New Column Series

The Ventral Striatum as an Interface Between the Limbic and Motor Systems

By Henk J. Groenewegen, MD, PhD
Introduction by Michael Trimble, MD, FRCP, FRPsych

INTRODUCTION

Over the next 2 years, *CNS Spectrums* will be publishing a series of articles on neuroanatomy. The purpose of these articles is to broaden knowledge and interest in neuroanatomy, with a special reference to some key brain structures that are important for neuropsychiatry. Interest in nuclear structures and hodology, in connectivity and circuitry between brain regions, and in neurochemical associations has increased in the last 3 decades due to new neuroanatomical staining methods, brain imaging, and new treatments, such as deep brain stimulation. These columns will enliven an understanding of the clinical neuroscience interface but also provide a solid framework of contemporary neuroanatomy for psychiatrists and neurologists.

The first in the series reviews the ventral striatum. Henk J. Groenewegen, MD, PhD, in a column dedicated to the late Lennart Heimer, MD, reveals the importance of this structure and its connectivity for a contemporary understanding of brain-behavior relationships. In earlier conceptions, the basal ganglia were solely related to motor function, uninvolved with emotion or cognition. This conception arose from a misunderstanding of basic neuroanatomy, which has been unravelled by careful neuroanatomical studies in the last 30 years with new tissue staining and tracing techniques. The basal ganglia are the main target structures of the limbic system, hence the motion in emotion.

THE VENTRAL STRIATUM

The ventral striatum is generally considered that part of the striatum that is connectionally associated with limbic structures, such as the amygdala, hippocampus, midline thalamus, and certain regions of the prefrontal cortex. In addition, the ventral striatum is strongly innervated by dopaminergic fibers from the ventral tegmental area (VTA [A10 cell group]), known as the mesolimbic dopamine system, and has the highest density of serotonergic inputs in the striatum. In its present connotation, the term

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"ventral striatum" was introduced in 1975 by Heimer and Wilson[1] to differentiate it from the dorsal, sensorimotor-related part of the striatum (ie, the caudate-putamen complex). This inclusion of ventrally located striatal tissue in a "unified" striatum, along with the recognition of connectionally associated pallidal elements in the substantia innominata and deep layers of the olfactory tubercle (ie, the ventral pallidum), has had great impact on the functional-anatomical concept of the basal ganglia. Whereas traditionally, the basal ganglia were thought to be primarily involved in sensory-motor functions,[1,2] it has now become accepted that the basal ganglia, as a result of their involvement in a set of parallel, functionally segregated basal ganglia-thalamocortical circuits, which primarily entertain the premotor and prefrontal cortical cortices, are also involved in cognitive and "limbic" functions.[2] Thus, in line with the characteristics of its inputs, the ventral striatum is functionally strongly associated with emotional and motivational aspects of behavior. Moreover, structural and functional disturbances of ventral striatal areas have been shown to be correlated with various forms of psychopathology, such as schizophrenia, addictive behavior, and obsessive-compulsive disorder.[3-7]

DORSAL VERSUS VENTRAL STRIATUM

It is important to note that the distinction between a dorsal and ventral striatum on the basis of specific cortical, thalamic, and dopaminergic inputs does not provide sharply defined borders between these striatal areas. To date, no other structural or functional markers uniquely characteristic for either of the two regions have been identified. In the literature, dorsal and ventral striatum have been virtually equalized with the distinction between the caudate-putamen complex and the nucleus accumbens, respectively.[8] However, the ventral striatum as defined on the basis of the aforementioned limbic inputs, as well as based on cyto- and chemoarchitectonic characteristics, occupies a more extensive striatal area than the nucleus accumbens alone and extends more dorsally and caudally into the ventral parts of the caudate nucleus and putamen.[8,9] Since most of our knowledge of the ventral striatum derives from data obtained in the nucleus accumbens, the remainder of this brief account primarily refers to this part of the ventral striatum. Ventral striatal areas outside the nucleus accumbens certainly deserve more attention in the future.

