The evolution of the basal ganglia

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Key Points/Objectives

*Cortico-basal ganglia loops are likely responsible for action selection of a wide variety of species-general and species-specific behaviors.

*The structures and connectivity of the basal ganglia are conserved throughout vertebrate evolution.

*There are subtle species differences in basal ganglia size, neurochemical makeup, and connectivity among vertebrates that, along with differences in the neocortex, may help to explain dramatic differences in behavioral repertoire.

Abstract

The importance of the basal ganglia for clinical, systems, and cognitive neuroscience is unrivaled. Surprisingly, these structures, which seem to have so many different functions in the human brain, are highly conserved across vertebrates. The subtle differences between species, however, may tell us a great deal about the evolution of the human brain.

1. Introduction

The basal ganglia are a fascinating set of structures and circuits situated roughly at the middle of the base of the brain. Because they have been implicated in a whole host of diseases, they have received an incredible amount of attention from clinicians and basic scientists alike. From an evolutionary perspective, they are highly conserved, to the degree that they are perhaps boring! However, as you will see, the extreme degree of this conservation raises its own sets of questions. Answering them may help us to understand fundamental principles of brain function and evolution.

Here, we will ask about the evolution of the basal ganglia. In doing so, we will cover basal ganglia structure and function, with a particular focus on comparative studies that may yield insights into species differences, both large and small.

2. What are the basal ganglia?

Different articles and textbooks provide varying lists of structures that constitute the basal ganglia, but the most common ones cited are the caudate, putamen, nucleus accumbens, olfactory tubercle, globus pallidus, subthalamic nucleus (STN), substantia nigra (SN), and ventral tegmental area (VTA). With the exception of the olfactory tubercle, which is a

paleocortical structure (Stephan, 1975), all of these are nuclei buried deep within the brain, and thus they have a fundamentally different structure than the layered cerebral neocortex (although they are anatomically intertwined with the neocortex, as we will see below). This leaves open the question: what qualifies as basal ganglia?

Because ontogeny so often recapitulates phylogeny, it is worth considering a developmental lens to define the basal ganglia. During early development, the neural tube forms three vesicles: the prosencephalon, mesencephalon, and rhombencephalon. The prosencephalon then splits into the telencephalon and diencephalon while the rhombencephalon splits into the metencephalon and myelencephalon, resulting in five total vesicles. Of the structures listed above, the caudate, putamen, nucleus accumbens, olfactory tubercle, and globus pallidus are all part of the telencephalon (along with the amygdala, olfactory bulb, and the rest of the cerebral cortex), while the subthalamic nucleus is part of the diencephalon (along with the thalamus, hypothalamus, and epithalamus), and the VTA and SN are part of the mesencephalon (along with other structures in the midbrain). For some developmental neurobiologists, the basal ganglia are necessarily part of the telencephalon (e.g., Medina et al., 2014; Smeets et al., 2000), and would encompass the caudate, putamen, nucleus accumbens, olfactory tubercle, and globus pallidus, but not the STN, VTA, or substantia nigra (SN). Of course, the circuits and functions of these latter structures are so intimately tied to the former that many researchers do label them ‘basal ganglia’ (Graybiel, 2000; Heimer, 1983; Mink, 2003), and this is likewise the list we will use. Some researchers also historically considered the claustrum, a telencephalic nucleus positioned between the putamen and the insula, as part of the basal ganglia (Brown and Marsden, 1998; Sherk, 1986), although this is not the dominant view currently, at least in part because of its strong, reciprocal connections with the cerebral cortex.

3. The organization of cortico-basal ganglia loops

Cortico-basal ganglia loops represent the fundamental organizing principle of the basal ganglia. Their basic architecture is well-described, and it has also been reviewed at every level elsewhere (Albin et al., 1989; DeLong and Wichmann, 2007; Gerfen, 2004; Haber, 2003) (FIGURE 1). In brief, nearly the entire cerebral cortex (with the likely exception of primary visual cortex (Saint-Cyr et al., 1990) projects topographically to the striatum, the main gateway to the basal ganglia. Other inputs to the striatum include those from the thalamus, substantia nigra, and amygdala. From there, the circuit splits into direct and indirect pathways through projections

to the internal globus pallidus (GPi)/substantia nigra pars reticulata (SNr) and external globus pallidus (GPe), respectively. The GPi and SNr project directly to the thalamus, which in turn projects to the cortex, constituting the direct pathway. The GPe projects to the STN, which in turn projects to the GPi and SNr, which project to the thalamus, which projects to the cortex, constituting the indirect pathway. Hence, both the direct and indirect pathways are part of cortico-basal ganglia loops, in which the circuit begins and ends in the cerebral cortex. A third pathway–the hyperdirect pathway–is composed of the projection directly from the cerebral cortex to the STN. This pathway (like the cortico-striatal pathway) is unidirectional, meaning the STN does not project back to the cerebral cortex.

Scientists have developed different frameworks for understanding the organization and functions of cortico-basal ganglia loops (FIGURE 2). Some are in conflict with each other, while others describe the loops at different levels and can thus coexist. The earliest organizing principle put forth to explain cortical-basal ganglia loops was funneling of information. Each basal ganglia relay station in the loop involves a smaller and smaller brain structure: the striatum is much smaller than the cerebral cortex; the pallidum and SNr are smaller than the striatum; the subthalamic nucleus is smaller than the pallidum and SNr. These are not subtle differences: for example, in the human brain, the striatum is ~60x the size of the subthalamic nucleus (Yelnik, 2002). Thus, one view of cortico-basal ganglia loops is as ‘funnels’ for information that must eventually reach the motor cortex. In this way, functionally distinct parts of the cerebral cortex could, through multisynaptic pathways, influence action (Kemp and Powell, 1971).

Another framework for explaining cortico-basal ganglia loops, in partial conflict with the funneling view, is that loops are parallel, segregated, and closed. Here, functionally distinct regions of the cerebral cortex project to different zones of the striatum, which then project to different zones of the pallidum, and so forth. In doing so, they create parallel, segregated loops for different functions (Alexander et al., 1986). These loops do not interact, so information is not integrated. For example, in monkeys, the dorsolateral prefrontal cortex projects to the dorsolateral head of the caudate, which then projects to the lateral dorsomedial GPi and the rostrolateral SNr, which then project to the ventralis anterior pars parvocellularis and mediodorsal pars parvocellularis nuclei of thalamus, which then project back to the dorosolateral prefrontal cortex. By contrast, the supplementary motor area projects to the putamen, which projects to the ventrolateral GPi and caudolateral SNr, which themselves project to the ventralis lateralis pars oralis and medialis of thalamus, which then project back to the supplementary

motor area. In this way, cortico-basal ganglia loops are closed (ending only where they began), parallel, and segregated in nature.

