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Review

The Basal Ganglia Over 500 Million Years

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The lamprey belongs to the phylogenetically oldest group of vertebrates that diverged from the mammalian evolutionary line 560 million years ago. A comparison between the lamprey and mammalian basal ganglia establishes a detailed similarity regarding its input from cortex/pallium and thalamus, as well as its intrinsic organisation and projections of the output nuclei. This means that the basal ganglia circuits now present in rodents and primates most likely had evolved already at the dawn of vertebrate evolution. This includes the 'direct pathway' with striatal projection neurons (SPNs) expressing dopamine D1 receptors, which act to inhibit the tonically active GABAergic output neurons in globus pallidus *interna* and substantia nigra *pars reticulata* that at rest keep the brainstem motor centres under tonic inhibition. The 'indirect pathway' with dopamine D2 receptor-expressing SPNs and intrinsic basal ganglia nuclei is also conserved. The net effect of the direct pathway is to disinhibit brainstem motor centres and release motor programs, while the indirect pathway instead will suppress motor activity. Transmitters, connectivity and membrane properties are virtually identical in lamprey and rodent basal ganglia. We predict that the basal ganglia contains a series of modules each controlling a given pattern of behaviour including locomotion, eye-movements, posture, and chewing that contain both the direct pathway to release a motor program and the indirect pathway to inhibit competing behaviours. The phasic dopamine input serves value-based decisions and motor learning. During vertebrate evolution with a progressively more diverse motor behaviour, the number of modules will have increased progressively. These new modules with a similar design will be used to control newly developed patterns of behaviour — a process referred to as exaptation.

Introduction

The forebrain structures concerned with the control of different patterns of behaviour in vertebrates include the pallium (corresponding to the mammalian cortex), the basal ganglia, the dopamine system, and the habenulae, the latter being important for the control of the different modulator systems. The basal ganglia is involved in selection of behaviour, motor learning and the control of dopamine neuron activity and value-based decisions. During the last few years, detailed knowledge of these structures has become available for lamprey [1–3], which represents the oldest group of now living vertebrates that diverged from the evolutionary line leading to primates some 560 million years ago [4] (Figure 1). The surprising conclusion is that the organisation of the basal ganglia in mammals (rodents, cats, and monkeys) is similar in great detail to that in cyclostomes (lampreys), suggesting that the organisation of the basal ganglia and related structures were present in the last common ancestor of all vertebrates.

In this review, we will make a detailed account of the organisation of the basal ganglia in lamprey (cyclostomes) and mammals. These are the two classes of vertebrates that have so far been explored in the greatest detail [3,5–14]. Subsequently, we will briefly consider the other classes, including birds, reptiles, amphibians, and fish.

Evolutionary Perspective — The Cambrian Explosion

Cyclostomes have evolved separately from mammals over more than 500 million years. It follows that when detailed similarities are demonstrated between forebrain circuits in the lampreys of today and those of mammals, these circuits were most likely already present at the dawn of vertebrate evolution (Figure 1). This was at the time of the Cambrian explosion when fossil records show the appearance of a multitude of now extinct species, but also the origin of different extant phyla like arthropods and molluscs, as well as vertebrates (cyclostomes). At this time, many of the molecular components of nerve cells had been designed (through evolution), including most ion channels, transmitters, and ionotropic and metabotropic receptors.

When comparing the organisation of the nervous systems of different phyla, a question that arises is whether specific features evolved independently, *de novo*, or had a common origin. With regard to the forebrain of arthropods and vertebrates, Strausfeld and Hirth [15] reported that there are striking similarities between a large number of transcription factors expressed in both phyla. Moreover, many aspects of the neural organisation of the vertebrate basal ganglia and corresponding structures in the arthropod (fruitfly) forebrain are similar. This implies a common origin; an annelid worm has been suggested as a candidate. Clearly, a worm, as much as any other creature, needs to have a neural machinery to decide about foraging, when and how to move etc. Although cyclostomes must be assumed to have evolutionary predecessors, we will focus here on a comparison within the vertebrate phylum.

The Organisation and Function of the Cyclostome and Mammalian Basal Ganglia

Control of Brainstem Motor Centres through Tonic Inhibition

The output structure of the basal ganglia is represented in both classes by substantia nigra *pars reticulata* (SNr) and globus

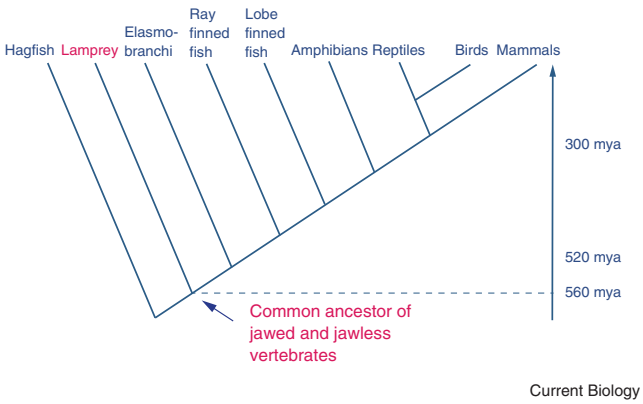


Figure 1. Phylogenetic tree of vertebrates.
The lamprey diverged from the vertebrate line 560 million years ago (mya). All key features of the basal ganglia had emerged already at this time point in evolution. (Adapted from [35].)

pallidus *interna* (GPi) [3,12,16]. They contain GABAergic projection neurons, which are tonically active at a rather high rate at rest, due to their inherent cellular properties [17]. As shown schematically in Figure 2, subclasses of these inhibitory neurons project to different motor centres in the brainstem that control, for example, eye movements, as the superior colliculus (optic tectum in early vertebrates), locomotion, posture, or other patterns of behaviour [18,19]. These projection neurons often send collaterals to the thalamus, which forwards information back to the cortex and striatum regarding the commands to brainstem centres, a form of efference copy [2,20]. There are also separate projections to the thalamus. The net effect of this arrangement is that during resting conditions the motor centres are under tonic inhibition (Figure 2), and it is only when subpopulations of neurons in the GPi/SNr are inhibited that the corresponding motor centres will be disinhibited and free to become active [3,12,18,21–26].

