

Review

The primate basal ganglia: parallel and integrative networks

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Abstract

The basal ganglia and frontal cortex operate together to execute goal directed behaviors. This requires not only the execution of motor plans, but also the behaviors that lead to this execution, including emotions and motivation that drive behaviors, cognition that organizes and plans the general strategy, motor planning, and finally, the execution of that plan. The components of the frontal cortex that mediate these behaviors, are reflected in the organization, physiology, and connections between areas of frontal cortex and in their projections through basal ganglia circuits. This comprises a series of parallel pathways. However, this model does not address how information flows between circuits thereby developing new learned behaviors (or actions) from a combination of inputs from emotional, cognitive, and motor cortical areas. Recent anatomical evidence from primates demonstrates that the neuro-networks within basal ganglia pathways are in a position to move information across functional circuits. Two networks are: the striato-nigral-striatal network and the thalamo-cortical-thalamic network. Within each of these sets of connected structures, there are both reciprocal connections linking up regions associated with similar functions and non-reciprocal connections linking up regions that are associated with different cortical basal ganglia circuits. Each component of information (from limbic to motor outcome) sends both feedback connection, and also a feedforward connection, allowing the transfer of information. Information is channeled from limbic, to cognitive, to motor circuits. Action decision-making processes are thus influenced by motivation and cognitive inputs, allowing the animal to respond appropriate to environmental cues.

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1. Introduction

The basal ganglia (BG) work in concert with cortex to orchestrate and execute planned, motivated behaviors requiring motor, cognitive, and limbic circuits. While best known for their motor functions, the BG are involved in several aspects of goal-directed behaviors, including not only its expression through the control of movement, but also the processes that lead to movement, including the elements that drive actions, such as emotions, motivation, and cognition. Indeed, regions within each of the BG nuclei are anatomically and physiologically associated with each of these functional circuits. Ventral regions of the basal ganglia play a key role in reward and reinforcement and are important in the development of addictive behaviors and habit formation (S Schultz, 1997; Wise, 1998; Koob, 1999; Rolls, 2000; Everitt et al., 2001). More central basal ganglia areas are

involved in cognitive functions such as procedural learning and working memory tasks (Mishkin et al., 1984; Phillips and Carr, 1987; Jueptner et al., 1997; Levy et al., 1997; Jog et al., 1999). Finally, the dorsolateral portion of the striatum, caudal to the anterior commissure is associated with the control of movement. Consistent with this topography, diseases affecting mental health, including schizophrenia, drug addiction, and obsessive compulsive disorder, are all linked to pathology in the basal ganglia, as are diseases affecting motor control (Stevens, 1973; Kalivas et al., 1993; McGuire et al., 1994; Breiter et al., 1996; Koob and Nestler, 1997; Pantelis et al., 1997; Kegeles et al., 2000; Menon et al., 2001; Rauch et al., 2001). The association of the basal ganglia with frontal cortical function along with its relationship to multiple neurological and psychiatric diseases emphasizes the importance of understanding the basal ganglia with respect to cortical function. Differentiation of frontal cortex and basal ganglia structures as they relate to human function and disease are best modeled from a combination of physiological, anatomical, and imaging studies in primates (both human and non-human). Thus, the present review describes

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the organization of the primate basal ganglia from the perspective of cortical function. In some situations, when necessary and indicated, data are presented from rodent work.

The BG includes the caudate n., putamen, and the globus pallidus and three closely related structures, the substantia nigra (SN), the ventral tegmental area (VTA), and the subthalamic nucleus (STh). Based on connectivity, histology, and functional considerations, the concept of the ventral striatum was introduced as the ventral extension of the striatum that includes the N. accumbens, the medial and ventral portions of the caudate n. and putamen, and the striatal cells of the olfactory tubercle (Heimer, 1978; Heimer et al., 1994). The ventral striatum contains a subregion, the shell. This region, which was first demonstrated in rodents (Zaborszky et al., 1985), is best distinguished by its lack of calbindin-positive staining (Martin et al., 1991; Meredith et al., 1996; Haber and McFarland, 1999). While the ventral and medial borders of the ventral striatum are relatively clear, the dorsal and lateral boundaries of the ventral striatum merge imperceptibly with the dorsal striatum (Fig. 1) (Haber and McFarland, 1999). The striatum is the main input structure to the basal ganglia. Its afferent projections are derived from three major sources: (1) cerebral cortex; (2) thalamus; and (3) brainstem. The striatum projects to the pallidal complex and to the substantia nigra, pars reticulata (SNr). The pallidal complex includes the external (GPe) and internal segments (GPi) of the globus pallidus and the ventral pallidum (VP), the pallidal segment connected to the ventral striatum. The substantia nigra (and VTA) contains the dopaminergic cells of the pars compacta (Snc/VTA), and the pars reticulata (SNr) (Fig. 2A). The outputs from the GPi and SNr

are to the thalamus, which then projects back to the cortex, completing what is referred to as the ‘direct’ cortico-basal ganglia pathway. The GPe is reciprocally connected to the STh, which in turn projects to the GPi. This is referred to as the ‘indirect’ cortico-basal ganglia pathway. For a comprehensive review of basal ganglia pathways (see Percheron et al., 1994; Graybiel, 1995; Parent and Hazrati, 1995; Parent et al., 2000; Middleton and Strick, 2002; Haber, 2003).

