HHS Public Access

Author manuscript

Neuroscience. Author manuscript; available in PMC 2017 June 26.

Published in final edited form as:

Neuroscience. 2014 December 12; 282: 248–257. doi:10.1016/j.neuroscience.2014.10.008.

The place of dopamine in the cortico-basal ganglia circuit

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Abstract

The midbrain dopamine neurons play a central role developing appropriate goal-directed behaviors, including the motivation and cognition to develop appropriate actions to obtain a specific outcome. Indeed, subpopulations of DA neurons have been associated with these different functions: the mesolimbic, mesocortical, and nigrostriatal pathways. The mesolimbic and nigrostriatal pathways are an integral part of the basal ganglia through its reciprocal connections to the ventral and dorsal striatum respectively. This chapter reviews the connections of the midbrain dopamine cells and their role in integrating information across limbic, cognitive and motor functions. Emphasis is placed on the interface between these functional domains within the striatum through corticostriatal connections, through the striato-nigro-striatal connection, and through the lateral habenula projection to the midbrain.

Keywords

functional integration; prefrontal cortex; lateral habenula; striatum; substantia nigra; ventral tegmental area

I. Introduction

A key component in developing appropriate goal-directed behaviors is the ability to first correctly evaluate different aspects of reward, including value versus risk and predictability, and inhibit maladaptive choices, based on previous experience. These calculations rely on integration of different aspects of motivation and cognition to develop and execute appropriate action plans. The midbrain dopamine (DA) neurons play a central role in these behaviors including reward, cognition, and motor control. Indeed, subpopulations of DA neurons have been associated with these different functions: the mesolimbic, mesocortical, and nigrostriatal pathways, respectively (Wullner et al., 1994, Sawaguchi, 1995, Goldman-Rakic, 1998, Wise, 2004). Recently, all DA cell groups have been associated with the development of reward-based learning, leading to goal-directed behaviors (Schultz, 2002).

The substantia nigra (SN) was first recognized in 1786 with the description of brain neuromelanin distribution (Vicq D'Azyr, 1786). The link to the motor system came much later with its association with Parkinson's disease (PD) (Brissaud, 1895, Bremer, 1920, Hassler, 1939). Collectively the work of several investigators than demonstrated that the cells contained DA, that DA was a neurotransmitter, and that these cells were depleted in Parkinson's disease (Ehringer and Hornykiewicz, 1960, Hornykiewicz, 1966, Bazelton et al., 1967). Around the same time DA was also linked to psychoses and subsequently addiction,

and behavioral disorders, see, (Baldessarini, 1985). With the visualization of DA neurons and the advances in connectivity and lesion methods in the 1960s, the subpopulations of DA neurons were associated with reward, cognition, or motor control: the mesolimbic (ventral tegmental area-VTA), mesocortical (VTA-retrorubral), and nigrostriatal (substantia nigra, pars compacta-SNc) pathways, respectively. Collectively these discoveries demonstrated that the DA cells are an integral part of the basal ganglia (BG). The VTA and SNc send a massive output to the striatum, the main input structure of the basal ganglia. Moreover, this is a bidirectional pathway, with the DA cells receiving a major input from the striatum.

Overall, the BG was best known for its relevance to motor functions, due to its role in movement control diseases. This concept dramatically changed in the last 35+ years to a more complex set of functions that mediate the full range of goal-directed behaviors, including emotions, motivation, and cognition. In the late 1970s, Heimer discovered that the nucleus accumbens, (NAcc), (a basal forebrain region associated with limbic function), and the surrounding area was actually part of the striatum and termed this the ventral striatum (VS). Moreover, he identified the cells that were located ventral to the anterior commissure as pallidal in nature and showed that they received input from the ventral striatum. These cells are referred to as the ventral pallidum (VP)(Heimer, 1978). Subsequently he and others showed that the VP projected to the medial dorsal (MD) thalamus and back to non-motor cortex, thus identifying a separate functional loop of the basal ganglia (Young III et al., 1984, Haber et al., 1985). The concept of several functional, yet separate cortical loops through BG was then expanded in primates (Alexander et al., 1990). While the notion that these circuits are anatomically segregated remains prominent in the field, the idea of a motivation-to-movement interface, rather than separate loops through BG circuits was developed soon after the discovery of the VS/VP circuit. Researchers interested in how motivation impacts learning and the development of habits, recognized that integration between functional circuits was necessary to carry out goal-directed behaviors (Mogenson et al., 1980, Percheron and Filion, 1991, Dickinson, 1994, Haber et al., 2000, Belin and Everitt, 2008, Leung and Balleine, 2013). Thus, the basal ganglia is now recognized to mediate the full range of behaviors leading to the development and execution of action plans, including the emotions, motivation, and cognition that drive them.

