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Cerebral hemisphere regulation of motivated behavior[1]

Larry W. Swanson*

The Neuroscience Program, Hedco Neuroscience Building, Rm. 428, University of Southern California, 3614 Watt Way, Los Angeles, CA 90089-2520, USA

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Abstract

The goals of this article are to suggest a basic wiring diagram for the motor neural network that controls motivated behavior, and to provide a model for the organization of cerebral hemisphere inputs to this network. Cerebral projections mediate voluntary regulation of a behavior control column in the ventromedial upper brainstem that includes (from rostral to caudal) the medial preoptic, anterior hypothalamic, descending paraventricular, ventromedial, and premammillary nuclei, the mammillary body, and finally the substantia nigra and ventral tegmental area. The rostral segment of this column is involved in controlling ingestive (eating and drinking) and social (defensive and reproductive) behaviors, whereas the caudal segment is involved in controlling general exploratory or foraging behaviors (with locomotor and orienting components) that are required for obtaining any particular goal object. Virtually all parts of the cerebral hemispheres contribute to a triple descending projection — with cortical excitatory, striatal inhibitory, and pallidal disinhibitory components — to specific parts of the behavior control column. The functional dynamics of this circuitry remain to be established.

Theme: Neural basis of behavior

Topic: Motivation and emotion

Keywords: Amygdala; Basal ganglia; Cerebral cortex; Hypothalamus; Motor behavior; Striatum

1. Introduction

Consciousness — thinking and feeling, the rational and emotional sides of our mental life — is, the clinical and experimental evidence would suggest, a product of activity in neural networks of the cerebral hemispheres. As a matter of fact, the notion that conscious or voluntary control of behavior is mediated by cerebral influences descending onto the paired sensorimotor nerves of the brainstem and spinal cord has evolved over a very long period of time. Threads of its history can be traced back several thousand years to Greco–Roman antiquity, especially in the work of Galen [48,156].

The basic structural plan and functional organization of most organs in the body are taken for granted by now — the kidney, heart, and stomach are good examples. But this does not apply to far and away the most important organ, the brain, and its paired cerebral hemispheres. Instead, there is not even a consensus list of parts for the brain, let alone a global scheme for classifying the parts and describing the basic plan of their interconnections or wiring diagram. In short, there remains an unfortunate lack of fundamental models describing how the brain works as a system [285].

The reason for this lack of understanding is simple: sheer complexity. Until the late 19th century, when the cornerstones of brain systems analysis — the neuron doctrine and theory of functional polarity [33,249] — were elaborated and became widely accepted, only a few parts of the brain were distinguished, and it was relatively easy to propose global models of brain structure–function (e.g. [77,173,332]). However, the introduction of the Golgi method, and of experimental degeneration methods for pathway tracing, in the latter half of the 19th century yielded orders of magnitude more information about brain structural organization. The situation was clear to Ramón y Cajal, who contributed far more than any other single investigator to our understanding of the vertebrate nervous

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*Tel. +1-213-740-5892; fax: +1-213-741-0561.

E-mail address: lswanson@usc.edu (L.W. Swanson).

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system. In 1909 he predicted that 'to extend our understanding of neural function to the most complex human physiological and psychological activities, it is essential that we first generate a clear and accurate view of the structure of the relevant centers, and of the human brain itself, so that the basic plan — the overview — can be grasped in the blink of an eye.' [33]

The latest neuroanatomy revolution started around 1970, and was based on a combination of axonal transport pathway tracing methods and immunohistochemistry (supplemented with hybridization histochemistry in the 1980s). It produced another avalanche of data on previously unknown neural connections — this time including neurotransmitters and their receptors — and a natural preoccupation with subjecting individual circuit elements to detailed analysis. Fortunately, these methods have clarified for the first time the basic connections of certain long obscure regions of the forebrain, including the hippocampus, amygdala, septum, and hypothalamus, so that the time may be opportune to reexamine from a synthetic perspective the overall organization of brain regions that control behavior — looking for simplifying principles instead of ever more subdivision and detail.

Eventually, a consensus description of nervous system organization will emerge, as happened long ago (basically in the 18th century) for the skeletal, muscular, circulatory, and other systems. The following synthesis is presented in the spirit of providing the crude outlines of at least one basic plan or model to rekindle discussion of this topic — and to stimulate the formulation of even better models. The analysis is based on four converging lines of evidence: development, gene expression patterns, circuit connectivity, and function, no one of which by itself is necessarily convincing. The ultimate model will be internally consistent yet comprehensive in terms of system components, and each component will be defined clearly and named unambiguously. A crippling handicap of systems neuroscience today is the confused, ambiguous state of the nomenclature used to describe brain structure, much of which is unavoidably based on historical accident rather than contemporary knowledge [285].

1.1. Motor system and the tripartite control of behavior

Before examining the structural organization and possible functional significance of what will be referred to as the behavior control column, and then the organization of cerebral inputs to the column, it is useful to outline a high level scheme for the nervous system control of behavior in general [292]. As a starting point, we assume that behavior is the product of, or is driven by, activity in the motor system — behavior is a function of activity in the motor system (Fig. 1). It seems incontrovertible that the behavior we observe in others is the product of somatic muscle contractions that in turn are controlled directly by activity in somatic motoneuron pools of the brainstem and spinal cord. In this Section we shall consider three key features of the motor system: (1) its neural inputs fall into three broad functional classes (sensory, cognitive, and behavioral state), (2) it is organized hierarchically, and (3) it has three divisions — somatic, autonomic, and neuroendocrine.

Turning first to the organization of neural inputs to the motor system, Cajal pointed out long ago that sensory systems generally have a dual projection within the central nervous system. One branch goes directly to the motor system, and the other goes (more or less directly) to the cerebral cortex, where sensations and perceptions are elaborated, and voluntary motor impulses are generated. For example, *dorsal root ganglion cell* axons branch within the spinal cord, with some collaterals innervating components of the intraspinal motor system and others innervating neurons that project to the thalamus and then

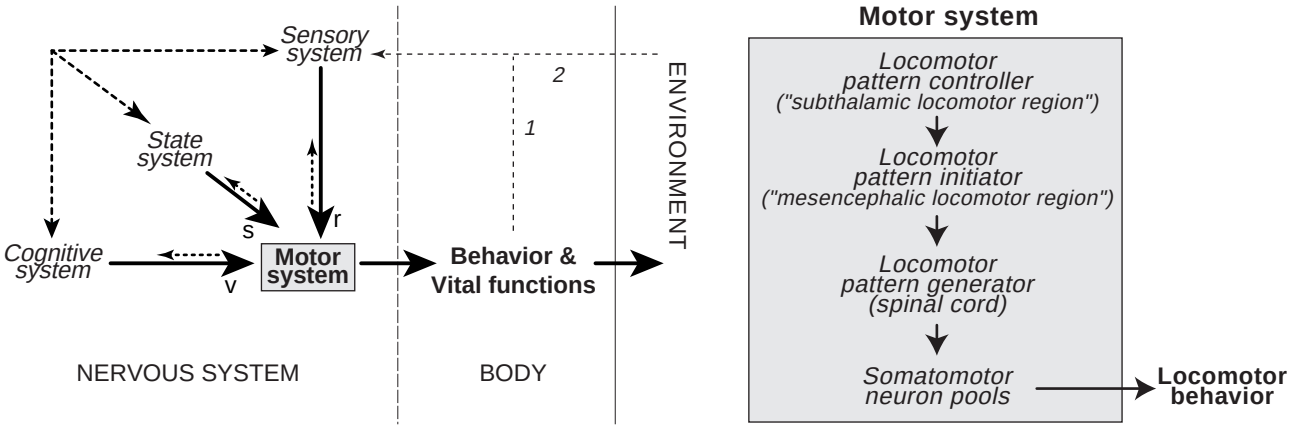


Fig. 1. Left. A basic schematic for nervous system functional organization. This model assumes that the motor system controls behavior and bodily vital functions, and that there are three classes of inputs to the motor system — cognitive, which is responsible for voluntary (v) control; sensory, which is responsible for reflex (r) control; and behavioral state, which is responsible for state (s) control. Note that the sensory, state, and cognitive systems share bidirectional connections, and that the results of internal (1) and external (2) behaviors feed back through the sensory system to influence future behaviors. Right. An example of how the somatic motor system is organized hierarchically, to control locomotion (see text for details).

cortex; and *retinal ganglion cell* axons branch to innervate the lateral geniculate-cortical projection and the superior colliculus-reticulospinal projection. Cajal illustrated this principle in a series of brilliant diagrams (see Fig. 2 for one of them), and established two fundamental classes of inputs to motoneurons, primary mediators of the behavior we observe in others: direct sensory inputs, which are responsible for the *reflex* initiation of behavior, and cortical inputs, which are responsible for the *voluntary* or conscious initiation of behavior and are informed by sensory and other information.

A third fundamental class of inputs to motoneurons gradually became recognized in the 20th century, and can no longer be ignored. This is the class of inputs arising from the still rather poorly understood brain system with intrinsic activity [327] that controls behavioral state — the sleep/wake cycle and levels of arousal within a particular state. Obviously, behavior is quite different when one is asleep or awake, and when awake there is a certain basic level of arousal or spontaneous activity that is independent of, though modulated by, sensory inputs.

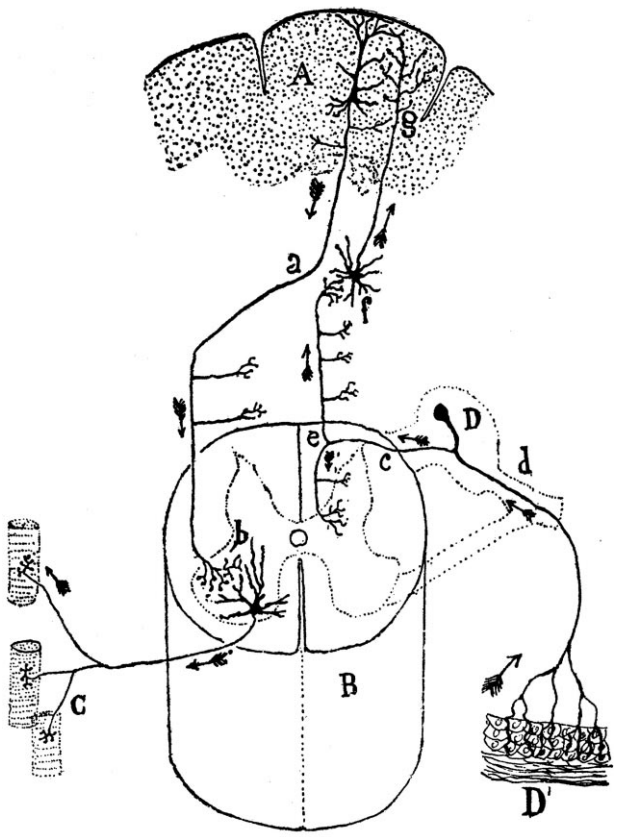


Fig. 2. One of Cajal's early circuit diagrams based on the Golgi method. It shows how sensory information is directed toward both the motor system and the cognitive system — and how there are two main inputs to the motor system. The peripheral, dendritic process (d) of a dorsal root ganglion cell (D) ends in the skin (D′), where sensory stimuli are detected. Impulses generated by the stimulus travel up the peripheral process (arrows) and then the central, axonal process (c), which bifurcates in the spinal cord (B). The descending branch generates collaterals in the spinal gray matter, which end on interneurons (not shown) that in turn innervate ventral horn motoneurons (shown for convenience on contralateral side near (b) that innervate muscle fibers (C). The other bifurcation branch of the central process ascends to another neuron (f) whose axon (g) in turn relays sensory impulses to the cerebral cortex (A). Psychomotor neurons in the cortex send via their axons (a) a second major class of inputs (b) to ventral horn motoneurons. From Ref. [31].

In summary, there are three major classes of inputs to the motor system: (a) sensory, which mediate reflex behavior; (b) cortical, which mediate cognition and voluntary behavior; and (c) behavioral state control (Fig. 1).

Turning now to the hierarchical organization of the motor system itself, the clinical observations and theories of John Hughlings Jackson over a century ago [301] pioneered the now generally held view that the motor system is organized hierarchically [28,306,328]. Nevertheless, after accepting by definition that motoneuron pools constitute the lowest level of the hierarchy, there is little or no consensus today about organizing principles and nomenclature for the higher levels. The basic idea is illustrated nicely, however, by what is known in a general way about the organization of the neural system that mediates and controls locomotor behavior [192,328,330]. The lowest or first level of the locomotor system is formed of course by a subset of motoneuron pools in the spinal cord ventral horn that innervates the limb muscles responsible for locomotor behavior (Fig. 1). The second major level is referred to as the locomotor pattern generator, which lies entirely within the spinal cord, near the motoneuron pools that it regulates. In fact, it is itself a hierarchy of increasingly complex motor pattern generators that coordinate and time muscle contractions across individual joints, then across multiple joints within a particular limb, and finally amongst all four limbs. A third major level is represented, at least in part, by an ill-defined region of the dorsal tegmentum known as the mesencephalic locomotor region, and rostroventral to this is a fourth major level in an ill-defined region of the caudal hypothalamus/rostral midbrain — the so-called subthalamic or hypothalamic locomotor region.

A crude though nevertheless useful understanding of functional differentiation between these major levels of the locomotor hierarchy has been gained by transecting the neuraxis at different rostrocaudal levels. The existence of a spinal *locomotor pattern generator* is demonstrated by the fact that whereas a spinal animal displays no spontaneous locomotor activity, coordinated limb movements characteristic of locomotion may be elicited when the limbs of such an animal are placed on a moving treadmill, thus providing somatic sensory input to the pattern generator [192,330]. Furthermore, undisturbed midbrain animals also show no spontaneous locomotor activity [88], although it can be elicited either by certain sensory stimuli (for example, auditory or nociceptive), or by experimental stimulation of the mesencephalic locomotor region [192,330], which apparently sends direct and indirect descending projections to the spinal locomotor pattern

generator. Viewed in this way, the mesencephalic locomotor region can be thought of as a *locomotor pattern initiator*. In contrast, undisturbed chronic hypothalamic animals do present spontaneous locomotor behavior, which by definition is not influenced or directed by cognitive inputs from the telencephalon because it has been removed or disconnected [88]. In the sense of providing a certain level of endogenous activity (perhaps some form of 'set-point'), the hypothalamic locomotor region can be thought of as a *locomotor pattern controller*, which generates spontaneous inputs (in an unknown way), ultimately, to the spinal locomotor pattern generator.

Although less understood, there is good evidence for conceptually similar central pattern generators for other complex motor behaviors, related for example to coordinated eye movements (centered in the midbrain), orofacial behaviors (centered in the dorsolateral hindbrain), and orientation of the head via the neck musculature (centered in the lower medulla and upper cervical spinal cord). It seems reasonable to postulate that these pattern generators are also influenced by higher levels of the motor hierarchy, namely pattern initiators and controllers.

In closing this section, we should point out that there are three divisions of the motor system. Thus far we have considered the well-known *somatomotor system*, which regulates the contraction of skeletal, striate, or voluntary muscle. The motoneuron pools for this system extend from the midbrain rostrally to the caudal end of the spinal cord. The second is the *autonomic visceromotor system*, where the first stage motoneurons form pools of preganglionic sympathetic and parasympathetic neurons; together they also stretch from the midbrain to the caudal end of the spinal cord, with a few gaps here and there. For the most part they innervate smooth muscle, cardiac muscle, and glands. The third is the *neuroendocrine secretomotor system*; its motoneuron pools are centered in and around the periventricular zone of the hypothalamus and they exert their influence throughout the body via the pituitary gland (Section 1.3). It seems reasonable to hypothesize that the second and third systems are hierarchically organized along the lines outlined for the somatomotor system. And as we shall see, the hypothalamus appears to contain mechanisms for coordinating appropriate responses in all three motor systems.

1.2. Basic organization of the forebrain

The fundamental plan of nervous system organization just presented — a motor system controlled by reflex, voluntary, and behavioral state inputs — is obviously a functional schema. On the structural side of the coin two distinct though not necessarily mutually exclusive plans for describing the central nervous system have become widely adopted [285]. One is based on comparative embryological considerations that date back to Malpighi in the 17th century. It contends that the vertebrate central nervous system consists of a series of primary, transversely arranged 'segments' that, from rostral to caudal, include the forebrain, midbrain, hindbrain, and spinal cord.The other structural model dates back even further to Vesalius in the 16th century and consists of three parts: a trunk or core that generates a series of paired cranial and spinal nerves (from an essentially continuous brainstem and spinal cord, respectively), and suprasegmental cerebrum and cerebellum.

Present unresolved ambiguity centers around how to define the brainstem and cerebrum in terms of forebrain, midbrain, and hindbrain divisions. From the functional schematic point of view (Fig. 1), the thalamus relays sensory information to the cognitive system in the cerebral hemispheres, and the hypothalamus is a key part of the neuroendocrine and autonomic motor systems, so these two forebrain areas can reasonably be included within the brainstem. On the other hand, there is a strong bias in the literature to treat the forebrain as a structural unit. Realistically, the extent to which these structural distinctions are artificial or inaccurate remains to be determined; there is no compelling evidence to support or reject either model at this time. For the sake of convenience, then, we shall now present a working hypothesis of basic subdivisions in the mammalian forebrain because they appear to play such critical roles in the expression of both voluntary and reflex behaviors.

The gradual progression from simple to complex morphology revealed during embryological development provides a time-honored way to appreciate the basic organizing principles of forebrain architecture (for reviews of the approach adopted here, see Refs. [7,9]). At early stages when neurulation occurs — when the neural plate fuses dorsally to form the neural tube — one can identify primary forebrain, midbrain, and hindbrain vesicles, with tiny paired optic vesicles evaginating from the presumptive hypothalamic region of the forebrain vesicle. The next major event in forebrain vesicle differentiation involves the formation rostrodorsally of an external groove, the hemispheric sulcus, which at least initially is complemented by an internal bulge, the torus hemisphericus. The hemispheric sulcus unambiguously divides the forebrain vesicle into three secondary vesicles — paired telencephalic vesicles (endbrain vesicles, with their incipient lateral ventricles) and diencephalon (interbrain, with its incipient third ventricle). This stage, which occurs in the four week human and eleven day rat embryo, is very instructive for understanding later development because the entire wall of the forebrain vesicle can be observed in a midsagittal view (Fig. 3) — the telencephalon has not yet begun its massive, complex, and still not fully understood process of evagination (Fig. 4).

So, as illustrated in Fig. 3, the midline sagittal view of the unevaginated forebrain vesicle is especially useful as the template for a fate map of subsequent differentiation (see Section 3.3.1). Shortly after the telencephalon and

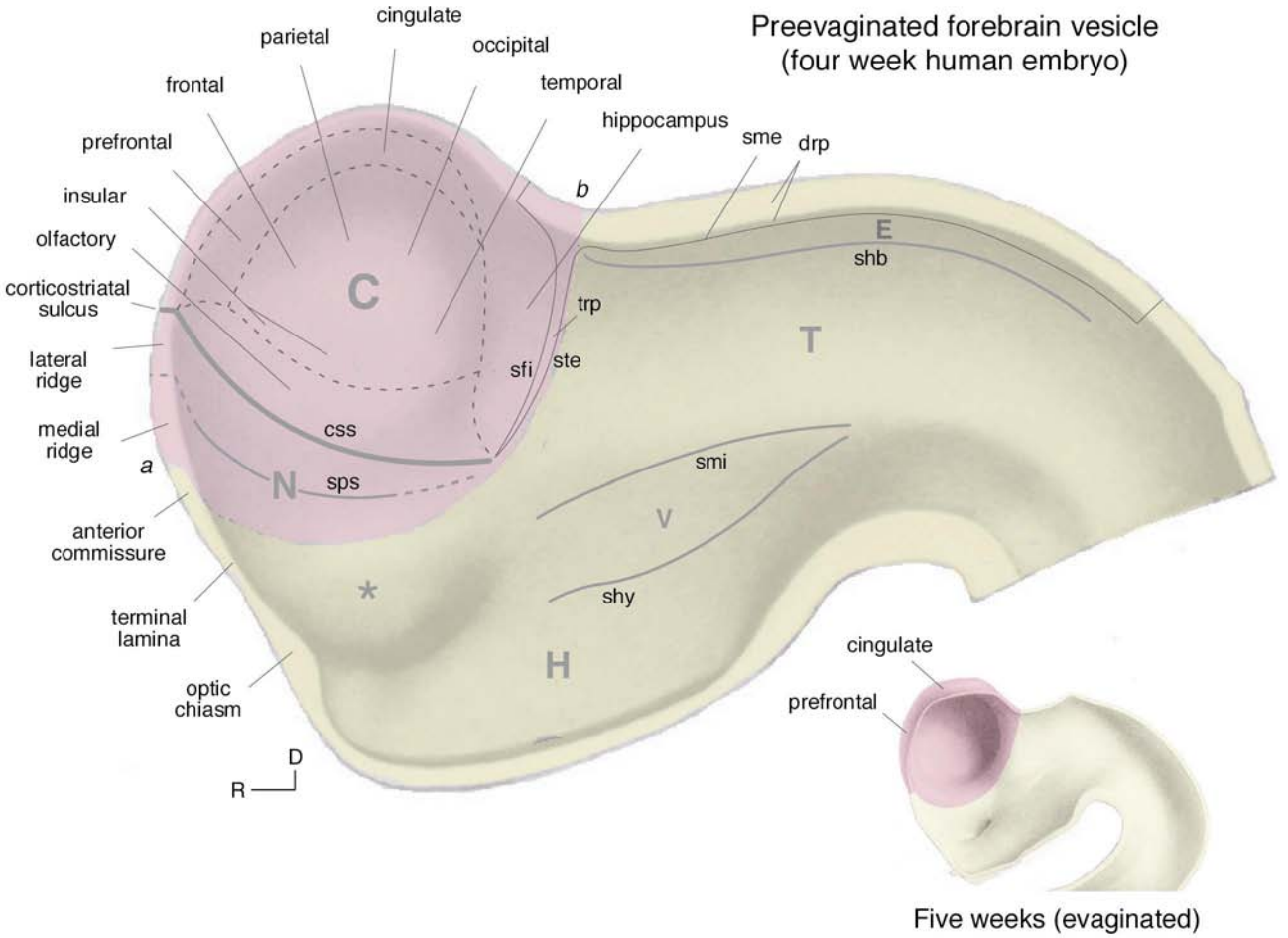


Fig. 3. Major forebrain subdivisions. A fate map of the major forebrain subdivisions projected onto the forebrain vesicle of a four week human embryo, before the telencephalic vesicle (pink) has evaginated to the extent it has a week later (inset, lower right). At the four week stage it is easy to envision qualitatively where the major regions of the cerebral cortex (C) will normally differentiate at later stages, as will the major 'longitudinal' divisions of the interbrain or diencephalon: the hypothalamus (H), ventral thalamus (V), dorsal thalamus (T), and epithalamus (E). The asterisk indicates the presumptive preoptic region, rostral (R) and dorsal (D) to the optic sulcus (gray streak extending from the optic chiasm). a–b indicates the junction between telencephalon and diencephalon (yellow), the presumptive interventricular foramen of Monro. Unless stated otherwise, all nomenclature in this article follows Refs. [9,282]. *Other abbreviations*: css, corticostriatal sulcus; drp, diencephalic roof plate; N, cerebral nuclei/basal ganglia; sfi, fimbrial sulcus; shb, habenular sulcus; shy, hypothalamic sulcus; sme, sulcus medullaris; smi, middle diencephalic sulcus; sps, striatopallidal sulcus; ste, sulcus terminalis; trp, telencephalic roof plate. Adapted with permission from Refs. [9,113].

diencephalon become distinguishable, two longitudinal grooves appear in the inner wall of the right and left halves of the diencephalic vesicle — the middle diencephalic and hypothalamic sulci. They define, in between, the ventral thalamus and a rostroventral extension of it that lies just caudal to the optic sulcus, where the first neurogenesis in the forebrain occurs. In this sense, diencephalic embryogenesis is fundamentally different from that in the hindbrain and spinal cord, where neurogenesis simply proceeds along a ventral to dorsal gradient.

Then the first obvious differentiation of the telencephalic vesicle occurs — the formation of a corticostriatal or corticobasal sulcus, which divides the vesicle neuroepithelium into an essentially dorsal pallial or cerebral cortical region, and an essentially ventral 'basal ganglia' or 'cerebral nuclei' region (Figs. 3 and 5). This internal sulcus forms because of neurogenesis in the ventral, presumptive nuclear or noncortical division of the telencephalon, which starts before neurogenesis in the cortical region. Around this time a third longitudinal sulcus (habenular) also appears in the diencephalon, just ventral to the roof plate; it separates presumptive epithalamus from presumptive dorsal thalamus.

The next and last stage of early forebrain development relevant here involves the appearance of an internal groove, the striatopallidal or interstriatal sulcus, that divides most of the presumptive basal ganglia region into ventromedial and dorsolateral ('ventricular') ridges (Figs. 3–5). Neurogenesis begins earliest in the ventromedial ridge, at least most of which goes on to form the globus pallidus, whereas the bulk of the dorsolateral ridge goes on to form the dorsal striatum (caudate and putamen) [87,142,302]. A specific model for how this occurs has been proposed (see Ref. [8], their Fig. 7).

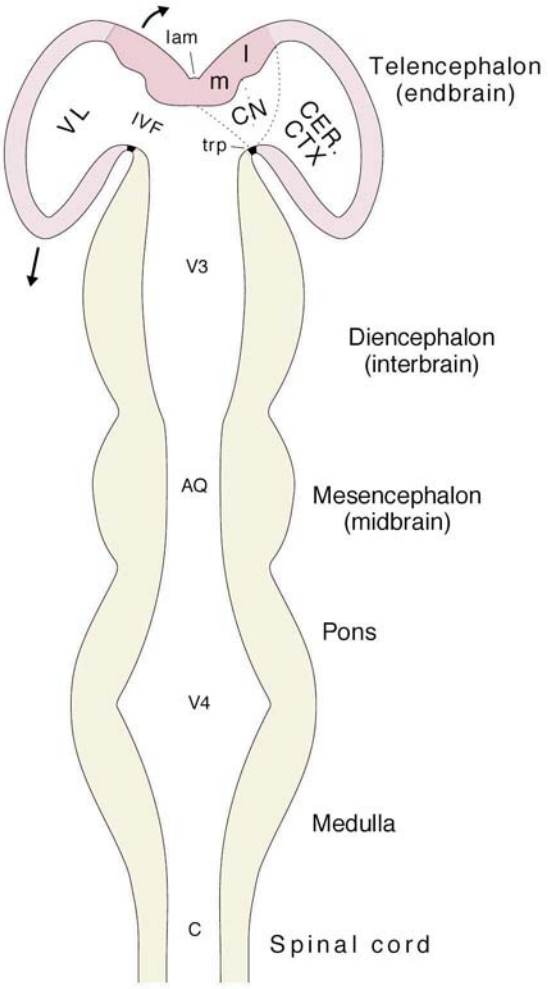


Fig. 4. The major divisions of the central nervous system in a horizontal section of a schematic neural tube with a straightened longitudinal axis. The cerebral hemispheres (pink) are rapidly evaginating (arrows), and their two divisions — cerebral cortex (CER. CTX), and cerebral nuclei/basal ganglia (CN), with their two differentiations, the medial (m) and lateral (l) ventricular ridges — are indicated. The major divisions of the ventricular system associated with major tissue divisions are also shown: central canal (C), fourth ventricle (V4), cerebral aqueduct (AQ), third ventricle (V3) and its rostromedial border the lamina terminalis (lam), and lateral ventricles (VL) with the associated interventricular foramina of Monro (IVF). *Other abbreviation*: trp, telencephalic roof plate (see Fig. 3). Adapted with permission from Ref. [278].

The situation in the telencephalic vesicle at this stage is complicated by the fact that the striatopallidal sulcus has not been traced to the rostral and caudal poles of the presumptive basal ganglia/cerebral nuclei region. This is of critical importance because the rostral pole forms the presumptive septal region whereas the caudal pole forms at least part (the noncortical part) of the amygdala (Fig. 3). Fundamental questions thus arise about the basic components of the septal region (are they striatal and/or pallidal?) and amygdala (are they cortical, striatal, and/or pallidal?). All that can be said with reasonable certainty on developmental grounds alone at this point in time is that the septal region is derived from the presumptive basal ganglia/cerebral nuclei region of the telencephalic vesicle, along with at least part of the amygdala. We shall examine this problem further in Section 3, where information about connections and neurotransmitter expression will be added to the developmental evidence.