CHARACTERISTICS OF THE VENTRAL STRIATUM/SHELL AND CORE OF THE NUCLEUS ACCUMBENS

As stipulated above, the cytoarchitectonic and chemoarchitectonic features of the dorsal and ventral striatum are basically similar, justifying the concept of the striatum as a functional-anatomical unit. Yet, the ventral striatum contains a greater diversity of neurotransmitters and neuroactive peptides than the dorsal striatum. The principal neurons of the ventral striatum are medium-sized, densely spiny projection neurons (MSN) that form >95% of the total population. The population of MSN falls largely into two categories: MSN containing γ-aminobutyric acid (GABA) and the neuropeptides substance P and dynorphin, and MSN containing GABA and enkephalin as neurotransmitters/modulators. The remaining population of ventral striatal neurons encompass cholinergic and a variety GABAergic interneurons, the latter co-storing various neuropeptides.[10] The differential distribution of neuroactive substances in the nucleus accumbens, along with the organization of afferent and efferent connections, has led to a distinction between the so-called shell and core subregions.[11-13] A well-accepted marker for the outer, crescent-shaped shell and the inner core subregion in a variety of species is the calcium-binding protein calbindin D28K, which is dense in the core and virtually absent in the shell.[11-14] Using these and other markers, it is clear that the shell and core subregions of the nucleus accumbens have a heterogeneous composition. Whereas the core shows in-homogeneities resembling the patch-matrix patterns in other parts of the striatum,[12,15] cytoarchitectonically it is homogeneous. In contrast, the shell subregion exhibits clustering of cells, some of these clusters containing cells with immature characteristics.[9,16] Furthermore, strong in-homogeneities exist in the distribution of various neurochemical substances and neurotransmitter receptors, among which μ-opioid (Figure 1) and dopamine $(D)_1$ and D_2 receptors, and these in-homogeneities differ from the patch-matrix configurations in the core and dorsal striatum.[17,18] Interestingly, the highest concentration of dopamine D_3 receptors in the brain is present in the shell of the nucleus accumbens.[19,20]

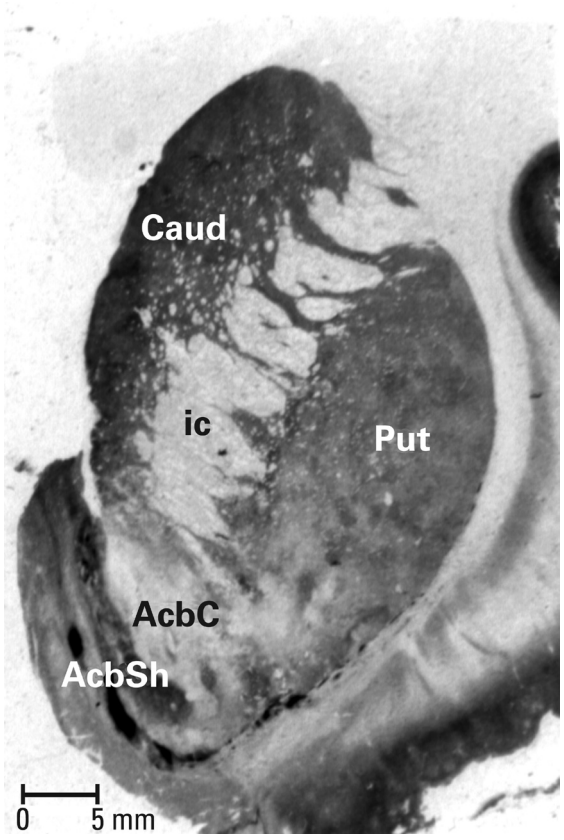
AFFERENT AND EFFERENT CONNECTIVITY OF SHELL AND CORE OF THE NUCLEUS ACCUMBENS

As in the caudate nucleus and putamen, cerebral cortical fibers form the main source of

glutamatergic inputs into the nucleus accumbens. These cortical inputs originate mainly in the medial orbitofrontal, anterior cingulate, and medial parahippocampal cortical areas (Figure 2).[12,21,22] In addition, the midline and intralaminar thalamic nuclei, the amygdala, and the hippocampal formation supply the accumbens with excitatory fibers (Figure 2). Extrinsic inhibitory GABAergic projections stem from the ventral pallidum.[23,24] The dopaminergic input to the nucleus accumbens originates in the VTA and medial part of the substantia nigra pars compacta. Its serotonergic input arises from the dorsal raphe nucleus. The output of the nucleus accumbens reaches the ventral pallidum, the medial part of the globus pallidus, and the dorsomedial part of the substantia nigra pars reticulata (Figure 2). Furthermore, accumbens fibers reach areas in the basal forebrain and mesencephalon that cannot be considered "classical" basal ganglia targets, such as the lateral preoptic area, the lateral hypothalamus, and the caudal mesencephalic regions (Figure 2).[12,23]

Considerable differences exist between the shell and core subregions in their input-output characteristics, although these differences are not absolute. Therefore, the core subregion receives inputs primarily from the dorsal parts

FIGURE 1.
Frontal section through the rostral part of the human striatum illustrating the pattern of μ-opioid receptor binding*[17]



* Note the differences in binding between the AcbSh and AcbC and the caudate nucleus and putamen.

