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Neural circuits and functional organization of the striatum

Abstract The basal ganglia and motor thalamic nuclei are functionally and anatomically divided into the sensorimotor, supplementary motor, premotor, associative and limbic territories. There exist both primary segregated basal ganglia-thalamocortical loops and convergence of functionally related information from different cortical areas onto these cortical basal ganglia-thalamocortical loops. The basal ganglia-thalamocortical loop arising from the sensorimotor area, supplementary motor area (SMA), premotor area and cingulate motor area provides distinct segregated subloops through the functionally distinct striatal, pallidal and thalamic regions with partial overlap. The subthalamic nucleus (STN) is also topographically organized. The ventrolateral part of the caudal 2/3 levels of the medial pallidal segment (GPi) projects to the primary motor area via the oral part of the ventral lateral thalamic nucleus (VLo) (Voa, Vop by Hassler's nomenclature). The thalamic relay nuclei of the GPi projection to SMA are identified in the transitional zone of the VApc (parvicellular part of the anterior ventral nucleus)-VLo and in the rostromedial part of the VLo. The thalamic nuclei relaying the cingulate subloop are not yet clearly defined. The supplementary motor subloop appears to be divided into the pre-SMA and SMA proper subloops. The premotor area is also divided into the dorsal premotor area subloop and the ventral premotor area subloop. It is suggested that the limbic loop consists of a number of subloops in the monkey as indicated by Haber et al. [67] and in rats [64]. We review here the microcircuitry of the striatum, as well as the convergence and integration between the functionally segregated loops. Finally, we discuss the functional implications of striatal connections.

Key words Basal ganglia · Cerebral cortex · Subthalamic nucleus · Thalamus · Supplementary motor area

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Introduction

In the past, the basal ganglia were considered as a site for integrating diverse inputs from the entire cerebral cortex and funneling these influences, via the ventrolateral thalamus, to the motor cortex [89]. However, more recently, based on anatomical and physiological findings, these structures are viewed as segregated parallel basal ganglia-thalamocortical circuits [3]. In addition to the five basal ganglia-thalamocortical circuits reported by Alexander et al. [3], functionally defined cortical areas appear to provide several subloops of the basal ganglia-thalamocortical circuits based on recent experimental data (for a review, see [106]). Groenewegen and co-workers [64] in the rat and Haber et al. [67] in the monkey have demonstrated a number of subloops of the limbic basal ganglia-thalamocortical loop. In this review we will describe a number of possible subloops, mainly motor-related loops, in relation to the topographic organization of the basal ganglia and thalamic nuclei, based on recent studies conducted in our laboratory. There exist both a primary segregated loop model and convergence of functionally related information from different cortical areas onto these cortical-basal ganglia loops. A major role of the basal ganglia is considered to integrate sensorimotor, associative, and limbic information to produce context-dependent behavior [61, 119].

We will briefly review the neural circuits of the striatum, and the convergence and integration between the basal gan-

glia-thalamocortical loops, and finally review the function of these striatal loops.

Microcircuits of the striatum

The striatum is the major input structure of the basal ganglia. Striatal neurons consist of medium-sized spiny neurons and aspiny neurons.

Spiny neurons

As many as 95% of striatal neurons are medium-sized spiny neurons [90]. The rest consist mainly of large neurons including large aspiny interneurons and a few large projection neurons [10, 11, 13, 20, 29]. The majority of spiny neurons are projection neurons [94], which contain GABA as a neurotransmitter together with a number of neuropeptides such as substance P (SP), enkephalin (ENK), dynorphin (DYN), and neurotensin (NT). The calcium-binding protein calbindin D-28k is also present in these neurons [18]. Spiny neurons containing ENK and expressing the D2 subtype of dopamine (DA) receptors project to the external segment of the globus pallidus (GPe), whereas those containing SP and DYN, and expressing D1 subtype project to the pars reticulata of the substantia nigra (SNr), and the internal segment of the globus pallidus (GPi) [45, 46, 50, 57, 84, 149]. Glutamic acid decarboxylase (GAD), the synthetic enzyme of gamma-aminobutyric acid (GABA) was immunohistochemically demonstrated in medium-sized projection neurons and interneurons as well as axon terminals [134]. Penny et al. [128] provided the first evidence for coexistence of GAD and SP within a single neuron (Fig. 1).

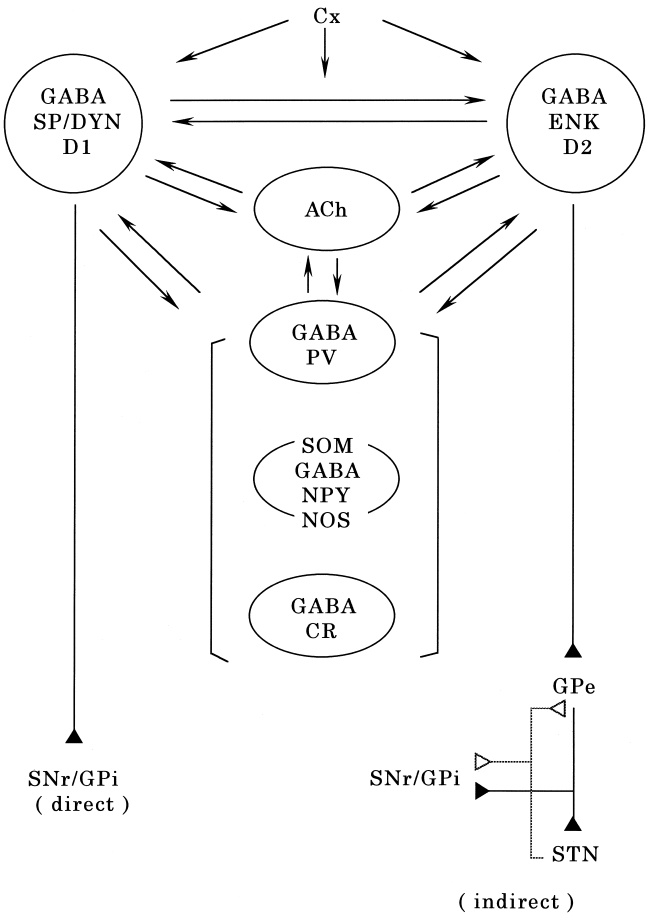

Fig. 1 Simplified diagram of striatal microcircuitry. Circles and ellipses indicate projection neurons and interneurons, respectively. For abbreviations see text.

