CHAPTER

The lamprey blueprint of the mammalian nervous system

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Brita Robertson, Andreas Kardamakis, Lorenza Capantini, Juan Pérez-Fernández, Shreyas M. Suryanarayana, Peter Wallén, Marcus Stephenson-Jones, Sten Grillner[1]

Department of Neuroscience, Karolinska Institutet, Solna, Sweden

[1]Corresponding author: Tel.: +46-8-52486900; Fax: +46-8-349544, e-mail address: sten..grillner@ki.se

Abstract

The basic features of the vertebrate nervous system are conserved throughout vertebrate phylogeny to a much higher degree than previously thought. In this mini-review, we show that not only the organization of the different motor programs underlying eye, orienting, locomotor, and respiratory movements are similarly organized, but also that the basic structure of the forebrain engaged in the control of movement is conserved. In the lamprey, which diverged already 560 million years ago from the vertebrate line of evolution leading up to primates, the basic components of the basal ganglia are similar to those of mammals in considerable detail. Moreover, the properties of the synaptic input are similar as well as transmitters/peptides in the direct and indirect pathway throughout the basal ganglia. The membrane properties of the striatal projection neurons with D1 and D2 receptors, respectively, are also similar, as are those of the pallidal output neurons. Our evidence suggests that the basal ganglia can be subdivided into functional modules controlling different motor programs, like locomotion and eye movements. What has happened during evolution is that the number of modules has increased in parallel with a progressively more complex behavioral repertoire. For value-based decisions, the circuitry through the lateral habenulae to the dopaminergic modulator neurons is also conserved, as well as the relay inhibitory interneurons involved. The habenular input is from a pallidal glutamatergic nucleus in lamprey as well as mammals, and this nucleus in turn receives input from the striosomal compartment within striatum and also from pallium (cortex in mammals).

Keywords

basal ganglia, striatum, dopamine receptors, selection, substantia nigra, optic tectum, habenula, reward, pallium

Progress in Brain Research, Volume 212, ISSN 0079-6123, http://dx.doi.org/10.1016/B978-0-444-63488-7.00016-1

The lamprey represents the first group of vertebrates to emerge, some 560 million years ago, at which point it diverged from the line of evolution leading up to primates including man (Kumar and Hedges, 1998). Recent findings have established that most aspects of both the forebrain and the brainstem–spinal cord are evolutionarily conserved (Ericsson et al., 2011, 2012, 2013; Grillner, 2003, 2006; Grillner et al., 2013; Jones et al., 2009; Stephenson-Jones et al., 2011, 2012a,b, 2013). In this mini-review, we provide the supporting evidence for this conclusion. We start with the motor infrastructure with networks coordinating different patterns of motor behavior at the brainstem–spinal cord level and then present detailed information at the forebrain level.

1 THE MOTOR INFRASTRUCTURE

1.1 THE BRAINSTEM–SPINAL CORD CONTROL OF LOCOMOTION

In all vertebrates, the networks coordinating locomotor movements are located in the spinal cord (Fig. 1). These networks contain sufficient information to coordinate the different muscles taking part in the locomotor cycle. Excitatory premotor interneurons play a critical role in generating the bursts of activity in different muscle groups, whereas the coordination between muscle groups depend on inhibitory or excitatory interaction between subgroups of interneurons. The excitatory V2a interneurons in rodents, amphibians (tadpole), zebrafish, and lamprey are central to the generation of burst activity (Eklöf-Ljunggren et al., 2012; Grillner, 2006; Hägglund et al., 2013; Roberts et al., 2012). In some species, the locomotor central pattern generator (CPG) is rhythmically active under resting conditions, even when the spinal cord has been transected, as in the dogfish (small shark) that spends its life swimming continuously (Grillner, 1974). The level of activity in the CPG is normally initiated from the locomotor command regions in the brainstem, e.g., the mesencephalic locomotor region (MLR) that, when activated, initiates locomotor activity in all groups of vertebrates. The higher the level of activity in MLR, the more excitation is mediated to the spinal CPGs and the faster the resulting locomotor activity. This is a convenient control system for higher centers, since they need not to worry about a detailed control and just need to generate a tonic signal that informs about the desired activity level, whereas all the detailed coordination is taken care of by the spinal networks themselves. The interface between MLR and the spinal cord is the reticulospinal projections that provide glutamatergic excitation of the CPG interneurons.

