Pergamon

PII: S0306-4522(99)00575-8

www.elsevier.com/locate/neuroscience

*Neuroscience* Vol. 96, No. 3, pp. 451–474, 2000

0306-4522/00 $20.00+0.00

## COMMENTARY

# THE CONNECTIONS OF THE DOPAMINERGIC SYSTEM WITH THE STRIATUM IN RATS AND PRIMATES: AN ANALYSIS WITH RESPECT TO THE FUNCTIONAL AND COMPARTMENTAL ORGANIZATION OF THE STRIATUM

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**Abstract**—This Commentary compares the connections of the dopaminergic system with the striatum in rats and primates with respect to two levels of striatal organization: a tripartite functional (motor, associative and limbic) subdivision and a compartmental (patch/striosome–matrix) subdivision. The topography of other basal ganglia projections to the dopaminergic system with respect to their tripartite functional subdivision is also reviewed. This examination indicates that, in rats and primates, the following observations can be made. (1) The limbic striatum reciprocates its dopaminergic input and in addition innervates most of the dopaminergic neurons projecting to the associative and motor striatum, whereas the motor and associative striatum reciprocate only part of their dopaminergic input. Therefore, the connections of the three striatal subregions with the dopaminergic system are asymmetrical, but the direction of asymmetry differs between the limbic versus the motor and associative striatum. (2) The limbic striatum provides the main striatal input to dopamine cell bodies and proximal dendrites, with some contribution from a subset of neurons in the associative and motor striatum (patch neurons in rats; an unspecified group of neurons in primates), while striatal input to the ventrally extending dopamine dendrites arises mainly from a subset of neurons in the associative and motor striatum (matrix neurons in rats; an unspecified group of neurons in primates). (3) Projections from functionally corresponding subdivisions of the striatum, pallidum and subthalamic nucleus to the dopaminergic system overlap, but the specific targets (dopamine cells, dopamine dendrites, GABA cells) of these projections differ. Major differences include the following. (1) In rats, neurons projecting to the motor and associative striatum reside in distinct regions, while in primates they are arranged in interdigitating clusters. (2) In rats, the terminal fields of projections arising from the motor and associative striatum are largely segregated, while in primates they are not. (3) In rats, patch- and matrix-projecting dopamine cells are organized in spatially, morphologically, histochemically and hodologically distinct ventral and dorsal tiers, while in primates there is no (bi)division of the dopaminergic system that results in two areas which have all the characteristics of the two tiers in rats.

Based on the anatomical data and known dopamine cell physiology, we forward an hypothesis regarding the influence of the basal ganglia on dopamine cell activity which captures at least part of the complex interplay taking place within the substantia nigra between projections arising from the different basal ganglia nuclei. Finally, we incorporate the striatal connections with the dopaminergic system into an open-interconnected scheme of basal ganglia–thalamocortical circuitry. © 2000 IBRO. Published by Elsevier Science Ltd.

*Key words:* basal ganglia, striatal compartments, dopamine, dendritic release, basal ganglia–thalamocortical circuitry, split circuit.

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*Abbreviations:* AChE, acetylcholinesterase; DA, dopamine, dopaminergic; EP, entopeduncular nucleus; GP, globus pallidus; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; NAcc, nucleus accumbens; PPD, preprodynorphin; SN, substantia nigra; SNC, substantia nigra pars compacta; SNR, substantia nigra pars reticulata; SP, substance P; STN, subthalamic nucleus; RRA, retrorubral area; VP, ventral pallidum; VTA, ventral tegmental area.

## 1. INTRODUCTION

The basal ganglia are a major neural system which receives inputs from virtually all cortical areas, and in turn affects the frontal cortex via its thalamic projections. The dopaminergic (DA) innervation of the basal ganglia plays a central role in a wide variety of motor, cognitive and emotional functions ascribed to the basal ganglia. This functional diversity is also reflected in the complexity of pathological conditions associated with DA dysfunction, such as Parkinson's disease, Tourette's syndrome and schizophrenia (e.g., Refs. 4, 47,48, 81, 86, 89, 166, 195, 213, 214, 226 and 267). The striatum is a major contributor of basal ganglia input to the DA system and the major recipient of DA input. The understanding of the organization of the connections between the two systems is essential for unraveling their role in normal and pathological states.

Descriptions of the connections between the striatum and the DA system have relied primarily on the regional subdivision of the striatum into caudate, putamen and nucleus accumbens (NAcc). During the last 15 years, much of the work on these connections has been influenced by the compartmental organization of the striatum, but the relationship between the two levels of organization has not been fully delineated. Yet a different principle of striatal organization, namely, functional subdivision imposed by corticostriatal projections, has dominated the descriptions of striatal connections with the frontal cortex (via the pallidum, nigra and thalamus), which provide the basis for models of basal ganglia–thalamocortical organization. The functional subdivision of the striatum, however, has received scant attention with regard to the connections of the striatum with the DA system (but see Refs. 107, 163, 164 and 165). In parallel, different subdivisions are used for describing the DA system. For example, while anatomists usually subdivide this system according to cytoarchitectonic criteria, behavioral neuroscientists tend to use a subdivision based on efferent projections of the DA system (e.g., mesostriatal and mesolimbic DA systems). As a result, there is presently an abundance of nomenclatures used in the description of the striatal connections with the DA system. Moreover, different nomenclatures are preferentially used by researchers from different fields. This complexity is compounded by the fact that the same terms are often used in rodent and primate research, although it is not always clear that these terms represent analogous areas/subdivisions.

In the present work, we survey and compare the connections of the DA system with the striatum in rats and primates. We review data on the organization of these connections with respect to a tripartite functional (motor, associative and limbic) subdivision of the striatum, as well as with respect to its compartmental (patch/striosome–matrix) subdivision, and combine the two levels of organization. In addition, we briefly review the topography of the projections of the other basal ganglia nuclei to the DA system, with respect to their tripartite functional subdivision. We then combine the anatomical organization of basal ganglia projections to the DA system with data on DA cell physiology in order to advance an hypothesis on the influences of the basal ganglia on DA cell activity. Finally, we incorporate the striatal connections with the DA system into an open-interconnected scheme[131,132] of basal ganglia–thalamocortical circuitry.

## 2. THE STRIATUM

The striatum is the main input structure of the basal ganglia. It is divided into the dorsal striatum (neostriatum), which includes most of the caudate and putamen, and the ventral striatum, which comprises the NAcc, the ventromedial parts of the caudate and putamen, and the striatal part of the olfactory tubercle. An important characteristic of the dorsal striatum is its patch (striosome in primates)/matrix compartmental organization. These compartments can be distinguished on the basis of the immunohistochemical distribution of several markers, including acetylcholinesterase (AChE), enkephalin, substance P (SP), DA, opiate receptors and calcium-binding protein (e.g., Refs. 68, 71, 72, 87, 89 and 97). The NAcc is divided into the "shell" and "core", which are cytoarchitectonically, physiologically and pharmacologically distinct, with the core resembling the caudate–putamen.[51,97,101,120,136,175,284,300,302] While extensive work has been devoted to the study of core–shell dichotomy in rats, the shell and core have only recently been demarcated in primates,[67,174,283] and it is still unclear whether these subterritories are equivalent to those in rats.[174] Although immunohistochemically distinct

compartments with features characteristic of patches and matrix have been demonstrated in the NAcc, their histochemical properties indicate that they are not equivalent to those in the dorsal striatum.[97,100,135,169,174,175,284,300]

### *2.1. The functional subdivision of the striatum*

The corticostriatal projections impose a functional organization upon the striatum and, subsequently, upon other nuclei of the basal ganglia (e.g., Refs. 4–7, 62, 109, 167, 196, 200, 213 and 216). While several versions of striatal subdivision have been proposed (e.g., Refs. 6, 7, 49, 109, 167, 213 and 216), we shall use here the tripartite anatomofunctional subdivision of the striatum into motor, associative and limbic, as delineated by Parent and Hazrati[196,200,202] in primates, and by Joel and Weiner[131] in rats. In primates, the motor striatum comprises the dorsolateral postcommissural putamen and a dorsolateral region in the caudate; it is innervated by the primary motor cortex, premotor cortex, supplementary motor area and postarcuate premotor area. The associative striatum comprises large parts of the putamen rostral to the anterior commissure, and most of the head, body and tail of the caudate; it receives input from associative areas of the cortex, including areas 8, 9, 10 and 46 of the prefrontal cortex. The limbic striatum comprises the NAcc and the most ventral parts of both the caudate and putamen; it receives extensive input from limbic structures, such as the hippocampus and amygdala, as well as from prefrontal areas subserving limbic and autonomic functions, i.e. the orbitofrontal cortex and anterior cingulate area.[6,7,109,196,202,247,248,296]

In the rat, the motor striatum comprises the lateral caudate–putamen; it is innervated by the lateral and medial agranular cortices,[20,171] which are analogous to primates' primary motor cortex and premotor areas.[2,17,36,57,160,161,188,189,209,224,279]. The associative striatum comprises the medial caudate–putamen; it is innervated by the anterior cingulate area,[98,249] which is analogous to primates' dorsolateral prefrontal cortex.[147,280] The limbic or ventral striatum receives extensive input from limbic structures, such as the hippocampus and amygdala, as well as from prefrontal areas subserving limbic and autonomic functions, i.e. orbital, infralimbic, prelimbic and agranular insular cortices.[20,97,98,120,124,150,171,186,187,250,274,280]

## 3. THE MESENCEPHALIC DOPAMINERGIC SYSTEM

The mesencephalic DA system is the largest DA system. The organization of DA neurons in rats and primates is generally similar, but there are some differences in the distribution of DA cells and in the extent of correspondence between DA cell groups and specific neuroanatomical regions.[15,58,63,78,113,173,179,234,242]. Although DA cells form a continuous group,[15,26,75,78,104,113,179,210,234,235,242] several parcellations of these neurons, based on different criteria, have been proposed.

Dahlstrom and Fuxe[43] divided the rat mesencephalic DA system into three cell groups: A8, A9 and A10. A10 cells are located in the ventral tegmental area (VTA), which is the ventromedial-most region of the midbrain. A9 neurons are located in the substantia nigra (SN), which is continuous medially with the VTA. Most neurons of the A9 group are found in the substantia nigra pars compacta (SNC), but some cells are also found ventrally within the substantia nigra pars reticulata (SNR). A8 cells are found in the retrorubral area (RRA), which lies caudal and dorsal to the SN.[43,63,271]

The three DA cell groups, A8, A9 and A10, can also be recognized in human and non-human primates, and they roughly correspond to the RRA, SNC and VTA, respectively.[26,63,78,113,127,172,179,210,234,235,242,271] The organization of the primate SNC is more complex than that of rats, and this complexity is paralleled by a proliferation of nomenclatures (for review, see Ref. 173). The nomenclature adopted here is based on the cytoarchitectonic subdivision of the ventral midbrain. Rostrally, DA neurons comprise a thin band dorsal to the SNR. At more central levels, DA neurons are arranged in the main horizontal band (the densocellular zone) from which columns (fingers) of DA cells penetrate ventrally into the underlying SNR. Dorsal to the main horizontal band, DA neurons are scattered in the pars mixta, which is probably specific to primates and is usually considered part of the SNC[15,65,66,111,128,154,207,215,271] (but see Langer *et al*.,[154] who suggest that the pars mixta also contains neurons belonging to A8, and McRitchie *et al*.,[172,173] who refer to this region as the parabrachial pigmented nucleus and suggest that it is part of the A10 cell group).

The anatomical division of the DA cells is considered to reflect differences in their efferent projections, with projections of A10 to the NAcc and other limbic areas comprising the mesolimbic DA system, and projections from A9 to the neostriatum comprising the nigrostriatal DA system (e.g., Refs. 11, 12, 43 and 279).