The morphology of the spiny neurons has been extensively studied by Golgi and intracellular labeling techniques [10, 23, 29, 35, 56, 90, 94, 155, 167]. These studies have shown that the primary dendrites are smooth, whereas secondary and tertiary dendrites are densely laden with spines [94] (Type I neurons of [29]). There is another type of projection neuron characterized by sparse dendritic spines, which are different from type I spiny neurons that have dense dendritic spines [11, 29, 56, 154, 155]. The distribution of dendrites may be limited by compartmental boundaries within the striatum [85]. Local axon collaterals, containing GABA, SP or ENK, make symmetric synaptic contacts mainly with the necks of spines or dendritic shafts of medium spiny neurons [43, 167].

Corticostriatal afferents form asymmetric synapses primarily with the head region of dendritic spines on medium spiny striatonigral neurons [16, 39, 40, 91, 155] (for review see [43, 149]).The nigrostriatal DA afferents immunoreactive (IR) for tyrosine hydroxylase (TH) make symmetric synaptic contact on the neck of dendritic spines and on the interspine shafts of distal dendrites of identified striatonigral medium spiny neurons [39]. About 6% of these synapses are on the cell body and proximal dendrites, 35% are on distal dendritic shafts, and 59% are on dendritic spines. The spines making contact with cortical afferents receive TH-IR boutons as well [39, 43]. Bouyer et al. [16] have shown that dendritic spines may receive synaptic input from both TH-IR terminals and degenerating terminals originating in the cortex. The major target of TH-IR boutons seem to be medium spiny neurons, with few inputs to other striatal cell types [16]. The majority of GAD-positive terminals form synaptic contacts with dendritic shafts or perikarya and only very few contact the dendritic spines (Fig. 2). This pattern of input is strikingly different from that of TH-IR terminals [131] or that in synaptic contact with striatonigral neurons [39]. It was suggested that this arrangement is designed to shunt or block passage of excitatory inputs from the head of the spine into the dendrite, without affecting the activity in the dendritic shaft of the cell body, i. e., the DA input would have a selective effect on inputs to spines [14]. DA afferents are located to sub-

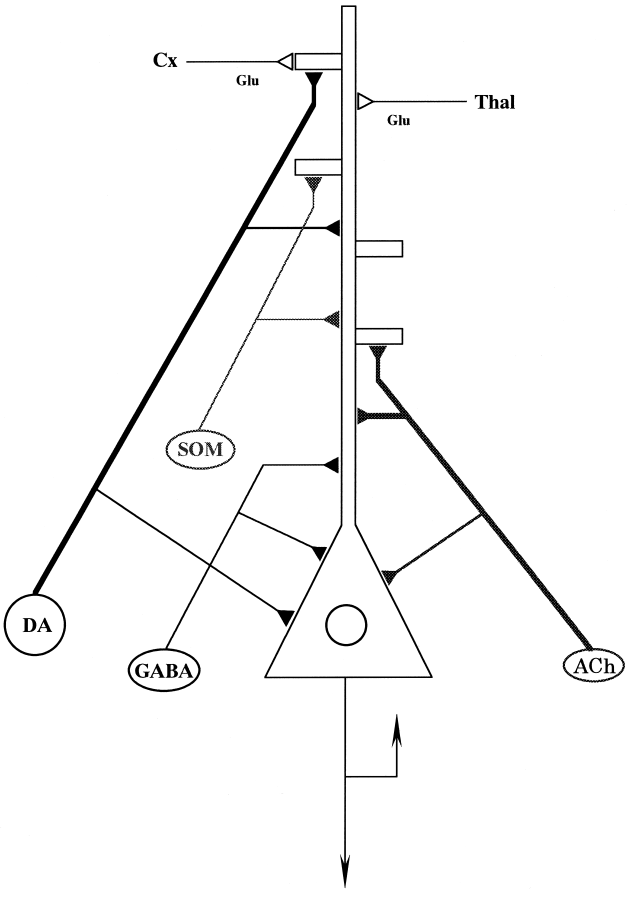

Fig. 2 Simplified diagram of the extrinsic and intrinsic inputs to a medium-sized spiny neuron of the striatum. Circles and ellipses indicate projection neurons and interneurons, respectively. For abbreviations see text.

serve a more specific modulation of afferent cortical inputs in the striatum [152].

Spiny neurons receive other afferents from striatal interneurons containing acetylcholine (ACh), somatostatin (SOM) and parvalbumin (PV) [43] (Fig. 1). The spiny neurons have local axon collaterals, which terminate on neighboring spiny neurons [43, 94, 155, 167]. Neurons giving rise to a direct pathway (striato-GPi/SNr) appear to be synaptically interconnected to neurons giving rise to indirect pathways (striato-GPe) [149, 153]. The feedback inhibition among spiny neurons seems to be weak [77]. The feedforward pathway through GABAergic interneurons seem to be powerful for spiny neuron inhibition [86] The major physiologic function of striatal efferent activity appears to be inhibition of tonically active GABAergic neurons in the globus pallidus (GP) and substantia nigra pars reticulata (SNr). Other extrinsic and intrinsic afferent synapses are situated in a position to regulate the effect of the corticostriatal excitatory input to the medium spiny neurons [43].

Aspiny neurons

Aspiny neurons (4 % of striatal neurons) have short axons and are interneurons in the striatum [10, 29]. GABAergic interneurons have been studied by light and electron microscopy using autoradiography of ^{3}H-GABA combined with Golgi staining [12]. These studies identified medium-sized GABAergic aspiny neurons and suggested these neurons form a local circuitry in the striatum. The GABAergic interneurons are incorporated into a feedforward inhibitory circuit in which they receive both extrinsic excitatory and intrinsic inhibitory inputs and their outputs inhibit both spiny projection neurons and interneurons [93]. GABAergic interneurons receive symmetrical synapses on the soma and proximal dendrites, while the distal dendrites mainly receive asymmetric synapses [12]. These interneurons have been divided into four major classes: large cholinergic neurons; GABAergic interneurons containing PV; GABAergic interneurons containing calretinin (CR); and a class of interneurons containing SOM, nicotinamide adenine dinucleotide phosphate (NADPH)-diaphorase (a marker for nitric oxide synthase, NOS), and NOS as well as GABA [86] (Fig. 1).