II. Overview of the basal ganglia circuitry

The striatum is the main input structure of the basal ganglia. Its afferent projections are derived from three major sources: 1. It receives a massive and topographic input from all of cerebral cortex; 2. The second largest input is derived from the thalamus; and 3. The third main input is from the brainstem, the largest from the midbrain DA cells. Striatal functional domains are derived from the topography of its cortical inputs. Thus, we briefly review the topography of those inputs here. In general, the cortical afferent projections terminate in a patchy and interdigitated manner (Künzle, 1975, Yeterian and Van Hoesen, 1978, Selemon and Goldman-Rakic, 1985, Kunishio and Haber, 1994, Chikama and Haber, 1995, Haber et al., 1995a, Yeterian and Pandya, 1998). Overall, cortical regions associated with reward and motivation, the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) project primarily to the ventral and medial part of the rostral striatum, including the medial wall of the caudate nucleus (Cd) and the medial putamen (Pu). In addition, the amygdala projects to

VS (Fudge et al., 2002). Dorsal prefrontal cortical (dPFC) areas project to the central striatum, and motor regions project to the dorsal lateral parts of the striatum, primarily caudal to the anterior commissure. However, despite this general topographic organization, embedded within these striatal territories are subregions containing convergent terminals between different reward-processing cortical areas, between these projections and those from the dPFC, and between the dPFC and rostral motor control areas (Haber et al., 2006, Calzavara et al., 2007) (Fig. 1). In other words, projections from different functional regions of cortex are not completely separated. Rather there are key areas within the striatum that receive these multiple inputs that may be particularly sensitive to synchronizing information across functional areas to impact on long-term strategic planning, and habit formation (Averbeck et al., 2014). Indeed, cells in the dorsal striatum are progressively recruited during different types of learning, from simple motor tasks to drug self-administration (Porrino et al., 2004, Graybiel, 2005, Volkow et al., 2006)}

The striatum, in turn, projects topographically to the pallidal complex, the VTA and SN (Haber, 2012). The outputs from the globus pallidus, internal segment (GPi)/SN then projects back to the cortex via the thalamus, completing the basic cortico-basal ganglia circuit. This is known as the direct pathway. The side loop, from the striatum via the globus pallidus, external segment (GPe) passes through the subthalamic nucleus to the GPi, and is referred to as the indirect pathway (Fig. 2). In addition, there are other projections of the striatum including those to the brainstem (Haber, 2012).

III. Organization of the midbrain DA cells in primates

The SNc has been divided into three groups: a dorsal (α) group, also referred to as the pars dorsalis; a main, densocellular (β) group; and a ventral (γ) group, or the cell columns (Olszewski and Baxter, 1982, Poirier et al., 1983, Francois et al., 1985, Halliday and Tork, 1986, Haber et al., 1995b). The dorsal group is composed of loosely arranged cells that extend dorsolaterally and circumvent the ventral and lateral superior cerebellar peduncle and the red nucleus. They are oriented horizontally, just dorsal to the densocellular region, with dendrites that stretch in a mediolateral direction that do not extend ventrally into pars reticulata. The dorsal cells merge with the immediately adjacent ventral tegmental area (VTA) forming a continuous mediodorsal band of cells. Both the VTA and the dorsal group are calbindin-positive (CaBP). This stain clearly demonstrates the merging of the VTA and the dorsal SNc cell groups. Together these cells are referred to as the dorsal tier DA cells (Fig. 3). In contrast, the ventral cell groups (the densocellular group and the cell columns) stand out as calbindin negative (Lavoie and Parent, 1991, Haber et al., 1995b, McRitchie and Halliday, 1995). These DA neurons are collectively referred to as the ventral tier (Fig. 3). Unlike the dorsal tier, their dendrites extend ventrally, deep into the pars reticulata. In addition to being calbindin-negative, they also express high levels for the D2 receptor and DA transporter (DAT) mRNAs. Importantly, the ventral tier cells are more vulnerable to degeneration in Parkinson’s disease and to N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced toxicity, while the calbindin-positive dorsal tier cell are selectively spared (Lavoie and Parent, 1991, Parent and Lavoie, 1993, Haber et al., 1995b).

IV. Connections

The main efferent projections of the midbrain DA system are to the striatum and cortex. Other projections include those to the thalamus, amygdala and hippocampus, and globus pallidus. The main afferent projections to the DA cells arise from the striatum and the brainstem pedunculopontine n. Other key afferent projections include those from the lateral habenula via the rostromedial tegmental nucleus (RMTg), the globus pallidus, and the superior colliculus. Each of these plays a key role in the regulation of the DA cells and processing of relevant or salient stimuli (Fig. 4).

