Convergence and Segregation of Ventral Striatal Inputs and Outputs

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ABSTRACT: The ventral striatum, which prominently includes the nucleus accumbens (Acb), is a heterogeneous area. Within the Acb of rats, a peripherally located shell and a centrally situated core can be recognized that have different connectional, neurochemical, and functional identities. Although the Acb core resembles in many respects the dorsally adjacent caudate-putamen complex in its striatal character, the Acb shell has, in addition to striatal features, a more diverse array of neurochemical characteristics, and afferent and efferent connections. Inputs and outputs of the Acb, in particular of the shell, are inhomogeneously distributed, resulting in a mosaical arrangement of concentrations of afferent fibers and terminals and clusters of output neurons. To determine the precise relationships between the distributional patterns of various afferents (*e.g.*, from the prefrontal cortex, the basal amygdaloid complex, the hippocampal formation, and the midline/intralaminar thalamic nuclei) and efferents to the ventral pallidum and mesencephalon, neuroanatomical anterograde and retrograde tracing experiments were carried out. The results of the double anterograde, double retrograde, and anterograde/retrograde tracing experiments indicate that various parts of the shell (dorsomedial, ventromedial, ventral, and lateral) and the core (medial and lateral) have different input–output characteristics. Furthermore, within these Acb regions, various populations of neurons can be identified, arranged in a cluster-like fashion, onto which specific sets of afferents converge and that project to particular output stations, distinct from the input–output relationships of neighboring, cluster-like neuronal populations. These results support the idea that the nucleus accumbens may consist of a collection of neuronal ensembles with different input–output relationships and, presumably, different functional characteristics.

INTRODUCTION: VENTRAL STRIATUM AND NUCLEUS ACCUMBENS

The term *ventral striatum* denotes an area of the striatum that receives inputs from such limbic structures as the hippocampus, entorhinal cortex, and amygdala, as well as dopaminergic afferents from the ventral mesencephalon. These striatal afferents are largely confined to the ventral and medial parts of the striatum, although in

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particular, in rostral and caudal striatal areas, some of these "limbic" afferents might reach also more dorsal parts of the striatum. Outputs from the ventral striatum reach ventral pallidal areas, the hypothalamus, the ventral tegmental area (VTA), the substantia nigra pars compacta and pars reticulata, and more caudal mesencephalic areas as the retrorubral area and the caudal mesencephalic tegmentum (for reviews, see refs. 1 and 2). The nucleus accumbens (Acb) is a nuclear mass in the rostroventral part of the ventral striatum bordered medially by the septum and ventrally by the olfactory tubercle (FIG. 1). Following the initial suggestion by Stevens[3] that the Acb plays a role in the pathophysiology of schizophrenia, over the past decades, this nucleus has been the focus of an increasing number of neuroanatomical, electrophysiological, and pharmacobehavioral studies. Important in this respect have also been the seminal papers by Heimer and Wilson,[4] proposing that the Acb forms an integral part of the striatum, and Mogenson *et al*.,[5] suggesting that the Acb is the neural substrate for limbic-motor interactions. In more recent years, the Acb has played a prominent role in theories of reward and motivation, and disturbances at the level of this nucleus have been implicated in a number of other affective disorders, such as schizophrenia and drug abuse.[6,7] More caudal parts of the ventral striatum, which appear to share many inputs and outputs with the Acb, have also received attention in this context. These areas, which include among others the so-called interstitial nucleus of the posterior limb of the anterior commissure (IPAC), are thought to belong to the territory of the extended amygdala[1] and are dealt with in other chapters in this volume.

NUCLEUS ACCUMBENS: SHELL–CORE DICHOTOMY

Within the Acb, primarily on the basis of (immuno)histochemical characteristics, a distinction can be made between a shell and a core region.[8–10] It is generally accepted that the differential distribution of the calcium-binding protein, calbindin D_{28K} (CaB), provides the most reliable distinction between shell and core[10,11] (FIG. 2). The medial, ventral, and lateral parts of the Acb, which are lightly to moderately immunoreactive for CaB, are considered to consitute the shell, whereas the central and dorsal parts of the Acb, which are more strongly immunoreactive for CaB belong to the core.[c] In accepting the differential distribution of CaB-immunoreactivity as a marker for shell and core, the lightly staining rostral part of the Acb must be included in the shell;[11] (see, however, ref. 12). It must further be noted, however, that

[c]The Acb core imperceptibly merges with the dorsally adjacent caudate-putamen complex. Connections of the patch and matrix compartments of the Acb core, summarized below, in most cases include the same compartments of the adjacent caudate-putamen, even though not explicitely stated in the text.