Large aspiny neurons contain choline acetyltransferase (ChAT) [13]. These cholinergic neurons (2 %) have a much wider distribution of their dendrites and axon collaterals and a large number of very thick dendritic stems branching rapidly into numerous branches. Distal dendritic branches are very numerous, thin and curved with varicosities [171]. The soma and proximal dendrites of cholinergic neurons in the striatum receive symmetrical synaptic input from SP-IR boutons, and these inputs were considered to arise from local axon collaterals of medium spiny neurons [15].

TH-IR axons make synaptic contacts with the somata and proximal dendrites of large ChAT-IR striatal neurons [95]. Moreover, TH-positive and ChAT-positive terminals form synapses with common dendrites of unlabeled striatal neurons [19]. The ChAT-IR boutons make symmetrical synaptic contact with the dendritic shafts (45 %), spines (34 %) and neuronal perikarya (20 %) of medium-sized densely spiny neurons [76], which were identified as striatonigral neurons [76]. Both DAergic and cholinergic synaptic boutons may have contact with the same medium spiny projection neurons; the interaction between DA and ACh would thus occur on the postsynaptic neurons (see [76]). The topography of cholinergic afferents of the dense spiny neurons is somewhat similar to that of the DA boutons originating from neurons in the SN [76]. Furthermore, 59 % of TH-IR boutons were in synaptic contact with dendritic spines, 35 % with the dendritic shafts and 6 % with the cell bodies of striatonigral neurons [39]. A parallel DA/ACh input to striatal spiny neurons has been proposed previously to account for the interaction between DA and ACh (Fig. 2).Thus, these neurons are able to sample inputs from large regions of the cortex or other afferent sources [21, 86].

The somata of cholinergic interneurons were found in both the matrix and the striosomes, and their dendrites often cross the boundaries between these compartments. The axons of these neurons tend to arborize in the matrix [60, 86]. The striatal cholinergic neurons may function as associative interneurons in the striatum [86]. The feedforward modulatory actions of their axons could be the key for the normally low spontaneous activities of the medium spiny neurons [21]. There are other cells with large somata that are not positive for ChAT. One class of these cells is the projection neuron [21]. Another consists of large instances of a class of GABAergic interneurons that contain PV (see [169]).

The PV-IR interneurons (3–5 % of striatal neuron population), subpopulations of GABAergic neurons, are slightly larger than the spiny neurons. The somata of PV neurons have a deeply indented nucleus. Gap junctions were found between two neighboring PV dendrites, and PV interneurons connected through gap junctions were considered to be activated synchronously by their inputs, and simultaneously to inhibit a large number of their target neurons [93]. The Ca-binding protein PV participates in Ca^{2+} and Ca^{2+} buffering in the neurons [71]. PV is found in neurons generating a continuous high-frequency firing such as cortical interneurons, reticular thalamic neurons and SNr neurons. These neurons are known to generate Ca spikes upon activation of neurons (see [93]). The GABAergic/PV-IR striatal neurons may correspond to the fast-firing striatal neurons that are easily excited by low levels of afferent stimulation [21]. The somata of spiny projection neurons are often outlined by a number of PV boutons. The somata of PV neurons were contacted by only a few synaptic boutons. The dendrites of PV neurons had more frequent synapses [93]. PV neurons receive inputs from the cerebral cortex, thalamus, SNc, and cholinergic and other PV interneurons [21, 93, 95]. Soma and dendrites of PV neurons make synaptic contact with axon terminals of cholinergic interneurons of the striatum [21]. All the PV immunoreactive boutons formed symmetrical synapses, and 50 % of these boutons were found on somata and proximal dendrites of PV interneurons [93]. PV boutons seldom form synapses with cholinergic interneurons of the striatum [21].

SOM-IR neurons are of the medium-sized aspiny interneurons (1–2 % of striatal neurons) [28, 162], and co-localized with neuropeptide Y (NPY) [151]. SOM-IR boutons form symmetrical synapses and contact on dendritic shafts and spines [162]. These neurons have three or four rather straight and relatively long dendritic arbors that exhibit spine-like appendages and fine tufted terminations, and have extensive axon collaterals within the striatum [43]. They correspond to the aspiny III neurons of DiFiglia et al. [28]. These neurons innervate mainly the matrix compartment, although their somata are found in both compartments, and their dendrites often cross compartmental boundaries [85]. Perikarya and proximal dendrites of SOM neurons receive both symmetric and asymmetric synapses, whereas more distal dendritic portions receive primarily asymmetric synapses [43, 162]. SOM/NOS-positive cells receive direct cortical inputs [164], and cholinergic [165] and DAergic [164] innervation. NOS-positive cells are likely to control local flow of blood in the striatum in response to cortical or pallidal inputs [6].

Neural circuits of the striatum

The striatum receives afferents from the cerebral cortex, substantia nigra (SN), thalamus, dorsal raphe nucleus, locus ceruleus, pallidum, STN, pedunculopontine nucleus (PPN) and other subcortical afferents as well as the hippocampus and the amygdala.

Striatal efferents

Corticostriatal projections

The striatum receives topographically organized cortical afferents from the functional and anatomical distinct areas with some overlap of projection fields. In general, the striatum is divided into the sensorimotor, associative and limbic striatum (Fig. 3). The sensorimotor striatum corresponds to the large dorsolateral part of the postcommissural part of the putamen (Put), the dorsolateral rim of the precommissural Put and the lateral part of the caudate nucleus (CN), and receives cortical afferents from the motor, premotor, supplementary and cingulate motor cortical areas as well as the somatosensory cortex [33, 75, 82, 97–99, 102, 113, 160, 161, 166].

The associative striatum occupies the major head of the CN (except its lateral part and dorsomedial to ventral parts), the middle parts of the body and the tail of the CN, and the precommissural Put as well as the ventromedial parts of the postcommissural Put. This striatum was identified histochemically on the basis of its calbindin content [38]. It receives cortical afferents from the associative cortical areas such as prefrontal, temporal, posterior parietal and preoccipital cortices as well as frontal eye field and supplementary eye field [24, 54, 55, 99, 100, 127, 129, 138, 142, 143, 156, 163, 172–175].