Overall, the simplest interpretation of a vast literature on forebrain embryology is that the telencephalic neuroepithelium differentiates into a topologically dorsal cerebral cortex and ventral cerebral nuclei (basal ganglia), which in turn differentiate into a dorsolateral striatum and ventromedial pallidum. On the other hand, the diencephalic neuroepithelium differentiates, to a first order of approximation, into a stack of four more or less longitudinal bands — hypothalamus, ventral thalamus, dorsal thalamus, and epithalamus. By and large, this view is based on more than a century's worth of morphological embryology. An understanding of the genomic program that assembles the neural plate and tube will undoubtedly lead to major new insights, although analysis of certain homeobox gene expression patterns already tends to confirm and clarify the location of certain fundamental borders, such as that between telencephalon and diencephalon (Fig. 6) and between cortex and basal nuclei (see [211]).

1.3. Basic organization of the hypothalamus

The majority of connections within the adult forebrain are accounted for by a familiar qualitative scheme: the dorsal thalamus projects topographically to the entire 'neocortex' (see [267]), which in turn projects topographically to the 'basal ganglia,' especially the striatum (see [84]). In contrast, whereas the hypothalamus is exceptionally important from the functional perspective — it is essential not only for survival of the individual but for the species as well — reasonably accurate data about its neural connections only began appearing with the neuroanatomy revolution of the 1970s, and the vague outlines of its basic structural organization — its place in the forebrain as a whole — are just now beginning to emerge [283].

The origins of deep interest in the hypothalamus can be traced to 1901 and Frölich's detailed account of the adiposogenital syndrome — excessive truncal obesity combined with genital atrophy, which was thought to be especially common in adolescent males [76]. Frölich himself attributed the symptoms to tumors associated with the pituitary gland, although over the next half century it became clear that the obesity and genital atrophy could be produced independently by localized experimental manipulation of the overlying hypothalamus (Fig. 7A), and it was also demonstrated that the hypothalamus has a profound influence on the autonomic nervous system, as well as on the output of the pituitary gland. Today, a wealth of functional evidence indicates that the hypothalamus plays an essential role in coordinating neuroendocrine, autonomic, and behavioral (somatomotor) responses neces-

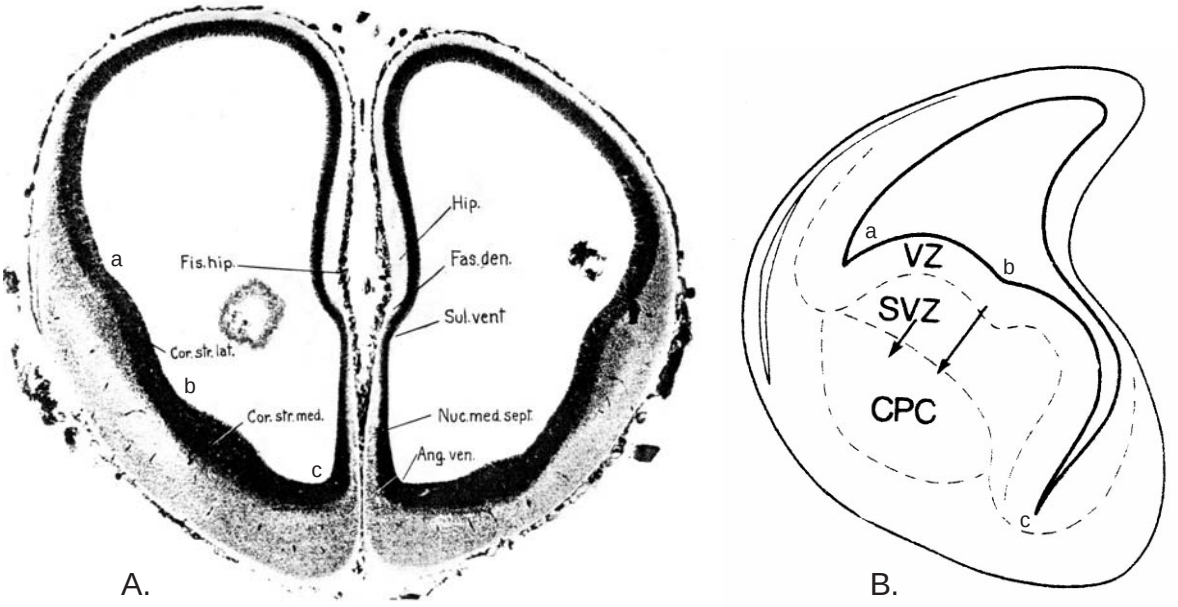


Fig. 5. Embryonic cortex and ventricular ridges. (A) Transverse section through the telencephalic vesicles of a 19 mm human embryo (about 8 weeks) showing the pallium or cortex (between a and the sulcus ventralis) and the two ventricular ridges — a dorsal or lateral ridge between a and b, and a ventral or medial ridge between *b* and *c*. The neuroepithelium is a black layer of varying thickness lining the ventricular cavity; a mantle layer of young neurons can be seen superficial to the neuroepithelium of the ventricular ridges, and in the most ventrolateral cortex just dorsal to a. (B) Transverse section of the left telencephalic vesicle at a later stage of development to show the further precocious growth of the mantle layer associated with the ventricular ridges — which begin bulging dorsally and partly obliterating the originally relatively huge lateral ventricle (from an embryonic day 16 hamster embryo). *Abbreviations*: a, corticostriatal sulcus; Ang. ven., ventral angle; b, striatopallidal sulcus; c, ventral angle; Cor. str. lat., lateral corpus striatum (striatum); Cor. str. med., medial corpus striatum (pallidum); CPC, caudoputamen; Fas. den., fascia dentata (dentate gyrus); Fis. hip., hippocampal fissure; Hip, hippocampus; Nuc. med. sept., medial septal nucleus; Sul. vent., ventral sulcus; SVZ, subventricular zone; VZ, ventricular zone (neuroepithelium). For clarity, the abbreviations a, b, and c have been added to the original figures. Part A adapted from Ref. [113], Part B adapted with permission from Ref. [302].

sary for survival of the individual and of the species (reviewed in Ref. [275]).

Before reviewing the structural organization of the hypothalamus, it is important to consider the fundamental evidence supporting the conclusion that in mammals this part of the brain controls the three basic classes of behavior that ethologists have shown are required for the survival of all animals: ingestive, defensive, and reproductive [306]. As pointed out in Section 1.1, chronic midbrain animals (with a complete transection of the neuraxis between forebrain and midbrain) display no spontaneous locomotor behavior when they are left undisturbed, whereas chronic hypothalamic animals (with telencephalon and thalamus removed or disconnected) are, if anything, hyperactive under quiet conditions. Furthermore, midbrain animals are completely aphagic and adipsic, cannot reproduce, and do not show spontaneous, completely integrated defensive behaviors [14,88]. In contrast, hypothalamic animals can regulate their body weight and body water by ingesting appropriate amounts of food and water from the environment (so long as they are readily available), can reproduce (females, at least), and can mount very effective and complete defensive responses, even to normally innocuous stimuli (Fig. 7B). This evidence, combined with a vast literature on the effects of hypothalamic stimulation and lesions [275], indicates that controllers for ingestive, defensive, and reproductive behaviors (as well as controllers for thermoregulatory behavior and the sleep/wake cycle) are found in the hypothalamus. It must be emphasized, however, that more or less complete 'fragments' of these global behaviors can be evoked in midbrain animals [14,88]. As with locomotor behavior (Fig. 1) these fragments are due to stimulation of individual motor pattern generators or initiators located within the midbrain, hindbrain, and spinal cord — motor pattern generators and initiators that presumably are somehow coordinated in specific ways by specific hypothalamic controllers at a higher level of the motor hierarchy. Knowledge of these individual motor pattern generators can be traced back almost 200 years to the discovery of a caudal medullary respiratory center by Legallois [144].

Let us now turn to the basic structural organization of the hypothalamus. The current view is that at least for descriptive purposes it is conveniently divided into three medial-to-lateral longitudinal zones (periventricular, medial, and lateral) as first suggested in 1940 by Crosby and Woodbourne [53]; and into four rostral-to-caudal levels or regions (preoptic, supraoptic or anterior, tuberal, and mammillary) as first suggested by LeGros Clark in 1938 [47]. To a first order of approximation, the neuroendocrine motor zone is centered in the periventricular zone, the medial zone contains a series of very well-defined nuclei

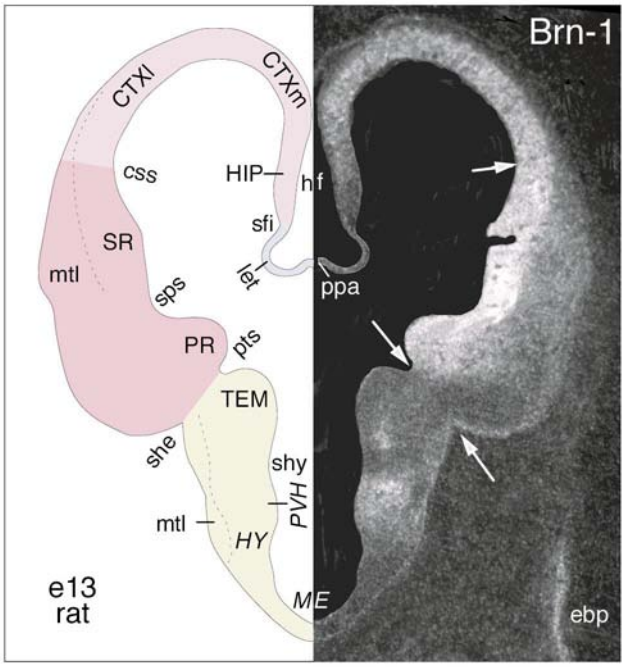


Fig. 6. Homeobox gene expression distinguishes telencephalon from diencephalon. This is a transverse section through the forebrain vesicle of an embryonic day 13 rat embryo. Brain-1 (Brn-1) is a POU-III homeobox gene, and an autoradiogram of its mRNA expression pattern is shown on the right side of the figure. The white arrows indicate the boundary between telencephalic and diencephalic vesicles, and it is clear that Brn-1 expression in the telencephalic vesicle at this stage of development stops at this boundary, although patches of expression are also seen in the presumptive hypothalamic paraventricular nucleus (PVH) and epibranchial placodes (ebp). Structural features seen at this level in an adjacent Nissl-stained section are drawn on the left, with the telencephalic vesicle indicated in pink and the diencephalic vesicle in yellow. *Other abbreviations*: css, corticostriatal sulcus; CTXl,m, cortex, lateral, medial regions; hf, hippocampal fissure; HIP, hippocampus; HY, hypothalamus; let, epithelial lamina; ME, median eminence; mtl, mantle layer; ppa, parahypophysial arch (adjacent to presumptive subfornical organ); PR, pallidal (medial ventricular) ridge; pts, pallidothalamic sulcus; sfi, fimbrial sulcus; she, hemispheric sulcus; shy, hypothalamic sulcus; sps, striatopallidal sulcus; SR, striatal (lateral ventricular) ridge; TEM, thalamic eminence. Adapted with permission from Ref. [7].

that serve to define the rostrocaudal levels, and the lateral zone is poorly differentiated, much like a rostral extension of the reticular formation [275]. However, a great deal of neuroanatomical evidence amassed in the last several years suggests that this basic scheme would benefit from certain refinements, especially in the region between the medial zone nuclei and the third ventricle (Fig. 8).

The *neuroendocrine motor zone* (Section 1.1) is the single most characteristic feature of the hypothalamus, and is certainly the best understood from a structure–function point of view [157,274]. It consists of distinct though partly interdigitated pools of secretomotor neurons that (a) send their axons to the posterior pituitary, where they release predominantly vasopressin or oxytocin (the magnocellular neurosecretory system), or (b) send their axons to the median eminence where they release hypophysiotropic hormones into a portal system for transport to the anterior pituitary, where they act on five classic endocrine cell types (the parvicellular neurosecretory system). The neuroendocrine motor zone is centered in the ventromedial diencephalon, in three contiguous differentiations of the hypothalamic periventricular zone: the neuroendocrine division of the paraventricular nucleus, the anterior periventricular nucleus, and the arcuate nucleus. Two major exceptions include the supraoptic and accessory supraoptic nuclei, which consist of magnocellular neuroendocrine neurons that migrate away from the periventricular zone during development; and the gonadotropin releasing hormone (GnRH) motoneurons, which are unique insofar as they are generated during development from the olfactory epithelium instead of from the third ventricular neuroepithelium, and come to lie scattered in the adult septal and preoptic regions.

The *hypothalamic medial nuclei* form a column of very distinct cell groups that, arranged from rostral to caudal, include the medial preoptic nucleus, anterior hypothalamic nucleus, descending division of the paraventricular nucleus, ventromedial nucleus (and adjacent tuberal nucleus), dorsal and ventral premammillary nuclei, and mammillary body. They form the greater part of the behavior control column discussed in Section 2.

The *hypothalamic lateral zone* remains poorly understood, and in the widest sense may be involved in the regulation of behavioral state and arousal mechanisms [275]. It would appear that the projections of the lateral preoptic area are distinct from more caudal regions of this zone (Ref. [272] and R.F. Thompson, L.W. Swanson, unpublished observations with PHAL), and recently it has become clear that the tuberal level of the lateral hypothalamic area is distinguished by separate populations of neurons that express melanin-concentrating hormone and hypocretin/orexin (see [25,130]), as well as corticotropin releasing hormone in response to dehydration [234,323]. This would suggest that the supraoptic or anterior, and the mammillary levels of the lateral zone may also have distinct features that remain to be characterized.

Finally, a *hypothalamic periventricular region* probably should be distinguished. In essence, it lies between the neuroendocrine motor zone and the medial nuclei proper, and it consists of two adjacent regions of the traditional longitudinal zones of the hypothalamus — neurons of the periventricular zone that are not neuroendocrine, and what remains of the medial zone after the large nuclei listed above (the 'medial nuclei proper') are removed. The reason for proposing a periventricular region defined in this way is that it would appear to constitute a *visceromotor pattern generator network* interposed between the neuroendocrine motor zone of the periventricular zone, preautonomic cell groups in the paraventricular nucleus, and the behavior control column in the medial zone [226,304]. As discussed in Section 7, this network receives inputs from the hypothalamic medial nuclei of the behavior

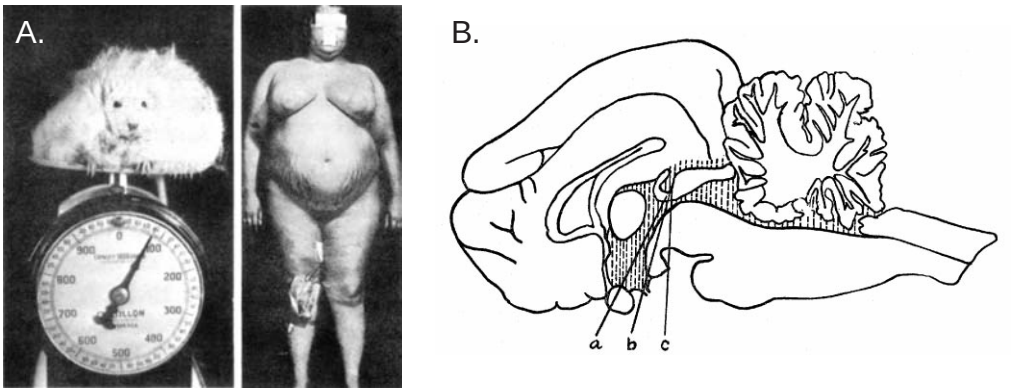


Fig. 7. Hypothalamic obesity. (A) Twenty-year-old female patient on the right suffered from a tumor confined to ventral and medial regions of the hypothalamus and displayed excessive hunger, thirst, and rage — and had lost her menstrual cycle — whereas obesity in the rat shown on the left was produced by an experimental lesion in the same general region of the hypothalamus. (B) Levels of central nervous system transection where animals can (a, b) and cannot (c) survive independently and display spontaneous behavior, including eating, drinking, and locomotion. Part A is reproduced with permission from Refs. [215,268], and Part B is reproduced with permission from Ref. [114].

control column, and projects to the neuroendocrine motor zone and preautonomic cell groups. In addition, it contains central rhythm generators such as the suprachiasmatic nucleus.

1.4. Perspective

Voluntary behavior is controlled directly by projections from the cerebral cortex to the somatic motor system. So it seems reasonable to focus an analysis of neural systems mediating this class of behavior on the reasonably well-known topographic map of the cerebral cortex, and on the less clear higher levels of the somatic motor system hierarchy. The overall organization of projections from the various thalamic nuclei to the entire cortical mantle is also firmly established, along with the organizing principles of outputs from the whole isocortex (neocortex) to the 'classical' basal ganglia (cerebral nuclei).

The rest of this paper deals with two major aspects of forebrain organization that remain problematic. First, how do certain long enigmatic regions including the hippocampus, amygdala, and septum (usually included within the 'limbic system') fit into the grand scheme of cerebral hemisphere organization? As a simple working hypothesis based on developmental, connectional, and neurotransmitter utilization criteria it is proposed that *all* parts of the cerebral hemispheres belong to either the cerebral cortex or to one or another division of the basal ganglia/cerebral nuclei — striatum or pallidum. Furthermore, it is proposed that there is a basic scheme of interconnections between the cerebral cortex, striatum, and pallidum, with differentiations or specializations of this prototypical circuit element in various morphologically and functionally distinct regions of the cerebral hemispheres. And second, what role does the hypothalamus play in regulating the expression of behaviors essential for survival of the individual and of the species as a whole? It is proposed that the hypothalamic medial nuclei form the rostral segment of a behavior control column extending through the ventromedial midbrain, and that as a whole this column receives a topographically organized input from virtually the entire cerebral hemisphere.

This analysis of forebrain organization relies heavily on a model of overall nervous system organization postulating that behavior is equivalent to activity in the motor system, which in turn is modulated by three classes of inputs — voluntary or cognitive, reflex or sensory, and behavioral state (Fig. 1). In this scheme, the hypothalamic medial nuclei are part of the behavior control column, and thus lie at the apex of the motor system hierarchy (Fig. 9), based on similarities with the hierarchical control of locomotor behavior (Fig. 1). Thus, it would be expected that the hypothalamic medial nuclei receive three classes of inputs: cognitive, sensory, and behavioral state [226], although this review focuses only on the first class — inputs from the cerebral hemispheres.

2. The behavior control column

It is convenient first to discuss a new concept, the 'behavior control column,' and then go on in Sections 3 and 4 to analyze how cerebral hemisphere inputs map onto it in a topographically organized way.

During the course of the last 15 years our laboratory has conducted a systematic analysis of axonal projections from the medial half of the hypothalamus, based on over 200 PHAL experiments in the rat [35–37,39,99,222,256, 303,324]. The results suggest three main conclusions:

(1) A series of very obvious cell groups in the rostral medial zone — including the medial preoptic nucleus, anterior hypothalamic nucleus, ventromedial nucleus (and a ventrolateral extension, the tuberal nucleus), dorsal premammillary nucleus, and ventral premammillary nu-

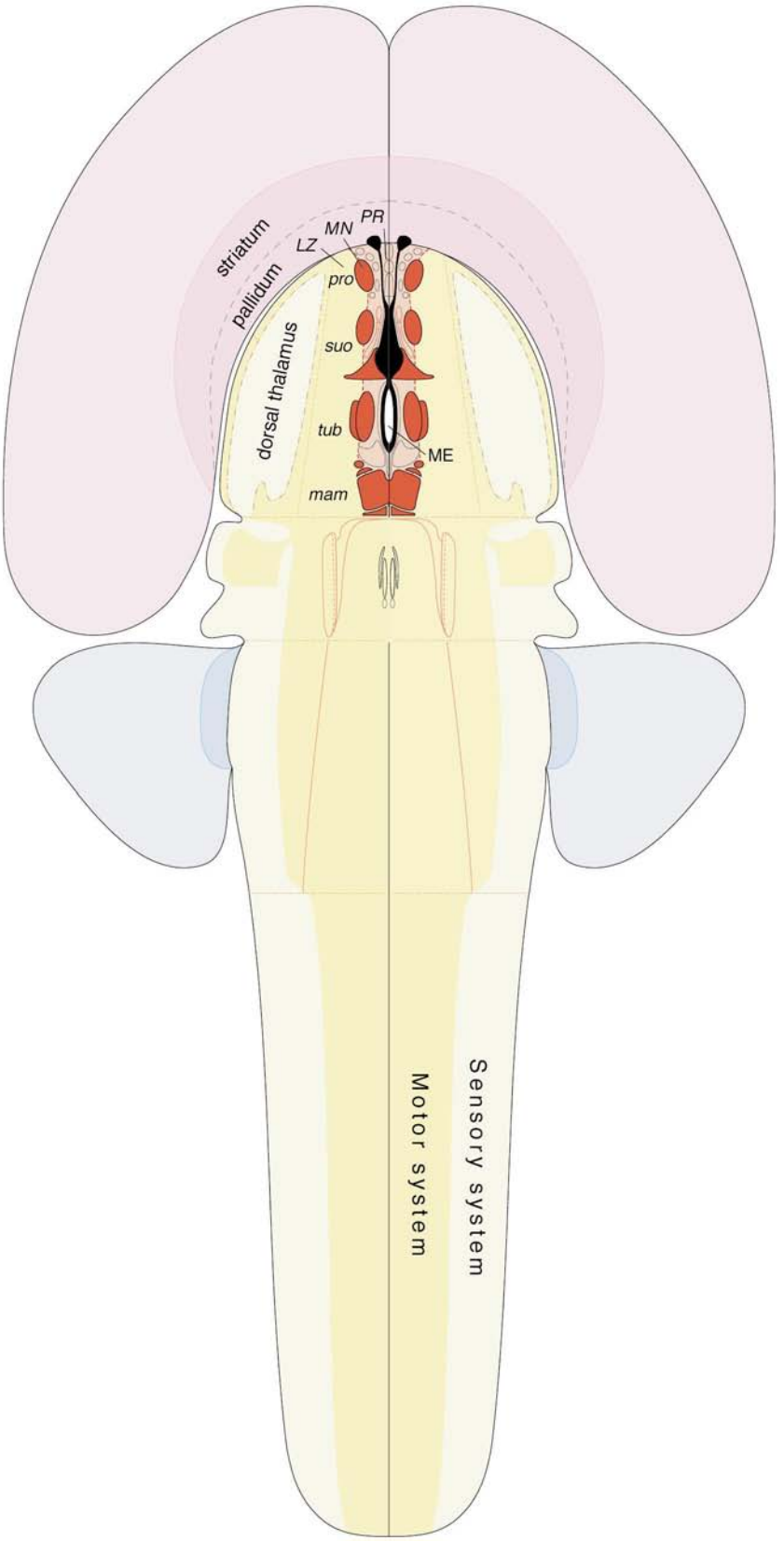


Fig. 8. Major features of hypothalamic cell group organization as seen on a flatmap of the rat central nervous system. The neuroendocrine motor zone is shown in black and the medial nuclei (MN) in dark red; the periventricular region (PR) is shown between them in light red, and the lateral zone (LZ) is shown in yellow, lateral to the medial nuclei. As discussed in the text, the periventricular region contains a visceromotor pattern generator network, and the medial nuclei form the rostral end of the behavior control column or network. In addition to these essentially longitudinal features, the hypothalamus can be divided into four transverse regions or levels, based on the characteristic medial nucleus residing within it — preoptic (pro), supraoptic or anteri or (suo), tuberal (tub), and mammillary (mam). The cerebrum is shown in pink, the cerebellum in blue, and the brainstem/spinal cord in yellow.

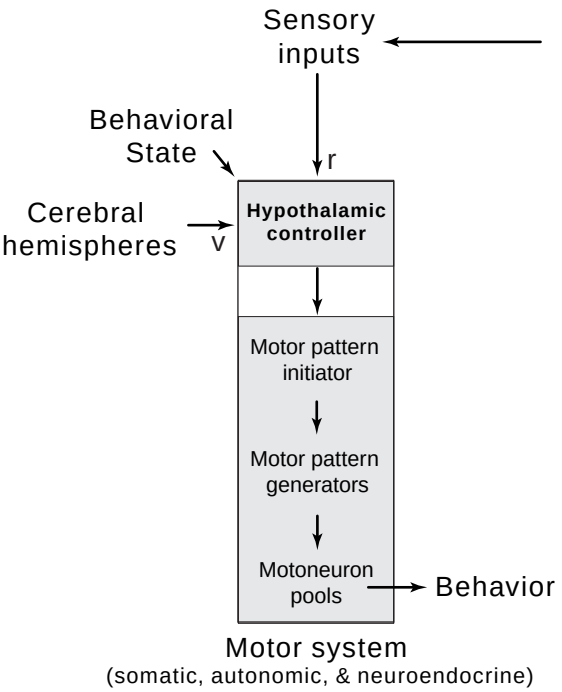


Fig. 9. A model of hypothalamic controllers at the top of the motor system hierarchy, with a trio of sensory, behavioral state, and cerebral hemisphere inputs (see Fig. 1). Although not shown for the sake of clarity, all three classes of inputs can go to all levels of the motor system hierarchy. *Abbreviations*: r, reflex; v, voluntary.

cleus (shown in red in Fig. 10) — all generate a dual projection, with a primary branch descending to the brainstem motor system and a secondary branch ascending to the thalamus [226]. This is, in principle, just like the projections of the caudally adjacent medial and lateral mammillary nuclei, which form the caudal medial zone of the hypothalamus. It has long been known from developmental studies that individual neurons in the mammillary nuclei send a descending axon to the brainstem tegmentum, and a collateral of this axon to the anterior thalamic nuclei [33,75,311]. It is also similar in principle to the caudally adjacent reticular part of the substantia nigra [39,226], which sends a branched projection to the brainstem motor system (including the deeper layers of the superior colliculus and reticular formation) and to the thalamus [16,266]; and it is similar to the adjacent ventral tegmental area, which sends projections to the brainstem motor system and thalamus, in addition to other sites (see [17,273]).

(2) The rostral medial zone nuclei just listed (medial preoptic, anterior hypothalamic, ventromedial and tuberal, and premammillary; red in Fig. 10) are interconnected in a massive, highly differentiated way, and other connectional and functional evidence indicates that they form critical parts of circuitry underlying the expression of reproductive and defensive behaviors, that is, social behaviors (involving interactions between animals) critical for survival of the species and the individual (Section 2.3).

(3) Overall, the evidence (Sections 1.3, 2.1–2.3) indicates that the ventromedial column of nuclei shown in Fig. 10 forms at least the core of a *behavioral control column* at the top of the motor system hierarchy (as defined in Figs. 1 and 9), and that this column may be divided into rostral and caudal segments. The *rostral segment*, from the medial preoptic to premammillary nuclei (the preoptic-premammillary segment) *plays a critical role in circuits regulating the three basic classes of goal-oriented behavior* common to all animals: ingestive, reproductive, and defensive; whereas the *caudal segment* (the mammillary-nigral segment; black in Fig. 10) *plays a critical role in circuits underlying the expression of exploratory or foraging behavior* in general. The rostral segment can be divided further into two major parts, one dealing with the social behaviors just mentioned, and another, the descending division of the paraventricular nucleus (PVHd; green in Fig. 10), dealing with ingestive (eating and drinking) behaviors, which we shall now consider in more detail.

2.1. Thirst as a model system (ingestive behavior)

The behavior control column is formed by a longitudinal array of cell groups whose functional significance is known at least in a general way. However, these cell groups are not ‘centers’ in some isolated, naive sense [180]. Rather, they are nodes in circuits, systems, or networks that mediate particular classes of behavior [275,293] — nodes that appear to act as controllers (or parts of controller networks) providing set-points or some baseline level of endogenous activity (Sections 1.1, 1.3). Furthermore, whereas the evidence strongly indicates that they are essential for the control of these behaviors, it is certainly not known at the present time whether or not there are nearby cell groups in the hypothalamus and midbrain that are also integral parts of the behavior control column. In short, while the behavior control column as defined in a preliminary way here appears to form an essential core of the associated circuitry, it may well include additional components.

For purposes of description and analysis, motivated behavior in general can be divided into three sequential phases — initiation, procurement, and consummatory [293]. In terms of defining underlying neural circuits, thirst has provided an unusually good model, in large part because so much is known about the physiology of body water regulation, and water intake in animals is so easy to measure and to manipulate with well-defined physiological stimuli [228,334]. Even more specifically, perhaps the best understood motivated behavior of all in terms of neural circuitry is drinking associated with a particular stimulus, hypovolemia, because at least one mechanism and site of initiation is known with certainty — high circulating levels of the peptide hormone angiotensin II acting on neuronal receptors in the subfornical organ [73,257,305].

