The Accumbens: Beyond the Core–Shell Dichotomy

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This article highlights recent discoveries related to the accumbens and closely associated structures, with special reference to their importance in neuropsychiatry. The development of "striatal patches" in the accumbens is reviewed in a series of pictures. Neuronal ensembles are discussed as potentially important functional-anatomical units. Attention is also drawn to recent discoveries related to the neuronal circuits that the primate accumbens establishes with the mesencephalic dopamine system. On the basis of histological and neurochemical differences, the accumbens has been divided into core and shell compartments. In the context of this article, the shell, which is an especially diversified part of the accumbens, is the subject of special attention because of its close relation to the extended amygdala and distinctive response to antipsychotic and psychoactive drugs.

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The purpose of this article is to highlight some major advances of the past several years that have profoundly changed our view not only of the accumbens, but of the anatomical organization of the basal forebrain in general. Discoveries related to the accumbens have played a significant role in this changing perspective. Since most progress emerged from experiments in the rat, this will be the immediate focus of our discussion. Translation of these insights to the primate accumbens, however, is proceeding apace, as is briefly discussed later in the article.

1. GENERAL OVERVIEW

Ever since Matthysse and Stevens focused attention on the mesolimbic dopaminergic (DA) system and its relation to schizophrenia in the early 1970s,[1,2] the accumbens has been a central structure in theories exploring the anatomical substrates of schizophrenia. However, clinical interest in the accumbens is based on more than its possible role in schizophrenia and other affective

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disorders. As a prominent part of the ventral striatum, and as a main target of the mesotelencephalic dopamine system, the accumbens is a natural focus for theories of reward and motivation, including aspects of drug abuse.[3–8]

Particularly in the work of Mogenson et al.,[9] the accumbens was envisioned as the "limbic-motor interface." Although this catchy phrase is sometimes invoked to describe the functions of the accumbens, the phrase is somewhat unsettling in the sense that the term *limbic* is rather murky; it lacks an adequate operational definition. Mogenson and his co-workers referred to the motivational processes that result in action or movements. In the context of this article it may be more important to emphasize that, whatever meaning one assigns to the term *limbic* and whatever role the accumbens plays in linking motivation to action, the accumbens is likely to share this role with several other structures of the basal forebrain, including especially the "extended amygdala" (see section 6).

Although the physiological and behavioral studies of the last 20 years have served to establish the accumbens as a pivotal structure in motivation and reward mechanisms, the anatomical discoveries related to the accumbens have provided the structural framework for this progress. The term *nucleus accumbens septi* was introduced by Ziehen[10] 100 years ago (see also introductory article by Chronister and DeFrance[11]), and for many years the accumbens remained in this uncertain relationship with the septum. In the mid-1970s, however, it became evident that the accumbens is an integral part of the striatal complex.[12,13] This assertion is reinforced by its developmental pattern (see section 2) and by the extrinsic connections of accumbens, which are reminiscent of those in the rest of the striatum.[14,15]

Based in part on the cortical input that the rat accumbens receives from allocortical and periallocortical areas (hippocampal formation, entorhinal area, and olfactory cortex), as well as from medial (anterior cingulate, prelimbic, infralimbic) and lateral (sulcal, agranular insular, and perirhinal) proisocortical areas, it is now customary to include the accumbens, together with the ventromedial part of caudate-putamen and the olfactory tubercle, in a larger entity referred to as the *ventral striatum* (see reviews by Alheid et al.[14] for primate and Heimer et al.[15] for rat). The identification of the ventral striatopallidal system,[12] in which the accumbens and its projections to a ventral extension of the pallidum (referred to as *ventral pallidum*) occupy a prominent position, added an important channel to the striatopallidal circuitry; in short, it demonstrated that the whole cortical mantle, and not only the neocortex, is interlinked with the basal ganglia. This added several corticostriatopallidothalamic circuits to the well-known corticostriatopallidothalamic loop by which information from various neocortical regions reaches the motor regions in the frontal lobe via synaptic relays in basal ganglia and thalamus. The corticosubcortical reentrant circuits related to the ventral striatopallidal system relay allocortical and periallocortical afferents via primarily the mediodorsal thalamic nucleus to the prefrontal cortex. This circuitry is in contrast to the ventral anterior–ventral lateral thalamic complex, with its output to the premotor cortex, which characterizes the channels through the dorsal portions of the striatopallidal system.[16]

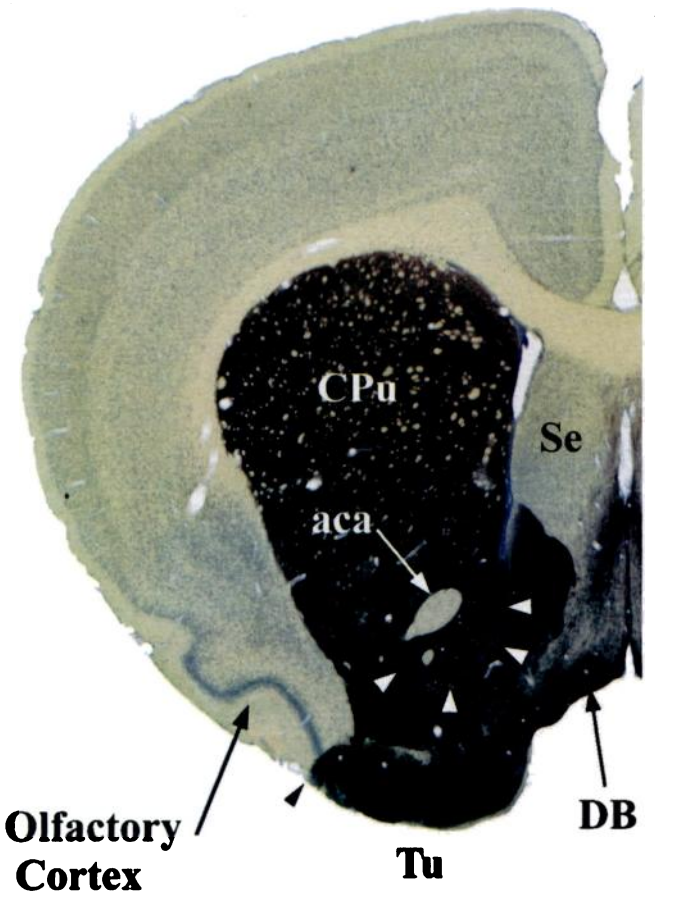
The identification of the corticosubcortical reentrant circuits that originate in various allocortical, periallocortical, and proisocortical areas and pass through the ventral striatopallidal system and the mediodorsal thalamus back to the prefrontal cortex has inspired several theoretical schemes attempting to explain various symptoms of neuropsychiatric disorders. Because these circuits have received considerable attention both in the preclinical and the clinical literature,[17–28] they will not be the focus of further discussion here. Suffice it to say that the nature of these circuits—that is, the extent to which they are "closed" (parallel and independent of each other) or "open" (interrelated with each other)—is still being debated (see reviews;[15,20,29,30] see also section 5).

Although the corticosubcortical reentrant circuits just mentioned are undoubtedly of great significance in the context of neuropsychiatric disorders, it should be emphasized that the basal ganglia, including the ventral striatopallidal system, establish several other interneuronal relations that are equally important. Among these are output channels via the internal pallidal segment and the reticular part of substantia nigra to various brainstem areas (reviewed[14,15,31]). Other axons interconnect the striatal complex with the mesencephalic dopamine neurons. Since the dopamine system occupies a central role in the etiology and pharmacotherapy of some of the most common brain disorders, including schizophrenia and Parkinson's disease, we will briefly outline in section 5 the neuronal circuits that the midbrain dopamine neurons establish with the striatal complex, including the accumbens. An important concept highlighted in that section, the modulation of the dorsal striatal complex by the ventral striatum via dopamine circuits, was first suggested on the basis of studies in the rat by Nauta et al.[32] As we shall see in section 5, this intriguing way of integrating information from ventral and dorsal parts of the basal ganglia via the ascending mesotelencephalic dopamine system is only one of several possible systems for integrating information from different sources within the basal ganglia.

Once the "striatal" nature of the accumbens was es-

tablished, its compartmental infrastructure became the focus of interest for a number of research groups, analogous with the intense interest in the compartmental organization of the dorsal striatum. Armed with a variety of immunohistochemical and in situ hybridization methods, receptor binding techniques, and increasingly more sensitive tract-tracing methods, workers gradually defined the compartmental or "patch-matrix" organization of the accumbens as similar, but not exactly parallel, to that elucidated for the dorsal striatum (the caudate-putamen).[28,33,34] In attempting to encompass the compartmental organization of ventral striatum in a structural theory of accumbens function, one hypothesis focuses on the existence of segregated clusters of neurons as neuronal ensembles that are characterized by different combinations of inputs and outputs that determine specific components of various behaviors.[35] The anatomical substrates for this theory will be discussed in section 3.

FIGURE 1. **Acetylcholinesterase-stained coronal section through the rat brain at the level of the olfactory tubercle. The section was counterstained with thionine. Note how the striatal complex (darkly stained with acetylcholinesterase) extends toward the ventral surface of the brain and includes not only the accumbens, but also large parts of the olfactory tubercle (Tu). The subdivision of the accumbens into a central core surrounded on its medial, ventral, and lateral sides by a shell is also evident. The border between the core and the shell is marked with *arrowheads*. The core extends into the dorsal part of the striatal complex (caudate-putamen; CPu), without sharp boundary. aca = anterior limb of the anterior commissure; DB = diagonal band; Se = Septum.**



The accumbens is directly continuous with the main dorsal part of the striatum, the caudate-putamen (Figure 1). It is generally agreed that the accumbens is an integral part of the striatal complex. It is obvious, however, that the accumbens has unique features compared with the rest of the striatal complex. For example, it can be divided into a central core that is surrounded on its medial, ventral, and lateral sides by a shell.[36] In most respects, the core cannot be easily distinguished from the rest of the caudate-putamen (Figure 1). The shell, on the other hand, has in addition to its striatal characteristics a number of features that are atypical for a striatal structure. Without directly dividing the accumbens into two different parts, some papers that appeared in the 1970s foreshadowed this important point (see, for example, Nauta et al.[32]). In addition to projections to ventral pallidum, the accumbens, especially its medial part, was characterized by projections to regions such as the bed nucleus of stria terminalis and lateral hypothalamus and to mesopontine targets caudal to the mesencephalic dopamine neurons.[33,37] It was later revealed that these projections, atypical for the striatum, originate primarily in the shell rather than in the core of the accumbens.[38]

Aside from having distinctive efferents, the core and the shell of the accumbens appear to receive distinctive cortical afferents from generally different cortical areas, suggesting functionally separate circuits.[21,22,28,39] In fact, the last few years have seen a rapidly increasing number of pharmacological and physiological studies in which the functional differences between the core and shell of the accumbens have been explored. These studies are especially relevant in the field of neuropsychiatry.

Ever since it was proposed, almost 20 years ago, that the accumbens plays an important role in reward mechanisms,[40] the function of dopamine and its interaction with neuronal elements in the accumbens have been central themes in drug abuse studies.[4,6,41,42] In the last few years it has been reported that many of the abused drugs (including cocaine, amphetamine, and morphine) preferentially stimulate the release of dopamine and increase the energy metabolism in the shell rather than the core.[43–45] Even nicotine seems to derive much of its addictive effect from interference with neuronal mechanisms in the shell of the accumbens.[46] Another drug that has received a lot of attention in recent years is methylenedioxymethamphetamine, bet-

ter known as "ecstacy." The physiological and pharmacological effects of "ecstasy" on the monoaminergic mechanisms in the brain, and in particular on the accumbens, have recently been reviewed in great detail.[47] As expected, there are significant differences between the core and the shell in their response to "ecstacy." The core–shell dichotomy also appears to be relevant in the context of antidepressant medication.[48]

Stress-induced activation of the dopamine systems in the brain[49,50] is another subject of considerable importance in neuropsychiatry. Several recent reports indicate that it is the neuronal circuits related to the shell rather than the core that are sensitive to stress[30,51–54] and that therefore may be related to symptoms of schizophrenia that are influenced by stress. In this context, it is especially interesting to realize that the shell rather than the core seems to be a primary target for antipsychotic drug action.[52,55,56] Because of the functional differences between the core and the shell and their apparent clinical relevance, we discuss in section 4 some of the many histochemical differences that exist between the core and the shell, including histochemical patterns altered by the administration of antipsychotic drugs.

Relevant to understanding the functional segmentation of the nucleus accumbens is the concept of the extended amygdala (see section 6). As originally proposed by Johnston[57] and elaborated in modern form by de Olmos, Alheid, and co-workers,[58–60] this structure stretches from the temporal lobe to the caudal portions of the accumbens. Portions of the ventral striatum, including part of the accumbens, are intimately related to the extended amygdala. In particular, we will explore the extent to which the accumbens, and especially parts of its shell, can be considered a transitional area between the striatal complex and extended amygdala. The identification of the core and shell of the accumbens and the continuing elaboration of the theory of the extended amygdala have significantly improved our understanding of basal forebrain anatomical organization. Because the core–shell dichotomy and the extended amygdala appear to be as relevant in the primate, including the human,[58,61–65] as they are in the rat, the continuing exploration of these structures is likely to be especially relevant to understanding the etiology and treatment of neuropsychiatric disorders.[58,66] As indicated above, many studies have focused attention on the shell of the accumbens as being of special relevance in drug abuse. The shell of the accumbens and the extended amygdala have many characteristics in common, so it is not surprising to learn that results obtained in recent experiments indicate that the extended amygdala is also an important structure in the context of drug abuse.[67–70]

2. SOME DEVELOPMENTAL ASPECTS

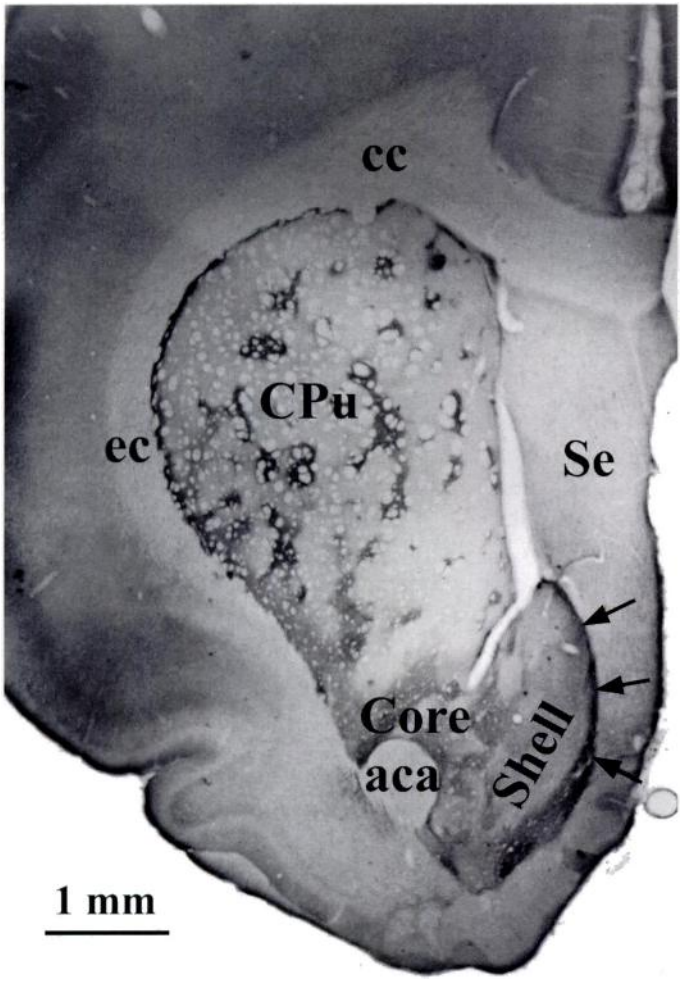
Developmental studies of specific brain structures can often yield insights into overall organizational features. For instance, early developmental and connectional studies[13] contributed to the recognition that the accumbens is more like the striatum than the septum. These studies, however, were performed prior to the recognition that the striatum is divided into "patch and matrix" compartments with different developmental histories and that the accumbens is divided into core and shell regions.