2. Functional organization of the basal-ganglia pathways

Frontal cortex is the main driving force of the BG as indicated by its massive topographically and functionally organized pathways. Together they control the ability to carry all aspects of goal directed behaviors including the motivation and cognition that drives and organizes them, along with their execution. Frontal cortex in primates can be divided into several functional regions: the orbital and medial prefrontal cortex (OMPFC), involved in emotions and motivation; the dorsolateral prefrontal cortex (DLPFC), involved in higher cognitive processes or ‘executive functions’; the premotor and motor areas, involved in motor planning and the execution of those plans (see the section below). Furthermore, prefrontal, premotor, and motor cortices are thought to be organized in a hierarchical manner, with motor cortex being the final step to action (Fuster, 2001). Functionally defined regions of frontal cortex project topographically through the basal ganglia, to thalamus, and back to cortex.

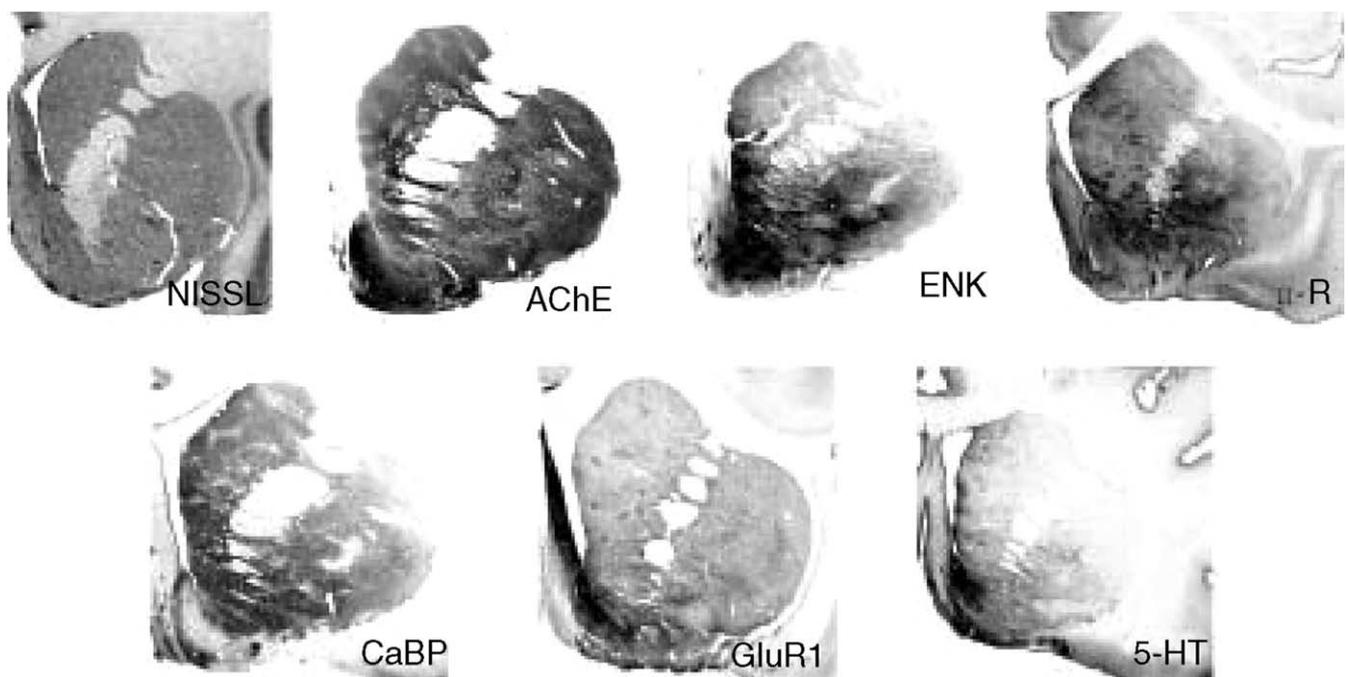


Fig. 1. Photomicrographs of the striatum at the level of the shell and core, immunostained for various transmitter-related molecules. AchE, acetylcholinesterase; CaBP, calbindin-28; ENK, enkephalin; GluR1, GluR1 AMPA receptor subunit; m-R, m-opiate receptor; 5-HT, serotonin.