A general approach to understanding the organization of

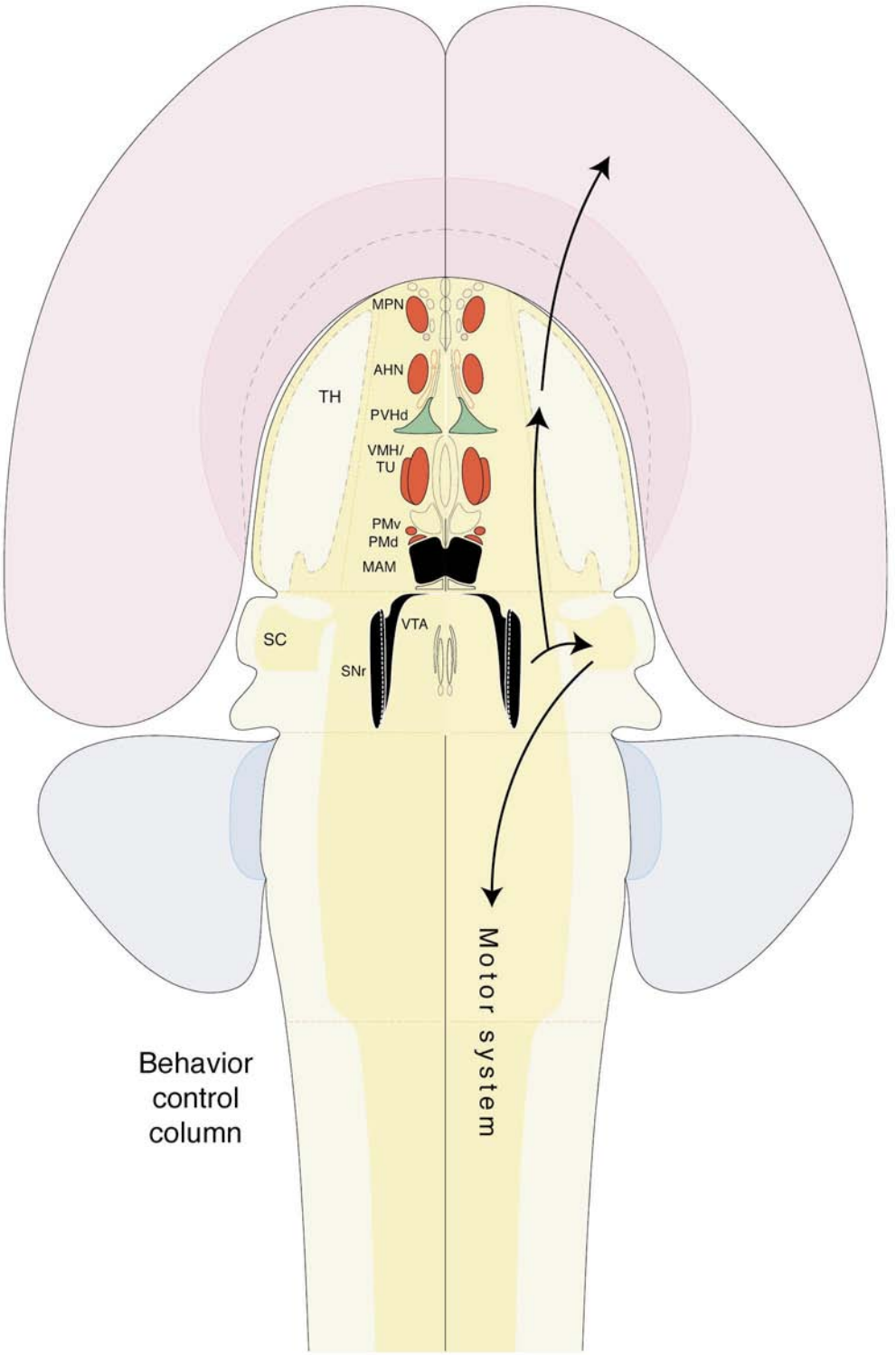


Fig. 10. An overview of the behavior control column, with the rostral segment in red and green, and the caudal segment in black. Almost all of the nuclei in this column generate a dual, typically branched projection — descending to the motor system on one hand and ascending to thalamocortical loops on th e other. *Abbreviations*: AHN, anterior hypothalamic nucleus; MAM, mammillary body; MPN, medial preoptic nucleus (lateral part in particular); PMd,v, premammillary nuclei, dorsal, ventral; PVHd, descending division of paraventricular nucleus; SC, superior colliculus, deeper layers; SNr, reticular substantia nigra; TH, dorsal thalamus; TU, tuberal nucleus; VMH, ventromedial nucleus; VTA, ventral tegmental area.

neural circuitry mediating a specific class of motivated or goal-oriented adaptive behavior — hypovolemic thirst and drinking — is illustrated in Fig. 11, which is based largely on evidence reviewed elsewhere [226,275–277,279]. The part of the behavior control column identified thus far with this activity is the descending (non-neuroendocrine) division of the paraventricular nucleus, and its descending projection to the periaqueductal gray and/or adjacent

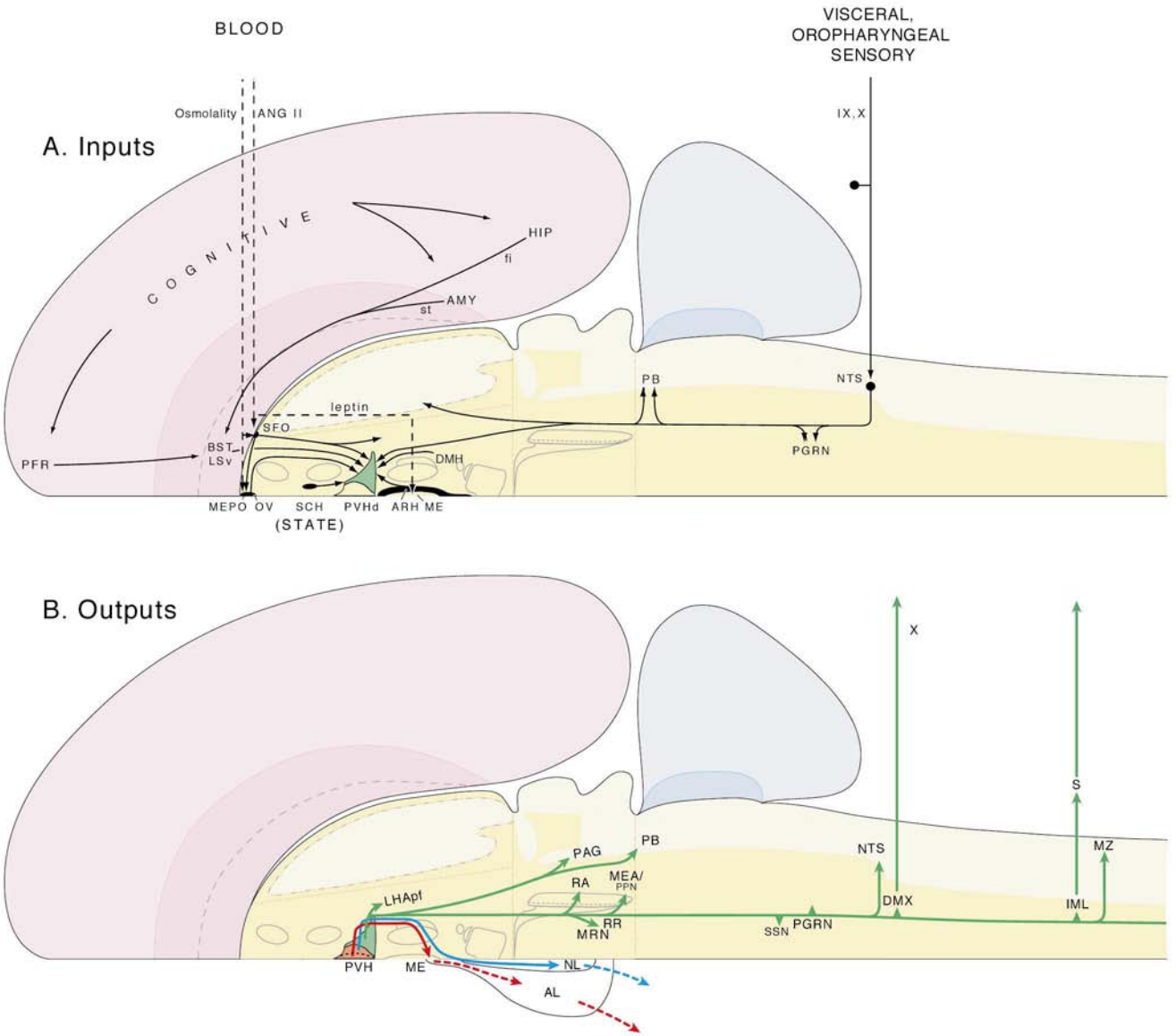


Fig. 11. Outline of circuitry involved in controlling thirst and drinking behavior. The scheme focuses on one member of the behavior control column, the descending paraventricular nucleus (PVHd), and its major inputs (A) and outputs (B). As discussed in the text, various classes of input play a key role in the initiation phase of the behavior, whereas outputs of the PVH are involved in the procurement and consummatory phases of the behavior, as well as in coordinating the appropriate visceral (neuroendocrine and autonomic) responses to maintain homeostasis during these latter phases, before enough water is located and ingested. The PVHd is perhaps the best established component of the hypothalamic thirst control network, although there are almost certainly others, which remain obscure at this point. Interestingly, the PVHd is a critical component of the hypothalamic hunger control network as well. *Other abbreviations*: AL, anterior lobe pituitary; AMY, amygdala; ANG II, angiotensin II; ARH, arcuate nucleus; BST, bed nuclei stria terminalis; DMH, dorsomedial nucleus; DMX, dorsal motor nucleus vagus; fi, fimbria; HIP, hippocampus; IML, intermediolateral preganglionic column; IX, glossopharyngeal nerve; LHApf, perifornical lateral hypothalamic area (tuberal level); LSv, ventral lateral septal nucleus; ME, median eminence; MEA, midbrain extrapyramidal area; MEPO, median preoptic nucleus; MRN, mesencephalic reticular nucleus; MZ, marginal zone; NL, neural (posterior) lobe pituitary; NTS, nucleus of the solitary tract; OV, vascular organ lamina terminalis; PAG, periaqueductal gray; PB, parabrachial nucleus; PFR, prefrontal region; PGRN, paragigantocellular reticular nucleus (ventrolateral medulla); PPN, pedunculopontine nucleus; RA, raphé nuclei; RR, retrorubral area; S, sympathetic ganglia; SCH, suprachiasmatic nucleus; SFO, subfornical organ; SSN, superior salivatory nucleus; st, stria terminalis; X, vagus nerve.

regions. The best evidence for this comes from lesions of the periaqueductal gray region (but not the medulla), which attenuate the primary polydipsia and subsequent hyperphagia elicited by noradrenaline injections in the paraventricular nucleus, whereas this is not the case for hypophysectomy (see [326]). The PVHd is undoubtedly not the only hypothalamic cell group that controls thirst (and hunger), there is, however, a great deal of evidence that it is at least an integral part of the control mechanism or network [145].

Thirst is initiated or modulated by a number of stimuli or influences. Sensory, essentially reflex, initiation is mediated in part by information from the vagus and glossopharyngeal nerves (related, for example, to car-

diovascular volume receptors, hepatic osmoreceptors, and a 'dry mouth'). This information is relayed, at least in part, by direct connections from the nucleus of the solitary tract to the PVHd, and by less direct inputs relayed from the nucleus of the solitary tract via the ventrolateral medulla (the lateral paragigantocellular reticular nucleus), projections to the PVHd that in part use norepinephrine, epinephrine, galanin, and neuropeptide Y as neurotransmitters [148,239,240]. All four substances induce primary polydipsia followed by hyperphagia when injected into the PVH (see [145]). Humoral sensory information (angiotensin II levels) is detected in the subfornical organ, which also projects directly to the PVHd, a pathway that, interestingly, also uses angiotensin II as a neurotransmitter [149]. In fact, the total output of the subfornical organ is of considerable interest because it innervates directly neuronal cell groups participating in all three classes of motor responses to hypovolemia — behavioral, autonomic, and neuroendocrine [275–277,291]. One of these cell groups surrounds the rostral end of the third ventricle, in and perhaps around the median preoptic nucleus and vascular organ of the lamina terminalis. Injections of angiotensin II into this general region elicit drinking [248,296], and the projection to it from the subfornical organ also contains angiotensin II [149]. Furthermore, this region, like the subfornical organ [253], is known to be osmoreceptive [24] (another humoral stimulus to thirst) and to project to the PVHd [97]. It should also be mentioned that there is a neuropeptide Y-containing projection from the hypothalamic arcuate nucleus to the PVH, and it is possible that circulating leptin entering through the nearby median eminence acts on this pathway to influence ingestive behavior responses associated with the PVHd (see [69]).

Not surprisingly, there are also presumed cognitive/voluntary and behavioral state inputs to the PVHd. Current evidence suggests that the former are relayed to the PVHd by the bed nuclei of the stria terminalis and ventral lateral septal nucleus, which in turn receive inputs from the prefrontal cortex, hippocampal formation, and amygdala (Ref. [226] and Section 4.2). Information about behavioral state, and in particular about the circadian cycle, may reach the PVHd directly from the suprachiasmatic nucleus, as well as from the latter via a relay in the subparaventricular zone [324]. In addition, there is a major input to the paraventricular nucleus from the nearby dorsomedial nucleus of the hypothalamus [303], which appears to be a critical node in the periventricular visceromotor pattern generator network (Sections 1.3 and 7).

In summary, it is useful to view motivation systems in terms of various classes of inputs (for example, sensory, cognitive, and behavioral state) to the motor system, in principle the way simpler, more traditional sensory-motor systems have been conceptualized. This approach has been outlined in some detail for one particularly clear example, hypovolemic thirst, but as we shall now see, it can be applied to defensive and reproductive behaviors as well.

2.2. Social behavior network (reproductive and defensive behaviors)

Pathway tracing methods demonstrate that there are two highly interconnected sets of nuclei in the rostral behavior control column (Fig. 12). One set [36,37,226,256] includes the lateral part of the medial preoptic nucleus, ventrolateral part of the ventromedial nucleus, and ventral premammillary nucleus. There is abundant evidence that these three cell groups form a core part of the sexually dimorphic circuit mediating reproductive behavior (see [254]), and each of them expresses abundant levels of estrogen receptor mRNA [255]. For example, the medial preoptic nucleus appears to be involved selectively in the expression of masculine sexual behavior whereas the ventrolateral ventromedial nucleus is important for the expression of feminine sexual behavior (in particular, the lordosis reflex).

In contrast, the other set includes the anterior hypothalamic nucleus, dorsomedial part of the ventromedial nucleus, and dorsal premammillary nucleus [37,39,222]. Abundant evidence reviewed elsewhere indicates that the circuitry established by these three cell groups plays a critical role in the expression of defensive behaviors, especially with respect to predators [34,51,225,226], and they all express abundant levels of androgen receptor mRNA [255].

The only major direct connection between these two sets of nuclei [37] is formed by a projection from the ventrolateral part of the ventromedial nucleus (part of the reproductive behavior network) and the anterior hypothalamic nucleus (part of the defensive behavior network). There are no known major direct connections between these six nuclei and the PVHd (part of the ingestive behavior network).

2.3. Exploration segment of the column (foraging behavior)

We have defined the caudal segment of the behavior control column as including the mammillary body, substantia nigra (reticular part), and ventral tegmental area — what at first sight might seem an odd grouping. The basic rationale is as follows. First, whereas the functional role of the ventral tegmental area is undoubtedly complex, there seems little doubt that it is an important node in the system that controls the expression of locomotor behavior (see [271]). Second, the reticular part of the substantia nigra undoubtedly plays a critical role in the expression of orienting movements of the eyes, head, and neck, and even of the upper limbs, via its massive projection to the deeper layers of the superior colliculus (e.g. [44,112,270,329]). And third, quite unexpected insights into the long enigmatic function(s) of the mammillary body have recently emerged (see [23,85,300]). Neurons in the mammillary body (and the anterior thalamic nuclei) display the features of 'head direction' or 'compass' cells, firing maximally

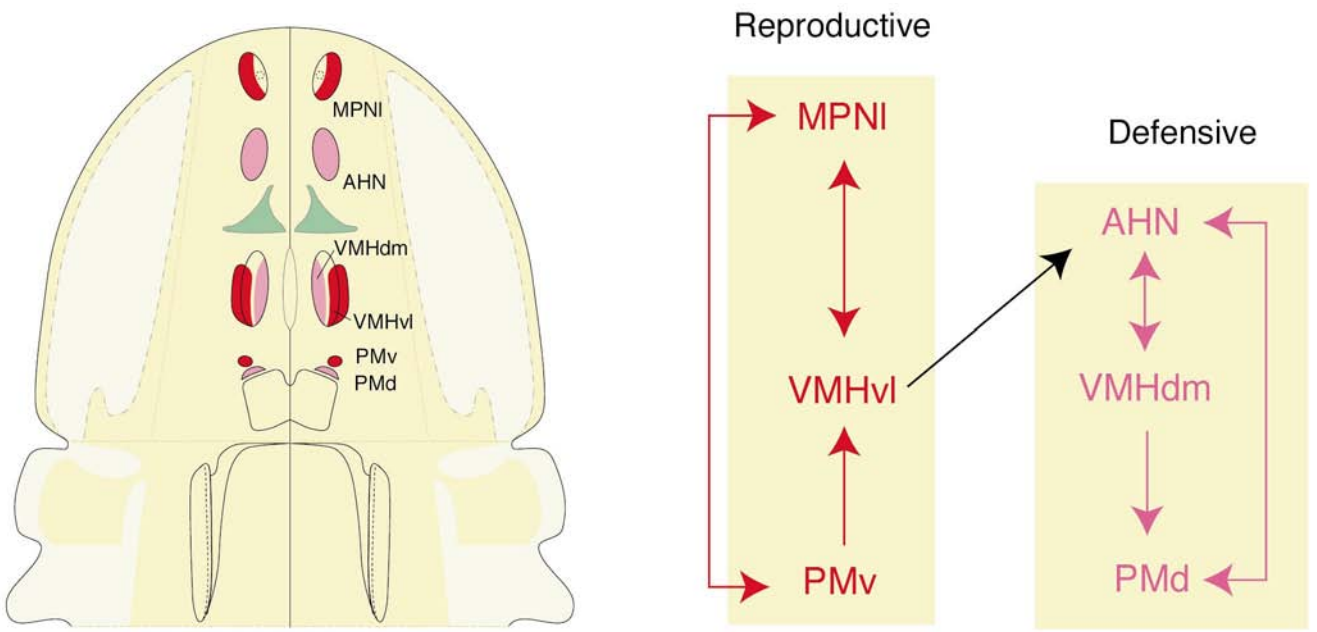


Fig. 12. Left. Cell groups of the rostral behavior control column. The descending paraventricular nucleus, which is involved in the control of eating and drinking (ingestive behavior, see Fig. 11) is shown in green. The rest of the cell groups play a major role in controlling two classes of social behaviors, that is, behaviors involving interactions between animals — reproductive (red) and defensive (magenta). Right. The organization of major direct connec tions between components of the rostral behavior control column. See text for details.

when the animal's head is pointed in a certain direction within the environment. Interestingly, whereas neurons with this basic neurophysiological profile were discovered in the subicular complex of the hippocampal formation, lesions there do not alter dramatically the physiological properties of head direction cells in the anterior thalamic nuclei, whereas lesions in this part of the diencephalon abolish head direction responses in the subicular complex. Preliminary evidence suggests that perhaps vestibular information about head orientation is relayed via the dorsal tegmental nucleus to the mammillary body (and/or anterior thalamic nuclei), and then on to the subicular complex [260,300]. It has been suggested that the mammillothalamic-cortical system containing head direction neurons is critically involved in elaborating a sense of direction [300].

Thus, a case can be made for the caudal behavior control column being involved critically in two basic aspects of exploratory or foraging behavior in general — locomotion and orientation of the eyes, head, and neck, with the reticular substantia nigra more involved in orienting movements and the mammillary body in orientation direction. By way of contrast, the rostral behavior control column appears to play a critical role in establishing particular goals, such as food or water, a mate, or escape from a predator.

3. A model of cerebral hemisphere organization

Having characterized the general structural and functional organization of a motivated behavior control column that can be thought of as lying at the apex of the motor system hierarchy in the upper brainstem, we shall now go on to consider how cerebral influences map onto the column. This will be facilitated by introducing a conceptually simple model of cerebral hemisphere organization, and later (in Section 6) comparing it briefly with other current ways of dealing with this problem. In essence, the model postulates that the cerebral hemispheres have only three parts — cortex, striatum, and pallidum — which generate a triple descending projection to the motor system — excitatory, inhibitory, and disinhibitory, respectively. The model is based on a combination of embryological, gene expression, connectional, and functional arguments.

3.1. Development and fast neurotransmitters

As discussed in Section 1.2, there is currently rather broad general agreement among neuroembryologists that the mammalian telencephalon (endbrain, cerebral hemispheres, and cerebrum are considered synonyms here) consists of two basic parts, a cortex dorsally and a nuclear mass ventrally (Figs. 3–6). As an extension of this view, most of the major human neuroanatomy textbooks of the last quarter century [42,186,195,331] have referred to the noncortical part of the adult cerebral hemisphere as the basal ganglia or basal nuclei (cerebral nuclei is used as a synonym here), although there is considerable disagreement about whether to classify certain parts of the cerebral

hemisphere as cortical or nuclear, or the problem is simply ignored (see Section 6).

A second, independent argument for a basic dichotomy between cerebral cortex and nuclei comes from extensive evidence [84] that most, if not all, cortical projection neurons (pyramidal cells) use glutamate as a fast, excitatory neurotransmitter, whereas in contrast the descending projections of two classic parts of the basal ganglia/cerebral nuclei (the caudate nucleus/putamen and the globus pallidus) use GABA as a fast, inhibitory neurotransmitter (Fig. 13). One postulate of the model outlined here is that in general descending projections of the basal ganglia/cerebral nuclei use GABA as an inhibitory neurotransmitter, and descending projections of cerebral cortex use glutamate as an excitatory neurotransmitter [206,226,295]. This is simply an application of the polytransmitter hypothesis that all neurons (at least at some stage of the life cycle) use either an excitatory amino acid or GABA as a neurotransmitter, along with various combinations of other peptides and molecules [281].

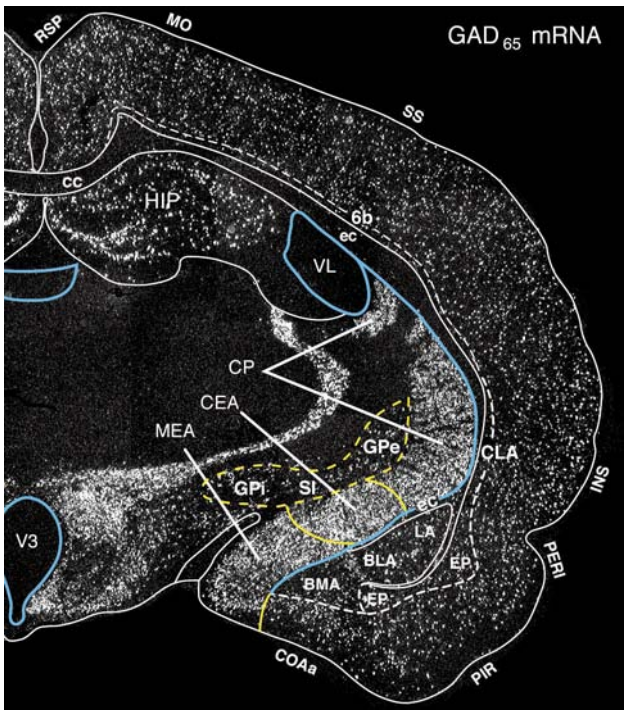


Fig. 13. The distribution of neurons expressing GAD65 mRNA in a transverse histological section through the rat forebrain. GAD65 (along with GAD67) is the enzyme that converts the default neurotransmitter glutamate to the neurotransmitter GABA. In the cerebral cortex, GAD is expressed in interneurons, whereas in the cerebral nuclei/basal ganglia it is expressed in descending projection neurons. Various cerebral nuclei regions as interpreted here are indicated with yellow; the lateral and third ventricular ependyma is shown in blue, along with the obliterated (ventral) part of the lateral ventricle (see Figs. 15, 17 and 18). This section corresponds approximately to the one shown in Fig. 17B. *Abbreviations*: BLA, basolateral amygdalar nucleus; BMA, basomedial amygdalar nucleus; cc, corpus callosum; CEA, central amygdalar nucleus; CLA, claustrum proper; COAa, anterior cortical amygdalar nucleus; CP, caudoputamen; ec, external capsule; EP, endopiriform nucleus; GPe,i, globus pallidus, external, internal segments; HIP, hippocampus; INS, insular cortex; LA, lateral amygdalar nucleus; MEA, medial amygdalar nucleus; MO, motor cortex; PERI, perirhinal area; PIR, piriform area; RSP, retrosplenial cortex; SI, substantia innominata; SS, somatosensory cortex; VL, lateral ventricle; V3, third ventricle; 6b, cortical layer 6b or 7 (subplate). From an in situ hybridization autoradiogram. Adapted with permission from Ref. [294].

In the mammalian cerebral cortex, glutamate appears to be used as a neurotransmitter by (all) pyramidal neurons whereas GABA is used by (many) interneurons but not by pyramidal cells. In a series of experiments with fundamental theoretical implications, Rubenstein and colleagues [11,12], and now others [143,202], have recently presented evidence that at least most GABAergic interneurons of the adult cerebral cortex are actually generated by the neuroepithelium of the ventricular ridges (which generate the basal ganglia/cerebral nuclei) at early stages of development and then migrate dorsally to the pallium (cortex) along tangential routes. These results imply another fundamental difference between the cerebral cortex and nuclei — this time with respect to developmental gene expression patterns, related to whether neurons use glutamate (a default neurotransmitter [281]) or GABA as a neurotransmitter. Perhaps during normal mantle layer formation in mammals, only the ventricular ridges generate neurons that retain the capacity to express glutamic acid decarboxylase (GAD), and thus synthesize GABA from glutamate, throughout life.

3.2. Triple projection to the motor system

Another postulate of our model is that the cerebral hemispheres generate a fundamental triple descending projection to the motor system, based on the ‘classical’ isocortical-striatal-pallidal model (see Sections 4 and 5 for references), and that the projections from structurally and functionally differentiated regions of the cerebrum are variations on this arrangement. The adult ‘minimal or prototypical circuit element’ (Fig. 14) consists of: (1) an excitatory (glutamatergic) projection from cortex to the brainstem and spinal cord motor system, with an excitatory collateral [146] to the striatum; (2) an inhibitory (GABAergic) projection from the striatum to the brainstem motor system, with an inhibitory collateral [197] to the pallidum; and (3) an inhibitory (GABAergic) projection from the pallidum to the brainstem motor system (with an inhibitory collateral [197] to the thalamus). Functionally, the pallidal projection is disinhibitory [227] because it is inhibited by the striatal input, which in turn is excited by the cortical input. The descending projection to the brainstem/spinal cord motor system from the isocortex (synonymous with neocortex, a term better left unused in light of unfounded evolutionary implications; see Section 6) arises primarily from layer 5, whereas the isocortical projection to thalamus arises predominantly from layer 6; cortical associational/commissural projections arise preferentially from supragranular layers 2 and 3 (see

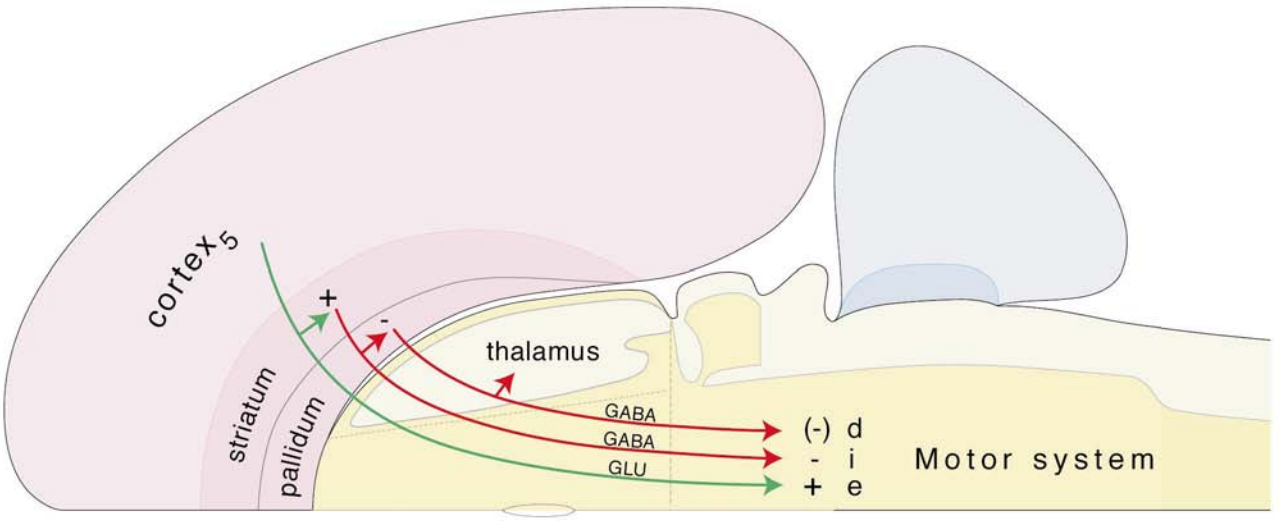


Fig. 14. Triple cascading projection from the cerebral hemispheres to the brainstem motor system. This minimal or prototypical circuit element consists of a glutamatergic (GLU) projection from layer 5 pyramidal neurons of the isocortex (or equivalent pyramidal neurons in allocortex), with a glutamatergic collateral to the striatum. This dual projection appears to be excitatory (e, +, green). The striatum then generates a GABAergic projection to the motor system, with a GABAergic collateral to the pallidum. This dual striatal projection appears to be inhibitory (i, −, red). Finally, the pallidum generates a GABAergic projection to the brainstem motor system, with a GABAergic collateral to the dorsal thalamus. This dual pallidal projection can be viewed as disinhibitory [d, (−)] because it is inhibited by the striatal input.