In the caudate, and to a lesser degree in the putamen, a striking feature of intrinsic organization is the presence of acetylcholinesterase-poor striosomes or opiate receptor–rich patches surrounded by a complementary stained "matrix."[71–73] These compartments appear to bear a regular relationship to the input-output structure of the dorsal striatum; for example, there are patches that target tegmental dopamine neurons. Studies examining the ontogeny of opiate receptor expression provide a means of tracking the development of striatal patches (striosomes) and help explain the adult configuration of these important structures.

The recent development of antibodies to the mu opiate receptor has facilitated immunohistochemical demonstration of the patch compartment (Figure 2) and helps to shed some light on the arrangement of these structures in the accumbens. Within the adult dorsal striatum, the patch compartment consists of two parts: elongated groups of neurons stained intensely but diffusely with mu receptor antibody, and a collection of similarly labeled neurons adjacent to the corpus callosum and external capsule, often termed the *subcallosal streak*. Within the ventral striatum, the core of the accumbens is partitioned into moderately stained and poorly stained regions, while much of the shell of the accumbens is diffusely immunoreactive. Along the most medial boundary of the shell is found a band of intense immunoreactivity somewhat reminiscent of the subcallosal streak in the dorsal striatum.

During development of the telencephalon, the lateral walls of the neural tube evaginate, forming mirror-image tubes straddling the diencephalon. Within each telencephalic tube, three broad regions of neuroepithelium, which surround a somewhat triangular-shaped lateral ventricle, can be delineated as precursors of large brain regions. The medial wall will give rise to the septum, hippocampus, and interconnecting fiber systems. The dorsal and dorsolateral walls will form the cerebral cortex, and the ventrolateral wall is thrown into two longitudinal ridges, the medial and lateral ganglionic eminences. It is generally agreed that the lateral

FIGURE 2. **Photomicrograph of a section through the rat striatum stained immunocytochemically with an antibody to the mu opiate receptor. Note the intensely stained patches and subcallosal streak in the caudate-putamen (CPu), the moderately stained areas in the core and portions of the shell of the nucleus accumbens, and the intensely stained band along the medial edge of the shell (*arrows*). aca = anterior limb of anterior commissure; cc = corpus callosum; ec = external capsule; Se = septum.**



ridge, also called the striatal ridge or eminence, will develop into the dorsal striatum, that is, the caudate-putamen (CPu), in the rat.[74]

However, the derivatives of the medial ganglionic eminence are still subject to debate. Recent atlases of neural development have designated the pallidum as a major derivative of the medial ganglionic eminence.[75,76] However, developmental studies of patterns of two major neuropeptide genes in the forebrain, preproenkephalin and preprotachykinin A, are consistent with the possibility that the medial ganglionic eminence gives rise to much of the extended amygdala,[77] as originally suggested by Johnston in 1923 (reviewed in Heimer et al.[66]).

These three broad regions of neuroepithelium differ in basic strategies of development. The rostral end of the medial wall undergoes an outside-to-inside pattern of migration; that is, the oldest septal neurons are found furthest from the ventricle, with younger neurons occupying positions progressively nearer the ventricle.[78] In the rat, the caudal end of the medial wall develops into the hippocampal formation through a complicated process of layering and infolding, and most neurons of the dentate gyrus are formed after birth.[79] Indeed, more recent studies have shown that, in the rat, dentate granule cells are continually born along the inner edge of the granule cell layer and migrate to the outer edge throughout life.[80] The dorsal and dorsolateral wall develop through an unusual inside-out process, whereby the oldest neurons occupy layers closest to the ventricle, forcing younger neurons to migrate through the older layer to reach more superficial layers of the cortex. As reviewed below, the lateral ridge of the ventrolateral wall (lateral ganglionic eminence) develops through a double migration, with early arising neurons first migrating to a position far away from the ventricle, then migrating back toward the ventricle. Migratory patterns of the derivatives of the medial ganglionic eminence are still being investigated.

On the basis of previous studies with ^{3}H thymidine that demonstrated that neurons of the patch compartment in general arise at an earlier time than the neurons of the matrix,[81] the origins of the patch and matrix compartments in striatum were reexamined by use of the thymidine analog bromodeoxyuridine (Brdu). This was injected into pregnant rats on either embryonic day 14 (E14) or E19 (the date of birth usually being E22). The earlier injection labels neurons in the patch compartment; matrix neurons are labeled by the later injection at E19. The E14-injected embryos were sacrificed either at 2 hours after injection or on E16, E19, or the day of birth (P0). E19-injected embryos were sacrificed either 2 hours after injection or on P0. Brains were removed, frozen, and processed for immunocytochemical localization of Brdu, as described previously.[82]

From these studies, our current model for the formation of the patch compartment in the dorsal striatum (Figure 3) has emerged. Specifically, the neurons that are the first to be formed migrate away from the neuroepithelium to occupy the developing field of the striatum. By E19, these neurons occupy much of the lateral and ventrolateral portion of the developing caudate-putamen. Neurons arising on E19 are restricted initially to the neuroepithelium but then begin to migrate ventrolaterally. By P0, these neurons have occu-

pied essentially the entire caudate-putamen. In so doing, they appear to surround and push the early-arising neurons back toward the lateral ventricle. The earlier-arising neurons clump together to form the distinct striosomes of the patch compartment. Presumably blocked by the boundary formed by the external capsule, the later-arising E19 neurons are unable to surround and displace early-arising neurons lying adjacent to this developing fiber tract. Thus, these early-arising neurons form the subcallosal streak. The early-arising neurons undergo two migrations, one away from the ventricle and a second, probably passive, migration back toward the ventricle. This results in an actual decrease in the distance between the ventricle and the

FIGURE 3. **Schematic model of the development of the patch-matrix organization of the rat dorsal striatum. Left-side sections at embryonic day 14 (E14), E19, and the day of birth (P0) are shown. *Filled circles* represent cells labeled by injection of bromodeoxyuridine at E14; *open circles* represent cells labeled by injection at E19. The *dashed lines* indicate the ventrolateral border of the neuroepithelium, as determined by counterstaining with basic fuchsin. Originating in the neuroepithelium adjacent to the lateral ventricle (LV), neurons initially migrate ventrolaterally into the developing field. Between E19 and P0, later-arising neurons invade the territory of the earlier-arising cells, surrounding and pushing them back in groups toward the ventricle; these groups become the patches, characterized in adults by several markers, including mu opiate receptors. Some early-originating neurons remain adjacent to the external capsule (ec) and corpus callosum (cc), presumably because the later-arising neurons are unable to surround them owing to the presence of these fiber tracts; these early-arising neurons form the subcallosal streak underneath the external capsule.**

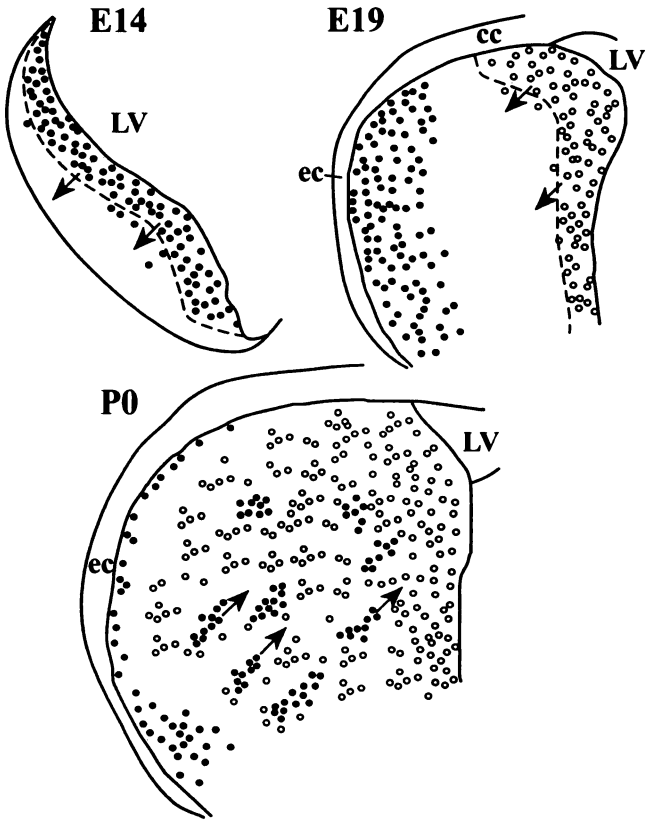
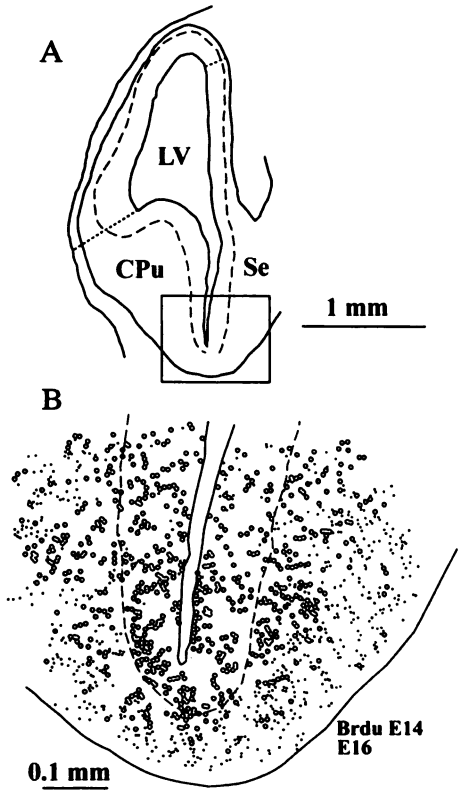


FIGURE 4. **Camera lucida drawings of a section through the left side of an E16 rat brain, following injection of bromodeoxyuridine (Brdu) at E14. The rectangle in the low-power view (A) indicates the region drawn in panel B. The *dotted lines* in A indicate the approximate boundaries that divide the telencephalic tube into three major regions: the medial wall, which will produce the septum, hippocampus, and related fiber systems; the dorsal and dorsal and dorsolateral wall, which will produce the neocortex; and the ventrolateral wall, which will develop into the striatum. Notice the deep ventricular groove between the developing striatum and septum; the wall of this groove will form the nucleus accumbens, with the lateral wall forming the core and the medial wall forming much of the shell. The *dashed lines* represent the borders of the neuroepithelium. In panel B, Brdu-labeled cells are plotted. *Solid dots* represent cells with intense, uniform labeling throughout the nucleus; *open circles* represent cells with intense spots of immunoreactivity in the nucleus. Note that E14-labeled cells fill all of the neuroepithelium and the developing field out to the external surface of the brain. CPu = caudate-putamen; LV = lateral ventricle; Se = septum.**



closest E14-labeled cells between days E19 and P0.[82]

As indicated above, the accumbens is also partitioned into mu receptor–rich and –poor areas, bounded medially by a mu receptor–rich stripe, perhaps analogous to the subcallosal streak. At E16, the lateral ventricle produces a deep crevice between the striatum and the septum (Figure 4A). The neuroepithelium on the lateral side of this slit is proposed to form the core of the accumbens, and the neuroepithelium on the medial and ventral sides likely produces much of the shell. At E16, neurons labeled at E14 fill all of the presumptive accumbens territory between the ventricle and the external surface of the brain (Figure 4B). By E19, the early-arising neurons have migrated out of the neuroepithelium but

FIGURE 5. Camera lucida drawings of sections through the left side of E19 rat brains following injection of bromodeoxyuridine (Brdu) at either E19 (B) or E14 (C). The low-power drawing (A) is from the same section shown in panel C; the rectangle in A shows the area plotted in C. Symbols for labeled cells are as in Figure 3. Note that the E19-labeled cells are restricted to the neuroepithelium and the E14-labeled cells occupy the adjacent developing field. aca = anterior limb of the anterior commissure; CPu = caudate-putamen; LV = lateral ventricle; Se = septum.