IV.1 Efferent projections

IV.1.1 The striatum—Both the dorsal and ventral tiers contribute to the DAergic-striatal pathway (Parent et al., 1983, Lynd-Balta and Haber, 1994b, a). Overall, there is a mediolateral topography to this projection, such that, the medial VTA/SN project to the medial striatum and the lateral VTA/SN to the lateral striatum. However, the dorsoventral topography is inverse. That is, the ventral SNc neurons project to the dorsal caudate nucleus and putamen and dorsal tier neurons project to the ventral parts of the striatum. Thus, the dorsal tier projects to the ventromedial striatum; the densocellular part of the ventral tier projects centrally and throughout different regions of the striatum; and the cell columns project primarily to the dorsal striatum. The shell region of the ventral striatum receives the most limited input, primarily derived from the VTA. The rest of the ventral striatum receives input from the entire dorsal tier. In contrast to the ventral striatum, the central striatal area (the region innervated by the dorsal prefrontal cortex) receives input from a wide region of the densocellular group. The ventral tier projects to the dorsal striatum, with the cell columns projecting almost exclusively to there. Importantly, the strength of projections to the striatum is not consistent throughout the striatum. In particular, the dorsolateral striatum receives the largest midbrain projection from cells throughout the ventral tier. In contrast the shell of the NAcc 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 (Fig. 5a) (Haber et al., 2000).

IV.1. 2 Cortex—The DA innervation of primate cortex is quite extensive. DA terminals in layer I, which are prevalent throughout cortex, provide a rather general modulation of many cells at the distal apical dendrites. The terminals in layers V–VI, on the other hand, are found in specific cortical areas and are in a position to provide a more direct modulation of cortical efferent projections, including corticostriatal and corticothalamic projections. (Lewis et al., 1987, Samson et al., 1990, Gaspar et al., 1992). Thus, parts of the striatum can be influenced by DA directly via the nigrostriatal pathway and indirectly via a nigrocortical/striatal pathway. The nigrocortical projection is more diffuse compared to the nigrostriatal system. The majority of DA cortical projections are from the parabrachial pigmented nucleus of the VTA and the dorsal SNc (Porrino and Goldman-Rakic, 1982, Levitt et al., 1984, Fallon and Loughlin, 1987, Lidow et al., 1991, Gaspar et al., 1992). Unlike the projection to the striatum, cells that send axons to functionally different cortical regions are intermingled with each other. Indeed, double label studies show that many cells send

collateral axons to different cortical regions (Gaspar et al., 1992). The ventral tier does not project extensively to cortex.

IV. 2. Afferent projections

IV.2.1 Striatum—While afferent control of dopaminergic neurons arises from a number of structures, the striatum is a major source. Like the VTA/SN projections to the striatum, those from the striatum to the midbrain are arranged in an inverse dorsal-ventral topography. That is, the dorsal aspects of the striatum terminate in ventral regions of the midbrain, while the ventral areas terminate dorsally (Szabo, 1979, Haber et al., 1990, Lynd-Balta and Haber, 1994b). Specifically, efferent projections to the midbrain from the ventromedial striatum, including the shell, terminate throughout an extensive dorsal region, including the VTA and the medial SNc. Thus the ventral striatum innervates a wide mediolateral range of dopaminergic cells. At central and caudal levels this projection field extends laterally and includes 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 projections to the midbrain are more limited and terminate in the ventrolateral midbrain in the pars reticulata, which includes some of the dopaminergic cell columns that extend into this region (Fig. 5b).

Thus, like the projections from the midbrain to the striatum, those from the striatum to midbrain differ in the proportion of cells projecting to each region. However, there is an inverse relationship. That is, in contrast to its relatively limited afferent midbrain input, the ventral striatum innervates a large area of the midbrain, including much of the dorsal tier and the densocellular area of the ventral tier and associated pars reticulata. However, the dorsolateral striatum, which has a relatively extensive midbrain input, projects to a limited midbrain region, primarily to the ventrolateral pars reticulata and the cell columns that invade this area (Haber et al., 2000).

IV.2.2. Cortex—There is a general acceptance of descending cortical projections to the substantia nigra. Cortical lesions result in reduced glutamate content in the rat substantia nigra as well as fiber degeneration in the cortico-nigral pathway (Afifi et al., 1974, Carter, 1980, Kornhuber, 1984). Retrograde tracing studies in rodents confirm these projections (Bunney and Aghajanian, 1976). However, these projections have been difficult to definitively demonstrate in primates. (Leichnetz and Astruc, 1976, Kunzle, 1978). While descending corticonigral fibers have been demonstrated with fiber degeneration and anterograde tracing techniques in primates, the authors in both studies point out that the results must be interpreted with care. Neither technique clearly showed that fibers actually terminated in the substantia nigra. A more recent study showed few fibers in the VTA/SN following small tracer injections confined to specific prefrontal areas. Importantly, those terminals were not limited to the VTA, but also found throughout the SN (Frankle et al., 2006). Thus, there are clearly cortical inputs to the midbrain DA cells. However, this projection does not appear to be as robust as other subcortical efferent projections.

