

The Concept of the Ventral Striatum in Nonhuman Primates

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ABSTRACT: The concept of the ventral striatum was first put forth by Heimer and Wilson to describe the extension of basal ganglia elements into the olfactory tubercle. The ventral striatum includes the conventional nucleus accumbens, which has been closely associated with reward and motivation. This paper uses the afferent connections to the ventral striatum to define this region in monkeys. Furthermore the shell and core subterritories are discussed with respect to their histochemistry and specific connections.

INTRODUCTION

This chapter addresses how the primate ventral striatum and the subterritories within it might be defined based on afferent connections from structures associated with reward and motivation. The nucleus accumbens is that part of the ventral striatum that has long been associated with the limbic system or with that group of structures thought to mediate motivational and emotional responses to environmental stimuli. This association is based on, among other things, its afferent connections from the amygdala and prefrontal cortical areas, considered to be involved in mechanisms of reward and positive reinforcement. The concept of the ventral striatum was originally developed in the classic paper by Heimer and Wilson in 1975 that describes the relationship between the nucleus accumbens and the olfactory tubercle in rats. The authors showed that striatal-like and pallidal-like elements of the olfactory tubercle constitute a ventral continuation of the striatum, and, therefore, together with the nucleus accumbens, these structures should be referred to as the ventral striatum.¹ Since then, the ventral striatum and its connections have been at the center of the reward circuit, and, as such, have been a research focus of the neurobiological mechanisms underlying drug addiction and mental disorders.²⁻⁴ Thus, our concept of the striatal region implicated in reward has evolved to include more than the traditional boundary of the nucleus accumbens, and it extends into the ventral forebrain.

SUBTERRITORIES OF THE VENTRAL STRIATUM

Recently, a subterritory of the ventral striatum, the shell region, has been identified dividing the ventral striatum into two parts, a medial/ventral shell region, and a

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central core region.⁵ Experiments aimed at delineating the functional significance of these two regions have been instrumental in understanding the circuitry underlying goal-directed behaviors, behavioral sensitization, and changes in affective states. Studies in rodents have been particularly important in demonstrating the organization of the shell and core and their relationship to distinct ventral striatal afferent and efferent projections. These studies provide critical information on how interactions between specific transmitter/receptor pathways mediate the transition between motivating stimuli and motor outcome.^{6–11} Whereas several transmitter and receptor distribution patterns distinguish the shell/core subterritories, calbindin-28 is the most consistent marker for the shell across species.¹²

In primates, as in rodents, the ventral striatum is divided into two territories: the inner core, which is calbindin rich, and the outer crescent-shaped shell, which is calbindin poor. Although a calbindin poor region marks the subterritory of the shell, staining intensity of other histochemical markers varies both within the shell and in distinguishing it from the core. These markers include enkephalin; acetylcholinesterase; neurotensin; the μ opiate receptor; the growth-associated protein, GAP-43; the AMPA subunits, GluR1, GluR2/3, and GluR4; the dopamine transporter; and serotonin. In general, compared to the core, the shell is rich in GluR1, GAP-43, acetylcholinesterase, μ receptor binding, serotonin, and substance P^{13–18} (FIG. 1). Substance P is distributed in patches throughout the striatum but is particularly dense in the shell. Acetylcholinesterase is very dense in the medial part of the shell. More laterally, however, the staining blends into the core and becomes indistinguishable from that observed in the remainder of the ventral striatum. Immunoreactivity for neurotensin is relatively low throughout the striatum; however, staining is dense in the medial rim of the shell. Enkephalin immunoreactivity is patchy throughout the striatum and does not show a remarkable differential pattern between the shell and core. Serotonin staining is dense in the shell, with the highest immunoreactivity in the medial dorsal portion. The dopamine transporter is relatively low throughout the ventral striatum, including the core. This pattern is consistent with the fact that the dorsal tier dopamine neurons express relatively low levels of mRNA for the dopamine transporter compared to the ventral tier.¹⁹ Whereas GAP-43 immunoreactivity is found throughout the adult striatum, the shell region stands out with the strongest antisera reaction. The μ receptor distribution is dense but patchy in the ventral striatum. There are dense patches in the medial and ventral shell, with the remainder remarkably free of receptor. By contrast, the core shows numerous patches of immunoreactivity that extend into the medial wall of the ventral caudate. Most of the excitatory amino acid receptors do not distinguish the dorsal striatum and ventral striatum. However, the AMPA receptor subunits do. The GluR1 subunit shows particularly dense immunoreactivity in the shell, with patches of reactivity in the core. By contrast, the GluR4 subunit shows weaker immunoreactivity in the shell than in the rest of the striatum. Taken together, neurotransmitters and receptors help distinguish the ventral and medial borders of the ventral striatum and the shell/core subterritories within it. However, the dorsal and lateral boundaries are more problematic. Here, the ventral striatum merges imperceptibly with the dorsal striatum.