In our cases area 46 projects to the intermediate part of the head CN and also to the precommissural part of Put. Caudally these terminations in the precommissural part were localized in the ventromedial part. At the level of the rostral end of the thalamus, the area 46 projection region in the Put was limited in its drosomedial margin. The frontal eye field (area 8) projects also to the intermediate part of the head CN, but this projection territory was shifted more dorsolaterally in comparison with the area 46 territory. The striatal territory of area 9 of the prefrontal cortex (PFC) was localized in the dorsal portion of the intermediate part of the head CN. Our findings of area 46 projections to the

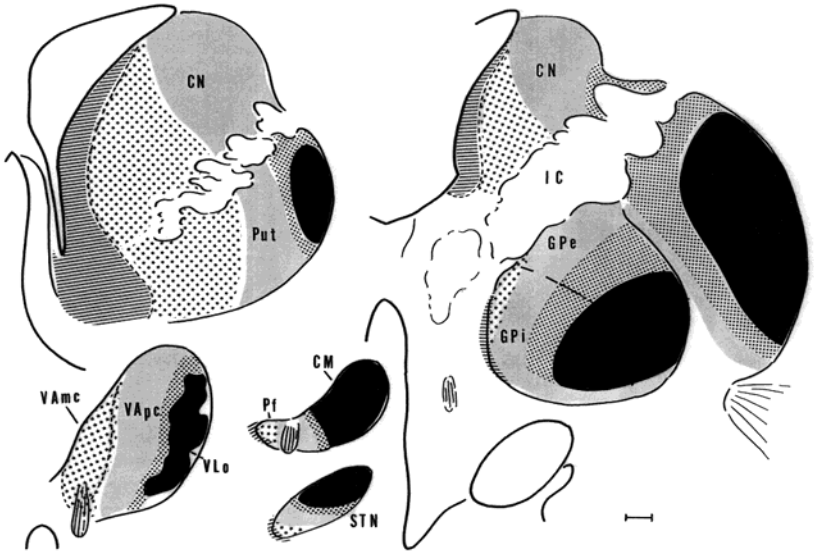

Fig. 3 Diagram showing the sensorimotor (black field areas), supplementary (dotted area), premotor (gray area), associative (star area), and the limbic (hatched) territories in the striatum, pallidum, subthalamic nucleus (STN), and the thalamus. *CM* centromedian nucleus, *Pf* parafascicular nucleus of the thalamus. For other abbreviations see text.

striatum are consistent with those of Selemon and Goldman-Rakic [142]; however, in our cases, these projections were denser ventrally in the head CN.

The limbic (or ventral) striatum occupies the dorsomedial margin to the ventral portions of the CN including the nucleus accumbens, and the ventromedial part of the precommissural Put. This striatum receives cortical afferents from allo- and peri-allocortical areas including the hippocampus, piriform, prelimbic (PL) and infralimbic (IL) cortices, and subcortical amygdala [7, 24, 31, 67, 96, 142, 163, 172, 176].

Nigrostriatal projections

Nigrostriatal DAergic fibers terminate upon striatal projection neurons, and DA appears to exert its effects directly upon these neurons. Terminations of these fibers form symmetric synapses predominately on the neck of dendritic spines [39]. In the early postnatal stage, striatal DA input is distributed in patches, and during subsequent development innervation of the matrix is completed [120]. The retrorubral region (A8) and SNc (A9) project to the dorsal striatum. The VTA (A10 DA cell group) projects to the ventral striatum as well as limbic forebrain areas, such as the septal area, prefrontal limbic cortex and the olfactory tubercle. Two sets of striatal projecting DA neurons are distinguished, a dorsal and ventral tier. The dorsal tier provides input to the striatal matrix compartment. Most of the dorsal tier neurons express calbindin in addition to DA. The ventral tier provides inputs to the striatal patch compartment. Neurons in this tier are situated in the ventral part of the SNc and in groups of cells embedded in the SNr [49, 78].

Thalamostriatal projection

In the monkey, the striatum receives major thalamic afferents from the centromedian-parafascicular complex, and the centromedian nucleus (CM) projects mainly to the Put, especially sensorimtor striatum, whereas the parafascicular nucleus (Pf) to the CN, associative striatum [36, 108, 136, 137]. The minor striatal projections arise from the intralaminar nuclei (Pc, CL), ventral anterior-ventral lateral nuclei (VA-VL), and the midline thalamic nuclei (for ref see [108]. The ventral striatum receives thalamic inputs mainly from the midline thalamic nuclei and the ventromedial margin of the Pf [53, 108, 115]. The thalamic input from CM preferentially appears to innervate striatofugal neurons, which give rise to the direct pathway in monkey, and frequent asymmetric synapses between CM terminals and striato-GPi neurons were found [147]. CM and Pf inputs terminate preferentially on the dendritic shafts of striatal neurons [137]. The topographic organization was demonstrated in the striatal projection from the motor thalamic nuclei [108]. The magnocellular part of ventral anterior thalamic nucleus (VAmc) and medial Pf project to the intermediate CN (associative striatum), the VApc and lateral Pf project to the dorsolateral CN and the rostromedial Put, and the VLo and CM project to the sensorimotor Put (Fig. 3). The striatal projection from CM was somatotopically organized. The dorsolateral, intermediate, and ventromedial portions of CM project, respectively, to the corresponding portions of the dorsolateral leg territory, intermediate arm territory and the ventromedial face territory of the Put receiving cortical afferents [108].

The Pf projects to the rostromedial part of STN, and to the limbic and associative territories in the striatum [136] and the pallidum [65]. Based our data [108, 115], the most ventromedial part of Pf provides a projection to the limbic

striatum, the lateral Pf to the lateral CN (premotor striatum), and the medial Pf provides a projection to the associative striatum (Fig. 3). The CM also projects slightly to the pallidal region supplied by the sensorimotor striatal territory [109, 150], and to the dorsolateral part of STN [136].

Subthalamostriatal projections

The striatum receives inputs also from the STN with topographic organization. The dorsolateral part of the STN projects to the sensorimotor Put, and the ventromedial STN to associative striatum [108, 124, 150]. The dorsolateral part of the STN was considered as a sensorimotor territory [81, 136] by virtue of its afferents from the motor cortex [68] and its projection to the sensorimotor area of the Put. The ventromedial and rostral portions of the STN, on the other hand, were considered associative-limbic territory [81, 123] by virtue of inputs from areas 6, 8 and 9 [68, 74, 156]. Since the most medial part of the STN receives afferents from the limbic cortex and the ventral striatum [62, 63, 66], this region corresponds to the limbic territory. Based on our data, we suggest topographical organization of the STN from the dorsolateral to the ventromedial portions of the STN in an orderly sequence of the motor, SMA, premotor, association, and limbic territories (Fig. 3). The motor territory of the STN is also somatotopically-organized [105].