A different division was advocated by Fallon and Moore[59] based on the finding that neurons of A10 and A9 are continuous in providing input to the forebrain (also see Ref. 282). They defined two sets of DA neurons: a dorsal tier located in the dorsal parts of the VTA and SNC and innervating ventral basal forebrain structures (e.g., olfactory tubercle, amygdala), the limbic striatum and the cortex, and a ventral tier located in the ventral parts of the VTA and SNC (including DA neurons in the SNR) and innervating more dorsal structures of the basal forebrain (e.g., the septum) and the neostriatum. In the last decade, much work has been devoted to the delineation of two tiers in rats and primates (e.g., Refs. 58, 69–75, 104, 154 and 173; see Section 4.2).

## 4. THE RELATIONS BETWEEN THE DOPAMINERGIC SYSTEM AND THE STRIATUM

### *4.1. The relations between the dopaminergic system and the functional subregions of the striatum*

This section examines the topographical relations of the DA system with the limbic, associative and motor subregions of the striatum in rats and primates. It should be noted that, while our definition of the limbic striatum coincides with the terms limbic or ventral striatum as they are used in the literature, this is not the case with regard to the motor and associative striatum. In primates, the conventional distinction is between the putamen and the caudate rather than between motor and associative striatum. In rats, the dorsal striatum (which comprises the two subregions) is either treated as one entity or divided according to spatial criteria (e.g., medial and lateral aspects), although some earlier divisions referred to the dorsolateral part of the dorsal striatum, which corresponds to part of the motor striatum in the present scheme, as the "non-limbic" striatum (e.g., Refs. 171 and 184). In order to discern the differential connections of the

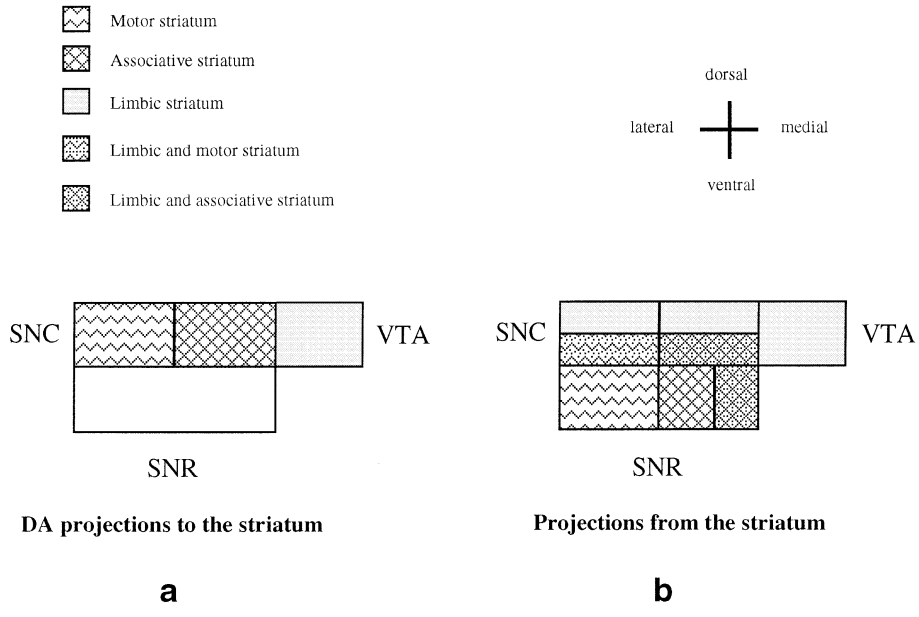


Fig. 1. A schematic representation of the localization of DA cells projecting to the motor, associative or limbic striatum (a), and of terminal fields in the SN and VTA arising from these striatal subregions (b) in the rat. For detailed explanation, see text.

motor and associative striatum with the DA system, we relied on descriptions and figures illustrating relevant results, on which we superimposed the tripartite subdivision of the striatum described above.

*4.1.1. Rats.* 4.1.1.1. The topographical organization of dopaminergic projections to the striatum. A subdivision of the DA system into groups projecting to the ventral or dorsal striatum was pioneered by Dahlstrom, Fuxe and their colleagues,[11,12,43] and retained in subsequent descriptions, although the subdivisions may differ in detail (e.g., Refs. 59, 279 and 282). Available data[3,18,29,52,59,74,97,103,114,185,252,262,282,298] indicate that the DA projections to the motor and associative striatum also arise from relatively distinct DA cell groups. The motor striatum is innervated mainly by the lateral SNC, the associative striatum mainly by the medial SNC and VTA, and the limbic striatum by the VTA with some contribution of the medial SNC. The RRA projects to all three striatal subregions (see Fig. 1a).

4.1.1.2. The topographical organization of the striatal projections to the dopaminergic system. The striatal projections to the DA system are also organized topographically. Striatal innervation of the VTA arises mainly from the limbic striatum, particularly from the NAcc shell;[19,99,120,185,219,286,297,303] the dorsal SNC is also innervated by the limbic striatum only, while the ventral SNC and the RRA are innervated by the three striatal subregions.[19,50,69,120,185,286,303] Striatonigral projections to the SNC and SNR maintain a rough mediolateral topography,[50,59,69,260] so that the motor striatum projects to the lateral SN; the associative striatum projects to the medial SN and the limbic striatum projects to a restricted area of the medial SNR[14,19,50,69,97,99,120,185,219,256,260,262,286,303] (see Fig. 1b).

Striatal projections to the SN are also directed to the SNR, where they synapse on the ventrally extending dendrites of DA cells located in the ventral SNC.[260,287] Although the mediolateral organization of striatal projections to the SNR is roughly maintained (e.g., Refs. 50, 59, 69 and 260), the degree of segregation between motor and associative striatal inputs in the SNR is not clear (e.g., Refs. 69 and 215). When considering this issue, it is important to distinguish between the organization of the dendritic fields of the SNC and SNR neurons. While the GABAergic neurons of the SNR have dendrites that extend over more than 40% of the mediolateral extent of the nucleus,[69] the ventrally extending dendrites of ventral SNC neurons are limited in the mediolateral dimension within the SNR. In addition to the larger dendritic fields of SNR compared with SNC neurons, striatal terminals in the SNR form synapses predominantly (77%) with distal dendrites.[256] These data suggest that there is a high degree of convergence in the inputs from the two striatal subregions to SNR neurons, whereas the inputs of the two striatal subregions to the ventrally extending DA dendrites are largely segregated.

*4.1.2. Primates.* 4.1.2.1. The topographical organization of dopaminergic projections to the striatum. DA cells projecting to the limbic striatum prevail in the VTA, RRA, pars mixta and in the medial part of the main horizontal band of the SNC,[109,163,164] whereas DA cells projecting to the rest of the striatum prevail in the main horizontal band of the SNC and in the ventrally extending DA columns, with only a minor contribution from the pars mixta, VTA and RRA.[65,109,118,128,130,154,164,197,205,208,258,268] However, attempts to outline the principles of the topographical organization of the nigral projections to the striatum have yielded contradictory descriptions[65,118,128,130,154,164,197,205,258,268] (for review, see Ref. 165). Recent data suggest that although different DA neurons project to the motor and associative striatum,[128,130,154,197,205,208,258] these projections arise from the entire rostrocaudal and mediolateral extents of the SN,[65,118,164,205,208,258,268] with interdigitating clusters of neurons innervating the two striatal subregions[128,130,154,205,208,258] (see Fig. 2a). A closer examination of the data reveals some regional quantitative differences between the projections to the motor and associative striatum. First, a decreasing proportion of neurons project to the associative versus motor

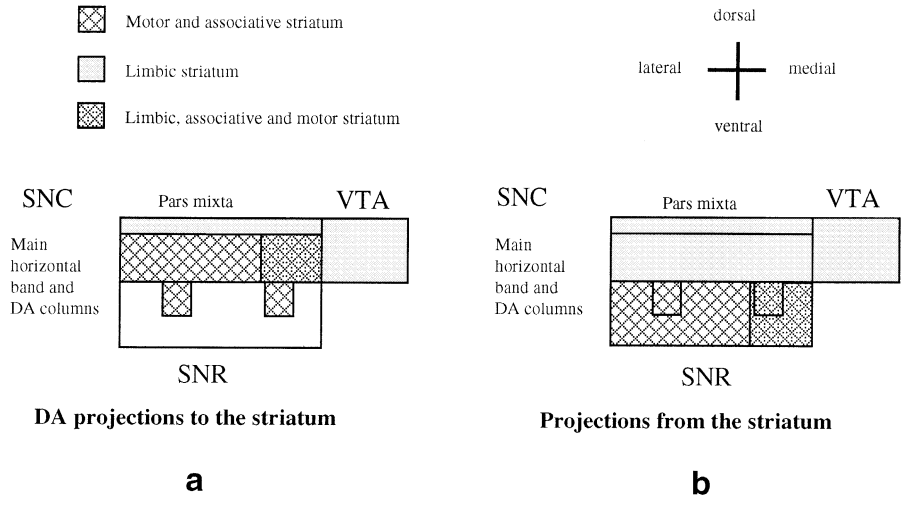


Fig. 2. A schematic representation of the localization of DA cells projecting to the motor, associative or limbic striatum (a), and of terminal fields in the SN and VTA arising from these striatal subregions (b) in the primate. For detailed explanation, see text.

striatum as one proceeds caudally in the SN,[65,118,205,208,258,268] and this difference is most pronounced in the caudal one-third of the SNC, which projects mainly to the motor striatum.[65,118,153,205,208,258,268] Second, the medial DA columns innervate the associative and motor striatum, whereas the lateral columns innervate mainly the motor striatum.[65,118,130,154,164,205,258]

Interestingly, these differences appear to be reflected in the relations between the degeneration of DA cells and the pattern of striatal DA loss in certain abnormal conditions. In Parkinson's disease, loss of midbrain DA neurons is most severe in the caudal and ventrolateral parts of the SNC,[60,80,82,225,295] and is associated with a greater DA depletion in the motor than in the associative striatum.[142,180,240] Likewise, in monkeys rendered parkinsonian after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine treatment, greater damage to the lateral than to the medial SNC was associated with a more severe DA depletion in the motor than in the associative striatum.[8,115,278]

4.1.2.2. The topographical organization of the striatal projections to the dopaminergic system. The limbic striatum projects to the VTA, RRA, pars mixta, the main horizontal band of the SNC and the medial SNR. Limbic striatal projections seem to spare the ventral and lateral regions of the SNR, including the ventrally extending DA columns.[104,106,163,165,249] Projections from the associative and motor striatum are directed mainly to the SNR, where they contact DA cells in the DA columns and the ventrally extending dendrites of DA cells of the main horizontal band of the SNC, with only minor projections to the main horizontal band itself.[118,165,201,202]

Attempts to delineate the principles of topographical organization of the striatonigral projections have yielded contradictory outcomes[66,118,197,215,217,249,258,276,277] (for review, see Ref. 165), and current data suggest that the associative and motor striatum project to the entire rostrocaudal and mediolateral extents of the SN[118,165,201,202] (see Fig. 2b). Several differences do seem to exist between the associative and motor striatonigral projections. In general, the associative striatal termination within the SNR is more massive than that of the motor striatum[201,202,258] (but see Ref. 118). In addition, there are regional differences in the densities of terminal fields from the two striatal subregions: (i) the associative striatum projects densely throughout the rostrocaudal extent of the SNR, whereas the projections from the motor striatum are denser more caudally;[118,197,258] (ii) the projections to the medial one-third of the SNR arise mainly from the associative and limbic striatum[61,118,165,197,249] (but see Smith and Parent,[258] who described projections from the motor striatum to the most medial SN); (iii) complementarily, the projections to the area of and ventral to the lateral DA columns arise mainly from the motor striatum.[118,258]

Goto *et al.*'s[82] findings in patients with striatonigral degeneration are of interest in this context. Calcineurin depletion in the lateral and ventral aspects of the SN was found in patients with greater degeneration of the lateral and caudal putamen (parts of the motor striatum), whereas in a patient whose caudate was also affected, calcineurin depletion was evident throughout the SN except for weak immunoreactivity in the medial SN. Since calcineurin is thought to reside in striatal axons,[82] these relations between striatal degeneration and loss of nigral calcineurin seem to be in accord with the organization of the striatonigral projections described above, namely, that the lateral and ventral aspects of the SN are innervated mainly by the motor striatum; other SN regions are also innervated by the associative striatum and the most medial SN is innervated in addition by the limbic striatum.