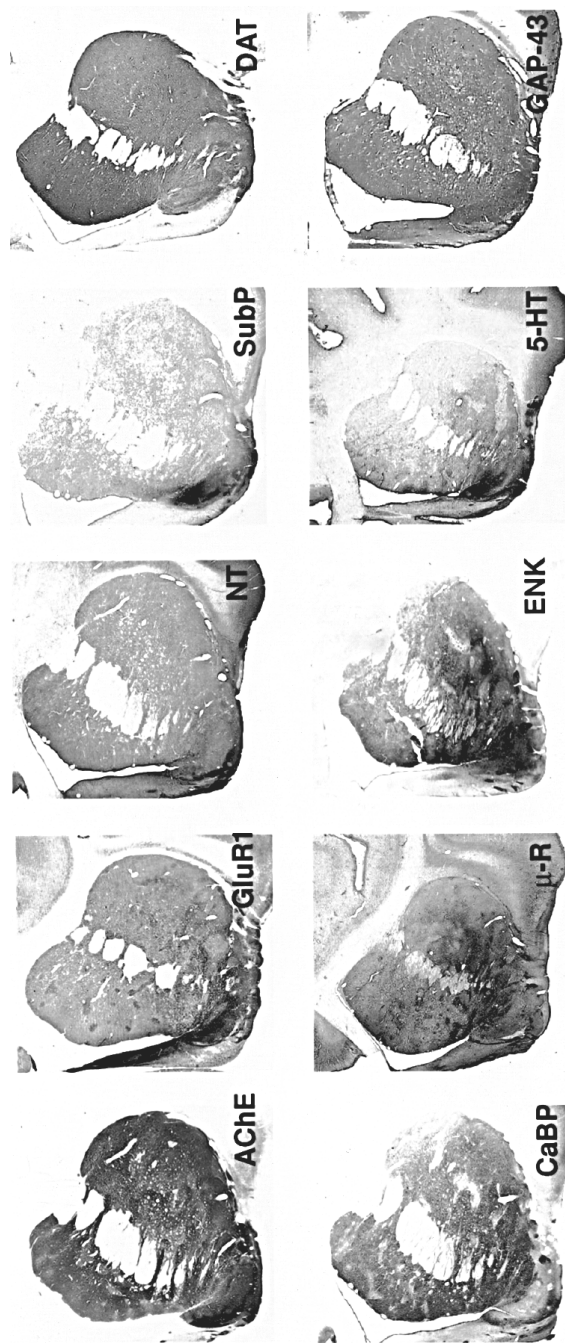


FIGURE 1. Photomicrographs of the striatum at the level of the shell and core, immunostained for various transmitter-related molecules. AChE, acetylcholinesterase; NT, neurotensin; SubP, substance P; DAT, dopamine transporter; CaBP, calbindin-28; μ -R, μ -opiate receptor; ENK, enkephalin; 5-HT, serotonin; GAP-43, growth-associated protein-43.

DISTINGUISHING THE VENTRAL FROM DORSAL STRIATAL TERRITORY

Several morphological characteristics are unique to the ventral striatum. It contains smaller and more densely packed neurons than the more homogenous dorsal striatum. Furthermore the organization of striosome (patch)-matrix compartments observed in the dorsal striatum is not characteristic of the ventral striatum. Instead, a complex relationship between transmitter systems exists that is not easily defined by a two-compartment system. Finally, unlike the dorsal striatum, the ventral striatum is invaded by many pallidal elements.^{13,20,21} Although these are important distinguishing features, neither these cytoarchitectonic distinctions nor histochemical markers indicate a clear boundary between it and the dorsal striatum. Thus, the border between the core and the dorsal striatum is ambiguous. Given the central importance of this region for understanding the motivational neuronal networks and the fact that it is the target of studies that focus on the underlying mechanisms of response to emotional stimuli, we set out to gain a better definition of what to include in the ventral striatal territory in nonhuman primates and how to distinguish it from the dorsal striatum.

Because the ventral striatum is considered to be that part of the striatum associated with "reward," an operational anatomic definition of its boundaries should be based on afferent projections from brain regions important for mediating the development of reward-associated responses. The main afferent projection to the striatum is from the cortex. Frontal cortical inputs to the striatum are massive and represent the defining feature of separate functional circuits.²²⁻²⁵ Information flow through the basal ganglia begins in functionally distinct regions of the frontal cortex as nodal points, with projections to anatomically distinct sectors of the striatum, the pallidum, the substantia nigra, and the thalamus. The thalamocortical pathway completes the circuit to frontal cortex. These pathways form functionally distinct loop systems that include the sensorimotor circuit (sensorimotor cortex); strategic planning and procedural memory circuit (dorsolateral prefrontal cortex); and the development of reward-associated responses, or the limbic circuit (medial and orbital prefrontal cortex, OMPFC). In addition to cortex, the other two main inputs to the striatum are from the thalamus and midbrain. All three afferent projecting systems are multifunctional, in that they contain distinct nuclear groups or regions, each involved specifically in sensorimotor, cognitive, or emotive processing. Our criteria for defining the ventral striatal region is that the afferent connections be derived from the OMPFC and thalamic and midbrain regions associated with reward, and exclude inputs from other cortical, thalamic, and midbrain regions. We used retrograde tracer techniques to characterize the afferent organization to the striatum from cortex, thalamus, and midbrain.²⁶⁻³⁰