Other striatal afferents

The striatum receives GABAergic afferents from the globus pallidus and possibly the substantia nigra pars reticulata (SNr) [149]. Based on our data, the striatum appears to receive vestibular input indirectly via the thalamic CM and central lateral nucleus (CL) [146].

Striatal efferents

Striato-pallidal projection

The striatum gives rise to efferent connections to the SN and the GPi (direct pathway), and the GPe (indirect pathway). In the monkey, the striatopallidal projection displayed a rostrocaudal, mediolateral and dorsoventral topography [69]. However, the CN was said to project rostrally and the Put caudally [125, 150]. Fibers from the CN and precommissural Put project principally to the dorsal third of GPe and GPi, whereas those from the postcommissural Put mainly to the ventral two-thirds of GPe and GPi [69]. The ventral (limbic) striatum is specifically connected to the ventral pallidum (VP) and the medial tip of the GPi [65]. According to Francois et al. [37], the associative striatum projects to the ventral part of the pallidum in addition to the dorsomedial pallidal region, and the sensorimotor striatal projects to the remaining central part of the pallidum [37]. Dual projections of striatal output were demonstrated in the pallidum and SN [22, 121, 168]. In the rat, striatopallidal projections have extensive axon arborizations in a region immediately adjacent to the striatum, and a second arborization zone in the central part of the pallidum, and these fibers arise from single striatal neurons [22].

Striatonigral projection

Striatonigral fibers arise from mainly a different population of spiny neurons than striatopallidal fibers but have the same neurotransmitters, namely, GABA, SP, ENK, DYN and NT. Almost all striatonigral fibers terminate in the SNr, but SP-IR fibers have been identified in both the SNr and the SNc. The GABAergic striatonigral fibers make symmetric synaptic contacts with the dendrites of either GABAergic SNr neurons or DAergic cells of the substantia nigra pars compacta (SNc) [47, 149].

It has been reported that the rostral and caudal parts of the striatum project, respectively, to the rostral and caudal parts of the SN [144, 158, 159]. However, the CN was said to project rostrally and the Put caudally [125, 150] in the SN. More recent work has reported a "rostrocaudal to mediolateral 90° shift" of the striatonigral pathway [37, 70]. The terminations of the striatonigral projection form a longitudinal band extending over the entire length of the SNr and SNc [37, 70]. Neighboring but separate regions of the striatum appear to have overlapping territories of nigral projection, especially in the caudal nigra [70]. However, Parent and co-workers [122] indicated no overlapping terminal fields in the SN and the pallidum in the squirrel monkey. The midlateral and middle DA cell groups in the SN receive inputs from the sensorimotor striatum, whereas the medial DA cell groups are preferentially related to the head of the CN and the rostral Put, corresponding to the association and limbic striatum [70]. According to Francois et al. [37], the whole pars reticulata and lateralis, and parts of the pars compacta, receive information from the associative striatum. The sensorimotor putaminonigral projection is organized in such a way that the rostrodorsal striatal regions project medially, while those of the caudoventral region project laterally [37]. Limbic striatal projections to the SN in monkeys are not as topographically arranged [65]. All parts of the ventral striatum terminate in the medial part of the SNr at rostral levels and extend laterally, over a wide region of the SNc more caudally [67]. Widespread influence was reported on the SN via the striatum, and subsequent nigrostriatal projections [67].

In our data, the associative striatum projects mainly to the SN with the small projection to the dorsomedial margin of the rostral GPe/GPi; the motor striatum (postcommissural Put) projects to the middle two-thirds of the medio-lateral extent of the SN, with predominance in its

lateral part, whereas the precommissural Put project to the remaining medial part of SN with partially overlapping terminals from the motor striatum in the middle part of the SN; the most ventral part of the Put projects to the lateral SN. Francois et al. [37] suggested convergence of the sensorimotor and associative striatal projections at the border of the two pallidal territories and in the central part of the pars reticualata/lateralis of the SN.

Neurons in the patch compartment project to the location of the ventral tier DA neurons, whereas neurons in the matrix compartment project to the location of GABA neurons in the SNr [41, 42, 48]. The calbindin selectively labels striatonigral neurons in the matrix compartment and not in the patches [48]. Calbindin-IR axon terminals of the matrix neurons were seen in the SNr. The striatal matrix compartment provides inputs directed to the thalamic projecting part of the entopeduncular nucleus (GPi in primates), whereas the patch compartment provides inputs to the habenular projecting part of the nucleus [133].

Basal ganglia-thalamocortical loops

Five proposed basal ganglia-thalamocortical circuits were reported by Alexander et al. [3]; those are the motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, and the anterior cingulate circuits. These circuits are partially closed-loop, with combination of open- and closed-loop, which arise from several separate but functionally related cortical areas, traverse specific portions of the basal ganglia and thalamus, and project back upon one of the cortical areas. For instance, the motor circuit arises from the SMA, arcuate premotor area, primary motor area, and somatosensory cortex, is transmitted largely through the Put and the motor thalamic nuclei, and ultimately projected back upon a single cortical region (SMA). According to these investigators, the motor circuit gains access to the SMA; however, our data suggest each motor-related cortical areas provides a proper motor circuit. At each level of the basal ganglia there is an apparent topographic organization in the projections from one level to the next with some overlap.