IV. 2. 3. Other inputs—Both the external segment of the globus pallidus (GPe) and the VP project to the substantia nigra The internal segment of the globus pallidus does not (Parent,

1986, Haber, 2012). The pallidal projection follows a similar organization, as does the striatonigral projection. The region of the GPe that receives input from the sensorimotor part of the striatum projects ventrally to the pars reticulata. The more rostral regions of the pallidum that receive input from the association areas projects more dorsally in the region of, and just ventral to, the DA cells. Finally, the VP projects dorsally, primarily to the densocellular region of the pars compacta (Haber et al., 1993). Thus the pattern of projection from the striatum to the pallidum and nigra is repeated again in the pallidal projection to the substantia nigra. In addition, there is a large projection from the pedunculopontine nucleus that terminates in the region of the DAergic cells bodies. These fibers appear to form close contacts with the cells and dendrites of the dorsal pars compacta (Lavoie and Parent, 1994). While there are several other smaller inputs to the VTA/SN, one that stands out because of its functional significance in the reward system, is the GABAergic projection from the rostromedial tegmental nucleus (RMTg). The RMTg receives a major input from the lateral habenula (LHb) and it is through this connection that the LHb has been shown to have a direct functional influence on DAergic neurons (Jhou et al., 2009). Specifically, negative reward signals from the LHb impact on the DA cells via the RMTg (Hong et al., 2011).

V. Significance of two subcircuits through the midbrain DA system

V. 1. Striato-midbrain-striato connections: the spiral

As indicated above, each functional region differs in its proportional projections that significantly alter their relationship to each other. The ventral striatum receives input from the areas involved in emotional processing, reward, and motivation. This includes the OFC, ACC, amygdala, and hippocampus. The ventral striatum receives a limited midbrain input, primarily from the VTA and dorsal tier. Yet, projections from this limbic area terminate widely in the midbrain, including the dorsal tier and the dorsal part of the ventral tier. The central striatum receives input primarily from areas involved in executive function and cognitive control. This includes areas 9 and 46. The central striatum receives input from the main part of the ventral tier and projects to a large area of the ventral tier. Finally, the dorsolateral part of the striatum is associated with motor control function. This receives a large midbrain input, but its projections to the midbrain are the most limited.

Thus, the size and position of the afferent and efferent connections for each system, together with the arrangement into three components, allow information from the limbic system to reach the motor system through a series of connections (Haber et al., 2000) (see Fig. 2.3.5). The dorsal tier projects back to the ventral striatum. However, the ventral striatum efferent projection to the midbrain extends beyond the tight ventral striatal/dorsal tier/ventral striatal circuit, terminating lateral and ventral to the dorsal tier. This area of terminal projection does not project back to the ventral striatum. Rather, cells in this region project more dorsally, into the striatal area that receives input from the dPFC. Through this connection, the same cortical information that influences the dorsal tier through the ventral striatum also modulates the densocellular region that projects to the central striatum. This central striatal region is reciprocally connected to the densocellular region. But it also projects to the ventral densocellular area and into the cell columns. Thus, projections from the dPFC, via the striatum, are in a position to influence cells that project to motor control areas of the

striatum. The dorsolateral striatum is reciprocally connected to the ventral densocellular region and cell columns. The confined distribution of efferent dorsolateral striatal fibers limits the influence of the motor striatum to a relatively small region involving the cell columns and the pars reticulata. 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 (Fig. 6). Through this spiral of inputs and outputs between the striatum and midbrain DA neurons, information can flow from limbic to cognitive to motor circuits, providing a mechanism by which motivation and cognition can influence motor decision-making processes and appropriate responses to environmental cues.

V. 2. The lateral habenula and RMTg

The lateral habenula (LHb) plays a central role in the reward circuit (Ullsperger and von Cramon, 2003, Matsumoto and Hikosaka, 2007, Hong and Hikosaka, 2008). LHb cells fire following a non-reward signal and are inhibited by reward-predicting stimuli. (Matsumoto and Hikosaka, 2007, Salas et al., 2010). They excite GABAergic cells in the RMTg that inhibit DA burst firing in response to reward (Christoph et al., 1986, Ji and Shepard, 2007). Relatively unknown until recently, this nucleus is now associated with several mental health disorders including depression, schizophrenia, and addiction (Shepard et al., 2006, Friedman et al., 2010, Ranft et al., 2010, Sartorius et al., 2010, Savitz et al., 2011, Winter et al., 2011). The main inputs to the LHb in primates are from forebrain areas; the lateral hypothalamus, the perifornical area, and from the GPi and the VP (Parent et al., 1981, Haber et al., 1993, Hong and Hikosaka, 2008, Bromberg-Martin et al., 2010, {Bromberg-Martin, 2010 #13259). Its main output is to the rostral median tegmental area (RMTg), central tegmental area (median raphe), and central grey (Herkenham and Nauta, 1979, Araki et al., 1988, Jhou et al., 2009, Brinschwitz et al., 2010). Although the LHb does not receive a significant direct cortical connection from reward-related regions, inputs from the lateral hypothalamus and pallidum may provide an indirect connection. Thus, the LHb receives input from areas that are associated with reward processing and in a position to convey this information to the midbrain DA cells via the RMTg.