Frontal Cortical Projections to the Striatum

The association of the frontal cortex with specific functions is well established. The orbital and medial prefrontal cortex (OMPFC) is involved in linking primary rewards with motivational and emotional features and plays a key role in the development of reward-guided behaviors. Lesions result in an inability to initiate and carry out goal-directed behaviors.³¹⁻³⁵ The recruitment of activity in the OMPFC with be-

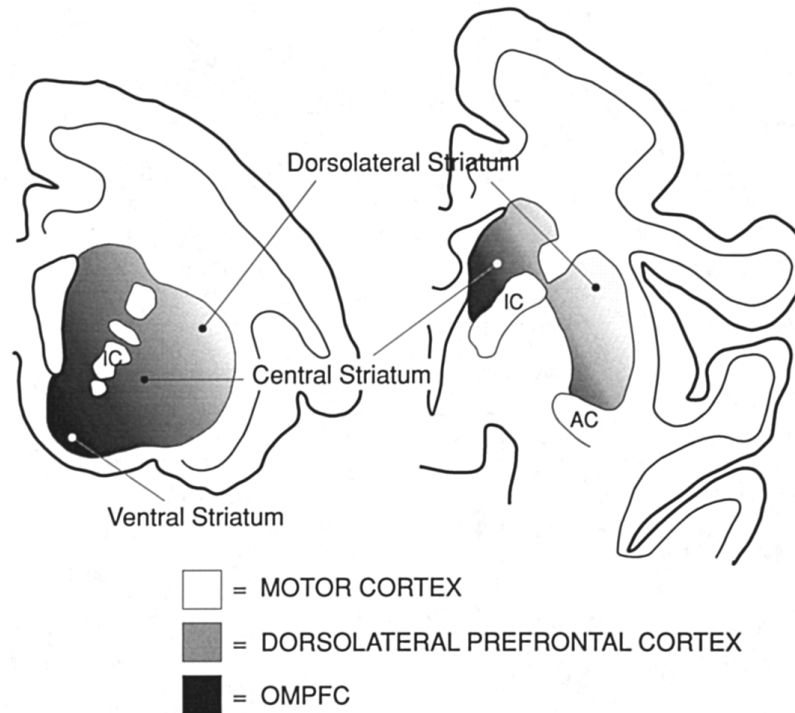


FIGURE 2. Schematic of corticostriatal topography.

haviors dependent on motivation and positive reinforcement is consistent with anatomical and physiological studies of the OMPFC. It receives input from, and can be stimulated by, olfactory, gustatory, and visceral sensations, all related to the assessment of palatable foods. These sensory afferent projections, coupled with visual input that associates food reward with an object, and inputs from the amygdala, attach emotional components to the primary reward.³⁶⁻⁴³ By contrast, motor, premotor, and supplementary motor cortices (areas 4, 6, and 8) are involved in motor and sensorimotor function and integration, and the dorsolateral prefrontal cortex (areas 46, 45, and 9) is involved in procedural learning and strategic planning.^{22, 25}

Projections from frontal regions form a functional gradient of inputs from the ventromedial sector through the dorsolateral striatum, with the OMPFC terminating in the ventromedial part, and the motor cortex terminating in the dorsolateral region (see FIG. 2). Within this gradient, our studies indicate that the cortical projections to the striatum are quite precise, and, depending on the location of relatively small injection sites, only specific cortical regions contain labeled cells (FIG. 3). In general, motor areas (areas 4, 6, and 8), but not from the OMPFC, project to the dorsolateral striatum. By contrast, the OMPFC (areas 24, 25, 32, 14, 13, and 12) projects to the ventral striatum, but not to the dorsolateral striatum. The dorsolateral prefrontal cortex (areas 9, 46, and 45) projects centrally, with little or no afferent projection to the calbindin-poor shell region or to the ventral rostral putamen, the ventral caudate nu-