Funneled vs parallel loops are in partial contradiction: obviously, projections either overlap, or they do not. Alexander, DeLong, and Strick (Alexander et al., 1986), in their landmark review paper on the subject, stress that funneling can and does occur within a loop, but not between loops. Functionally related, but potentially quite physically distant, cortical regions (such as the dorsolateral prefrontal cortex, posterior parietal cortex, and arcuate premotor area) can be part of the same loop, and will thus have highly overlapping projections to the striatum.

Other authors have emphasized the integrative and hierarchical nature of cortico-basal ganglia loops (Balleine et al., 2015; Haber, 2003). They point out how widespread many of the terminal fields are within the basal ganglia loops. For example, the territory occupied by striatal terminal fields from many frontal areas appears far out of proportion to what would be expected of a point-to-point, nonoverlapping, topographic projection (Haber et al., 2006). This creates intricate patterns of overlap, such that some zones of the striatum appear highly integrative, while others are less so. Indeed, there are some areas of the striatum that receive projections from *all* prefrontal regions (Averbeck et al., 2014). The dopaminergic neurons of the substantia nigra pars compacta (SNc) and VTA exchange reciprocal connections with the striatum, and they do so in a way that appears to impose a hierarchical structure on the basal ganglia as a whole via closed and open loops. This is another opportunity for potential integration in the basal ganglia, and it also may impose hierarchical organization on basal ganglia-mediated behaviors.

3.1. Limbic, associative, and sensorimotor loops through the basal ganglia

Regardless of the degree of integration across cortico-basal ganglia loops, one common simplification is to split the loops into three groups: limbic, associative, and sensorimotor. For example, the ventromedial striatum receives projections from limbic and motivational structures, such as the ventromedial prefrontal cortex, hippocampus, and amygdala. It is sometimes referred to as the limbic striatum. The central striatum receives projections from parts of the cerebral cortex associated with cognition, such as the dorsolateral prefrontal cortex. It is sometimes referred to as the associative striatum. The dorsolateral striatum receives projections from parts of the cerebral cortex associated with sensorimotor functions, including primary

motor and somatosensory cortices. It is sometimes referred to as the sensorimotor striatum (FIGURE 3).

Although now the limbic cortico-basal ganglia loops are widely appreciated, historically, our understanding of them lagged our understanding of associative and sensorimotor loops. In fact, in the first half of the 20th century, neuroscientists tended to view the nucleus accumbens as part of the olfactory system, rather than as part of the striatum (Salgado and Kaplitt, 2015). Connectivity studies were particularly convincing in regard to establishing the true role of the nucleus accumbens (Heimer et al., 1982; Nauta et al., 1978). The limbic loops involve projections from limbic regions of the cortex, along with the amygdala, to the nucleus accumbens, which projects to the ventral pallidum (which has both GPi and GPe -like components), which then projects to the mediodorsal nucleus of thalamus. These circuits parallel those from the dorsal striatum. The nucleus accumbens constitutes part, but not all, of the ventral striatum and is composed of a shell and a core. The shell of the nucleus accumbens is easily differentiated from the rest of the striatum on histochemical and connectivity grounds: it is high in calretinin, substance P, serotonin, and acetylcholinesterase and low in calbindin (Meredith et al., 1996). Importantly, the core of the nucleus accumbens, while relatively easy to distinguish from the shell, merges imperceptibly with the caudate and putamen. Thus, some investigators use the term “ventral striatum” to refer not only to the nucleus accumbens, but also to the territories of the caudate and putamen receiving inputs from reward-related structures, primarily those from the orbital and medial prefrontal cortices and the reward-related thalamus and midbrain (Haber and McFarland, 1999).

The central and associative striatum have a compartmental organization (Crittenden and Graybiel, 2011). The striosomes (also called patches) form islands in the larger framework of the striatal matrix. Striosomes stand out from the matrix as having high levels of substance P, mu-opioid receptors, and calretinin, and low levels of enkephalin, calbindin, and acetylcholinesterase, among others (Bolam and Izzo, 1988; Graybiel and Ragsdale, 1978). These compartments receive preferential input from different parts of the cerebral cortex, with striosomes receiving stronger input from limbic cerebral cortex and matrix receiving stronger input from sensorimotor areas. Output from striosomes vs matrix is also preferential: striosomes project to the dopamine-rich SNc, while the matrix does not. Shared projections to the pallidum often target different subpopulations of cells.

The hyperdirect pathway, from the frontal cortex to the subthalamic nucleus directly, is also topographically organized, with limbic and motivational regions such as the ventromedial prefrontal cortex projecting to the ventromedial STN, cognitive/associative regions such as the

dorsolateral prefrontal cortex projecting to the middle of the STN, and sensorimotor regions such as primary motor cortex projecting to the dorsolateral STN (Haynes and Haber, 2013).

The final link in the loops, the projection from the thalamus to the cortex, is surprisingly obscure. That is, we know a great deal about the thalamocortical projection in general; however, which thalamic neurons receive inputs from the GPi/SNr, and are thus capable of closing the cortico-basal ganglia loop, is unclear. This is an especially challenging problem to solve, because it requires careful, multisynaptic tract-tracing. Older views, focused on movement, were that the only portion of the loop that completely closed was the motor portion. In other words, it was thought that the basal ganglia directed its output only to the motor and premotor cortices (Kemp and Powell, 1971). Taking advantage of the transneuronal properties of the herpes simplex virus type 1 (HSV1) (Strick and Card, 1992), Strick and colleagues were able to identify some output channels in nonhuman primates. Injections into the primary motor cortex, the supplementary motor area, frontal eye fields, dorsolateral prefrontal cortex, and the ventral premotor area all resulted in (retrograde, transsynaptic) labeling in the GPi/SNr, demonstrating that these cortical areas are the targets of basal ganglia-thalamic output (Hoover and Strick, 1993; Lynch et al., 1994; Middleton and Strick, 1994). Additional studies showed basal ganglia outputs to the inferotemporal cortex (Middleton and Strick, 1996). Beyond this limited set of regions, at this point, which cortical regions do and do not receive basal ganglia output are unclear.