VI. Summary and conclusion

Functional Considerations

The ability to maintain focus in the execution of specific behaviors and the ability to adapt appropriately to external and internal cues are key deficits in basal ganglia diseases that affect these aspects of motor control, cognition, and motivation. Thus, a system that contains separate circuits to mediate various functions to maintain focus in coordinating actions maybe important. However, to have a system that was designed only with parallel and segregated circuits, without interaction between those networks is not adaptive. Cross-talk between functional circuits is critical for adjusting behaviors based on new information for the overall learning process. We now know that the basal ganglia plays a central role in this process. Indeed, reward and associative functions are not clearly and completely separated within the striatum. Consistent with human imaging studies, reward-responsive neurons are not restricted to the ventral striatum, but rather are found throughout the striatum. Moreover,

cells responding in working memory tasks are often found also in the ventral striatum (Levy et al., 1997, Hassani et al., 2001, Takikawa et al., 2002, Watanabe et al., 2003, Tanaka et al., 2004, Li and Daw, 2011, Cooper et al., 2012, Isomura et al., 2013).

As described above, embedded within limbic, associative, and motor control striatal territories are subregions containing convergent terminals between different reward-processing cortical areas, between these projections and those from the dPFC, and between the dPFC and rostral motor control areas. These nodes of converging terminals represent hubs within the striatum that may be particularly sensitive to synchronizing information across functional areas to impact on long-term strategic planning, and habit formation (Averbeck et al., 2014). Functionally, cells in the striatum are progressively recruited during different types of learning (Graybiel, 2005, Lehericy et al., 2005, Pasupathy and Miller, 2005, Pennartz et al., 2009). Convergent fibers from cortex within the ventral striatum, taken together with hippocampal and amygdalo-striatal projections, place the ventral striatum in a key entry port for processing emotional and motivational information that, in turn, drives basal ganglia action output.

The striatal output impacts directly on the DA cells through the striato-nigro-striatal connection and indirectly through the pallidal-LHb-RMTg pathways. One can hypothesize that initially the nodal points of interface between the reward and associative circuits, for example, send a direct coordinated signal to DA cells. This pathway is in a pivotal position for temporal training DA cells. In turn, these nodal points may be further reinforced through the burst firing activity of the nigrostriatal pathway, thus transferring that impact back to the striatum. Moreover, since the midbrain DA neurons project to a wider dorsal striatal region, information is transferred to other functional regions during learning and habit formation (Volkow et al., 2006, Porrino et al., 2007, Belin et al., 2009) Indeed, when the striato-nigro-striatal circuit is interrupted, information transfer from Pavlovian to instrumental learning does not take place (Belin and Everitt, 2008). In addition, striatal output also modulates the midbrain DA cells indirectly through its connection to the GP/VP, LHb, and RMTg. This signal appears to be transmitted non-topographically from throughout the GPi. Thus, it is likely to represent more generalized information about the state of the striatum. Yet the result is an inhibition of DA cells in response to negative reward. Taken together, the complexity of the striato-nigra system is a key factor in developing appropriate responses to environmental cues and for adapting behaviors accordingly.

Acknowledgments

This work was supported by the NIMH grant MH045573-24.

Abbreviations

ACC	anterior cingulate cortex
BG	basal ganglia
CaBP	calbindin-positive
Cd	caudate nucleus

DA	dopamine
dPFC	dorsal prefrontal cortex
GPe	globus pallidus, external segment
GPi	globus pallidus, internal segment
LHb	lateral habenula
NAcc	nucleus accumbens
OFC	orbitofrontal cortex
Pu	putamen
PD	Parkinson's disease
RMTg	rostromedial tegmental nucleus
SN	substantia nigra
SNc	substantia nigra, pars compacta
SNr	substantia nigra, pars reticulata
VP	ventral pallidum
VS	ventral striatum
VTA	ventral tegmental area