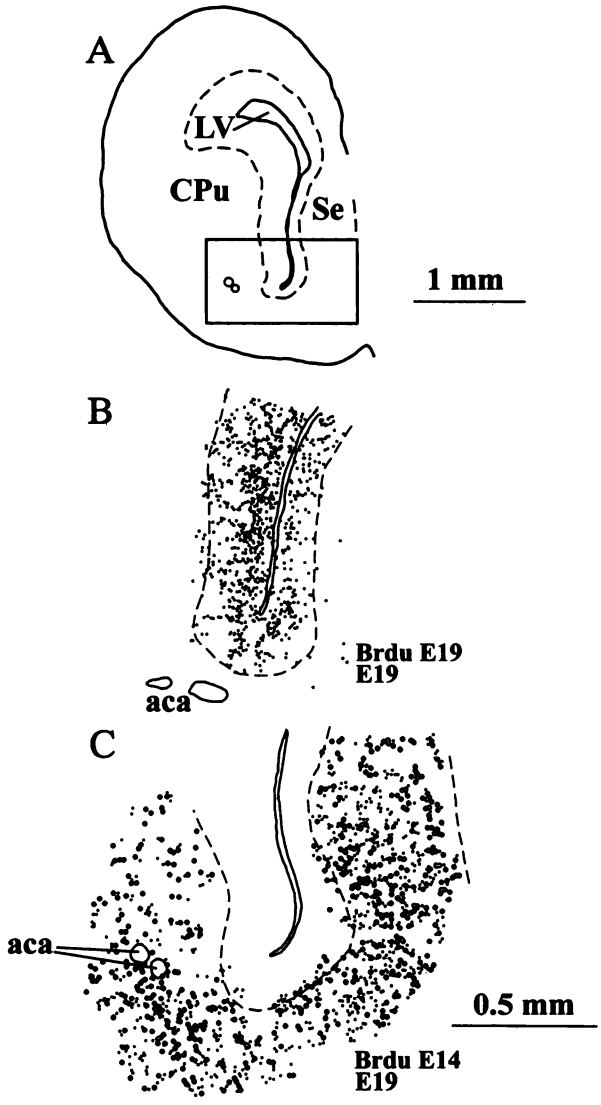
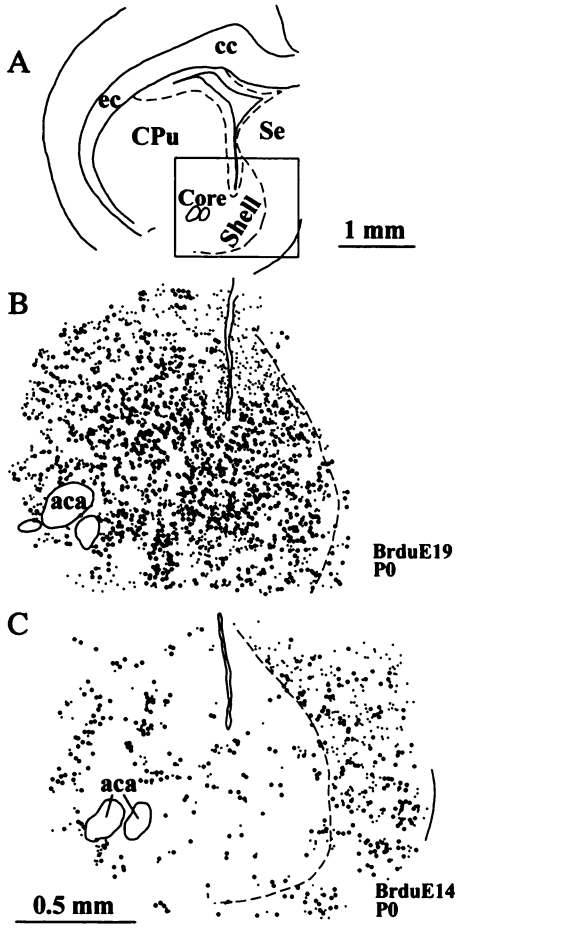


FIGURE 6. Camera lucida drawings of sections through the left side of P0 rat brains, following injection of bromodeoxyuridine (Brdu) at either E19 (B) or E14 (C). The low-power drawing (A) is from the same section shown in panel C; the rectangle represents the area plotted in C. Symbols for labeled cells are as in Figure 3. Note that the E19-labeled cells occupy the entire core of the accumbens but are rarely found in the septum (Se) or diagonal band of Broca. Far fewer E14-labeled cells are found in the accumbens. Within the core, note the groups of labeled cells, which may be similar to the groups of early developing neurons that form the patches in the caudate-putamen. Within the shell, labeled cells tend to be more isolated, although some accumulation along the medial boundary of the shell is evident. The solid line along the medial edge of the drawing in C represents the midline. aca = anterior limb of the anterior commissure; cc = corpus callosum; CPu = caudate-putamen; ec = external capsule.



continue to occupy the entire region of the presumptive accumbens developing field (Figure 5C). The neuroepithelium at this age is filled with newly labeled cells (Figure 5B). Thus, neurons originating at E14 and at E19 occupy exclusive but adjoining fields in the E19 accumbens rather than being separated by a substantial gap such as that found in the caudate-putamen at this age (Figure 3). By P0, the later-arising neurons have migrated out of the neuroepithelium to occupy most of the developing accumbens (Figure 6B). Within the core of the accumbens are groups of early-arising neurons, reminiscent of the patches of the caudate-putamen (Figure 6C); fewer such groups are found in the shell of the accumbens. Along the medial edge of the shell is a discontinuous band of early-arising neurons, although it is not as distinct as the subcallosal streak.

These results suggest that similar developmental processes occur in the dorsal and ventral striatum, at least in the accumbens. In both regions, neurons originate in the neuroepithelium and migrate away from the ventricle into the developing field. In the caudate-putamen and, to some extent, in the core of the accumbens, later-developing neurons surround and push earlier-arising neurons in groups back toward the ventricle. Early-developing neurons form lateral (subcallosal streak) and, to some extent, medial boundaries of the striatum (medial edge of the accumbens shell). The lateral boundary, however, is delimited by the external capsule, whereas the medial boundary appears to be formed primarily by early-arising septal neurons, which may exert repulsive forces on the migration of the later-developing accumbens cells.

3. ENSEMBLES OF NEURONS IN THE ACCUMBENS: DIFFERENT COMBINATIONS OF INPUT AND A VARIETY OF TARGETS

Most, if not all, of the afferent fibers to the accumbens show heterogeneous patterns of distribution, and the accumbens' projection neurons that reach particular targets are also heterogeneously distributed. These inhomogeneous patterns can, to a large degree, be related to the distinction between the accumbens shell and core regions, as well as to patch-matrix patterns in the core of the accumbens. Furthermore, the nucleus accumbens is an integral part of a larger unit, the ventral striatum, and so there are few, if any, afferent projections that are restricted to the accumbens; most of the terminal fields are continuous dorsally into the ventral and medial parts of the caudate-putamen complex or ventrally into the striatal elements of the olfactory tubercle. In a caudal direction, terminal fields of several afferent systems are continuous into various parts of the extended amygdala, including the bed nucleus of the stria terminalis, the subpallidal portions of the extended amygdala, and the interstitial nucleus of the posterior limb of the anterior commissure (see section 6). Likewise, populations of projection neurons in the accumbens in most instances blend into neighboring regions of ventral striatum and/or extended amygdala.

Functional Aspects of Accumbens Neurons

Medium-sized spiny neurons form the major class of neurons (around 95% in the rat and 70% in the primate) of the striatum, and, as in the dorsal striatum, these cells constitute the output neurons of the accumbens. The remaining accumbens neurons are larger and aspiny or sparsely spined interneurons. They include the cholinergic interneurons and a variety of peptidergic interneurons,[83] as well as a less well studied complex of smaller neurons that generally occur more frequently medially, ventrally, and along the margins of the striatum.[14,84–86]

The medium-sized projection cells are among the most densely spined neurons in the brain, which suggests that a major function of these cells is the integration of information from different sources. Physiologically, medium-sized spiny neurons tend to be "silent," and it has been shown that a large proportion of these cells, like their counterparts in the dorsal striatum,[87] exhibit two distinct states in their resting membrane potential: an "up state" with a resting membrane potential of approximately –55 mV, close to the threshold for generating action potentials, and a hyperpolarized "down state" with a resting membrane potential of –85 to –90 mV.[35,88]

When these neurons are in their up state, they may generate bursts of spikes. Neurons that are in the hyperpolarized down state must first be brought into the up state, as for example by the activity of one of the excitatory inputs of the accumbens, before firing of these neurons can be elicited, as for example by a second excitatory input. Lesions of the cerebral cortex may cause medium-sized striatal neurons to be in a permanent down state,[87] whereas lesions of the fornix-fimbria, which interfere with input from the hippocampus formation, may have similar effects on accumbens neurons.[88] When the latter effects occur, excitation of prefrontal afferents of the accumbens does not lead to firing of accumbens output neurons, as is normally the case. This has led O'Donnell and Grace[88] to suggest that the hippocampal afferents "gate" the prefrontal throughput in the accumbens.

Similar gating mechanisms have recently been suggested for the amygdala and prefrontal afferents at the level of the accumbens.[89] Interactions between hippo-

campal and amygdaloid inputs of the accumbens, with respect to both short-term (paired pulse facilitation) and long-term (long-term potentiation and long-term depression) plastic processes, have also been described.[90]

Specific Relationships of the Thalamic and Amygdaloid Afferents With the Prefrontal Cortex–Ventral Striatal System

Considering these interactions, it may be assumed that the activity in a combination of distinct afferent sources will to some degree determine the output of the accumbens. As indicated earlier, excitatory inputs to the rat accumbens originate in allocortical, periallocortical, and proisocortical areas, as well as in the midline thalamic nuclei and basal amygdaloid complex.[91] In the present context, the organization of the midline thalamic, basal amygdaloid, and hippocampal inputs will be described in some detail. For all three sources of input to the accumbens, it has been shown that they also project, in a topographical fashion, to proisocortical prefrontal areas.[92–96] Furthermore, the midline thalamic and the basal amygdaloid projections have been clearly shown to be organized so that specific parts of these nuclei project to both an area in the prefrontal cortex and a region in the ventral striatum (including the accumbens) that are, in turn, connected by way of prefrontal corticostriatal projections (Figure 7A and B).[21,95,96] Through such an arrangement, a particular region of the ventral striatum may be reached by excitatory inputs from either of two sources (see Figure 7B): a specific midline thalamic nucleus, such as the paraventricular nucleus, or a specific part of the basal amygdaloid complex, such as the caudal parvicellular basal nucleus. These inputs can occur

FIGURE 7. Schematic representation, in two sagittal views of the rat brain, of the relationships of the ventral striatum. In A, the relationships of the intermediodorsal thalamic nucleus (IMD) with the lateral prefrontal cortex (agranular insular area; AI) and the lateral part of the nucleus accumbens (Acb lat) are shown. These parts of the prefrontal cortex and the nucleus accumbens are connected to each other by way of corticostriatal projections. The IMD projects also to the rostral part of the basal amygdaloid complex, in particular to the rostral magnocellular basal nucleus (Bmg), which in turn projects to the lateral parts of the prefrontal cortex and the nucleus accumbens. In B, similar arrangements are depicted for the paraventricular thalamic nucleus (PV), the medial part of the prefrontal cortex, the medial part of the nucleus accumbens (Acb med), and the caudal parvicellular basal amygdaloid nucleus (Bpc). CPu = caudate-putamen complex, dorsal striatum; MD = mediodorsal thalamic nucleus; PL/IL = prelimbic/intralimbic; SNr = substantia nigra pars reticulata; VP = ventral pallidum.

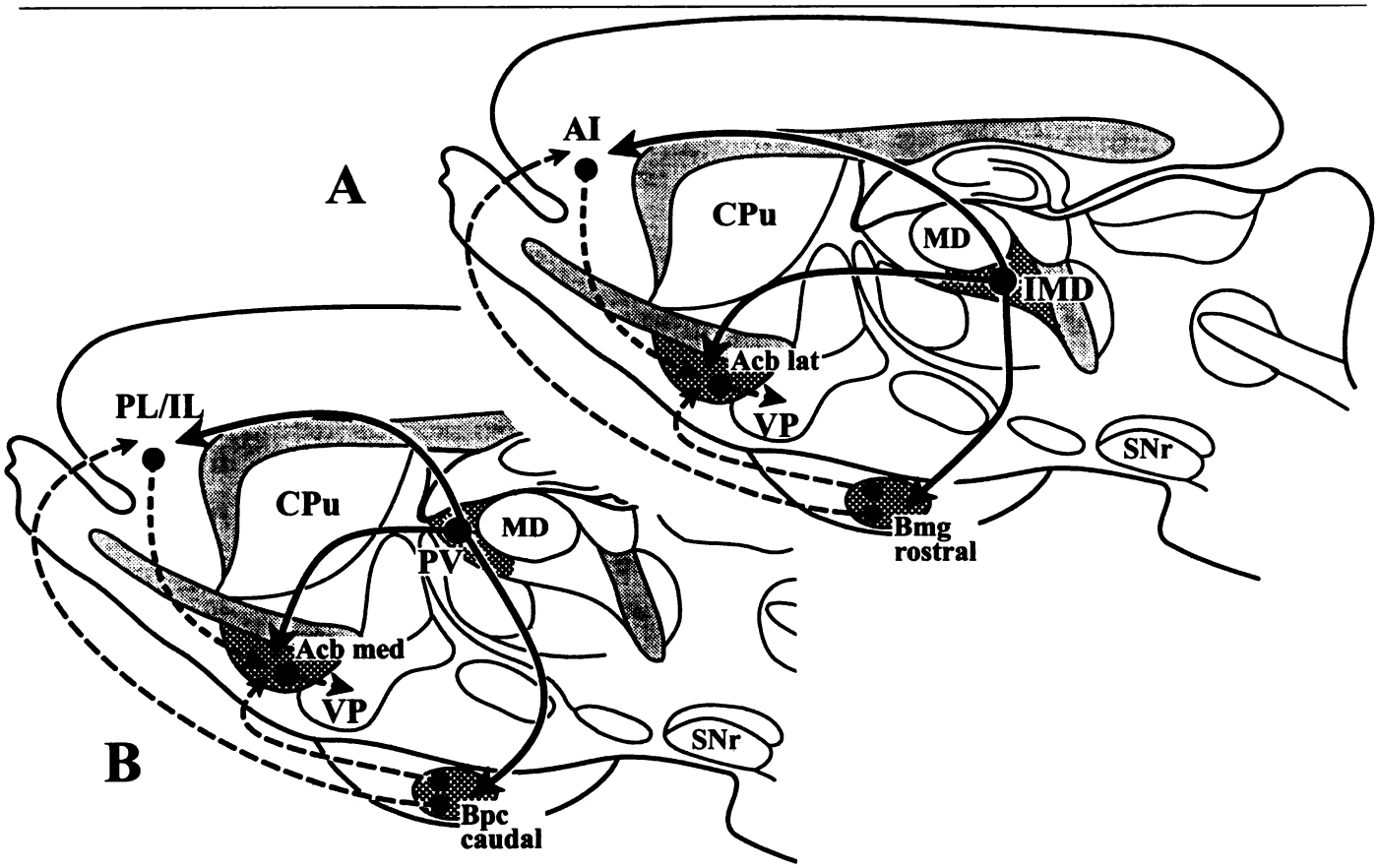
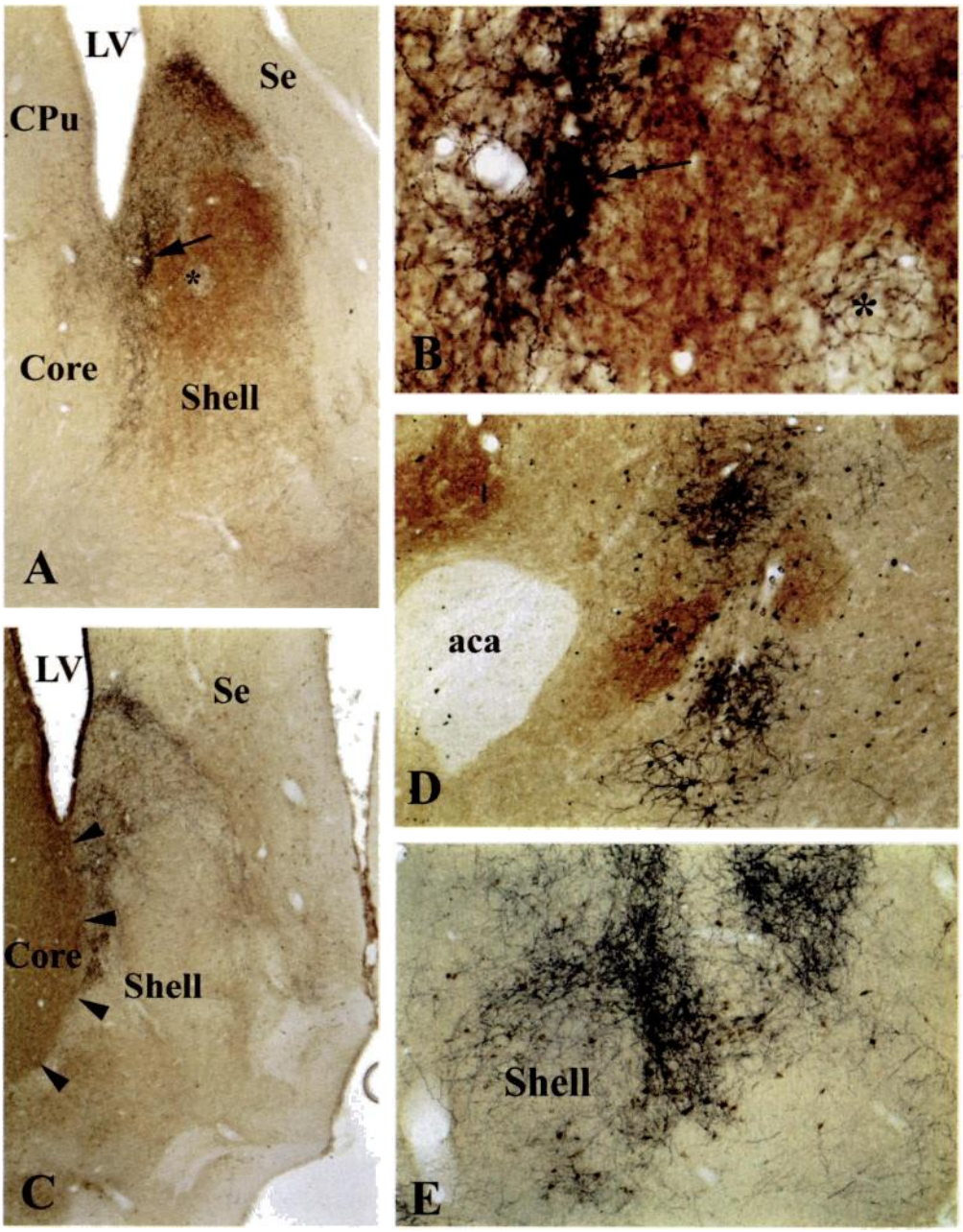