The Direct and Indirect Pathways for Initiation and Suppression of Movements

The input structure of the basal ganglia, the striatum, contains 95% GABAergic spiny striatal projection neurons (SPNs) [7,27]. They are of two types. The first expresses dopamine D1 receptors (D1R), is excited by dopamine, and projects directly to the output neurons of the basal ganglia (SNr and GPi) [28,29]. These neurons represent the 'direct pathway' through the basal ganglia (Figure 2). The second type expresses dopamine D2 receptors (D2R) and is instead inhibited by dopamine. They are part of what is often called 'the indirect pathway' (Figure 3) and send projections via the inhibitory globus pallidus *externa* (GPe) and the excitatory subthalamic nucleus (STN), which in turn targets the output level of the basal ganglia (GPi and SNr). The net effect of the indirect pathway is to enhance the activity of neurons in GPi/SNr and thus to provide additional inhibition of the motor centres that are innervated by these nuclei. Whereas the direct pathway provides inhibition of GPi/SNr, and thereby disinhibits the motor centres, the indirect pathway instead strengthens this inhibition and prevents motion [1,7,10,30,31].

Recent studies show that this basic organisation is also present in cyclostomes [3,6,12,13,32]. The diagram in Figure 3 shows the key features of the basal ganglia that apply to both cyclostomes and mammals. To the right is a table comparing the detailed factual knowledge between the two groups. As can be appreciated, the organisation, connectivity and cellular components are virtually identical. Only the presence of different subtypes of striatal interneurons remains unclear — although two subtypes have been identified in lamprey [5,33].

The Basal Ganglia of Amniote and Anamniote Vertebrates are Similar

For a long time it had been assumed that the basal ganglia in amniotes (mammals, birds and reptiles) was much more developed than in anamniotes (amphibians, fish and cyclostomes) [34–36]. The large similarities between the oldest group of anamniotes (lamprey) and mammals [3] have, however, invalidated this assumption (Figure 3). We will now look in greater detail at this neural organisation.

Striatum — Intrinsic Circuitry and Input–Output Relations

Compartments within Striatum

The striatum, the input stage of the basal ganglia, can be subdivided into the ventral striatum or nucleus accumbens in mammals, which has input from the limbic areas and hippocampus in particular, and the dorsal striatum. In rodents, the dorsal striatum, also referred to as neostriatum, can be subdivided into a dorsomedial and a dorsolateral part, and in primates and humans into caudate nucleus and putamen. Finally, in lamprey the striatum forms only one entity. All parts of the striatum are further subdivided in a mosaic of compartments referred to as striosomes and matrisomes, in both lamprey and mammals [13,37,38]. They were discovered through their particular histochemical characteristics, and both contain D1R- and D2R-expressing SPNs. The SPNs of the striosomes inhibit the activity of the dopamine neurons, whereas the matrisomes take part in the control of movement via the direct and indirect pathways [37]. The striosomes can be regarded as related to a circuit of value-based decisions [39–41], as they influence the level of activity in the dopamine neurons in contrast to the matrisomes, which influence movements (see also below). However, collaterals of the GABAergic SNr neurons have also been reported to affect the activity of the dopaminergic SNc neurons [42]. Both compartments contain SPNs characterised by a large dendritic tree with numerous spines.

Input from Thalamus, Cortex/Pallium and GPe

The striatum was named as such because of the fact that large numbers of fibres from the cortex/pallium to the brainstem and spinal cord pass through this structure, rendering it a striated impression [43]. The projection pattern from the lamprey pallium to the midbrain, brainstem and spinal cord is very similar to that of the rodent cortex [44]. Different parts of the cortex project to specific parts of the striatum according to a topical arrangement [45]. Many cortical/pallial 'pyramidal tract' axons (PT in Figure 3, lower left) projecting to the brainstem and spinal cord give off collaterals to neurons within striatum that synapse exclusively on the many spines of SPNs [44,46,47]. This means that the PT commands to the brainstem and spinal cord will also affect the striatum. There is in addition a subset of pyramidal neurons that have intratelencephalic axons (IT in Figure 3, lower left) projecting to the contralateral cortex/pallium, but they also target

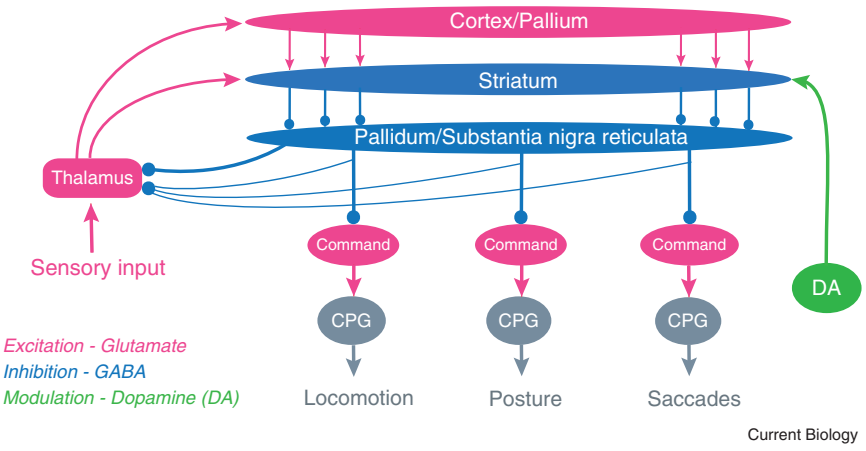


Figure 2. Connectivity of the 'direct pathway' of the basal ganglia.
The output level pallidum/substantia nigra *pars reticulata* contains tonically active inhibitory neurons (blue colour) that target different brainstem centres for locomotion, posture and saccadic eye movements and also thalamus that in turn excites (red colour) both cortex and striatum. Efference copies of pallidal information to brainstem centres are sent to thalamus. Excitatory synapses are red with an arrowhead and inhibitory synapses have a bulb ending (blue). The dopamine innervation (DA) targets striatum and regulates the responsiveness of striatal neurons. (CPG, central pattern generator.)

the SPN spines but remain within the striatum [44,46,47]. Their synapses on SPNs are larger than those made by PT axons. In mammals, it has been suggested that these latter pyramidal neurons would tend to project preferentially to D1R SPNs [48], but this view has been challenged [49–51].