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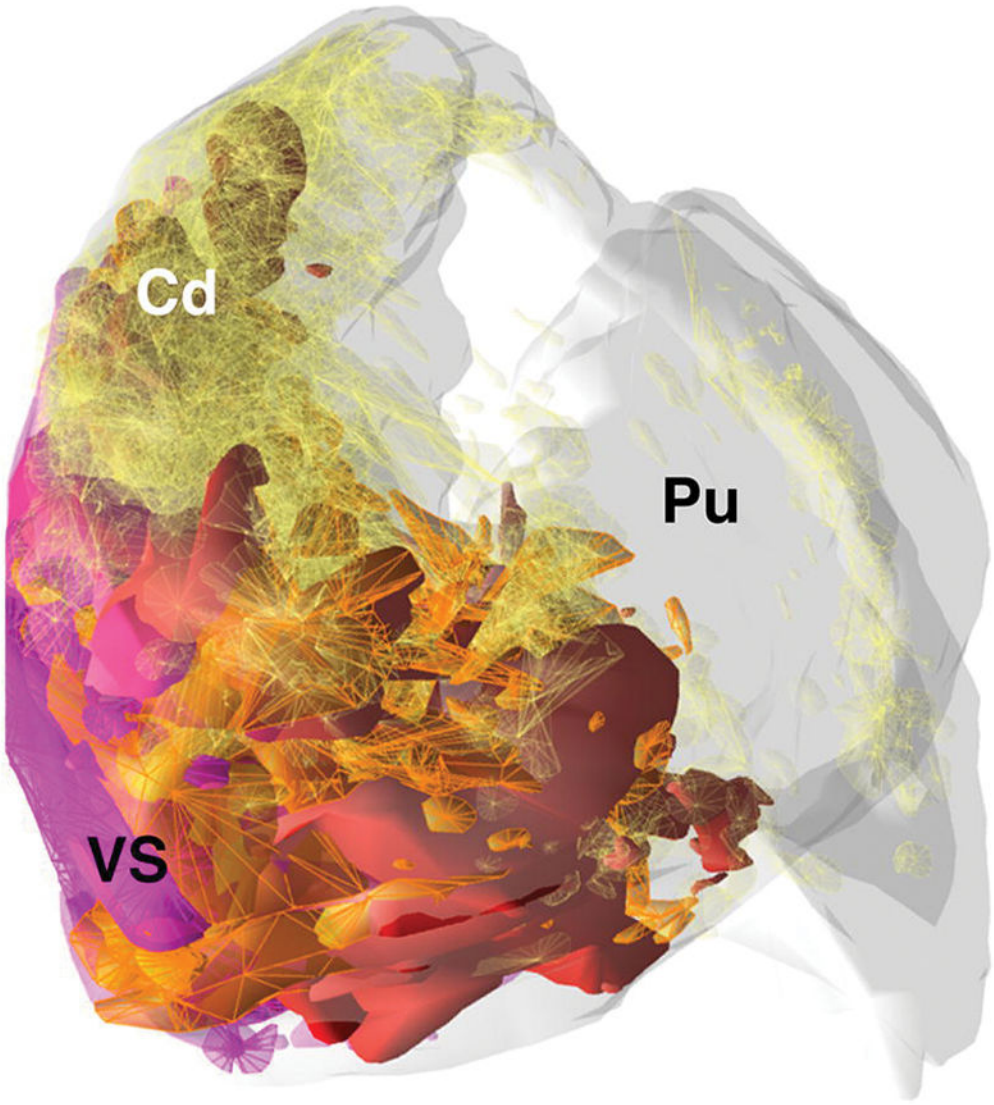

Figure 1.

Medio-frontal view of a 3-D striatal reconstruction illustrating convergence of inputs from PFC. red=inputs from ventromedial prefrontal cortex; dark orange=inputs from orbitofrontal cortex; light orange=inputs from dorsal anterior cingulate cortex; yellow=inputs form dorsal prefrontal cortex. Cd=caudate nucleus; Pu=putamen; VS=ventral striatum. (Figure adapted from (Haber and Behrens, 2014))