FIGURE 1. Photomicrographs of two transverse sections through the rat Acb stained for Nissl substance (**A**, rostral; **B**, caudal). Note the inhomogeneous distribution of cells and the existence of clusters of neurons (arrowhead in **A**). In **B**, arrows mark the border between shell (AcbSh) and core (AcbC); compare with FIGURE 2. The large arrowhead in **B** indicates the major island of Calleja. ac, anterior commissure; CPu, caudate-putamen complex; OT, olfactory tubercle.

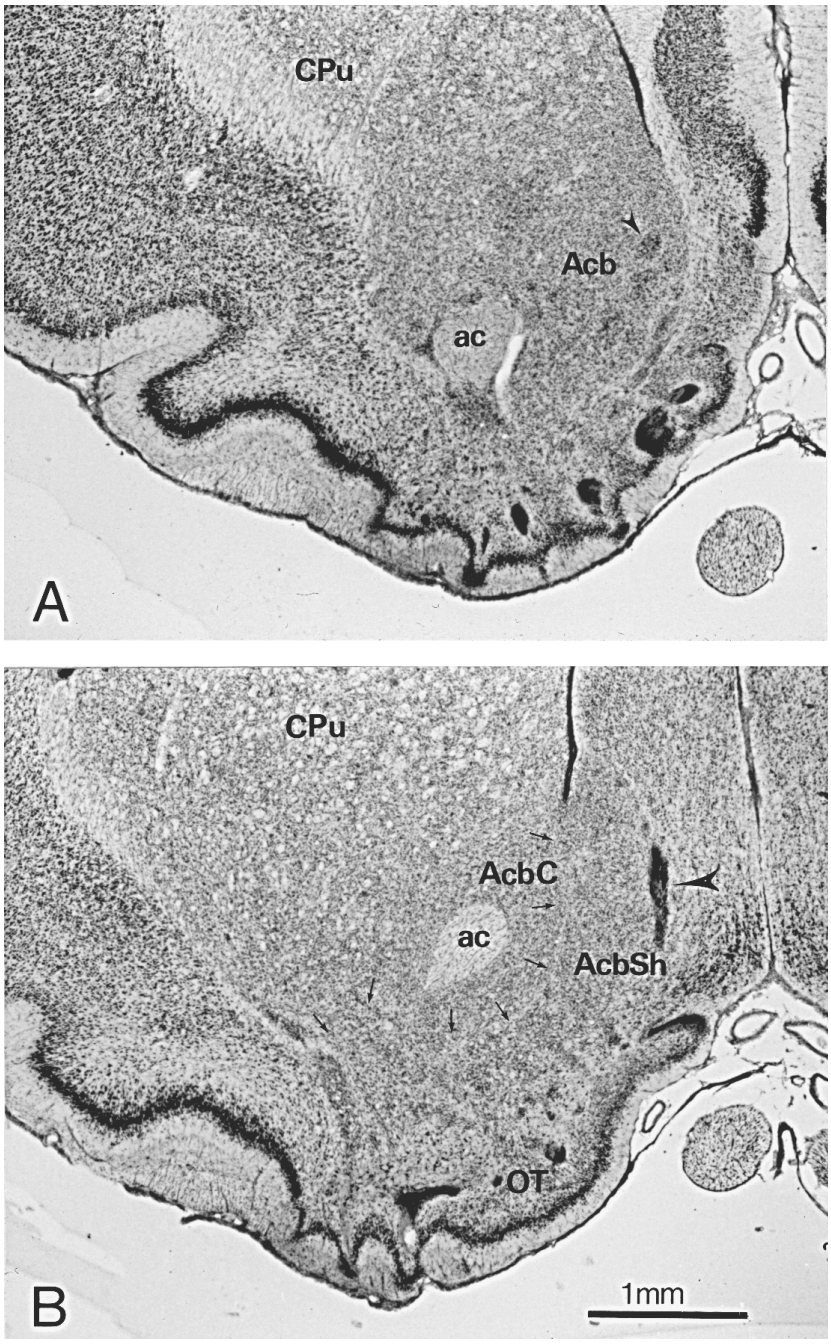

CPu
Acb
ac
A
CPu
AcbC
ac
AcbSh
OT
1mm
B

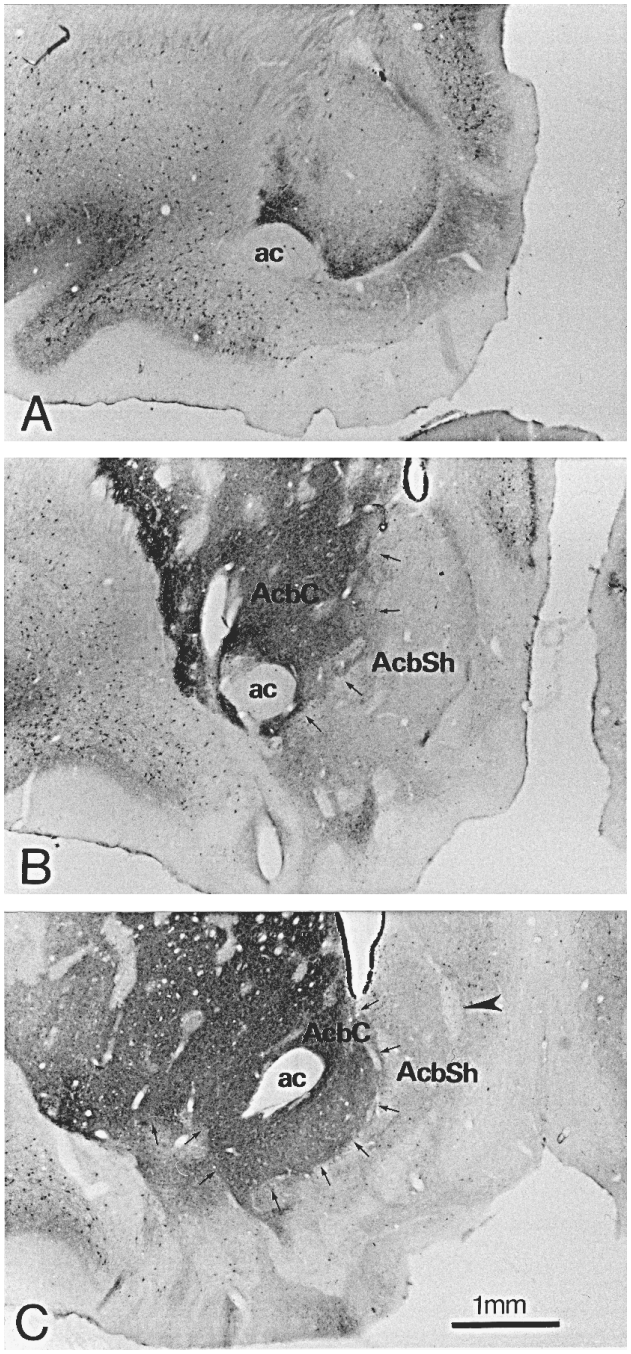
TABLE 1[a]

	CaB	ENK	NAL	DA	D_1	D_2	D_3	SP	NT
CORE	+++	++	+	++	++	++	+	++	++
patch	++	+++	+++	+				+++	+++
matrix	+++	++	+	++				++	+
"rostral zones"	+++	+++	+++	+				+	
SHELL	++	+++	+	+++	+++	+	++	+++	+++
cell clusters	+	+	+++	+				+	+
cone-shaped area	++	+++	++	+++				+++	+++

[a]The distribution of a limited number of neurochemical substances and neurotransmitter receptors in shell and core of the Acb (grey rows), and identifiable "compartments" therein,[9,10] is represented in a three-level scale: +++, dense; ++, moderate; +, weak. The distribution of the dopamine receptors D_1, D_2, and D_3 has not been described in such detail that a further subdivision within the shell and core is justified. For the various substances, the references contain the original data. CaB, calbindin D_{28K};[9–11,13] ENK, enkephalin;[9,14] NAL naloxon;[14] DA, dopamine;[9] D_1, dopamine D_1 receptor;[15] D_2, dopamine D_2 receptor;[15] D_3, dopamine D_3 receptor;[16] SP, substance P;[9,10] NT, neurotensin.[17,18]

both shell and core exhibit distinct inhomogeneities for cellular density (FIG. 1) and CaB-immunoreactivity (TABLE 1; FIG. 2). The lateral shell exhibits a moderate immunoreactivity for CaB, whereas medial, ventral, and rostral shell areas show much lower levels of CaB-immunoreactivity. Within the medial shell, cell cluster areas in Nissl-stained sections exhibit almost no CaB-immunoreactivity, whereas in its caudo-dorsal part, collections of CaB-immunoreactive neurons are present.[10] The core of the Acb, much like the ventromedial parts of the adjacent caudate-putamen complex, contains distinct areas of low CaB-immunoreactivity which coincide with the striatal patches expressing high concentrations of μ-opioid receptors.[19,20] TABLE 1 summarizes the differential distribution of a number of neurochemical substances and neurotransmitter receptors in the various parts of the Acb shell and core. At least five, but presumably more, different compartments can be recognized in the Acb. It must be noted that, for a variety of substances and receptors that are not represented in this table, also, inhomogeneous patterns of distribution have also been described, but that a complete picture of the precise mutual relationships between these patterns is still largely lacking.