[123,147]). Recall that the brainstem part of the motor system, as defined here, includes the hypothalamus (e.g. Fig. 9).

3.3. A basic taxonomy of parts

Thus far we have suggested that embryological, neurotransmitter, and connectional evidence all converges to indicate that the cerebral hemispheres present two basic divisions, cortex and nuclei, and that the latter have two subdivisions, striatum and pallidum. This brings us to the crux of the problem — how might all of the various parts of the cerebral hemispheres be classified as either cortical, striatal, or pallidal, and how does the triple descending projection to the motor system apply to this classification? The answers to these two questions are, of course, entirely interrelated. For the sake of clarity, the classification scheme for parts we have arrived at thus far will be discussed now, followed in the next Section by an analysis of the connectional evidence. Here there are two concerns: what are the major divisions of the cerebral cortex, and what are the major divisions of the cerebral nuclei/basal ganglia?

3.3.1. The cerebral cortex (cortical plate and claustrum)

The general outlines of areal differentiation in the mammalian cerebral cortex are widely appreciated, although a comprehensive account of the cerebral hemispheres needs to deal with a rather obscure but critical topic — the nature and full extent of the claustrum. But first, the traditional cerebral cortex: more or less obvious differences in lamination patterns have led to parcellation of the cortical mantle into areas or fields. As an obvious example, there is a clear difference in lamination between olfactory and somatic sensorimotor cortical areas (Fig. 15). Although alternative schemes are available [129], the one used here is derived from the classical work of Brodmann [78]. We have developed a graphical way to show the cortical areal map in a topographically accurate way (where the surface area of particular cortical fields is maintained along with correct borders between fields) for the rat [8,278,282] (Fig. 16) and human [280], and references to the primary literature for the various cortical areas may be found in Ref. [282]. The flatmap approach is based on embryology, and in principle it is a fate map of the neural plate, which topologically is a flat sheet, one cell thick. At early stages of the neural tube, it is easy to appreciate how the presumptive cortical protomap could be visualized on a flat sheet, before the telencephalic vesicles evaginate (Fig. 3).

There are only a few points about regions included in the cerebral cortex that merit comment here, and they revolve around the admittedly unusual olfactory region, which is unique because it is the only part of the cerebral hemispheres to receive direct input from a (sensory) cranial nerve. First, along with Brodmann [78] we include the olfactory bulb (main and accessory) in the cerebral cortex, and in fact regard it as the primary, unimodal olfactory area (analogous, say, to area 17 or the primary, unimodal visual area) because it is in direct receipt of olfactory information from the olfactory nerve. In this view, mitral cells are modified pyramidal cells, which of course use glutamate as a neurotransmitter [252]. And second, following recent trends, we include laminated parts

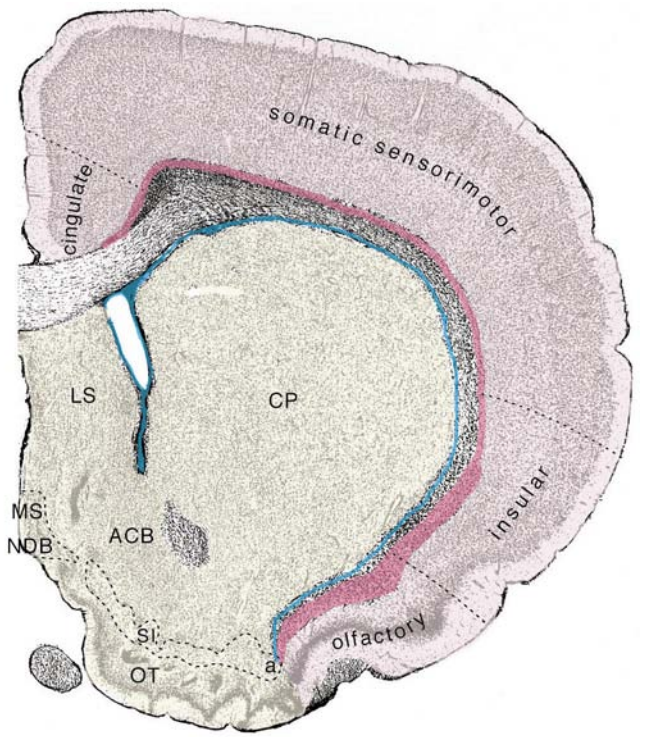


Fig. 15. Cerebral cortex versus basal ganglia/cerebral nuclei. This is a transverse Nissl-stained histological section through the adult rat telencephalon to show the disposition of cerebral cortex (pink) versus cerebral nuclei/basal ganglia (yellow). Notice how differentiated cortical lamination patterns can be; for example, compare somatic sensorimotor cortex with olfactory cortex. Correspondingly, note how differentiated various regions of striatum can be; for example, compare caudoputamen (CP) with olfactory tubercle (OT). The claustral division of cerebral cortex is shown in darker pink, deep to the traditional cortical plate, and the lateral ventricular ependyma with its obliterated ventral extension are shown in blue. This section corresponds to level A in Fig. 17. *Other abbreviations*: a, corticostriatal sulcus (obliterated, see Fig. 5); ACB, nucleus accumbens; LS, lateral septal nucleus; MS, medial septal nucleus; NDB, nucleus of the diagonal band; SI, substantia innominata. Photomicrograph from Ref. [282].

of the amygdala on the surface of the hemisphere as components of the (olfactory) cortex [294]. They include the well-known cortical 'nucleus' of the amygdala and 'nucleus' of the lateral olfactory tract, along with the more obscure postpiriform transition area and piriform-amygdalar area — all of which appear to contain classical pyramidal neurons that use glutamate as a neurotransmitter. These four parts of the amygdala, along with the piriform area, anterior olfactory 'nucleus,' and tenia tecta might be thought of as the secondary olfactory region of cortex.

The claustrum has remained problematic for almost 200 years, although we have advanced a working hypothesis that while based on indirect evidence at least provides a unifying concept. According to this view (see Refs. [282,294] for citations) the claustrum proper, which lies between the six classical layers of the insular lobe and the ventral extension of the corpus callosum or external capsule (Figs. 16A and 17D), is derived embryologically from the cortical subplate, and thus amounts to a layer variously called 6b or 7. Ventral to the claustrum proper lies the endopiriform 'nucleus,' which more often than not has been regarded as a ventral division of the claustrum, deep to the three classical layers of the piriform area and just superficial to the rostroventral end of the extreme capsule (Fig. 17A). Dorsal to the claustrum proper, recent work has identified in rodents a very distinct though thin layer 6b or 7 that stretches all the way dorsomedially into the cingulate gyrus and may well be derived from the cortical subplate (see [63,282,310,312,315]).

The suggestion here is that a cortical subplate region, which becomes progressively thinner from ventral to dorsal (Fig. 17A), consists of the endopiriform nucleus, claustrum proper, and layer 6b/7, respectively. The final component is the most speculative, but follows Meynert's original suggestion in 1867 [170–172] that the basolateral complex of the amygdala is a thick, caudoventral extension of the claustrum. Recent Golgi analyses have emphasized the pyramidal cell-like morphology of projection neurons in this complex (e.g. [161]), which probably use glutamate rather than GABA as a neurotransmitter (see [54,161]), and it is possible to arrange the various parts of the basolateral complex in positions deep to various olfactory (amygdalar) and temporal cortical areas [294], just superficial to the caudoventral end of the external capsule (Fig. 17B, C).

To summarize, our working hypothesis suggests that the claustral complex (basolateral amygdalar nuclei, endopiriform nucleus, claustrum proper, and isocortical layer 6b/7) is derived embryologically from the cortical subplate region deep to the cortical plate, and that its projection neurons use glutamate as a neurotransmitter.

3.3.2. The cerebral nuclei (striatum and pallidum)

According to our simple model of the cerebral hemispheres, everything that is not cortical (as defined in the flatmap of Fig. 16) is either striatal or pallidal. In a seminal paper, Heimer and Wilson [104] stressed the utility of distinguishing between dorsal and ventral regions of the basal ganglia with very similar connectional patterns (Fig. 19). According to this now widely accepted view, the caudate nucleus and putamen form the dorsal striatum, which projects to the globus pallidus or dorsal pallidum; whereas in contrast the nucleus accumbens, striatal fundus, and olfactory tubercle form the ventral striatum, which projects to the substantia innominata or ventral pallidum broadly conceived. More recently, we have expanded this approach to suggest that there are also medial and caudorostral regions of the basal ganglia/cerebral nuclei.

As reviewed in detail elsewhere [224,225,282,295], the lateral and medial divisions of the septal region appear to form a medial component of the basal ganglia/cerebral nuclei. Cajal [32] long ago suggested that the lateral septal nucleus, with its medium spiny stellate neurons, constitutes

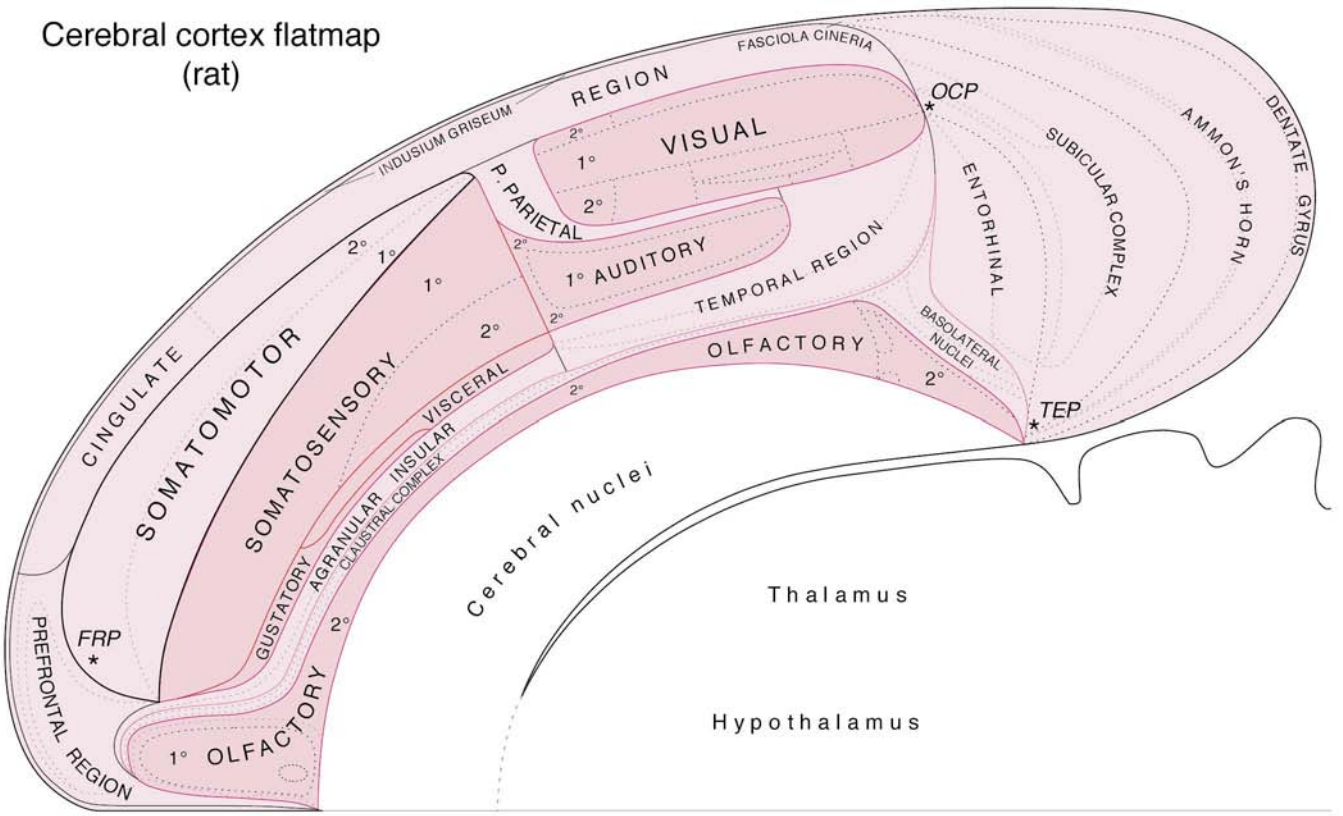


Fig. 16. A flatmap of the rat cerebral cortex. In this projection, surface areas and boundary conditions are accurate (at least qualitatively), so that shapes and distances are inevitably distorted. In principle, this is a topological transformation of the cerebral cortex as observed in the unevaginated telencephalic vesicle, early in embryonic development (see Fig. 3). *Abbreviations*: FRP, frontal pole; OCP, occipital pole; TEP, temporal pole. Adapted from Ref. [282].

the striatum for hippocampal cortex. It is now known that there is a topographically organized projection from Ammon's horn cortex and subiculum proper to the lateral septal nucleus (Section 4), that the medium spiny neurons there are GABAergic (as in the dorsal and ventral striatum), and that there is a projection from the lateral septal nucleus to the medial septal/nucleus of the diagonal band complex. It seems obvious that the latter, with its mixture of GABAergic and cholinergic neurons is a medial differentiation of the substantia innominata that is specialized with respect to connections with the hippocampal formation [124,169,232].

We have also revived older suggestions that the central and medial nuclei of the amygdala (along with the anterior amygdalar area and intercalated nuclei [175]) form a caudal region of the striatum, as reviewed elsewhere [294]. This view is based in part on embryological considerations (Section 1.2), in part on the fact that their projection neurons are GABAergic (see Fig. 13), and in part on their connections (Section 4.2). One of these connections is a prominent GABAergic input to the bed nuclei of the stria terminalis, which itself has GABAergic descending projections — leading us to suggest, along with embryological evidence, that the bed nuclei form a rostral differentiation of the pallidum (Fig. 19, Section 4.2, and Ref. [295]) related to amygdalar parts of the caudal striatum.

3.3.3. Overview of cerebral regional anatomy

The regional anatomy of the adult cerebral hemispheres is exceptionally difficult to appreciate. However, its general organization is much simpler to understand if one begins early in development with the unevaginated telencephalic vesicle and its presumptive cortical region and two ventricular ridges (Fig. 5) — and then assumes that the former generates the cerebral cortex proper (the cortical plate) and claustral complex (the subplate), whereas the latter generate the striatum and pallidum. The basic process involved in this morphogenesis is illustrated schematically in Figs. 5, 6 and 18. Perhaps the single most important feature to consider in mammals is the tremendous growth of the lateral (striatal) ventricular ridge, which leads to extensive obliteration of the originally relatively huge lateral ventricle (Fig. 5A), starting ventrally at the corticostriatal sulcus (a in Figs. 5 and 18) and extending progressively more dorsal over time (blue line in Fig. 18). The locations in the adult rat telencephalon of the obliterated lateral ventricle and its ventral tip, the former corticostriatal sulcus, are shown in Figs. 15 and 17. Note in these figures that the

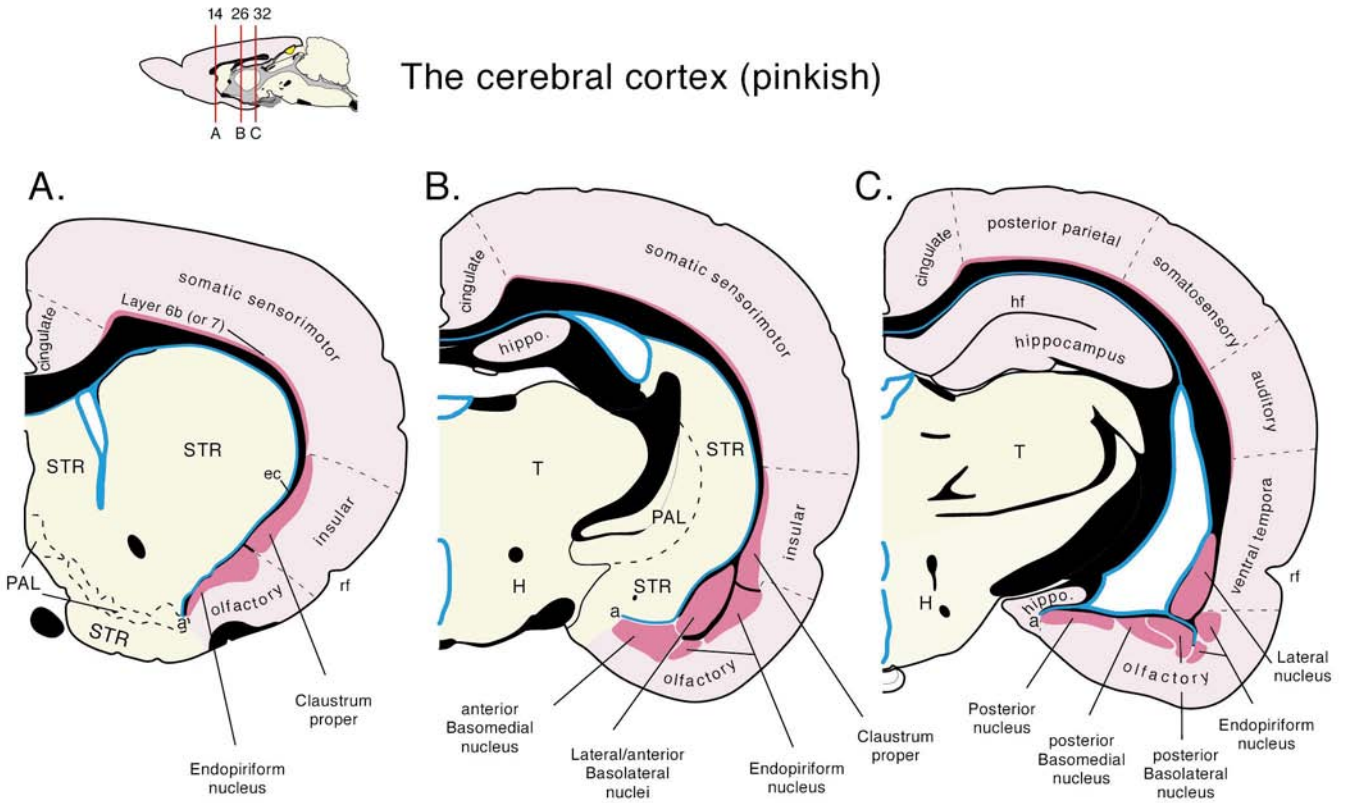


Fig. 17. Adult cortical plate versus subplate. The relationship between cerebral cortex proper (the cortical plate, light pink) and the claustral complex (the cortical subplate, darker pink), as seen in three transverse sections through the adult rat forebrain. The approximate location of the sections, which are arranged from rostral (A) to caudal (C), is indicated in the schematic sagittal outline at the upper left, which also shows corresponding atlas levels in Ref. [282]. As in Figs. 13, 15 and 18, the ventricular ependyma, and the obliterated lateral ventricle, are indicated in blue. A Nissl-stained section for level A is shown in Fig. 15; and the distribution of GAD-expressing neurons at about level B is shown in Fig. 13. *Abbreviations*: a, obliterated corticostriatal sulcus; ec, external capsule; H, hypothalamus; hf, hippocampal fissure; hippo., hippocampus; PAL, pallidum; rf, rhinal fissure; STR, striatum; T, thalamus. Drawings adapted from Ref. [282].

latter indicates the border between cerebral cortex and cerebral nuclei/basal ganglia as defined in this article.

4. Cerebral inputs to the behavior control column

Based on the general classification of cerebral parts just outlined we can see how the triple descending projection (Fig. 14) is organized topographically with respect to the various components of the behavior control column (Fig. 10). In this Section the defining [269], primary, or major projection from a cortical area to the striatum, or from a region of the striatum to the pallidum, will be described to emphasize organizing principles. A more detailed account of cerebral connections, which recognizes that a particular cortical area may project to multiple sites within the striatum (and pallidum), and that a particular striatal region may project to multiple sites within the pallidum, will be presented in Section 5.

4.1. To the exploration (caudal) segment

It is instructive to begin with the familiar isocortical to dorsal striatum to dorsal pallidum projection system as a prototype. A topographically organized projection from most of the isocortex to the entire caudoputamen was first demonstrated in 1961 by Webster [325], and since that time it has become clear [59,166] that major contributors include the visual, auditory, somatosensory, and gustatory areas, the somatomotor areas, the orbital cortex and cingulate region, and posterior parietal and temporal association areas (Fig. 20A). Pyramidal cells in this broad region of cortex that project to the brainstem and spinal cord motor system are concentrated in layer 5, use glutamate as a neurotransmitter, and generate a glutamatergic collateral to the dorsal striatum (see [84,123,146,147]). In terms of basal ganglia/cerebral nuclei inputs to the behavior control column, there is a topographically organized GABAergic projection from the caudoputamen to the substantia nigra (see [59]), and most of these axons generate a GABAergic collateral in the globus pallidus (see [197]) — and then there is a dense GABAergic projection from the globus pallidus (both segments) to the substantia nigra [102,262,265,298]. For the sake of completeness it should be pointed out that widespread regions of the prefrontal, premotor, and a-

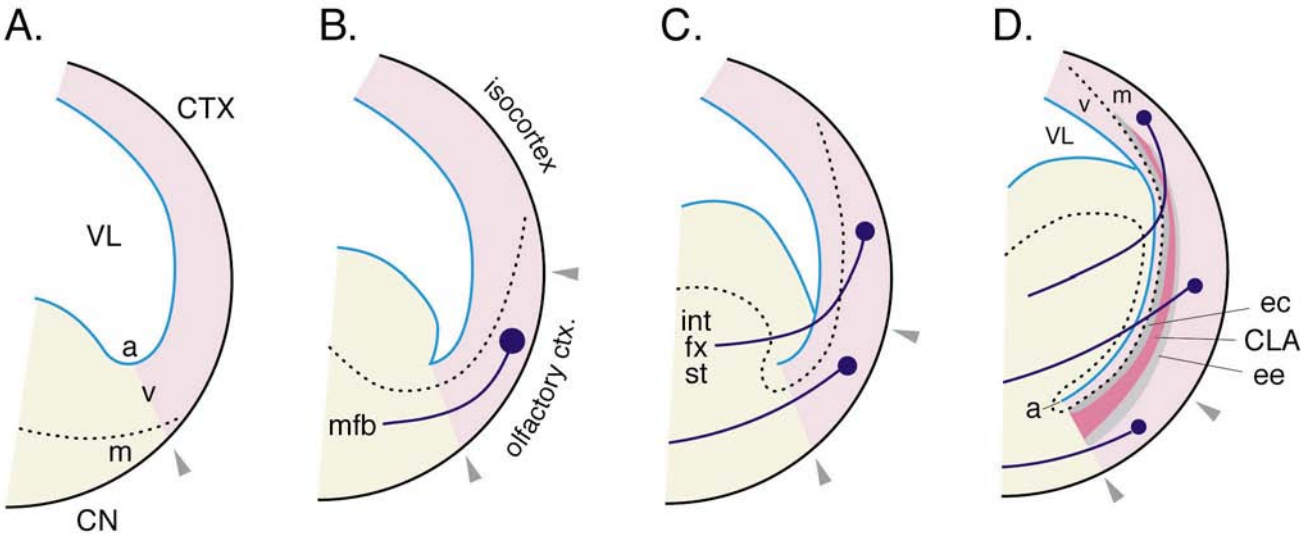


Fig. 18. Development of mature lateral ventricle shape. This sequence of cartoons illustrates how a great deal of the lateral ventricle's (VL) wall (in blue) becomes obliterated during embryogenesis, as the dorsal ventricular ridge of the cerebral nuclei/basal ganglia (CN, in yellow) grows dorsally with the massive thickening of its mantle layer (m). Ventricle obliteration begins ventrally at the corticostriatal sulcus (a; see Figs. 3, 5, 6, 13, 15 and 17) and gradually extends dorsally (B–D). Axonal projections from the olfactory cortex and immediately adjacent regions that differentiate near the cerebral nuclei/basal ganglia, descend in the medial forebrain bundle (mfb), ventral to the obliterated lateral ventricle (B–D). Descending projections from other, more dorsal regions of cortex pass through the earlier obliterated lateral ventricle in the internal capsule (int), fornix system (fx), and stria terminalis (st). As descending, association, and commissural projections form, they construct a deep fiber system consisting of the external (ec) and extreme (ee) capsules, just superficial to the ventricular layer of the neural tube (v). It would appear that the claustral complex (CLA), the remnant of the cortical subplate, differentiates within this deep fiber system, and that it becomes progressively thinner from ventral to dorsal (D). Adapted with permission from Ref. [294].

	Dorsal	***Ventral***	***Medial***	***Caudorostral***
STRIATUM	CP	ACB FS OT	LSC	MEA CEA AAA IA
PALLIDUM	GPe GPi	SI MA	MS/DBB	BST

Fig. 19. A simple scheme for topographic regionalization of the basal ganglia/cerebral nuclei. *Abbreviations*: AAA, anterior amygdalar area; ACB, nucleus accumbens; BST, bed nuclei stria terminalis; CEA, central amygdalar nucleus; CP, caudoputamen; FS, striatal fundus; GPe,i, globus pallidus, external, internal segments; IA, intercalated amygdalar nuclei; LSC, lateral septal complex; MA, magnocellular (preoptic) nucleus; MEA, medial amygdalar nucleus; MS/DBB, medial septal/nucleus of the diagonal band complex; OT, olfactory tubercle; SI, substantia innominata.

granular insular regions of cortex also send a glutamatergic projection directly to the substantia nigra (see [137,183]). This is the basic triple descending projection from the cerebrum to the motor system (including the behavior control column) discussed in Section 3.2, and it tends to course through the internal capsule/lateral forebrain bundle fiber system [282] (Fig. 20A). Other brainstem projections of the caudoputamen and globus pallidus are discussed in Section 5.1.

Let us now compare this arrangement with defining

Fig. 20. Differentiations of the triple projection to the motor system (Fig. 14) from various regions of the cerebral hemisphere. Inputs to components of the behavior control column (Fig. 10), at the top of the motor system hierarchy (Figs. 1 and 9), are stressed. Parts A–C deal with inputs to the caudal segment of the column, whereas parts D and E show inputs to the rostral segment of the behavior control column. *Abbreviations*: ACB, nucleus accumbens; AHN, anterior hypothalamic nucleus; AOB, accessory olfactory bulb; ap, ansa peduncularis; BST, bed nuclei stria terminalis; CA1,3, fields of Ammon's horn; CEA, central amygdalar nucleus; CP, caudoputamen; DG, dentate gyrus; fi, fimbria; FS, striatal fundus; fx, postcommissural fornix; GP, globus pallidus; lfb, lateral forebrain bundle (internal capsule, cerebral peduncle) system; LHAcl, lateral hypothalamic area, caudolateral region; LS, lateral septal complex; MAM, mammillary body; mct, medial corticohypothalamic tract; MEA, medial amygdalar nucleus; mfb, medial forebrain bundle system; MPNl, medial preoptic nucleus, lateral part; MS/DBB, medial septal/diagonal band nuclei; NLOT, nucleus lateral olfactory tract; OT, olfactory tubercle; PM, premammillary nuclei; PVHd, descending paraventricular nucleus; SI, substantia innominata; st, stria terminalis; SUBv, ventral subiculum; TT, tenia tecta; VMH, ventromedial hypothalamic nucleus.