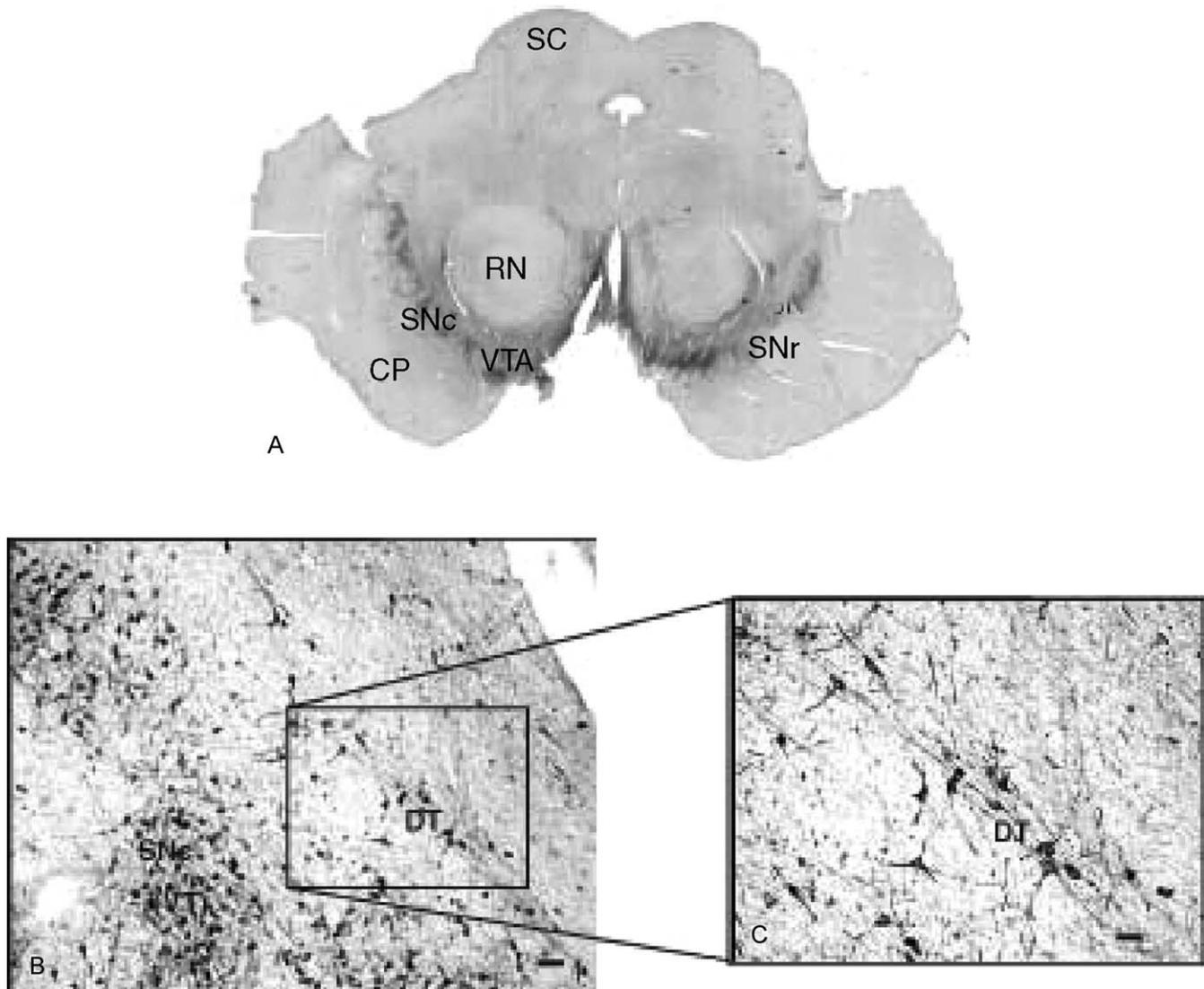


Fig. 2. Photomicrographs of the tyrosine hydroxylase (TH) positive-staining in the midbrain. (A) A coronal section through the humans midbrain, illustrating the distribution of the dopamine cells in the substantia nigra and adjacent ventral tegmental area. CP, cerebral peduncle; RN, red nucleus; SC, superior colliculus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; VTA, ventral tegmental area. (B) TH-positive fibers and cells of dorsal and ventral tiers. Scale = 100 μ m. The cells and processes of the dorsal tier indicated by the box are shown magnified in (C) revealing the horizontal arrangement of their dendritic processes. Scale = 50 μ m. VT, ventral tier; DT, dorsal tier.

2.1. Functional and anatomical organization of cortical-striatal pathways

The association of different frontal regions with particular functions is derived from multiple sources including physiological and connective studies, lesions, and imaging studies in both human and non-human primates. While frontal regions have been associated with different behaviors for some time, the understanding of how different aspects these behaviors are specifically related frontal regions continues to evolve. Thus, for example, motor cortices continue to be defined by their physiology and connectivity (Kunishio and Haber, 1994; Lu et al., 1994; Dum and Strick, 1996; Matelli and Luppino, 1996; Picard and Strick, 1996; Tanji and Mushiake, 1996; Strick et al., 1998; Schieber, 1999a;

Schieber, 1999b; Kakei et al., 2001; Dum and Strick, 2002). Caudal motor areas, including motor cortex (M1); supplementary motor area (SMA); caudal cingulate motor area, (CMAc); and caudal premotor area (PM) areas, are most closely involved with movement execution, are highly microexcitable, closely timed to the execution of movement, and send direct descending projections to spinal motor nuclei. Rostral motor areas, including PreSMA, CMAr, and rostral PM areas, project to caudal motor area, are involved in sequence generation, and motor learning, and are less microexcitable than the caudal motor areas, but more so than the prefrontal cortex. Their temporal firing pattern is less directly associated with movement than the caudal motor areas. These motor areas projection topographically to the striatum (Kemp and Powell, 1970; Kunzle, 1975; Kunzle,

1977; Kunzle, 1978; Aosaki et al., 1994b; Flaherty and Graybiel, 1994; McFarland and Haber, 2000). Projections from M1 terminate almost entirely in the dorsolateral putamen, caudal to the anterior commissure. There are few terminals rostral to the anterior commissure. The caudal premotor area projects to a striatal region that is just adjacent to M1 projections, extending only slightly into the caudate n. The rostral premotor areas terminate in both the caudate n. and putamen, bridging the two with a continuous projection. This projection extends more rostrally than those from the motor cortex, although not into the rostral pole of the striatum. Thus, both caudal and rostral areas occupy much of the putamen caudal to the anterior commissure. This area receives overlapping projections from parietal areas associated with somatosensory function, resulting in a sensory-motor area that is somatotopically organized. Physiological and imaging studies support the involvement of this striatal region in sensorimotor control and motor plans (Aldridge et al., 1980; DeLong and Georgopoulos, 1981; Alexander and DeLong, 1985a,b; Alexander and DeLong, 1986; Kimura, 1986, 1990; Kermadi and Joseph, 1995; Hikosaka et al., 1996; Boecker et al., 1998). Thus, the premotor and motor areas (and the frontal eye fields) mediate different aspects of motor behavior, including planning, learning, and execution, which are in turn reflected both anatomically and physiologically in the central and lateral caudate n. and in the central, dorsal, and lateral putamen, respectively.