Cortical Area	Ventromedial Cases							Central			Dorsolateral Cases									
	82	28	33	13	94W	38	35	89	94L	96	39	32	44	43	45	29	37	66L	102	
4	-	-	-	-	-	-	-	-	-	-	++	-	++	++	++	++	++	++	++	
6	-	-	-	-	-	-	-	++	-	-	++	++	++	++	++	++	++	+	+	
24c	-	-	-	-	-	-	-	++	++	++	++	++	++	++	++	++	++	++	++	
8	-	-	-	-	-	-	-	++	++	++	++	-	+	+	++	-	-	-	-	
9	-	-	-	-	-	-	-	++	+	+	-	-	-	-	-	-	-	-	-	
45/46	-	-	-	-	-	-	+	++	++	++	-	-	-	-	-	-	-	-	-	
12	-	+	++	++	++	++	++	++	++	++	-	-	-	-	-	-	-	-	-	
11	-	-	++	++	-	++	++	+	+	+	-	-	-	-	-	-	-	-	-	
13	-	-	+	-	++	++	++	++	+	-	-	-	-	-	-	-	-	-	-	
13a/b	-	++	++	++	++	++	++	++	+	-	-	-	-	-	-	-	-	-	-	
24a/b	-	+++	+++	+++	++	+++	+++	+++	+	++	-	+	-	-	-	-	-	-	-	
32	+	+++	+++	+++	+	++	+++	+++	-	-	-	-	-	-	-	-	-	-	-	
14	++	++	++	++	++	+	-	++	-	-	-	-	-	-	-	-	-	-	-	
1a	+++	++	++	++	++	++	-	-	-	-	-	-	-	-	-	-	-	-	-	
25	+++	+++	+++	+++	+	++	++	+	-	-	-	-	-	-	-	-	-	-	-	

FIGURE 3. Corticostriatal projections. Relative density of retrogradely labeled neurons in frontal cortical areas after injections of retrograde tracers into ventral, central, and dorsolateral striatal regions.

cleus, and the medial wall of the rostral caudate nucleus. Thus, the ventral striatum in primates can be viewed as that part of the striatum that receives prefrontal lobe input from the OMPFC but not from the dorsolateral prefrontal cortex or the sensorimotor cortex.

Thalamic Projections to the Striatum

Projections to the striatum from the thalamus are derived from the midline, the intralaminar nuclei, and the ventral tier nuclear group. The midline thalamic nuclei are most closely associated with the limbic system by virtue of their connections to the amygdala, hypothalamus, and cingulate cortex. The ventral tier nuclei and the centromedian nucleus of the intralaminar group are most closely aligned with the motor system via their connections to the motor and premotor cortex. Finally, the parafascicular nucleus of the intralaminar group and the dorsomedial nucleus are associated with the dorsolateral prefrontal area.^{44,47} Although the boundaries within the intralaminar group are difficult to define, the more lateral portions of the intralaminar complex are connected to the motor cortex, whereas the medial regions are connected to the prefrontal areas. The midline nuclei and the medial parafascicular nucleus project to the ventral striatum, whereas the ventral tier and the centromedian nucleus project to the dorsolateral "sensorimotor" striatum. The midline thalamic nuclei and medial part of the parafascicular nucleus do not project to the

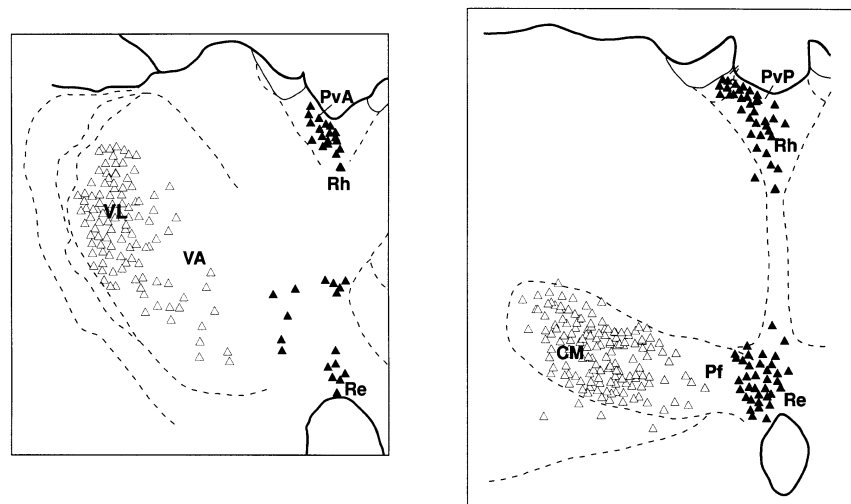


FIGURE 4. Thalamostriatal projections. Distribution of labeled cells in the thalamus after injections of retrograde tracers into the dorsolateral and ventral striatum. Filled triangles, distribution of cells labeled following ventral striatal injection sites; unfilled triangles, distribution of cells labeled following dorsolateral injection sites. CM, center median nucleus; Pf, parafascicular nucleus; PvA, anterior paraventricular nucleus; PvP posterior paraventricular nucleus; Rh, rhomboid nucleus; Re, nucleus reuniens; VA, ventral anterior nucleus; VL, ventral lateral nucleus.

dorsal striatum, and, conversely, the centromedian nucleus and the ventral tier nuclei do not project to the ventral striatum. In contrast to the ventral striatum, the dorsolateral striatum receives input from the lateral intralaminar nuclei (FIG. 4). These thalamostriatal projections support the notion that inputs to the striatum are organized along functional domains, with the ventral striatum receiving its thalamic input from the neurons located on or near the midline.