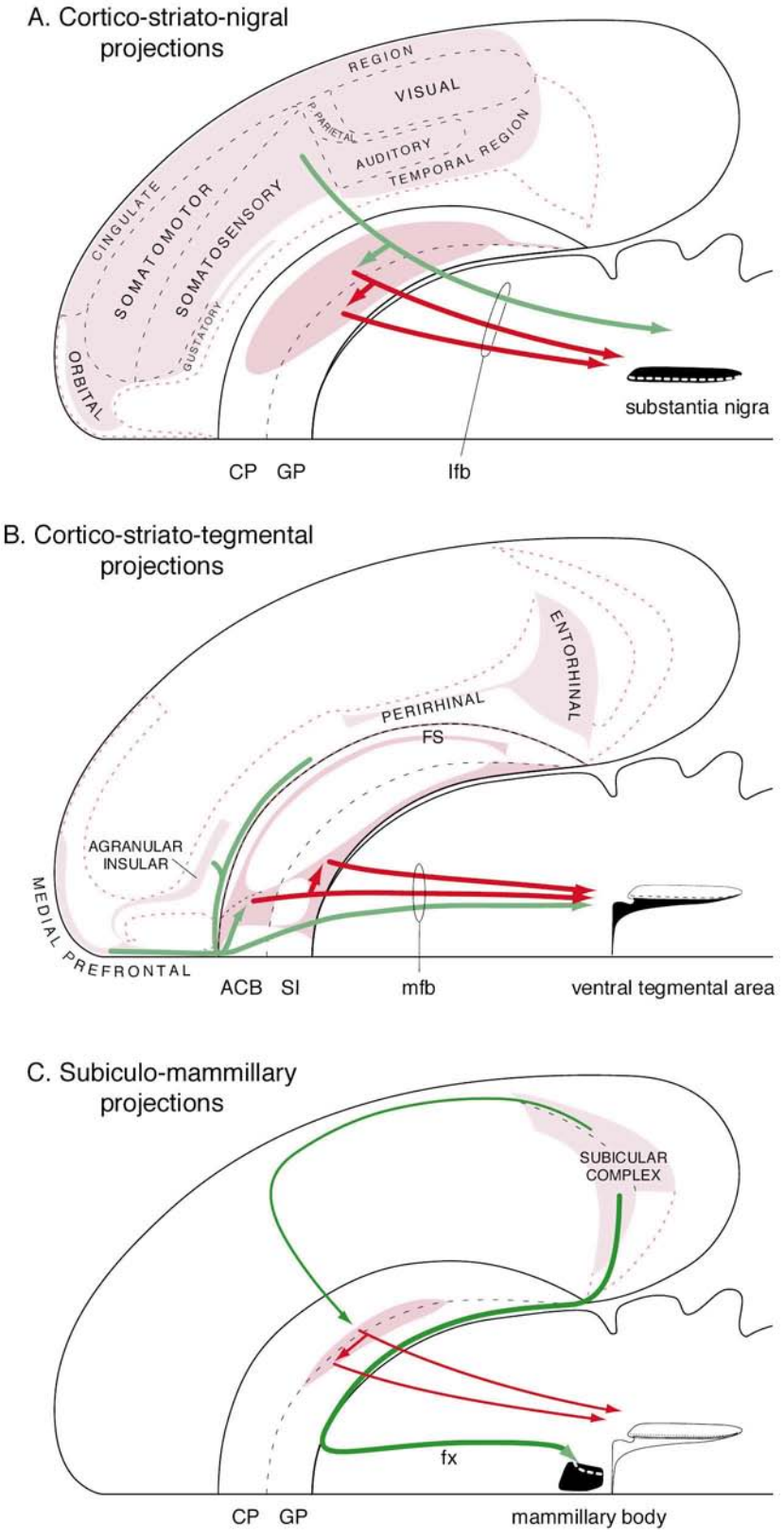

A. Cortico-striato-nigral projections
REGION
VISUAL
AUDITORY
TEMPORAL REGION
CINGULATE
SOMATOMOTOR
SOMATOSENSORY
GUSTATORY
ORBITAL
substantia nigra
CP
GP
lfb
B. Cortico-striato-tegmental projections
ENTORHINAL
PERIRHINAL
FS
AGRANULAR INSULAR
MEDIAL PREFRONTAL
ACB
SI
mfb
ventral tegmental area
C. Subiculo-mammillary projections
SUBICULAR COMPLEX
fx
CP
GP
mammillary body

Fig. 20.

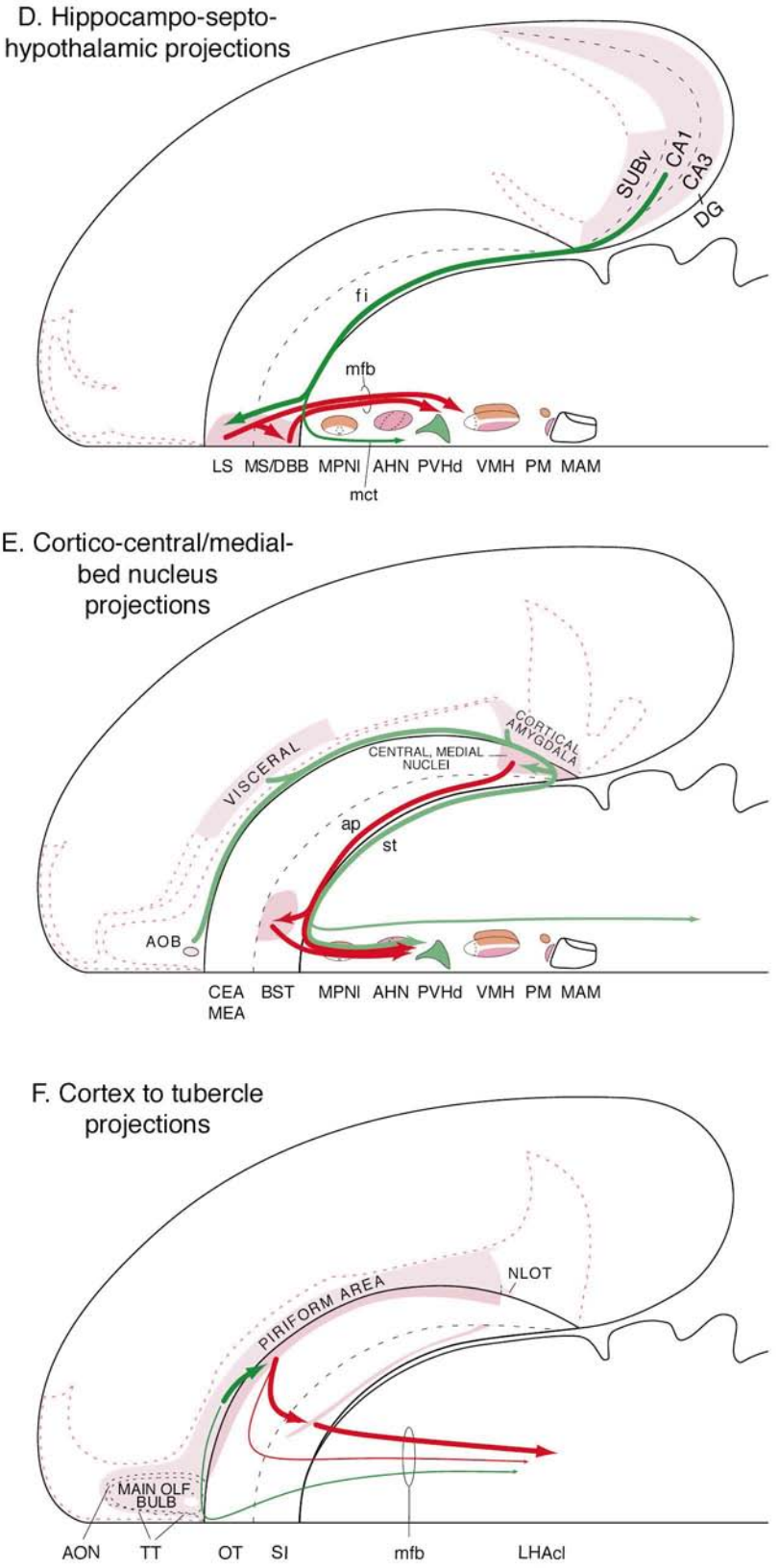


Fig. 20. (*continued*)

cortical inputs to the ventral striatum, and in particular with defining inputs to its major component, the nucleus accumbens (Fig. 20B). These inputs arise predominantly in the entorhinal area of the hippocampal formation [308] and adjacent perirhinal area of the inferior temporal association region [168], and in the medial prefrontal region and caudally adjacent agranular insular region [19]. Then, the nucleus accumbens sends dense projections to the substantia innominata and to the ventral tegmental area component of the behavior control column [104,105,188,287], projections that are GABAergic (see [126]). And finally, the substantia innominata (ventral pallidum in the sense of Fig. 19) sends a presumably GABAergic projection to the ventral tegmental area, and other brainstem regions (see [92]). Fibers associated with this component of the triple descending projection from the cerebrum tend to course through the medial forebrain bundle system [282] rather than the lateral forebrain bundle system (Fig. 20A, B).

Thus far we have examined the major triple descending cerebral input to the substantia nigra and ventral tegmental area. Defining inputs to the third component of the caudal segment of the behavior control column, the mammillary body, are associated with yet another region of cortex, the subicular complex of the hippocampal formation (Fig. 20C). Interestingly, it is this region and not Ammon's horn (the hippocampus proper) that projects through the postcommissural fornix in a topographically organized way to the mammillary body (see [132,286,288,316,317]). The subicular complex has a very light and limited projection to the striatum [316,317]. In particular, it appears to innervate a narrow vertical band of the caudoputamen adjacent to the lateral wall of the lateral ventricle (J.M. Wyss, personal communication). The exact projections of this dorsal striatal zone to the nuclei of the caudal behavior column zone, and to the pallidum, remain to be determined.

As discussed in Section 2.3, the ventral tegmental area plays a role in controlling locomotor behavior, the substantia nigra in orienting movements of the eyes, head, and neck, and the mammillary body in the orientation direction of the head — all important components of exploratory or foraging behavior.

4.2. To the goal (rostral) segment

The lateral septal complex or medial striatum receives a topographically organized input from fields CA1-3 of Ammon's horn or the hippocampus proper, as well as from the subiculum proper, via the precommissural fornix [225,286,288] (Fig. 20D). In addition, a small component of the postcommissural fornix, the medial corticohypothalamic tract, extends ventrally behind the anterior commissure to innervate most hypothalamic components of the behavior control column, including the medial preoptic, anterior hypothalamic, ventromedial, ventral premammillary, and medial mammillary nuclei; this projection arises mostly from the ventral half of the subiculum (see [40,132,286]). The lateral septal complex in turn sends a descending, presumably GABAergic, projection to the medial septal/diagonal band complex (medial pallidum) and to most components of the rostral behavior control column (see [225,289]). Because of the highly topographic nature of projections from the hippocampus to the lateral septal complex, and from the latter to the behavior control column, it would appear that different dorsoventral zones within the hippocampus (and in particular field CA1) influence different functional components of the behavior control column [223,225] (Fig. 21).

Next we come to cortical areas sending their most dense striatal inputs to the central and medial amygdalar nuclei — the caudal striatum (Fig. 20E; also see Fig. 24 below). By far the most dense striatal projection of the accessory olfactory bulb (primary pheromonal cortex) is to the medial amygdalar nucleus [242], which also receives massive inputs from areas of cortex associated with the amygdala (cortical 'nucleus' and postpiriform transition and piriform-amygdalar areas) (see [162,165]) — all of which in turn receive massive inputs from the main or accessory olfactory bulb [242]. Perhaps the most dense striatal projections from the visceral area and adjacent posterior agranular insular area are to the central nucleus, which also gets heavy inputs from the amygdala-related cortical regions just mentioned as projecting massively to the medial amygdalar nucleus (see [162,165]). The medial and central nuclei send a dense GABAergic projection to the bed nuclei of the stria terminalis or rostral pallidum (see [38,141,206,247]), and the medial nucleus also projects to all components of the rostral behavior control column except the descending paraventricular nucleus and dorsal premammillary nucleus (see [38]). Finally, the bed nuclei of the stria terminalis project to much of the behavior control column (see [289]), although the details remain to be analyzed.

And last, there is the most idiosyncratic part of the cerebrum, associated with the main olfactory bulb (Fig. 20F). The main olfactory bulb, and three principal cortical recipients of its output, the anterior olfactory nucleus, tenia tecta, and piriform area (see [208,241]), all project heavily to an unusual differentiation of the (ventral) striatum, the olfactory tubercle (see [98,152,208]). The main olfactory bulb does not project outside the cerebral hemispheres; and at best the only brainstem projections of the anterior olfactory nucleus, tenia tecta, and piriform area consist of light inputs to the caudal lateral hypothalamic area (see [210]), and to the central part of the thalamic mediodorsal nucleus (from the piriform area) [210]. The olfactory tubercle part of the ventral striatum has only one major projection — to the immediately underlying substantia innominata [152], although there is a lighter projection to the caudal lateral hypothalamic area from layer 3 [210].

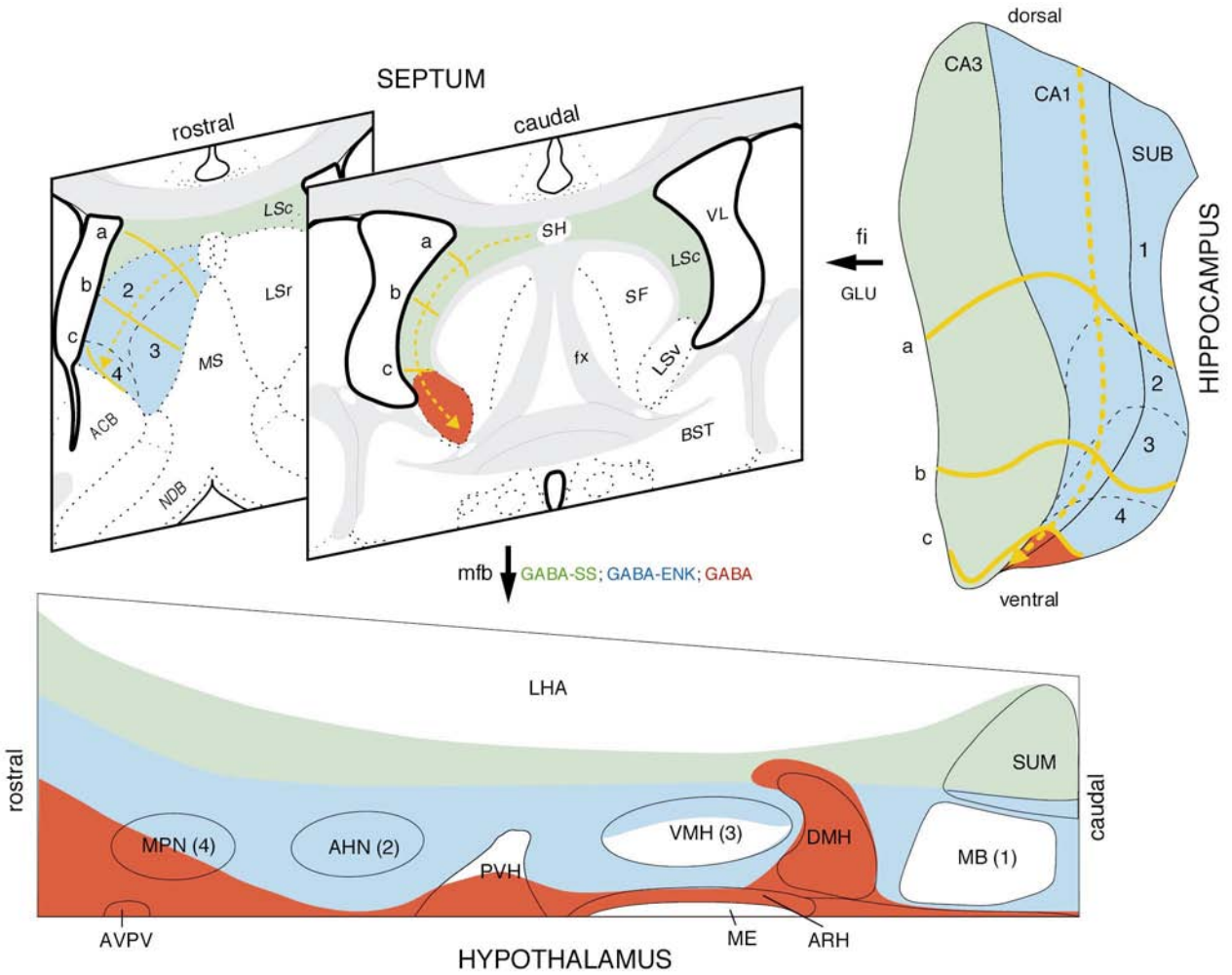


Fig. 21. Hippocampal inputs to the behavior control column. The hippocampal cortex (Ammon's horn and subiculum proper) projects topographically upon the lateral septal nucleus (medial striatum), which in turn projects topographically upon the hypothalamus, including the rostral behavior control column (also see Fig. 20D). The unfolded, flattened hippocampus is shown in the upper right, and field CA3 projects preferentially to the caudal lateral septal nucleus (LSc), which in turn projects massively to the supramammillary nucleus (SUM). In contrast, field CA1 and the subiculum (SUB) project preferentially to the rostral lateral septal nucleus (LSr), which in turn projects topographically to the behavior control column. For example, zone 2 in field CA1/SUB projects to a restricted region of the LSr (rostral section through the SEPTUM, upper left), which in turn projects preferentially to the anterior hypothalamic nucleus (AHN), part of the defensive behavior control subsystem (Fig. 12). *Other abbreviations*: ACB, nucleus accumbens; ARH, arcuate nucleus; AVPV, anteroventral periventricular nucleus; BST, bed nuclei stria terminalis; DMH, dorsomedial nucleus; ENK, enkephalin; fi, fimbria; fx, fornix; GLU, glutamate; LSv, ventral lateral septal nucleus; MB, mammillary body; ME, median eminence; mfb, medial forebrain bundle; MPN, medial preoptic nucleus; MS, medial septal nucleus; NDB, nucleus of the diagonal band; PVH, paraventricular nucleus; SF, septofimbrial nucleus; SS, somatostatin; VL, lateral ventricle; VMH, ventromedial nucleus. Reprinted with permission from Ref. [223]; copyright 1996 American Association for the Advancement of Science.

The precise region of pallidum (substantia innominata) receiving input from the olfactory tubercle has not been analyzed with modern anterograde tracing methods; presumably it sends descending GABAergic fibers through the medial forebrain bundle.

5. Differentiations of the descending projection system

It is clear from the preceding Section (Fig. 20) that whereas the triple descending projection model applies qualitatively to virtually all parts of the cerebral hemispheres, quantitative aspects of the model are differentiated in various regions. Furthermore, the triple descending model is based on a 'minimal circuit element' analysis — almost all parts of the cerebral hemispheres have additional connections that were not described. Because these other connections are often used to argue that particular cerebral components contribute to the formation of unique systems (Section 6) it is important to consider what is actually known about the circuitry of the classical part of the cerebral hemispheres — the isocortical-dorsal striatopallidal system.

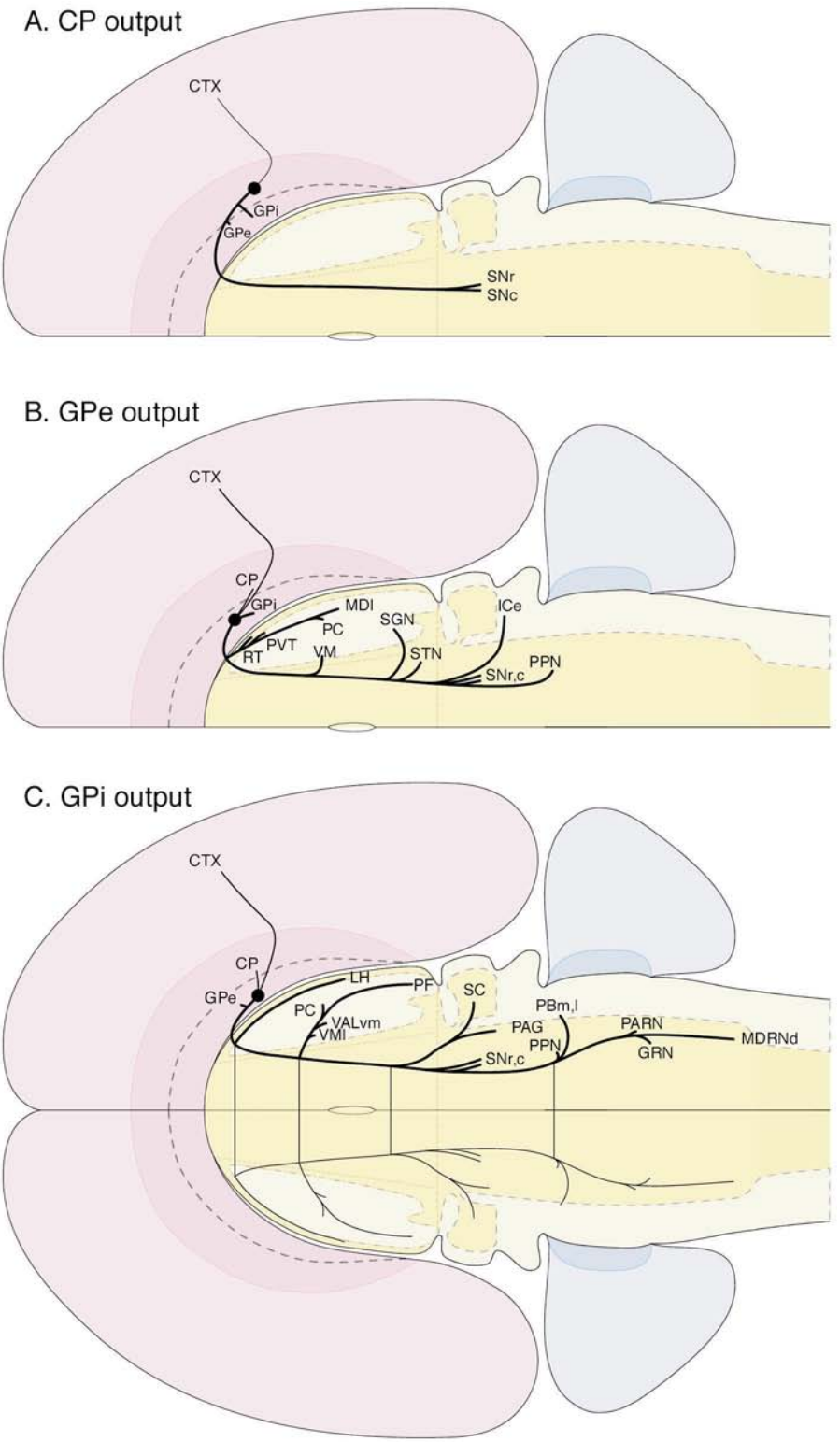


Fig. 22. The major known outputs of the classical dorsal striatopallidal system in rat, as documented in the text. *Abbreviations*: CM, central medial nucleus; CP, caudoputamen; CTX, cerebral cortex; DR, dorsal raphé; GPe,i, globus pallidus, external, internal segments; GRN, gigantocellular reticular nucleus; ICd,e, inferior colliculus, dorsal, external nuclei; LDm, lateral dorsal nucleus, medial region; LH, lateral habenula; MAN, medial accessory nucleus; MDl, mediodorsal nucleus, lateral part; MDRNd, medullary reticular nucleus, dorsal part; NTS, nucleus solitary tract; PAG, periaqueductal gray; PARN, parvicellular reticular nucleus; PBl,m, parabrachial nucleus, lateral, medial divisions; PC, paracentral nucleus; PF, parafascicular nucleus; PPN, pedunculopontine nucleus/midbrain extrapyramidal area; PRN, pontine reticular nucleus; PVT, paraventricular nucleus thalamus; RNd, red nucleus, dorsal region; RTrv, reticular nucleus thalamus, rostroventral region; SC, superior colliculus, deeper layers; SGN, suprageniculate nucleus; SI, substantia innominata; SNc,r, substantia nigra, compact, reticular parts; STN, subthalamic nucleus; VALrm,vm, ventral anterior–lateral complex, rostromedial, ventromedial regions; VMl, ventral medial nucleus thalamus, lateral region; VTA, ventral tegmental area; ZI, zona incerta.

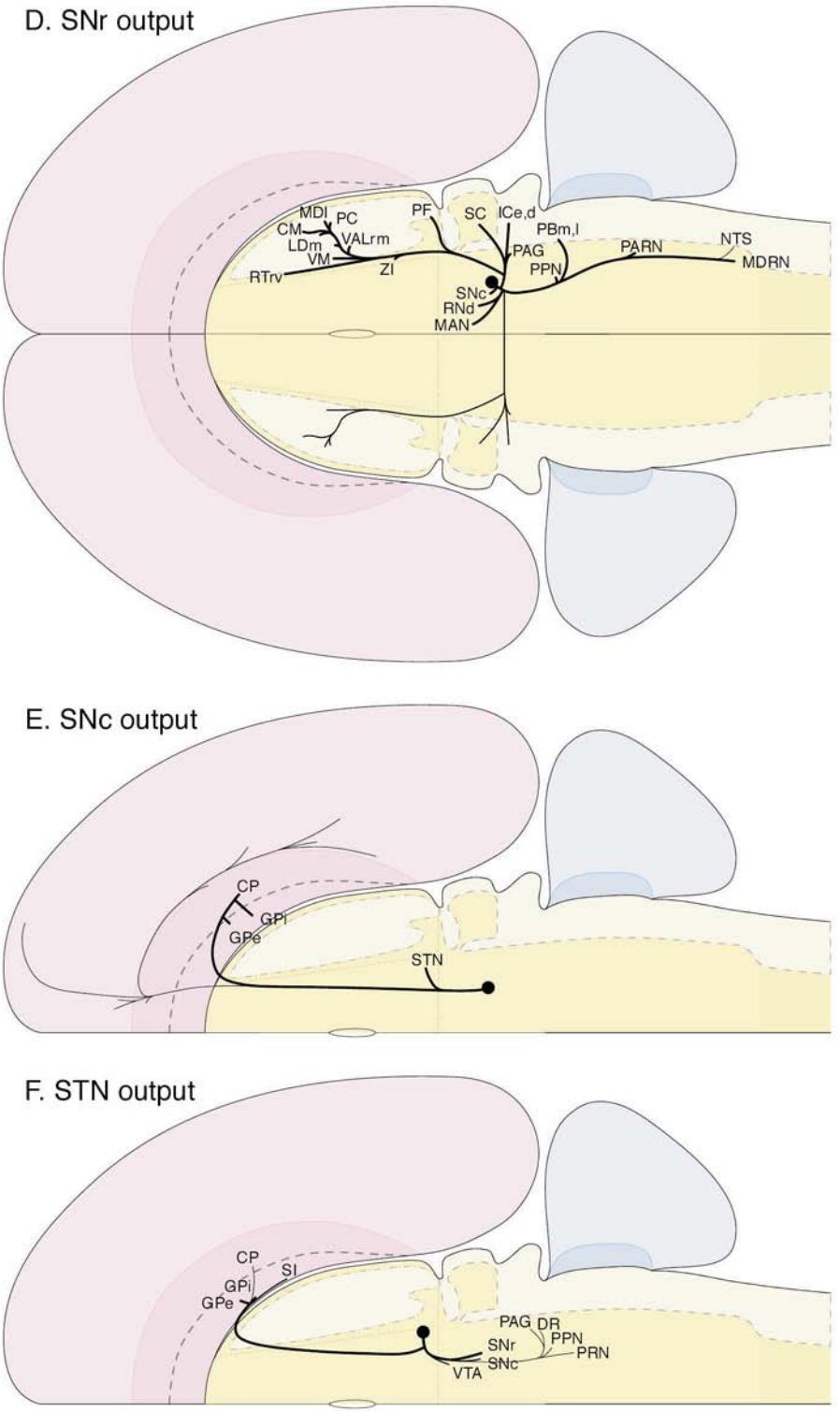


Fig. 22. (*continued*)

5.1. Total output of the dorsal striatopallidum

The total output of the caudoputamen is refreshingly simple: it innervates both the internal (medial) and external (lateral) segments of the globus pallidus, and both the compact and reticular parts of the substantia nigra (Fig. 22A). Many neurons send axon collaterals to both segments of the globus pallidus and the substantia nigra (see [197]), although there is evidence to suggest that by and large separate neurons project to the compact and reticular

parts of the substantia nigra [82]. In addition, the caudoputamen sends a light projection to the isocortex [62].