*4.1.3. The relations between the dopaminergic system and the functional subregions of the striatum in rats and primates: summary.* In both rats and primates (Figs 1a, 2a), the DA projections to the limbic versus motor and associative striatum arise from relatively distinct groups of neurons. In rats, the VTA projects almost exclusively to the limbic striatum, the RRA and the medial SNC innervate all three striatal subregions, and the lateral SNC and DA cells in the SNR innervate the motor and associative striatum only. In primates, the VTA, RRA and pars mixta project almost exclusively to the limbic striatum, the medial part of the main horizontal band of the SNC innervates all three striatal subregions, and DA columns and the lateral part of the SNC innervate the motor and associative striatum only. In rats, the groups of DA cells projecting to the associative versus motor striatum are also largely segregated, residing in the medial and lateral SNC, respectively. In primates, these two sets of neurons are organized in interdigitating clusters,

although the caudal one-third of the SNC and the lateral DA columns appear to project preferentially to the motor striatum.

In both rats and primates (Figs 1b, 2b), the projections from the limbic striatum to the DA system only partially overlap the projections from the motor and associative striatum. The VTA and dorsal SNC (pars mixta in primates) are innervated by the limbic striatum; the ventral SNC (main horizontal band in primates) is innervated by the three striatal regions, and DA neurons in the SNR (DA columns in primates) are innervated mainly by the motor and associative striatum. In rats, the projections from the motor and associative striatum are largely segregated, terminating in the lateral and medial SN, respectively. In primates, these projections interdigitate, although the lateral and ventral aspects of the SN appear to be innervated preferentially by the motor striatum. In both, limbic striatal projections are directed primarily to DA cell bodies and proximal dendrites, whereas the projections from the associative and motor striatum are directed mainly to the ventrally extending DA dendrites in the SNR.

Comparing Figs 1a with 1b and 2a with 2b, it is evident that in both rats and primates the limbic striatum projects to the DA regions from which it receives DA input, as well as to the DA regions projecting to the motor and associative striatum. Moreover, the main striatal input to the latter regions arises from the limbic striatum. In rats, the associative and motor striatum are reciprocally connected with the medial and lateral regions of the ventral SNC. It is considerably more difficult to discern, in primates, the extent to which the motor and associative striatum reciprocate their own DA input. However, a comparison between the organization of the striatonigral and nigrostriatal projections for each striatal subregion reveals the following. (1) The main output of the motor striatum is directed to areas from which it receives its main DA innervation, i.e. the more caudal SNC and lateral DA columns. (2) Motor striatal projections seem to be the main source of striatal input to the caudal and lateral SN, since the limbic striatum does not project to these regions and the associative striatal projections to these regions seem to be less dense than projections from the motor striatum. (3) Associative striatal projections are distributed over wide areas of the SN and thus overlap with areas which contain DA cells projecting to the associative as well as to the motor striatum. There is thus an anatomical basis for reciprocal connections between the motor and associative striatum and the DA system, and it is also possible that projections from the associative striatum terminate on DA cells projecting to the motor striatum and vice versa.

In studies reporting anterograde and retrograde labeling resulting from the same injection, some correspondence is usually found between striatal terminal fields in the SN and the clusters of retrogradely labeled nigral cells, supporting the existence of reciprocal connections between the striatum and the DA system (rats: Refs. 59 and 69; primates: Refs. 107, 118, 197 and 258). However, such correspondence is not perfect, since labeled nigral cells can be found outside the terminal field or the terminal field can include unlabeled nigral cells. As pointed out by Hedreen and DeLong[118] and Haber and Lynd-Balta,[107] this suggests that DA cells projecting to one striatal region can receive innervation from a different striatal region. A review of relevant papers[107,118,197,258] suggests that, in primates, the associative striatum may have some influence on the DA input to the motor striatum.

Finally, there is also some support for both reciprocal and non- reciprocal connections at the electron microscopic level. Somogyi *et al.*[260] found, in rats, striatal boutons which form synapses with nigrostriatal neurons, pointing to reciprocal connections between the dorsal striatum and the DA neurons of the SN. Groenewegen *et al.* found that ventral striatal fibers and terminals establish close appositions with DA cell bodies and dendrites in the SNC[97] as well as with ventrally extending DA dendrites in the SNR,[99] and Somogyi *et al.*[260] found that ventral striatal boutons contact perikarya and dendrites of nigral neurons projecting to the dorsal striatum, supporting the existence of a pathway from the ventral striatum, via nigral DA cells, to the dorsal striatum.

It can be concluded that, in rats and primates, the limbic striatum can influence its own DA input as well as the DA input to the motor and associative striatum, while the associative and motor striatum can influence only part of their DA input. While the former is merely a refinement of the long known fact that the connections of the limbic striatum with the DA system are asymmetrical in that this subregion innervates a wider area of the DA system than the area from which it receives its innervation (e.g., Refs. 99, 106, 109, 128, 130, 164, 165, 177, 185, 202 and 266), the latter indicates that the connections of the motor and associative striatum with the DA system are also asymmetrical, but in a reversed direction, because these areas innervate a more restricted area of the DA system than the area from which they receive their innervation.

### *4.2. The relations between the dopaminergic system and striatal compartments*

*4.2.1. Rats.* Gerfen[69,71,72,74,75] pioneered the view that the compartmental organization of the striatum is the most important characteristic for understanding the striatal relationships with the DA system. Using retrograde and anterograde tracer injections in subregions of the SN, Gerfen showed that most of the striatal neurons projecting to the SNR are located in the matrix compartment, while most of the striatal neurons projecting to the SNC are located in the patch compartment,[68,69] and that dopaminergic projections from the dorsal SNC are directed mainly to the matrix compartment whereas dopaminergic projections from the SNR are directed mainly to the patch compartment.[75] Consequently, Gerfen divided the SNC into dorsal and ventral tiers according to their differential projections to the matrix and patch compartments (see Fig. 3a). Since the DA cells of the VTA and RRA were found to project only to the matrix, they were included in the dorsal tier.[70,72–75] Thus, according to Gerfen's division, the dorsal tier includes the VTA, RRA and the dorsally located neurons in the SNC (the dorsal tier of the SNC), and the ventral tier includes ventral SNC neurons (the ventral tier of the SNC) and DA neurons located in the SNR, mainly in its ventral and caudal parts.[69,70,74,75,77,98,270,287] [1] In addition, Gerfen established the idea that the two striatal compartments have differential relations with the SN.[68–72,74,75] Striatal patch neurons preferentially innervate cell bodies and proximal dendrites of ventral tier neurons (including DA neurons in

[1]Gerfen's delineation of ventral and dorsal tiers differs from that of Fallon and Moore.[59] In Fallon and Moore's scheme, the ventral tier consists of the ventral parts of the VTA and SNC, while the dorsal tier consists of the dorsal parts of these structures. In Gerfen's scheme, the ventral tier is confined to the ventral SNC, while the dorsal tier includes the dorsal SNC and the entire VTA.

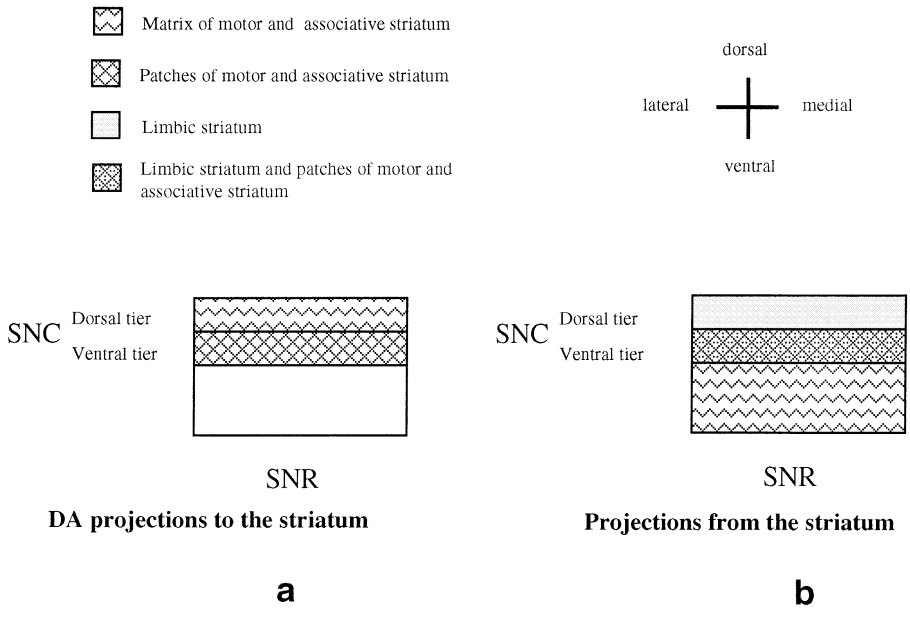


Fig. 3. A schematic representation of the localization of DA cells projecting to the patch or matrix compartments of the motor and associative striatum (a), and of terminal fields in the SN and VTA arising from these compartments and from the limbic striatum (b) in the rat. For detailed explanation, see text.

the SNR), while striatal matrix neurons innervate SNR GABAergic neurons and the dendrites of the ventral tier DA neurons that extend ventrally into the SNR[68,69] (see Fig. 3b).

Although Gerfen's view of the relations between the SN and the striatal compartments is widely accepted in the literature, additional tracing data supporting his observations are lacking. As pointed out by Gerfen,[68,69,75] the determination of the organization of the striatonigral and nigrostriatal projections with respect to the striatal compartmental organization is difficult because there is no technique which enables the injection of a tracer specifically to only one of the striatal compartments and because it is difficult to confine tracer injections to either the dorsal or ventral tier of the SNC, or to prevent spread of tracer from the SNC to the SNR (see Refs. 97 and 153 for comments on this issue). Thus, the extant techniques do not have the resolution to satisfactorily determine the nigral targets of projections arising from matrix versus patch neurons, as well as the areas in which matrix- and patch-projecting DA neurons reside.

Several lines of evidence, however, give indirect support to Gerfen's scheme. The existence of two components of the nigrostriatal projections has been inferred from the findings that the DA innervation of the striatum first develops in distinct "islands" and only later extends diffusely across the entire striatum, and that the regions of termination of the islandic DA fibers correspond to patches[74,88,162,182,223,241,301] (but see Ref. 285). Moreover, following lesion of patch-projecting DA cells in newborn rats, the spared matrix-projecting DA cells were similar in their location, morphology and chemistry to dorsal tier DA cells of intact rats.[74] It remains unclear whether this subdivision of the nigrostriatal system continues to be reflected in the organization of DA neurons in the mature brain, although there are morphological differences between DA fibers within patches and those within the matrix which suggest that this may be the case[74] (but see Ref. 114).