3.2. Neurotransmitters and neuromodulators in the basal ganglia

Cortico-striatal projections are glutamatergic and tonically inactive. Striatopallidal projections are GABAergic and tonically inactive. Thus, selective firing of the cortex activates striatal neurons, which in turn deactivate GPi/SNr neurons. Those GPi/SNr neurons are tonically active, so inhibiting them has the capacity to reduce their firing. GPi/SNr projection neurons are also GABAergic, so they inhibit the firing of thalamic cells. The net effect of cortical excitation of the direct pathway is thus to *disinhibit* the thalamus, which then has an excitatory effect on the cortex. By contrast, GPe neurons, which are also tonically active and GABAergic, inhibit STN neurons, which in turn excite the GPi/SNr. Thus, the net effect of the indirect pathway will be to inhibit the thalamus, and thus, the cortex.

Dopamine, originating primarily in the SNc and the VTA, is released onto striatal neurons expressing either D1 receptors or D2 receptors. D1 receptors are mostly excitatory, while D2 receptors are mostly inhibitory. D1-expressing striatal neurons project preferentially to the

GPi/SNr as part of the direct pathway, while D2-expressing striatal neurons project preferentially to the GPe as part of the indirect pathway. Thus, whether through exciting the direct pathway or inhibiting the indirect pathway, the net effect of dopamine is to excite the thalamus, and, ultimately, the cortex. This explains why dopaminergic cell loss in Parkinson's Disease is so devastating for movement: a reduction of dopamine will lead to underactivation of the direct pathways and overactivation of the indirect pathways, both of which will reduce neuronal activity in circuits that generate movements.

The main midbrain dopaminergic cell regions are the retrorubral area (RRA), SNc, and VTA. The SNc is divided into dorsal (pars dorsalis), main (densocellular, and ventral (cell columns) groups (Haber, 2014). Importantly for this discussion, the dorsal cells merge with those of the VTA and retrorubral area (RRA); moreover, they are all calbindin-positive. Thus, the VTA, RRA, and dorsal group are collectively referred to as dorsal tier dopaminergic cells. The calbindin-negative SNc main and ventral groups are referred to as ventral tier dopaminergic cells. The two tiers show a number of additional distinctions: the ventral tier is more susceptible to cell loss during the early stages of Parkinson's Disease (Damier et al., 1999), ventral tier dendrites extend into the SNr, and the two tiers show different gene expression (Monzón-Sandoval et al., 2020). They also have different projection patterns. Both the dorsal and ventral tier dopaminergic neurons project to the striatum, but they do so in a reverse topography: dorsal tier neurons project to the ventral striatum, while ventral tier neurons project to the dorsal striatum. The shell of the nucleus accumbens has a fairly restricted set of inputs from the VTA specifically (part of the dorsal tier). Dopaminergic projections to the cerebral cortex are mainly from the dorsal tier.

Serotonin also acts on much of the basal ganglia. The cell bodies producing serotonin are found within the raphe nuclei, which are spread throughout the medulla, pons, and midbrain. The latter two sets of groups are called the dorsal raphe nuclei, and they provide most of the serotonergic input to the forebrain. Serotonin neurons reach the basal ganglia via the medial forebrain bundle (Parent et al., 2011). Serotonin neurons innervate all basal ganglia nuclei, with the densest innervation of the substantia nigra. Serotonin labeling in the striatum is heterogeneous, potentially preferentially innervating matrix over striosomes.

3.3. Conclusion

Having covered in moderate detail the structures and pathways forming the cortico-basal ganglia loops, as well as the various frameworks and controversies associated with them, we

are now in a better position to understand the ways in which these circuits are (and are not) different across species.

4. The evolving basal ganglia

As we shall see below, the basal ganglia are fascinating in part because of how conserved they are during vertebrate evolution. The description above of the circuitry composing cortico-basal ganglia loops has been primarily constructed using data from mice, rats, macaques, and humans. Obviously, all of these are mammalian species, and they appear to share the core circuits of cortico-basal ganglia loops. This leaves open two major lines of inquiry. First, how far back in phylogenetic history do the basal ganglia reach, and is this different according to structures and connections? Second, are there quantitative, rather than qualitative, differences even among closely related species in basal ganglia structure and function?

4.1. Phylogeny of the basal ganglia

In the last two decades, we have come to realize that the basal ganglia architecture described above likely reaches back 550 million years, such that all modern-day vertebrates share this fundamental blueprint. How scientists came to this conclusion requires a close look at a funny-looking jawless fish, the lamprey. Early studies suggested that only some vertebrates had basal ganglia structures similar to those found in mammals. In particular, the seeming absence of a pallidum in lampreys was used as evidence of potential mammalian specificity (Murakami et al., 2005, 2001; Osorio et al., 2005). In addition, an indirect pathway had not been uncovered in non-mammalian, non-avian species. Indeed, the basal ganglia were thought to be fundamentally different in amniotes (such as mammals, birds, and reptiles) than nonamniotes (such as amphibians and fish) (Smeets et al., 2000).

Studies in the lamprey largely invalidated these views. We focus on the lamprey because it represents the earliest divergence from the rest of vertebrate evolution amongst extant species. Thus, features present in lamprey and in other studied vertebrate species (birds, mammals, etc.) were likely present at the onset of vertebrate evolution. Of course, there is always the possibility that the same circuit evolved independently in different lineages, as the lamprey has been evolving for just as long as the human. However, as Grillner and Robertson

(2016) point out, this is not simply a case of a single shared feature. As we will see, there are shared connections, channels, transcription factors, and so forth, reducing the likelihood that convergent evolution accounts for the similarities across vertebrates.

Electrophysiological and anatomical evidence have converged to show the presence of direct and indirect basal ganglia pathways in lampreys (Grillner and Robertson, 2016; Stephenson-Jones et al., 2011; Stephenson-Jones et al., 2012). For example, injections of retrograde tract-tracers into the putative lamprey pallidum result in labeled cells in the striatum, and injections of anterograde tract-tracers in the striatum result in terminal fields in the putative pallidum (Stephenson-Jones et al., 2011). The putative pallidal region also contains fibers positive for enkephalin and substance P, and these fiber populations are separable. Most of the neurons in this region are tonically active at rest, inhibitory, and project to brainstem motor structures. A subset of cells within the putative pallidum project to another region with features that match the STN. All of this evidence is consistent with the mammalian direct and indirect pathways; although GPi and GPe are intermingled in lamprey, their cell populations are divisible and match those of the mammal. The earlier studies suggesting the absence of a pallidal structure were likely performed too early in lamprey development to distinguish these cell types.