Besides innervating densely both parts of the substantia nigra [102,262,265], the external globus pallidus sends inputs to the subthalamic nucleus (see [187]), pedunculopontine nucleus/'midbrain extrapyramidal area' [21,182,229], and external nucleus of the inferior colliculus [181] in the brainstem, and to at least five nuclei in the rat thalamus [43,46,131,246,297] aside from the ventral medial nucleus [108,245] (Fig. 22B). Furthermore, the external globus pallidus projects locally to the internal globus pallidus [131] and caudoputamen [212,265], as well as to the cerebral cortex [232,236].

The output of the internal segment of the globus pallidus, which is often called the entopeduncular nucleus in nonprimates, is even more extensive than that from the external segment (Fig. 22C). In addition to both parts of the substantia nigra, it projects in the brainstem to the deeper layers of the superior colliculus, periaqueductal gray, pedunculopontine nucleus/midbrain extrapyramidal area, parabrachial nucleus, parvicellular reticular nucleus, and dorsal part of the medullary reticular nucleus (see [298]). In the rat thalamus, the internal globus pallidus innervates adjacent regions of the ventral anterior–lateral complex and ventral medial nucleus [43,313], the paracentral and parafascicular nuclei of the intralaminar group [298], and the lateral habenula [200,298]. Whereas the projections of the caudoputamen and external globus pallidus are unilateral, the descending projections of the internal globus pallidus are bilateral, although the contralateral pattern is considerably lighter than the ipsilateral pattern [298]. Finally, the internal globus pallidus sends projections to the external globus pallidus and caudoputamen [298], and rather widespread regions of the cerebral cortex [232,236].

Because the substantia nigra is so closely associated with the dorsal striatopallidal region and forms a part of the behavior control column, it is worth considering its total projection pattern as well. The neural output of the reticular part of the substantia nigra (GABAergic neurons) is considerably more extensive than commonly acknowledged (Fig. 22D). In addition to its well-known projection to intermediate layers of the superior colliculus [83,118,221], it also projects to the inferior colliculus [322,337] and periaqueductal gray [83,118,221,337]; to the parabrachial nucleus [58,83] and nucleus of the solitary tract [321]; to the compact part of the substantia nigra [100], and to the red nucleus [338] and medial accessory nucleus [17,58] bordering the rostral tip of the oculomotor nucleus. The reticular substantia nigra has rather widespread inputs to the reticular formation, including the pedunculopontine nucleus/midbrain extrapyramidal area [17,83,86], parvicellular reticular nucleus [45,321,339], and medullary reticular nucleus [45,321,339]. In the rat thalamus, the reticular substantia nigra has a well-known, massive input to the ventral medial nucleus [50,83,108], but it also has substantial inputs to at least half a dozen other cell groups including medial regions of the ventral anterior–lateral complex [58,233]; medial regions of the lateral dorsal nucleus [58,83]; lateral part of the mediodorsal nucleus [17,83]; central medial [58,83], paracentral [58,83], and parafascicular [49,58] nuclei of the intralaminar group; and finally the reticular nucleus [58,193] and zona incerta [58,321]. It should also be noted that projections from the reticular substantia nigra to the tectum, periaqueductal gray, and dorsal thalamus are bilateral, although the contralateral component is relatively light (see [83,337]).

The projections of the compact part of the substantia nigra (dopaminergic neurons) are much simpler than those of the reticular part (Fig. 22E). They appear to be entirely ascending and ipsilateral, with the vast majority ending in the nearby subthalamic nucleus [70,79,83,213], both segments of the globus pallidus [79,150], and finally the caudoputamen (see [10,79,159]). In addition, there is a much lighter input to the nucleus accumbens and olfactory tubercle (ventral striatum), the perirhinal and ectorhinal areas of the ventral temporal cortex, the anterior cingulate area, and the olfactory bulb, anterior olfactory nucleus, piriform area, and cortical amygdalar nucleus (see [22]).

For the sake of completeness, we shall end this Section with a brief overview of projections from the subthalamic nucleus (Fig. 22F), which is intimately related to the circuitry of the dorsal striatopallidum and substantia nigra. Developmentally, the subthalamic nucleus is a caudal differentiation of the lateral hypothalamic area (see [7]), and it generates descending and ascending projections, but curiously has no known input to the thalamus. Its ascending projections go heavily to both segments of the globus pallidus [133,185,199,218], moderately to the substantia innominata [91,185,218], and lightly to the caudoputamen [133,185]. Its descending projections go heavily to both parts of the substantia nigra [133,218,263] and the ventral tegmental area [91,263]; and lightly to the pedunculopontine nucleus/midbrain extrapyramidal area [101,133,185] and to the periaqueductal gray, dorsal nucleus of the raphé, and pontine reticular nucleus [133]. The subthalamic nucleus appears to contain a rather complex population of glutamatergic neurons with highly collateralized axons [199,238,261].

One obvious conclusion that emerges from this review is that the external and internal segments of the globus pallidus and the reticular part of the substantia nigra each have multiple projection targets in both the dorsal thalamus and parts of the brainstem with at least some relationship to the motor system broadly conceived.

5.2. Multiple striatopallidal targets of single cortical areas

It is obvious from the literature that many cortical areas

send a divergent projection to the striatum, and that a more limited expanse of cortex projects to the pallidum as well as the striatum.

Individual cortical areas may send a divergent input to one or more regions of the striatum. At a high level of resolution, studies of individual barrels in the vibrissal region of the rat primary somatosensory area demonstrate that a single cortical column sends divergent projections to multiple regions of the caudoputamen [6], and it has even been shown that a single barrel generates two types of only partly overlapping terminal fields within the caudoputamen — one diffuse and the other discrete [335]. Furthermore, other parts of the primary somatosensory cortex in rat, such as the forelimb (Fig. 23A) and hindlimb representations, also project to multiple zones or lamellae within the caudoputamen [29]. A similar arrangement is found in projections from the monkey somatosensorimotor cortex to the dorsal striatum (see [74,299]).

At a lower level of resolution, it is also clear that a number of cortical fields project to more than one region of the striatum (Fig. 24). For instance, the prelimbic area (PL) of the medial prefrontal cortex projects to the dorsal, ventral, medial, and caudal striatum (Fig. 23B) as defined on regional grounds in Fig. 19. In fact, virtually all parts of the striatum are involved in this type of divergent projection from one cortical area or another (Fig. 24). The most extreme example known to date is the infralimbic area (ILA), the most ventral component of the medial prefrontal cortex, which projects to all nine of the major striatal regions identified here.

In addition to innervating multiple sites in the striatum, some cortical areas project to the pallidum as well (Fig. 25). Such cortical inputs involve all regions of the pallidum as defined topographically in Fig. 19 — dorsal, ventral, medial, and rostral. It is clear, however, that a much more restricted expanse of the cortical mantle projects to the pallidum than to the striatum.

5.3. Striatopallidal inputs to cerebral cortex

We have seen that most of the cerebral cortex projects massively to the entire striatum, and that a restricted part of the cortex projects relatively lightly to most if not all of the pallidum. Kodama first reported in 1928–29 [138] a projection travelling in the opposite direction, and since the later introduction of combined retrograde transport/histochemical methods it has become clear that a substantial pallidal projection consisting of at least three cell types (cholinergic, GABAergic, and unidentified) innervates essentially the entire cortical mantle in a broadly topographic way, and that the striatum also projects to cortex, although much less prominently (Fig. 26). Qualitatively, the substantia innominata, and both segments of the globus pallidus innervate the isocortex; the magnocellular (preoptic) nucleus innervates olfactory cortex; the medial septal complex innervates the hippocampal formation, orbitofrontal cortex, and cingulate gyrus; and the bed nuclei innervate the medial prefrontal cortex, the ventral hippocampus, and olfactory regions of the claustral complex. In contrast, the dorsal (caudoputamen) and medial (lateral septal complex) striatum project very lightly to the isocortex and hippocampus, respectively, whereas certain parts of the caudal striatum project rather substantially mostly to olfactory-related areas of cortex.

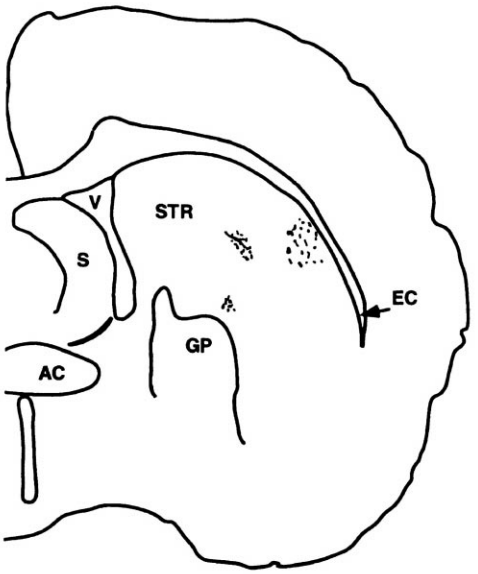
5.4. Differential projections from single striatal regions

There are clear differentiations or specializations of the triple descending projection to the motor system associated with different regions of the striatopallidum (Section 4; Fig. 20). A simple example makes the point that differentiation or specialization can occur within a particular region of the striatopallidum as well. The example involves the familiar isocortical-dorsal striatopallidal projection and a comparison between the output of motor cortex regions influencing eye and neck musculature on one hand, and orofacial musculature on the other (Fig. 27). Not surprisingly, the topographic organization of motor cortex is preserved in its projections to the caudoputamen, which in turn projects topographically to the internal globus pallidus, which in turn projects topographically to the reticular substantia nigra. But here the organization takes an interesting turn. The eye/neck motor area projects to the superior colliculus as do related regions of the internal globus pallidus and reticular substantia nigra; whereas in contrast the orofacial motor cortex projects to the parvicellular reticular nucleus, along with the topographically related parts of the internal globus pallidus and reticular substantia nigra. In the parlance of Section 1.1, the superior colliculus contains a motor pattern generator (or perhaps a motor pattern initiator) for eye and head orienting movements controlled in part by the substantia nigra, whereas the parvicellular reticular nucleus contains a motor pattern generator for orofacial behavior, controlled in part by a different region of the substantia nigra.

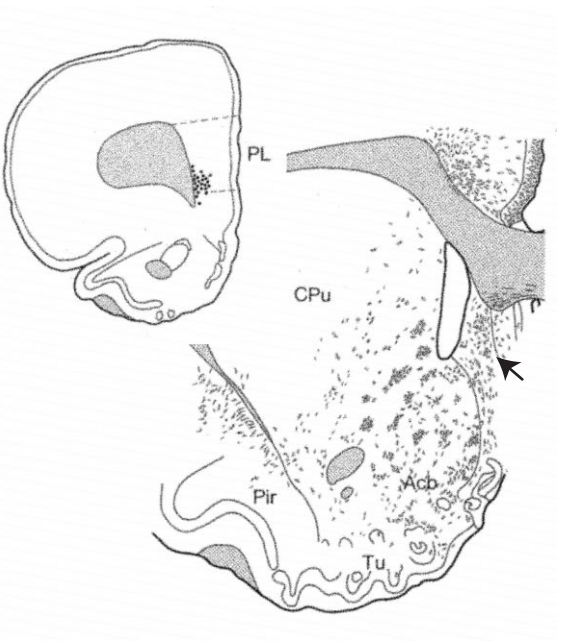
5.5. Complex intra-striatopallidal connections

It is becoming increasingly clear that the intrinsic circuitry of the cerebral nuclei/basal ganglia is much more complex than previously recognized, and that this is just as much a feature of the dorsal striatopallidum as it is of the ventral, medial, and caudorostral regions. For ease of description known intrinsic connections will be divided into projections (a) between striatal regions, (b) from striatal regions to multiple pallidal regions, (c) between pallidal regions, and (d) from pallidal regions to striatal regions.

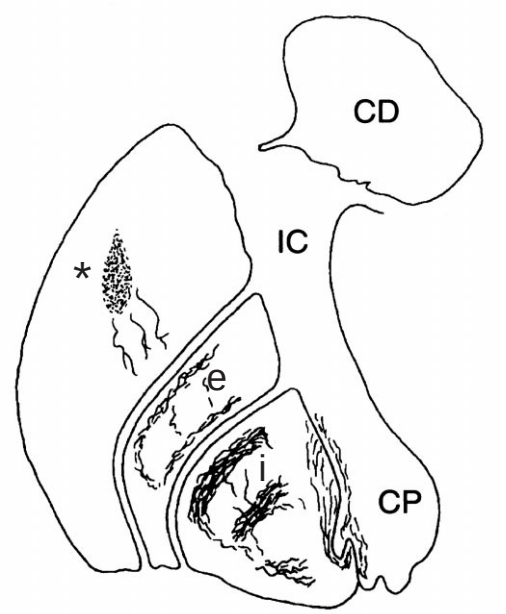
As noted above (Section 5.2; Fig. 24) some cortical areas project to several distinct regions of the striatum, and



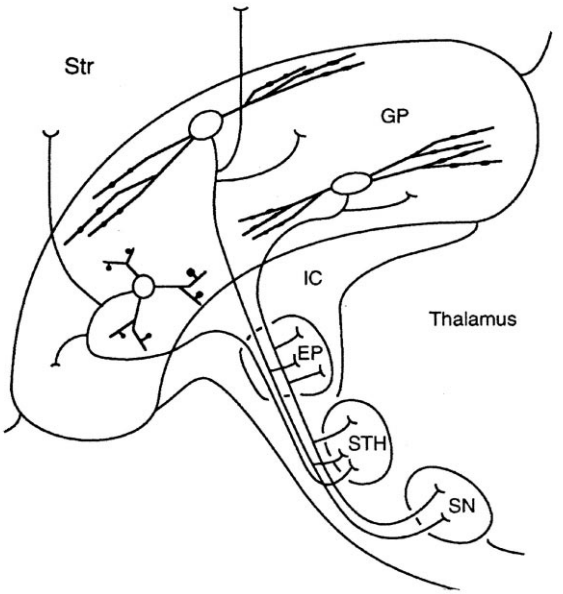
A. Forelimb somatosensory area to striatum



B. Prelimbic area to striatum



C. Sensorimotor striatum to pallidum



D. External pallidum to striatum and pallidum

Fig. 23. Illustrations of differentiations within isocortical-dorsal striatopallidal connections. (A) The forelimb region of the primary somatosensory cortical area in the rat projects to at least three widely separated patches or columns in the caudoputamen or dorsal striatum (STR), as seen in this transverse section through the level of the anterior commissure (AC), demonstrated with the anterograde tracer Fluoro-Ruby. (B) The prelimbic area (PL) of the rat medial prefrontal region projects to multiple regions of the striatum, including the caudoputamen (CPu), nucleus accumbens (Acb), olfactory tubercle (Tu), and lateral septal nucleus (arrow, added here for clarity). Demonstrated in frontal sections (injection site is in smaller diagram at upper left) with the PHAL method. (C) The complex banded projection from somatosensorimotor regions of the putamen (upper left) to the external (e) and internal (i) segments of the globus pallidus in the monkey as demonstrated with the PHAL method (an asterisk, *, to mark the injection site, and the letters e and i have been added here for clarity). (D) A cartoon indicating the complex nature of intrinsic and extrinsic projections of the external segment of the globus pallidus (GP) in the rat. *Other abbreviations*: CD, caudate nucleus, putamen; CP, cerebral peduncle; EC, external capsule; EP, entopeduncular nucleus, internal globus pallidus; IC, internal capsule; Pir, piriform area; S, septum; SN, substantia nigra; STH, subthalamic nucleus; Str, striatum; V, lateral ventricle. Part A is reproduced with permission from Ref. [29], Part B is reproduced with permission from Ref. [19], Part C is reproduced with permission from Ref. [199], and Part D is reproduced with permission from Ref. [135].

		CP	ACB	FS	OT	LSC	MEA	CEA	AAA	IA	References
Cortex proper	ACA	3+	1+								[15]
	ORB	3+		1+	1+						[19]
	ECT	3+	1+	1+							**
	PL	3+	3+		3+	1+		1+	1+		[15,19,164]
	ILA	1+	3+	2+	2+	2+	2+	1+	2+	1+	[15,19,119,164]
	AIv	2+	3+	2+	2+		1+	2+	1+		[19,164,165]
	AId	3+	3+					1+	1+		[19,164,165]
	PERI	2+	3+	3+	1+						[168]
	ENT	1+	3+	2+	2+		1+			1+	[139,163,264,290]
	PIR			1+	3+				1+		[152]
	AON		1+		2+						[152]
	SUB		2+			3+	2+	2+		2+	[40,93,288]
	CA1		1+			3+					[288]
	AIp	1+	1+	3+	1+		2+	3+	2+		[162,165,336]
	GU/VISC	3+	1+	3+				3+	1+	1+	[162,165,336]
	TR		3+	2+	3+	2+	3+	3+	2+	2+	[165], *
	PAA		2+	2+	3+		3+	3+	3+	2+	*
	COAa			1+	1+		3+		2+	1+	[205]
	COApl		2+	1+	1+	2+	2+	2+	1+	1+	[35]
	COApm		2+	2+	2+	1+	3+	1+	2+	2+	[35]
Claustral complex	EPd		1+	1+	2+		1+		1+	1+	[18,141], *
	PA		2+	1+	1+	3+	3+	1+			[35]
	BMAp		3+	1+	1+	1+	2+	3+			[205]
	BMAa		2+	3+	1+	1+	3+	3+	2+		[205]
	BLAp	1+	3+	1+	1+			1+			[134,141]
	LA	1+	2+					2+			[141,160,204,207]
	BLAa	3+	3+	1+	3+						[134,141,204]

Fig. 24. Anatomical evidence for cortical areas projecting to multiple striatal regions in rat. *, H.-W. Dong, G.D. Petrovich, L.W. Swanson, unpublished observations; **, R. Burwell, personal communication. *Abbreviations*: AAA, anterior amygdalar area; ACA, anterior cingulate area; ACB, nucleus accumbens; AId,p,v, agranular insular area, dorsal, posterior, ventral parts; AON, anterior olfactory nucleus; BLAa,p, basolateral nucleus amygdala, anterior, posterior parts; BMAa,p, basomedial nucleus amygdala, anterior, posterior parts; CA1, hippocampal field CA1; CEA, central nucleus amygdala; COAa,pl,pm, cortical nucleus amygdala, anterior, posterolateral, posteromedial parts; CP, caudoputamen; ECT, ectorhinal area; ENT, entorhinal area; EPd, dorsal endopiriform nucleus; FS, striatal fundus; GU/VISC, gustatory/visceral areas; IA, intercalated nuclei amygdala; LA lateral nucleus amygdala; LSC, lateral septal complex; MEA, medial nucleus amygdala; ORB, orbital area; OT, olfactory tubercle; PA posterior nucleus amygdala; PAA, piriform-amygdalar area; PERI, perirhinal area; PIR, piriform area; PL, prelimbic area; SUB, subiculum; TR, postpiriform transition area.

To	From	References
GPe	Frontal cortex	[184]
GPi	Frontal cortex	[184]
SI	ILA, PL, ORB, AI, PIR, PAA, TR, ENT	[19,95,236]
MA	ENT	[120]
MSC	AH (very light)	[81,307]
BST	AOB, ILA, PL, GU/VISC, SUBv, COA, TR, PAA, BMA, BLAp, PA	[119,163,242,288] [35,141,165,205], *

Fig. 25. Anatomical evidence for projections from cerebral cortex to pallidum in rat. *, H.-W. Dong, G.D. Petrovich, L.W. Swanson, unpublished observations. *Abbreviations*: AH, Ammon's horn; AI, agranular insular area; AOB, accessory olfactory bulb; BLAp, basolateral nucleus amygdala, posterior part; BMA, basomedial nucleus amygdala; BST, bed nuclei stria terminalis; COA, cortical nucleus amygdala; ENT, entorhinal area; GPe,i, globus pallidus, external, internal segments; GU/VISC, gustatory/visceral areas; MA, magnocellular (preoptic) nucleus; MSC, medial septal complex; ORB, orbital area; PA, posterior nucleus amygdala; PAA, piriform-amygdalar area; PIR, piriform area; PL, prelimbic area; SI, substantia innominata; SUBv, ventral subiculum; TR, postpiriform transition area.

the anatomical evidence indicates that at least some distinct regions of the striatum project to others. Thus, the nucleus accumbens projects to the caudoputamen [309], the striatal fundus projects to the central amygdalar nucleus [96], and the medial amygdalar nucleus projects to the central amygdalar nucleus, anterior amygdalar area, olfactory tubercle, striatal fundus, and lateral septal complex [38]. In addition, the obscure anterior amygdalar area and intercalated amygdalar nuclei appear to project to the nucleus accumbens, striatal fundus, and olfactory tubercle; to the central and medial amygdalar nuclei; and perhaps to the caudoputamen ([194]; H.-W. Dong, G.D. Petrovich, L.W. Swanson, unpublished observations].

Thus far we have emphasized a 'prototypical' triple descending projection from different regions of the cerebral hemispheres — with a particular region of striatum innervating a particular region of pallidum. However, there is a wide range of variation on this theme because a majority of striatal regions project to multiple pallidal

	From	To	References
Striatum	CP	Isocortex (very light)	[62]
	LSC	AH (very light)	[225]
	MEA	Olfactory (heavy), HF/PFC/AI (light)	[38]
	AAA	AON, PIR, TTd, ILA, ORB, AIp, ENT, CA1v, COAa, COApl, PAA, TR, BMA, LA, PA	*
	IA	AON, PIR, ENT, CA1v, COA, TR, PAA, BMA, LA	*
Pallidum	GPe	Widespread cortex	[89,232,236]
	GPi	Widespread cortex	[89,232,236]
	SI	Widespread cortex	[89,232,236]
	MA	Olfactory cortex	[272]
	MSC	HF, OFC, CG	[80,289]
	BST	ILA, PL, CA1v/SUBv, TR, ENT, BLA, BMA, PA	[64,65,66,287],

Fig. 26. Anatomical evidence for projections from basal ganglia/cerebral nuclei to cerebral cortex in rat. *, H.-W. Dong, G.D. Petrovich, L.W. Swanson, unpublished observations. *Abbreviations*: AAA, anterior amygdalar area; AH, Ammon's horn; AIp, agranular insular area, posterior part; AON, anterior olfactory nucleus; BLA, basolateral nucleus amygdala; BST, bed nuclei stria terminalis; CA1v, hippocampal field CA1, ventral region; CG, cingulate gyrus; COAa,pl, cortical nucleus amygdala, anterior, posterolateral parts; CP, caudoputamen; ENT, entorhinal area; GPe,i, globus pallidus, external, internal segments; HF, hippocampal formation; IA, intercalated nuclei amygdala; ILA, infralimbic area; LA, lateral nucleus amygdala; LSC, lateral septal complex; MA, magnocellular (preoptic) nucleus; MEA, medial amygdalar nucleus; MSC, medial septal complex; OFC, orbitofrontal cortex; PA, posterior nucleus amygdala; PAA, piriform-amygdalar area; PFC, prefrontal cortex; PIR, piriform area; PL, prelimbic area; SI, substantia innominata; SUBv, ventral subiculum; TR, postpiriform transition area; TTd, dorsal tenia tecta.

	GPe	GPi	SI	MSC	MA	BST	References
CP	X	X					[196]
ACB	X		X				[287,309]
FS			X			X	[5]
OT							
LSC							
MEA			X			X	[38,141]
CEA			X			X	[141]
AAA	X		X	X	X	X	*
IA			X	X			*

Fig. 28. Anatomical evidence for striatal regions projecting significantly to multiple regions of the pallidum. *, H.-W. Dong, G.D. Petrovich, L.W. Swanson, unpublished observations. *Abbreviations*: AAA, anterior amygdalar area; ACB, nucleus accumbens; BST, bed nuclei stria terminalis; CEA, central nucleus amygdala; CP, caudoputamen; FS, striatal fundus; GPe,i, globus pallidus, external, internal segments; IA, intercalated nuclei amygdala; LSC, lateral septal complex; MA, magnocellular (preoptic) nucleus; MEA, medial nucleus amygdala; MSC, medial septal complex; OT, olfactory tubercle; SI, substantia innominata.

regions (Fig. 28). In fact, the olfactory tubercle (ventral striatum) and lateral septal complex (medial striatum) seem to be the only exceptions to this organizational feature. The projection from the somatic sensorimotor region of the putamen to multiple (at least six) regions of the globus pallidus in the monkey provides an unusually nice illustration of how differentiated they can be (Fig. 23C).

There is also considerable evidence for significant projections between different regions of the pallidum. The external globus pallidus projects to the internal globus

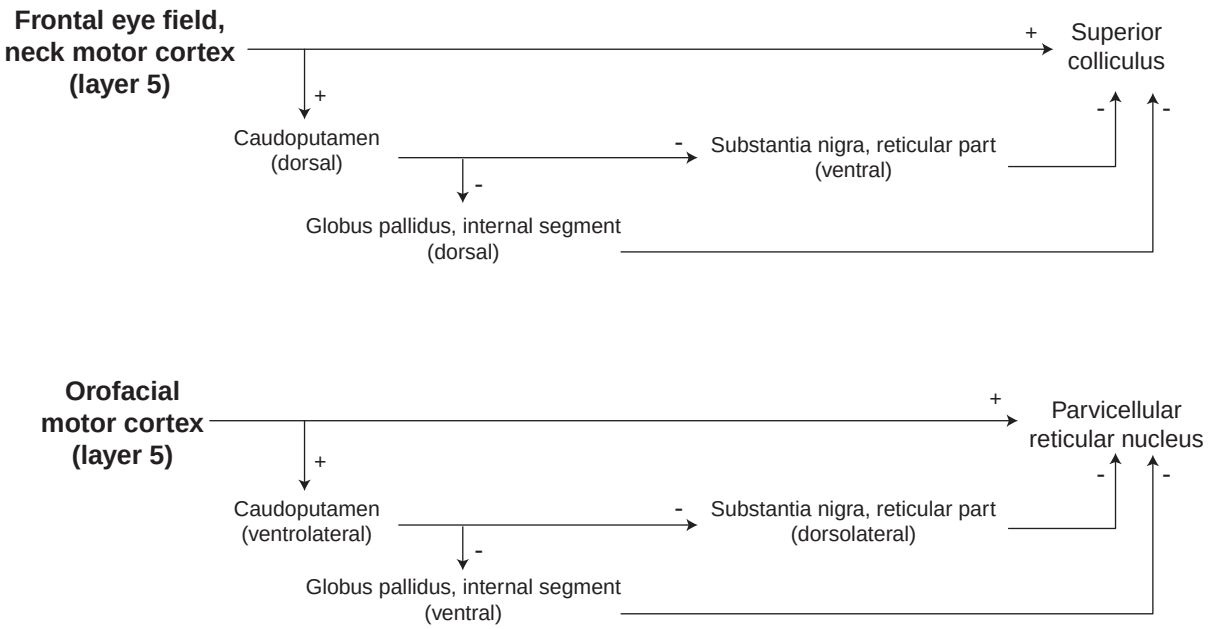


Fig. 27. Differential, topographically organized projections from two regions of rat somatomotor cortex to dorsal striatum, globus pallidus, and brainstem motor system, based on the work of Takada and colleagues [298].

From	To	References
GPe	CP	[212,265]
GPi	CP	[298]
SI	CP, ACB, OT, FS, LSC, CEA, MEA, AAA	[92,96]
MA	OT, AAA, MEA	[272]
MSC	LSC	[151]
BST	CP, ACB, OT, FS, LSC, CEA, MEA	[65,289]

Fig. 29. Anatomical evidence for projections from pallidum to striatum in rat. *, H.-W. Dong, G.D. Petrovich, L.W. Swanson, unpublished observations. *Abbreviations*: AAA, anterior amygdalar area; ACB, nucleus accumbens; CEA, central nucleus amygdala; CP, caudoputamen; FS, striatal fundus; GPe,i, globus pallidus, external, internal segments; LSC, lateral septal complex; MEA, medial nucleus amygdala; OT, olfactory tubercle; SI, substantia innominata.

pallidus [131] (Fig. 23D) and vice-versa [298], the substantia innominata projects to the bed nuclei of the stria terminalis [96], the magnocellular (preoptic) nucleus projects to the medial septal complex [272], the latter projects to the bed nuclei [80,289], and the latter project to the substantia innominata and globus pallidus [64,95].

Finally, each of the six major regions of the pallidum identified here projects more or less densely to one or more regions of the striatum (Fig. 29). In fact, it seems likely that most if not all of the striatum receives at least some input from the pallidum.