Support for the existence of two types of striatal cell populations, one projecting to the GABAergic neurons and to the ventrally extending DA dendrites in the SNR and the second projecting to DA cell bodies and proximal dendrites in the SNC, can be derived from the differential distribution of calbindin-positive fibers, which are dense in the SNR and absent in the SNC,[70,73,121,173] as well as from the differential distribution of preprodynorphin (PPD) and preprotachykinin in the SN, with denser PPD in the SNC compared with the SNR and a reverse pattern for preprotachykinin.[159] Moreover, if calbindin is a selective marker of striatonigral projections arising from the matrix (see Refs. 54, 73 and 162), its differential distribution in the SN suggests that matrix neurons correspond to the first type of striatal neurons. Similarly, if PPD is a marker of patch neurons, a possibility raised by Lee *et al.*[159] based on the patchy distribution of striatal neurons with intense PPD immunoreactivity, then the differential distribution of PPD in the SN suggests that patch neurons correspond to the second type of striatal neurons.

Finally, analysis at the electron microscopic level revealed morphological differences between striatal terminals contacting DA cell bodies and proximal dendrites and those contacting SNR cells and ventrally extending DA dendrites. Thus, Somogyi *et al.*[260] described two types of striatal boutons in the SN. Type 1 forms synapses mainly on dendritic shafts of SNR neurons and less frequently with dendrites, located in the SNR, of nigrostriatal neurons. Type 2 contacts perikarya and proximal dendrites, mainly in the SNC, including perikarya and proximal dendrites of nigrostriatal neurons. Similarly, there are morphological differences between ventral striatal terminals contacting perikarya and those contacting dendrites of DA cells,[260] pointing to a different ventral striatal origin of these terminals. Given that there are two sets of NAcc neurons, one projecting preferentially to DA neurons of A8, A9 and A10 and the other to the GABAergic neurons of the SNR,[19,97] and that ventral striatal fibers and terminals establish close appositions with ventrally extending DA dendrites in the SNR,[99] it is possible that, also in the ventral striatum, there is one set of neurons which is analogous to patch neurons (i.e. project to DA cell bodies) and another set which corresponds to matrix neurons (i.e. project

to the GABAergic neurons of the SNR and to the ventrally extending DA dendrites).

The ventral and dorsal tiers can be distinguished according to additional criteria outlined by Gerfen, namely, their cell morphology, chemistry and afferent connections. Thus, dorsal tier neurons have horizontally oriented dendrites while ventral tier neurons have in addition vertically oriented dendrites which extend into the SNR.[59,70,74,75,173,287] Most dorsal tier neurons express the calcium-binding protein, calbindin, while neurons of the ventral tier do not.[70,73,74,174] The dorsal tier is innervated by the ventral striatum while the ventral tier is innervated by the ventral and dorsal striatum.[69]

*4.2.2. Primates.* Several of the criteria used for distinguishing the ventral and dorsal tiers in rats have been adopted for this purpose in primates. However, although primate DA cells are believed to be arranged in a dorsal and a ventral tier (e.g., Refs. 104, 111, 154 and 173), there is no (bi)division of the primate DA system that results in two areas which have all the morphological, chemical and afferent/efferent characteristics of the two tiers delineated in rats.[164,173] As a result, there are several schemes for the organization of two tiers in the primate DA system, depending on the specific criterion used.

4.2.2.1. Calbindin cell staining. Using differential distribution of calbindin-negative and calbindin-positive DA neurons, Haber and colleagues[104,111,163–165] concluded that the areas containing calbindin-positive neurons, i.e. the RRA, VTA and pars mixta, comprise the dorsal tier, while the areas containing calbindin-negative neurons, i.e. the main horizontal band of the SNC and the ventrally extending DA cell columns, comprise the ventral tier. Similar distribution was found in several other studies of non-human primates,[73,156,199] as well as in humans. Yamada *et al.*[295] found only calbindin-negative neurons in the alpha layer and in the ventral part of the beta layer of the SNC (according to the terminology of Ref. 193), which are contained within the ventral tier, while calbindin-positive neurons were found in the VTA and in the dorsal part of the beta layer of the SNC, which are contained within the dorsal tier. Gibb[79] and McRitchie *et al.*[173] also found no calbindin-positive cells in areas corresponding to the ventral tier (ventral and dorsal tiers in McRitchie *et al.*'s and Gibb's schemes), while other DA cell groups contained both calbindin-positive and calbindin-negative neurons.

Haber and colleagues showed that the two tiers are also distinguished by dendritic orientation, so that dendrites of dorsal tier neurons stretch in a mediolateral direction, whereas dendrites of ventral tier neurons are also oriented ventrally, filling much of the SNR and reaching its ventral border[104,111,163–165] (also see Ref. 199). However, although many studies in human and non-human primates report that DA neurons extend their dendrites ventrally into the SNR,[15,66,79,80,104,157,173,215,217] the correspondence between these neurons and the DA neurons which are calbindin negative is not clear. In humans, some studies report that the region containing neurons with ventrally extending dendrites extends throughout the SN and is co-extensive with the calbindin-negative region,[104,173] while others report that the former area is more restricted than the latter.[79,80,210] In non-human primates, the region containing neurons with ventrally extending dendrites is located in a restricted area within the calbindin-negative region, i.e. the rostral two-thirds of the SNC.[15,66]

The dorsal and ventral tiers as delineated by calbindin cell staining can also be distinguished by low and high levels, respectively, of several DA-related markers, including mRNAs for the $D_2$ receptor, the DA transporter and tyrosine hydroxylase.[16,104,111,163–165] Additional DA-related markers used to distinguish two tiers in the DA system yielded subdivisions which do not correspond to the two tiers delineated by Haber and colleagues. Thus, Murray *et al.*[180] reported that mazindol-binding sites are low in the dorsal tier of the SNC and high in the ventral tier of the SNC and in the VTA, which is part of the dorsal tier as defined by Haber and colleagues. Gibb[79,80] delimited a ventral tier showing low melanin content and a dorsal tier showing high melanin content, but both were contained within the ventral tier as defined by Haber and colleagues.

4.2.2.2. Differential projections to the striosome and matrix compartments. Graybiel *et al.*[91] found differences in the DA innervation of striosomes and matrix in the mature human brain, supporting the existence of two components of the nigrostriatal projections in primates, one projecting to the matrix and the other to striosomes. However, attempts to delineate groups of matrix- and striosome-projecting neurons in the primate SN have been less successful.

Gerfen *et al.*[73] suggested that calbindin can be used as a marker of the matrix nigrostriatal system, with calbindin-positive cells innervating the matrix and calbindin-negative cells innervating the patches. However, as pointed out by Lynd-Balta and Haber,[164] most of the projections to the striatum in primates arise from the ventral tier of the SNC as delimited by calbindin-negative DA cells, and only sparse projections arise from the dorsal tier, which contains calbindin-positive cells (see Section 4.1.2.1). Consequently, the dorsal tier is unlikely to provide the sole DA input to the striatal matrix and, therefore, the differential innervation of the striatal compartments cannot coincide with the division of nigral DA cells into dorsal and ventral tiers on the basis of calbindin cell staining.[164]

Graybiel and colleagues[128,130,153,154] conducted an extensive investigation of the spatial, cytoarchitectonic and histochemical characteristics of striosome- and matrix-projecting DA neurons. A series of studies using retrograde tracer injections to demonstrate DA projections to the striatum failed to find the simple relations between striatal compartments and different subdivisions of the SNC (into AChE-poor and AChE-rich compartments, and into a medial, cell-rich half and a lateral, cell-sparse half)[128,130] found earlier in cats.[129] Using anterograde tracer injections into different parts of the DA system, Langer and Graybiel[153] found that A8 and the pars mixta (at least its caudal part) project preferentially to the matrix, whereas the lateral part of the main horizontal band with its ventrally extending DA columns projects preferentially to striosomes. However, A8 and pars mixta do not contribute much to the DA innervation of the dorsal striatum.[65,109,118,128,130,154,164,197,205,208,258,268] As for the main horizontal band, labeling of both compartments (albeit with different intensities) appeared after all anterograde tracer injections in the SN, leading Langer and Graybiel[153] to caution that all the injected regions may contain striosome- and matrix-projecting neurons.[153]

Several studies found that the SNC region which contains

DA cells with vertically oriented dendrites is contained within the SNC region in which most of the nigrostriatal cells reside (i.e. the area containing calbindin-negative cells),[15,66,79,80,210] suggesting that there may be two regions differing in their dendritic orientation, one projecting to striosomes and the other to the matrix. However, this conflicts with the above findings that neurons projecting to striosomes or to the matrix do not reside in distinct regions. According to other studies, the SNC region which contains DA cells with vertically oriented dendrites coincides with the calbindin-negative SNC region,[104,173] suggesting that most nigrostriatal neurons have vertically oriented dendrites. It seems, therefore, that cell morphology also cannot differentiate between striosome- and matrix-projecting cells.

Using the distribution of SP as a marker for the termination area of dorsal striatal afferents in the human SN, Haber and Groenewegen[104] found no SP staining in the dorsal tier, patchy staining in the ventral tier (both delineated by calbindin cell staining) and more even staining in the SNR. This led them to suggest that, in analogy with the relations between DA cells and striatal compartments in rats, DA cells in the SP-free zone (presumably not innervated by the neostriatum) would project to the matrix, while DA cells that lie enmeshed in SP fibers (presumably innervated by the neostriatum) would project to striosomes.

4.2.2.3. Differential termination of matrix- and striosome-arising projections in the substantia nigra. Based on the above finding, Haber and Groenewegen[104] speculated that, in analogy to rats, the DA cells in the ventral tier that lie within SP fibers are innervated by striosomes only. However, they argued that because the area of overlap between SP-positive fibers and DA cells increases from rat through non-human primate to human, a parallel increase in the relative ratio of striosomes to matrix area should be expected. Since the latter is not the case, they concluded that, in primates, matrix neurons also contribute to the striatal projections to DA cells. There are numerous reports, however, that the distribution of SP-positive fibers in rats, non-human and human primates is similar[27,73,79,125,170,173,210,290] (but see Ref. 207), enabling the retention of Haber and Groenewegen's original suggestion that the striatal projections to DA cells arise only from striosomes.

While there is no marker at present for fibers arising from patches (although PPD is a possible candidate;[159] see Section 4.2.1), calbindin is considered a selective marker of striatonigral projections arising from the matrix.[54,73,199,222] Examination of the relevant studies indicates that the distribution of calbindin-positive fibers is similar in rats and human and non-human primates, with calbindin-positive fibers restricted mainly to the SNR[70,73,79,111,121,173] (but see Ref. 199). It is therefore likely that striatal innervation of DA cells arises mainly from the striosomal compartment with no or only minor contribution from the matrix compartment, which projects preferentially to the SNR. The existence of two such subpopulations of striatal neurons is supported by findings of morphological differences between striatal fibers innervating the DA cells and those innervating the GABAergic neurons of the SNR,[201,290] which suggest that they may have a distinct origin in the striatum.[201]

*4.2.3. The relations between the dopaminergic system and striatal compartments in rats and primates: summary*. In rats, there are two subpopulations of nigrostriatal DA neurons, one projecting to patches and the other projecting to the matrix, and these subpopulations correspond to the ventral and dorsal tiers of the SNC, respectively. These two tiers can be distinguished according to cell morphology (dendritic orientation) and chemistry (calbindin cell staining). In primates, calbindin cell staining can delimit a ventral and a dorsal tier which occupy similar locations within the DA system as the corresponding tiers in the rat. Specifically, the dorsal SNC, RRA and VTA contain calbindin-positive cells, whereas the ventral SNC and SNR contain only calbindin-negative cells. However, these tiers do not coincide with striosome- and matrix-projecting cell subpopulations. Rather, these subpopulations are composed of intermingled clusters of neurons of each type. Moreover, striosome- and matrix-projecting DA cells cannot be differentiated according to the morphology of their dendrites nor by any other marker tested to date (e.g., AChE staining), although SP may be a promising candidate.