What of invertebrates? Can only vertebrates lay claim to the basal ganglia? In an important review, Strausfeld and Hirth (2013) presented evidence that different components of the arthropod central complex share foundational features with those of the vertebrate basal ganglia, including developmental origins and transcription factors. Arthropods are animals with segmented bodies and an exoskeleton. This phylum includes crustaceans and flies. They diverged from the phylogenetic lineage that includes humans roughly 600 million years ago. The central complex has three main components; the fan-shaped body, the ellipsoid body, and the protocerebral bridge. The arthropod fan-shaped body has a modular structure that mirrors that of the striatum; the arthropod ellipsoid body contains GABAergic neurons with widespread and reciprocal projections that seem to mirror those of the pallidum. Although likely not matched in all the connective, electrophysiological, and anatomical properties with those of the vertebrate basal ganglia, it seems clear that many of the basal ganglia's precursors were present in the last common ancestor of arthropods and vertebrates.

The striosome/matrix compartmental organization is also present across all mammalian species thus far analyzed (Hamasaki and Goto, 2019). Even the ratio of striosome to matrix volume (15:85) is the same across mammalian species (Johnston et al., 1990). Although non-mammalian vertebrates likely have similar cell classifications, they do not appear to be compartmentalized as they are in mammals.

4.2. What does this mean for basal ganglia function?

The extraordinary conservation of basal ganglia circuits over evolutionary history seems like it ought to give us clues to the function(s) these circuits serve. In other words, what is the purpose of such conserved structures and pathways? The basal ganglia have been implicated in functions as diverse as movement, learning, language, tool use, motivation, and planning. However, there have been attempts to unify these disparate functions under common basal ganglia theories.

A great deal of focus in this space has been on action selection (Park et al., 2020): that is, choosing one behavior or set of behaviors over others (Redgrave et al., 1999). This includes roles for both movement selection and refinement (Middleton and Strick, 2000). The direct and indirect pathways, in this conceptualization, are responsible for promoting and inhibiting the desired and undesired movements, respectively. At rest, the GPi and SNr are tonically active, blocking signals to the thalamus that would lead to movement. Activation of direct pathway neurons of the striatum by specific cortical projection populations would release this block on the desired movement, while activating indirect pathway neurons of the striatum would suppress unwanted movements. Indeed, converging lines of evidence suggest that the direct and indirect pathways activate simultaneously (Cui et al., 2013), supporting this view. The architecture of the basal ganglia may be particularly well-suited to the selection problem (Redgrave et al., 1999): competitors are positioned to influence motor output (thalamic projections are widespread to motor structures); basal ganglia inputs have the capacity to signal urgency; priority must be attained through interconnections; competing actions must be inhibited (achieved through tonic inhibition of motor plans until one is selected). However, much of the basal ganglia seem concerned not with movement per se, but with cognitive and motivational functions. How do these fit into an overarching theory of action selection?

One common viewpoint is that cortico-basal ganglia loops can arbitrate among behaviors at a relatively high level. In other words, it may be the responsibility of the cerebral cortex to instantiate the specific movements responsible for a behavioral plan, but the basal ganglia may choose the particular behavioral plan (O'Reilly and Frank, 2006). Thus, as the repertoire of behaviors expands, the cortex and its inputs to the basal ganglia would expand, but the function of the basal ganglia (arbitration) remains the same. This allows for motivational and cognitive behaviors to be selected by the basal ganglia, as well.

‘Behavior’ is a far-reaching term that somehow manages to encompass both buying a car and grasping a coffee cup, and everything in between. One hypothesis is that cortico-basal ganglia loops adjudicate amongst behaviors at a different, higher level than cortico-cortical circuits (Cisek, 2022). Specific actions may be grouped into a relatively small number of classes (such as feeding or defensive behavior). The basal ganglia would then arbitrate among these higher-level classes according to the state of the individual, while cortico-cortical projections would choose among specific actions or movements. One advantage of this hypothesis (which is elaborated upon in Cisek’s chapter in volume 2) is that it is concordant with the massive convergence of cortical input at the level of the striatum.

One illuminating area of research into basal ganglia function consistent with this view involves language. Comparative studies of the FOXP2 gene have revealed intriguing differences across brain areas and species. FOXP2, a transcription factor expressed during development in many cortical projection neurons and medium spiny neurons (among others) in many species, has been linked to language and speech. Humans with mutations in the FOXP2 gene have difficulties with the movements necessary to produce speech as well as with expressive and receptive language (Watkins et al., 2002). Similarly, a disruption in FOXP2 during development in songbirds impairs song learning (Haesler et al., 2007). In mice, which lack the complex vocalizations found in humans and songbirds, FOXP2 is associated with motor skill learning. Specifically, expressing the human version of FOXP2 in mice leads to dendritic changes and plasticity within cortico-basal ganglia circuits, specifically (Enard, 2011). Thus, motor skill learning in mice, language learning in humans, and song learning in birds can all be mediated via the same basal ganglia mechanism.

4.3. Nomenclature

One notable impediment to comparative progress is nomenclature across species. It is unreasonable to expect that, for example, a human researcher seeking to understand a result from rodent optogenetics will realize that the entopeduncular nucleus is the direct pathway homologue of the primate GPi. Infuriatingly, even the term ‘basal ganglia’ is a misnomer, as a ‘ganglion’ is a group of neurons in the *peripheral* nervous system, not the central nervous system (Sahin et al., 2020). These structures would be more appropriately referred to as ‘basal nuclei.’

An impressive effort to resolve these issues was demonstrated by the Avian Brain Nomenclature Forum (Anton Reiner et al., 2004; A Reiner et al., 2004). For much of the 20th

century, the bird telencephalon was thought to lack a neocortex, instead consisting of a neostriatum (equivalent to mammalian caudate/putamen), archistriatum (equivalent to amygdala), and hyperstriatum (thought to be specific to birds, this was considered to be an enlargement of the basal ganglia). Increasing knowledge of shared cell types and projections led to revisions to the understanding of homologies, including the apparent existence of a neocortex homologue in the previously named hyperstriatum. However, nomenclature was still severely mismatched in avian vs mammalian literatures. The Forum established consensus to rename existing avian structures to more closely align with known homologies, while still leaving open structures with ambiguous homologies. In so doing, the avian paleostriatum augmentatum and paraolfactory lobe were renamed the lateral and medial striatum, respectively. The paleostriatum primitivum was renamed the globus pallidus. The neostriatum and hyperstriatum were given the names nidopallium and mesopallium+hyperpallium, because their precise homologies with the mammalian neocortex are unknown.

5. A comparative analysis of the mammalian basal ganglia

Given the extraordinary degree of basal ganglia conservation across species, particularly across mammals, is there anything to be learned by examining species differences in these structures? We would argue that subtle differences in basal ganglia organization help to reveal clues about basal ganglia function across species. Unfortunately, in this regard, we are limited to the species that have been studied for any given question, which are most typically humans, nonhuman primates, rats, and mice. Thus, most of this section will focus on these species.