FIGURE 8. Color photomicrographs of double-immunostained sections, showing the relationships of afferent fiber systems with each other or with the output neurons of the accumbens. A: Transverse section through the caudal accumbens showing fibers from the caudal basal amygdaloid complex *(black)* with those from the midline paraventricular thalamic nucleus *(brown)*. In B, a higher magnification of part of this section is shown; *asterisk* and *arrow* indicate similar positions in A and B. Note that in the dorsomedial part of the accumbens, close to the septum (Se), fibers from the amygdala and the thalamus overlap, whereas more ventrally there exists an almost complete segregation between the two fiber systems, most clearly illustrated in B. Areas avoided by the brown thalamic fibers are specifically innervated by the black amygdaloid afferents *(asterisk and arrow)*. C: Photomicrograph shows the relationship of the afferents from the caudal basal amygdaloid complex *(black fibers)* with the distribution of immunoreactivity for the calcium-binding protein calbindin D_{28K}, which marks the shell/core division of the accumbens *(arrowheads)*. D: Transverse section through the rostral part of the accumbens, double-stained for enkephalin immunoreactivity (to show the accumbens compartments) and neurons retrogradely labeled from a small injection of a retrograde tracer in the ventral pallidum. Note the clustering of retrogradely labeled neurons (in this case outside the enkephalin-positive patches *[asterisk]*). E: Transverse section from the ventromedial accumbens, double-stained for anterogradely labeled fibers from the basal amygdaloid complex *(black)* and neurons retrogradely labeled from an injection in the mesopontine tegmentum. Note the close association of the labeled fibers and the clusters of projection neurons. aca = anterior limb of the anterior commissure; CPu = caudate-putamen; LV = lateral ventricle.



both directly and indirectly through thalamocortical or amygdalocortical and subsequent prefrontal corticostriatal projections, as for instance from the ventral prelimbic and infralimbic areas (see Figure 7B). The midline paraventricular thalamic nucleus, in addition, projects to the caudal basal amygdaloid complex, which provides this nucleus yet another indirect route to reach the same region in the ventral striatum (Figure 7B).

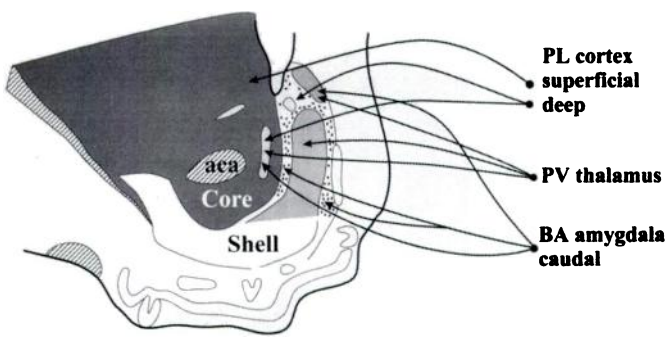
These arrangements of connections between the midline thalamus, the basal amygdaloid complex, and the prefrontal cortex–ventral striatal system indicate that these structures are interconnected in a distributed way.[25] Activity in the midline thalamic and basal amygdaloid nuclei may in this way have a profound influence on the activity of the prefrontal cortex–ventral striatal system. Determining whether the hippocampus is involved in a similar way in this distributed network will require further detailed study.

Convergence and Segregation of Afferents of the Accumbens

The previous subsection describes some of the general "rules" in the connections between different structures that project to the accumbens; the precise patterns of overlap and segregation of these afferents appear to be rather complicated. In general, the projections to the nucleus accumbens from the cerebral cortex, the hippocampal formation, the basal amygdaloid complex, and the midline thalamus are topographically organized.[39,97–100] For example, the ventral subiculum of the hippocampal formation projects to the medial part of the accumbens, most dominantly in the caudomedial shell, whereas progressively more dorsal parts of the subiculum project to successively more lateral and rostral parts of the accumbens.[99] Likewise, the projections from the basal amygdaloid complex show a mediolateral topography: the caudal part of the parvicellular basal nucleus projects to the caudomedial accumbens (Figure 8C), whereas, at the other extreme, the rostral part of the magnocellular basal nucleus projects primarily laterally. The hippocampal projections are more restricted (largely to the shell and to the medial and rostrolateral parts of the core[99,101]) than those of the basal amygdaloid complex, which involve the shell, the entire core, and extensive parts of the caudate-putamen complex.[100,102] Therefore, only in a rather restricted part of the accumbens—predominantly in the medial and rostral shell and in the medial core—may interactions between hippocampal and amygdaloid inputs take place. Furthermore, in view of the topography in both afferent systems, only specific subsystems of these afferents may converge; for example, the ventral subiculum and the caudal part of the basal amygdaloid complex may converge in the caudomedial accumbens, whereas the dorsal subiculum and the rostral basal amygdaloid complex both target the rostrolateral part of the accumbens. Even within these regions of the accumbens, which receive terminations from both the hippocampus and the amygdala, the terminal fields do not necessarily completely overlap, such that areas with particular cytoarchitectural or immunohistochemical characteristics may receive inputs either from the hippocampus or from the amygdala, but not from both.[103]

Similar patterns of overlap and segregation have been found for other sets of afferents of the accumbens. For example, in the caudomedial part of the shell, the afferents from the ventral prelimbic area and the caudal basal amygdaloid nucleus overlap extensively, but the terminal fields of these two afferents are largely segregated from the projection area occupied by the fibers from the paraventricular thalamic nucleus (Figure 8A and B). However, all three afferents converge in the patches of the medial part of the core (Figure 9).[104] In part, the specific areas of convergence and segregation can be recognized in the cytoarchitecture or chemoarchitecture of the accumbens, for example in cell-dense regions (within which appear clear cell clusters) or cell-poor regions in the shell.[104]

FIGURE 9. Convergence and segregation of accumbens afferents. Schematic representation of the relationships of three fiber systems of the medial part of the accumbens: the prelimbic area (PL) of the prefrontal cortex, the midline paraventricular thalamic nucleus (PV), and the caudal part of the basal amygdaloid complex (BA). *Black dots* mark a cell cluster zone as seen in Nissl-stained sections; *gray shades* indicate the immunoreactivity patterns of the calcium-binding protein calbindin D_{28K} in the shell and core. Prelimbic cortical and caudal basal amygdaloid fibers project to the cell cluster zone. Paraventricular thalamic fibers project to the moderately cellular zone and show a light, homogeneous calbindin immunoreactivity. All three afferent systems converge in the patches of the core, which are characterized by light calbindin staining. Note that the deep and superficial layers of the prelimbic area project to different areas in the accumbens. aca = anterior limb of the anterior commissure. Modified from Wright and Groenewegen.[104]



Neuronal Ensembles in the Accumbens: Projections to a Multitude of Targets

The above data on the topographical organization of different afferent fiber systems suggest that within the accumbens a patchwork of heterogeneously distributed inputs from various sources exists. The results of injections with retrograde tracers in target areas of the accumbens have shown that the output neurons are inhomogeneously distributed and, to a certain degree, organized in clusters (Figure 8D and E).

An important question is to what extent these clusters of output neurons receive specific sets of inputs; that is, to what extent are there specific input/output channels through the accumbens? Preliminary results from experiments in which injections of anterograde tracers in one of the input structures of the accumbens were combined with injections of retrograde tracers in one of its targets indicate that, indeed, clusters of output neurons may receive rather specific sets of inputs (Figure 8E).[103] These anatomical results support the idea that the accumbens consists of a collection of neuronal ensembles that may be differentially recruited under different functional or behavioral circumstances.[35]

The output from the neuronal ensembles in the accumbens has the potential to directly engage a number of functional-anatomical circuits. Via output to the ventral pallidum, which in turn projects to the mediodorsal thalamus, the accumbal ensembles have direct access to the thalamo-prefrontal circuitry.[21,28] Projections from, especially, the shell of the accumbens to the central division of the extended amygdala and the lateral hypothalamus[31,38,105] provide access to a multitude of autonomic and somatomotor targets, which are part of the anatomical substrate for goal-directed behaviors. Projections from the accumbens to the basal forebrain corticopetal cholinergic projection neurons[106,107] may provide a means for accumbens to affect cortical arousal, attention, and cognitive functions.[58,108] As discussed in more detail in section 5, the accumbens also projects to the dopaminergic neurons in the ventral tegmental area and the pars compacta of the substantia nigra, and it may also have input to the pars reticulata, either directly or indirectly via a relay in the ventral pallidum.[109–112]

This short review of the accumbens' most prominent output channels gives an idea of the many functions and behavioral acts that are likely to be controlled or activated by the neuronal ensembles in the accumbens. To what extent such neuronal ensembles indeed exist as distinct anatomical and functional units remains to be seen. How and under what circumstances are these neuronal ensembles activated, and can they influence each other?