In rats, the ventral and dorsal tiers can also be distinguished according to hodological criteria; both tiers project to the motor and associative striatum, but only the ventral tier is innervated by these striatal regions. In primates, only the ventral tier projects to the motor and associative striatum, and projections from these striatal regions are not directed to the entire ventral tier (as delimited by calbindin cell staining), but only to restricted subregions within it, i.e. DA cells that lie enmeshed in SP fibers. These relations may suggest that these DA cells correspond to ventral tier DA cells in rats.

In rats and primates, striatonigral projections directed to DA cells or to the SNR can be differentiated on the basis of fiber morphology and calbindin fiber staining, suggesting that these projections originate from different subsets of striatal neurons. In rats, there is some evidence that these two subsets correspond to patches and matrix, whereas in primates such evidence is presently lacking.

It can be concluded that, while in rats several lines of evidence point to differential relations between patch and matrix striatal neurons and the ventral and dorsal tiers of the SNC, in primates there is no direct evidence for differential relations of two sets of DA cells with the striatal compartments, although there are no data which contradict the existence of such relations.

We would like to end this section with a cautionary note. The terms ventral and dorsal tiers are widely employed in the primate literature, often with the implicit assumption that these two tiers have all the characteristics ascribed to them in rats. In view of the above, it is clear that more attention should be given to the nomenclature employed.

### *4.3. Combining topography and compartmentalization in rats and primates*

*4.3.1. Dopaminergic projections to the striatum.* In rats, the dorsal tier innervates all three striatal subregions. More specifically, the medial aspect of the dorsal tier (i.e. the VTA) provides the main DA input to the limbic striatum, the central aspect of the dorsal tier (medial part of the dorsal SNC) provides the main DA input to the matrix neurons of the associative striatum, and the lateral aspect of the dorsal tier (lateral part of the dorsal SNC) innervates the matrix neurons of the motor striatum. The medial and lateral aspects of the ventral tier innervate the patches of the associative and motor

striatum, respectively. In primates, like in rats, the DA projections to the limbic striatum arise from a relatively distinct group of neurons. However, there is no segregation between DA cells projecting to the motor versus associative striatum, nor between DA cells projecting to matrix versus striosomes. In addition, while in rats matrix- and patch-projecting DA cells are distinguished by calbindin cell staining, this marker does not distinguish between such cells in primates. Rather, calbindin cell staining differentiates between DA cells projecting to the limbic striatum (calbindin-positive cells) versus associative and motor striatum (calbindin-negative cells).

*4.3.2. Striatal projections to the dopaminergic system.* In rats, the projections to DA cell bodies and proximal dendrites arise mainly from the limbic striatum, which projects to both the dorsal and ventral tiers (except for the group of DA cells located in the SNR). In contrast, the projections of the associative and motor striatum (arising from patches) to DA cell bodies and proximal dendrites are restricted to the ventral tier, to its medial and lateral aspects, respectively. The reverse is true with regard to striatal projections to the ventrally extending dendrites of DA cells. Most of these projections arise from the matrix of the associative and motor striatum, and are directed to the medial and lateral SNR, respectively, whereas limbic striatal projections are restricted to the most medial SNR. In the three striatal subdivisions, different sets of neurons project to the DA cell bodies and proximal dendrites or to the ventrally extending DA dendrites. In the motor and associative striatum, these sets correspond to the patch and matrix compartments, respectively.

In primates, as in rats, the main striatal input to the DA cell bodies arises from the limbic striatum, which projects to most of the DA system (except for the more lateral and ventral parts of the SN), with some contribution from a specific (as yet unspecified) set of neurons in the motor and associative striatum, which projects to subregions within the main horizontal band and to the DA columns. As in rats, the input to the ventrally extending DA dendrites arises mainly from a (so far unspecified) set of motor and associative striatal neurons, with a minor projection from the limbic striatum which is directed to the most medial SNR. The projections to ventrally extending DA dendrites in the SNR arise mainly from striatal areas which are innervated by the corresponding DA cells.

*4.3.3. Striatal–dopaminergic system–striatal connections.* In both rats and primates the following observations can be made. (1) The limbic striatum reciprocates its DA input and in addition innervates most of the DA neurons projecting to the associative and motor striatum. (2) The motor and associative striatum reciprocate part of their DA input. (3) The DA cells which project to the motor and associative striatum can be divided into three subgroups: a group innervated only by the limbic striatum (dorsal tier in rats; neurons in the SNC which lie in the SP-free zone in primates), a group not innervated by the limbic striatum (in the more lateral SN), and a group innervated by the limbic striatum and the motor or associative striatum (ventral tier in rats; neurons in the SNC enmeshed within SP fibers in primates).

In rats, the organization of the connections between the dorsal striatum and the DA system can be further specified with respect to striatal compartmental organization. It is common to stress the reciprocal connections between the ventral tier and striatal patches. However, ventral tier neurons are also innervated by matrix neurons (which project to their ventrally extending dendrites) and by the limbic striatum (which projects to their cell bodies and proximal dendrites). Thus, the DA input to the patches of the associative striatum is under the influence of the limbic striatum and the patches and matrix of the associative striatum. Similarly, the DA input to the patches of the motor striatum is under the influence of the limbic striatum and the patches and matrix of the motor striatum. In contrast to the patches, the matrix of the associative and motor striatum do not reciprocate their DA input, which arises from the medial and lateral dorsal tier, respectively; rather, these DA regions are innervated by the limbic striatum only.

There are several differences between rats and primates. (1) In rats, projections directed to the ventrally extending dendrites can influence only patch-projecting neurons, while in primates they can influence striosome- and matrix-projecting neurons. (2) As a result, in primates, matrix neurons of the motor and associative striatum may have more influence on their DA input than matrix neurons in rats. (3) In rats, the SN region not innervated by the limbic striatum (i.e. DA cells located in the more lateral SNR) contains only patch-projecting neurons, while the analogous region in primates (the lateral DA columns) is characterized by preferential projections to the motor striatum and not by differential projections to the striatal compartments. (4) In primates, the associative striatum may have some influence on the DA input to the motor striatum.

## 5. PROJECTIONS TO THE DOPAMINERGIC SYSTEM FROM OTHER NUCLEI OF THE BASAL GANGLIA

In addition to the massive striatal projections, the DA system receives basal ganglia inputs from the pallidum, the subthalamic nucleus (STN) and the SNR.

### *5.1. The functional subdivision of the pallidum and subthalamic nucleus*

Parent and Hazrati[196,200,202] showed that, in primates, the tripartite subdivision of the striatum is maintained at the pallidal level, so that the pallidum can also be divided into motor, associative and limbic subregions. The motor subregion of the external segment of the globus pallidus (GPe) comprises the ventrolateral two-thirds of the postcommissural GPe; the motor subregion of the internal segment of the globus pallidus (GPi) comprises the ventrolateral two-thirds of the postcommissural GPi; the associative GPe comprises most of the globus pallidus (GP) at anterior commissural levels and the dorsomedial one-third of the postcommissural GPe; the associative GPi comprises the dorsomedial one-third of the postcommissural GPi; the limbic pallidum comprises the ventral pallidum (VP), the ventromedial rim of the rostral GPe and the medial tip of the GPi (for a similar subdivision, see Ref. 109).

Anatomical data indicate that, also in rats, the tripartite subdivision of the striatum is maintained at the level of the entopeduncular nucleus (EP; the rat analog of the primate GPi), GP (the rat analog of the primate GPe) and VP. Since the projections from the striatum to the EP are topographically organized, preserving the mediolateral and dorsoventral coordinates,[64,120,178,181,185] we[131] had previously divided the EP into motor and associative subregions in the lateral and

medial regions of the nucleus, respectively. Likewise, since the striatal projections to the GP are topographically organized, preserving the mediolateral, rostrocaudal and dorsoventral coordinates,[140,178,294] the lateral GP corresponds to the motor GP, while the medial GP corresponds to the associative GP. The VP is innervated by the ventral striatum[9,19,97,98,105,110,120,178,302] and therefore corresponds to the limbic pallidum.

There is still a controversy regarding the extent of segregation of striatal projections in the SNR (e.g., Refs. 66, 69, 109, 118, 165, 201, 202 and 215). Parent and Hazrati[201,202] concluded that the projections of the three striatal subregions overlap extensively in the SNR (for a similar conclusion, see Ref. 109; for discussion of this controversy, see Ref. 131 and Section 4.1.1.2).

With regard to the STN, we[132] had previously proposed that the primate STN may be subdivided into motor, associative and limbic subregions, each projecting to corresponding areas of the striatum, GPe and GPi. More specifically, the dorsolateral two-thirds of the rostral two-thirds of the STN and most of the caudal one-third of the STN project to the motor pallidum and motor striatum, and thus comprise the motor STN. The ventral and medial parts of the rostral two-thirds of the STN project mainly to the associative pallidum, associative striatum and SNR, and to a lesser extent to the limbic pallidum. These parts of the STN comprise the associative STN and the limbic STN. The exact definition of the limbic STN according to relevant STN efferents is still unclear, since the extent of the STN field which projects to the VP is still controversial[109,203] (see Ref. 132).

In the rat, the subthalamic projections to the GP, EP and striatum are topographically organized, preserving the mediolateral coordinates and inverting the dorsoventral coordinates (GP: Refs. 21, 94, 144 and 281; EP: Refs. 21, 24, 94 and 144; striatum: Refs. 94 and 144), suggesting that each STN subregion projects to functionally corresponding subdivisions of the pallidum, EP and striatum. Therefore, the rat STN can also be subdivided into three subregions, with the lateral STN comprising the motor STN, and the medial STN comprising an associative and a smaller limbic region of the STN, in its ventrolateral and dorsomedial parts, respectively.

The following sections will describe the organization of basal ganglia projections to the DA system in rats and primates with regard to this tripartite subdivision.

### 5.2. Rats

*5.2.1. Pallidal projections to the dopaminergic system.* The VP provides the main pallidal input to the DA cells.[96,99,105,254–256,297] The medial VP, which is innervated by the NAcc shell, projects to the VTA and the lateral VP, which is innervated by the rest of the limbic striatum, projects to the SNC and RRA.[96,99,297] In addition to its projections to the DA system, the VP, like the limbic striatum, projects to the most medial SNR.[25,96] However, unlike the limbic striatum, the VP contacts mainly perikarya of DA cells and not their ventrally extending dendrites.[25,96,99]

The GP (which comprises the motor and associative pallidum) innervates mainly the SNR, with relatively minor projections to the SNC. The pallidonigral projections are topographically organized, with the motor pallidum innervating the lateral SN and the associative pallidum innervating the medial SN.[23,25,34,76,96,105,219,254–256,262] The dorsal pallidum, unlike the dorsal striatum, does not seem to contribute much to the innervation of the ventrally extending DA dendrites, since most of its synapses in the SNR are with soma (54%) and proximal dendrites (32%),[254–256] suggesting that it contacts primarily the GABAergic cells of the SNR. There is also a minor projection from the EP to the SN which terminates mainly in the SNR.[116]

*5.2.2. Subthalamic projections to the dopaminergic system.* The organization of STN projections to the SN seems to comply with the organization of the other basal ganglia projections:[76,94,144,145] the associative and limbic STN project to the medial SNR, while the motor STN projects to the lateral SNR.[21,94,144,145,281] This is supported by Kitai and Kita's[145] observation that there are neurons in the STN which project, via axon collaterals, to nigral and pallidal areas which are innervated by the same striatal subregion. The data are not sufficient to conclude whether STN input is restricted to the dendrites of SNR neurons or also reaches the ventrally extending DA dendrites. Although anatomical studies indicate that the subthalamic innervation of the SNC, VTA and RRA is very sparse,[35,94,144,145,281] there is electrophysiological evidence for direct projections from the STN to DA cells.[38,194,253]