FIGURE 2. Photomicrographs of three transverse sections through the Acb, immunostained for CaB. **A,** rostral; **C,** caudal. Arrows in **B** and **C** indicate the border between shell (AcbSh) and core (AcbC) of the Acb. Note that the shell shows much less CaB immunoreactivity than the core but that the shell is inhomogeneous in itself, exhibiting moderate immunoreactivity in the lateral shell and almost no immunoreactivity for CaB in its medial part (compare also FIG. 4A). The large arrowhead in **C** indicates the major island of Calleja. The core, exhibiting mostly high levels of CaB, contains, in addition, patches of light or moderate levels of immunoreactivity for CaB. The rostral part of the Acb (**A**), with the exception of a lateral region, is lightly immunoreactive for CaB and has been included in the shell on the basis of this characteristic by Jongen-Rêlo *et al.*[11] ac, anterior commissure.


ac
A
AcbC
AcbSh
ac
B
AcbC
ac
AcbSh
1mm
C

RELATIONSHIPS OF AFFERENTS AND EFFERENTS WITH SHELL AND CORE

The Acb receives inputs from the hippocampal region, basal amygdaloid complex, prefrontal cortex, midline and intralaminar thalamus, ventral pallidum, the dopaminergic ventral tegmental (A10) and retrorubral (A8) cell groups, the serotonergic median raphe nucleus, and the noradrenergic A2 cell group in the nucleus of the solitary tract.[1,21,22–24] The projections of none of these structures are restricted to the Acb, but they extend either into the ventrally adjacent striatal parts of the olfactory tubercle and/or into the dorsally adjacent caudate-putamen complex and more caudal ventral striatal areas. Within the Acb, the projections of most of these afferent structures are inhomogeneously distributed, and they show particular relationships with the shell and core, or subregions therein (FIG. 3). However, there are no afferent systems that are exclusively related to either Acb shell or core. Thus, whereas the projections from the hippocampal subicular and CA1 regions predominently target the medial, ventral, and rostral parts of the Acb shell, these hippocampal projections also extend into the medial part of the Acb core (refs. 21 and 22; and Beijer and Groenewegen, unpublished observations).

Likewise, the medial entorhinal area projects predominently to the Acb shell, but these projections are by no means restricted to the shell, and they appear to also invade the Acb core. The lateral entorhinal area projects primarily to the Acb core but targets also the lateral part of the shell (ref. 25; and Beijer and Groenewegen, unpublished observations).

Afferents from different nuclei of the basal amygdaloid complex terminate in different parts of the Acb in a highly complex arrangement.[24] Whereas the caudal part of the parvicellular basal nucleus sends fibers predominently to the dorsomedial shell, it targets, in addition, the patches in the core. The rostral part of the magnocellular basal nucleus sends fibers to the lateral part of the Acb shell and, additionally, to the patches of the lateral Acb core. The midrostrocaudal part of the accessory basal nucleus issues fibers to the ventral part of the shell as well as to the matrix of the core. The caudal parts of the accessory basal and the magnocellular basal nuclei project to the ventromedial shell, whereas these nuclei have additional projections to the patches in the medial core of the Acb.[24]

The thalamic projections from the midline and intralaminar thalamic nuclei to the Acb likewise show specific arrangements in projecting to distinct parts of the Acb shell and either the patch or matrix compartments in the Acb core.[22,26] The anterior part of the thalamic paraventricular nucleus has a strong projection to the medial shell, as well as to the patches in the medial core of the Acb. More posterior parts of the paraventricular nucleus send fibers to more ventral and lateral parts of the shell. The intermediodorsal thalamic nucleus, a caudal representative of the midline thalamic nuclei, projects heavily to the Acb core, in particular targeting the matrix and avoiding its patches. The projections from the rostrally located parataenial nucleus include predominantly the ventral and rostral parts of the shell, avoiding its most medial and lateral parts. Additional projections reach the Acb core, but these are less dense and not strictly bound to either patch or matrix. The central medial thalamic nucleus and the medial part of the parafascicular nucleus send fibers to the rostral part of the Acb core and, in addition, extensively to the medial part of the caudate-putamen complex.[22,26]

The projections from different areas in the prefrontal cortex to the Acb are also topographically arranged. Moreover, the detailed arrangements with respect to specific compartments within the shell and core appear to depend upon the layer of origin of the prefrontal cortical projections.[13,23,27] The infralimbic cortex projects to a peripheral, band-like region in the medial and ventral parts of the shell, as well as to a region including the lateral part of the medial shell and the medial part of the core of the Acb. The lateral shell receives its cortical inputs predominantly from the ventral agranular insular area in the depth of the rostral part of the rhinal sulcus. The deep laminae (deep layer V) of the ventral prelimbic area send fibers to the dorsomedial part of the shell, as well as to the patches of the Acb core; its superficial laminae (superficial layer V and layer III) project to the matrix of the core. Similar arrangements exist for the deep versus superficial projections from the dorsal prelimbic area to, respectively, the patch and matrix compartments of the Acb core.[23, 27] However, the projections from the dorsal prelimbic area extend further rostrally into the Acb and more dorsally into the medial caudate-putamen than those from the ventral prelimbic area. The dorsal agranular insular area in the lateral part of the prefrontal cortex primarily projects to the core of the Acb and extensive parts of the ventral caudate-putamen. Superficial layers project more heavily to the matrix, deep layers to the patches of the core.[23, 28] The projections from the dorsal agranular insular and the dorsal prelimbic areas to the Acb core, in part, overlap in caudal parts of the Acb, but the dorsal prelimbic area tends to project more medially and rostrally in the Acb than the dorsal agranular insular area.