Based on our data in monkeys, the motor loop appears to be divided into the sensorimotor, dorsal and ventral premotor, SMA-proper, pre-SMA, and the cingulate motor subloops. The sensorimotor subloop arises from the primary motor and sensory areas, projects to the postcommissural part of the Put (motor Put), then projects to the ventrolateral parts of the caudal 2/3 GPi, and finally projects back to the motor cortex via the thalamic VLo [113, 114, 116]. The premotor subloop arises from the premotor area, projects to the lateral part of the CN and the ventromedial rim of Put, and then to the dorsomedial parts of the GPi, and finally projects back to the premotor area via the medial part of VApc. The SMA subloop arises from the SMA, and projects to the dorsomedial Put as well as the lateralmost CN (Fig. 4), and then to the GPi regions between the premotor area and primary motor area territories of the GPi, and finally projects back to the SMA via the VApc-VLo [113, 114]. Our data suggest that the SMA subloop is further subdivided into the pre-SMA and SMA proper subloops, the former situates in the dorsomedial portion and the latter in the ventrolateral portion of the SMA territory in the pallidum. The thalamic region relaying the pre-SMA information appears to be lateral VApc, and that of the SMA proper to the rostromedial VLo as well as the transitional zone of the VA-VLo [106, 116]. In electrophysiological studies, the GPi-thalamic neurons projecting to SMA were indicated mainly in the VApc and the rostral portion of VLo [80].

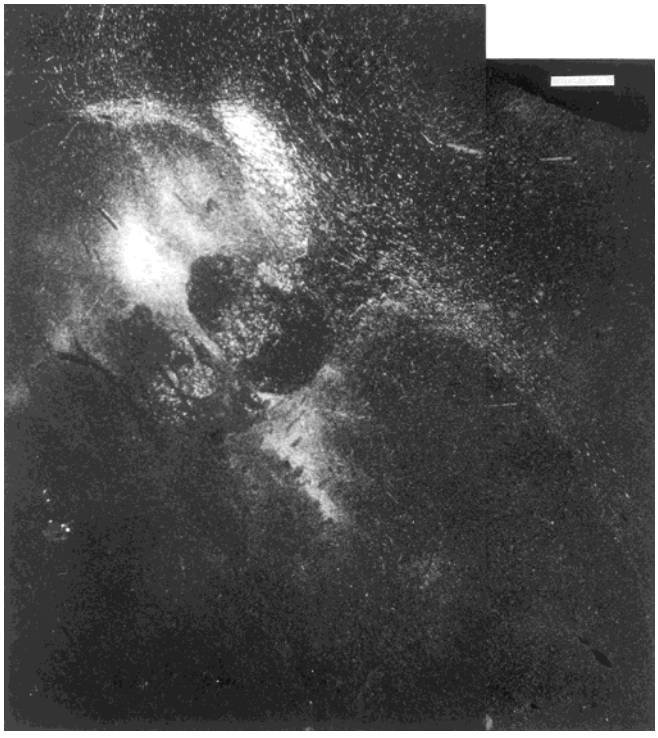

Fig. 4 Dark-field autoradiograph of an isotope demonstrating labeled terminals in the lateral part of the caudate nucleus and dorsomedial part of the putamen following ^{3}H-leucine injection into the supplementary motor area. Scale bar = 1 mm.

Following injections of the subunit B of cholera toxin (CTB) in the primary motor area and of biotinylated dextran amine (BDA) in the ventrolateral part of the GPi, BDA-labeled terminal arborizations were observed surrounding the VLo neurons labeled retrogradely with CTB. We also demonstrated electron microscopically monosynaptic contacts of the GPi afferents on the VLo neurons projecting to the primary motor cortex [87]. Following ^{3}H-leucine injections in the primary motor area, anterogradely labeled terminals were seen in the VLo in addition to the oral part of ventral posterolateral nucleus (VPLo), whereas the labeled terminals were demonstrated in the lateral

VApc with an injection in the SMA proper [111]. BDA injections in the rostromedial VLo or in the remaining major VLo, resulted in labeled terminals mainly in the superficial and deep layers of SMA proper or primary motor area, respectively [116]. Since Schell and Strick's [140] paper was published, it has long been thought that the sensorimotor information from the GPi is conveyed exclusively to the SMA. We have reported the VLo projection to the primary motor area [107], but it took a long time to publish these papers [87, 110, 111, 113] due to the controversial interpretation. Now, it has been shown also by other groups that the pallido-recipient part of the thalamus in the macaque monkey projects directly to the primary motor area [26, 72, 117]. Electrophysiological studies indicated GPi-thalamic neurons projecting to the motor area are located mainly in VLo [117]. Recently, this linkage was confirmed by Hoover and Strick [73] using the technique of retrograde transneuronal transport of *Herpes simplex* virus.

The premotor subloop is further divided into the ventral and dorsal subloops. Following ^{3}H-leucine injection into the ventral premotor area, labeled terminals were limited to the ventromedial zone of the Put, ventral to the facial territory, and in the ventral part of the VApc, while ^{3}H-leucine injection within the ventromedial Put resulted in labeled terminals in the ventromedial to ventral part of the GPi/GPe. Wheat germ agglutinin-conjugated horseradish peroxidase (WGA-HRP) injection in the ventral part of VApc and the involvement of the lateral part of the medial part of ventral lateral nucleus (VLm) resulted in retrogradely labeled cells in the dorsomedial to ventral part of GPi [114]. Based on these findings, and since the ventral premotor area connects with the ventral part of the VApc, and partially with the VLm [111], we suggest that the ventral premotor subloop sends information through the ventromedial Put, the medial to ventral GPi, and the ventral VApc/VLm, and finally back to the ventral premotor area. Similarly our data suggest the presence of a distinct dorsal premotor subloop, as the dorsal premotor area connects with the dorsomedial part of the VApc, and this VApc region receives GPi afferents from the dorsomedial part of the GPi [112].

The limbic striatum relays the limbic loop through the ventral pallidum or medial part of rostral GPi, and the magnocellular part of dorsomedial nucleus (MDmc) or VA, and projects back to the limbic cortical areas. This loop is divided into three subloops, the medial and orbitofrontal circuits and the anterior cingulate subloop [65, 67]. Orbital and medial PFC projects primarily to the medial and central part of ventral striatum but not to the lateral ventral striatum [67]. The orbitofrontostriatal projection extends throughout the head and body of the CN [67, 142]. Topographically, areas 32 (PL) and 25 (IL) project to the shell and medial ventral striatum while cells from area 13a and 13b project to the medial ventral striatum, and cells in area 13 project centrally [67]. The cingulate gyrus (areas 24a, b, 23a) projects to the medial part of the ventral striatum [96]. Midline thalamic nuclei project densely to the medial ventral striatum and to the shell [53]. Our data demonstrated topographic inputs to the ventral striatum from the medial prefrontal cortex (IL, PL), midline thalamic nuclei, Pf and from the lower brainstem (solitary-vagal nuclear complex) [115]. A number of subloops, in the rat, were demonstrated in the limbic basal ganglia-thalamocortical circuits [64].