Midbrain Dopamine Projections to the Striatum

The midbrain dopamine neurons are divided into two groups: a dorsal tier and a ventral tier. The dorsal tier includes both the dorsal substantia nigra, pars compacta (SNc) and the contiguous ventral tegmental area (VTA). Cells in this region are oriented horizontally and are calbindin positive. The ventral tier cells are calbindin negative and include both the densocellular cell group and the cell columns that extend deep into the pars reticulata (FIG. 5a). Inputs to all striatal regions are from the entire rostrocaudal extent of the substantia nigra. The midbrain input to the sensorimotor-related striatum is from the ventral tier of dopaminergic neurons, both the densocellular region and the cell columns. The dorsal tier (the VTA and the dorsal SNc) do not project here.³⁰ Within the densocellular region, groups of cells that project to the sensorimotor striatum are found in the lateral two thirds; these cells do not extend to its medial border with the VTA. The projections to the ventral striatum originate primarily from the medial half of the midbrain neurons, but from both the dorsal and ventral tiers. However, it is only the densocellular region of the ventral tier that projects here: the cell columns do not.^{30,48} The midbrain projections to the central region of the striatum are derived from a wide range of dopaminergic neurons in both the dorsal and ventral tiers. The majority come from the densocellular part of the ventral tier, but some come also from the dorsal SNc. Thus, three groups of neurons can be distinguished: the dorsal tier, which projects to the ventral striatum; the cell columns, which project to the dorsolateral striatum; and an intermediate area, the densocellular part of the ventral tier, which projects primarily to the central striatum (FIG. 5b). However, within the densocellular group, there is some intermingling of cells that project to different striatal territories. This results in a large area of the striatum that is modulated by inputs from the densocellular group.

Summary of Corticostriatal Topography

Based on the afferent projections from cortex, thalamus, and midbrain, we can define the ventral striatum as that part of the striatum that receives inputs from the OMPFC but not from motor, premotor, or supplementary motor regions of the frontal cortex and few, if any, from areas 9 and 46. In addition, the amygdala, the most widely recognized structure associated with emotional behavior projects extensively to the ventral striatum.^{49–54} Our experiments demonstrate that, in contrast to the ventral striatum, there were no labeled cells in the amygdala following retrograde tracer injections into the dorsolateral (sensorimotor) striatum. It receives input from the midline thalamic nuclei and the medial-most part of the intralaminar nuclear group. The lateral part of the intralaminar nuclei and the ventral lateral nucleus do not project here. Finally, the dorsal tier of the midbrain dopamine neurons and the dorsal part of the densocellular group project to the ventral striatum. By contrast, the cell