The thalamic input equals that of the cortical input and represents some 45% of the glutamatergic input to striatum in rodents and originates in particular from the intralaminar nuclei [52]. The central lateral nucleus targets the spines, while the parafascicular nucleus targets mainly the dendritic shafts [53]. Both in rodents and lamprey, the thalamic synapses display activity-dependent depression, so that their synaptic potentials decrease progressively in amplitude, whereas corticostriatal synapses are of the facilitating type and the synaptic potentials instead increase in amplitude [54–56]. One may speculate that the fast information via the thalamic route to the striatum provides an initial response for fast action, and that it is subsequently decreased, while the response via the longer cortical/pallial route would lead to a more elaborated response and hence take over through the facilitating synapses.

One subtype of GABAergic neuron (arkypallidal) within GPe enters the striatum with an extensive axonal arbour that targets the dendritic shafts as well as the spines of SPNs [57,58]. They may also contact striatal interneurons. These neurons obviously feed back information from GPe to striatum and they display reciprocal activity to that of the GPe neurons that instead project to the STN and form part of the indirect pathway. The arkypallidal neurons were recently shown to provide a stop signal to activity in the striatum [59]. These neurons have been characterised in rodents, and whether they exist in other vertebrates needs to be explored.

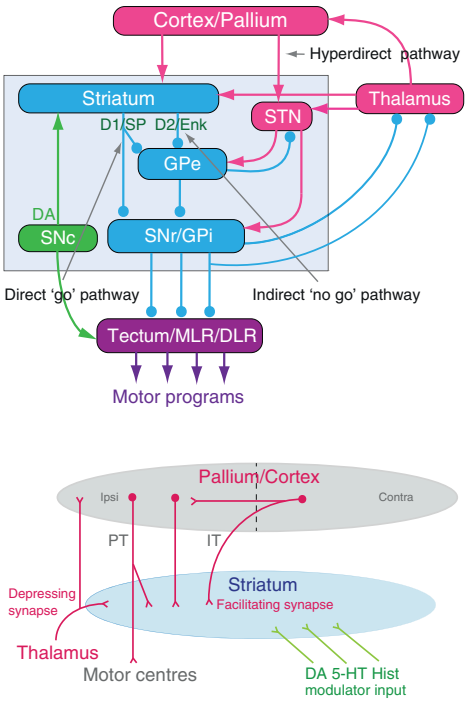
D1 and D2 Receptor-Expressing SPNs

The D1R- and D2R-expressing SPNs controlling the direct and indirect pathways appear to have very different functions — one initiating movements and the other suppressing movements — although the role of the indirect pathway is not fully elucidated. Their general morphology is similar but not identical. The D2R-SPNs that also express enkephalin have a somewhat smaller dendritic tree and display higher excitability than D1R-SPNs at rest [60,61]. When the dopamine system is turned on, the D1R-SPNs (also substance P-expressing) receive further excitation, whereas the D2R-SPNs are instead inhibited. This applies to both mammals and lamprey [6,32,61,62]. The SPNs of both subtypes interact synaptically via mutual inhibition targeting the distal dendrites. This means that the interacting SPNs can influence the dendritic processing within a given SPN. In the extensive dendrites with numerous spines, complex processes take place, including long-term potentiation (LTP) and long-term depression (LTD) [54,63]. The dendritic processing seems to be the target of this synaptic interaction, rather than regulating the frequency of action potentials, which instead is the role of fast-spiking interneurons targeting the soma level [64]. The membrane properties of SPNs are characterised by a subtype of potassium channels (the inward rectifiers, Kir), which are open under resting conditions and hyperpolarise the cells [5,65–67]. If, however, a cell is depolarised to levels close to generating action potentials, the Kir channels will be closed due to their voltage dependence. This leads to an increase in excitability, which is a hallmark of SPNs, defining their cellular properties. They thus represent the converse of the spontaneously active SNr/GPi neurons.

Striatal Interneurons

In addition to the two types of SPNs expressing D1R or D2R, there are several subtypes of interneurons representing approximately 5% of the total number of cells in the striatum in rodents [7]. They are all GABAergic, except for the large aspiny cholinergic cells that project to the SPNs and exert their action through muscarinic receptors. They become inhibited by bursts of activity in the dopamine neurons [68–70]. Enhanced dopamine activation of the SPNs, in combination with a decreased muscarinic activation (via m4 receptors), will promote synaptic plasticity in input synapses from cortex and thalamus [70]. In mammals, the cholinergic neurons are tonically active, even referred to as TANs (tonically active neurons) in primates [71,72]. The interaction between cholinergic interneurons has another possible dimension in that a train of activity in the cholinergic neuron can, via nicotinic receptors located on the dopamine terminals, lead to a release of dopamine [73]. In lamprey, cholinergic neurons have been described histochemically, and there is also a presence of extracellular acetylcholine-esterase [33,74]. As yet, no recordings have been made from the cholinergic neurons in lamprey.