Individual output channels are concerned with distinct aspects of behavior [103]. Some channels, such as the sensorimotor loop, may subserve motor control. Other output channels, such as the SMA loop, may be concerned with higher order aspects of motor behavior, such as the generation of sequential movements based on internal cues. Output channels related to the PFC may be involved in cognitive aspects of behavior such as working memory (see [103]). Information originating in different parts of the cortex may remain segregated in several parallel pathways that pass through the striatum to the pallidum or SN, and finally gains access to multiple cortical areas via thalamic nuclei.

Recently, several routes were provided for the flow of cortical information along indirect pathways of the basal ganglia [153]. The direct cortico-STN projection seems to play an important role in movement control [118]. The GPe-GPi projection was demonstrated in addition to the indirect projection via the STN. This projection makes synaptic contact mainly with the perikarya of GPi [145]. Reciprocally interconnected groups of neurons in the GPe and STN innervate, via axon collaterals, the same population of neurons in the GPi [153]. The GPe also innervates the reticular nucleus of the thalamus. Based on our data, neurons receiving this input were reciprocally connected with the CM of the thalamus [88]. Individual neurons in the basal ganglia output nuclei appear to receive convergent synaptic input from both direct and multiple indirect pathways [153]. Increased inhibition of neurons in the basal ganglia target nuclei is likely to be associated with cessation of selected movements and possibly the suppression of nonselected movements [2, 27]

Compartment

The striatum can be divided into two compartments, the striosomes and the matrix, based on mu-opiate receptor binding studies and acetylcholinesterase histochemistry [58, 130]. The extrastriosomal matrix is a principal target of cholinergic modulation in the striatum, whereas the striosomal system receives a weaker innervation by ChAT-positive fibers. The cholinergic innervation of the matrix is dense in the sensorimotor region of the striatum. The compartments also have different connections. The striosomes receive cortical afferents from limbic cortices and related areas, while the matrix receives cortical afferents from the neocortex [30, 41, 132]. Cortical inputs to these compartments originate in different sublayers of layer V [44]. The matrix receives cortical afferents mainly from the superfi-

cial part of layer V and supragranular layers, while the striosomes receive afferents from the deep part of layer V. However, more detailed analysis revealed that most cortical areas provide inputs to both the patch and matrix compartments [44]. The relative density of input to the patch compartment is higher than periallocortical areas, such as IL and PL, and neocortical areas have a relatively greater input to the matrix compared to the patch compartment. Neurons of the striosomes project mainly back to the SNc while those of matrix project mainly to the pallidum and SNr [41, 49, 59, 79]. The extrastriosomal matrix thus projects to regions that give rise to the basal ganglia-thalamocortical loops and the extraloop connections to the brainstem. These two striatal compartments may be linked functionally by interneurons that contain both SOM and NPY [41]. Matrix neurons containing SP mainly project upon the GPi/SNr, while those containing ENK project mainly upon the GPe [60]. Striosome neurons projecting to the SNc contain mainly SP [1, 25, 60].

Convergence and integration

Interactions between the functionally segregated basal ganglia-thalamocortical loops could overlap at different levels, such as the cerebral cortex, striatum, pallidum, STN, SN, thalamic nuclei and the PPN. Opposite conclusions, overlap or interdigitation, were reported on the converging corticostriatal projections [142, 176], and on the converging nigral projections from the sensorimotor and association striatum [37, 150]. Smith and Parent [150] interpreted the patchy terminal fields from the two sources as interdigitating, whereas Francois et al. [37] suggested an integration of both associative and sensorimotor functions at a neuronal level in the middle third of the SN. Pallidal neurons located at the border of the two territories are also considered to receive inputs from both the associative and sensorimotor components [37], as the dendritic arborizations of the pallidum are vary widely, are discoidal in shape, and oriented parallel to the dorsolateral pallidal border [170].

Integration of the diverse information from the pallidum was described in the STN [81] or at the synaptic level of the neurons in the STN and entopeduncular nucleus [9]. The outputs from different regions of the ventral pallidum also exhibit extensive overlap in the SN, and the SN was considered to be an important region for integrating different ventral striatal regions [66]. The ventral striatum can influence subsequent motor output. Interactions between different basal ganglia-thalamocortical circuits may also occur at the level of the thalamus and the PPN [153]. Limbic and associative GPi territories project to the common thalamic nuclei, including the VApc, dorsal VL, and the rostrodorsal part of the Pf [148]. However, in our studies these GPi projections maintained segregations also at the thalamic levels with minor overlap (in preparation).

Graybiel and colleagues suggested a reorganization of the cortical information in the patterns of divergence of cortico-striatal inputs and reconvergence in the striatopallidal projections (divergence-reconvergence pattern) [32–34]. Somatotopically similar parts of different cortical areas provide input to overlapping striatal regions [33], which in turn reconverge in the projections of the striatum to both pallidal segments [32]. Divergence was considered to be a device for associative processing [102]. According to Flaherty and Graybiel [34], the temporary divergence may increase lateral interactions between sensorimotor matrisomes, as well as between matrisomes and striosomes. A given cortical region sends input to multiple sites in the striatum so that novel associations can be set up between different groups of inputs before the inputs reconverge at the level of the pallidum [34]. The interaction of the striatal input system between other matrisomes and strisomes could be a substrate for associative learning in the basal ganglia [34].

The convergence of basal ganglia and cerebellar projections are suggested at the thalamic levels [26, 116, 135, 139]. Our data suggest the overlap in the lateral part of the VLo thalamic nucleus with the GPi afferents from the ventrolateral part of the caudal GPi and the cerebellar afferents from the ventral part of the cerebellar dentate nucleus. On the other hand, the hand/arm motor area and adjacent arcuate premotor area receives strong superficial thalamocortical projections as well as the deep thalamocortical projections from the VApc-VLo [116]. We consider that these cortical areas receive convergent afferents from the GPi and cerebellar dentate nucleus via the VLo, and play a role in the control of hand/arm complex movements [116]. Further studies are needed to clarify whether or not single thalamic neurons projecting to motor and arcuate premotor areas directly receive the dual pallidal and cerebellar inputs.