More detailed anatomical studies of the type described in this section would facilitate the solution to these questions, and such investigations must also be carried to the ultrastructural level in order to investigate potential convergence of various afferents on single projection neurons in the accumbens.[113–115] In fact, the elucidation of the microanatomy of the accumbens and of the rest of striatum is an essential component in efforts to understand how information is being processed in the basal ganglia.[116,117]

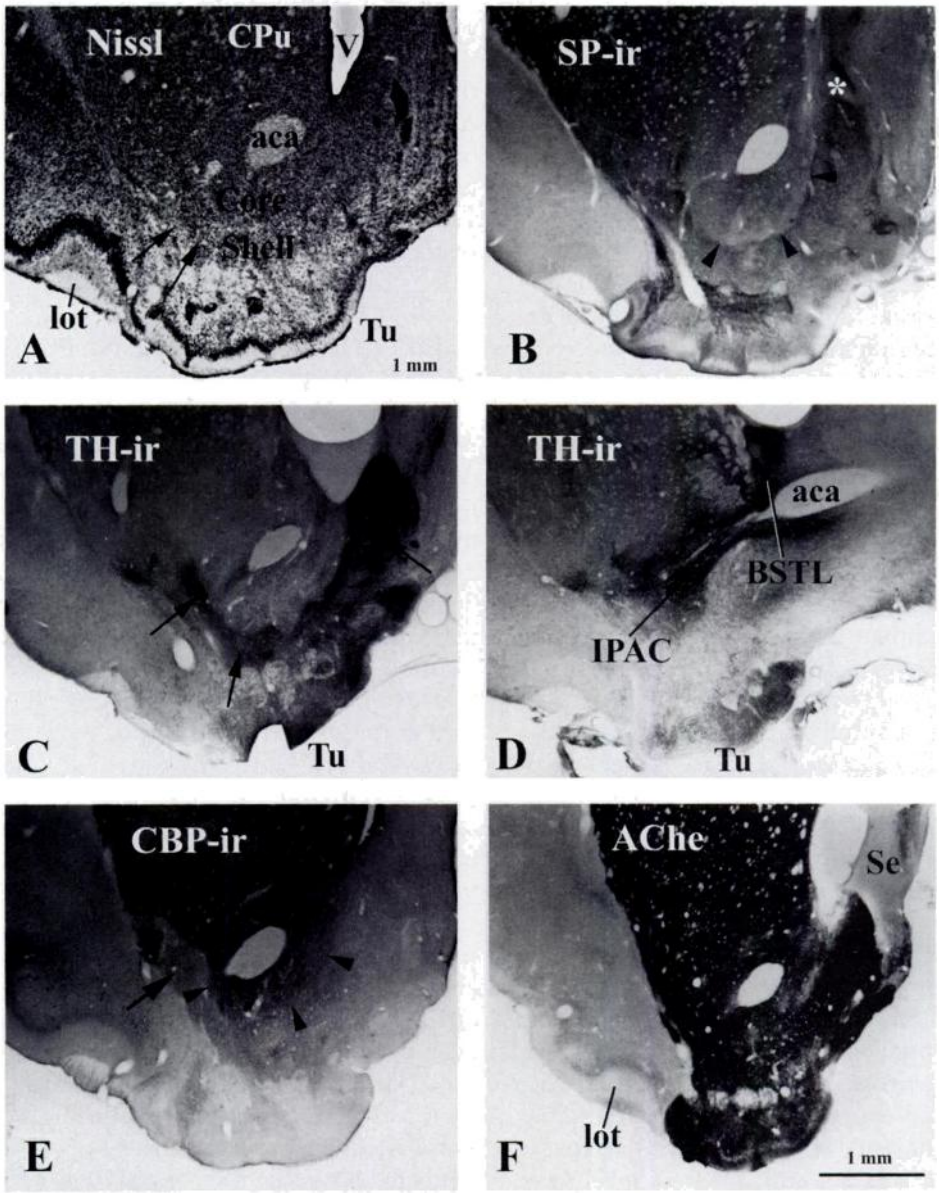
On the functional level, a multidisciplinary approach is needed, as indicated by Pennartz et al.,[35] in which pharmacological, electrophysiological, and behavioral experiments are used in different combinations and under different conditions (for example, in live, freely moving animals, or in brain slices). When determining the actual placement for electrodes or pipettes used in these experiments, it is no longer enough to refer to rostral versus caudal, or lateral versus medial accumbens; the placement of the electrode or pipette tip will have to be described in relation to the various subdivisions of the accumbens as revealed in histological or histochemical stains.

4. THE CHAMELEON-LIKE NATURE OF THE SHELL OF THE ACCUMBENS

A conventional Nissl-stained preparation (Figure 10A) demonstrates that it is difficult to distinguish boundaries between any of the striatal components. As a chameleon blends into its background, the accumbens appears to blend into the rest of the striatum. Careful inspection, however, reveals some subterritorial patterns of organization even in Nissl-stained material. For example, the lateral part of the shell is characterized by lower cell density (arrows in Figure 10A) than the adjacent core. On the other hand, by examining preparations stained with substance P immunoreactivity (Figure 10B), one can make the point that the shell is a rather uniform structure having rather well-defined boundaries, except perhaps towards parts of the olfactory tubercle and the extended amygdala (see section 6).

Although the histochemical differences between the core and the shell, and within the shell itself, will be emphasized in this section, it is also important to point out that in some histochemical stains it is difficult or even impossible to detect a difference between core and shell. Although the case is somewhat exceptional, this is for instance true in regard to binding sites for amylin.[118] The histochemical stain for this peptide, incidentally, tends to show that the central division of the extended amygdala, or at least its IPAC component, is closely

FIGURE 10. Coronal sections through the rat brain that illustrate organizational features of the accumbens at a level where both core and shell are present. A: Nissl-stained preparation. Note that striatal structures, including the accumbens core and shell, caudate-putamen (CPu), and olfactory tubercle (Tu), exhibit similar cell densities and are not clearly delimited from each other. Careful observation distinguishes subterritories: a particularly conspicuous boundary is evident between the core and lateral shell, which has a noticeably lesser cell density *(arrows)*. B: Substance P immunoreactivity (SP-ir). The shell exhibits moderately dense immunoperoxidase product that extends uniformly from its most dorsomedial to the most lateral parts. Whereas a sharp boundary exists between the core and shell *(arrowheads)*, it is difficult to identify a boundary between the core and the dorsally adjoining caudate-putamen. Note that a module lacking SP-ir is present dorsomedially *(asterisk)*. C: Tyrosine hydroxylase immunoreactivity (TH-ir) 2 days following injection of 6-hydroxydopamine into the ventral mesencephalon. Note that immunoreactivity is preserved in the shell *(arrows)* and the medial part of the olfactory tubercle (Tu). D: Following the same lesion, the TH-ir innervation is preserved also in the lateral bed nucleus of stria terminalis and in the interstitial nucleus of the posterior limb of the anterior commissure (BSTL and IPAC) as well as in the central nucleus of the amygdala (not shown), in contrast to adjacent parts of the caudate-putamen. E: Calbindin D_{28K} immunoreactivity (CBP-ir). Staining is robust in the core, whereas the shell is characterized by relatively weak CBP-ir. The boundary between core and shell is indicated by *arrowheads*. CBP-ir intensity can be seen to be greater in the lateral *(arrow)* than in the medial part of the shell. F: Acetylcholinesterase (ACh) reaction, which demonstrates that the shell has a stronger reaction than the core. The staining is very strong in the dorsomedial and lateral parts of the shell, which have between them an intermediate sector with a reaction of moderate intensity. aca = anterior limb of the anterior commissure; lot = lateral olfactory tract; Se = septum; V = ventricle. The scale bar shown in A applies also to B–E.



related to the accumbens. (IPAC abbreviates "interstitial nucleus of the posterior limb of the anterior commissure"; see section 6.)

That certain neurochemical consistencies exist throughout the shell, distinguishing it from most surrounding structures, is also shown in a preparation where the monoamine-selective neurotoxin 6-hydroxydopamine (6-OHDA) was injected into the ventral tegmental area and revealed a differential vulnerability of the tyrosine hydroxylase immunoreactive (dopaminergic) innervation in the core and shell, in the sense that the shell is more resistant than the core and the adjoining caudate-putamen[119] (Figure 10C). The same is true as well for the medial part of the olfactory tubercle (Figure 10C and D) and parts of the extended amygdala, including especially the lateral bed nucleus of stria terminalis and the interstitial nucleus of the posterior limb of the anterior commissure (BSTL and IPAC in Figure 10D), as well as the central amygdaloid nucleus (not shown). In other words, the caudomedial part of the shell blends into some other part of the basal forebrain without forming a clear border. The extended amygdala (including the IPAC) and its relation to the accumbens are discussed in section 6.

A similarly transient retention of shell dopamine innervation is observed following 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administration,[120] ventral mesencephalic ibotenic acid injections,[119] and methamphetamine administration.[121] In the accumbens core and caudate-putamen, dopamine innervation is rapidly eliminated by the toxin, thus indicating a fundamental difference between the dopamine innervation in the shell of the accumbens and that of the core and caudate-putamen. Following ventral mesencephalic 6-OHDA lesions, the differential resistance of the dopamine innervation is not the same throughout the entire shell: the loss of fibers in the lateral part of the shell is more pronounced than in the medial part (Figure 10C). This suggests that the fundamental difference between the dopamine innervation in the shell and core may also to some extent characterize the dopamine innervations of the medial and lateral parts of the shell. It is noteworthy that the dopamine innervation of core and caudate-putamen in the vicinity of the lateral shell is rapidly lost following 6-OHDA administration.

As indicated above, few histochemical preparations actually reveal uniform neurochemical features throughout the shell.[122–124] Rather, most neurochemical markers of the shell tend in varying degrees to distinguish medial, lateral, and, occasionally, intermediate parts of the shell. Calbindin immunoreactivity, for example, is very light in the dorsomedial shell, but in more ventral and lateral parts of the shell that happen to be adjacent to other structures that stain very strongly for calbindin, namely the accumbens core and lateral parts of the caudate-putamen, the shell calbindin immunoreactivity also is somewhat stronger (Figure 10E). Thus, one observes neurochemical gradients in the shell, indicating heterogeneity among the different parts of the shell.

This point is nicely shown with acetylcholinesterase histochemistry, particularly if the reaction has been carried out with a light touch (Figure 10F). In a section that was incubated for a short time in substrate, acetylcholinesterase staining is exceedingly strong in the dorsomedial and lateral parts of the shell but much less prominent in the intermediate shell. In other words, acetylcholinesterase staining serves to identify the dorsomedial part of the shell as an area that is likely quite different from the remainder of the shell. In this regard, it is interesting to note that the caudomedial part of the shell is also the part that has many features in common with the extended amygdala. However, except in the IPAC component of the extended amygdala, which is directly continuous with the shell, the two structures do not share strong acetylcholinesterase reactivity (see section 6).

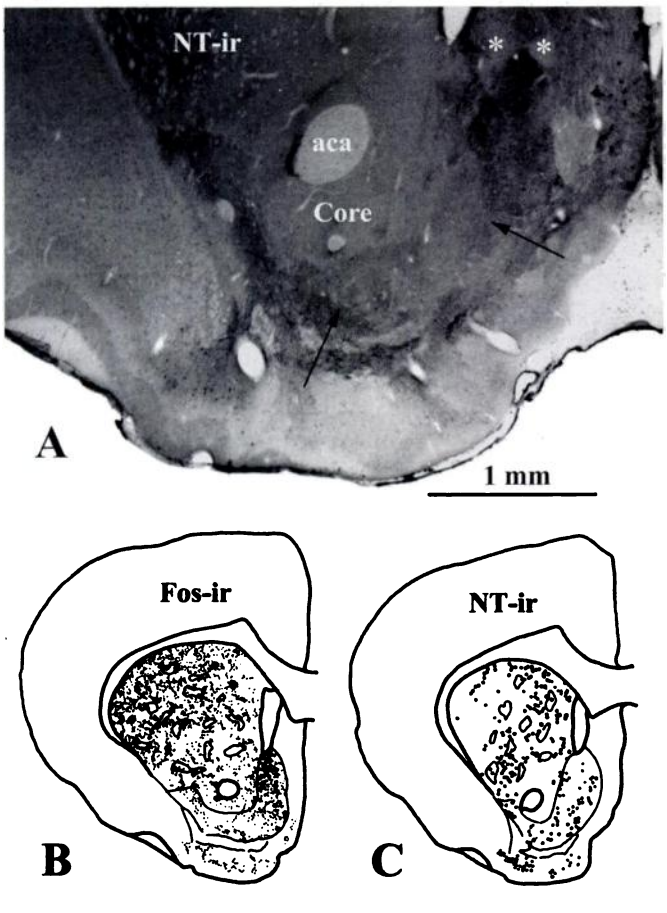
Response of the Shell to Antipsychotic and Psychoactive Drugs

The contrast between neurotensin negative and positive patches in the dorsomedial shell is enhanced by treatments with a variety of drugs, including antipsychotics. Figure 11A shows neurotensin immunoreactivity in the accumbens after administration of the antipsychotic drug haloperidol, which gives a clear image of the entire shell. In this kind of preparation, a dorsomedial part of the shell is observed in which the organization is conspicuously modular. Because the microenvironments seem to be so mutable under these circumstances, the studies by Groenewegen and his colleagues, which were discussed in the previous section, become especially relevant. The neurochemical environments of these specialized districts are to some extent distinct, while the boundaries between them are likely quite vague. Nevertheless, one can easily generate hypotheses regarding ways by which the different neurochemical environments in the subterritories might affect the functions of neurons. For example, the propensity of neurons to shift into the "up state" from the hyperpolarized state and hence increase the probability of firing (as reviewed in the previous section) could very well differ between these regions, which would certainly differentially regulate cortical throughput in these regions.

Laterally in the shell (Figure 11A), one also sees a clear,

albeit more homogeneous, enhancement of the neurotensin staining pattern. Between the dorsomedial and lateral shell, there is an intermediate region within which input-output relationships are unclear. It is interesting that neurotensin immunoreactivity is enhanced considerably by typical antipsychotic drugs medially and laterally in the shell, but minimally in this intermediate region. This pattern is similar to the pattern observed in material exhibiting strong acetylcholinesterase activity (Figure 10F). It was shown that this intermediate region may correspond to an area of heightened D_3 dopamine receptor mRNA[125] and that haloperidol, putatively acting through the D_3 receptor, tends to blunt the synthesis of proneurotensin mRNA specifically in this region.[126] Thus, the possibility becomes real that the relatively weak neurotensin immunoreactivity in this intermediate part of the shell is related to a specific receptor interaction (see also Figure 11B in Zahm[127]).