5.1. Mammalian cortico-striatal circuits

Importantly, available evidence suggests that limbic, associative, and sensorimotor cortico-basal ganglia loops are remarkably similar across primates and rodents (Voorn et al., 2004). Across species, cortical regions project to unique but overlapping territories, with projections from limbic regions occupying the ventromedial striatum, projections from associative regions occupying the central striatum, and projections from sensorimotor regions occupying the dorsolateral striatum. This ventromedial to dorsolateral gradient is also present in dopamine uptake rates (Calipari et al., 2012), in the topography of connectivity with midbrain

dopamine neurons, and in functions as they related to value-based decision-making (Burton et al., 2015) (Figure 3).

Despite this shared organization, we know that there are dramatic differences in the cerebral cortex across species. This means that cortical input to the basal ganglia is different across species, and requires some attention (Smeets et al., 2000).

Balsters and colleagues (Balsters et al., 2020) examined the relationship between the striatum and different cortical and subcortical regions through resting-state fMRI in mice, macaques, and humans. On the basis of anatomical connectivity, the mouse striatum was subdivided into three segments: the medial caudoputamen, the lateral caudoputamen, and the nucleus accumbens. On the basis of resting-state fMRI functional connectivity, the homologues of these regions were portions of the human posterior putamen (lateral caudoputamen) and nucleus accumbens (medial caudoputamen and mouse nucleus accumbens). However, 85% of human voxels did not correspond to any mouse voxels (by contrast, only 31% of human voxels were unassigned in the comparison with macaque). These unmatched voxels were located mainly in the human associative striatum and showed functional connectivity with the prefrontal cortex, particularly the dorsolateral prefrontal cortex, and associated structures. Thus, by virtue of its prefrontal afferents, much of the human striatum must be considered dissimilar to the mouse striatum, even if the foundational architecture of the striatum remains similar across species.

In another comparison between macaques and humans using structural connectivity, primary motor cortex and frontal eye fields showed greater overlap in their connectivity with the striatum in humans than macaques (Neggers et al., 2015). This was accompanied by a posterior shift in these cortico-striatal terminal fields. The authors posit that this could be due to the relative enlargement of the prefrontal cortex in the human, along with greater human simultaneous control of hand and eye movements (such as in tool use or gesturing). With increasing space in the striatum necessarily dedicated to the prefrontal cortex, motor projections may have shifted and converged.

Anatomical connectivity (tract-tracing) in rats and macaques reveals that broad ventromedial to dorsolateral projection patterns are preserved across species (Heilbronner et al., 2016). That is, ventral and medial frontal cortices in both rats and monkeys project to the ventromedial striatum, while dorsal and lateral frontal cortices in both rats and monkeys project to the dorsolateral striatum. Connectivity profiles reveal many similarities: in projections from the medial and lateral orbitofrontal cortices in both species, and from the ventromedial prefrontal cortex in both species. However, the projection from the rostral dorsal anterior cingulate cortex

is far more extensive in the macaque than in the rat, suggesting species divergence in this circuit.

Hamasaki and Goto (Hamasaki and Goto, 2019) asked about the volume of the striatum and the neocortex across 76 mammalian species (proportional to whole brain volume). The striatum's volume was relatively constant across species, scaling with total brain volume. However, the proportional volume of the neocortex *also* ranges dramatically across species, as do the relative sizes of different specific areas within the neocortex (Frahm et al., 1982). Hamasaki and Goto (2019) interpret their findings in the light of the potential integrative function of the cortico-striatal projection. Because the expanded neocortex projects to the relatively unexpanded striatum, the cortico-striatal projection may play a more integrative role in some species, like humans, than in others.

5.2. The anterior limb of the internal capsule

By far the greatest morphological difference in the basal ganglia across mammals is only tangentially related to the basal ganglia themselves: the internal capsule. This is a white matter bundle that bisects the caudate and the putamen/globus pallidus in primates. The axons of the internal capsule connect the cerebral cortex with the thalamus, brainstem, spinal cord, and subthalamic nucleus. It is divided into an anterior and a posterior limb, with a distinctive genu (knee / bend) at the transition point. In rodents, the anterior limb of the internal capsule–the portion carrying prefrontal fibers–is not present, so the caudate and putamen form a single nucleus: the caudoputamen. Note that these fibers (the ones connecting the prefrontal cortex with the thalamus, subthalamic nucleus, and brainstem) do of course exist in rodents, but they are not encapsulated within a discrete bundle. Instead, they are embedded within fascicles inside the caudoputamen (Coizet et al., 2017).

There is very little information in the literature as to when, phylogenetically, this change could have come about. The tree shrew, dog (*Canis lupus*), cat (*Felis catus*), opposum (*Monodelphis domestica*), sheep (*Ovis aries*) (Ella and Keller, 2015), bat (*Phyllostomus discolor*) (Radtke-Schuller et al., 2020), and at least 5 species of primates have a separate internal capsule (Datta et al., 2012; Mikula et al., 2007; Ni et al., 2018), while at least 3 species of rodents have fascicles embedded in the striatum. Critically, even though the rabbit brain shares many features with the rodent brain (lissencephalic, hippocampus situated dorsally), it does have a separate caudate and putamen (Carman et al., 1963). This is somewhat surprising, as rodents and lagomorphs only diverged ~62 million years ago. The brains of the armadillo and

echidna (*Tachyglossus aculeatus*), however, each contain a single caudoputamen (Cherupalli et al., 2017; FERRARI et al., 1998). Based on known mammalian phylogenomics, a clear pattern of evolutionary history of these two morphologies does not emerge (Murphy et al., 2021) (FIGURE 4).

5.3. A closer look at dopamine

A great deal of work, particularly in rodent models, has begun to tease apart the various functions of dopaminergic neurons in the VTA and SNc. Along with more advanced computational models and links to ever-more-complex behaviors has come an understanding that dopaminergic neurons occupying different territories within these structures may have different functions. Thus, it is increasingly important to understand the relationship between the topography of midbrain dopaminergic neurons in different species.