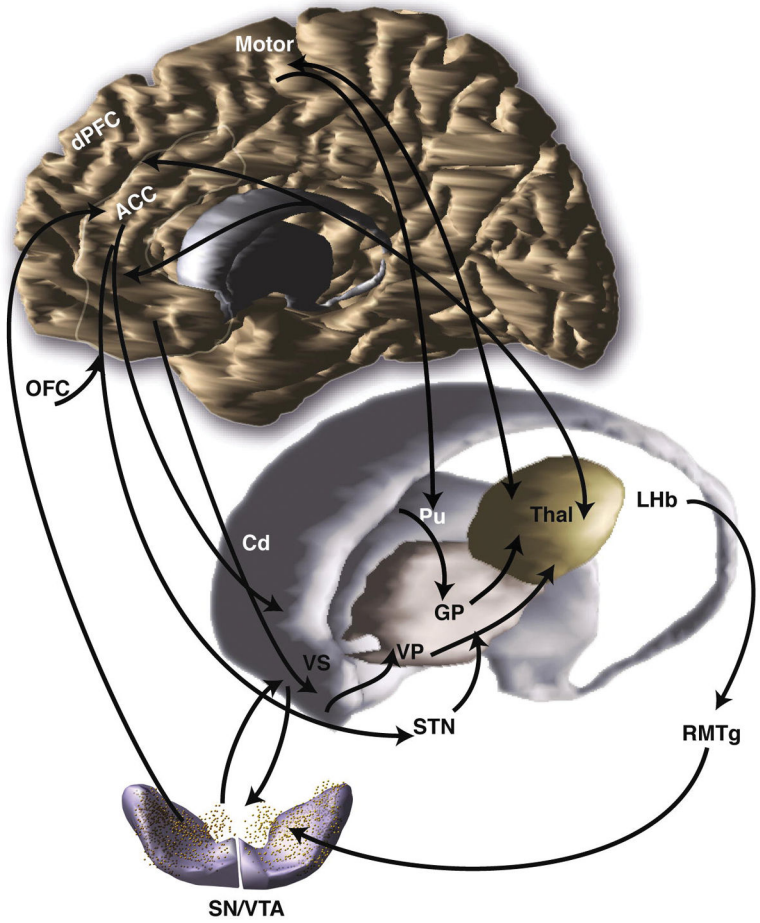

Figure 2.

Schematic illustrating key structures and pathways of the basal ganglia. Note: brainstem motor connections are not illustrated to simplify the figure. Cd=caudate nucleus; ACC= anterior cingulate cortex; dPFC=dorsal prefrontal cortex; GP=globus pallidus; LHb=lateral habenula; OFC=orbital frontal cortex; Pu=putamen; RMTg=rostromedial tegmental nucleus; SN=substantia nigra; STN=subthalamic n.; Thal=thalamus; VP=ventral pallidum; VS=ventral striatum; VTA=ventral tegmental area.

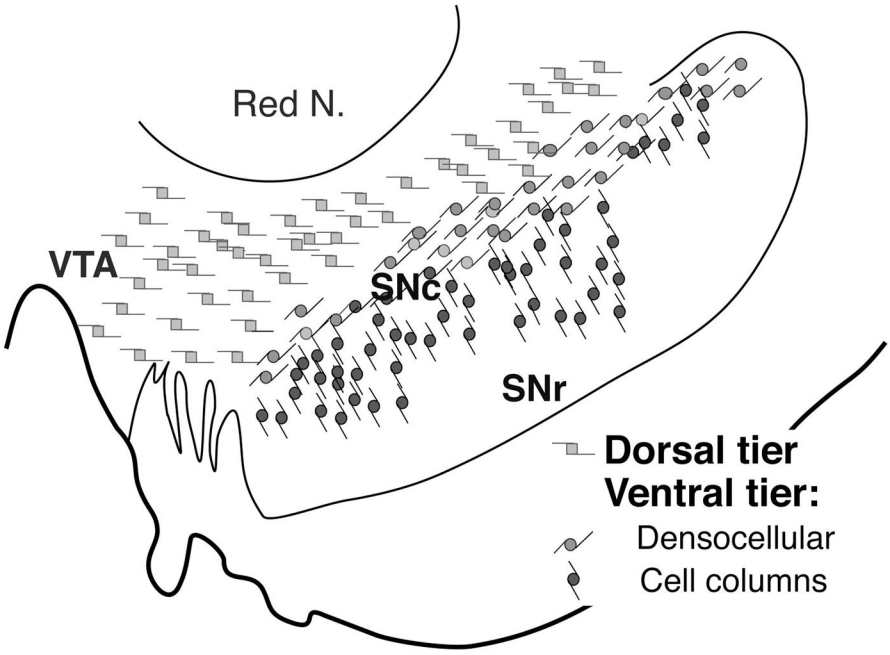

Figure 3.
Schematic of the midbrain dopamine neurons, illustrating the dorsal and ventral tiers. SNc=substantia nigra, pars compacta; SNr=substantia nigra, pars reticulata; VTA=ventral tegmental area.

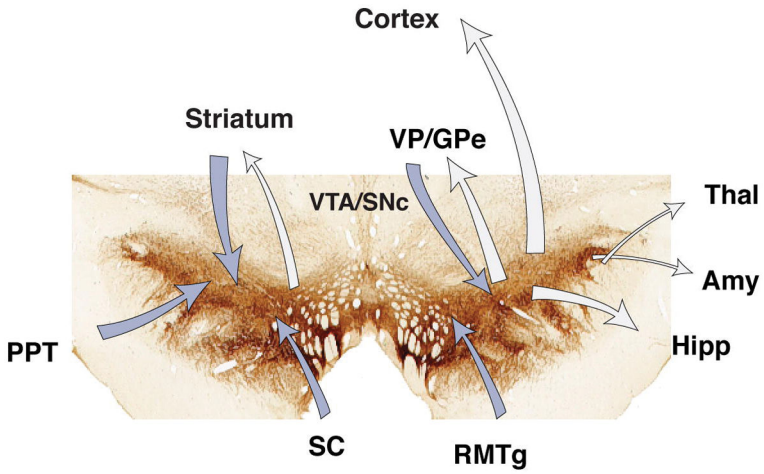

Figure 4.