FIGURE 11. **A: Neurotensin immunoreactivity (NT-ir) following administration of haloperidol. NT-ir is strong dorsomedially and laterally in the shell and weak to moderate in an intermediate zone of the shell *(between arrows)*. The dorsomedial sector contains modules with weak NT-ir *(asterisks)*. B and C: Diagrams of frontal sections through the rat brain showing the distributions of Fos (Fos-ir; B) and neurotensin (C) immunoreactive neurons at 2 and 24 hours, respectively, following administration of haloperidol (2 mg/kg). Neither marker is present in appreciable quantity in control brains. Note that haloperidol induces robust Fos immunoreactivity in the dorsomedial shell and dorsolateral caudate-putamen (B). Following haloperidol administration, NT-ir neurons are more numerous in lateral parts of the shell and in a band extending from the dorsomedial to the ventrolateral caudate-putamen (C).**

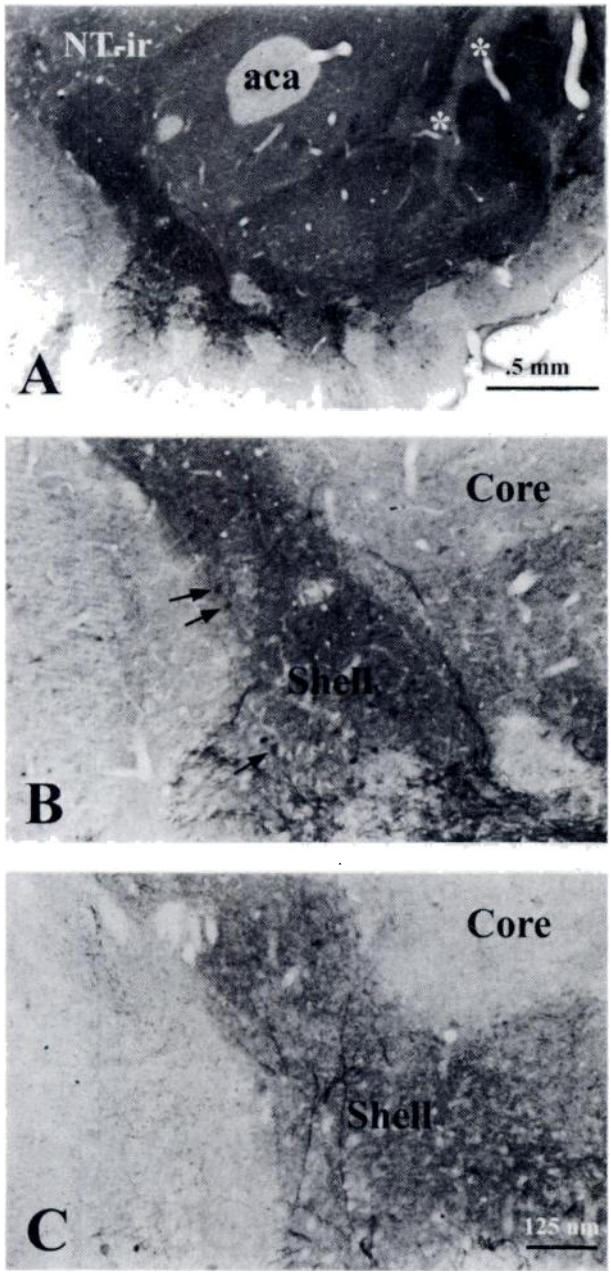


The response of the immediate-early gene, c-*fos*, and its protein product, Fos, following administration of antipsychotic drugs[52,128–130] is a useful tool for identifying neurons that have been stimulated by the drug. The diagram in Figure 11B shows a large amount of the immunoperoxidase product for Fos in a rat sacrificed 2 hours after administration of haloperidol. Whereas Fos is virtually absent from the striatum of control brains, the haloperidol-treated animal exhibits intense Fos reaction in the dorsomedial shell as well as throughout the core and caudate-putamen, particularly dorsolaterally. Considering the recent advances in the treatment of schizophrenia based on the use of so-called atypical antipsychotic drugs, it is especially interesting to note that such drugs, as exemplified by clozapine, produce an equally robust response in the dorsomedial shell but fail to elicit significant Fos immunoreactivity in the caudate-putamen.[52,56,129]

A complementary picture emerges from preparations showing perikaryal neurotensin immunoreactivity, which is of considerable interest in view of the proposed transcriptional regulation of neurotensin by Fos[131] and a considerable literature suggesting that neurotensin and dopamine coregulate each other in the basal ganglia (recently reviewed in Lambert et al.[132]). Figure 11C shows that following administration of haloperidol, the distribution of neurotensin-immunolabeled neurons is very weak in the dorsomedial shell but is stronger laterally in the shell, which is the converse of what is observed for Fos immunoperoxidase product following the same drug treatment (Figure 11B). Inasmuch as Fos and neurotensin exhibit the most robust histochemically detectable responses so far observed in striatum following antipsychotic drug treatments, it is noteworthy that a complementarity characterizes their distributions and serves to further distinguish the dorsomedial and lateral part of the accumbens shell in functional-anatomical terms.

Following administration of amphetamine, which results in increased stimulation of striatal dopamine receptors, one observes moderate numbers of very strongly labeled neurotensin immunoreactive neurons in the lateral, but not the dorsomedial part of the shell

FIGURE 12. **A: Neurotensin immunoreactivity (NT-ir) following administration of *d*-amphetamine (4 mg/kg at 4, 14, and 24 hours prior to sacrifice). The shell exhibits dorsomedial and lateral sectors in which the immunoreactivity is strong and an intermediate sector in which it is moderate. Also note the numerous immunoreactive cell bodies in the lateral shell, which are absent from control brains. The dorsomedial shell exhibits modules with weak immunoreactivity *(asterisks)*. B: Enlargement of the lateral shell, showing NT-ir neurons *(arrows)*. C: Section through the lateral shell (corresponding approximately to the area shown in B) from brain treated with *d*-amphetamine and SCH 39166, a dopamine D_1 receptor antagonist. Note relative paucity of NT-ir neurons. aca = anterior limb of the anterior commissure.**



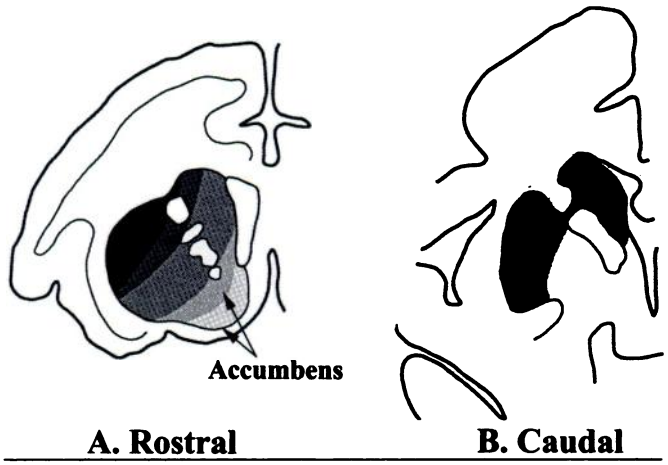
(Figure 12A and B). This response can be blocked by a dopamine D_1 antagonist (Figure 12C). Yet again, something quite different appears to be happening in the medial and lateral parts of the shell. Although this response is not observed at all in the medial shell, it is seen in the rostral part of the olfactory tubercle and caudodorsal parts of the caudate-putamen (D. S. Zahm and M. A. Welch, unpublished data).

5. ORGANIZATION OF THE PRIMATE STRIATUM AND ITS RELATION TO THE MESENCEPHALIC DOPAMINE NEURONS

The Ventral Striatum in the Primate

In the primate brain, including that of the human, the accumbens is more or less synonymous with the fundus striati, which appears as a broad continuum between the caudate nucleus and the putamen underneath the rostral part of the internal capsule (Figure 13). The accumbens of the primate, like that of the rat, is a prominent part of the ventral striatum, which in addition includes the rather ill-defined primate olfactory tubercle, as well as the rostroventral parts of the caudate nucleus and putamen.[22] The primate striatum, like the striatal complex in the rat, may be divided into separate domains based on cortical input (Figure 13). Cortical

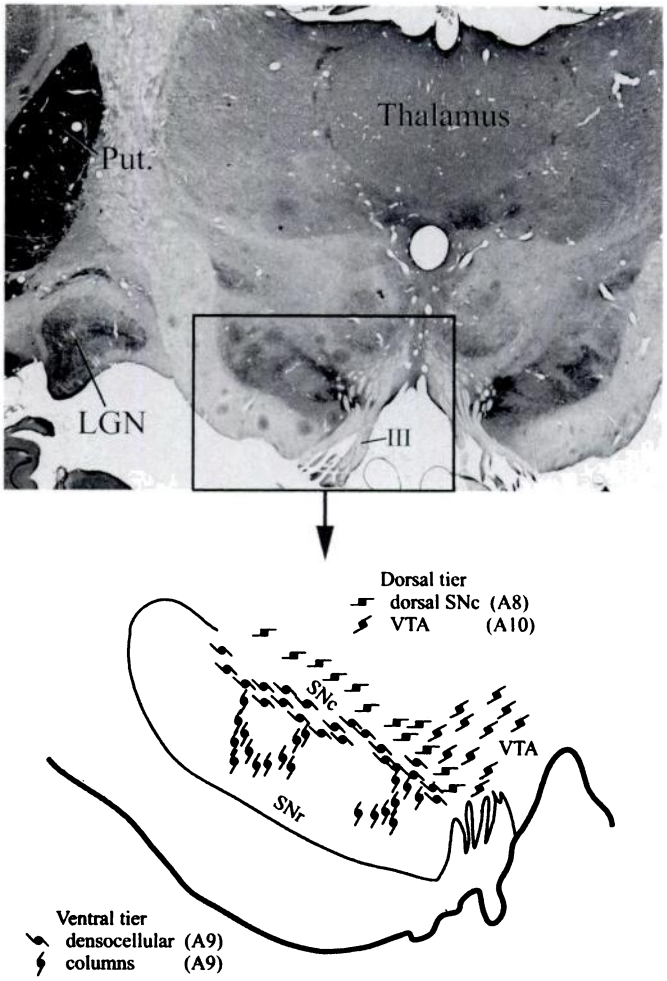
FIGURE 13. **Schematic representation of the "functional" map of the striatum based on cortical input. Levels of overlap are indicated by intermediate shades of gray. *Light gray:* input from allocortical and periallocortical regions (hippocampus formation, entorhinal area, and olfactory cortex), proisocortical regions (anterior cingulate gyrus, orbitofrontal and insular regions), and some isocortical orbitofrontal and inferior temporal gyrus association areas. All of these areas are sometimes referred to as "limbic-related cortex." *Medium gray:* input from a wide range of association cortices. *Dark gray:* input from the sensorimotor cortex, the supplementary motor area, and the frontal eye field.**



afferents to the ventral striatum (light gray in Figure 13; see also Haber et al.[22]) originate in allocortical and periallocortical regions (hippocampal formation, entorhinal area, and olfactory cortex), proisocortical regions (anterior cingulate gyrus, orbitofrontal and insular regions), the cortical-like basal amygdaloid complex, and some isocortical orbitofrontal and inferior temporal gyrus association areas. The accumbens in primates, like that in rats, is divided into core and shell subterritories. The core is continuous with the rest of the striatum, whereas the shell, which can be distinguished from the rest of the ventral striatum by its relatively low levels of calbindin (CaBP) immunoreactivity,[64] surrounds the core at its medial and ventral borders.

The cingulate and prefrontal-orbitofrontal cortical input, as well as the thalamic afferents to the core and shell of the accumbens and to the rest of ventral striatum, in the primate have recently been described in considerable detail in a series of papers by Haber and her collaborators,[22,133,134] which should be consulted for further details. The dorsolateral part of the striatum receives inputs from sensorimotor cortex, supplementary motor area, and the frontal eye fields (dark gray in Figure 13). The large central area of the rostral striatum and much of the caudate nucleus posterior to the commissure receive inputs from a wide range of association cortices, as well as direct afferents from primary and secondary visual and auditory cortices. For a discussion of the primate corticosubcortical reentrant circuits via the basal ganglia and the thalamus back to cortex, the reader is referred to Alexander et al.[16,17] and to Hoover and Strick.[135] In the following segments we will turn our attention to the mesotelencephalic dopamine system and its interaction with the accumbens and the rest of the striatum.

FIGURE 14. Schematic drawing of the base of the left cerebral peduncle to show the distribution of dopaminergic cells in the substantia nigra and ventral tegmental area. Put. = putamen; LGN = lateral geniculate nucleus; SNc = Subtantia nigra pars compacta; SNr = substantia nigra pars reticulata; VTA = ventral tegmental area.



Mesencephalic Dopamine Neurons

As indicated in Figure 14, the dopamine cells of the substantia nigra pars compacta (SNc) are closely associated and almost imperceptibly merge with the immediately adjacent dopamine cell groups of the ventral tegmental area. Based on the phenotypic characteristics, the midbrain dopamine neurons can be divided into a dorsal tier and a ventral tier. The dorsal tier, whose cells are CaBP positive, includes both the dorsal substantia nigra pars compacta and the contiguous ventral tegmental area. The ventral tier includes cells in both the densocellular and the ventral group that form cell columns penetrating deep into pars reticulata. The ventral tier cells are CaBP negative and have relatively high levels of expression for dopamine transporter and the D_2 receptor. The main projections of both groups of dopamine neurons are to the striatum and to cortex. The dorsal group of the SNc is composed of loosely arranged cells, extending dorsolaterally to circumvent the ventral and lateral aspects of the superior cerebellar peduncle and the red nucleus. These dorsal neurons are oriented horizontally, just dorsal to a dense cluster of neurons referred to as the densocellular region, and form a continuous band with the ventral tegmental area. The dendrites of this dorsal group stretch in a mediolateral direction, and they do not extend into the ventral parts of the pars compacta or into the substantia nigra pars reticulata. In contrast, the dendritic arborizations of the densocellular region are oriented ventrally and penetrate the major portion of the pars reticulata in primates.

FIGURE 15. Composite drawing of the midbrain projection to the striatum in two rostrocaudal views. Whereas the dorsal tier of dopaminergic neurons projects to the ventral striatum, the densocellular part of the ventral tier projects throughout the striatum. ac = anterior commissure; C = caudate; ic = internal capsule; Pu = putamen; SNc = substantia nigra pars compacta; VP = ventral pallidum; VTA = ventral tegmental area.

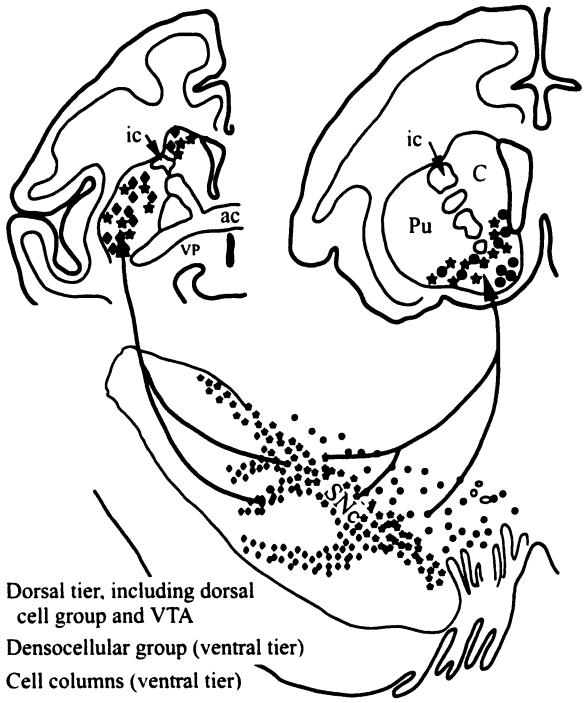
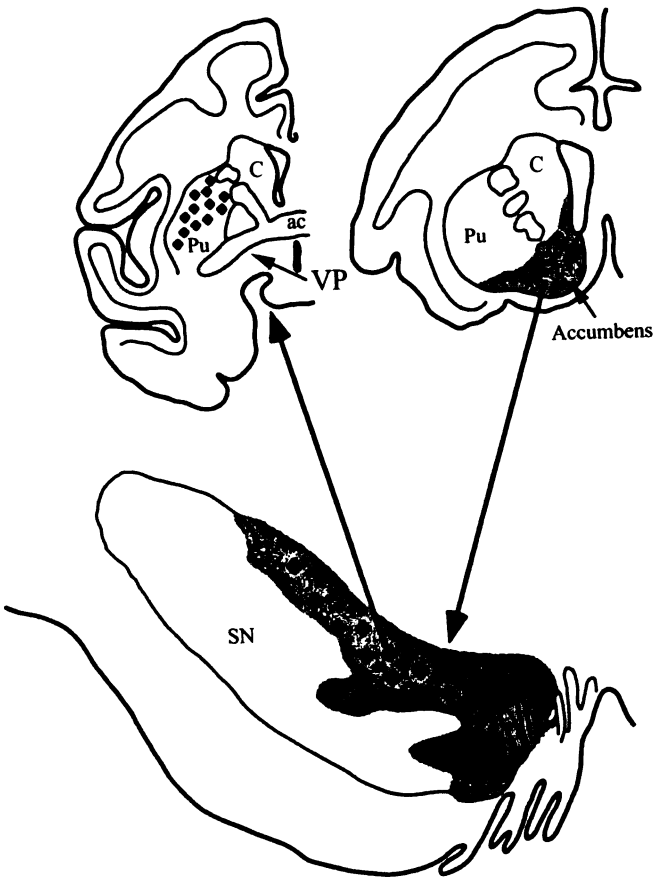


FIGURE 16. Schematic figure to show how the ventral striatum might be able to modulate the dorsal striatum by projecting to substantia nigra neurons *(diamonds)* that in turn project to dorsal striatum. ac = anterior commissure; C = caudate; Pu = putamen; SN = substantia nigra; VP = ventral pallidum.