Prefrontal cortical regions (DLPFC and OMPFC), are the least microexcitable of frontal cortex (Fuster, 1997). The DLPFC is involved in working memory, set shifting, and strategic planning, often referred to as ‘executive functions’ (Passingham, 1995; Goldman-Rakic, 1996; Smith and Jonides, 1997; Fuster, 2000, 2001). The DLPFC projects most densely to the rostral striatum including both the caudate n. and the putamen, rostral to the anterior commissure. The rostrocaudal extent of this projection is large and topographically organized. While there are few terminals in the central and caudal putamen posterior to the anterior commissure, the caudate n. does remain innervated (Selemon and Goldman-Rakic, 1985; Arikuni and Kubota, 1986). Physiological, imaging and lesion studies support the idea that the head of the caudate n. is instrumental in delayed tasks, particularly in specific working memory tasks (Battig et al., 1960; Butters and Rosvold, 1968; Hikosaka et al., 1989; Apicella et al., 1992; Partiot et al., 1996; Levy et al., 1997; Elliott and Dolan, 1999). Taken together, the caudate n., and in particular the head of the caudate n., is involved in working memory and strategic planning processes, working together with the DLPFC in mediating this function. The DLPFC has close connections with the orbital and medial prefrontal cortex (Carmichael and Price, 1996b; Petrides and Pandya, 1999; Barbas, 2000; Passingham et al., 2002).

Orbital prefrontal cortex is involved in the development of reward-based learning and goal-directed behaviors (Butter and Snyder, 1972; Benevento et al., 1977; Rolls and Baylis, 1994; Meunier et al., 1997; Baxter et al., 2000; Hikosaka and

Watanabe, 2000; Schultz et al., 2000). This area receives input from multimodal sensory regions and is closely linked to the medial prefrontal cortex (Carmichael and Price, 1996a; Carmichael and Price, 1996b). Lesions of the orbital and medial prefrontal areas result in an inability to initiate and carry out goal-directed behaviors, and lead to socially inappropriate and impulsive behaviors (Rolls et al., 1980; Eslinger and Damasio, 1985; Fuster, 1989; Cummings, 1995; Filley, 1995). The lateral orbital regions, areas 13 and 12, and dysgranular insular cortex project to the central and lateral parts of the ventral striatum (Kunishio and Haber, 1994; Haber et al., 1995b; Chikama et al., 1997; Ferry et al., 2000). Medial orbital areas 13a/b and 14 projects to the medial wall of the caudate n., extending ventralward into the n. accumbens, lateral to the shell region. This area receives an additional dense innervation from the medial prefrontal cortex (the anterior cingulate cortex). The medial prefrontal cortex, receives particularly dense innervations from the orbital prefrontal cortex, the amygdala, and the hypothalamus and is important in the expression of emotion (Carmichael and Price, 1995; Mayberg et al., 1999). The shell receives the densest innervation from medial areas 25, and 32 and from agranular insular cortex. Together, the orbital and medial prefrontal cortex projects primarily to the rostral striatum, including the n. accumbens, the medial caudate n., and the medial and ventral rostral putamen. This projection extends caudally and occupies a small ventromedial portion of the caudate n. and the most ventral and medial part of the putamen (Pandya et al., 1981; Kunishio and Haber, 1994; Haber et al., 1995b; Chikama et al., 1997; Ferry et al., 2000; Freedman et al., 2000; Fudge and Haber, 2002). Together, we refer to this area as the ventral striatum (Haber and McFarland, 1999). In addition, the ventral striatum receives input from the amygdala and hippocampus (Russchen et al., 1985; Fudge et al., 2002). Consistent with input from the OMPFC, physiological and imaging studies demonstrate the important role of the ventral striatum in the development of reward-based learning and in mental health diseases (Apicella et al., 1991; Breier et al., 1992; Kalivas et al., 1993; Bowman et al., 1996; Tremblay et al., 1998; Wise, 1998; Robbins and Everitt, 1999; London et al., 2000; Everitt et al., 2001; Hassani et al., 2001; Menon et al., 2001). In summary, projections from frontal cortex form a “functional gradient of inputs” from the ventromedial sector through the dorsolateral striatum, with the medial and orbital prefrontal cortex terminating in the ventromedial part, and the motor cortex terminating in the dorsolateral part (Fig. 3).

2.2. The thalamostriatal projection

As seen with the cortico-striatal projection, thalamostriatal inputs are also topographically and functionally organized. The midline and intralaminar nuclei are the source of the most widely reported thalamostriatal projections (Jones and Leavitt, 1974; Nakano et al., 1990; Sadikot

1982; Parent and DeBellefeuille, 1983; Ilinsky et al., 1985; Giguere and Goldman-Rakic, 1988; Haber et al., 1993; Ilinsky et al., 1993; McFarland and Haber, 2002). Thus, the functional topography of cortex that is maintained through cortical connections to the striatum, is likely to be continued from the striatum to the pallidum/SNr, from these output structures to the thalamus, and finally, back to cortex.