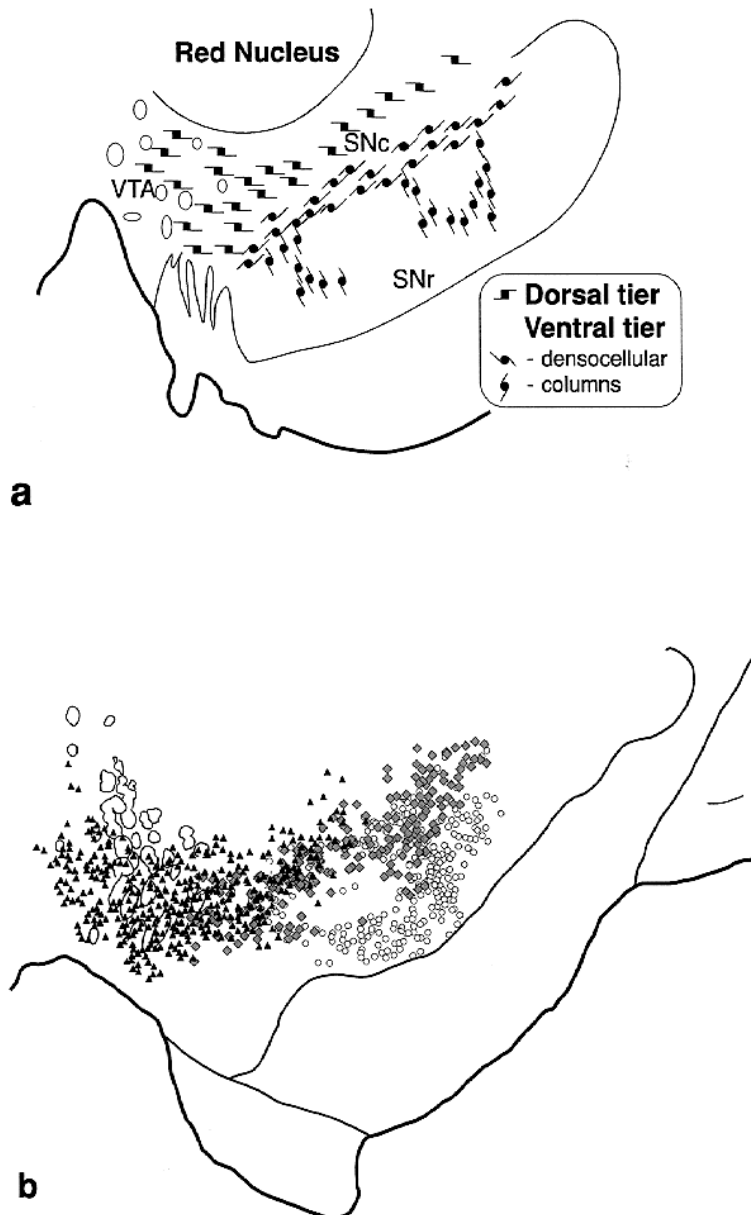


FIGURE 5. a: Schematic of the substantia nigra in the tiers of the midbrain dopamine neurons. VTA, ventral tegmental area; SNc, substantia nigra, pars compacta; SNr, substantia nigra, pars reticulata. **b:** Midbrain striatal projections. Distribution of labeled cells in the midbrain after injections of retrograde tracers into the dorsolateral and ventral striatum. Filled triangles, distribution of cells labeled following ventral striatal injection sites; filled diamonds, distribution of cells labeled following central injection sites; unfilled circles, distribution of cells labeled following dorsolateral injection sites.

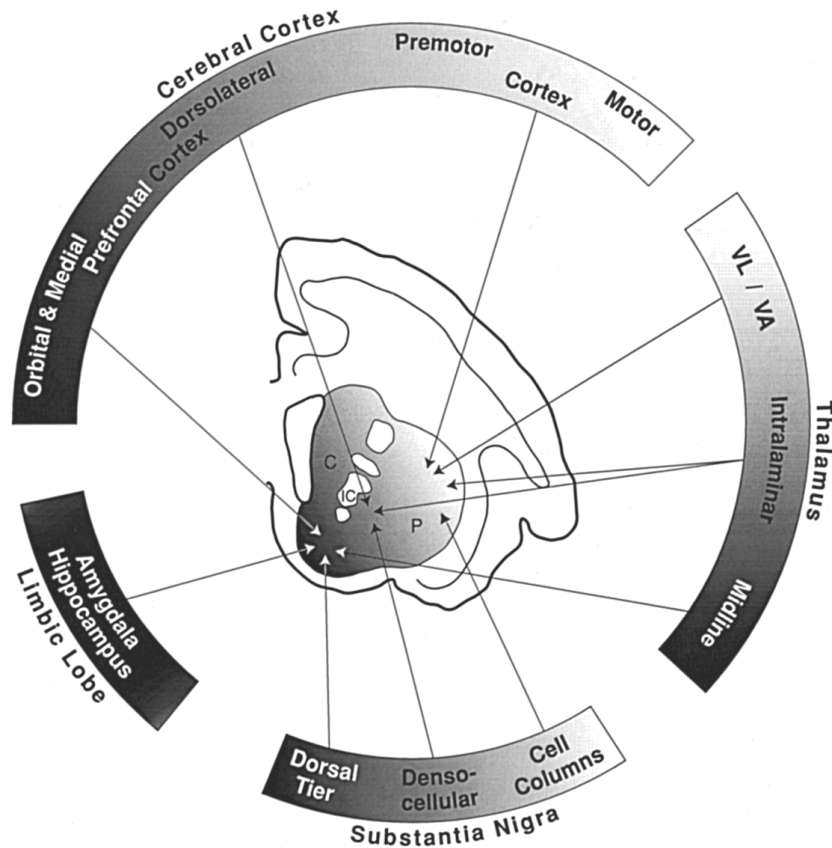


FIGURE 6. Summary diagram illustrating striatal territories based on inputs from specific cortical, thalamic, and midbrain regions.

columns do not. The ventral striatum receives little, if any, input from the dorsolateral prefrontal cortex. However, at the junction between the ventral striatum and the central striatum, projections from the OMPFC and dorsolateral prefrontal cortex do overlap. This transition region also receives mixed innervation from the intralaminar nuclei of the thalamus and the densocellular midbrain group (FIG. 6).