*5.2.3. Nigral projections to the dopaminergic system.* Anatomical and electrophysiological studies demonstrated direct projections from the GABAergic projection neurons of the SNR to the DA cells of the SNC.[13,44,112,272] Moreover, electrophysiological data suggest that these projections can affect a restricted region of the SNC, just dorsal to the stimulated SNR neurons.[112]

### 5.3. Primates

*5.3.1. Pallidal projections to the dopaminergic system.* The pallidal projections arise mainly from the VP, which also innervates a small region of the medial SNR.[108,109] Although these projections may not be organized topographically,[108] it seems that, at least for some pallidal subregions, interconnected regions of the ventral striatum and VP project to the same region of the DA system. Thus, a medial (neurotensin-positive) region of the VP projects extensively to the VTA, and its nigral projections are restricted to the pars mixta only,[108] while other VP regions project to both the pars mixta and the main horizontal band of the SNC. In addition, the nigral projections of the NAcc shell, which is interconnected with the medial VP,[106,261] seem to be restricted to the pars mixta only, while other ventral striatal regions project to both the pars mixta and the main horizontal band.[106,165]

Projections from the GPe are directed to the SNR,[53,109,117,198,204,208,259] where they form dense networks that closely surround the soma and proximal dendrites of SNR neurons,[203] suggesting that pallidal projections are not a major source of input to the ventrally extending DA dendrites. Although data on the topographical organization of the pallidonigral connections are sparse, results of several studies suggest that the associative GPe projects to the entire SNR,[117,198,204,208] while the motor GPe projects to the lateral SNR.[53]

*5.3.2. Subthalamic projections to the dopaminergic system.* The subthalamonigral fibers arise mainly from the ventral

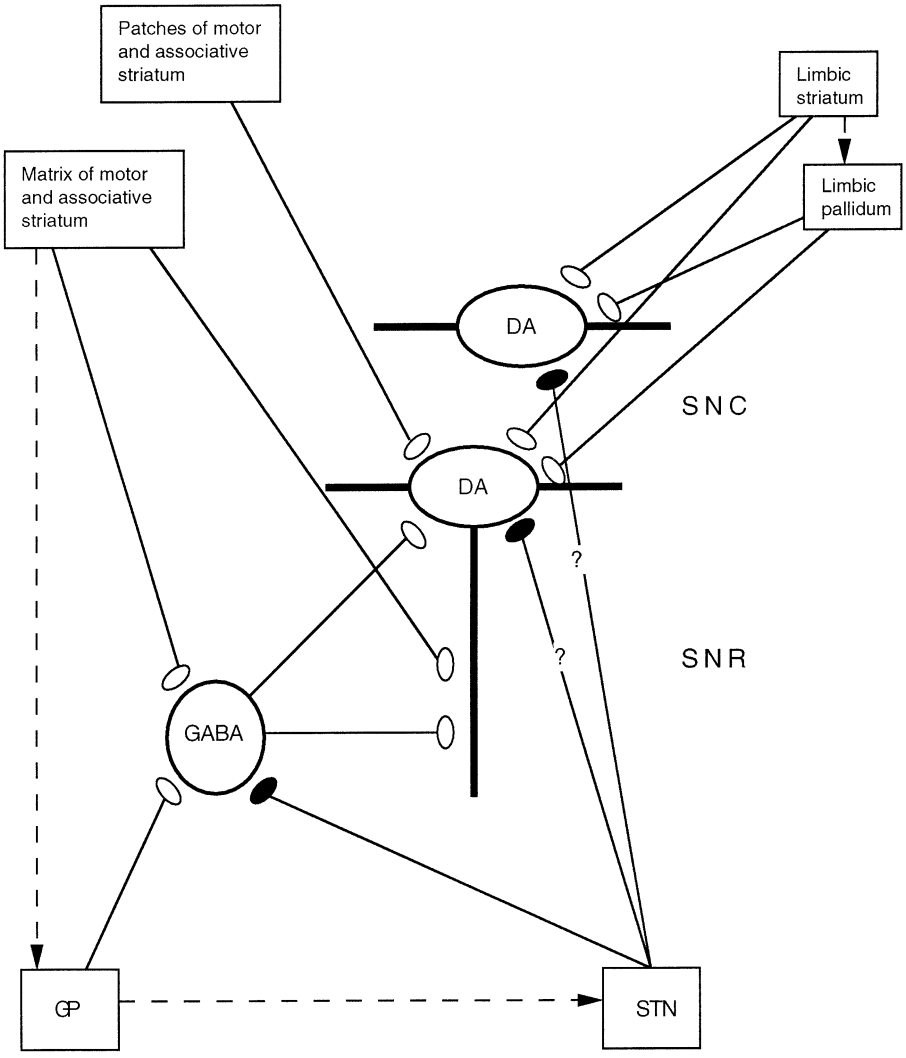


Fig. 4. A schematic representation of the different targets in the SN (DA cell bodies and proximal dendrites, ventrally extending DA dendrites, SNR GABAergic neurons) of projections arising from the basal ganglia nuclei in the rat. Open ellipse: inhibitory synapse; filled ellipse: excitatory synapse. Dashed lines depict some of the connections between the basal ganglia nuclei. For detailed explanation, see text.

STN[206,257] and terminate primarily in the SNR, although some fibers ascend along the DA cell columns of the SNC that invade the SNR. Thus, the STN is in a position to influence mainly non-dopaminergic cells in the SN, but may also influence DA cells.[33,183,198,200,203,206,208,216,257] STN projections seem to display a crude mediolateral topography, with the medial STN projecting to the medial SN and the lateral STN projecting to the lateral SN.[183,203,206,257]

### *5.4. Basal ganglia projections to the dopaminergic system: summary*

In both rats and primates, the projections from functionally corresponding subdivisions of the striatum, pallidum and STN to the DA system overlap (although the data on primates are less clear cut), but the specific targets (DA cells, DA dendrites, GABA cells) of these projections differ. The limbic subregions of the striatum and pallidum provide the main basal ganglia input to the cell bodies and proximal dendrites of most of the DA system. The SNR, a specific subset of neurons in the motor and associative striatum (patch neurons in rats), and probably the STN also project to DA cells. The main basal ganglia input to the ventrally extending DA dendrites in the SNR arises from SNR neurons and from a specific subset of neurons in the motor and associative striatum (matrix neurons in rats), with only minor contributions from the pallidum and STN. The STN, pallidum, and a specific subset of neurons in the motor and associative striatum (matrix neurons in rats) synapse on SNR GABAergic neurons (see Fig. 4).

## 6. FUNCTIONAL IMPLICATIONS: BASAL GANGLIA INFLUENCES ON DOPAMINE CELL ACTIVITY

The synaptic organization of the DA innervation of the striatum and the effects exerted by DA on striatal neurons have been extensively reviewed (e.g., Refs. 83, 102 and 202). We will focus here on the influence of the basal ganglia on DA cells, with an emphasis on the differential inputs to cell bodies and proximal dendrites of nigral DA neurons and to their ventrally extending dendrites. Since much more is known on the subcellular targets of basal ganglia projections to the SN and on dendritic DA release in rats, the present discussion is restricted to this species.

### 6.1. Physiology of dopamine cells

DA cells have been shown to exhibit two spontaneously occurring electrophysiological states: single spiking, in which the majority of cells are found, and burst firing.[30,84,134,137,272,291] The cells can rapidly switch between these two states, and this switch has been suggested to constitute the basic mechanism for changing the influence of DA cells on their targets.[30,134,194,269] DA cell switching is most likely to be the result of excitatory input and/or removal of inhibitory input to DA cells. Thus, stimulation of the prefrontal cortex or STN, as well as local application of glutamate or *N*-methyl-D-aspartate, were found to induce bursting of DA cells,[38,39,134,137,194,251,253,264] and blockade of $GABA_A$ receptors in the SNC was found to increase burst firing in DA neurons.[195,272]

The latter indicates that tonic activation of $GABA_A$ receptors is of major importance in suppressing burst firing. Since such tonic GABAergic input probably arises from SNR neurons,[13,30,85,112,137,146,251,265,272,291] inhibition of SNR neurons is expected to lead to disinhibition of burst firing in SNC DA neurons.[13,137,146,291] Descending GABAergic afferents (e.g., striatal and pallidal) can inhibit the tonic GABAergic input to the DA cells by stimulating $GABA_A$ receptors located on SNR neurons, and thus indirectly facilitate the switching of DA neurons to the bursting mode.[13,137,146,291] In addition to indirect stimulation of DA cells, descending GABAergic afferents directly inhibit these cells via $GABA_B$ receptors.[137,146,251,265,272,291] This inhibition does not seem to play a major role in the tonic suppression of burst firing, because blockade of $GABA_B$ receptors results in a minor change of burst firing in SNC neurons.[55,195,272] Thus, descending GABAergic afferents exert two contrasting effects on the activity of DA cells, namely, direct inhibition or indirect stimulation. Which of the two effects predominates depends on the specific target of the afferents (i.e. DA or SNR cells), as well as on their relative activation. Administration of low levels of GABA, or low levels of $GABA_A$ agonists, into the SN, as well as weak stimulation of the striatum, result in disinhibition of DA cells, while administration of $GABA_B$ agonists or high levels of $GABA_A$ agonists into the SN, as well as stronger striatal stimulation, are needed to observe the direct inhibitory effect.[30,137,146,238]

Another factor which regulates DA cell activity is DA released from DA dendrites; the latter inhibits DA neurons, probably via activation of $D_2$ autoreceptors.[28,37,40,93,137,192,220,227,232,251,264,273,291,305] It has been suggested that this inhibitory effect acts to increase the likelihood of a switch to a bursting mode;[30,93] however, there is evidence that DA and $D_2$ agonists decrease bursting of DA cells (for review, see Ref. 194). Whatever the effect of dendritically released DA on DA cell activity, it is evident that factors affecting its release can indirectly affect the activity of DA cells.

*6.1.1. Factors affecting dendritic dopamine release.* The ionic mechanisms underlying DA dendritic release (e.g., the degree to which it is calcium dependent, depolarization mediated, sensitive to tetrodotoxin, etc.),[37,93,119,139,190,227,233] as well as the relation between dendritic release and DA cell firing (e.g., Refs. 40, 93, 191 and 192), remain controversial. Bunney *et al.*[30] suggested that dendritic release occurs when DA cells switch from the single-spiking mode to the bursting mode. Accordingly, stimulation of the cortex or presentation of physiologically significant stimuli (such as food), which result in the bursting of DA cells,[84,85,137,151,251] also increase dendritic release.[37,305]

Dendritic DA release is inhibited by DA via activation of $D_2$ autoreceptors, and this effect is thought to be similar to, though weaker than, the DA inhibitory effect on DA release from terminals.[30,137,139,191,192,305] There are contradictory findings concerning the effects of GABA on dendritic release (e.g., Refs. 37, 40, 137 and 146), which are probably due to the existence of several GABAergic systems in the SN and the different effects of $GABA_A$ and $GABA_B$ receptor stimulation. Stimulation of $GABA_B$ receptors decreases dendritic release, while low, but not high, doses of $GABA_A$ agonists increase dendritic release.[40,137,146] In addition to its direct effects on DA dendrites, GABA can indirectly affect dendritic release via its influence on the activity of DA cells. Kalivas[137] concluded that descending GABAergic afferents can directly inhibit DA dendritic release via stimulation of $GABA_B$ receptors, and indirectly stimulate DA release (by removing tonic GABAergic input) via activation of $GABA_A$ receptors (also see Ref. 251; for review of the effects of other neurotransmitters on dendritic DA release, see Ref. 137).