Functional aspect of the striatum

In addition to the control of movements, the basal ganglia are involved in a variety of cognitive and mnemonic functions in the generation and execution of context dependent behaviors (for a review see [153]). The striatum, major recipient nucleus of the basal ganglia, filters information from various cortical areas and subcortical regions. It is engaged in the neuronal integration of motivational processes into behavioral output. Subcortical and cortical limbic structures, which are directly linked to reward [83, 104], predominantly project to the limbic (or ventral) striatum.

The complex functions, such as cognitive and behavioral functions, seem to result from the integration exerted by the spiny neurons between glutamatergic inputs arising from the cortex and DAergic afferents from the SNc. This integration might occur in the dendritic spines. Striatal synaptic plasticity, induced by repeated cortical activation,

has been proposed as possible cellular bases of learning and memory in the brain [17]. Activation of mGluRs (metabotropic glutamate receptors) might be implicated in long-term changes in corticostriatal synaptic transmission [17]. Activation of both glutamate (Glu) and DA receptors is required for the generation of the synaptic plasticity (LTD) in the striatum, and these two transmitters are considered to play a crucial role in the storage of information within the basal ganglia (see [17]). The function of DA on striatal neurons is mediated by two DA receptor subtypes, D1 and D2 receptors [51]. D1 and D2 receptors cooperate in the modulation of basal ganglia activity. Long-term potentiation (LTP) and long-term depression (LTD) have been demonstrated in the striatum [17], and both LTD and LTP in the striatum, with the cooperative action of D1 and D2 receptors, may play a role in the regulation of motor learning as well as in the control of complex behavioral activity related to basal ganglia functioning [17].

Repeated cortical stimulation of cholinergic neurons is functionally effective, as these cells exert a tonic control on the activity of spiny neurons and integrate information originating from Glu and DA inputs [86]. Cholinergic neurons in the striatum have been considered as interneurons relaying inputs from DAergic afferents to the spiny neurons (for reviews see [86, 101]). Striatal cholinergic neurons may function as associative interneurons in the striatum [86]. Different subtypes of muscarinic receptors are implicated in the inhibitory control of the release of GABA and Glu within the striatum [157]. GABA acting on receptors located on GABAergic and Glu fibers is of great importance in the physiology of the striatum. Cortical Glu inputs to the GABAergic neurons produce the excitation of these neurons and subsequent increase in the release of GABA in the striatum. Increased striatal GABA concentration reduces the release of Glu in this structure by activating $GABA_B$ (bicuculline-insensitive) receptors on cortical Glu terminals [17]. The striatum receives serotoninergic excitatory input [126] from the raphe dorsalis nucleus [8]. Serotonin (5-HT) in the striatum was thought to exert a metabolic regulatory function on the biosynthesis of neuropeptides rather than act as an ion channel modulator. Central 5-HT neurons are able to produce DA from exogenous L-DOPA [5]. Striatal neuropeptide systems are involved in the regulation of motor programs and they may also be involved in the control of mood as well as self-administration behavior and behavioral sensitization [4].

The context-dependent activity in the basal ganglia is acquired through behavioral learning [92]. Many DA neurons in the midbrain respond to novel and attractive stimuli and they specifically respond to reward stimuli during the learning stages of operant conditioning or spatial delayed-response tasks [141]. Striate neurons acquire task-related activity through learning and the acquired activity almost disappears with selective lesions in nigrostriatal DA system (see [92]). In the very design of corticostriatal connections, there appears to be an inherent conditionality [92]. Evidence for plasticity of neuronal responsivity has been demonstrated both in the striatum and midbrian DA containing cell groups that project to it [61, 141]. The basal ganglia appear to participate in the initiation of movement in a behavioral context-dependent manner.

Normal behavior appears to be dependent on a balance in the output of the direct striatonigral system and the indirect, striatopallidal system [1, 27]. The model of neurologic dysfunction of the basal ganglia suggests that increased output of the indirect pathway (striatopallidal), relative to that in the direct pathway (striatonigral), results in akinesia as occurs in Parkinson's disease. Conversely, increased output of the striatonigral pathway, relative to the striatopallidal pathway, is thought to result in hyperkinetic syndromes, as occurs in dystonia, Huntington's chorea and Tourette's syndrome (for a review see [47]).

DAergic cells in the mesencephalon project to the forebrain and influence neuropeptide levels. A decrease in DA action in the striatum, with either neuroleptic treatment or with 6-hydroxydopamine (6-OHDA)-induced dopamine striatal deafferentation, results in an increase in ENK peptide and mRNA levels in GABA-containing striatopallidal projection neurons that also express dopamine D2 receptor but a decrease in SP-IR and mRNA levels in striatonigral projection neurons expressing the D1 receptor [46, 51, 177]. In situ hybridization studies demonstrated that striatopallidal neurons contain mRNA encoding ENK and striatonigral neurons contain mRNAs encoding both DYN and SP [50]. Peptide levels in striatal neurons are regulated by DA receptor-mediated mechanisms. It is suggested that DA exerts a tonic inhibitory control, mediated via D2 receptors, over ENK-containing striatopallidal output neurons. Levels of ENK and SP are oppositely modulated by DA [52, 177]. These opposite effects by DA appear to be related to the differential expression of D1 and D2 dopamine receptor subtypes by neurons that express these peptides [51]. Thus, mRNA encoding the D1 dopamine receptor subtype is localized in striatonigral neurons and the mRNA encoding the D2 dopamine receptor subtype is localized in striatopallidal neurons [51, 50]. It is suggested that gene regulation in striatopallidal and striatonigral neurons is organized in different ways by the activation of DA receptor subtypes [51].

Acetylcholine, released from interneurons within the striatum, has an important role in the regulation of striatal function. Such regulation is in part mediated through ACh muscarinic receptors, which show a complex distribution pattern in striatal neuron populations. A balance between the levels of DA and cholinergic activity appears to be necessary for normal striatal function [76]. An imbalance between levels of activity of ACh is associated with Parkinson's disease, and the balance and movement abnormalities can be modified by either elevating DA levels with L-DOPA or by reducing the actions of ACh with ACh receptor antagonists. The reverse is true for Huntington's-like movement abnormalities, which are associated with an im-

balance in favor of DA [76]. Crucial to this scheme is the fact that DA tonically inhibits the release of ACh in the striatum (for review see [101]). The true functional network is more complex, as the striatum contains a variety of neurotransmitter candidates (for detail see [76]).

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