1.2 RESPIRATORY CONTROL

In mammals, a critical part of the control system is the pre-Bötzinger complex. Excitatory neurons in this nucleus interact to generate burst activity and this can take place even when all inhibition has been blocked. Moreover, these interneurons have crossed branches, which coordinate the pre-Bötzinger CPGs on both sides of the

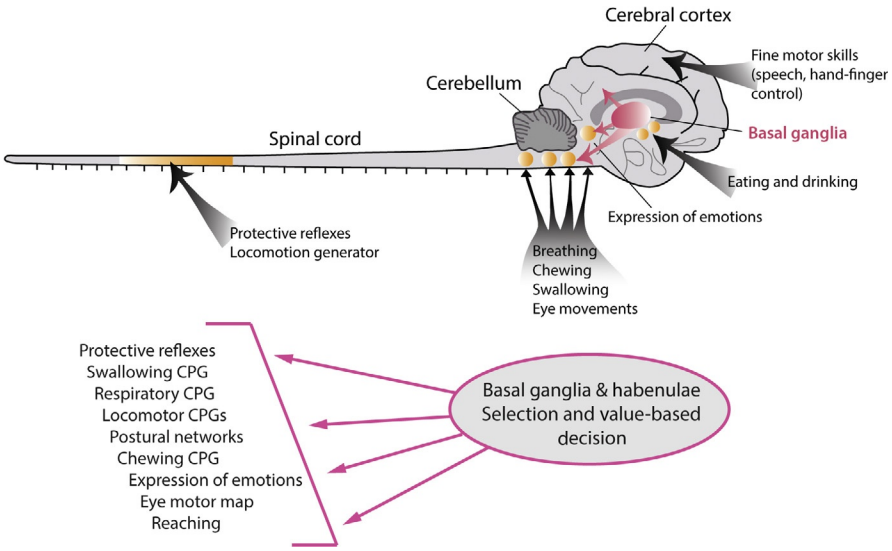

FIGURE 1

Common motor infrastructure from lamprey to man. Throughout the vertebrates, several basic motor behaviors are controlled by neuronal networks (CPGs) located in the brainstem (e.g., swallowing, breathing) and the spinal cord (e.g., locomotion). The basal ganglia are similarly organized in lamprey and primate and play a crucial role in the selection of motor behaviors. The addition of a well-developed cerebral cortex in primates provides a locus for networks controlling fine motor skills. In the lower part of the figure, there is a list of different motor programs from simple protective reflexes to the more complex motor maps for eye and orienting movements. One structure that determines when a given motor program should be active/selected is as indicated the basal ganglia. The habenula and its control of dopamine neurons are important for value-based decisions.

brainstem. When the pre-Bötzinger complex is incapacitated, the respiratory activity in rodents vanishes (see Feldman and del Negro, 2006). The final coordination of the different inspiratory and expiratory muscles is coordinated by downstream premotor interneurons, and in this process, inhibitory interaction is also important.

On the other evolutionary extreme, the lamprey, the respiratory activity is similarly controlled by a group of glutamatergic neurons in the paratrigeminal respiratory group (pTRG). A blockade of activity in pTRG terminates respiratory activity, whereas the burst activity can continue when inhibitory activity is blocked (Cinelli et al., 2013; Gariépy et al., 2012; Mutolo et al., 2011). The activity level in the pTRG is, however, also influenced by cholinergic, GABAergic, and peptidergic (substance P) input to this nucleus (Cinelli et al., 2013; Mutolo et al., 2011). These are the same modulators that are also playing an important role in the rodent pre-Bötzinger CPG. The basic organization of the core burst-generating mechanism thus appears to be very similar.

1.3 THE CONTROL OF EYE, ORIENTING, AND EVASIVE MOTOR BEHAVIOR IN THE OPTIC TECTUM/SUPERIOR COLLICULUS

The optic tectum, which is referred to as the superior colliculus in mammals, with its layered structure (Nieuwenhuys and Nicholson, 1998), gets a direct site-specific projection from the retina in all vertebrates. This retinotopic map is distributed over the surface of the tectum, and aligned with this sensory map, there is a motor map with tectal efferents that, when activated, will produce eye or orienting/evasive movements (Isa and Hall, 2009; Jones et al., 2009; Kardamakis et al., 2012, 2013; Saitoh et al., 2007). Stimulation at a given point in the motor map will produce an eye movement in a certain direction and of a specific amplitude that will move the eye to a given point of interest. Superimposed on this eye movement, there will be a subsequent orienting movement of the head in the same direction. Another part of the efferent output instead elicits evasive movements. During the locomotion, in any species, it will be critical to continuously avoid bumping into objects whether walking in the street or for a bird flying through the foliage of a tree. These evasive movements are thus a critical part of adaptive motor behavior.