The Mesotelencephalic Dopamine Projections

The projections of the dopamine neurons to the striatum are more loosely organized than the corticostriatal projections with respect to their functional domains. The dorsal tier projects to the ventral striatum.[62] The cell columns that penetrate into pars reticulata project primarily to the dorsolateral (sensorimotor) striatum. The densocellular part of the ventral tier, however, projects throughout the striatum (Figure 15). In particular, the central part of the densocellular region of the ventral tier projects to both the ventral and dorsal parts of the striatum. Within the center of this midbrain region, there is an intermingling of cells that project to different striatal territories, thereby allowing a large area of the striatum to be modulated by inputs from this midbrain region. Therefore, in contrast to cortical projections to the striatum, there is not a simple point-to-point relationship between different groups of substantia nigra neurons and the different functional domains of the striatum. The majority of midbrain dopamine cells projecting to the cortex arise from both the ventral tegmental area and the dorsal group of the pars compacta throughout its rostrocaudal extent.[136,137] The densocellular region and the ventral groups of the substantia nigra do not appear to project heavily to cortex. Thus the dorsal tier, but not the ventral tier, of midbrain neurons gives rise to the dopamine-cortical projection.

In summary, the dorsal tier neurons project to a limited region of striatum—in particular, to the ventral striatum. However, the dorsal tier neurons project widely throughout cortex. In contrast, the ventral tier cells project widely throughout the striatum but do not project to cortex.

Projections to the Midbrain Dopamine Neurons

The striatum projects massively back to the substantia nigra[138] (see also the review by Alheid et al.[14]). Ventral striatonigral inputs terminate in the medial pars reticulata and much of the densocellular part of the pars compacta. It is important to note that the ventral striatal

fibers terminate throughout a wide mediolateral extent of the densocellular region of the ventral tier.[139,140] Thus, the ventral striatal input to the substantia nigra is in a position to influence a large population of dopamine neurons that in turn project to the dorsal striatum (Figure 16). This important concept was first developed on the basis of experimental studies in the rat.[32,141] The dorsolateral striatonigral inputs to the substantia nigra, on the other hand, terminate ventrally in the pars reticulata, and therefore are not in a position to influence a large population of dopamine neurons.[32,142] Descending projections from the central nucleus of the amygdala also terminate in a wide mediolateral region of dopamine cells, primarily in the dorsal pars compacta and in the densocellular regions.[143] In addition, cells from the bed nucleus of the stria terminalis and the sublenticular part of the extended amygdala project to the dorsal tier (S. N. Haber, unpublished observations). Thus, like the ventral striatum, the extended amygdala may therefore be able to influence a wide range of dopamine neurons, and it may thus have direct access to striatal and cortical structures by way of the mesencephalic dopamine neurons (see also Gonzales and Chesselet[144]).

The simple scheme shown in Figure 16 illustrates a way whereby pieces of information that originally come from different parts of the cerebral cortex can be integrated via a nigrostriatal feedback loop. However, there are other possibilities whereby functionally diverse information might be integrated in the basal ganglia, such as by local circuit neurons within the striatum or via "open" corticosubcortical reentrant circuits through the basal ganglia.[109,145] Yet another possibility has recently been proposed by Bevan and his collaborators,[109] who traced descending projections from dorsal and ventral pallidal territories to individual neurons in substantia nigra in a combined light-electron microscopic study. They found that individual neurons in both the pars compacta and the pars reticulata do receive input from both the dorsal and the ventral pallidum. In other words, stimuli from different parts of the striatopallidal system may converge on single neurons in the substantia nigra. However, some caution is needed, since it is difficult to make tracer injections in the ventral pallidum without involving neurons in the extended amygdala. (See Figure 6 in Heimer et al.[31])

6. ACCUMBENS AND EXTENDED AMYGDALA

Although the amygdaloid complex is often treated as a monolithic structure in summary behavioral assessments of forebrain function, it is a highly differentiated region with many nuclei (reviewed by Alheid et al.[59]), and ample evidence suggests distinct functions for subgroups of these nuclei. The nuclei of the *basolateral complex* (lateral, basolateral, and basomedial nuclei), for example, may function to some degree as cortical areas. Although lacking a clear laminated appearance, they appear to be made up of generally pyramidal-like cells with a neurohistochemical makeup similar to the nearby areas of cortex. The basolateral complex shares reciprocal connections with a variety of cortical areas and projects to dorsal and ventral striatum.[102] This projection might heuristically be considered as a kind of corticostriatal projection. Also contributing to the innervation of ventral striatum are various other cortical-like *superficial nuclei* such as the anterior cortical nucleus, the nucleus of the lateral olfactory tract, and the posterior cortical nuclei. Distinct from the superficial nuclei and the basolateral complex are central and medial amygdaloid nuclei (the *centromedial amygdala*); these nuclei seem to be the main relays for amygdaloid information routed to the hypothalamus, although they do not have exclusive rights to this role. The central nucleus, moreover, is the main source of amygdaloid projections to autonomic and somatomotor areas of the brainstem.

Extended Amygdala

Over the past two decades, it has become increasingly clear that neuronal cell groups composing central and medial amygdaloid nuclei are not bounded by the arbitrary borders that are generally used to depict the limit of the amygdaloid body. Rather, more or less continuous columns of cells extend from these two nuclei through the sublenticular areas (just below the globus pallidus) and within the fascicles of the stria terminalis in order to merge with the bed nucleus of the stria terminalis. In fact, the symmetries between the cells, connections, and neurochemistry of the bed nucleus of the stria terminalis and the centromedial amygdala are so strong that it has become convenient to talk of the interconnecting cells and the bed nucleus of the stria terminalis as an extension of the amygdala into the basomedial forebrain,[60,146,147] an "extended amygdala."[58,59] This situation is illustrated in a schematic fashion in Figure 17. Insofar as the portions of this structure related to the central amygdala and those most closely related to the medial amygdala have distinctive efferent targets, it is practical to partition the extended amygdala into "central" and "medial" divisions (shown in yellow and green, respectively, in Figure 17), with the central division possessing the most direct projections to the lateral hypothalamus and brainstem (represented by the light yellow arrow in Figure 17) and with efferents from the medial division of the extended amygdala massively favoring the medial hypothalamus (repre-

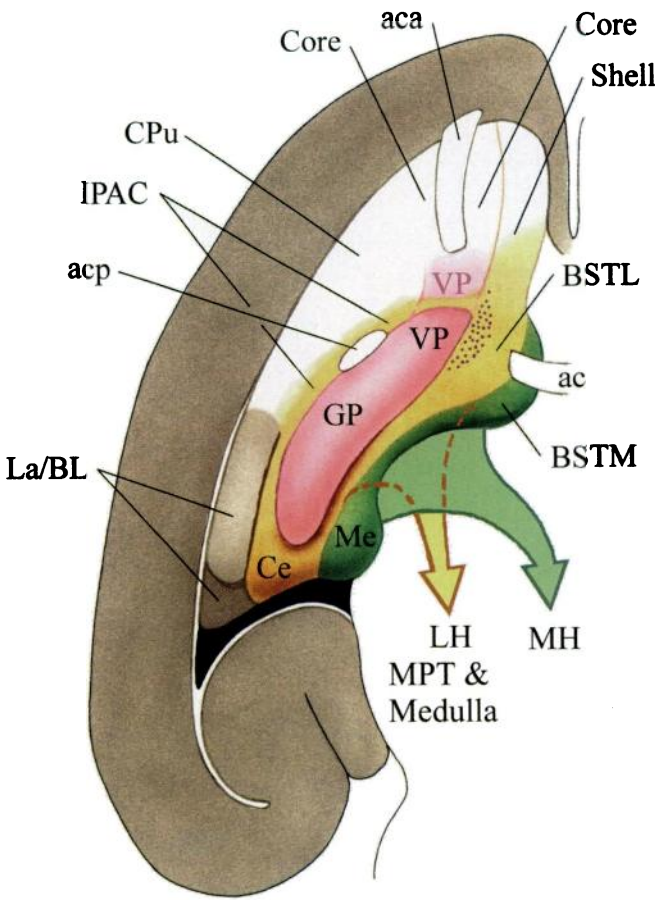


FIGURE 17. Schematic, partly three-dimensional drawing of the basal forebrain of the rat in horizontal view. The major subcortical forebrain structures—the striatum *(white)*, represented by the caudate-putamen (CPu) and the core and shell of the accumbens; the pallidum *(pink)*, represented by the globus pallidus (GP) and the ventral pallidum (VP); and the extended amygdala with its two subdivisions, the central *(yellow)* and medial *(green)* divisions—form large diagonally oriented "columns." Note that the core of the accumbens can generally be easily distinguished from the shell; there is a distinct border between the core and shell of the accumbens, whereas the core is directly continuous with the rest of the striatum without any clear border dividing the two parts. The *yellow*-colored central division of the extended amygdala continues without sharp boundary into the caudomedial part of the shell, which can be considered a transitional area between the striatum and the extended amygdala. The IPAC (interstitial nucleus of the posterior limb of the anterior commissure) component of the extended amygdala (shown in *yellow* since it appears to constitute a subdivision of the central extended amygdala) has traditionally been included in the caudate-putamen or striatum. The ventral extension of the globus pallidus (the ventral pallidum) is sandwiched between the striatum, the main part of the extended amygdala, and the rostral arm of the extended amygdala (the IPAC). In order not to compromise the rendition of the core–shell dichotomy of the accumbens, the rostroventral extension of the ventral pallidum into the deep part of the olfactory tubercle has only been implied with a gradually disappearing *pink* color underneath the core of the accumbens. The *broad arrows* illustrate how the two divisions of the extended amygdala are characterized by, in general, different efferent targets. Whereas the medial extended amygdala is closely related to the medial hypothalamus (MH), the central extended amygdala provides the main output to the lateral hypothalamus (LH) and to somatomotor and autonomic centers in the brainstem. aca = anterior limb of the anterior commissure; acp = posterior limb of the anterior commissure; BSTL = lateral bed nucleus of stria terminalis; BSTM = medial bed nucleus of stria terminalis; Ce = central amygdaloid nucleus; La/BL = lateral and basolateral amygdaloid nuclei; Me = medial amygdaloid nucleus; MPT = mesopontine tegmentum.

sented by the light green arrow in Figure 17; the stria terminalis and its accompanying cell groups are not indicated in the schematic illustrations in Figure 17).

In the context of a review of the accumbens, it is the central division that is the most immediately relevant. Particularly similar to the shell of the accumbens,[38] the central division of extended amygdala makes extensive projections to the lateral hypothalamus and to the mesopontine tegmentum (see review by Alheid and Heimer[105]). Another similarity to the accumbens is that the central division of extended amygdala receives a dense innervation from the basolateral complex of the amygdala; however, as with the shell of the accumbens, this appears to preferentially originate in the posterior (parvicellular) part of the basolateral amygdala. The anterior (magnocellular) part of the basolateral amygdala seems to have a more exclusive relation to the dorsal striatum and to lateral portions of the ventral striatum.[102]

Transitions Between Accumbens and Extended Amygdala

One territory where the histochemistry of the accumbens and central division of extended amygdala seem to blend is in the caudal aspects of the accumbens, particularly its shell division. This zone, which is adjacent to the rostral face of the lateral bed nucleus of the stria terminalis (BSTL), is indicated by a gradually fading yellow color in Figure 17. The caudal aspects of the accumbens are also separated from the sublenticular

FIGURE 18. A series of coronal sections through the rat forebrain stained for angiotensin II to show the strong immunoreactivity in the caudomedial shell of the accumbens (A and B) and its continuity with interstitial nucleus of the posterior limb of the anterior commissure (IPAC in C) and the bed nucleus of stria terminalis (BST in D) at the level of the crossing of the anterior commissure (ac). aca = anterior limb of the anterior commissure; acp = posterior limb of the anterior commissure; cc = corpus callosum; Cpu = caudate-putamen; GP = globus pallidus; LV = lateral ventricle; Se = septum; Tu = olfactory tubercle.

