain. Not surprisingly, this paradigm shift has met with some resistance, as discussed elsewhere (76, 77).

The question of whether the extended amygdala is a useful concept was debated during a discussion by Swanson and Alheid at a recent symposium (78). According to Swanson, the central-medial amygdala represents a striatal structure for which the bed nucleus of stria terminalis serves as a pallidal counterpart. A larger number of studies, however, have corroborated Johnston's original idea of a continuum involving the central-medial amygdala and the bed nucleus of stria terminalis (8). Since anatomical and histochemical differences between this continuum and the striatal-pallidal system appear to be significant, we (47, 76, 77) and others (e.g., reference 75) have argued that the continuum involving the central-medial amygdaloid bed and nucleus of stria terminalis should be identified as a macroanatomical system in its own right. Swanson thinks that these differences are not prominent and specific enough to justify the definition of the extended amygdala as a system separate from the striatal-pallidal system. As usual in situations in which differences of opinion are concerned, the proof will be shown in later findings. As indicated, a growing number of researchers have accepted the notion that the extended amygdala is a useful concept.

The extended amygdala has been accepted as a useful concept in investigations of drug addiction and other specific behaviors, ranging from fear and anxiety to sexual and appetitive behavior (32), and it is slowly gaining a foothold in other fields related more directly to psychiatry (79–81). Much would be gained if scientists and clinicians interested in the amygdaloid complex would include the bed nucleus of stria terminalis (which is a large structure in the human brain) in their imaging studies of the amygdala.

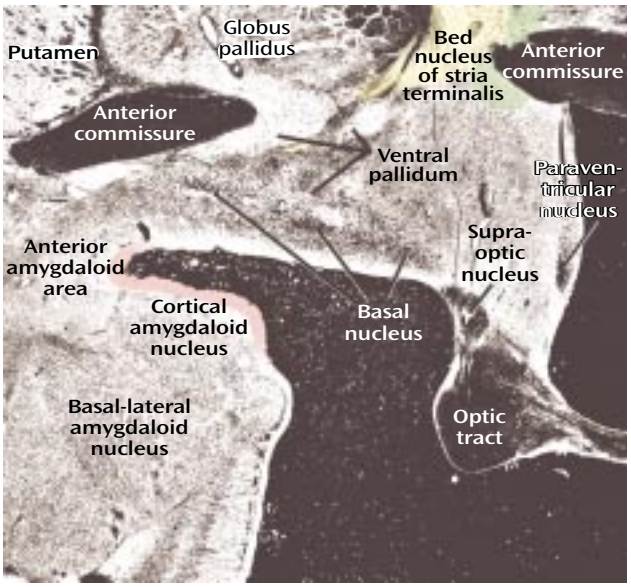
There are a number of reasons to pay special attention to the extended amygdala in the context of neuropsychiatric disorders. Many receptors (e.g., for vasopressin, oxytocin, androgens) and neuropeptides (e.g., cholecystokinin, enkephalins, angiotensin II, somatostatin, neurotensin, opioid peptides) that have attracted special attention in

FIGURE 11. The Extended Amygdala, Shown in Isolation From the Rest of the Human Brain[a]



[a] The central division of the amygdala is in yellow, and the medial division is in green. Note that the lateral basal cortical amygdala is not part of the extended amygdala. The supracapsular region of the extended amygdala, i.e., the supracapsular bed nucleus of stria terminalis, is depicted as a continuum, although the cell bodies, especially in the medial division, do not form continuous columns. Associated dendrites and neuropil, however, are likely to form such columns. (Modified from earlier work [47], copyright Elsevier, Amsterdam; graphic by Medical and Scientific Illustration, Crozet, Va.)

FIGURE 12. Klüver-Barrera Stained Coronal Section of the Human Basal Forebrain at the Level of the Crossing of the Anterior Commissure[a]



[a] The large hyperchromatic cells of the basal nucleus of Meynert form particularly large conglomerates at this level. The pink region in the temporal lobe indicates the olfactory bulb distribution to the cortical amygdaloid nucleus. (Modified from work by Sakamoto et al. [84], copyright Elsevier, Amsterdam.)

the study of neuropsychiatric disorders (82) are characteristic of one or both divisions of the extended amygdala. Androgen-receptive neurons, which are prevalent in the medial division of the extended amygdala, are of apparent importance for determining sexual behavior but are also well known for their involvement in aggressive behavior. Neurons that contain corticotrophin-releasing factor, which are especially prominent in the central division of the extended amygdala, are relevant in physiological responses to stress and for their apparent involvement in major depression and anxiety disorders. These and other features, which make the extended amygdala particularly important in the context of neuropsychiatric disorders, have been discussed in review articles (7, 63, 82, 83). Since the extended amygdala, like the ventral striatum, contains an abundance of small-celled islands (47), my earlier discussion regarding the small-celled islands is relevant also in regard to the extended amygdala.