Fast-spiking GABAergic interneurons are present in both lamprey and mammals [5,75–78], somewhat similar to cortical basket cells. They target the soma of the SPNs and will thus control whether a spike can be initiated or not [79]. The fast-spiking



	Lamprey	Mammals
Input to striatum		
Cortical IT-type	+	+
Cortical PT-type	+	+
Thalamus	+	+
Dopamine	+	+
5-HT	+	+
Histamine	+	+
Striatal spiny projection neurons (SPN)		
D1R/SP	+	+
D2R/Enk	+	+
Spiny dendrites	+	+
Kir	+	+
GABA	+	+
DARPP32	+	+
Rest hyperpol.	+	+
Striatal interneurons		
Cholinergic	+	+
Fast spiking (FS)	+	+
Subtypes of FS	?	+
Output pathway SNr/GPi		
Spontaneous activity	+	+
Direct input D1R/SP SPN	+	+
GABA	+	+
Parvalbumin	+	+
Indirect loop		
GPe	+	+
Direct input from D2R/Enk SPN	+	+
GABA	+	+
Subthalamic nucleus	+	+
Glutamate	+	+
Spontanous activity	+	+
I_h	+	+

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Figure 3. The organisation of the basal ganglia is almost identical throughout vertebrate phylogeny — from lamprey to primates.

Top left: the striatum consists of GABAergic neurons (blue colour) and also Globus Pallidus *externa* (GPe), Globus Pallidus *interna* (GPi) and Substantia Nigra *pars reticulata* (SNr). SNr and GPi represent the output level of the basal ganglia, which projects via different subpopulations of neurons to optic tectum (superior colliculus), the mesencephalic (MLR) and diencephalic (DLR) locomotor command regions and other brainstem motor centres, and also back to thalamus with efference copies of information sent to the brainstem. The indirect loop is represented by the GPe, the subthalamic nucleus (STN) and the output level (SNr/GPi) — the net effect being an enhancement of activity in these nuclei. The striatal neurons of the direct pathway to SNr/GPi express the dopamine D1 receptor (D1) and substance P (SP), while the indirect pathway neurons in striatum express the dopamine D2 receptor (D2) and enkephalin (Enk). Excitatory glutamatergic neurons are represented in red and GABAergic structures in blue colour. Also indicated is the dopamine input from the substantia nigra *pars compacta* (SNc, green) to striatum and brainstem centres. Lower left: many cortical/pallial axons projecting to the brainstem and spinal cord (PT) give off collaterals to neurons within striatum. There is a subset of pyramidal neurons that have intratelencephalic axons projecting to the contralateral cortex/pallium (IT) that also target the striatum. To the right: a table depicting the key features of the basal ganglia organisation that are found in both mammals and lamprey. So far, subtypes of fast-spiking striatal interneurons have not been demonstrated in the lamprey.

interneurons have brief action potentials and can fire at high frequency. In mammals, they are connected through gap junctions at the soma level [80]. The cortex can also activate these neurons, which provides a way of indirectly shutting off the SPNs. The same fast-spiking interneurons can provide inhibition of both subtypes of SPNs (D1R and D2R) [64,81].

The cholinergic and the fast-spiking interneurons may each represent roughly 1% of the neuronal population in the striatum of rodents. In addition, other subtypes of interneurons, representing the remaining 3%, have recently been defined in mammals and include the neuroglioform as well as NOS-, 5-HT_{3A}- and TH-expressing neurons [82,83]. In contrast to the other subtypes of interneurons, much less is known of the role of these neurons within striatum. It is unknown whether they exist in lamprey. The overall role of the different subtypes of interneurons in striatum remains far from being clear in either mammals or lamprey.

Nkx2.1 in Lamprey and Other Vertebrates

The GPi and SNr constitute the output stage of the basal ganglia. Both structures are present in lamprey and mammals and they appear to have partially overlapping targets [3,11,12]. Although the physiology, immunohistochemistry and tracing studies confirmed the presence of globus pallidus in lamprey, a study by Murakami *et al.* [84] had indicated that in contrast to all other vertebrate groups, the expression of the pallidal homeobox transcription factor Nkx2.1 was absent in the lamprey forebrain — a study that led a number of investigators to conclude that the pallidum was missing in lamprey [84–87]. Recently, however, researchers from the Kurutani laboratory, who earlier showed the absence of Nkx2.1 in the lamprey pallidum, could demonstrate that Nkx2.1 is indeed present [88], and this controversy is thus resolved.

Neurons of GPi/SNr

The GPi/SNr cells are tonically active at a high rate, although their neurophysiological characteristics differ somewhat, dependent on their targets [10]. The spontaneous activity is inherent in that it does not depend on excitatory input. They have an extensive dendritic tree, which is arranged in a discoid fashion, perpendicular to the direction of the input fibres from e.g. the striatum [11].

As has been noted above, different subpopulations of cells target different motor centres, including the superior colliculus/optic tectum, centres for the control of locomotion, posture, swallowing, chewing, and other structures [18,22,24,26,89,90]. At rest all the different motor centres are kept under tonic inhibition; that is, the basal ganglia can determine if a motor behaviour should be allowed to manifest itself or be kept inhibited.

Is One Main Role of the GPi/SNr-Thalamo-Cortical Loops to Provide Efference Copy Information to Cortex/Pallium and Striatum?

The output axons of GPi/SNr that project to the different brainstem motor centres also provide collaterals to the thalamus (70% or more; Figures 2 and 3), to forward information to the cortex/pallium or the striatum [11,91], in the form of an efference copy of the commands issued. These thalamic neurons,

however, also receive input from other sources including the cortex [92,93]. In the primate literature, the main focus has been on the loops formed through the projections to the thalamus and back to the cortex, and the direct projections to the brainstem have often been neglected [94–97], perhaps due to the prevailing 'cortico-centric' view of brain function. It should be recalled that mammals like rodents, rabbits and cats have a seemingly normal basic movement repertoire when devoid of the entire neocortex, provided that the basal ganglia remain intact [98]. Cats, for example, can move around, search for food and explore different routes in a graceful way.

In the treatment of Parkinson's disease, electrolytic lesions were made in the thalamic relay nucleus that receive input from GPi/SNr, which resulted in an improved control of hand movement, but all other motor symptoms remained unchanged [99]. These findings imply that the basic motor functions do not crucially depend on thalamic feedback to cortex/pallium [2]. No apparent cognitive deficits were reported. These results suggest that a major role of the thalamic feedback may be to provide efference copy information to the cortex/pallium about the basal ganglia commands to brainstem motor centres [2,20,92]. In lamprey, projections from SNr/GPi to the pallium/striatum via the thalamus are also present [12].