SPECIFICITY OF PROJECTIONS TO THE VENTRAL STRIATUM

OMPFC Projections

The OMPFC includes the anterior cingulate cortex, medial and lateral orbital cortex, and agranular insular cortex (Ia).⁵⁵ Based on clinical, behavioral, and connective studies, the OMPFC can be divided into general areas: a medial prefrontal region (areas 25, 24a/b, and 32), a medial orbital region (areas 13a/b, 11, and 14),

and a lateral region (areas 12, 13m, and 13l). Areas 25 and Ia are most closely linked to connections with the amygdala. Areas 24 a/b, 14, and 13a/b are in a pivotal position. Like areas 25 and Ia, they receive input from the amygdala, albeit less. Area 13 receives the least input from the amygdala. Thus, these prefrontal cortical areas are arranged, such that areas 24 a/b and 13a/b provide a bridge between areas receiving a dense projection from the amygdala and those that do not.^{38,39}

Our retrograde studies show that the shell receives the densest OMPFC innervation from medial areas 25, 14, and 32, 24a/b, and Ia. The medial shell has the most limited inputs, which are from areas 25, 14, and Ia. In addition to afferent projections from these areas, the ventral shell receives input from areas 24 a/b and area 32. Medial areas 25, 14, 24, and 32 also project to the medial wall of the caudate nucleus. This area of the caudate nucleus also receives a dense innervation from areas 13a/b and from parts of the dysgranular insular cortex. By contrast, the central and more

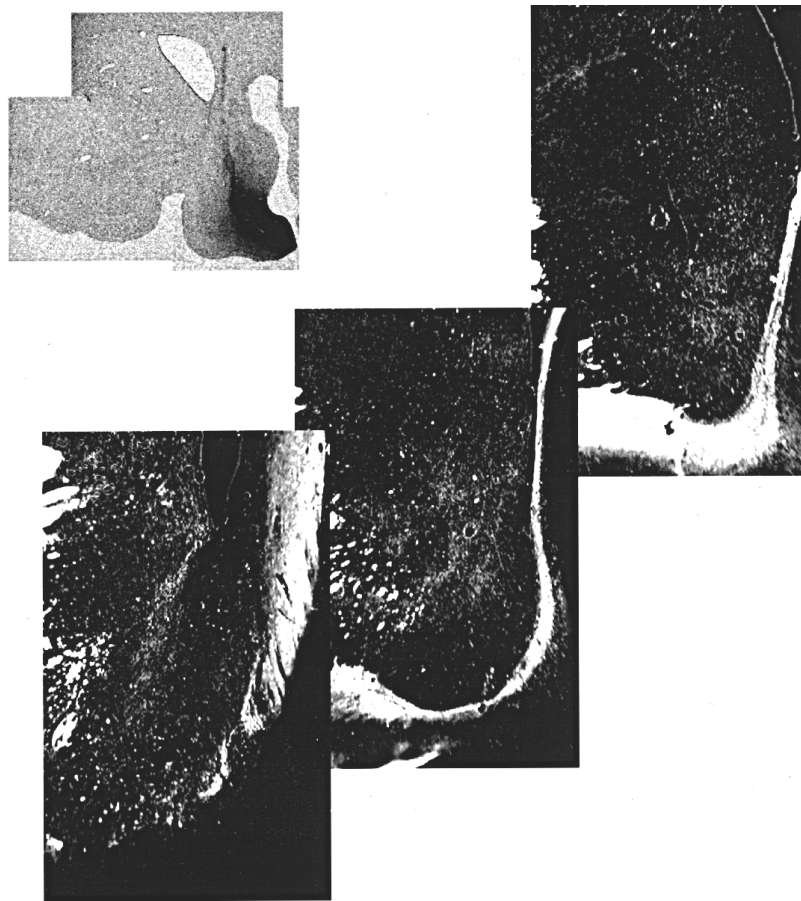


FIGURE 7. Fiber distribution in the rostral striatum following an anterograde tracer injection into the medial prefrontal cortex.

lateral core receives fewer inputs from areas 25 and Ia, and a denser projection from lateral OMPFC regions, areas 13 and 12, and the dysgranular insular cortex.^{26–28} It is of interest to note that the part of the cingulate cortex, area 24c, that is closely connected to motor areas does not project to the ventral striatum.

Injections of anterograde tracers confined to areas 14 and 13a of the OMPFC confirmed the retrograde experiments. Clusters of fibers are distributed in the ventral striatum, just rostral to and at the level of the anterior commissure. There were no terminals in the dorsolateral striatum. Fibers are primarily located in the core, with a few patches in the shell. The densest projection field was along the medial wall of the ventral caudate nucleus. Fibers extend rostrally through the rostral caudate nucleus (FIG. 7). Here, they are no longer limited to the ventral part of the striatum, but they appear in the central regions as well. In summary, the CaBP-poor shell region receives the most limited OMPFC projection. This projection is derived primarily from medial areas 25, 32, 24a/b, and from Ia. The core receives more widespread OMPFC projections. Of particular interest is that the OMPFC projection extends dorsally and rostrally from the conventionally defined nucleus accumbens into the ventral caudate nucleus and throughout a large part of its rostral pole.