5.6. Striatopallidal inputs to the thalamus

We will close this Section with a brief review of pallidal and striatal projections to the thalamus (Fig. 30), which of course projects back to the cerebral cortex thus closing a cortico-striatopallidal-thalamocortical loop, broadly defined. Confining the discussion to rats, the anatomical evidence demonstrates that each of the six major regions of the pallidum identified here projects to both the dorsal and ventral thalamus. Overall, the pallidum innervates at least seven nuclei in the dorsal thalamus (Fig. 30) and two in the ventral thalamus. As far as the latter are concerned, all regions of the pallidum except the external globus pallidus are known to innervate substantially the lateral habenula, and the external pallidum and substantia innominata project to the reticular nucleus (see references in Fig. 30). In contrast, striatal projections to thalamus are considerably more limited. They seem to arise almost exclusively from medial and caudal regions of striatum, and mainly end in the paraventricular and paratenial nuclei, the nucleus reuniens, and the medial part of the mediodorsal nucleus (Fig. 30).

6. Other models of basal ganglia/cerebral nuclei organization

In the first sentence of a 1966 paper that many regard as a foundation stone of contemporary thinking about basal ganglia organization, Nauta and Mehler [187] wrote, ‘The fiber projections of the corpus striatum have been the subject of intensive study and controversy for almost a century.’ As a matter of fact, the confusion has a much longer history than that and is perhaps as deep now as it has ever been. Some understanding of how the current situation evolved may help solve the problem eventually. Where helpful, archaic nomenclature will be referenced to the fundamental model of central nervous system divisions presented in Fig. 4.

The oldest approach is based on the gross anatomy of the adult human brain, and it is easy to trace the first major breakthrough to Willis [332], who in 1664 identified and named the *corpus striatum*, which lay deep within the cerebrum, surrounded by cortex and bounded caudally by our diencephalon. However vague the description, his striate body is essentially the same as the region we refer to here as the basal ganglia/cerebral nuclei/striatopallidum. Unfortunately, this is an empty appeal to historical precedence in light of a bewildering proliferation of definitions for these terms between then and now [285]. Only 20 years later Vieussens [319] went to the opposite extreme by renaming Willis’s striate bodies the *corpora striata inferiora* (essentially the anterior striate bodies) and then extending the concept to include a *corpora striata suprema* (essentially the posterior striate bodies), corresponding to our diencephalon, and a *corpora striata media*, encompassing the rest of our brainstem. By the early 19th century two great neuroanatomists, Reil [217] and Gall [77], almost simultaneously adopted an intermediate view — they referred to the anterior striate body (Willis’s striate body) and posterior striate body (our diencephalon) as the anterior and posterior parts of the great cerebral nucleus or ganglion, respectively. In 1876 Ferrier [71] introduced the term ‘basal ganglia’ as synonymous with the great cerebral nucleus or ganglion (encompassing Willis’s corpus striatum and our diencephalon), but most leading 20th century neuroanatomists who use the terms basal ganglia or basal nuclei at all mean it to indicate the noncortical parts of the cerebral hemisphere, or Willis’s *corpora striata* [42,52,111,186,195,331]. As we shall see below, contemporary neuroscientists and neurologists have tended to adopt a very different, systems-oriented approach to the basal ganglia.

Embryology has had a most profound influence on how we think about the basic parts of the central nervous system, and it was Baer [13] in the early 19th century who made the fundamental generalization that the neural tube of all vertebrates shows three primary vesicles, forebrain, midbrain, and hindbrain, and that the forebrain subsequently differentiates into paired endbrain vesicles (cerebral hemispheres, telencephalon) and an interbrain vesicle (diencephalon). However, further parceling of the telencephalic vesicle has been and remains problematic. In 1859 Reichert [216] suggested that the embryonic human telencephalic vesicle may be divided simply into a thin

A. From striatopallidum & behavior control column (BCC) **To thalamus**

striatum	pallidum	rostral BCC	caudal BCC		References
CEA MEA LSC	BST SI GPe	MPNI VMHvl/TU PMv AHN VMHdm PMd		PVT	[36-39,92,178,214,222,225,256,289,297]
LSC	BST MSC SI	VMHvl PMv AHN PMd		PT	[36,37,39,80;92,178,222,256,289]
MEA LSC	BST SI	MPNI VMHvl/TU PMv AHN VMHdm PMd	VTA	RE	[17,36-39,92,178,222,225,256,289]
		PMd	MAM	ATN	[39,75]
			SNr	LDm	[58,83]
CEA MEA	BST SI	PMv	VTA	MDm	[17,36,38,92,214,289], *
	GPe		SNr VTA	MDl	[17,43,46,83]
	MSC MA SI			MDc	[80,92,110,209,289]
			SNr VTA	CM	[17,58]
	GPe GPi		SNr	PC	[43,46,58,298]
	SI GPi			PF	[92,298]
	GPe			SGN	[246]
			SNr	VM	[58,233]
	GPi			VMl	[298]
	GPi			VALvm	[298]
			SNr	VALrm	[58,233]

B. From thalamus **To cerebral cortex**

														References
PVT			PL ILA		AId,p			PERI	ENT		SUBv		TT	[see 20]
PT			ILA	ORBm	AIv				ENT					[see 20]
RE		ACA	PL ILA				ECT	PERI	ENT	SBC	RSP	SUBv	CA1v TR TT	[see 226]
ATN	MOs	ACA		ORBvl		VIS	TE ECT	PERI	ENT	SBC	RSP	SUBd,v	TT	[see 220,250]
LDm		ACA				VISs			ENT	SBC	RSP			[318]
MDm		ACA	PL	ORBm	AId,v									[90,140]
MDl	MOs	ACA												[90,140]
MDc				ORBl	AIv									[90,140]
CM		ACA	PL											[see 20]
PC	MOs	ACA		ORBl	AId									[see 20]
PF	SSp,s MOp,s	ACA	PL											[see 20]
SGN						AUDp,s								[see 109]
VM VMl VALvm VALrm	most isocortex					most isocortex								[108,109]

Fig. 30. A summary of anatomically defined projections (A) from the striatopallidum and behavior control column to the dorsal thalamus, as well as (B) from these regions of dorsal thalamus to the cerebral cortex, as seen in the rat. *Abbreviations*: ACA, anterior cingulate area; AId,p,v, agranular insular area, dorsal, posterior, ventral parts; ATN, anterior nuclei thalamus; AUDp,s, primary, secondary auditory areas; BST, bed nuclei stria terminalis; CA1v, ventral hippocampal field CA1; CEA, central nucleus amygdala; CM, central medial nucleus; ECT, ectorhinal area; ENT, entorhinal area; GPe,i, globus pallidus, external, internal segments; ILA, infralimbic area; LDm, lateral dorsal nucleus, medial region; LSC, lateral septal complex; MA, magnocellular (preoptic) nucleus; MAM, mammillary body; MDc,l,m, mediodorsal nucleus, central, lateral, medial parts; MEA, medial nucleus amygdala; MOp,s, primary, secondary motor areas; MPNl, medial preoptic nucleus, lateral part; MSC, medial septal complex; ORBl,m,vl, orbital area, lateral, medial, ventromedial parts; PC, paracentral nucleus; PERI, perirhinal area; PF, parafascicular nucleus; PL, prelimbic area; PMd,v, premammillary nuclei, dorsal, ventral; PT, paratenial nucleus; PVT, paraventricular nucleus thalamus; RE, nucleus reuniens; RSP, retrosplenial area; SBC, presubiculum, postsubiculum, parasubiculum; SGN, supragenicular nucleus; SI, substantia innominata; SNr, reticular substantia nigra; SSp,s, primary, secondary somatosensory areas; SUBv, ventral subiculum; TE, temporal association areas; TR, postpiriform transition area; TT, tenia tecta; TU, tuberal nucleus; VALrm,vm, ventral anterior–lateral complex, rostromedial, ventromedial regions; VISs, visual areas, secondary; VMl, ventral medial nucleus, lateral region; VMHdm,vl, ventromedial nucleus hypothalamus, dorsomedial, ventrolateral parts; VTA, ventral tegmental area.

upper wall (mantle or pallium) and a thicker basal mass. However, the greatest embryologist of the latter 19th century, His, proposed in the ‘official’ tabulation of anatomical nomenclature, the 1895 *Basle Nomina Anatomica* (*BNA*) [115], that there are three divisions of the telencephalon: pallium or cortex, rhinencephalon or olfactory brain (see Ref. [258] for a history of the term rhinencephalon), and corpus striatum, which he extended caudally to include all of the hypothalamus except the mammillary body (even though the hypothalamus, including the preoptic region, is derived from third ventricular neuroepithelium). Contemporary developmental neuroscience has not, until very recently, been particularly concerned with global accounts of telencephalon generation. It seems generally acknowledged that there are cortex and basal ganglia or nuclei, but problematic regions like the amygdala and septum are typically ignored or treated uncritically.

The possible existence of additional telencephalic divisions, such as the rhinencephalon, has led to endless

confusion for over a hundred years, and raising the possibility that they may be eliminated as superfluous is a primary goal of this review. Exactly how His defined the rhinencephalon in terms of today's extensive parceling of the forebrain is impossible to say. But it is clearly associated with two other lines of thought that have had considerable influence, at least for a while. The first is the concept of the limbic system, which evolved out of Broca's detailed account of a 'great limbic lobe' forming a complete ring around medial regions of the cerebral hemisphere in all mammals [26]. According to Broca, this ring processes olfactory information, which is routed dorsally into the cingulate gyrus where associations with pain and pleasure may be formed, and caudally into the hippocampal gyrus where olfactory discrimination may take place [243] — it was Cajal who suggested that the hippocampal gyrus is a high order olfactory association cortex involved in forming olfactory memories [33]. Many years later the limbic lobe concept was revived and greatly expanded by MacLean. In 1952 he suggested [154] that the limbic lobe and the subcortical regions with which it interconnects are involved in the elaboration and expression of emotions, and used the term limbic system in referring to this functional circuitry. This was an expansion on his seminal proposal three years earlier [153] that there is a basic dichotomy within the cerebrum: the limbic lobe constitutes a phylogenetically ancient ring of medial cortex subserving emotional ('what we feel') functions, whereas the more lateral neocortex subserves primarily cognitive ('what we know') functions. MacLean's original definition of the limbic system included a continuous ring of cortical structures (olfactory cortex, hippocampal formation, cingulate gyrus, and subcallosal gyrus), along with a group of subcortical areas with which they were known at the time to interconnect (amygdala, septum, hypothalamus, habenula, anterior thalamic nuclei, and 'parts of the basal ganglia'). Despite growing uneasiness with the limbic system concept — mainly because its exact structural components and functions have now become so vague (e.g. [27]; but see [155]) — it remains in widespread use for lack of a viable alternative [284].

MacLean's arguments rely in part on evolutionary thinking, which has provided yet another way of viewing the basic components of the brain, and of the telencephalon in particular. Probably the main intellectual stimulus came at the beginning of the 20th century from Edinger [68], who proposed in a very general way that there is a part of the brain, the palaeëncephalon (old brain) that is common to and basically unchanged throughout all vertebrates, and a neëncephalon (new brain) that is encountered in a very rudimentary way in amphibians and becomes huge in birds and especially mammals. The old brain is responsible for reflex and instinctive behaviors, and its telencephalon consists essentially of rhinencephalon and corpus striatum, whereas the new brain is responsible for connecting associations and elaborating anticipatory behavior, and it consists essentially of the pallium or cortex as defined at the time. Edinger's younger colleague Kappers [128] is responsible for elaborating this concept and introducing nomenclature still widely used in part today — usually without recognizing its theoretical foundations and implications. Starting with a basic dichotomy between pallium (cortex) and corpus striatum, Kappers distinguished oldest (paleo-), old (archi-), and new (neo-) components of each — thus, paleopallium (paleocortex) and paleostriatum, archipallium (archicortex) and archistriatum, and neopallium (neocortex) and neostriatum. According to this scheme, paleocortex corresponds roughly to olfactory cortex, archicortex to the hippocampus, and neocortex to the rest; whereas paleostriatum refers to the globus pallidus, archistriatum refers to the amygdala, and neostriatum to the caudoputamen. The basic premises of this vague theory have certainly never been proven — in fact there is now good evidence for the equivalent in teleost fish of a pallium that contains regions associated with sensory modalities other than olfactory [67,189] — and it is interesting to note that Eliot Smith, who actually introduced the concept of 'archipallium' in 1901 [258], wrote a strong disclaimer less than a decade later [259].

The importance of neuroanatomical nomenclature ought to be evident by now, and the utility of abandoning misleading or arbitrary names in favor of more accurate ones is clear in principle but difficult and slow to come in practice. A nice example is provided by the term 'lentiform nucleus,' which was introduced by Burdach [30] in the early 19th century, and which refers to a very obvious gross anatomical feature of the primate cerebral hemisphere. We now know that the lentiform or lenticular 'nucleus' consists of the globus pallidus and only part of the dorsal striatum, the putamen. From every perspective (except primate gross anatomy) this is an arbitrary and very misleading parcellation: it makes considerably more sense on functional, developmental, and connectional grounds to combine the putamen and caudate nucleus as dorsal striatum, in distinction to the globus pallidus or dorsal pallidum (Sections 1.2, 3.3.2, 4.1 and 5.1).

We have argued that the same basic principle applies to the terms 'amygdala' [294] and 'septum' [295] — in light of modern connectional and functional data, they refer to gross anatomical regions that arbitrarily group structures associated with different functional systems. And the same really applies to the paleo-, archi-, neo-terminology for cortex and 'striatum' (i.e., corpus striatum). Obviously, no clear, primary, topographically organized circuitry has been established between paleocortex (olfactory cortex) and paleostriatum (globus pallidus), or between archicortex (hippocampus) and archistriatum (amygdala as a whole), although such is the case for neocortex and neostriatum, which partly explains their continued widespread use. However, it seems illogical to use them when the basic premise upon which they were coined is so doubtful. Better terms at this point would be isocortex [320] and

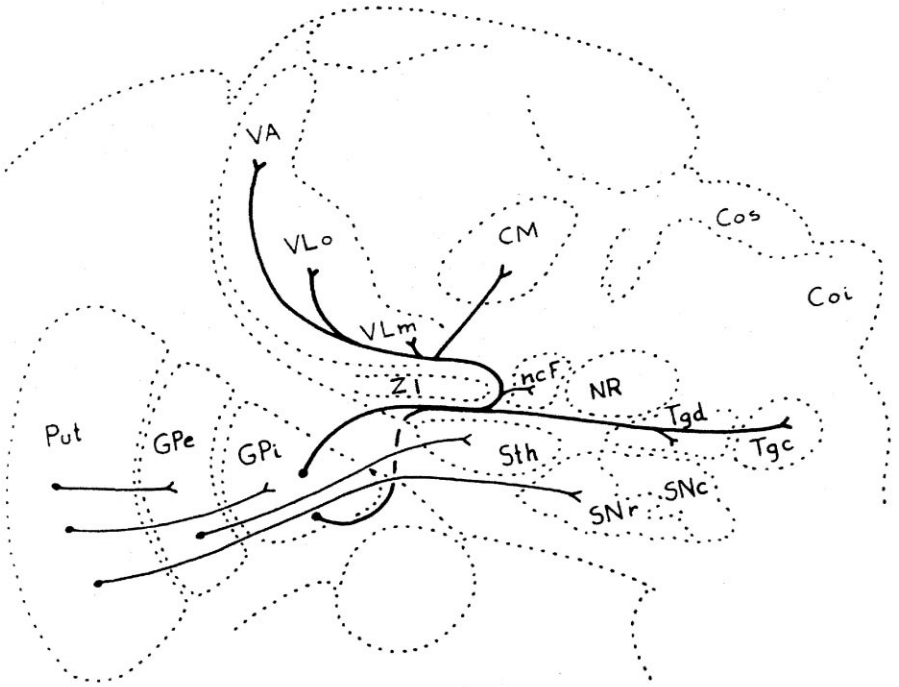
dorsal striatum [104]. The fate of the term limbic system remains to be seen. Rhinencephalon is fine as long as it is defined in terms of what we now know are clearly parts of olfactory cortex and cerebral nuclei, just as one might refer to parts of the visual or auditory systems within the cerebral hemispheres as the visual brain or auditory brain [111].

As mentioned at the beginning of this section, the 1966 paper by Nauta and Mehler on projections of the monkey lentiform nucleus provides a good starting point for contemporary thinking about cerebral hemisphere organization in general, and basal ganglia/cerebral nuclei organization in particular. Using the first genuinely new experimental pathway tracing method of the 20th century, they demonstrated unequivocally that the striatum (putamen) projects to the globus pallidus and reticular substantia nigra; that the external globus pallidus innervates the subthalamic nucleus; and that the internal globus pallidus has a complex double projection — one to multiple regions of the thalamus and the other to several parts of the midbrain tegmentum, including the fields of Forel and a region extending around the rostral pole of the red nucleus, and another region that includes the pedunculopontine nucleus and the midbrain extrapyramidal area of Rye and colleagues [229]. Thus, they established a dual output of the basal ganglia (Fig. 31A) — to the thalamus and to regions of the brainstem including the subthalamic nucleus, substantia nigra, rostromedial tegmentum (centered in the field of Forel), and perhaps the area of the pedunculopontine nucleus as defined by Olszewski and Baxter [191] in the human brainstem.

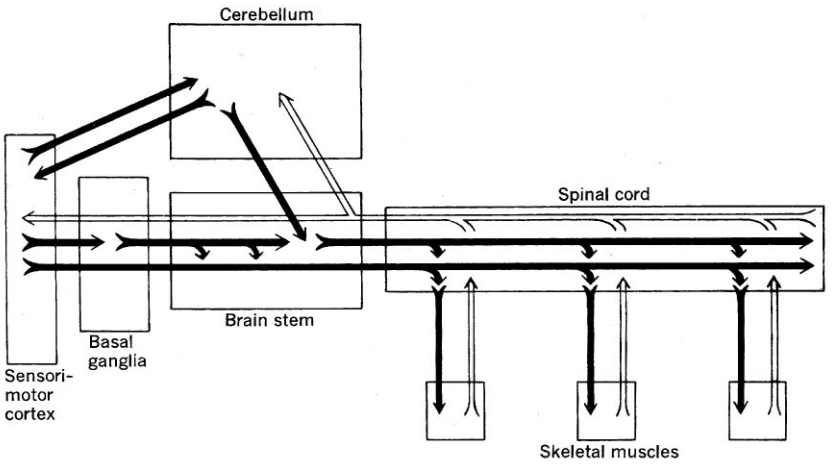
Two subsequent reviews, both with a physiological/clinical rather than anatomical focus, set the stage for current models of basal ganglia organization. The first, by Henneman [106,107], appeared in Mountcastle's prestigious *Medical Physiology*, and it dealt exclusively with basal ganglia projections to the brainstem motor system, essentially ignoring projections to the thalamus (Fig. 31B). In addition, he defined the most important components of the basal ganglia as including the caudate and putamen (striatum) and the globus pallidus of the forebrain, and what were said to be the closely related subthalamic nucleus, substantia nigra, and red nucleus — a systems-based definition. No citations to the anatomical literature were provided, although it seems clear that he, like certain other neurologists (see [60]), applied the term basal ganglia to what had earlier been referred to as the core of the extrapyramidal system or the striatal system [41,125,136]. The second review was by DeLong and Georgopoulos [57], and it appeared seven years later in the prestigious *Handbook of Physiology*. Here basal ganglia projections to the thalamocortical loop were emphasized instead (Fig. 31C). They followed Henneman's systems and clinically-oriented definition of the basal ganglia (which included the caudoputamen and globus pallidus, along with the subthalamic nucleus and substantia nigra — and sensibly not the red nucleus), but they went considerably further. They also emphasized the topographic organization of projections through cortico-basal ganglia-thalamocortical loops, and 'The existence of segregated pathways through the basal ganglia indicated by anatomical and physiological studies . . . '

This approach, which has been updated periodically ever since (e.g. [1,3,4,122,174,203,269]) (Fig. 32) has been immensely valuable in focusing research onto a manageable number of cell groups and their interconnections, and is surviving basically intact in the most popular neuroscience textbooks [55,176]. Nevertheless, it has been noted (e.g. [2,190,231]) that there are problems when it is taken too literally. First, the bulk of internal pallidal projections to the 'motor' thalamus in rat, cat, and monkey are actually collaterals of axons to the brainstem tegmentum (the region of the pedunculopontine nucleus/midbrain extrapyramidal area, in particular) (see [72,103,198,200, 201,313]), and the same probably applies to reticular substantia nigra projections to 'motor' thalamus and brainstem (e.g. superior colliculus and reticular formation) (see [16,199,266]). It would appear, in fact, that more neurons in the internal pallidum of the monkey project to the tegmentum than to the thalamus [103], and that the pallidotegmental projection is more differentiated in monkeys than in rats [199,251]. Second, whereas the pedunculopontine nucleus/midbrain extrapyramidal area projects to the subthalamic nucleus and globus pallidus, it also has well documented projections to the spinal cord and a large expanse of the reticular formation known to play a role in somatomotor responses (the oral and caudal parts of the pontine reticular nucleus and gigantocellular reticular nucleus in particular) (see [94,121,158,179,230,333]). Taken together, the first two points suggest that in mammals projections to the thalamocortical loop and brainstem motor system from the internal pallidum and reticular substantia nigra mostly arise from the same population of neurons in each cell group. Third, in view of all the projections of the globus pallidus and reticular substantia nigra (Fig. 22), restricting the 'basal ganglia' to just the dorsal striatopallidum, subthalamic nucleus, and substantia nigra seems too extreme at both the telencephalic and brainstem levels, and arbitrary as well at the brainstem level. And fourth, the current standard model only considers adequately the dorsal striatopallidum. As an aside, if this model were applied as well to the ventral, medial, and caudorostral striatopallidum as envisioned here, then it would include the whole of the behavior control column (see Figs. 20 and 33). From a systems point of view, this is perfectly reasonable, but it would certainly provide an even more novel definition of the basal ganglia — and one should as well add a series of cell groups analogous to the subthalamic nucleus.

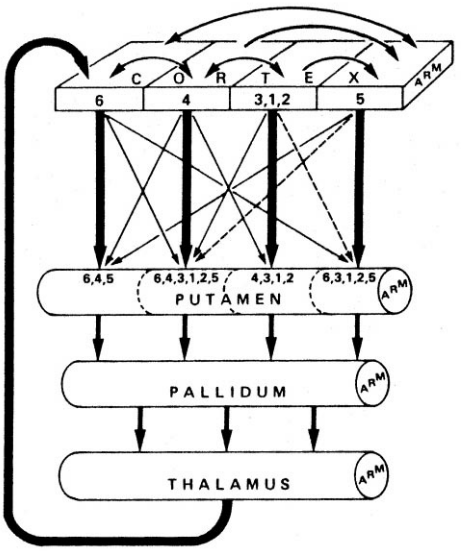
One other concept dealing with general principles of cerebral hemisphere architecture — the extended amygdala — is relevant to this discussion. In a recent book on the



A. Nauta and Mehler 1966



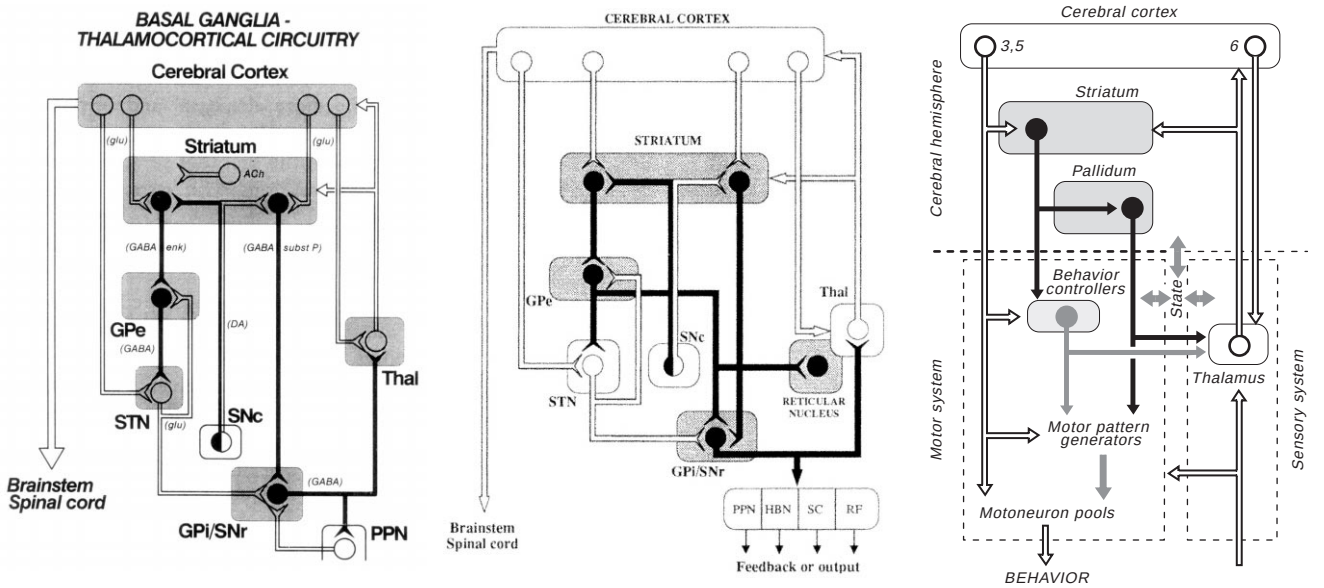
B. Henneman 1974



C. DeLong and Georgopoulos 1981

Fig. 31. Three seminal views on the fundamental organization of circuitry associated with the basal ganglia. (A) The neuroanatomical results of Nauta and Mehler [187] in the monkey showed multiple projections from the putamen (Put) and globus pallidus to the thalamus, subthalamic nucleus, and midbrain. In this diagram, the brainstem is shown in a sagittal projection and the basal ganglia (lentiform nucleus — putamen and globus pallidus) in a frontal pl ane. (B) In this functionally oriented diagram, Henneman [106] emphasized projections from the basal ganglia to the brainstem and spinal cord skeletomotor system. (C) Here, DeLong and Georgopoulos [57] stressed cortico-striatopallido-thalamocortical loops. *Other abbreviations*: CM, centre médian; Coi, Cos, inferior, superior colliculi; GPe,i, globus pallidus, external, internal segments; ncF, nucleus of the fields of Forel (prerubral field); NR, red nucleus; SNc,r, substantia nigra, compact, reticular parts; Sth, subthalamic nucleus; Tgc, Tgd, pedunculopontine nucleus, pars compacta, pars dissipata; VA, ventral anterior nucleus; VLm,o, ventral lateral nucleus, medial, oral parts; ZI, zona incerta. All three figures are reproduced with permission.

topic [167], de Olmos and Heimer [61] have traced its history and outlined its major features. In brief, the extended amygdala consists of four highly interconnected telencephalic cell groups — the central and medial amygdalar nuclei, and then two major extensions, the caudal substantia innominata (the sublenticular part, which