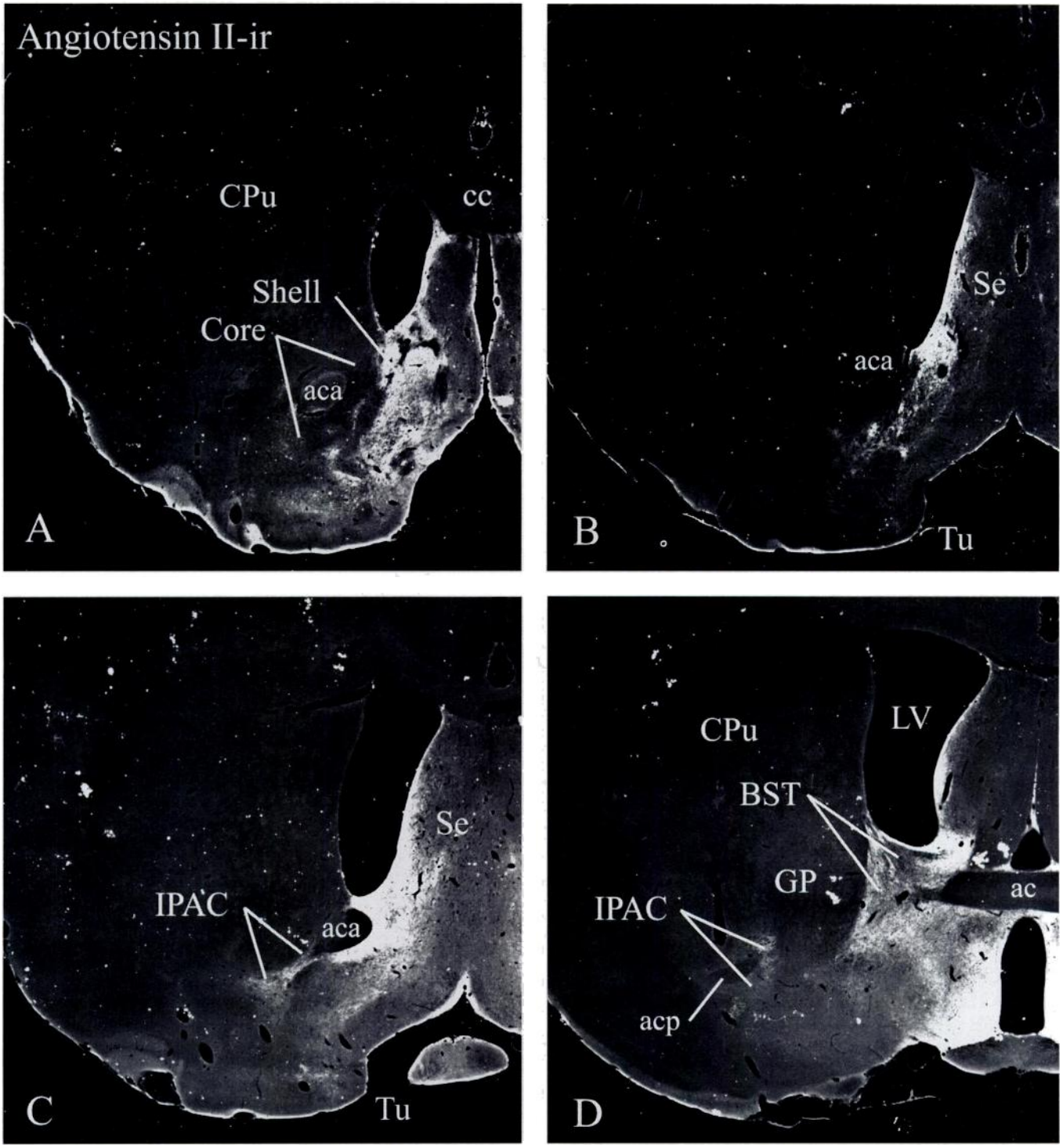
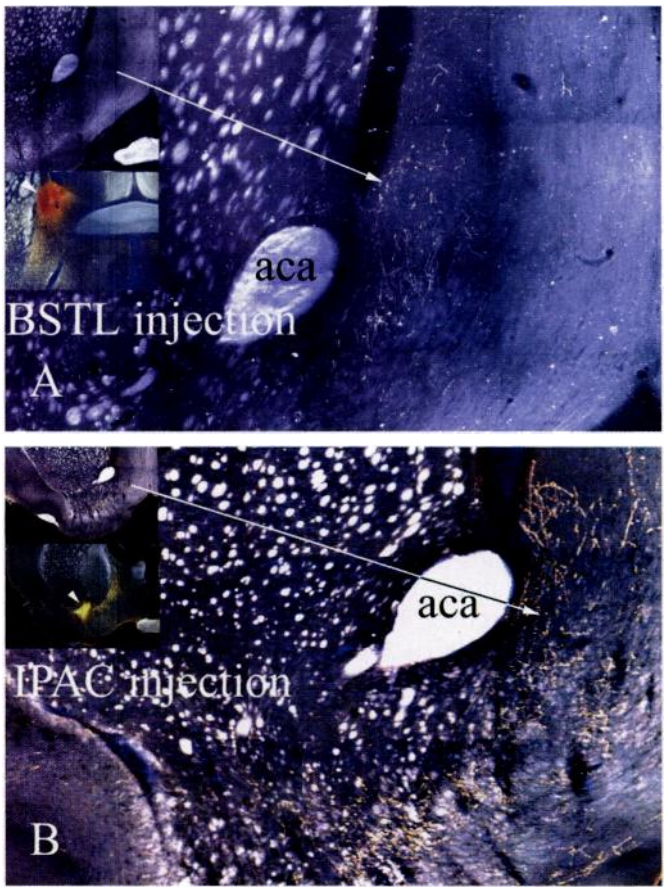


FIGURE 19. **Anterograde labeling of the accumbens after phytohemagglutin-stimulated lymphocyte (PHA-L) injections in the extended amygdala. A: PHA-L injection in the lateral bed nucleus of the stria terminalis (BSTL). The injection site is shown in the lower inset; the upper inset is a wider view of the area of termination. B: PHA-L injection in the interstitial nucleus of the posterior limb of the anterior commissure (IPAC). The injection site is again shown in the lower inset, with a wider view of the section above. aca = anterior limb of the anterior commissure.**



portions of the extended amygdala by the ventral extension of the pallidum (VP in Figure 17). Histochemically, these areas are rather rich in acetylcholinesterase but somewhat lighter than the dorsal striatum generally or the more rostral portions of the shell of the accumbens; these caudomedial zones of accumbens are also immunoreactive for angiotensin II (Figure 18) and enriched in a number of neuropeptides (such as neurotensin, cholecystokinin, and opioid peptides), which also distinguish extended amygdala from nearby dorsal or ventral striatum. The presence of vasopressin/oxytocin receptors[148,149] also distinguishes the caudomedial accumbens and the extended amygdala from the rest of striatum.

In terms of connections, these caudal shell areas are closely interconnected with the central division of the extended amygdala. Projections from the caudal shell regions reach the lateral bed nucleus of the stria terminalis, the sublenticular portions of extended amygdala, and the central nucleus of the amygdala.[32,38] The extended amygdala appears to reciprocate these projections: the lateral bed nucleus of stria terminalis and the IPAC component of the extended amygdala project to the caudal shell of the accumbens medially and ventrally (Figure 19), as well as laterally across the rear face of the accumbens, and the central amygdaloid nucleus projects with a less dense projection medially in the shell.[39] Because of the relay to the amygdala, these caudal areas of the accumbens are in a position to funnel information from medial prefrontal cortex, insular cortex, and hippocampal formation to the central division of the extended amygdala. It also is notable that afferents relayed to the central division of the extended amygdala through these caudal areas of the accumbens shell should be strongly affected by the dense dopaminergic innervation of these areas, in addition to the conspicuous, but less dense, dopaminergic terminations seen in the lateral bed nucleus of the stria terminalis, in the central division of the sublenticular extended amygdala, and in the central amygdaloid nucleus.

Given the many histochemical similarities and strong interrelations between the caudal shell areas of the accumbens and the extended amygdala, it may seem tempting to include the caudomedial shell of the accumbens within the boundaries of the extended amygdala. On the other hand, the medial shell, like the rest of the accumbens, appears to have a well-developed projection to the ventral pallidum, which in turn projects to the mediodorsal thalamus (see review by Heimer et al.[15]). The caudomedial shell, therefore, is an integral part of a significant ventral striatopallidothalamocortical loop, and from this point of view it is more similar to other striatal or basal ganglia structures than to the extended amygdala. One approach to this problem is to consider the caudal areas of accumbens—and in particular its caudomedial shell area, which has the closest neurochemical and hodological relations with the extended amygdala—as "transitional" with this latter structure.[58,59] That is to say, for the most part we cannot simply separate or define borders between neurons that seem to participate in striatopallidal circuits and those that participate in circuits typical of the central division of the extended amygdala.

The Interstitial Nucleus of the Posterior Limb of the Anterior Commissure (IPAC)

IPAC, which was illustrated in coronal section in Figures 10D, 18, and 19 and in the schematic drawing in

Figure 17, is represented by collections of neurons that, in the rat, accompany the posterior limb of the anterior commissure across the face of the pallidum. It has traditionally been included in the caudate-putamen (striatum), as reflected by terms such as *fundus striati*[150] or *subcommissural striatal pocket*, when viewed in coronal rat brain sections. As explained below, however, the term *interstitial nucleus of the posterior limb of the anterior commissure*[146] seems more appropriate. This term reflects its general association with the posterior limb of the anterior commissure and has the virtue of being neutral with respect to its association with the striatum or amygdala. It is also in keeping with the rather reasonable tradition of accepting the nomenclature proposed by the first individual to identify a novel anatomical structure.

The reasons for introducing a short discussion of IPAC in the context of the accumbens are manifold. As indicated in Figures 17 and 18, IPAC, like the rest of the central division of the extended amygdala, is directly continuous with the caudal aspects of the accumbens, and it shares with the caudal medial shell area of the accumbens reciprocal interconnections with other parts of the central extended amygdala (Figure 19).[32,59,151–153] It also appears to contain the same variety of histochemical markers (including angiotensin II, neurotensin, secretoneurin, opioid peptides, vasopressin, and oxytocin receptors), as well as androgen and estrogen receptors (for references, see Alheid et al.[59] and Heimer et al.[66]), that serve to distinguish the extended amygdala from the adjacent striatal territories. However, like the rest of the accumbens and ventral striatum, IPAC is also characterized by significant acetylcholinesterase staining and by an especially great density of dopamine terminals, which, like the dopamine terminals in the caudomedial shell (see section 4, Figure 10C and D), are relatively more resistant to toxic or surgical manipulation than the dopamine terminals in the rest of the accumbens. In contrast to other parts of the ventral striatum, including the caudomedial shell of the accumbens, IPAC does not appear to have any significant projections to ventral or dorsal pallidum,[154] and it thus may not be part of the corticostriatopallidothalamic circuitry. Therefore, even though IPAC has stronger acetylcholinesterase reaction and a greater density of dopamine terminals than other parts of the extended amygdala, it nonetheless appears to be an integral part of the extended amygdala, and from this point of view it is a little different from the caudomedial shell of the accumbens, which we defined as a transition area between the basal ganglia and extended amygdala.

IPAC, like the rest of the continuum formed by the central extended amygdala, and the shell of the accumbens for that matter, has a number of features that are highly relevant in the context of neuropsychiatric disorders. This subject has been discussed at some length in a recent article by several of the present authors[66] and will not be dwelt upon here. Suffice it to say that the IPAC component of the extended amygdala and its continuation into the shell of the accumbens belong to some of the most densely dopamine-innervated parts of the basal forebrain. This particular corridor, therefore, is likely to be of special interest in evaluating therapeutic agents targeting dopamine receptors or drugs of abuse that are known to interact strongly with dopaminergic mechanisms. Although the theory of the extended amygdala appears to be as relevant in the primate brain, including the human,[61,63] as it is in the rat, the special segment represented by IPAC still remains to be adequately described in the primate.

7. CLOSING REMARKS

It appears that the term *nucleus accumbens septi* does not adequately describe this important part of the basal forebrain; in fact, the accumbens can hardly be referred to as a nucleus, since, with the major exception of clear boundaries towards the septum and the anterior olfactory areas, it cannot be clearly demarcated either from nearby parts of ventral striatum or from parts of the extended amygdala. When it was acknowledged that the accumbens is an integral and major part of the ventral striatum, it was only a matter of time before the corticosubcortical reentrant circuits through the accumbens were described and quickly adapted to theories intended to help explain major symptoms in various neuropsychiatric disorders. Gradually the patch-matrix organization of the accumbens has been clarified, and, as has been reviewed to some extent in this article, additional discoveries are now being made that make it possible to propose hypotheses based on the anatomical connections of ensembles of neurons within different parts of the accumbens and to analyze subpopulations of neurons as to their potential involvement in the drug treatment of neuropsychiatric disorders and in some aspects of drug abuse.

The recent anatomical discoveries related to the accumbens, including the identification of the core–shell dichotomy and its relevance in the context of connectional arrangements and immunohistochemical staining patterns, have added another level of sophistication to our understanding of the organization of basal forebrain functional-anatomical systems in general. Of special note was the realization that many of the features that distinguish the shell, especially its caudomedial

part, from the core and the rest of striatum are also characteristic of the central division of the extended amygdala.[58] As a way of summarizing our understanding of the nature of the accumbens and its position in the overall organizational scheme of the basal forebrain, we would like to refer again to the schematic drawing in Figure 17. Although such schemes carry the risk of oversimplification, they nonetheless provide for overall perspectives, which are otherwise difficult to obtain.

Since a sharp border does not exist between the core of the accumbens and the rest of the striatal complex (caudate-putamen), and since the core parallels in almost every aspect the rest of the striatum, it is difficult to escape the conclusion that the accumbens is an integral part of the striatal complex. However, as indicated by a fine line in Figure 17, and as illustrated in many of the previous figures, there is a rather distinct border between the core and the shell of the accumbens. Although the shell has many striatal features that justify its inclusion in the notion of the ventral striatum, the shell is also endowed with very specific characteristics, atypical of the striatum, that justify the subdivision of the accumbens into two major subterritories as defined by the core–shell dichotomy.

The accumbens and its relevance to neuropsychiatric disorders cannot be brought into perspective without some appreciation of the theory of the extended amygdala. As indicated by the gradually fading yellow color in Figure 17, parts of the accumbens, especially its caudomedial shell, serve as areas of transition to the central division of the extended amygdala (in yellow). Together, the shell of the accumbens and the extended amygdala form an extensive forebrain continuum of apparent importance in neuropsychiatry (for further discussion of this subject, see Alheid and Heimer[58] and Heimer and co-workers[66]). The shell of the accumbens is similar, although not identical, to the central division of the extended amygdala, with which it is directly continuous and with which it appears to share histochemical and connectional features. These shared features include an especially high density of dopamine terminals and many similar inputs from areas in the prefrontal-orbitofrontal cortex and medial temporal lobe, including the hippocampal formation and the large "cortical-like" basolateral amygdaloid complex. These cortical regions are precisely the ones that appear to be prominently involved in many neuropsychiatric disorders, including especially those characterized by emotional derangements and associated viscero-endocrine and behavioral symptoms, such as Alzheimer's disease, schizophrenia, depressive disorders, and obsessive-compulsive disorder.

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