The three main dopaminergic cell groups of the basal ganglia (described above: SNc, VTA, RRA) are “remarkably homologous” across rodents and primates (McRitchie et al., 1996). However, there are differences in connectivity patterns. In rodents, dopaminergic projections to the cerebral cortex originate almost exclusively in the VTA, whereas, in primates, dopaminergic projections to the cerebral cortex can also be found in the RRA and medial SNc (Williams and Goldman-Rakic, 1998). One hypothesis is that dopaminergic projections to the lateral prefrontal cortex in primates were paralleled by a lateral expansion of the dopaminergic cells of origin (Gaspar et al., 1992). The dopaminergic projection to the cerebral cortex differs between rodents and primates in other ways as well. Essentially all of the primate cerebral cortex is innervated by dopaminergic fibers, although some portions denser than others, but there are swaths of rodent cortex without dopaminergic innervation (Berger et al., 1991). The laminar distribution is also both more regionally variable and more concentrated in layer I in primates than in rodents.

6. A comparative analysis of the primate basal ganglia

Humans’ closest ancestors were nonhuman primates. It thus stands to reason that we can learn a great deal about the evolution of the *human* basal ganglia specifically by looking at differences across extant primate species. As we have emphasized above for mammalian basal ganglia evolution, these differences are likely to be subtle. Still, even subtle differences could

give us hints about human brain evolution and the functions of different basal ganglia structures and circuits.

In an analysis of brain structure volume differences across humans, chimpanzees, bonobos, gorillas, orangutans, and gibbons and a variety of Old World- and New World monkeys, the human striatum was found to be significantly smaller than predicted based upon the anthropoid trend line, while most human limbic regions were larger (Barger et al., 2014). Similarly, in a direct comparison between humans and rhesus macaques, the human striatum is less enlarged than expected relative to overall brain size (Yin et al., 2009). These results are concordant with those discussed above for broader mammalian trends: the expansion of the human neocortex has outpaced the expansion of the striatum, which may lead to greater opportunity for integration.

In an analysis of tyrosine hydroxylase density in different basal ganglia nuclei across six primate species (human, chimpanzee, gorilla, macaque, baboon, capuchin), Raghanti and colleagues (2016) found that humans have higher density of dopaminergic innervation in the medial caudate than other primates, including great apes. They connect this finding with language and speech functionality in the region. Similarly, another study found that, relative to other primates, humans have higher levels of dopaminergic innervation in both the ventral striatum and the ventral pallidum (Hirter et al., 2021).

With regard to cholinergic systems, monkeys (capuchin, baboon, macaque) have more cholinergic interneurons with simple bipolar neuronal morphology in the basal ganglia, whereas hominoids have a greater preponderance of multipolar neurons (Stephenson et al., 2017). Multipolar cholinergic interneurons may be related to motor and cognitive functions, with bipolar neurons linked to autonomic and sensory functions. Because of the well-established link between striatal acetylcholine and learning, it seems plausible that these species distinctions may be related to the evolution of learning capabilities.

Humans also have denser neuropeptide Y innervation of the nucleus accumbens, but not of the neocortex or even the dorsal striatum (Raghanti et al., 2014). This amino acid seems to be at least partially responsible for hedonic eating (Rezitis et al., 2022).

Raghanti and colleagues (2018) have collected and synthesized these neurochemical results to suggest a particular trajectory of hominoid evolution. They posit that neurochemical evolution resulted in a human-specific profile in the striatum: high dopamine, serotonin, and neuropeptide Y along with low acetylcholine. They further show that an inchoate form of this profile is present in early hominids, but is quite different from what is seen in other primates. In doing so, they touch on fundamental questions of how the human brain came to be so unique,

and what is so unique about it. They argue that this neurochemical pattern leads to greater cognitive control over potentially volatile social emotions, reduced aggression, high drive toward external rewards, high social conformity, and greater information-gathering about the environment. The advantage of this theory is that, by positing that a confluence of neurochemical factors in the basal ganglia were necessary to form human social systems, seemingly subtle inter-species differences could potentially have substantial evolutionary impact.

7. Disorders of the human basal ganglia

Although one reason to perform comparative studies of the basal ganglia is to understand their evolution, another is to establish the suitability (or not) of nonhuman animal models of human disease. Indeed, the basal ganglia are a major source of pathophysiology across neurological and psychiatric disorders. Having reviewed in detail the evolution, structure, and function of the basal ganglia, we turn finally to dysfunction.

The two most prominent disorders of the basal ganglia are Parkinson's Disease and Huntington's Disease, which have opposite symptomatology. Parkinson's Disease, caused by degeneration of midbrain dopamine neurons, leads to loss of movement. Huntington's Disease, a genetic condition inherited in an autosomal dominant fashion, leads to degeneration of striatal neurons and ultimately excess movement.

However, as we learned above, the basal ganglia are not solely involved in movement. Dysfunction of the basal ganglia is strongly associated with emotional and cognitive deficits, as well. This can be easily observed in Parkinson's and Huntington's Disease: patients report significant cognitive and emotional problems that interfere with quality of life. Often, these symptoms are overlooked in favor of the more obvious movement problems associated with these disorders.

The neurotoxins 1-methyl-4-phenyl-1,2,3,6,-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) can mimic the effects of Parkinson's Disease by destroying dopaminergic neurons in nonhuman animal models. Exposed animals demonstrate both motor and cognitive/emotional deficits (Tadaiesky et al., 2008). Transgenic rodent models of Huntington's Disease carrying the mutant *HTT* gene also recapitulate key aspects of the disorder. However, failures in clinical trial translation from rodents to humans has emphasized the need for large animal models of this disease (Howland et al., 2020). Given the conserved

nature of basal ganglia structures and circuits, it is unclear whether what is needed is just larger brains or some (subtle) change in neuroanatomy across species.

Equally importantly, all psychiatric disorders seem to involve prominent basal ganglia disruption, although the details of the circuits affected and their aberrations depend upon the particular disorder and/or symptomatology. In many cases, these seem to rely on the limbic portions of the cortico-basal ganglia loops, and thus are centered on the ventral striatum and ventral pallidum rather than their dorsal, more movement-related counterparts. Furthermore, the disruptions are often tightly linked to projections from cortical regions involved in emotion and reward. For example, obsessive-compulsive disorder is characterized by enhanced functional connectivity between the orbitofrontal cortex and the ventral striatum (Abe et al., 2015).

From a comparative perspective, mental health disorders can be quite challenging to model in nonhuman animals. There have of course been many attempts to model various aspects of mental health conditions in nonhuman animals (Nestler and Hyman, 2010), but these have largely been seen as inadequate. With a shift in focus to modeling specific cognitive, emotional, circuit, and behavioral deficits, rather than the whole disorder (as in the US National Institute of Mental Health Research Domain Criteria, RDoC), it may be possible to gain clarity on how nonhuman animal models can be useful in understanding mental health.