The Basal Nucleus of Meynert

The most conspicuous and best-known component of the basalis region is the basal nucleus of Meynert (colored red in Figure 8, image B), which contains a mixture of cholinergic and γ-aminobutyric acid (GABA)-ergic corticalpetal neurons. This widely dispersed, more or less continuous collection of aggregated and nonaggregated neurons stretches from the septum-diagonal band in the rostral region of the forebrain to the caudal part of the globus pallidus. Since collections of the large hyperchromatic cells of this system are strikingly displayed in Nissl preparations (Figure 12), the basal nucleus of Meynert has sometimes been used as a synonym for the substantia innominata or simply been referred to as the nucleus of the substantia innominata.

Cortical afferents to the basal nucleus come primarily from the greater limbic lobe, whereas basal nuclei projections, which are important for cortical arousal and attention mechanisms (85), reach the entire cerebral cortex. These anatomical and physiological features signify the importance of the basal nucleus in the context of neuropsychiatric disorders (86).

Although the most well-known clinical correlation in regard to the basal nucleus is Alzheimer's disease, in which there is usually pronounced depletion of neurons in the basal nucleus, other degenerative disorders with frequent involvement of this nucleus include Parkinson's disease, Korsakoff's disease, and Down's syndrome. It is important to realize, however, that these disorders also involve other parts of the brain. It hardly needs mentioning that the substantia nigra shows pronounced changes in Parkinson's disease, whereas in Alzheimer's disease, pathological changes in the hippocampus and parahippocampal gyrus are pathognomonic (87). The hallmarks of Alzheimer's disease also include paranoid delusions, hallucinations, and psychomotor agitation—symptoms commonly found in schizophrenia (88). These symptoms, which apparently occur independent of the degree of dementia, can be correlated with pathological involvement of structures in the medial-temporal lobe, including the amygdala, which are characterized not only by connections with surrounding regions of the temporal lobe and the orbital-frontal cortex but also downstream projections to the ventral striatal-pallidal system, the extended amygdala, and the basal nucleus of Meynert.

Conclusions

The ventral striatal-pallidal system and extended amygdala, major components of the new anatomy of the basal forebrain, have been used to guide studies of a variety of specific emotional functions and adaptive behaviors ranging from fear-anxiety and addiction-reward to sexual behavior and appetitive behavior (32), and they have rejuvenated studies of brain development and comparative neuroanatomy (e.g., 78, 89). The most important reason for neuropsychiatrists to be concerned with these two macro-anatomical systems relates to the fact that they, together with the basal nucleus of Meynert and the precommissural septum (in the paraterminal gyrus) (Figure 6), serve as output channels for activities originating in the greater limbic lobe, the various parts of which are by far the most important cortical regions implicated in emotional and motivational functions of the brain.

How these output channels of the greater limbic lobe organize and integrate cortically derived information

with input from other brain regions (e.g., the thalamus and brainstem) to produce the different aspects of emotional-motivational behavior and how in neuropsychiatric dysfunction they contribute to disintegrated behavior will provide a greater challenge for the foreseeable future. In the final analysis and regardless of the field of inquiry—physiology, pharmacology, molecular biology, behavior or clinical medicine, not to speak of brain imaging—investigations and theoretical discussions of emotional-motivational as well as cognitive symptoms will have to be explained in the context of the anatomy of the basal forebrain.

This new anatomy has exposed the fallacy of the popular limbic-versus-basal-ganglia dichotomy that is still part of the textbook lore of clinical neurology. Since the entire cerebral cortex, including the hippocampus, the olfactory cortex, and major parts of the amygdala, projects to the basal ganglia, all major telencephalic disorders are, to some extent at least, disorders of the basal ganglia. However, the new anatomy of the basal forebrain has a more important and far-reaching message: the great divide between neurology and psychiatry has no anatomical basis. In other words, a reasonable understanding of the new anatomy of the basal forebrain will go a long way toward explaining the increasingly well-known fact that major brain disorders are characterized by both neurological and psychiatric symptoms.

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