Indirect and Hyperdirect Pathways — GPe and STN

The GPe is anatomically separated from the GPi in mammals and receives input from the D2R-expressing SPNs, which in turn project to the STN. In other non-mammalian vertebrates, from lamprey to birds, the GPe cells that receive input from D2R SPNs are mixed with the GPi cells, which receive input from D1R SPNs [3,35,100,101]. The output targets of GPe and GPi neurons are, however, similar in the different classes of vertebrates. Functionally, the basis for the D1R and the D2R pathways to GPi and GPe thus remain the same [3,7,13,31,92].

The connections between the GABAergic GPe neurons that contact the excitatory STN neurons are reciprocal, and this arrangement can result in oscillatory activity [102], which is more pronounced in the absence of dopamine, and thus represents one possible source of the symptoms in Parkinson's disease [103–105]. The STN cells project in turn to GPi and provide further drive to these cells (Figure 3), hence resulting in an enhanced inhibition of the motor centres. An increased activity in D2R SPNs will thus decrease the inhibition produced by the GPe neurons on the STN, and therefore increase STN activity, and thereby also that of the GPi. These represent the main components of the indirect pathway, the function of which is to inhibit movements [30,31,106]. There is also other related connectivity from the GPe directly onto the GPi/SNr neurons [107]. A decreased activity of GPe will result in increased GPi activity, conforming to the indirect pathway effects.

The STN neurons also receive direct input from the cortex/pallium and from the thalamus, and the net effect of activating the STN will be an activation of the GPi, and therefore inhibition of the particular motor centre that is the target of this pathway. This is also referred to as the 'hyperdirect pathway' [108,109], which rapidly can terminate a given motor act. The STN neurons express D5 receptors [110], a subtype of the D1-receptor family, and an activation of the dopamine system will thus provide additional excitability of the STN pathway, also affected in Parkinson's disease. An enhanced dopamine drive will thus facilitate the D1R SPNs of the direct pathway and at the same time the hyperdirect pathway, allowing for a rapid termination of motor acts.

STN is also present in lamprey, with input from both identified GPe neurons and from the pallium, and thus both the indirect and the hyperdirect pathways have been present from very early on in vertebrate evolution [3,44]. The primate STN is subdivided into several areas, one related directly to motor tasks and others to emotional and cognitive functions [111]. This relates to the different roles of the basal ganglia and the STN in the control of different aspects of behaviour. STN is the target of deep brain stimulation, now a common form of therapy, which has helped thousands of patients through a marked reduction of the motor deficits in Parkinson's disease [112]. Deep brain stimulation, like DOPA therapy, has side effects outside the motor sphere that can be ascribed to effects on emotional and cognitive control.

In addition to the arkypallidal subpopulation of GPe neurons projecting back to striatum (see above) [58], the more common type of GPe neuron projecting to STN also sends collaterals innervating the fast-spiking interneurons in striatum [113]. In GPe, a third subtype of neuron has recently been described that co-expresses cholinergic markers and GABA [114]. The latter neurons are similar to those of nucleus basalis that project directly to the frontal cortex. This appears to be a distinct population from those of the indirect pathway. Whether these projections are present in other classes of vertebrates is as yet unknown.

The Action of Modulator Systems on Striatum and Directly on Brainstem Motor Centres

Among the different modulator systems that impinge on striatum in lamprey and mammals, the dopamine system has been studied in the greatest detail. It is conserved regarding the projection pattern from substantia nigra *pars compacta* (SNc) and the ventral tegmental area (VTA) to striatum, the STN, other basal ganglia structures, and the projections to motor centres in the midbrain, like optic tectum/superior colliculus [115] (Figure 4). The dopamine neurons are tonically active at a low rate under resting conditions, which sets the responsiveness of SPNs in striatum [62]. Too little dopamine is associated with difficulty to initiate movements, as in Parkinson's disease, and too much dopamine leads instead to hyperkinesias and movements that are initiated without the conscious intention of the individual. This demonstrates a very critical role to the dopamine system in the control of motor behaviour. Depletion of dopamine as caused by the toxins MPTP or 6-OH-dopamine gives rises to hypokinesias, and the same types of symptoms are observed in humans, rodents, amphibians, teleosts and lamprey [116–122].

The dopamine neurons are activated by unexpected (salient) stimuli, but also in the context of reward [123,124]. These dopamine signals are important during motor learning and to evaluate if a movement has been successful or not. The dopamine signal can help strengthen the input synapses to striatum. This can be regarded as a very fundamental property of the nervous system, since it is critical for any animal to be able to learn and strengthen useful motor patterns. The converse is also true, in that less successful or harmful motor patterns should be disfacilitated, as when the dopamine activity is depressed. These actions of dopamine provide the basis for reinforcement learning. The

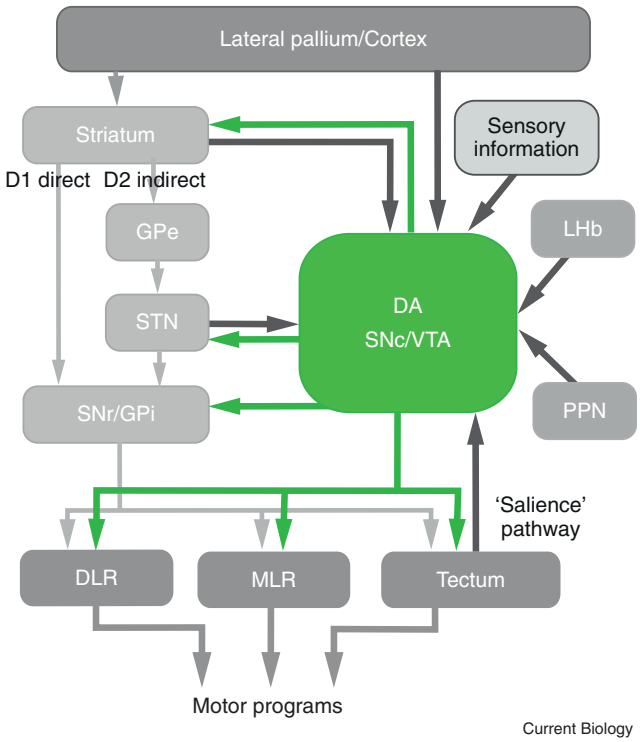

Figure 4. Efferent and afferent connectivity of the SNc.
The connectivity between the SNc and other basal ganglia subnuclei is evolutionarily conserved, as well as the inputs from the lateral pallium, habenula, PPN and optic tectum. In addition, as observed in mammals, the SNc receives multiple sensory inputs. In the lamprey, these originate from the olfactory bulb, tectum, octavolateral area and the dorsal column nucleus. Apart from input to striatum, SNc also sends projections to several motor output nuclei.