Caud=caudate nucleus; ic=internal capsule; Put=putamen; AcbC=core of the nucleus accumbens; AcbSh=shell of the nucleus accumbens.

Voorn P, Brady LS, Berendse HW, Richfield EK. Densitometrical analysis of opioid receptor ligand binding in the human striatum–I. Distribution of mu opioid receptor defines shell and core of the ventral striatum. *Neuroscience*. 1996;75:777-792.

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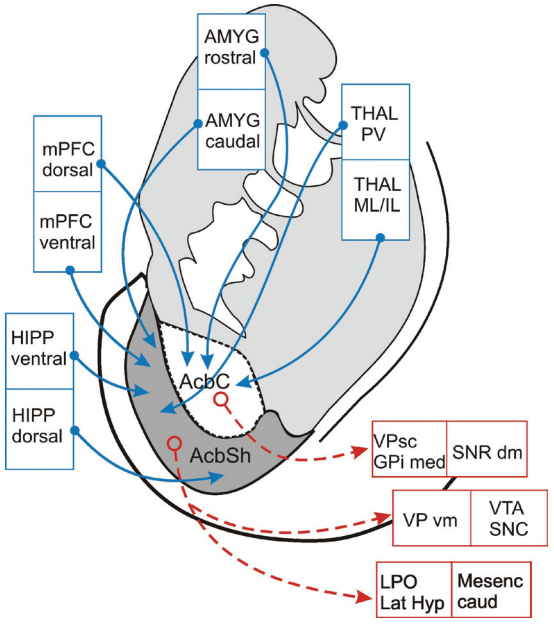
FIGURE 2.
Schematic drawing of the inputs and outputs of the shell and core of the nucleus accumbens (see also Figure 1)*



* Dopaminergic, serotonergic, and noradrenergic inputs have been omitted from the drawing. Note that virtually all structures, although via different subdivisions or subnuclei, project to both shell and core.

AcbSh=shell of the nucleus accumbens; AcbC=core of the nucleus accumbens; AMYG=amygdala; THAL=thalamus; PV=paraventricular thalamic nucleus; mPFC=medial prefrontal cortex; ML/IL=midline and intralaminar thalamic nuclei; HIPP=hippocampal formation; VPsc=subcommissural part of the ventral pallidum; med=medial; GPi=internal segment of the globus pallidus; SNRdm=dorsomedial part of the substantia nigra pars reticulata; VPvm=ventromedial part of the ventral pallidum; VTA=ventral tegmental area; SNC=substantia nigra pars compacta; LPO=lateral preoptic area; Lat Hyp=lateral hypothalamus; Mesenc caud=caudal mesencephalic regions.

Groenewegen HJ. *CNS Spectr*. Vol 12, No 12. 2007.

of the medial prefrontal cortex (dorsal prelimbic and anterior cingulate areas), the parahippocampal cortex, the caudal midline and rostral intralaminar thalamic nuclei, and the anterior part of the basolateral amygdaloid nucleus (Figure 2). In its outputs, the core parallels the dorsal striatal projection patterns by sending fibers to the dorsal, subcommissural part of the ventral pallidum (evidently a ventral extension of the external segment of the globus pallidus), the medial part of the internal segment of the globus pallidus, and the dorsomedial part of the substantia nigra pars reticulata (Figure 2).[25,26] The subcommissural ventral pallidum is in reciprocal connection with the dorsomedial part of the subthalamic nucleus.[27] The medial areas of the internal globus pallidus and substantia nigra project to the ventromedial and mediodorsal thalamic nuclei and via this thalamic relay reach the medial and orbital prefrontal areas that project to the core of the nucleus accumbens, closing one of the "limbic" basal ganglia-thalamocortical circuits.[2,12,21]