There is a clear, reciprocal point-to-point relationship between the Acb and the ventral pallidum: the medial shell and the core project to the ventromedial and the dorsal parts of the ventral pallidum, respectively.[29–31] In addition, the lateral shell projects to the ventrolateral part of the ventral pallidum (ref 31; and Groenewegen and Wright, unpublished observations). The return projections from the ventral pallidum to the Acb are organized in a comparable topographical fashion.[22,32]

The relationships of the Acb with the dopaminergic and nondopaminergic cell groups in the ventral mesencephalon are rather complex. Whereas the A10 cell group in the VTA projects predominantly to the medial and ventral parts of the shell, its fibers are by no means restricted to this area and terminate also in the medial core and adjacent regions of the caudate-putamen complex. Within the medial shell, an inhomogeneous distribution of dopaminergic fibers is apparent: whereas the cone-shaped area contains the highest density of dopaminergic fibers, the cell clusters that border this region receive virtually no such fibers (TABLE 1).[33] The retrorubral A8 cell group projects more laterally in the Acb, whereas the A9 projections in the Acb do not reach further ventrally than the core.[22,34,35] The accumbal projections to the ventral mesencephalon are arranged as follows. The medial shell sends fibers to the medial VTA; more lateral parts of the shell, that is, its ventromedial and ventral parts, innervate the lateral part of VTA, the dorsal tier of the substantia nigra pars compacta and the retrorubral area. A small number of fibers extend even further caudally to reach the midbrain tegmentum and lateral part of the central grey matter.[2,29,35,36] For the projections from the core, a distinction must be made between the patch and matrix compartments. The patches project to the substantia nigra pars compacta; the matrix sends fibers to a restricted dorsomedial part of the pars reticulata.[29,35,37–39]