same dopamine neuron can send branches to both striatum and the brainstem motor centres [125]. This means that when the activity of the dopamine neurons is enhanced, not only the direct pathway neurons with D1R-receptors but also the D1R-expressing neurons in tectum or in the MLR will be facilitated to promote the initiation of movement [125,126].

Activation of Dopamine Neurons — Role of Habenulae, PPN and Cortex

The phasic control of the dopamine neurons is of critical importance. It results in an enhanced activity in a reward situation, and conversely a decrease in the absence of an expected reward. The dopamine neurons receive input from several structures, including striatum, cortex/pallium, the lateral habenulae, and the pedunculopontine nuclei (PPN; Figure 4) [115,127–129], which regulate their activation [130]. A recent report shows that the dopamine neurons can progressively increase their level of activity, as when a rodent approaches the location of, for example, food [131]. Recent data also show that even under natural movements, the dopamine neurons exhibit a burst of activity each time a new bout of locomotor activity is initiated [10]. The dopamine neuron population in rodents and monkey is heterogeneous [132–134]. SNc can be subdivided into a medial part, where neurons relate to reward, and a lateral part, in which the pattern of activation instead is related to aversive behaviour [135]. In VTA, one subpopulation of dopamine neurons projects to the frontal lobe, and another to the ventral striatum [136]. This means that the previous notion that dopamine neurons represent a uniform group has to be revised. In lamprey, the dopamine neurons are located in the nucleus of the posterior tubercle, which corresponds to SNc with regard to detailed input and output projections, but may also partially represent VTA [115]. Whether the lamprey dopamine neurons can be further subdivided into subpopulations remains to be established.

The lateral habenulae contains three different compartments in the lamprey and likely also in mammals, each of which is concerned with the control of the level of activity in either dopamine, 5-HT or histamine neurons (Figure 5) [13,129]. The dopamine neurons receive a direct projection from lateral habenulae and also a disynaptic inhibitory control via the rostromedial tegmental nucleus (RMtg) [13,137]. There is thus a potential for both facilitation and inhibition of the dopamine neurons. The striosomal compartment of striatum provides direct inhibition of dopamine neurons [138], but as shown in lamprey it also projects to the habenulae-projecting part of globus pallidus (GPh) [13,129]. GPh is excitatory and thus will activate the lateral habenulae that will feed information to the dopamine neurons [13,128]. GPh also receives input from cortex, the limbic system, and thalamus in both lamprey and rodents [13,128,139]. This means that there is a potential for an intricate regulation of the dopamine neurons, which also relates to signalling aversive behaviour [140]. The medial habenula with projections to two separate interpeduncular nuclei and further to the periaqueductal grey/central grey is present in lamprey, zebrafish and mammals [129]. Recent data on zebrafish show its role in fear responses [141].

The 5-HT and Histamine Systems are Conserved

In addition to the dopamine system, 5-HT neurons in the raphe nuclei project to striatum in both lamprey and mammals (Figure 5) [33,142–144]. Similarly, the histamine system, originating in hypothalamus, projects to striatum [55,145,146]. The histamine system shows diurnal variation, with an enhanced activity during daytime, which also influences striatal excitability via presynaptic H3 receptors [55]. There also appears to be input from hypothalamus, at least to the rodent ventral striatum, and it is thus possible that the hypothalamic centres for foraging and other hypothalamic functions [147] can influence striatum and the threshold for eliciting different patterns of behaviour.

Value-Based Decisions — Motor Learning

Figure 6 shows two schemes, the lower representing the circuitry discussed so far from matrisomes in striatum concerned with the control of motion via the direct and indirect pathways. The upper diagram is concerned with the control of the dopamine neurons from the striosomes. As discussed above, GPh receives inhibitory input from striosomes [13] and excitatory input from pallium/cortex orbitofrontal, the limbic system and thalamus [139]. GPh will in turn control the lateral habenulae and thereby the level of activity in the dopamine neurons. This circuit is apparently well-suited to contribute to the control of the level of activity in the dopamine neurons. When it comes to evaluation of whether an action has been successful or not, GPh neurons are known to be modulated in relation to aversive behaviour in both primates and rodents [140,148,149]. In lamprey, GPh neurons are also excitatory and have the same connectivity [129].