8. Conclusion

The basal ganglia are remarkable for many reasons: their diversity of functions, their significance in psychiatric and neurological disorders, and, most importantly to us, their extraordinary conservation across vertebrates. As we have seen, conservation of structure certainly does not mean uniformity of structure. The cortico-basal ganglia loops encompass limbic, associative, and sensorimotor functions, and the compartmentalization of the striatum creates added complexity. Conservation of structure also does not necessarily mean conservation of function. With the expansion of the cerebral cortex, functions (like language processing) may likewise be added to the striatum. However, they may still exist under the information processing umbrella of action selection. Intriguingly, the additional integration within the basal ganglia that may be necessitated by cerebral cortical expansion may further alter the nature of basal ganglia function. Similarly, even subtle alterations in neurochemical profiles, when combined, may have been impactful in human evolution.

FIGURES

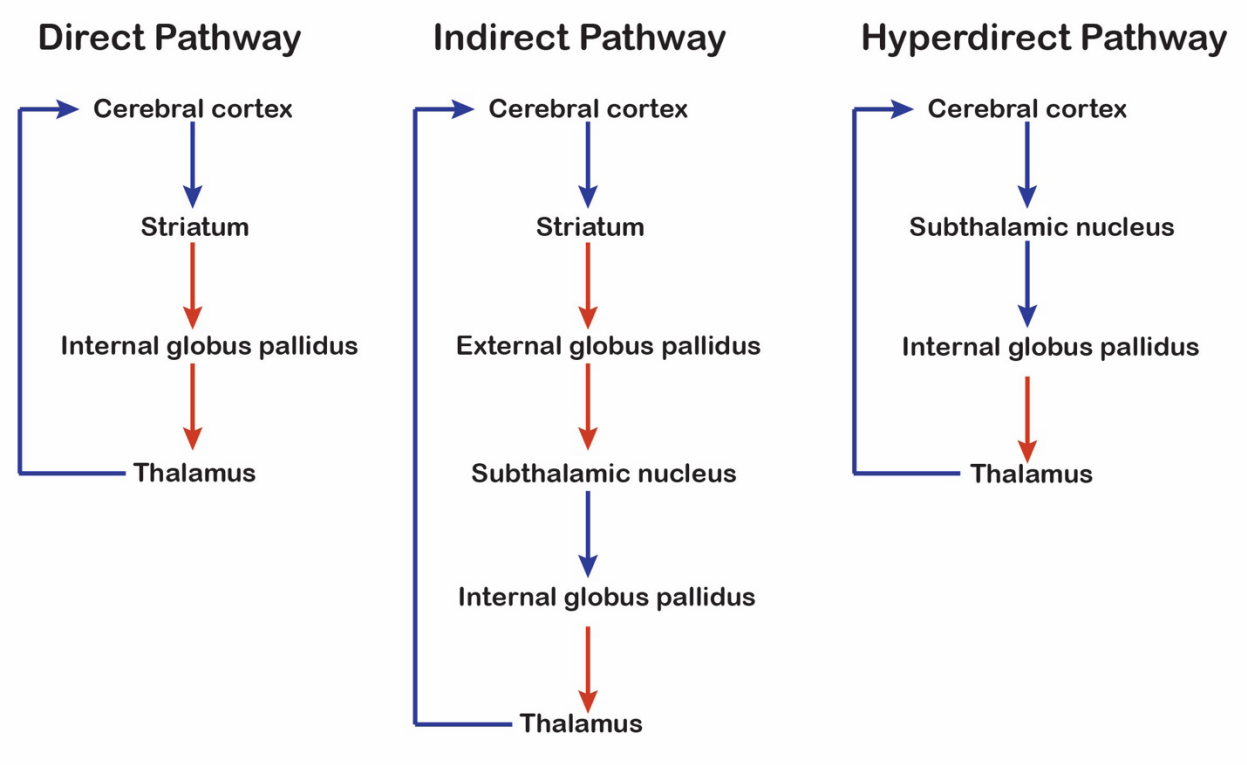

Figure 1: Cortico-basal ganglia pathways, simplified. Red arrows represent inhibitory connections; blue arrows represent excitatory connections.

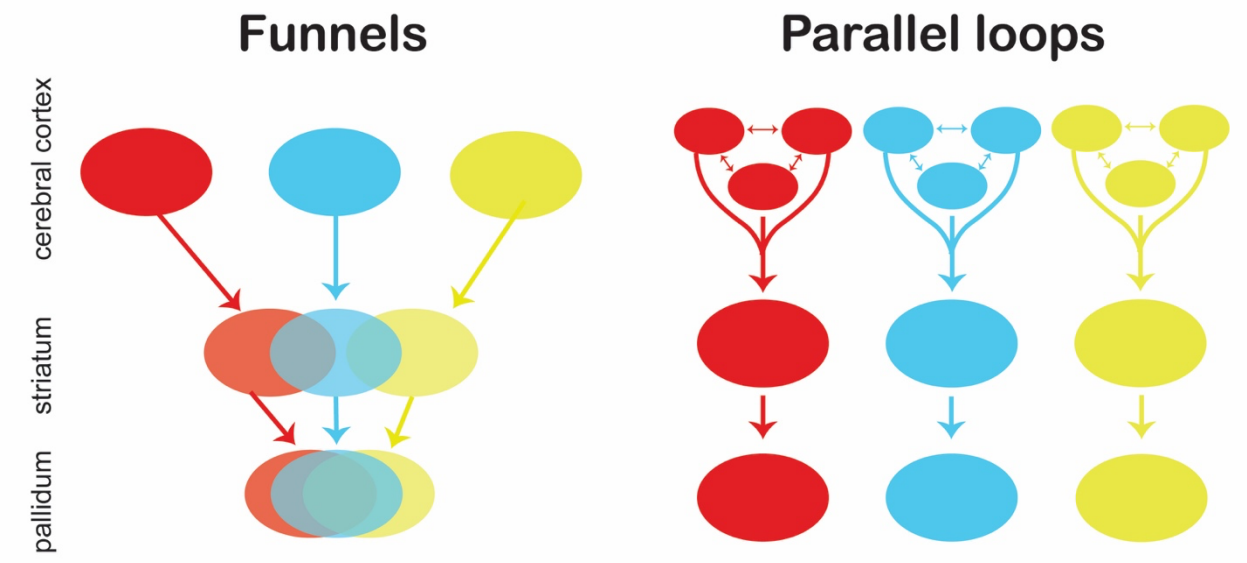

Figure 2: Graphical depictions of funneling vs parallel, segregated pathways in cortico-basal ganglia loops. Different ovals represent representations of different cortical regions. Ovals with the same color at right are functionally related but discrete regions.