The microcircuitry of tectum is also conserved throughout vertebrate phylogeny. In the superficial layer, the retinal afferents are located and they synapse directly or indirectly on the dendrites of the efferent output neurons, which are located in the deep layer of tectum. In addition, the retinal afferents activate GABAergic interneurons that disynaptically will inhibit the output level (Isa and Hall, 2009; Kardamakis et al., 2012). There is, in addition, a widespread inhibition of efferent neurons that are not targeted by the site-specific excitation (Kardamakis et al., 2013). Also in this case, from lamprey to mammals, there is a striking similarity between the organization of the optic tectum with its intrinsic circuitry and of the input and output levels.

1.4 GENERAL COMMENTS ON THE MOTOR INFRASTRUCTURE

The neural control of locomotion, respiration, and eye and orienting/evasive movements represent three well-studied examples of different types of motor programs, but there are in reality a whole range of standard motor patterns used for feeding, swallowing, control of body orientation (posture), grasping movements, and protective reflexes of different types (see Fig. 1). In most cases, the basic modes of operation of these circuits have been conserved, although of course adapted to the particular morphology of a given species.

2 THE FOREBRAIN CONTROL OF THE BRAINSTEM–SPINAL CORD MOTOR PROGRAMS

Having all these motor programs available for activation to produce a variety of patterns of behavior, it is clear that there is a need for a mechanism that determines which motor program(s) should be active at a given point of time. In this context, the basal ganglia in lamprey as well as in mammals play an important role. We have

recently shown that the organization of the basal ganglia and its different components are virtually identical in lamprey and mammals, a finding that was unexpected and very surprising (see Fig. 2; Stephenson-Jones et al., 2011, 2012b).

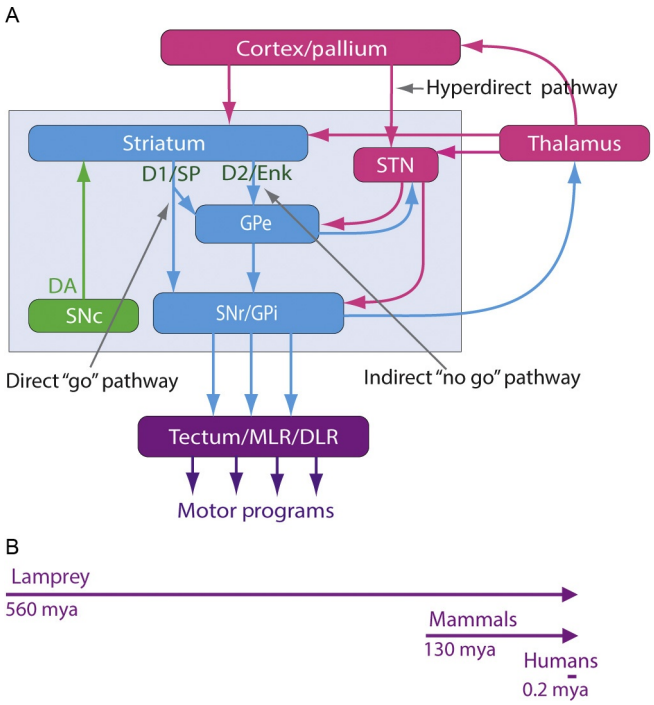

FIGURE 2

The organization of the basal ganglia is almost identical throughout vertebrate phylogeny—from lamprey to primates. (A) The striatum consists of GABAergic neurons (blue color; light gray in print version), as 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, and it projects via different subpopulations of neurons to tectum (superior colliculus), the mesencephalic (MLR), and diencephalic (DLR) locomotor command regions and other brainstem motor centers, and also back to thalamus and cortex (pallium in lower vertebrates). The indirect loop is represented by the GPe, the subthalamic nucleus (STN), and the output level (SNr/GPi). The striatal neurons of the direct pathway to SNr/GPi express D1R and substance P (D1/SP), while the indirect pathway neurons in striatum express D2R and enkephalin (D2/Enk). Excitatory glutamatergic neurons are represented by red color (dark gray in print version). Also indicated is the dopamine supply from the substantia nigra pars compacta (SNc; green; light gray in print version). (B) *The vertebrate lineage is represented*. The lamprey diverged from the main vertebrate line already 560 million years ago (mya), and mammals emerged only some 130 mya and humans some 0.2 mya. Yet the design of the basal ganglia is conserved from lamprey to primates.