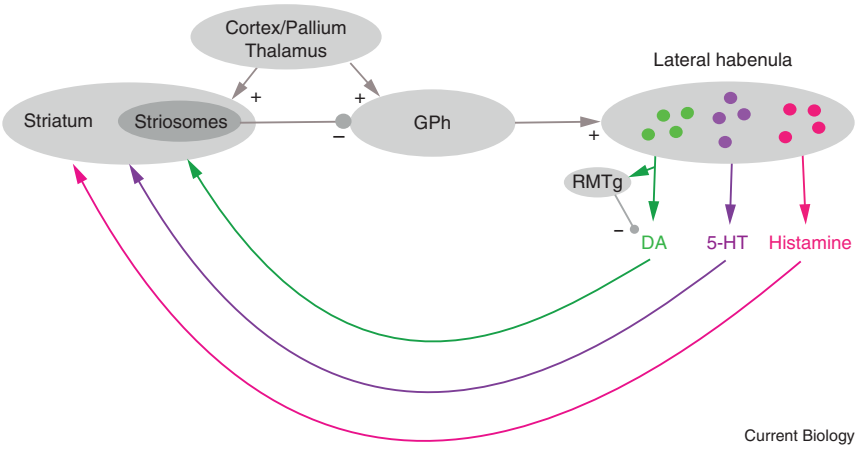

Figure 5. Circuitry for evaluation.
The striosomal compartment in striatum projects to the glutamatergic GPh [3], which targets the lateral habenula. The lateral habenulae contains three different compartments in the lamprey, and likely also in mammals, each of which is concerned with the control of the level of activity in either dopamine (DA), 5-HT or histamine neurons. The dopamine neurons receive a direct projection from the lateral habenulae and also a disynaptic inhibitory control via the rostromedial tegmental nucleus (RMtg). All three modulatory systems send direct projections back to striatum.

The phasic control of the dopamine neurons is crucial in respect to motor learning, and it should be noted that there are several additional inputs to the dopamine neurons (Figure 4) from, for example, the PPN and other structures that in primates exhibit reward-related activity [127]. Different groups of PPN neurons project to SNc, sending expected reward signals to the medial SNc and sensorimotor/alerting signals to the lateral SNc [130]. An enhanced activity in the dopamine neurons can facilitate synaptic plasticity as in LTP or LTD [63,150]. These are thus important components of motor learning, another important aspect of forebrain function.

There is a fuzzy distinction between learned movements and innate motor patterns including respiration, posture or locomotion [151–153]. In human locomotion, for instance, the standard leg movements can be modified and one can learn to walk on high heels or like Charlie Chaplin. This is a form of learned modification of an innate motor program — in some sense a 'habit' has been formed. A somewhat more complex movement is when you learn to stretch out the hand towards the light switch in a given location even in a dark room. A habit is formed and you may later stretch out the hand towards the presumed location of the light switch even when it has been moved — although you may in reality be aware that this is the case. One can finally make completely new patterns of motor coordination like when learning to bicycle, perform a somersault or play the violin. In all these cases, one most likely utilises elements of the intrinsic motor repertoire, but sequenced in a new way for a given individual. These movements are sometimes referred to as goal-directed, but in reality the different motor patterns underlying a habit may of course be recruited to achieve a certain goal. Humans excel in combining different aspects, such as grasping an object, while at the same time moving at a fast speed. This ability is markedly incapacitated in Parkinson's disease [154,155]. This finding suggests that the basal ganglia is of critical importance for this form of intricate coordination between different motor patterns.

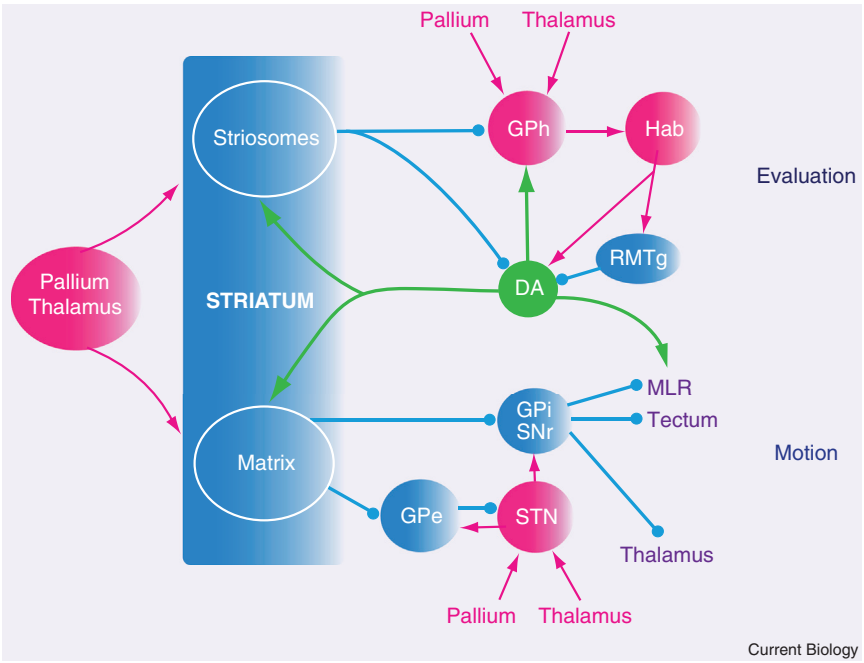

Figure 6. Overview of the basal ganglia/habenular circuits underlying the control of motion and evaluation.
The lower part of the diagram shows that the matrix component of striatum projects to both globus pallidus *interna* and substantia nigra *pars reticulata* (GPi/SNr), and further to the brainstem motor programs. In addition, it shows the indirect pathway with GPe (globus pallidus *externa*) and the subthalamic nucleus (STN). The colour code is blue for GABAergic, red for glutamatergic and green for dopaminergic neurons (DA). The evaluation circuit in the upper part of the diagram contains the lateral habenula (Hab) with its projection to dopamine neurons directly and indirectly via the GABAergic RMTg. The lateral habenula has input from the glutamatergic habenula-projecting globus pallidus (GPh), which in turn is excited from pallium and thalamus, whereas it receives inhibition from the striosomal compartment of striatum. Dopamine neurons also send projections to the mesencephalic locomotor region (MLR) and tectum.