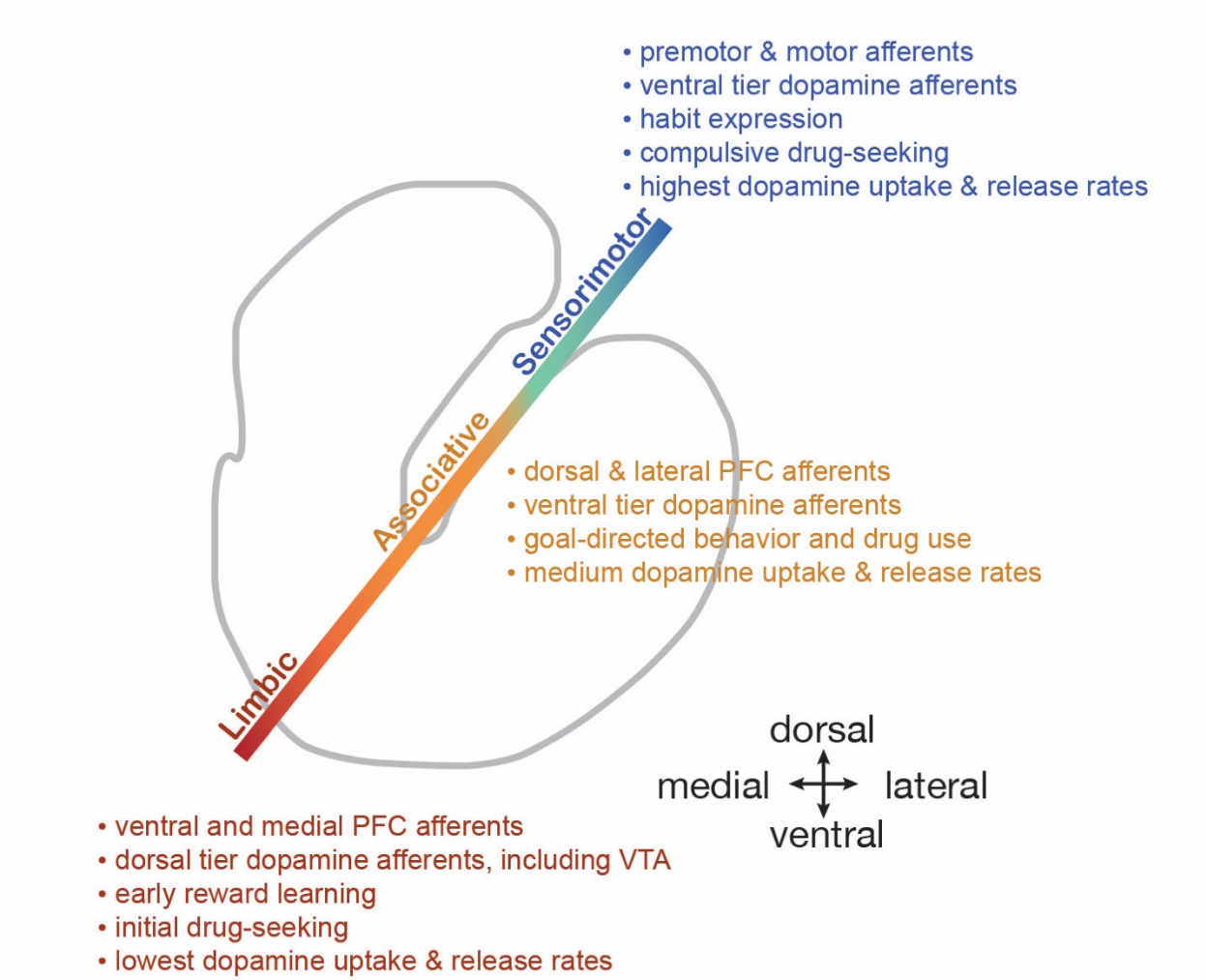

Figure 3: Ventromedial to dorsolateral gradients in the striatum. Striatal gradients can be found in frontal cortical and dopaminergic projections, dopamine release and uptake rates (Siciliano et al., 2014), functionality during reward-guided decision-making (Burton et al., 2015), and stages of addiction to drugs of abuse (Everitt and Robbins, 2013). There are additional structural and functional gradients omitted.

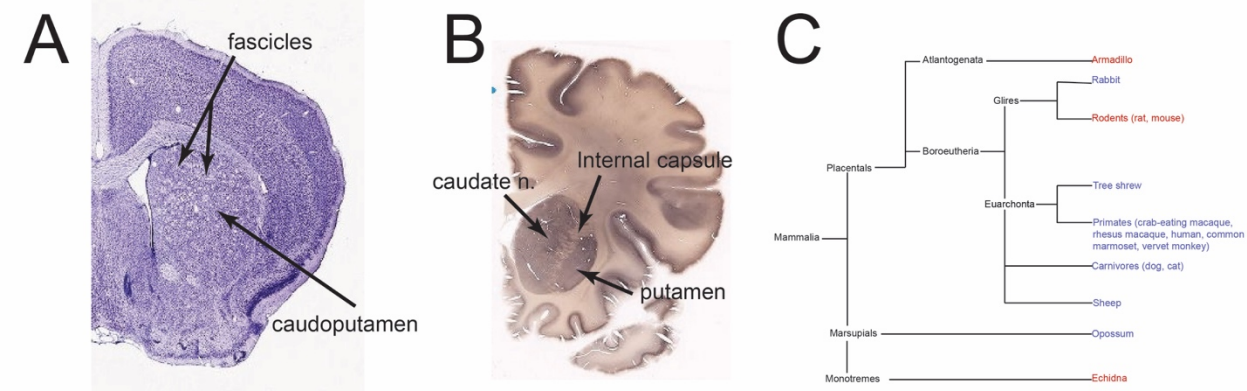

Figure 4: The anterior limb of the internal capsule is distributed through fascicles in the rodent brain (A), but it is encompassed within a discrete bundle dividing the caudate from the putamen/GP in the primate (human) brain. (B). An examination of this bundle's morphology across brains of different species does not reveal an obvious phylogenetic history (C). Red text indicates species with a fasciculated anterior limb of the internal capsule, blue text indicates a discrete bundle. For a more detailed phylogenetic tree of placental mammals, see Murray and Wise (this volume). Abbreviation: n., nucleus. Mouse brain image from Allen Mouse Brain Atlas (Dong, 2008) https://connectivity.brain-map.org/static/referencedata. Human brain image from BRAINSPAN: Atlas of the developing human brain https://www.brainspan.org/static/atlas

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