Schematic illustrating the connections of the midbrain dopamine neurons. Grey arrows=inputs; light grey arrows=outputs; Arrows represent general input and outputs and are not intended to represent topography. Amy=amygdala; GPe=globus pallidus, external segment; Hipp=hippocampus; PPT=Pedunculopontine nucleus; rostromedial tegmental nucleus=RMTg; SC=superior colliculus; SNc=substantia nigra, pars compacta; Thal=thalamus; VP=ventral pallidum; VTA=ventral tegmental area.

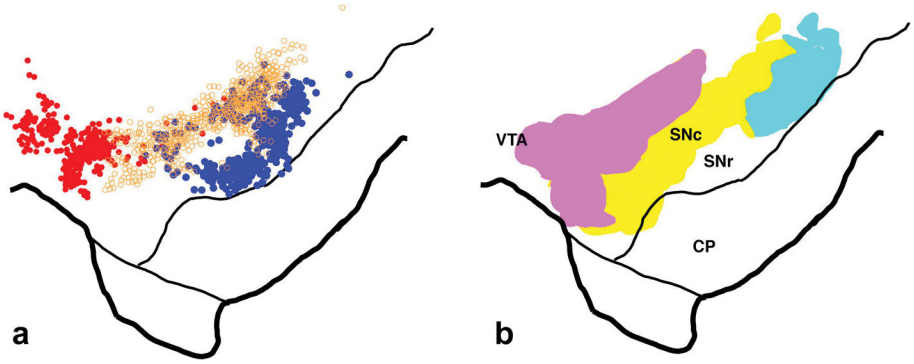

Figure 5.

Schematic of the midbrain illustrating the projections to (a), and from (b) the striatum. a. the distribution of cells projecting to the ventromedial, central and dorsolateral striatum to the midbrain. Red=cells projecting to the ventromedial striatum (limbic region, note some cells are outside the midbrain projection area and likely receive inputs from other regions), orange=cells projecting to the central striatum (association region); blue=cells projecting to the dorsolateral striatum (motor region). b. the distribution of terminal fields from the ventromedial, central and dorsolateral striatum to the midbrain. Pink=terminal field from the ventromedial striatum (limbic region), yellow=terminal field from the central striatum (association region); blue=terminal field from the dorsolateral striatum (motor region). Note: these projections do overlap to some extent. CP=cerebral peduncle; SNc=substantia nigra, pars compacta; SNr=substantia nigra, pars reticulata; VTA=ventral tegmental area.

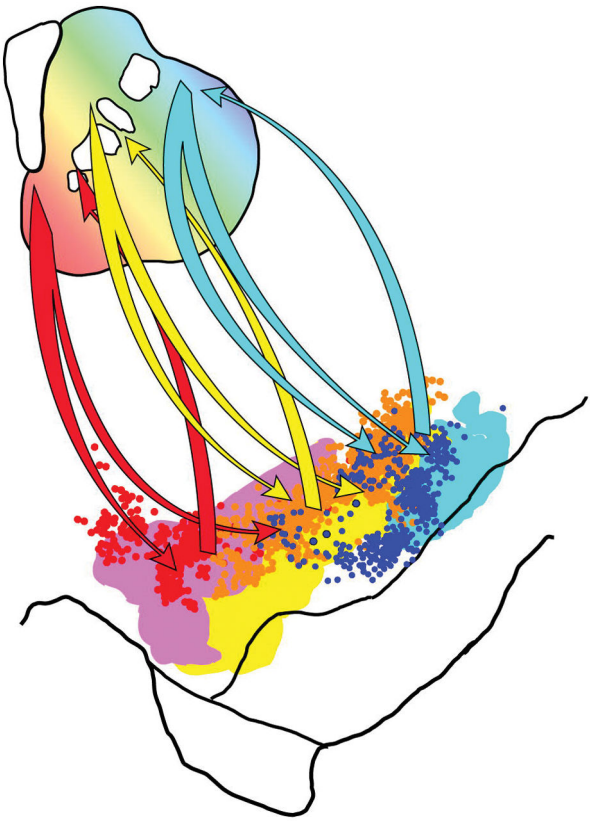

Figure 6.

Schematic illustrating the complex connections between the striatum and substantia nigra/ventral tegmental area. The arrows illustrate how the ventral striatum can influence the dorsal striatum through the midbrain dopamine cells. Colors represent functional regions of the striatum, based on cortical and subcortical inputs. Midbrain projections from the ventral striatum (red) project to both the VTA and ventromedial SNc. Projections from the VTA/medial SN project, not only back to the ventral striatum, but also more laterally to impact on more dorsal striatal regions, forming the first part of a feed forward loop (or spiral). The spiral continues through the striato-nigro-striatal projections through which the ventral striatum impacts on cognitive and motor striatal areas via the midbrain dopamine cells. red=inputs form the limbic areas; yellow=inputs form the dPFC; green/blue=inputs motor control areas; circles=cells projecting to the striatum, outlines=striatal projection fields.