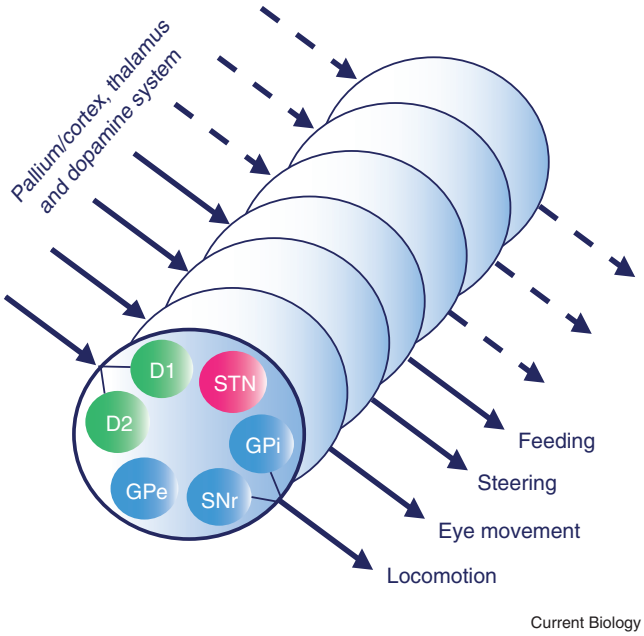

Figure 7. Conceptual scheme of a modular organisation of the basal ganglia, with one module for each type of motor program.
Each module would contain the D1R and D2R projection neurons and the components of the direct and indirect pathway GPi (includes also SNr), GPe and STN. Each module would be activated if sufficient drive occurs from neurons in pallium/cortex and thalamus. The responsiveness of the modules would be determined by the tonic dopaminergic drive. Whereas the lamprey has a limited behavioral repertoire, mammals and particularly primates have a very varied and versatile motor repertoire.

Fish, Amphibians, Reptiles and Birds — The Interphase Between Lamprey and Mammals

As mentioned above, most basal ganglia key features were thought to have evolved within the amniote classes [34,36,101]. However, since the lamprey, the earliest anamniote, has the basal ganglia developed in exquisite detail, this longstanding assumption is incorrect. In select species the details can possibly vary to some degree, but it can be assumed that in general the design will be very similar in all vertebrates. This is also supported by studies using classical anatomy, immunohistochemistry, tracing techniques, electrophysiology and more recently the expression of different transcription factors. In the different classes of vertebrates the main components of the basal ganglia have been demonstrated, although the knowledge may be fragmentary in some groups [100,156–162]. In all vertebrate classes, including lamprey, the pallidal regions contain large GABAergic cells and express the pallial homeobox transcription factor Nkx2.1 [88,156,158,162,163]. In songbirds there appears be a somewhat special arrangement in terms of the interaction between striatum and different components of the pallium during the song-learning phase [164–166].

Possible Differences Between the Lamprey and Mammalian Basal Ganglia

The projection neurons from cortex/pallium of the PT-type (Figure 3) have the same target areas in the brainstem and spinal cord in mammals and lamprey. However, their soma–dendritic morphology differs in that the mammalian PT neurons typically have one, sometimes two, apical dendrites targeting the molecular layer, while the lamprey PT cells have two main dendrites that ramify profusely as they approach the molecular layer [44,167]. Clearly they pick up information from a much broader area in the lamprey pallium than the apical dendrites in the rodent cortex.

With regard to the interneurons in striatum, we know that there are cholinergic interneurons and fast-spiking interneurons in both lamprey and rodents [5,64,74]. We have not recorded from the cholinergic interneurons and we do not know if they have the same reciprocal relationship to the firing of the dopamine neurons as in mammals [69]. During the last few years a number of subtypes of striatal neurons, such as neuroglioform, NOS-, 5-HT_{3A}- and TH-expressing neurons [82,83], have been identified in rodents, but their function remains to be determined in mammals. Whether they exist in lamprey is as yet unclear.

Overarching Control — Conceptual Model

The inference from what we have discussed so far is that in striking detail the basal ganglia of vertebrates are arranged in a practically identical way with the same building blocks and connectivity (e.g., direct, indirect and hyperdirect pathways), and with the same transmitters, peptides and ion channels. The role of the vertebrate basal ganglia in the control and selection of behaviours is obvious. Since both the direct and indirect pathways are conserved throughout vertebrate phylogeny, it would appear likely that the basal ganglia circuit for selection of behaviour provides a good solution that has not been possible to improve further during evolution, at least with regard to these central and basic features.

The tiny striatum of the lamprey only has to deal with a rather limited behavioural repertoire such as locomotion, steering, foraging, eye movements and control of body orientation. Figure 7 summarizes a conceptual model of the basal ganglia. As we have indicated earlier (Figure 2), the basal ganglia can be subdivided into modules involved in the control of a variety of motor programs such as locomotion, different eye movements and feeding. Neurons of both the direct and indirect pathway are activated during initiation of a given behaviour [2,10,31,168,169]. Whereas the direct pathway will initiate behaviour through disinhibition of the appropriate motor centre, the indirect pathway can be assumed to suppress competing patterns of behaviour. For instance, one cannot turn left and right at the same moment. Each module will thus contain the D1R- and D2R-expressing SPNs as well as their downstream elements. Whether a module will be activated or not depends on the activation of the SPNs from thalamus and pallium (cortex), and the responsiveness of the SPNs depends on the concurrent dopamine activation, the tonic level as well as the phasic activation known to occur [10] as different movements are initiated.

During vertebrate evolution the size of the basal ganglia has expanded to a very large structure in primates, with the striatum being subdivided in several compartments linked to the control of different patterns of behaviour. What seems to have happened is that the basal ganglia has expanded in parallel with a progressively enlarged and refined behavioural repertoire. In other words, in parallel there would also be a progressive increase in the number of behavioural modules. But the design of each of these modules may have remained the same throughout

vertebrate phylogeny, although the number of modules has increased. This suggests that these circuits represent a successful solution to the control of behaviour that has remained relatively untouched by evolution. For development this process is called exaptation [3] — that is, evolution through a progressive increase of the number of identical circuits used to control new emerging patterns of behaviour, a process somewhat similar to how the number of cortical columns have increased from mice to men.

Concluding Remarks

A finding that has important implications is that the basic features of the forebrain organisation discussed here appear to be conserved throughout vertebrate phylogeny, indicating that it represents critical elements in terms of decision-making and selection of behaviour and reward mechanisms. This also means that many of these mechanisms can be studied in a variety of vertebrate model systems and that the results can be expected to be applicable to vertebrates in general rather than being species-specific.

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