*6.1.2. Effects of dopamine released from dendrites.* In addition to direct regulation of DA cell activity, DA released from dendrites can modulate the GABAergic influences on DA cells.[10,37,42,93,137,152,228,263,288,289]. Cheramy *et al.*[37] concluded that DA released from dendrites exerts an excitatory effect on SNR projection neurons and regulates the presynaptic release of GABA from striatonigral terminals. Later studies reported that DA increases the activity of SNR projection neurons,[93,137,158,288] probably via activation of $D_2$ receptors located on these neurons.[93,158] In addition, exogenous and endogenous DA attenuates the inhibitory effect of GABA on SNR projection neurons, as well as their response to striatal stimulation.[288,289] DA can also influence GABA release in the SN, with stimulation of $D_1$ increasing and that of $D_2$ decreasing GABA release.[1,93,137,228,263] In addition, increased release of GABA was reported following activation of $D_1$ receptors located on GABAergic terminals in the SNR,[137,221,228,236,263] which are most likely of striatal origin, because most $D_1$ receptors in the SNR are located on striatonigral terminals.[10,221,236]

It follows from the above that dendritic DA has two opposing effects on the GABAergic neurons of the SNR. On the one hand, it exerts a direct excitatory effect on these neurons, via $D_2$ receptors, and attenuates the inhibitory effects of the striatonigral projection on these neurons. On the other hand, it increases, via $D_1$ receptors, GABA release from striatonigral terminals, thus exerting an indirect inhibitory effect on SNR neurons. The latter effect may be more pervasive under physiological conditions, because the injection of amphetamine into the SNR, which leads to release of DA from dendrites, decreased the activity of SNR neurons,[275] and this effect was blocked by $D_1$ but not $D_2$ antagonists.[275]

### 6.2. Effects of the basal ganglia on the dopaminergic system

In view of the above, it appears that the basal ganglia can influence the activity of DA cells in three ways: (i) inhibit the activity of DA cells via direct projections to DA cell bodies and proximal dendrites; (ii) disinhibit DA cells by inhibiting SNR neurons, thus removing the latter's tonic inhibitory input

to DA cells; (iii) influence the activity of DA cells by affecting dendritic DA release. We suggest that each of the different basal ganglia nuclei influences DA cell activity in some of these ways, depending on its specific targets in the SN.

The limbic striatum and limbic pallidum exert a direct inhibitory effect on most DA cells. Patch neurons of the motor and associative striatum exert such an effect on ventral tier DA cells. Such an inhibitory effect in turn reduces dendritic DA release.

Matrix neurons of the motor and associative striatum, and matrix-like projections of the limbic striatum, inhibit SNR GABAergic cells. This (i) disinhibits DA cells, and thus facilitates burst firing of DA cells, and (ii) disinhibits dendritic DA release, which can be further increased by the increased bursting of the DA cells. Increased dendritic release may be attenuated by the direct inhibitory projections of matrix neurons to the ventrally extending DA dendrites. Thus, the projections of matrix neurons can affect dendritic DA release in opposite directions. However, while the striatonigral projections are widely distributed, SNR projections to the SNC are spatially restricted, so that an SNR neuron can influence mainly DA neurons located above it.[112] Consequently, the disinhibitory effect of the striatal projections is expected to be limited to a small population of DA neurons contacted by the inhibited SNR cells and to DA dendrites in their vicinity, and therefore to be more localized than the direct inhibitory effect. As a result, DA concentration will increase in restricted areas, i.e. in the vicinity of inhibited SNR neurons, while DA concentration in other regions will not be affected, or may even be reduced. Increased DA concentration in restricted areas may either increase further the tendency of the corresponding DA cells (i.e. those which were disinhibited by the activation of the striatonigral projection) to fire in bursts, or serve to limit bursting of the disinhibited DA cells.

It should be noted that patch and matrix neurons of the motor and associative striatum exert opposite effects on the activity of patch-projecting DA neurons, namely, direct inhibition and indirect excitation (following inhibition of SNR cells), respectively. Similarly, the two sets of neurons have opposite effects on dendritic DA release in the SNR. Thus, patch neurons can reduce dendritic release via their effect on DA cell activity, whereas matrix neurons can increase dendritic release via their effect on SNR GABAergic cells. Since dendritic DA release within the SNR can modulate (probably facilitate; see below) matrix-originating striatonigral transmission, both compartments can apparently contribute to such modulation.

The motor and associative pallidum provide an inhibitory input to the SNR, directed mainly to SNR GABAergic neurons. These neurons also receive excitatory input from the STN.[229,253] Pallidal and subthalamic neurons are tonically active, suggesting that they provide tonic inhibitory and excitatory inputs, respectively, to the GABAergic cells of the SNR, and thus determine the level of tonic activity of SNR cells.[143,229,253] Since SNR cells provide tonic inhibitory input to DA cells and dendrites, the pallidal and subthalamic projections apparently participate in the regulation of the baseline level of DA cell activity and dendritic release. This contrasts with the phasic influences (inhibitory and excitatory) exerted by striatal projections on DA cell activity and dendritic release. The excitatory subthalamic input to SNR neurons may serve to limit the inhibitory influence of the striatonigral projections, since STN lesion was found to increase the inhibition of SNR neurons following striatal stimulation.[143] In addition to its inhibitory effects on DA cells via its excitatory effects on SNR neurons, the STN is considered to be directly involved in the induction of burst firing in DA neurons.[38,194,253] The indirect inhibitory and direct excitatory effects of the STN are likely to be tonic and phasic, respectively (also see below).

### *6.3. Summary: an hypothesis*

Activity in a set of striatal neurons (triggered, for example, by corticostriatal input) is expected to result in the following.

(1) Matrix neurons will provide inhibitory input to DA dendrites and SNR neurons. A subset of these SNR neurons which receive a sufficient amount of converging striatal inputs will phasically reduce their activity. As a result, DA cells and dendrites which receive tonic inhibitory input from this subset will be disinhibited, increasing the likelihood of burst firing and of dendritic release. Increased DA release will modulate bursting in DA cells and increase the signal-to-noise ratio in striatonigral transmission because it will (i) increase GABA release from the active striatal terminals in the regions of inhibited SNR cells, but not in other SNR regions innervated by the active matrix neurons, and (ii) excite SNR neurons in the vicinity of the inhibited SNR cells, thus increasing the contrast between the inhibited SNR cells which transmit striatal information and other SNR cells.

(2) Matrix cells projecting to the GP will phasically inhibit a subset of GP neurons, which will lead to a phasic disinhibition of STN neurons. As a result, a subset of DA cells will receive an increased excitatory input (from the STN) and are likely to increase bursting. This increased bursting will be limited by the activation of a set of SNR neurons which will receive reduced inhibitory (from the GP) and increased excitatory (from the STN) input. In addition, since the topographical organization of the striato-, pallido- and subthalamonigral projections indicates that these SNR neurons also receive striatal inhibitory input, pallidal and subthalamic inputs are also expected to contribute to the sharpening of striatonigral transmission.

(3) Patch neurons will provide inhibitory input to DA cells to which they project.

(4) “Patch-like” limbic striatal neurons will provide inhibitory input to DA cells to which they project, whereas “matrix-like” limbic striatal neurons will have a disinhibitory effect (via inhibition of SNR GABAergic neurons) on a subset of DA cells. It should be noted that the former can influence DA projections to the motor, associative and limbic striatum, whereas the latter effect is restricted to regions of the DA system which project to the limbic striatum. Another disinhibitory effect of limbic striatal neurons stems from inhibition of VP GABAergic neurons which project to the DA system. This disinhibitory effect can affect the entire DA system. It remains an open question whether limbic striatal neurons projecting to the VP and/or SNR are distinct from those projecting to DA cells; were this the case, two sets of limbic striatal neurons would exist, one, “patch-like”, directly inhibiting DA cells, and the other, “matrix-like”, indirectly facilitating DA cells, via inhibition of SNR and/or VP neurons.

To summarize, the activity of striatal neurons can either suppress DA cell activity directly or promote bursting in a

subset of DA cells indirectly. The direct inhibitory influences arise from patch and limbic striatal neurons, whereas the indirect facilitatory influences arise from matrix and limbic striatal neurons; the latter may be different from limbic striatal neurons which exert direct inhibitory effects. Both the direct and indirect influences of motor and associative striatal inputs are restricted to patch-projecting DA cells,[2] whereas those arising from the limbic striatum can affect the entire DA system.[3]

The above hypothesis has interesting implications for two of the central functions ascribed to striatal DA input, namely, governing striatal learning[90,102,122,123,141,176,211,212,243,246,292,293] and enabling the execution of well-learned behaviors[22,32,41,86,92,141,148,149,218,230,231,239] (but see Ref. 246). We suggest that the direct inhibitory effect exerted by each striatal region on its DA input provides a mechanism which restricts striatal learning in well-learned situations, whereas the indirect facilitatory effect provides a mechanism for the maintenance of an optimal striatal DA level needed for the execution of well-learned behaviors. With regard to the former, it has already been suggested that cessation of DA cells' response when rewards become predictable is the result of inhibitory input to these cells[245,246] arising from striosomes[123] or from the limbic striatum.[293] The present hypothesis underscores the distinction between the inhibitory inputs arising from patches and from the limbic striatum: whereas patch neurons can restrict learning only in the striatal region within which they reside, limbic striatal neurons can restrict learning in the entire striatum. A similar distinction applies to the indirect facilitatory effect which maintains the striatal DA level necessary for performing well-learned acts. Again, whereas projections arising from the motor and associative striatum can affect only the DA input to their patch compartment, projections arising from the limbic striatum may affect DA input to both compartments in all three striatal subregions. The limbic striatum has been charged with a role in motivation and goal-directed behavior (e.g., Refs. 31, 32, 56, 138, 155, 212, 237, 239, 243 and 244) since its identification as a "limbic–motor interface" by Nauta *et al.*[185] and Mogenson *et al.*[177] The present hypothesis imbues the "limbic–motor interface" with the ability to influence learning and execution of learned behaviors in the motor and associative striatum so as to adjust them to the motivational state of the organism and to foster the attainment of the current goal (for a detailed exposition, see Ref. 133).

In addition, the present hypothesis directs attention to several relatively neglected effects of DA within the SNR and, in particular, its role in sharpening the transfer of striatal information via the SNR. Interestingly, the source of SNR DA is a small subset of DA neurons which are the only DA neurons to receive projections from the motor and associative striatum (i.e. ventral tier neurons). This suggests that projections from the motor and associative striatum to the DA system have the capacity to modulate the effects of DA within the SNR, and in this way modulate the transfer of their output via the SNR.

[2]The organization of striatonigral projections in rats suggests that matrix neurons can affect DA input to patch neurons, but not their own DA input. It is still possible, however, that the effects exerted by matrix neurons on the DA system extend to the matrix compartment as a result of some kind of direct interaction between the two striatal compartments.

[3]As noted in Section 6, data on dendritic release in primates are scant. However, even if the mechanisms governing such release and its effects were similar in primates and rats, an important difference would remain due to the different relations between the striatal compartments and the DA system in the two species. Specifically, the data suggest that, in primates, nigrostriatal DA cells which have ventrally extending dendrites project to both striatal compartments. Therefore, while, in rats, dorsal striatal projections to the SNR can affect the activity of patch-projecting DA cells only, in primates the associative and motor striatal projections to the SNR would affect the activity of DA cells projecting to the striosomes and matrix of these striatal regions.