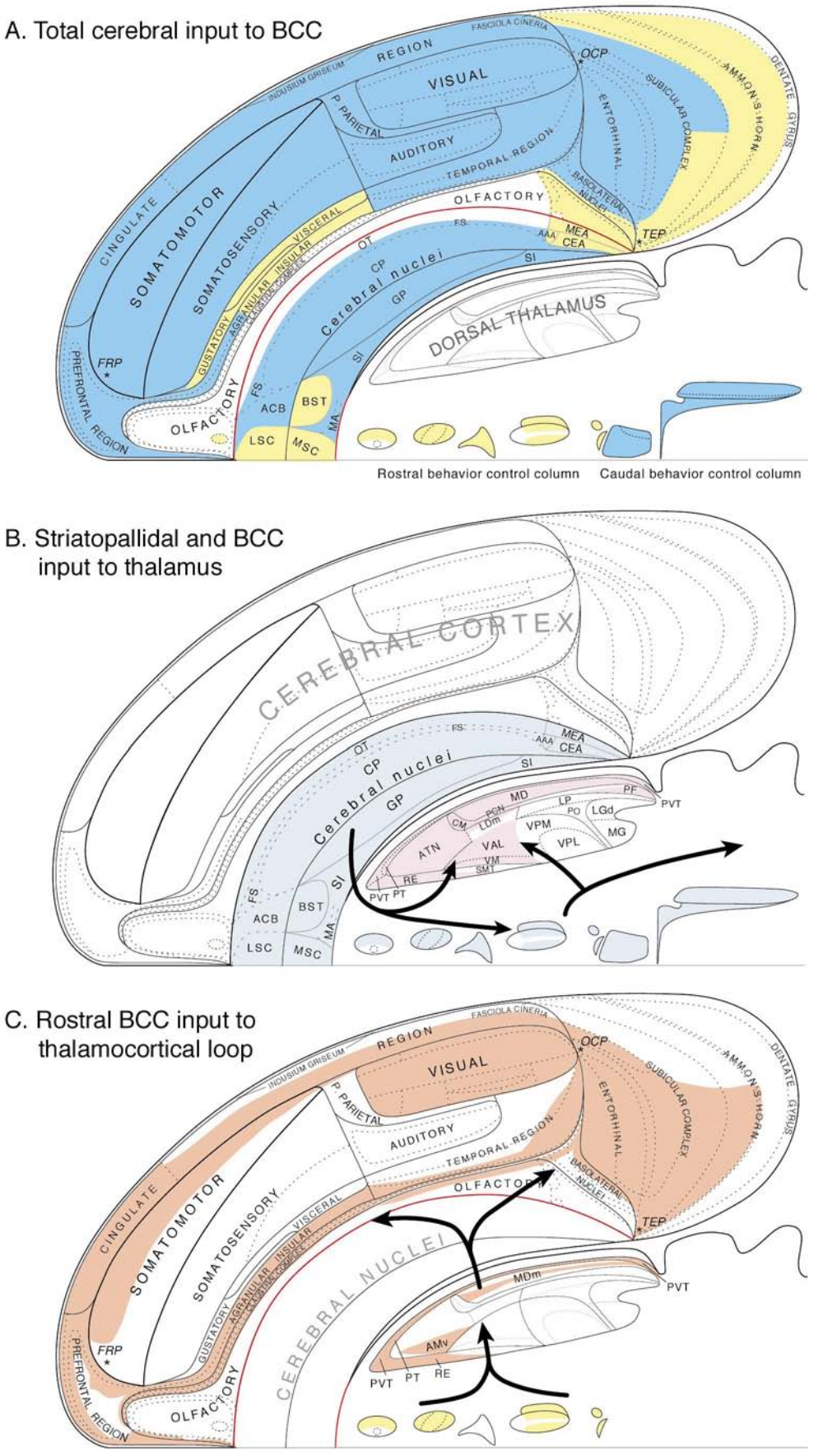


A. Alexander et al. 1990 B. Smith et al. 1998 C. Here

Fig. 32. Three more recent views of basal ganglia circuitry. (A) The widely influential model of basal ganglia organization introduced by Alexander, Crutcher, and DeLong in 1990 [3]. Excitatory pathways are indicated by open circles and lines, inhibitory pathways by filled circles and lines. Although it has been suggested [56] that the internal segment of the globus pallidus and the reticular part of the substantia nigra form a single nucleus, analogous to the caudate nucleus and putamen (forming the dorsal striatum), there is no clear developmental evidence to support this view. (B) A recent update by Smith and colleagues [261] of the Alexander, Crutcher, and DeLong model shown in (A). The most substantial difference is the addition of 'output' at the bottom right. (C) A refinement of this model based on the evidence reviewed here. This version emphasizes the extensive collateralization of key pathways, including those arising in layers 3 and 5 of the cerebral cortex, in the striatum, and in the pallidum. This version also places the striatopallidum within the broader context of sensory-motor and state control systems (see Fig. 1). For clarity, certain important components associated with the dorsal striatopallidal system have not been shown. They include the compact substantia nigra and subthalamic nucleus, which have mostly intrinsic connections, although the compact substantia nigra at least may someday be viewed as part of the behavioral state system. It will be interesting to see whether there are analogous cell groups associated with the ventral, medial, and caudorostral striatopallidal systems (Fig. 20B–F). *Abbreviations*: ACh, acetylcholine; DA, dopamine; glu, glutamate; GPe,i, globus pallidus, external, internal segments; HBN, habenula; PPN, pedunculopontine nucleus; RF, reticular formation; SC, superior colliculus; SNc,r, substantia nigra, compact, reticular parts; STN, subthalamic nucleus. Parts A and B reproduced with permission.

is actually the only part ventrally adjacent to the globus pallidus itself) and the bed nuclei of the stria terminalis. This anatomical unit is part of the telencephalon, but is fundamentally different from the dorsal and ventral striatopallidum because (a) most importantly, it does not participate in a thalamocortical feedback loop, (b) its components are highly interconnected by long 'associative' pathways, (c) its functions are related to the autonomic and neuroendocrine systems, and (d) it shows certain neurochemical specializations. However, it is known (Fig. 30;

Fig. 33. Three different aspects of forebrain organization. (A) Virtually the entire cerebral hemispheres (cortex and basal nuclei) — with the notab le exceptions of many olfactory cortical areas and the dentate gyrus — project in a topographically organized way to the behavior control column (BCC). Cerebral inputs to the rostral segment of the column are indicated in yellow, and those to the caudal segment in blue. See Fig. 20 for details about the overall organization of these projections. (B) Essentially the entire striatopallidum (cerebral nuclei/basal ganglia) generates a branched projection to the dorsal thalamus and behavioral control column, which in turn generates a branched projection to the dorsal thalamus and brainstem motor system. The parts of the thalamus innervated by the cerebral nuclei and behavior control column are indicated in pink. As a whole, they send a topographically organized projection to essentially the entire cerebral cortex (Fig. 30). (C) This map illustrates the thalamocortical projection (in light red) influenced by pathways from the rostral segment of the behavior control column (yellow). Note that the ring of cortex influenced by the rostral behavior control column is rather different than the set of cortical and striatopallidal regions that project to the rostral behavior control column (yellow in part A). A larger version of the cortical map is shown in Fig. 16. *Abbreviations* (not in Fig. 16): AAA, anterior amygdalar area; ACB, nucleus accumbens; AMv, anteromedial nucleus, ventral part; ATN, anterior thalamic nuclei; BST, bed nuclei stria terminalis; CEA, central nucleus amygdala; CM, central medial nucleus; CP, caudoputamen; FS, striatal fundus; GP, globus pallidus; LGd, dorsal lateral geniculate nucleus; LP, lateral posterior nucleus; LSC, lateral septal complex; MA, magnocellular (preoptic) nucleus; MDm, mediodorsal nucleus, medial part; MEA, medial nucleus amygdala; MG, medial geniculate nucleus; MSC, medial septal complex; OT, olfactory tubercle; PCN, paracentral nucleus; PF, parafascicular nucleus; PO, posterior complex thalamus; PT, paratenial nucleus, PVT, paraventricular nucleus thalamus; RE, nucleus reuniens; SMT, submedial nucleus thalamus; SI, substantia innominata; VAL, ventral anterior–lateral complex; VM, ventral medial nucleus; VPL, ventral posterolateral nucleus; VPM, ventral posteromedial nucleus.


A. Total cerebral input to BCC
INDUSIUM GRISEUM
REGION
FASCIOLA CINERIA
OCP
VISUAL
P PARIETAL
AUDITORY
TEMPORAL REGION
ENTORHINAL
SUBICULAR COMPLEX
AMMON'S HORN
DENTATE GYRUS
BASOLATERAL NUCLEI
OLFACTORY
CINGULATE
SOMATOMOTOR
SOMATOSENSORY
VISCERAL
AGRANULAR INSULAR
GUSTATORY
F.S.
AAA
MEA
CEA
TEP
OT
CP
SI
Cerebral nuclei
GP
DORSAL THALAMUS
FRP
PREFRONTAL REGION
OLFACTORY
FS
ACB
BST
MA
LSC
MSC
Rostral behavior control column
Caudal behavior control column
B. Striatopallidal and BCC input to thalamus
CEREBRAL CORTEX
F.S.
AAA
MEA
CEA
OT
CP
SI
Cerebral nuclei
GP
MD
PF
PVT
LP
PO
LGd
PCN
CM
LOm
VPM
MG
ATN
VAL
VPL
VM
SMT
RE
PVT
PT
FS
ACB
BST
MA
LSC
MSC
C. Rostral BCC input to thalamocortical loop
INDUSIUM GRISEUM
REGION
FASCIOLA CINERIA
OCP
VISUAL
P PARIETAL
AUDITORY
TEMPORAL REGION
ENTORHINAL
SUBICULAR COMPLEX
AMMON'S HORN
DENTATE GYRUS
BASOLATERAL NUCLEI
OLFACTORY
CINGULATE
SOMATOMOTOR
SOMATOSENSORY
VISCERAL
AGRANULAR INSULAR
GUSTATORY
TEP
CEREBRAL NUCLEI
MDm
PVT
AMv
PVT
PT
RE
FRP
PREFRONTAL REGION
OLFACTORY

Section 5.6) that both the caudal substantia innominata and the bed nuclei project to the thalamus, and it is easy to place the four nuclei of the extended amygdala within the framework of a 'caudorostral' striatopallidum with projections to the motor system as well (Fig. 20F; Section 4.2). The fact that these four cell groups are interconnected in a complex way is not unusual in terms of other basal ganglia/cerebral nuclei/striatopallidal regions (Figs. 23, 28 and 29; Section 5.5). On the other hand, it is true that the circuitry associated with these four nuclei has special functional significance — we would suggest that the medial amygdalar nucleus is a striatal region specialized for relaying pheromonal information to the (hypothalamic) motor system, whereas the central amygdalar nucleus is a striatal region specialized for relaying cortical information to the autonomic system [294]. Neurochemical specializations help characterize all differentiated regions of the cerebral hemispheres. For a further discussion of the extended amygdala (see [38]).

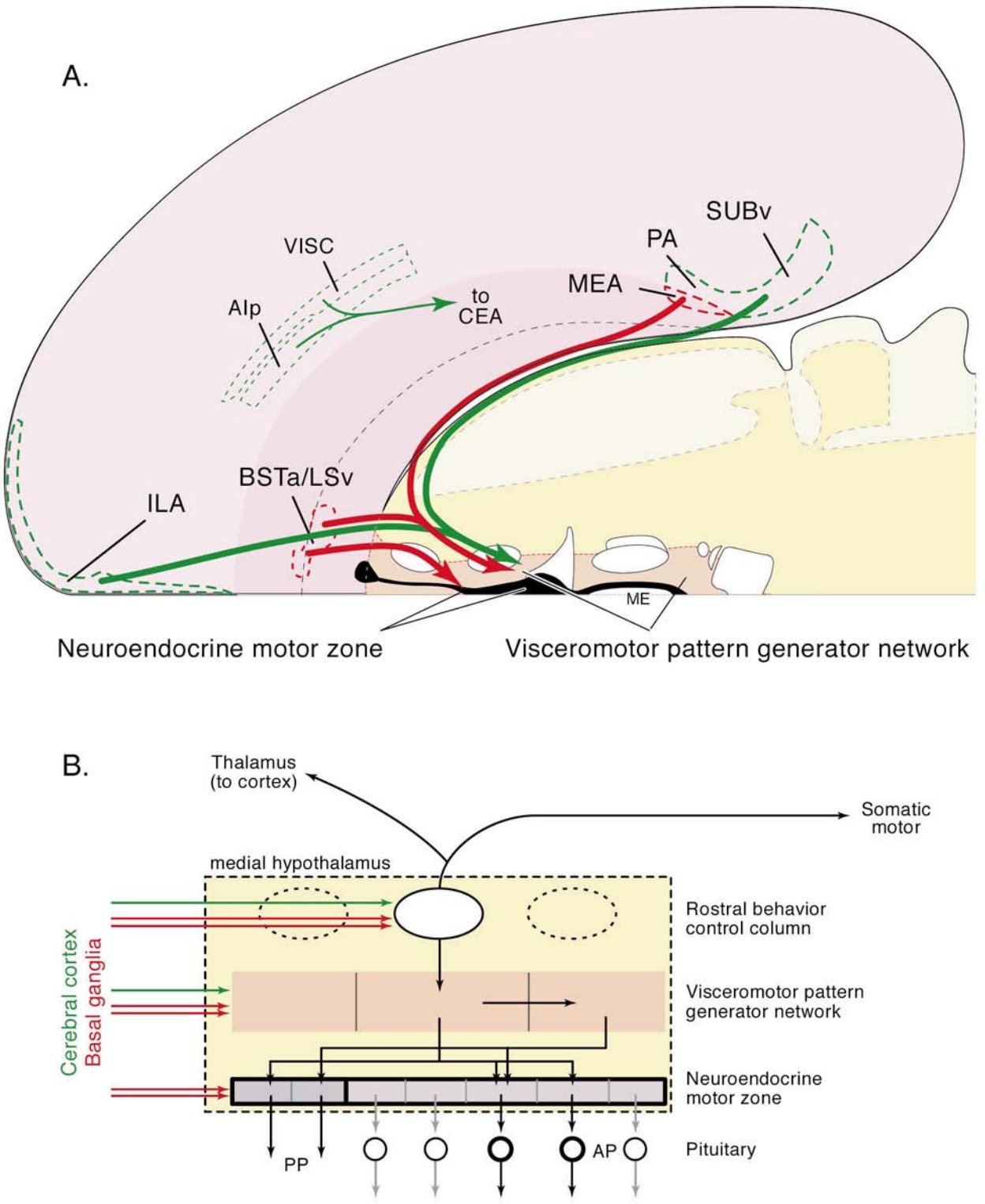
7. Conclusions

Developmental, gene expression, connectional, and functional evidence converges to suggest that the cerebral hemispheres have three basic parts — cortex, striatum, and pallidum — and that they generate two major outputs, a triple cascading projection to the motor system on one hand and projections to thalamocortical feedback loops on the other. For descriptive purposes the basal ganglia/cerebral nuclei can be parceled into dorsal, ventral, medial, and caudorostral striatopallidal regions based on gross anatomy (Fig. 19). This is not, however, a particularly useful way of viewing cerebral hemisphere architecture from a functional perspective because individual regions may themselves be quite differentiated. For example, primary visual and primary somatomotor areas of cortex, which have very different functions, both project to the dorsal striatum (caudoputamen), whereas the ventral striatum has been defined as containing such morphologically and functionally diverse components as the nucleus accumbens and olfactory tubercle. A better way to approach understanding the cerebral hemispheres is to begin with a structure/function parceling of the cortical mantle, and then follow the organization of primary and secondary projections from this map through the striatum and pallidum (Fig. 20). Each cortical area displays a characteristic lamination pattern (compare primary visual and olfactory areas, for example), and this is reflected in structural differentiations of striatal and pallidal regions influenced by that cortical area (compare caudoputamen with olfactory tubercle, for example).

The cerebral hemispheres project to all levels of the somatic motor system hierarchy, from alpha motoneuron pools at the bottom, to motor pattern generators, to motor pattern initiators, to the motor pattern (behavior) controllers at the top, which are emphasized in this review (Fig. 1). Basically, we have presented evidence to support the generalization that at a minimum the cerebral hemispheres generate a triple projection to the motor system, with an excitatory component from the cortex, an inhibitory component from the striatum, and a disinhibitory component from the pallidum (Fig. 14). In fact, most of the cerebrum participates in a triple projection to the behavior control column in ventromedial regions of the upper brainstem (Figs. 9, 20 and 33). Like the basal ganglia/cerebral nuclei themselves, the behavior control column sends a descending input to (lower levels of) the motor system, as well as an input to the thalamocortical projection system (Figs. 10 and 33B).

The behavior control column as we have defined it consists of rostral and caudal segments. The caudal segment includes the mammillary body, reticular substantia nigra, and ventral tegmental area, and it appears to be involved in signaling or regulating the direction of head orientation, of orienting movements of the eyes, head, and upper limbs, and of locomotor activity — in other words, key components of exploratory or foraging behavior in general. By way of contrast, the rostral segment includes the medial preoptic, anterior hypothalamic, descending

Fig. 34. Cerebral hemisphere inputs to the neuroendocrine and autonomic motor systems. *A.* Only two substantial inputs have been identified from the cerebral hemispheres directly to the region of the neuroendocrine motor zone; they arise in the adjacent anterior bed nuclei of the stria terminalis (BSTa) and ventral lateral septal nucleus (LSv). However, these two regions, along with the infralimbic area (ILA), ventral subiculum (SUBv), posterior amygdalar nucleus (PA), and medial amygdalar nucleus (MEA) project to the visceromotor pattern generator network surrounding the neuroendocrine motor zone. The central amygdalar nucleus (CEA) projects to the caudal bed nuclei of the stria terminalis and brainstem nuclei associated with the autonomic system (not shown). The central nucleus receives inputs from many cortical areas (see Fig. 24), but two of the most dense inputs are from the visceral area (VISC) and ventrally adjacent posterior agranular insular area (AIp). *B.* A model of basic hypothalamic organization. The neuroendocrine motor zone, centered along the third ventricle, has pools of magnocellular neurosecretory neurons projecting to the posterior pituitary (PP), and pools of parvicellular neurosecretory neurons related via the median eminence (ME) to the five classic cell types of the anterior pituitary (AP). In the periventricular region surrounding, and interdigitating with, the neuroendocrine motor zone there is a visceromotor pattern generator network organized such that it is in a position to generate patterns of pituitary hormone secretion, as well as coordinated patterns of activity in preautonomic neurons of the PVHd (the latter not shown for simplicity). The rostral segment of the behavior control column consists of distinct medial nuclei with a typical pattern of outputs. Most of these nuclei generate a dual projection to the brainstem motor system and to the dorsal thalamus, as well as a medially-directed projection to the visceromotor pattern generator network. The function of the lateral zone of the hypothalamus is less clear, but it is probably involved in the control of behavioral state and levels of arousal. The medial hypothalamus receives inputs from the cerebral hemispheres, as well as from the various sensory systems [226] and the state control system (the suprachiasmatic nucleus is just one example [324]).



paraventricular, ventromedial, and premammillary nuclei — which are involved in controlling the three fundamental classes of motivated behavior necessary for survival of the individual and species: ingestive, reproductive, and defensive. Thus, the rostral segment of the behavior control column appears to be involved in accomplishing specific goals, whereas the caudal segment appears to play a critical role in the expression of exploratory or foraging behaviors used to attain any and all goal objects. The rostral segment projects to a rostromedial zone in the thalamus that includes the nucleus reuniens, the paraventricular and paratenial nuclei, the ventral anteromedial nucleus, and the medial mediodorsal nucleus — which together in turn project to a ring of cerebral cortex that

includes a large expanse of the cingulate, orbitofrontal, agranular insular, and hippocampal regions (Figs. 30 and 33C). Interestingly, this ring of cortex only partly overlaps the region of cortex that projects to the rostral segment, mostly by way of the striatopallidum (yellow in Fig. 33A).

In the last twenty years, models of basal ganglia function have tended to focus on evidence from primates and on 'segregated' thalamocortical feedback loops involving motor, premotor, and prefrontal cortical areas, while major projections to the somatic motor system have tended to fade into the background. Nevertheless, anatomical evidence from rat, cat, and monkey indicates that most neurons in the internal globus pallidus (and reticular substantia nigra) generate a branched projection to the thalamus and to the brainstem motor system, with the thalamic input arising as collaterals of thicker descending parent axons to the brainstem (Section 6). Potential inputs to the motor system from the internal globus pallidus include the reticular substantia nigra, deeper layers of the superior colliculus, periaqueductal gray, pedunculopontine nucleus/midbrain extrapyramidal area, parvicellular reticular nucleus, medullary reticular nucleus, and gigantocellular reticular nucleus (Fig. 22C; Sections 5.1 and 6). The reticular substantia nigra projects to most of these areas, as well as to the external and dorsal inferior colliculus, red nucleus, and a nearby oculomotor-related cell group, the medial accessory nucleus (Fig. 22D). Unfortunately, most of these descending projections have not been examined yet with the most sensitive neuroanatomical methods for the primate central nervous system, where distances and volumes are much greater than in the rat. As shown clearly for the massive internal globus pallidus to pedunculopontine nucleus/midbrain extrapyramidal area projection, these methods for the primate include the retrograde tracer fast blue [103] and the anterograde tracer biotinylated dextran amine [231,251].

As pointed out in the Introduction (Section 1.1), the motor system has three divisions — somatic, autonomic, and neuroendocrine — and we have just discussed the fact that voluntary control of the somatic motor system is mediated by extensive, topographically organized inputs from the cerebral hemispheres. It is now becoming clear that there are also interconnected parts of the cerebral hemispheres that generate characteristic triple projections to the autonomic and neuroendocrine motor systems (Fig. 34A). First, let us consider briefly the cerebral autonomic system. The visceral area and ventrally adjacent posterior agranular insular area of cortex project massively to the central amygdalar nucleus of the caudal striatum (Section 4.2), and it in turn has direct projections to components of the brainstem autonomic system, including preganglionic parasympathetic cell groups [117]. In addition, the central nucleus projects to the bed nuclei of the stria terminalis (rostral pallidum) [141], which also has descending projections to the brainstem autonomic system [116,177,244]. This set of connections would seem to define at least an important core part of a cerebral subsystem concerned with regulating autonomic motor system output, although there are undoubtedly other important components that have direct connections with brainstem autonomic centers, including the medial prefrontal [177,314] and insular [127,177] cortical areas. Furthermore, two brainstem visceroSensory cell groups, the nucleus of the solitary tract [219,235] and parabrachial nucleus [237], project directly to most if not all of these telencephalic sites in the rat at least.

And second, let us review briefly the outlines of cerebral components of the neuroendocrine system (Fig. 34A). To date, there is substantial neuroanatomical evidence for two adjacent regions of the striatopallidum — the ventral lateral septal nucleus and anterior bed nuclei of the stria terminalis — projecting directly to the region of neuroendocrine motoneuron pools in the periventricular hypothalamus [225]. However, the medial amygdalar nucleus [38] of the caudal striatum, and the infralimbic [119], ventral subicular [40], and posterior amygdalar [35] regions of cortex also project substantially to the ventral lateral septum/anterior bed nuclei, as well as directly to the visceromotor pattern generator network in the periventricular region of the hypothalamus. Together, these six regions appear to form important components of a cerebral network that may influence the output of the neuroendocrine motor system, either directly via secretomotor motoneuron pools, or indirectly via an adjacent visceromotor pattern generator network (Fig. 34B).

With this evidence about possible cerebral inputs to the neuroendocrine motor system in hand, it is now possible to outline a model of basic hypothalamic organization (Fig. 34B). Starting with the rostral behavior control column (concerned with ingestive, reproductive, and defensive behaviors), we have seen that it receives a triple descending input from the cerebral hemispheres and then generates a dual output to the somatic motor system and thalamocortical system. On the other hand, individual nuclei of the rostral behavior control column send few in any direct inputs to the neuroendocrine motor zone. Instead, they tend to project to the medially adjacent visceromotor pattern generator network in the periventricular region, and it in turn projects massively and in a complex way to the neuroendocrine motor zone — producing patterns of hormone secretion from the anterior and posterior (neural) lobes of the pituitary gland. Neuroanatomical evidence to date suggests that the visceromotor pattern generator network receives a triple descending input from the cerebral hemispheres (cortical excitatory, striatal inhibitory, and pallidal disinhibitory), whereas significant inputs directly to the neuroendocrine zone appear restricted to the striatopallidum (and are presumably GABAergic).

In closing, it is essential to underline the fact that the model of brain architecture outlined here is based mostly on structural evidence and gene expression patterns in the

rat, where such information is by far most complete. However, the model remains incomplete. For example, the lateral hypothalamus undoubtedly plays a major role in controlling behavior (perhaps especially behavioral state), and yet its structural organization remains poorly understood. More importantly, almost nothing is known about the functional dynamics of the circuitry outlined here — what are the precise functional roles of each component in each subsystem, and how are behavioral priorities involving different subsystems established? But most importantly, we have almost no direct evidence about the organization of this circuitry in the human brain, where pathological changes result in such devastating neurological and psychiatric afflictions. All we can do at this point is superimpose the circuitry determined experimentally in animals onto renderings of the human brain (Fig. 35), and

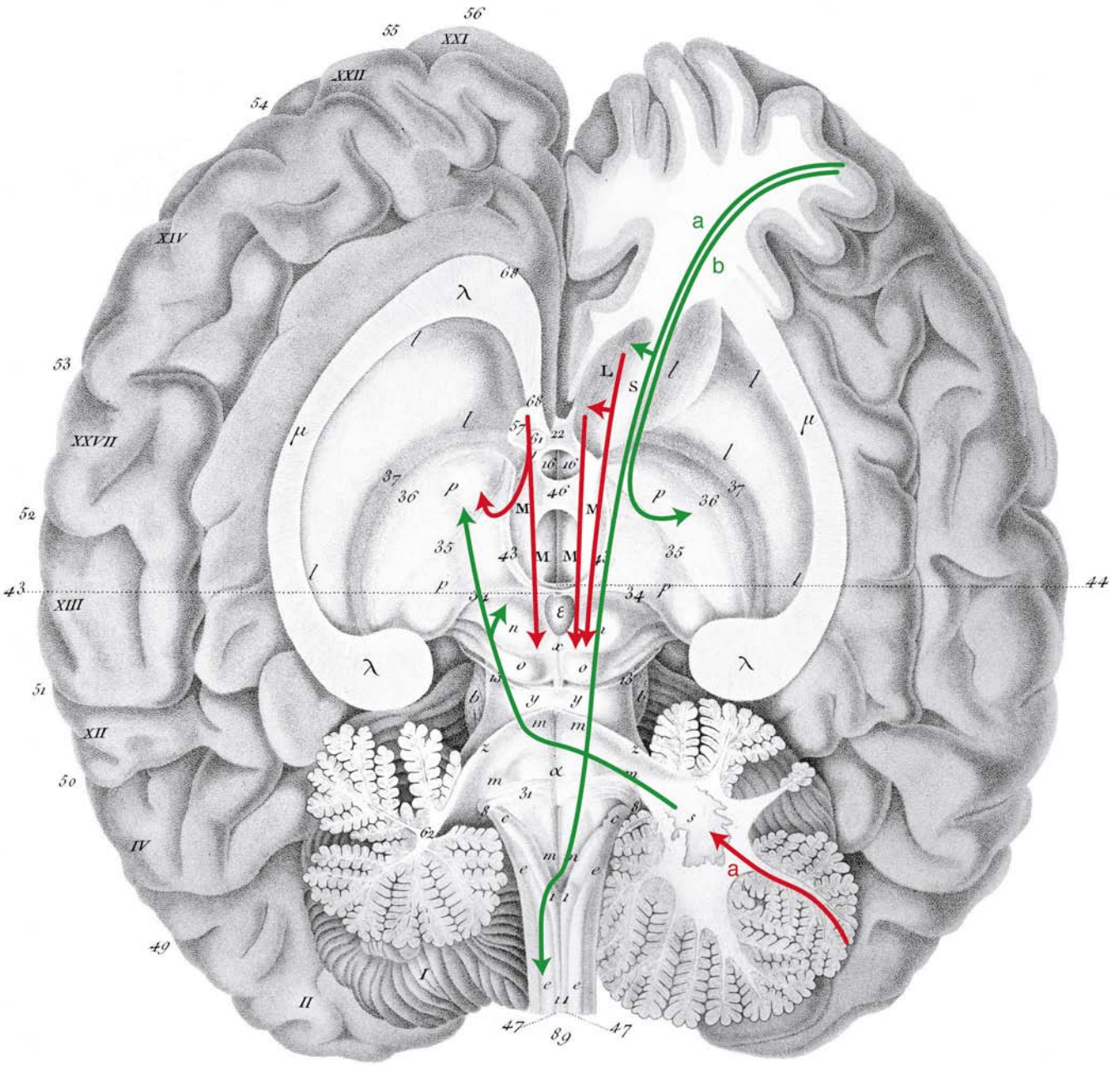


Fig. 35. The triple cascading projection from the cerebral hemispheres superimposed on a drawing of the human brain viewed from above. In this preparation, which is from Gall and Spurzheim [77], the corpus callosum and cerebellum have been bisected, the cerebral and cerebellar hemispheres have been pulled apart like opening a book to reveal the striatopallidum and brainstem, and the rostromedial pole of the frontal lobe has been sliced off to reveal the pattern of gray and white matter. For comparison, the projection (red *a*) from cerebellar cortical Purkinje cells to cerebellar nuclei (*s*) to thalamus (*p*) is also shown. Excitatory pathways are in green, inhibitory in red. The green *a* indicates the corticospinal tract, which arises from layer 5 pyramidal cells, and sends a collateral to the striatum (near *L*), whereas the green *b* indicates the corticothalamic projection, which arises mainly from layer 6 pyramidal cells. *S* indicates the internal capsule. Compare with Fig. 14 from the rat.

hope that principles emerging from comparative analyses have some qualitative validity.

8. The following references can be found in Figs. 24-26+28-30

[5]; [15]; [18]; [20]; [65]; [66]; [81]; [89]; [90]; [93]; [109]; [110]; [120]; [134]; [139]; [140]; [151]; [160]; [163]; [164]; [178]; [184]; [196]; [204]; [205]; [207]; [209]; [214]; [220]; [250]; [264]; [290]; [307]; [318]; [336]

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