The output level of the basal ganglia (globus pallidus interna, GPi, and substantia nigra pars reticulata, SNr) consists of GABAergic neurons that in both rodents and lamprey target different brainstem motor centers (Ménard et al., 2007; Robertson et al., 2006; Takakusaki, 2008). These GABAergic neurons are tonically active at a high rate during resting conditions and keep the different motor centers under tonic inhibition, whether for instance in tectum or the locomotor command centers (Hikosaka and Wurtz, 1983; Ménard and Grillner, 2008; Stephenson-Jones et al., 2011, 2012b; Takakusaki, 2008). When a given motor center is relieved from inhibition, this can be sufficient to release the specific motor center that has been disinhibited. It thus appears that the basal ganglia in this specific role govern through a global inhibition of the different motor centers. In addition, part of the efferent control from GPi/SNr is channeled via thalamus back to motor centers in cortex.

The input level of the basal ganglia, the striatum, receives input in approximately equal amounts directly from thalamus and from pallium (cortex in mammals; Doig et al., 2010), and the prominent dopaminergic input from the lamprey counterpart of substantia nigra pars compacta (SNc)/ventral tegmental area (VTA) (Pombal et al., 1997). In both mammals and lamprey (see Fig. 2), the efferents of striatum, the medium spiny neurons (MSNs), are of two types: one with dopamine D1 receptors (and substance P) that projects directly to the output level (SNr/GPi) and another that expresses D2 receptors (enkephalin) and instead projects via the internal basal ganglia nuclei (globus pallidus externa, GPe, and the subthalamic nucleus, STN) to the output level (Ericsson et al., 2013; Gerfen and Surmeier, 2011; Robertson et al., 2012; Stephenson-Jones et al., 2012b). An increased activity in the D1 direct pathway will lead to a suppression of the output at the GPi/SNr level, whereas an enhanced activity in the indirect D2 pathway will instead lead to an enhanced activity at the output level and thus a more intensive inhibitory output activity from GPi/SNr (Hernandez-Lopez et al., 1997; Surmeier et al., 2007). Both D1 and D2 MSNs are, in contrast to the spontaneously active GPi/SNr neurons, difficult to activate, since they express inward rectifier potassium channels (Kir) that remain open at a hyperpolarized level and are only closed when the cell receives sufficient excitation from thalamus and/or pallium (cortex) (Ericsson et al., 2011; Shen et al., 2007). The thalamic input is glutamatergic with depressing synapses, whereas the cortical input, also glutamatergic, instead is facilitating (Ding et al., 2008; Ericsson et al., 2012). Even at the detailed level with regard to connectivity, expression of particular types of ion channels, transmitter receptors or neuropeptides, the lamprey, and the mammalian basal ganglia are organized in a practically identical way. Thus, the basal ganglia with all its intricate details have been invented by evolution already 560 million years ago when the lamprey diverged from the evolutionary line leading up to mammals.

Our view of the basal ganglia in relation to the mechanism of selecting motor programs is that there are a set of functional modules in the basal ganglia that control each pattern of behavior, like locomotion, steering, eye movements, and feeding. Each of these modules contains the elements of both the direct and indirect pathways (see Fig. 3). The activation of the direct pathway (D1/substance P, MSNs) from either thalamus or cortex leads to a disinhibition of the pallidal output neurons that in

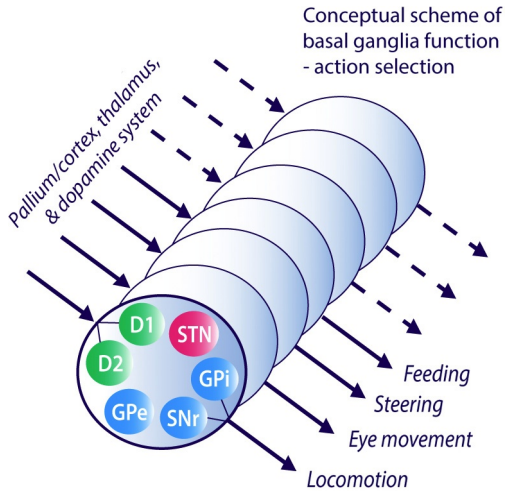

FIGURE 3

Conceptual scheme of a modular organization 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 (see Fig. 2A). 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 would have a limited behavioral repertoire, mammals and particularly primates have a very varied and versatile motor repertoire.