2.4. Parallel versus integrative circuits

The basal ganglia are connected with frontal cortex in a series of functional modules that maintain a relative consistent anatomical and physiological organization, leading to the concept of parallel processing of cortical information through segregated BG circuits (Heimer et al., 1982; Alexander et al., 1986; Middleton and Strick, 2002). This concept of parallel circuits allows models of function derived from one circuit to be extended to the other circuits. One such model (derived from the motor circuit), focuses on the role of the BS in the selection and implementation of appropriate action while inhibiting unwanted ones (Alexander and Crutcher, 1990; Mink, 1996). This model assumes that the behavior has been learned and the role of the basal ganglia is to carry out a coordinated action. However, recent evidence demonstrates that the BG are also critical in mediating the learning process by reinforcing new behavioral-guiding rules. Of particular importance is its role in reinforcement and adaptation to accommodate the past in predicting future outcomes. This is a critical component in forming behavioral responses (Owen et al., 1993; Aosaki et al., 1994a; Passingham, 1995; Wise, 1998; Bar-Gad and Bergman, 2001). Communication across functionally distinct circuits is required for this to occur. This communication is critical in order to continually evaluate and adjust to stimuli throughout the development of behaviors. Thus, models based on solely on parallel processing, do not address how information can be transformed across functional regions in order to help implement the learning and adaptability that is necessary in the development of goal-directed behaviors. Indeed, physiological, behavioral, and imaging studies support the role of the basal ganglia in this process (Grafton and Hazeltine, 1995; Hikosaka et al., 1995; Jaeger et al., 1995; Doyon et al., 1997; Hikosaka et al., 1998; Jog et al., 1999; Everitt et al., 2001; Letchworth et al., 2001). While BG pathways are generally topographically organized through the one-way cortico-BG circuits, as reviewed above, other parts of the neural network argue against parallel processing as the only organizational rule.

An emerging literature in primates as well as in rodents supports the idea that there are pathways by which information from separate cortico-basal-ganglia loops can influence each other (Percheron and Fillion, 1991; Francois et al., 1994; Joel and Weiner, 1994; Bevan et al., 1996; Bevan et al., 1997; Joel and Weiner, 1997; Groenewegen et al., 1999a; Groenewegen et al., 1999b; Haber et al., 2000; Bar-Gad and Bergman, 2001; McFarland and Haber, 2002).

For example, while projections from cortex terminate in a general topography through the BG structures, the dendrites and axons within each structure often cross functional boundaries. This has been suggested to be one mechanism that integrates information across regions. Thus, for example, the dendritic arbors in the GP are extensive and extending beyond functional domains. In this way, distal dendrites from one region invades an adjacent functional area. Another mechanism is through a convergence of terminals from functionally adjacent fields onto progressively smaller basal-ganglia structures (Percheron and Fillion, 1991; Yelnik et al., 1997; Yelnik, 2002). The fact the adjacent areas overlap in function is not surprising. Many cortical areas are tightly linked to the immediately adjacent cortex. Thus, 'edges' of functionally identified regions are likely to process mixed signals. Furthermore, the interface between functional circuits increases with the complexity of interconnections within the intrinsic BG circuitry and with the compression of pathways to successively smaller structures (Smith et al., 1998; Bar-Gad and Bergman, 2001).

A third mechanism is through complex non-reciprocal arrangements between structures (Joel and Weiner, 1997; Haber et al., 2000; McFarland and Haber, 2002). These pathways provide a directional flow of information between regions. For example, the idea that the limbic striatum could influence motor output was first demonstrated in rodents via the striato-nigro-striatal (SNS) pathway. These studies demonstrated, both at the light microscopic level and at the EM level, pathways by which the ventral striatum could influence the dorsal striatum via the midbrain dopamine neurons (Nauta et al., 1978; Somogyi et al., 1981). The possibility of a second feedforward loop has also been proposed by which the shell of the ventral striatum could influence the core through striato-pallido-thalamic pathways (Zahm and Brog, 1992). In addition, connections of the subthalamic n. to the two pallidal segments are in a position to allow associative regions to influence both limbic and motor areas (Joel and Weiner, 1997). As such, mechanisms by which information can 'flow' through functional circuits exists and are fundamental (along with the parallel circuits) for understanding how the execution of goal-directed actions evolves from reward and cognition, shaping final motor outcomes. Two examples of neuronal network systems that extend beyond connecting adjacent regions are the striato-nigro-striatal network and thalamo-cortico-thalamic network. These networks provide a potential continuous feedforward mechanism of information flow. In this way, limbic pathways can interact with cognitive pathways, which, in turn, interact with to motor pathways.

2.5. The striato-nigro-striatal network

While behavioral and pharmacological studies of dopamine pathways have lead to the association of the mesolimbic pathway and nigrostriatal pathway with reward

and motor activity, respectively, more recently both of these cell groups have been associated with the development of reward-based learning, the acquisition of newly acquired behaviors, and plasticity (Ljungberg et al., 1991; Anglade et al., 1996; Hollerman and Schultz, 1998; Schultz, 1998; Bonci and Malenka, 1999; Matsumoto et al., 1999; Berke and Hyman, 2000; Song and Haber, 2000). The midbrain dopamine cells project to the striatum and also receive striatal output. Based on anatomical criteria, the midbrain dopamine neurons are divided into two tiers: a dorsal tier and a ventral tier (Fig. 4A) (Francois et al., 1985; Francois et al., 1987; Lavoie and Parent, 1991; Parent and Lavoie, 1993; Haber et al., 1995a; Francois et al., 1999). The cells of the dorsal tier include the dorsal SNc, the contiguous VTA, and retrorubral cell group (Figs. 2 and 4). The ventral tier cells include most of the SNc (a denso-cellular group and the cell columns). There is an inverse dorsal-ventral topographic organization to the midbrain striatal projection. The dorsal and medial dopamine cells project to the ventral and medial parts of the striatum, while the ventral and lateral cells project to the dorsal and lateral parts of the striatum (Carpenter and Peter, 1972; Szabo, 1979, 1980;