## 7. THE DOPAMINERGIC SYSTEM AND THE OPEN-INTERCONNECTED ORGANIZATION OF BASAL GANGLIA CIRCUITRY

In the last 15 years, the basal ganglia have been viewed as "components of basal ganglia–thalamocortical circuits that are organized in a parallel manner and remain largely segregated from one another, both structurally and functionally" (Ref. 6, p. 119; also see Refs. 5, 7, 47, 95, 97 and 213). Each circuit receives input from several separate but functionally related cortical areas, traverses specific regions of the striatum, GPi, SNR and thalamus, and projects back upon one of the frontocortical areas providing input to the circuit. Within each circuit, striatal output reaches the basal ganglia output nuclei (SNR and GPi) via a "direct" pathway and via an "indirect pathway" which traverses the GPe and STN.[4–6,46,214]

While the principle of parallel segregated organization has become central to research and theoretical approaches aimed at understanding normal and abnormal brain functions,[4,45,47,81,86,87,89,94,98,126,196,213,214,226,267] it has been repeatedly recognized that integration between different basal ganglia–thalamocortical circuits is essential for producing coherent behavior, as well as the wide variety of symptoms which are associated with basal ganglia dysfunction (e.g., Refs. 62, 95, 98, 109 and 168). Recently, we presented a new scheme of basal ganglia–thalamocortical organization, namely, the "split circuit" scheme, which emphasizes an open-interconnected as opposed to closed-segregated architecture of the basal ganglia–thalamocortical circuits.[131] A split circuit contains one frontocortico-striatal pathway and two striato-frontocortical pathways. One of the striato-frontocortical pathways re-enters the frontocortical area of origin, thus forming a "closed circuit", and the other leads to a frontocortical area which is the source of a different circuit, thus forming an "open pathway".

Using the tripartite subdivision of the striatum and pallidum, we described a motor, an associative and a limbic split circuit (Fig. 5). The associative split circuit contains a closed associative circuit that re-enters the associative prefrontal cortex and an open associative pathway that terminates in the premotor cortex, which projects to the motor striatum. The motor split circuit contains a closed motor circuit that re-enters motor and premotor cortical areas and an open motor pathway that terminates in the associative prefrontal cortex. Since only the striatonigral portion of this pathway belongs exclusively to the motor circuit, whereas the nigro-thalamo-cortical portion is also part of the associative split circuit, we termed the striatonigral portion an "open motor route". The limbic split circuit contains a closed limbic circuit that re-enters the limbic prefrontal cortex, an open limbic pathway that terminates in the associative prefrontal cortex, i.e. an "open limbic route", and possibly an additional open limbic pathway which terminates in the motor/premotor cortices (via the rostromedial GPi). Thus, the three split

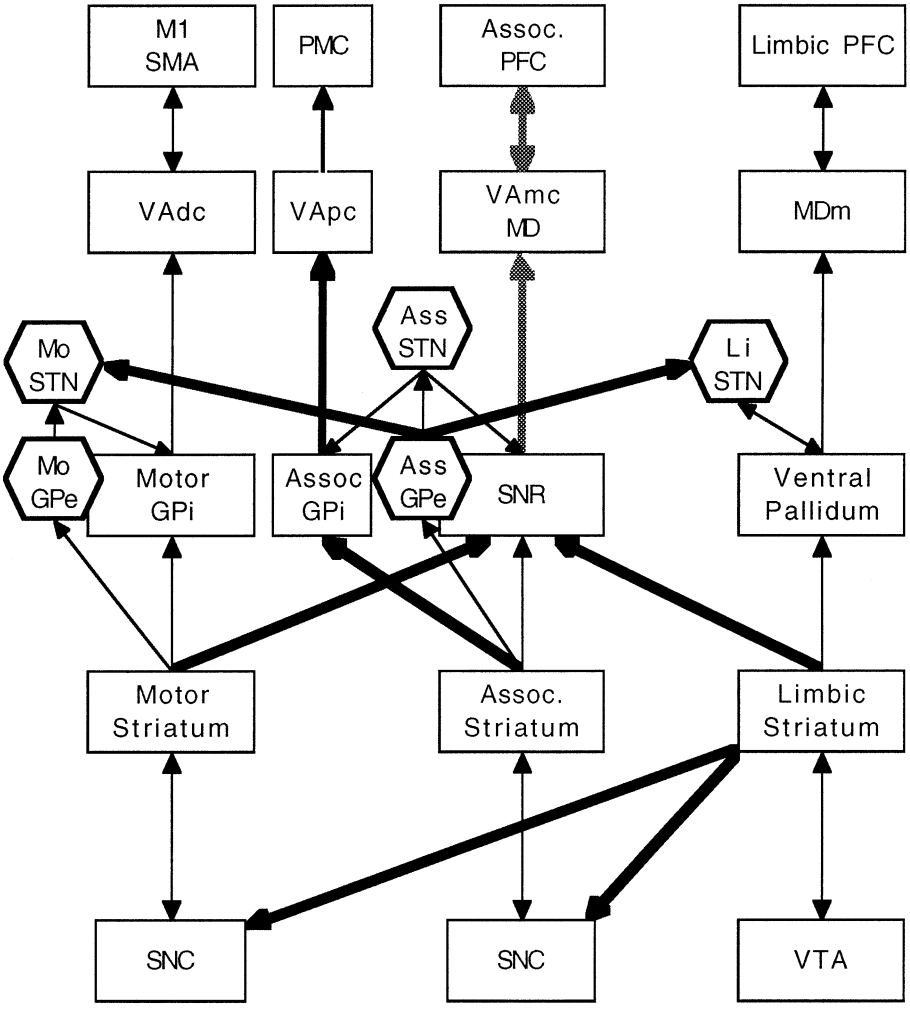


Fig. 5. A summary diagram of the structural organization of the motor, associative and limbic split circuits. Each split circuit contains a closed circuit and an open route or an open pathway. Included within each of the closed circuits as well as within the open associative pathway is a direct and a closed indirect pathway. In addition, the associative split circuit contains an open indirect pathway which connects it with the motor split circuit, and possibly an open indirect pathway which connects it with the limbic split circuit. Each split circuit has a closed loop with the DA system, and in addition there are two open loops connecting the limbic split circuit with the motor and the associative split circuits. This structural organization enables four modes of between-circuit interaction: via open pathway, via open route, via open indirect pathway and via open loop. It is noteworthy that the three split circuits differ in their modes of connectivity. Thus, the motor split circuit is connected to the associative split circuit at the level of the SNR (via an open route). The associative split circuit is connected to the motor split circuit at the level of the cortex and pallidum (via the open associative pathway and the open indirect pathway, respectively). The associative split circuit may also be connected to the limbic split circuit at the level of the pallidum (via an open indirect pathway). The limbic split circuit is connected to the associative split circuit at the level of the SNR and the striatum (via an open route and an open loop, respectively), and to the motor split circuit at the level of the striatum (via an open loop). The limbic split circuit may also be connected to the motor split circuit at the level of the cortex (via an open limbic pathway). It is likely that these differences in the levels of connectivity between the split circuits have functional significance.[133]. "Closed circuit": a striato-fronto cortical pathway that re-enters the frontocortical area which is the source of cortical input to this striatal subregion. "Open pathway": a striato-fronto cortical pathway that terminates in a frontocortical area which innervates a different striatal subregion. "Open route": the striatonigral portion of an open pathway. "Closed indirect pathway": an indirect pathway (striatum–GPe–STN–GPi/SNR) which connects functionally corresponding subregions of the basal ganglia, i.e. which terminates in the same subregion of the basal ganglia output nuclei as the direct pathway. "Open indirect pathway": an indirect pathway (striatum–GPe–STN–GPi/SNR) which connects functionally non-corresponding subregions of the basal ganglia, i.e. which terminates in a different subregion of the basal ganglia output nuclei than the direct pathway. "Closed loop": a loop (striatum–DA system–striatum) which terminates in the striatal subregion from which it originates. "Open loop": a loop (striatum–DA system–striatum) which terminates in a different striatal subregion than that from which it originates. Pathways connecting between circuits are demarcated in thick lines. The GPe and STN appear within hexagons for clarity of presentation. Ass, associative; Lim, limbic; MD, mediodorsal thalamic nucleus; MDm, medial mediodorsal thalamic nucleus; MI, primary motor cortex; Mot, motor; PFC, prefrontal cortex; PMC, premotor cortex; SMA, supplementary motor area; VAdc, ventral anterior thalamic nucleus, dencicellular subdivision; VAmc, ventral anterior thalamic nucleus, magnocellular subdivision; VApc, ventral anterior thalamic nucleus, parvicellular subdivision. Note that corticostriatal projections are not depicted.

circuits are interconnected via their open routes or open pathways.

It should be noted that open pathways connecting different subregions of the limbic striatum have been described by Zahm *et al.*[299,300,304] In particular, these authors have drawn attention to a major open pathway within the limbic circuit originating from the shell subterritory of the NAcc and terminating in cortical areas projecting to the core subterritory.

The open-interconnected principle also governs the organization of indirect pathways.[132] Thus, similarly to striato-frontocortical pathways, there are two types of indirect pathways. An indirect pathway terminating in the

same GPi/SNR subregion as the direct pathway forms a "closed indirect pathway", which contributes to segregated processing. An indirect pathway terminating in a different GPi/SNR subregion than the direct pathway forms an "open indirect pathway", which contributes to integrated processing. There is a closed indirect pathway within the motor, associative and limbic closed circuits, as well as within the open associative pathway. In addition, there is an open indirect pathway which connects the associative striatum to the motor GPi and possibly an open indirect pathway connecting the associative striatum to the VP.

The connections between the striatum and the DA system have long been recognized as not obeying the parallel segregated principle, because the ventral striatum can influence the DA input of the dorsal striatum. Accordingly, several authors suggested that these connections provide a major mode of between-circuit integration (e.g., Refs. 99, 106, 109, 128, 130, 164, 165, 177, 185, 202 and 266). However, the connections of the striatum with the DA system have not been incorporated into the existing schemes of basal ganglia–thalamocortical circuits.

The split circuit scheme can easily accommodate the connections of the basal ganglia with the DA system, due to its emphasis on the open-interconnected nature of the circuits. Thus, the basic design of the connections of the basal ganglia with the DA system is that of a "loop" comprising the projections from a striatal subregion to a subregion of the DA system and from this subregion to a striatal subregion. A loop which terminates in the striatal subregion from which it originates forms a "closed loop", and thus contributes to segregated processing. A loop which terminates in a different striatal subregion than that from which it originates forms an "open loop", and thus contributes to integrated processing. The application of the concept of closed and open loops to the data surveyed here allows the conclusion that each of the split circuits contains a closed loop, and in addition, the limbic split circuit is the source of two open loops, one connecting it to the associative striatum and the other connecting it to the motor striatum. As detailed by Haber *et al.*,[108,109] an additional means by which the limbic circuit can interact with the motor and associative circuits is provided by the connections of the limbic pallidum with the DA system, since the limbic pallidum innervates regions of the DA system which provide DA input to the motor and associative striatum.

A summary diagram of the structural organization of the motor, associative and limbic split circuits, including their indirect pathways and their connections with the DA system, is presented in Fig. 5. The major feature emerging from the connectivity depicted here is that the connections of the basal ganglia with the thalamus and the cortex, as well as the connections between the different nuclei of the basal ganglia (i.e. those involving the STN and the DA system), provide a neural substrate for the transfer of information within as well as between basal ganglia–thalamocortical circuits. Thus, the same sets of connections, striato-frontocortical, striato-pallido-subthalamo-pallidal/nigral, or striatal–DA system–striatal, subserve either segregated or integrated processing, depending on the specific target of the connections. This reinforces the view that the organization of the basal ganglia–thalamocortical circuitry is better described as open-interconnected rather than closed-segregated, as captured by the concept of split circuit.

*Acknowledgements*—We are indebted to Prof. H. Groenewegen for critical reading of the manuscript. We also thank our anonymous referees for their constructive comments.

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(*Accepted* 2 *December* 1999)