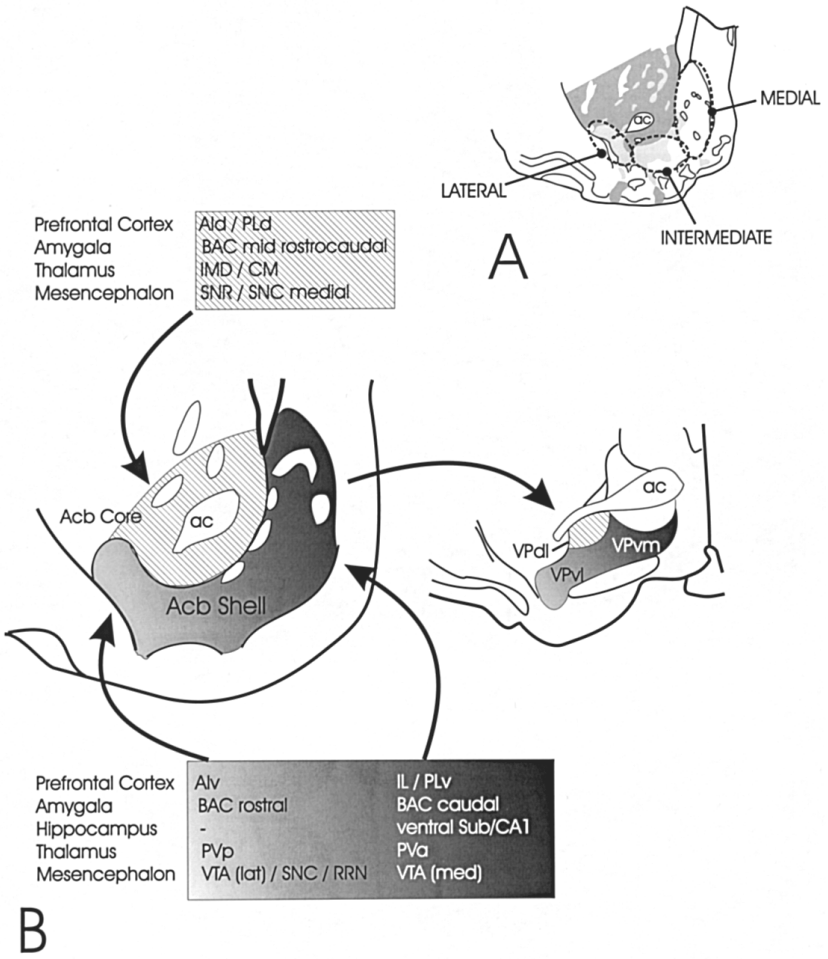


FIGURE 3. Tentative subdivision of the Acb shell and the topographical arrangements of inputs and outputs of the Acb. **A:** In a drawing of a transverse CaB-stained section through the Acb, the subdivision of the shell into medial, lateral, and intermediate parts is indicated. **B:** The broad topography of the main afferents and the ventral pallidal efferents of the core and the medial and lateral parts of the shell is represented in a transverse section through the Acb (left) and the ventral pallidum (right). ac, anterior commissure; Acb, nucleus accumbens; AId, dorsal agranular insular cortex; AIv, ventral agranular insular cortex; BAC, basal amygdaloid complex; CA1, cornu Ammonis field 1; CM, central medial nucleus; IL, infralimbic cortex; IMD, intermediodorsal nucleus; PLd, dorsal prelimbic cortex; PLv, ventral prelimbic cortex; PVa, anterior paraventricular nucleus; PVp, posterior paraventricular nucleus; SNC, substantia nigra pars compacta; SNR, substantia nigra pars reticulata; Sub, subiculum; VPdl, dorsolateral ventral pallidum; VPvl, ventrolateral ventral pallidum; VPvm, ventromedial ventral pallidum; VTA, ventral tegmental area.

An important distinction between the Acb core and shell is that the latter, at least its medial part, sends projections to the lateral preoptic and lateral hypothalamic areas.[29,31,40]

SUBDIVISIONS OF THE SHELL OF THE NUCLEUS ACCUMBENS

Taking together the immunohistochemical differentiation, for example, for CaB immunoreactivity, and the differential arrangements of afferents and efferents of the shell of the Acb, it may be suggested that this region consists of at least three subregions. Thus, a distinction can be made between a medial, a ventral, and a lateral shell (FIG. 3A). The medial shell, with its reciprocal relationships with the VTA and its strong input from the anterior paraventricular thalamic nucleus, the ventral subiculum, and the caudal basal amygdaloid nucleus, is clearly distinct from the lateral shell, which has more direct relationships with the substantia nigra pars compacta, the posterior paraventricular thalamic nucleus, and the rostral magnocellular basal amygdaloid nucleus (FIG. 3B). As discussed above, the ventral, intermedate part of the shell receives, at least to a large degree, inputs from yet another set of afferents, among which are the dorsal subiculum and midrostrocaudal parts of the basal and accessory basal amygdaloid nuclei. The borders between the ventral part of the shell on the one hand and the medial and lateral parts of the shell on the other hand are not sharp, and, as yet, no immunohistochemical markers have been described that distinguish clearly between these areas in the shell. Yet, their specific input–output relationships suggest an involvement in different functional aspects of the Acb.

Within the medial shell further distinctions should probably be made, in view of the heterogeneities in the distribution of neurochemical substances, neurotransmitter receptors, and afferent and efferent connections (see refs. above and, e.g., 41 and 42). Purely for descriptive reasons, the terms ventromedial and dorsomedial shell have been introduced (e.g., refs. 13 and 42). Functional studies indicate that the ventromedial shell may indeed be a distinct r egion of the Acb.[43]

Both neuroanatomical[12,44,45] and functional studies[46,47] suggest that there exist also rostrocaudal differences within the Acb. Zahm and Heimer,[12] on the basis of an efferent connectivity pattern distinct from the "typical" projections patterns of both shell and core, designated the rostral part of the Acb as the so-called "rostral pole." Further studies are needed to substantiate the specific identity of the rostral part of the Acb, distinct from shell and core.

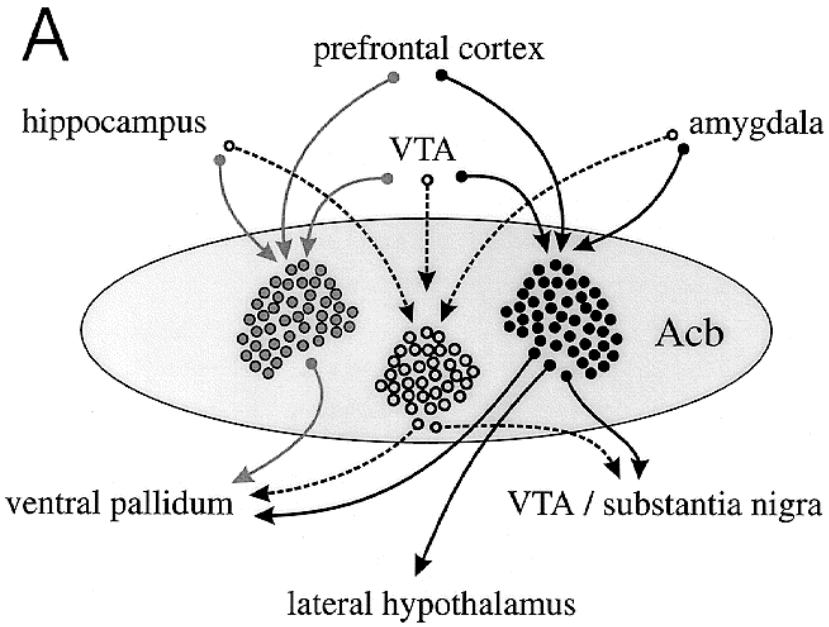
SHELL OF THE NUCLEUS ACCUMBENS: COLLECTION OF ENSEMBLES OF NEURONS?