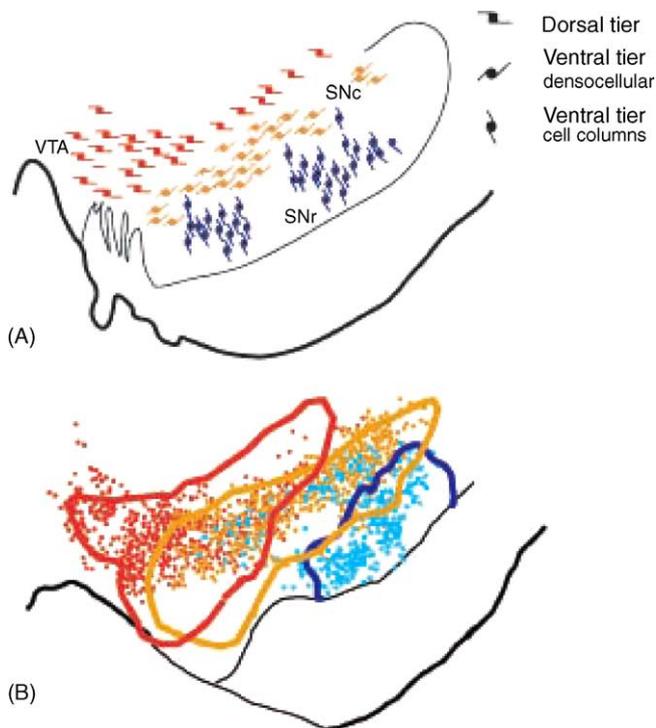


Fig. 4. Schematic through the midbrain. (A) Schematic demonstrating the arrangement of the different dopaminergic cell groups in the midbrain. The dorsal tier includes the ventral tegmental area, and the retrorubral cell groups; the ventral tier includes the denso-cellular cells and the cell columns. DAT, dopamine transporter; D2R, D2 dopamine receptor; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine; PD, Parkinson's disease; VTA, ventral tegmental area; SNr, substantia nigra pars reticulata; SNc, substantia nigra pars compacta. (B) Schematic illustrating the functional organization of striatal afferent and efferent projections. The color scheme follows the functional organization of cortico-striatal projections (see Fig. 3).

Parent et al., 1983; Hedreen and DeLong, 1991; Lynd-Balta and Haber, 1994a,b; Francois et al., 1999; Haber et al., 2000). The shell region of the ventral striatum receives the most limited midbrain input, primarily derived from the VTA. The rest of the ventral striatum receives input from the entire dorsal tier from the most medial and dorsal part of the denso-cellular group. The central striatal area (the region innervated by the DLPFC) receives input from a wide region of the denso-cellular group. The ventral tier projects to the dorsolateral striatum, with the cell columns projecting almost exclusively to there. The dorsolateral striatum receives the largest midbrain projection, while the ventral striatum receives the most limited dopamine cell input. Thus, in addition to an inverse topography there is also a differential ratio of dopamine projections to the different striatal areas. Projections from the striatum to the midbrain are also arranged in an inverse dorsal-ventral topography. The dorsal aspects of the striatum terminate in the ventral

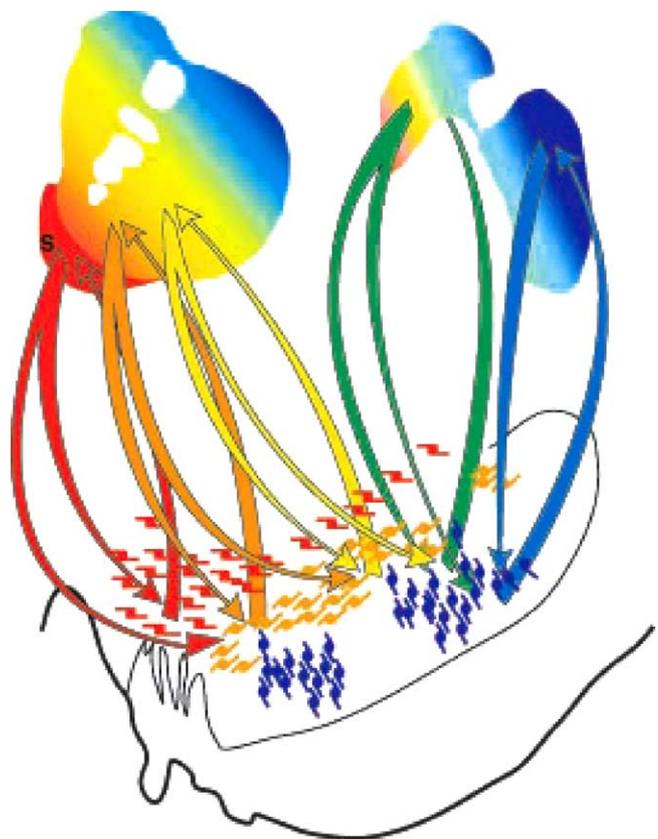


Fig. 5. Diagram of the organization of striato-nigro-striatal (SNS) projections. The colored gradient in rostral and caudal schematics of the striatum illustrates the organization of functional cortico-striatal inputs (see Fig. 3). Midbrain projections from the shell target both the VTA and ventromedial SNc (red arrows). Midbrain projections from the VTA to the shell form a "closed," reciprocal SNS loop (red arrow). Projections from the medial SN feed-forward to the core forming the first part of a spiral (orange arrow). The spiral continues through the SNS projections (yellow and green arrows) with pathways originating in the core and projecting more dorsally (blue arrows). In this way ventral striatal regions influence more dorsal striatal regions via spiraling SNS projections. IC, internal capsule; S, shell.

regions of the midbrain, while the ventral areas terminate dorsally (Szabo, 1967, 1970, 1980; Haber et al., 1990; Selemon and Goldman-Rakic, 1990; Hedreen and DeLong, 1991; Lynd-Balta and Haber, 1994c; Parent and Hazrati, 1994). Projections from the ventromedial striatum terminate throughout an extensive dorsal region, including the VTA and the medial SNc, along with the medial pars reticulata. The ventral striatum projects not only throughout the rostrocaudal extent of the substantia nigra, but also innervates a wide mediolateral range of dopaminergic cells including much of the densocellular SNc. The central striatum projection terminates more ventrally, primarily in the ventral densocellular region (and associated pars reticulata). The dorsolateral striatum projection terminates in the ventrolateral midbrain in the pars reticulata and in the dopaminergic cell columns that extend into this region.