turn releases a given motor program. The responsiveness of the striatal neurons is determined by the level of tonic dopaminergic input to striatum; too little dopamine results in a hypokinetic syndrome, like Parkinson´s in both lamprey and mammals (Thompson et al., 2008), while too much results in hyperkinesia and nonintentional release of movements. One role of the indirect pathway (D2/enkephalin, MSNs) is to suppress competing movements, e.g., you cannot turn left and right at the same time (Cui et al., 2013; Kravitz et al., 2010).

The basic organization of these modules must have evolved to control the limited behavioral repertoire of cyclostomes early in vertebrate evolution, and this detailed organization has not changed significantly over the next 500 million years or more. What most likely has happened is that the number of modules has instead increased as the behavioral repertoire has expanded progressively during evolution to the ultimate level expressed in humans.

One aspect of the basal ganglia is thus the mechanism discussed above relating to action selection (Grillner et al., 2005; Redgrave and Gurney, 2006). It should not be forgotten that a major role also relates to motor learning. This contains two aspects: (1) the formation of new motor programs as when we learn to bike or acquire a new habit (Graybiel, 2008) and (2) the actual process of learning the new motor task and

the mechanism used to evaluate whether the performance is optimal or needs further elaboration. In the latter aspect, the dopamine system is assumed to play a role in promoting synaptic plasticity in the input synapses to striatum (Kreitzer and Malenka, 2005; Schultz, 2007).

2.1 THE CONTROL OF DOPAMINE NEURONS FROM THE LATERAL HABENULAE

The dopamine system plays a prominent role in the control of the basal ganglia, and another important aspect is how the activity of the dopaminergic neurons is controlled. One major feature is that there is an increased activity during reward situations (Schultz, 2007) and a decreased activity when an expected reward does not occur. There is a relation to aversive behavior also (Hikosaka, 2010). One critical control is from the lateral habenulae that provide excitation to a subgroup of dopamine neurons in mammals as well as to a GABAergic rostromedial tegmental nucleus (RMTg) that instead inhibits another subgroup of dopamine neurons (Lammel et al., 2012). In the lamprey, we know that there is a direct projection from the lateral habenulae to dopamine neurons in SNc and VTA, while there is also an indirect pathway via RMTg to dopamine neurons that can provide inhibition (see Fig. 4; Stephenson-Jones et al., 2012a). The neural substrate for a dual control is thus present also in lamprey, but it is not yet known if there are subpopulations of dopamine neurons with different functions.

Another critical part is the control of the habenular nuclei. In lamprey, there is a separate nucleus (the habenula-projecting globus pallidus, GPh; Fig. 4), which is glutamatergic and activates the habenula (Stephenson-Jones et al., 2013). The GPh neurons receive in turn inhibitory control from the striatum, but excitatory input from both thalamus and pallium. Moreover, the striatal control is from a separate compartment within striatum referred to as striosomes (Fig. 4). Mammals do not have a distinct GPh, but the neurons projecting to the lateral habenulae are located in one part of the entopeduncular nucleus in rodents and in primates in the periphery of the GPi (Hong and Hikosaka, 2008; Shabel et al., 2012). Whether the input to GPh from striatum is from the striosome compartment also in mammals has yet to be determined.

The control of dopamine neurons from the lateral habenulae and in turn from striatum and cortex can be regarded as an evaluation circuit that decides whether a given motor act has been successful and combined with reward, or if it instead has failed. Figure 4 shows in lamprey what can be regarded as two separate circuits: one involved in the selection of different motor programs that originates from the matrix compartments and another that is involved in evaluation or value-based decisions. It is clear that all species need to have a mechanism that determines if an action has been rewarding or not. This applies to a variety of actions whether selecting food or considering more esoteric aspects of life.

The circuitry from the medial habenulae to the interpeduncular nucleus and the periaqueductal gray that mediates fear/flight responses is also conserved. The circuitry has been identified in lamprey, zebrafish, and mammals (Agetsuma et al., 2010; Herkenham and Nauta, 1979; Stephenson-Jones et al., 2012a).