Thalamic Projections to the Striatum

All regions of the ventral striatum receive dense projections from the midline thalamic nuclei and from the medial parafascicular nucleus.²⁹ The midline nuclei include the anterior and posterior paraventricular, parataenial, rhomboid, and reuniens thalamic nuclei. The shell of the nucleus accumbens receives the most limited projection. The medial shell is innervated almost exclusively by the anterior and posterior paraventricular nuclei and the medial parafascicular nucleus. The ventral shell receives input from these nuclei as well as from the parataenial, rhomboid, and reuniens midline groups. The medial wall of the caudate nucleus receives projections, not only from the midline and the medial intralaminar nuclei, but also from the central superior lateral nucleus, and a limited input from the magnocellular subdivision of the ventral anterior nucleus. By contrast, the central core receives a limited projection from the midline thalamic nuclei, predominantly from the rhomboid nucleus. It also receives input from the parafascicular nucleus and the central superior lateral nucleus. In summary, midline nucleus thalamic input to the medial shell is mostly confined to a specific group of cells. The ventral shell receives a more widespread midline nucleus afferent projection. Additional thalamic nuclear groups project to the medial wall of the caudate nucleus. Finally, the central core receives the smallest midline thalamic projection.

Midbrain

The neurons innervating the shell of the nucleus accumbens originate from the dorsal tier of mesencephalic neurons, including the dorsal SNc and the VTA.⁴⁸ These cells project to all ventral striatal regions. The ventral tier (densocellular part) also projects throughout the ventral striatum, with the exception of the medial shell region. This projection is derived from the medial and dorsal part only (primarily the VTA), and it varies in intensity in different ventral striatal regions. The ventral shell receives a very limited projection from the densocellular group, from cells located

in the most medial and dorsal region. The midbrain projections to the medial wall of the caudate nucleus is from a wider medial-lateral range of the densocellular group, but are located in its dorsal portion. The central and lateral core region derives the least amount of its afferent projection from the dorsal tier. More laterally and ventrally placed cells of the ventral tier project to the core, compared to the shell or medial wall of the caudate nucleus. Injections of retrograde tracers into the rostral striatum label the most dorsal group of densocellular neurons. Thus the topography of the midbrain-ventral striatal projection is such that input to the medial shell is derived only from the dorsal tier. Input to the ventral shell is primarily from the dorsal tier, with only a few cells that project there from the medial, dorsal densocellular group. Both the dorsal tier and the dorsal densocellular group project to the medial wall of the caudate and to the central and lateral core.

THE VENTRAL STRIATAL TERRITORY

Taken together, the ventral striatum in primates encompasses a large ventromedial region, the bulk of which extends from the anterior commissure to the rostral pole of the caudate nucleus. The shell receives the most limited input from the cortex, thalamus, and midbrain. This input is from areas 32, 25, 14, and 1a, the midline thalamic nuclei, and the dorsal tier of the midbrain dopamine neurons. Each of these areas is most closely aligned with other brain structures that mediate emotional responses, including the amygdala and hypothalamus. Within the shell there is a relative difference in afferent projections to the medial and ventral parts. The medial region, just beneath and medial to the ventricle, receives the most restricted input, which is derived almost entirely from areas 25 and 1a, the paraventricular midline thalamic nucleus, and the medial dorsal tier (the VTA) of the midbrain. In addition to these regions, the ventral shell receives input from areas 24a/b and 13a/b, the rhomboid and parataenial midline thalamic nuclei, and a limited input from the medial densocellular midbrain group. The medial wall of the caudate nucleus receives input from the same areas as the shell but also from additional cortical, midbrain, and thalamic areas that do not project extensively to the shell. These include other OMPFC areas, denser labeling in nonmidline thalamic regions, and wider spread input from the densocellular group of midbrain neurons.

These studies illustrate that although the inputs to the shell region in primates are more restricted than to other parts of the ventral striatum, they are not unique. Medial OMPFC areas innervate the shell and medial caudate nucleus. In addition, more lateral areas, 13 and 12, project throughout the core. The midline thalamic nuclei project most densely to the medial caudate nucleus and to the shell region. In addition, however, the medial caudate nucleus also receives a dense innervation from several thalamic nuclei (i.e., the ventral anterior nucleus) that do not project to the shell. Finally, the shell receives input from the dorsal tier of the midbrain dopaminergic neurons but not from the ventral tier. By contrast, both the dorsal and ventral tier neurons project to the rest of the ventral striatum. Thus in monkeys we can define a relatively small shell region that receives a specific and limited afferent projection most closely linked to the amygdala and hypothalamus. However, extending beyond the CaBP-negative borders is a more extensive area that also receives inputs from

areas associated with reward. FIGURE 6 illustrates the more restricted inputs to the shell region that blend with additional inputs in the medial ventral striatum. The connectional similarities between the shell and the medial wall of the caudate nucleus suggest that although the medial wall is not CaBP negative, it may be a transitional zone between the shell and the core.

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