The shell receives inputs from ventrally located medial prefrontal areas (infralimbic and ventral prelimbic), the midline paraventricular thalamic nucleus, posterior parts of the basolateral amygdaloid nucleus, and the subiculum and CA1 regions of the hippocampal formation (Figure 2). In addition to dopaminergic and serotonergic inputs, the caudomedial shell receives, as the only striatal area, significant numbers of noradrenergic fibers, most likely stemming from noradrenergic cell groups in the caudal brainstem.[28] Through its outputs, the shell targets the ventral and medial parts of the ventral pallidum and adjacent lateral preoptic area. Shell fibers reach the lateral hypothalamus, the dopaminergic cell groups in the VTA and dorsal tier of the substantia nigra pars compacta and, more caudally in the mesencephalon, the region of the pedunculopontine nucleus (Figure 2). Via the ventral pallidum, the shell is involved a reentrant "limbic" basal ganglia-thalamocortical circuit that also entertains the mediodorsal thalamic nucleus and medial prefrontal areas.[12] Through the projections to the VTA and adjacent substantia nigra pars compacta, the shell may be in a position to influence the dopaminergic inputs to other parts of the striatum, in this way forming a neuronal substrate for the integration of activity in various parallel, functionally segregated basal ganglia-thalamocortical circuits.[29,30] In primates, an elaborate spiraling circuitry of striatonigrostriatal projections has been described.[31] Thus, ventral striatal areas project to medially located dopaminergic cell groups that, in addition to projecting back to the same striatal area, project to dorsally adjacent striatal areas. This shift in projections is a repeating pattern, which leads to the involvement of progressively more dorsal striatal areas and successively more laterally located dopaminergic cell groups in the substantia nigra.[31]

NOTES ON THE FUNCTIONS OF THE VENTRAL STRIATUM

Based on the character of the afferents of the nucleus accumbens, this part of the ventral striatum may be viewed as a site for integration of signals with emotional content (amygdala); contextual information (hippocampus); motivational significance (dopaminergic inputs); information about the state of arousal (midline thalamus); and executive/cognitive information (prefrontal cortex). The accumbens' outputs, directly or via ventral pallidal and dopaminergic and nondopaminergic nigral relays, lead to brain areas involved in basic functions, such as feeding and drinking behavior (lateral hypothalamus); motivational behavior (VTA and nigral dopaminergic neurons); locomotor behavior (caudal mesencephalon); and more complex cognitive and executive functions (via medial thalamic nuclei to the prefrontal cortex). Thus, Morgenson and colleagues'[32] original concept of the nucleus accumbens as a functional interface between the limbic and motor systems, in general terms, is still valid. However, current insights are, of course, much more differentiated. In particular, the functional differentiation between the shell and core has received much attention in the past 2 decades. Primarily based on animal experimental work, it may be concluded that the shell stands out from the core and the rest of the striatum through its involvement in the expression of certain innate, unconditioned behaviors, such as feeding or defensive behavior.[33-39] The shell and core subregions play important but distinct roles in Pavlovian and instrumental conditioned learning that may be potentiated by psychostimulants.[40-48] The core subregion seems to be preferentially involved in response-reinforcement learning, whereas the shell is not involved in motor or response learning, per se, rather, it integrates basic biological "drives" with the viscerolimbic and motor-effector systems. Dopamine

in the nucleus accumbens may have a role in enhancing the gain by which conditioned stimuli and contexts exert control over behavior.

CONCLUSION

The ventral striatum forms an integral part of the striatum based upon cytoarchitectonic and chemoarchitectonic characteristics and the general patterns of afferent and efferent connections. It is a specific region of the striatum in the sense that it forms the crossroad between limbic, cognitive, and motor systems. As previously discussed, experimental animal studies have shown that the ventral striatum plays an important role in several forms of behavioral learning. Shell and core form structural and functional distinct subregions of the nucleus accumbens as the "central" part of the ventral striatum. Information about ventral striatal functioning in the human brain is unfortunately scarce.[49] The dysfunction of this part of the striatum has been associated among individuals with schizophrenia,[6,7,50,51] obsessive-compulsive disorder,[5] depression, and drug addiction.[4,52-54] Preliminary positive effects of deep brain stimulation in the region of the nucleus accumbens in cases of otherwise intractable obsessive-compulsive behavior have been reported.[49,55] Whether these findings forebode a development in which the ventral striatum becomes a surgical or pharmacologic target for therapeutic interventions in various neuropsychiatric diseases remains to be seen. ***CNS***

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In the next "Brain Regions of Interest," Scott Zahm, PhD, will discuss the Ventral Tegmental Area.