When considered separately, each pathway of the system (striato-nigral or nigro-striatal pathway) creates a loose topographic organization demonstrating that the VTA and medial SN are associated with the limbic system, and the lateral and ventral SN are related to the associative and motor striatal regions. However, the ascending and descending limb for each functional area of the striatum differs in their pro-

portional projections. The ventral striatum receives a limited midbrain input, but projects to a large region. In contrast, the dorsolateral striatum receives a wide input, but projects to a limited region. Thus the ventral striatum influences a wide range of dopamine neurons, but is itself influenced by a relatively limited group of dopamine cells. In contrast, the dorsolateral striatum influences a limited midbrain region, but is affected by a relatively large midbrain region. In addition, for each striatal region there is one reciprocal and two non-reciprocal connections with the midbrain. Dorsal to the reciprocal connection lies a group of cells that project to the striatal region, but does not receive projections from it. Ventral to the reciprocal component lies efferent terminals without an ascending reciprocal connection. Finally, these three components for each SNS projection system occupy a different position within the midbrain. The ventral striatum system lies dorsomedially, the dorsolateral striatum system lies ventrolaterally, and the central striatum system is positioned between the two (Fig. 4B) (Haber et al., 2000). With this arrangement, information from the limbic system can reach the motor system through a series of connections. The ventral striatum, which receives input from the OMPFC sends an efferent projection to the midbrain that extends beyond

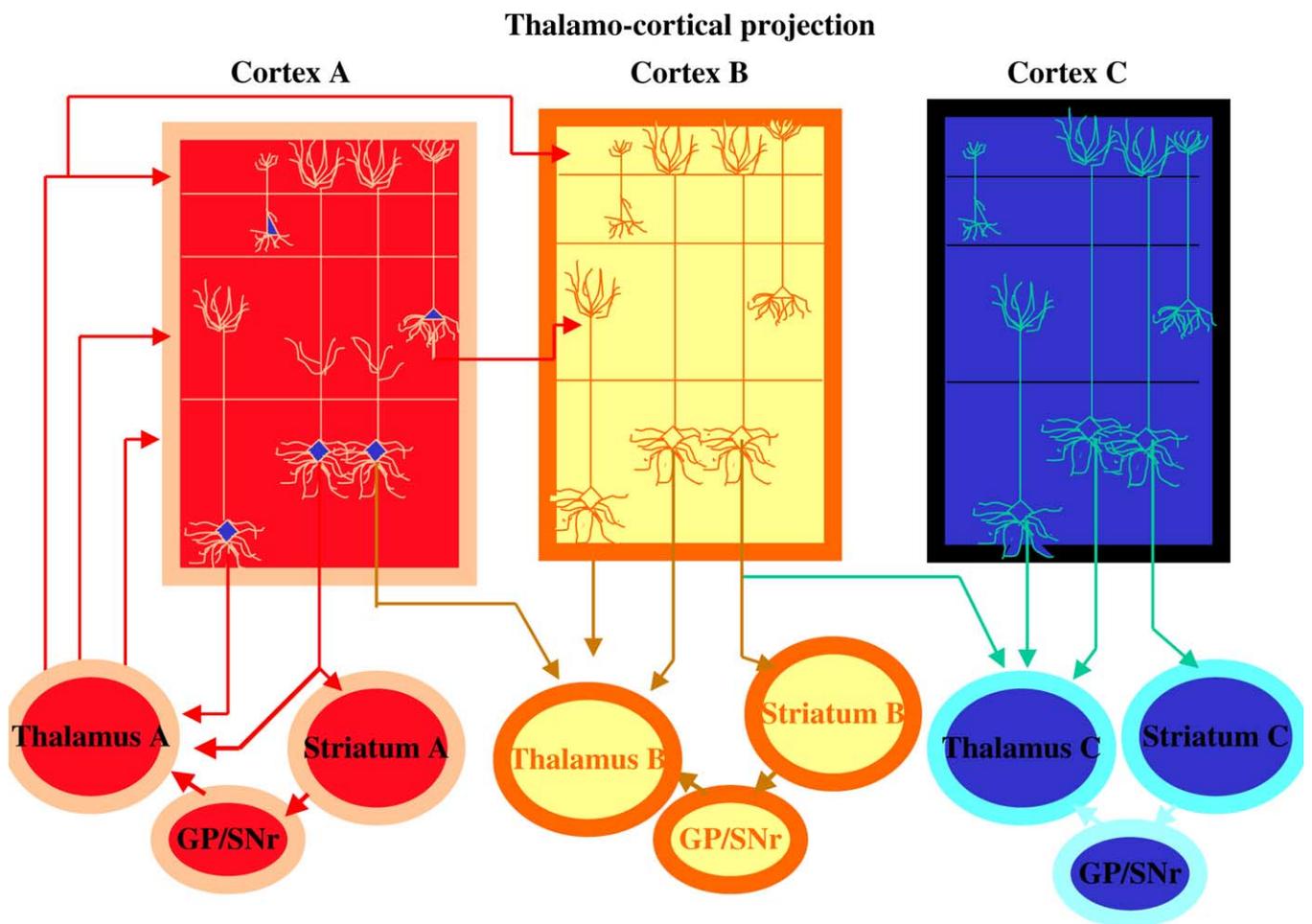


Fig. 6. Diagram of the organization of thalamo-cortico-thalamic projections. Through the non-reciprocal cortico-thalamic projection, cells in layer V may also interface with other cortico-basal ganglia circuit by projecting to a thalamic region that is part of another circuit system.