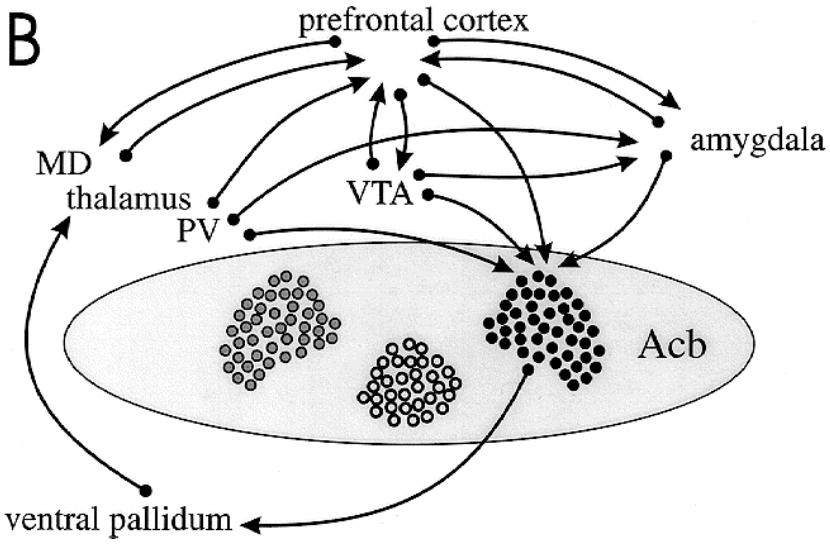
The immunohistochemical and tract-tracing data reviewed above indicate that the shell and core of the Acb should not be considered as anatomical and functional units but rather that they can be further subdivided into different subregions. Thus, the medial, intermediate, and lateral parts of the shell of the Acb, as well as the medial and lateral parts of the core, receive different combinations of inputs from cortical and subcortical sources and project to different pallidal, hypothalamic, and mesenceph-

alic targets. Moreover, within these subregions of the shell and core, the terminal fields of different sources of inputs and the neurons that give rise to different outputs are very heterogeneously distributed.[2,13,24,28,35,48,49] This leads to intricate relationships of various afferent systems in different parts of the Acb. For example, the results of double anterograde tracing experiments have shown that within the medial shell and core of the Acb the inhomogeneously distributed afferents from the anterior paraventricular thalamic nucleus, the caudal parvicellular basal amygdaloid nucleus, and the ventral prelimbic and infralimbic cortices form intricate patterns of convergence and segregation.[13] Similar arrangements of convergence and nonconvergence appear to exist in the lateral parts of the shell and core of the Acb with respect to afferents from the other parts of the midline thalamus, basal amygdaloid complex, and the (lateral) prefrontal cortex.[28] The results of retrograde tracing experiments, with small injections of retrograde tracers in one of the projection areas of the Acb, show that the Acb output neurons are organized in a clustered fashion.[2,35,49] An important question, that largely remains to be answered, is if and how the cluster-like organization of output neurons is related to the heterogeneous mosaic of convergent and segregated inputs of the Acb. In other words, to what extent does this organization reflect the existence of specific input–output channels through the Acb? Preliminary results of experiments, in which rats were injected with an anterograde tracer in one of the input structures of the Acb combined with a retrograde tracer in one of the Acb target areas, indicate that indeed particular clusters of output neurons may receive rather specific sets of inputs.[48,49]

In view of the wide range of behavorial aspects in which the Acb is presumed to play a role, Pennartz *et al*.,[50] in a recent review, argued that the nucleus consists of a collection of neuronal ensembles, or groups, with different functional and behavioral connotations. An ensemble is thought to be formed by a population of Acb neurons that is temporarily and (nearly) synchronously activated by a specific set of excitatory inputs. The coherent activity of these inputs could thus lead to the activation of a particular set of outputs of the Acb. Each distinct ensemble may be capable of generating a spatiotemporally coded output that is transferred to a set of target structures characteristic for this ensemble, and hence may induce behavioral effects that are specifically linked to this particular ensemble; [50] (see also O'Donnell *et al*., this volume). It is not a prerequisite for the idea of the existence of neuronal ensembles in the Acb that such ensembles of neurons are "bound" to a cluster of spatially closely related neurons. However, it is tempting to speculate that the experimentally shown clusters of output neurons in the above-mentioned retrograde tracing experiments, which receive different and specific combinations of converging inputs, form the anatomical substrates of such ensembles (FIG. 4A). Because only a strong exci-

FIGURE 4. Schematic representation of the input–output relationships of clusters of neurons in the shell of the nucleus accumbens. **A:** Different clusters of neurons (ensembles?) receive different combinations of converging inputs and project to distinct targets, including the ventral pallidum, the lateral hypothalamus, and the ventral mesencephalon. **B:** The various (limbic) cortical and subcortical structures that project to the Acb are strongly and, in a number of cases, reciprocally interconnected. Note that the Acb, via the ventral pallidum and the mediodorsal thalamic nucleus is involved in a closed thalamocortical–basal ganglia loop.[1,2] VTA, ventral tegmental area. Acb, nucleus accumbens; MD, mediodorsal thalamic nucleus; PV, paraventricular thalamic nucleus.


A
prefrontal cortex
hippocampus
amygdala
VTA
Acb
ventral pallidum
VTA / substantia nigra
lateral hypothalamus


B
prefrontal cortex
MD
thalamus
PV
VTA
amygdala
Acb
ventral pallidum

tatory input is thought to be able to electrophysiologically activate striatal output neurons (see below), it is important to realize that the major cortical, thalamic, and limbic inputs of the Acb have extensive, and in most cases, reciprocal interconnections (FIG. 4B). This extensive interconnectivity of the afferent structures of the Acb could be the anatomical basis for the temporarily coherent and synchronous activation of the populations of neurons that constitute the ensembles in the Acb (FIG. 4).

As indicated above, for an understanding of the way in which ensembles of Acb neurons may be activated, it is of great interest to consider the specific physiological properties of the Acb output cells, that is, the medium-sized spiny neurons. These spiny output neurons, both in the caudate-putamen complex [51] and the Acb, [52] have a bistable membrane potential, that is, they are mostly in a state with a hyperpolarized membrane potential of −85 to −90 mV ("down state"), but occasionally they reach a state with a relatively depolarized membrane potential of approximately −55 mV ("up state"). Only in neurons in the up state, of which the membrane potential is close to the spike threshold, can firing of action potentials be induced; neurons in the down state are physiologically "silent." It is thought that excitatory inputs from a particular source can bring striatal output neurons from the down state into the up state, but that excitatory inputs from yet another source are necessary to induce firing activity.[50–52] For example, hippocampal activation may bring Acb output neurons in their up state and, in this way, facilitate the throughout of prefrontal cortical activity via the Acb, as observed by O'Donnell and Grace,[52] in an intracellular electrophysiological study. Following lesions of the hippocampal afferents to the Acb, the Acb output neurons remain in their down state, and prefrontal cortical activition is not able to evoke Acb neuronal firing. Therefore, O'Donnell and Grace[52] have suggested that hippocampal inputs "gate" the prefrontal cortical throughput through the Acb. In an extracellular electrophysiological study, investigating the interactions between hippocampal and amygdaloid afferents in the Acb, Mulder *et al.*[53] found that amygdaloid activation facilitates hippocampal throughput through the nucleus but that, in contrast, hippocampal activation may close a gate for amygdaloid inputs. Although the observations of O'Donnell *et al.*[52] and Mulder *et al.*[53] cannot be completely reconciled with each other, they suggest that various afferents of the Acb interact with each other at the level of the output neurons, one of the possible consequences being that two or more afferents have to be active in temporal and spatial coherence to activate output neurons of the Acb. In that respect, it is of great importance to study in detail the input–output patterns at the level of the Acb, in order to understand the various possible interactions of inputs and, in this way, the activation or modulation of a multitude of outputs of the nucleus.

CONCLUDING REMARKS

The above reviewed data, with respect to the functional anatomical organization of the Acb, as part of the ventral striatum, indicate that this nucleus consists of various different subregions (e.g., medial and lateral shell and core, etc.) and that within these subregions functionally distinct ensembles of neurons exist, possibly organized in anatomical compartments and activated by specific sets of afferents that are primarily derived from (subregions of) limbic structures. It is thus important to note

that the Acb neuronal ensembles must be viewed in close association with groups of neurons in prefrontal cortical, amygdaloid, and midline/intralaminar thalamic structures (as described above), which, in turn, have strong mutual interconnections (FIG. 4B). Such interconnections between structures that are afferent to the Acb may be crucial for the spatially and temporally coherent activation of the presumed ensembles in the Acb. How and under which functional circumstances the Acb neuronal ensembles are activated, and whether they can influence each other, are all important questions that need to be answered in order to further our understanding of the functional anatomy of the nucleus accumbens.

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