it reciprocal connection, terminating lateral and ventral to it. This terminal region projects to the central (or associative) striatum. The central striatum is reciprocally connected to the densocellular region but also projects to the ventrally and thus in a position to interact with cell projecting to the dorsolateral (or motor) striatum. Taken together, the interface between different striatal regions via the midbrain DA cells is organized in an ascending spiral interconnecting different functional regions of the striatum and creating a feed forward organization (Fig. 5). Information can thus be channeled from the shell to the core, to the central striatum, and finally to the dorsolateral striatum. In this way, information flows from limbic to cognitive to motor circuits.

2.6. Thalamo-cortico-thalamic interface

The thalamic-cortical pathway is the last link in the circuit and is often treated as a simple ‘one-way relay’ back to cortex. However, this pathway does not transfer information passively but rather plays a key role in regulating cortical ensembles of neurons through its projections to different cortical layers and by non-reciprocal cortico-thalamic projections (Jones, 1985; Sherman and Guillery, 1996; Castro-Alamancos and Connors, 1997; McFarland and Haber, 2002). Like the SNS system, the thalamo-cortico-thalamic system is in a critical position for integrating information across functional circuits. While cortico-thalamic projections to specific relay nuclei are thought to follow a general rule of reciprocity, cortico-thalamic projections to VA/VL and central MD sites, as seen in other thalamocortical systems, are more extensive than thalamocortical projections (Sherman and Guillery, 1996; Deschenes et al., 1998; Jones, 1998; Darian-Smith et al., 1999; Murphy et al., 1999; McFarland and Haber, 2002). Furthermore, they are derived from areas not innervated by the same thalamic region, indicating non-reciprocal cortico-thalamic projections to specific basal-ganglia relay nuclei. Although each thalamic nucleus completes the cortico-basal-ganglia segregated circuit, the non-reciprocal component is derived from a functionally distinct frontal cortical area. For example, the central MD has reciprocal connections with the lateral and orbital prefrontal areas and also a non-reciprocal input from medial prefrontal areas; VA has reciprocal connections with dorsal premotor areas, and caudal area DLPFC and also a non-reciprocal connection from medial prefrontal areas; and VLo has reciprocal connections with caudal motor areas along with a non-reciprocal connection from rostral motor regions. The potential for relaying information between circuits through thalamic connections, therefore, is accomplished through the non-reciprocal cortico-thalamic pathways (Fig. 6). Thus, similar to the basal-ganglia-thalamic relay nuclei appear to mediate information flow from higher cortical “association” areas of the prefrontal cortex to rostral motor areas involved in “cognitive” or integrative aspects of motor control to primary motor areas that direct movement execution.

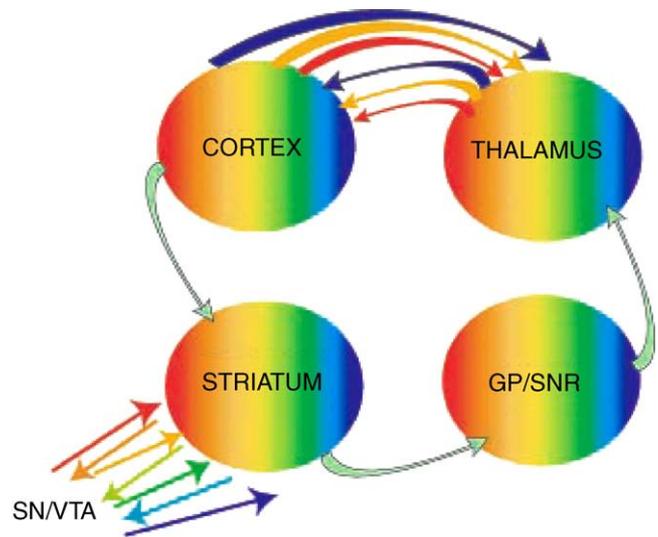


Fig. 7. Schematic illustrating two potential mechanisms for relaying and integrating information within the cortico-basal-ganglia circuitry. Information from distinct cortical regions could be processed separately, and in parallel through functionally-related neurons (green arrows). Information from these distinct, parallel pathways could be integrated in two ways: (1) by spiraling connections between the midbrain dopamine cells and the striatum; and (2) via thalamo-cortico-thalamic projections.

2.7. A role for both parallel circuit and integrative networks

Within each area of connected cortico-BG structures, there are both reciprocal connections linking up regions associated with similar functions (maintaining parallel networks). However, in addition, there are non-reciprocal connections linking up regions that are associated with different cortical-BG circuits (Fig. 7). The development and modification of goal-directed behaviors require continual processing of complex chain of events, which is reflected in the feedforward organization of both the striato-nigral connections and the thalamo-cortical connections. Information can thus be channeled from limbic, to cognitive, to motor circuits, allowing the animal to respond appropriate to environmental cues. Parallel circuits and integrative circuits must work together, so that the coordinated behaviors are maintained, and focused (via parallel networks), but also can be modified and changed according the appropriate external and internal stimuli (via integrative networks). Indeed, both the inability to maintain and to focus in the execution of specific behaviors, as well as the inability to adapt appropriately to external and internal cues, are key deficits in basal ganglia diseases which affect these aspects of motor control, cognition and motivation.

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