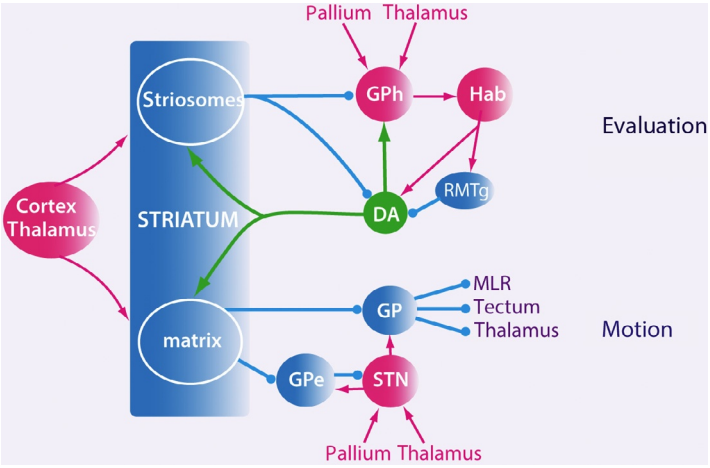

FIGURE 4

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 (GP, includes also SNr) and the brainstem motor programs. In addition, it shows the indirect pathway with GPe (globus pallidus externa) and the subthalamic nucleus (STN). The color code is blue (dark gray in print version) for GABAergic, red (gray in print version) for glutamatergic, and green (gray in print version) for dopaminergic neurons (DA). The evaluation circuit in the upper part of the diagram contains the lateral habenulae (Hab) with its projection to dopamine neurons directly and indirectly via the GABAergic RMTg. The lateral habenulae 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.

2.2 PALLIUM AND THE LAYERED NEOCORTEX

In mammals, the neocortex (mammalian pallium) has distinct layers, which define for instance where the output neurons to the striatum and the spinal cord are located and where the different types of input from thalamus terminate. The pallium in lower vertebrates and birds does not, however, have the layered structure of the mammalian cortex (Nieuwenhuys and Nicholson, 1998). Nevertheless, there appears to be a similar organization of the input to pallium from different parts of thalamus. The output from pallium targets the striatum, STN, and brainstem including tectum in lamprey (Ocana et al., 2012) as well as in mammals. Moreover, stimulation of one area in pallium can trigger orienting, eye, locomotor, and mouth movements in lamprey, and similarly in higher vertebrates. It is noteworthy that mammals like cats, rodents, and rabbits without a neocortex (surgically removed), but with all other parts of the forebrain intact, can survive for years. They have a complex behavioral repertoire and can display goal-directed movements (Bjursten et al., 1976). They move around in a normal way and perform exploratory movements and can find their way out of a maze. When they need food, they identify the location of the food and move to this

place and start eating. In a T-maze, they can learn where the food is located, which means that there is a certain element of memory, even though neocortex is removed. They have, however, difficulties in interpreting the surrounding world, and if kept in a colony of intact cats, they are unable to evaluate who is friend or foe. They usually respond by attacking, and will do so successfully, which of course requires a very well adapted motor repertoire. These actions must be under the control of striatum and primarily its thalamic input. The experiments show that as long as the basal ganglia are preserved, goal directed, and adaptable, behavior can be produced by the nervous system.

The layered cortex is often thought to be critical for higher cognitive functions that have evolved in mammals and particularly in primates. One caveat, however, is the fact that the most advanced group of birds (ravens, crows, and jays) are reported to make tools to catch food (also an ability of chimpanzees) and have the ability to plan and a very good memory for faces and locations of food (Raby et al., 2007). They thus have a capacity for complex aspects of behavior mostly attributed primarily to monkeys and in some respects even apes. Although they do not have a layered cortex, their pallium is well developed.

3 CONCLUSION

The general structure of the nervous system from the basal ganglia and habenula in the forebrain to the motor networks in the brainstem–spinal cord had already been developed at the onset of vertebrate evolution and has been maintained throughout vertebrate phylogeny.

ACKNOWLEDGMENTS

Swedish Research Council, Grant Number: VR-M-K2013-62X-03026, VR-NT 621-2007-6049, European Union FP7 “Select-and-Act” 201716, Cortex Training Programs and Moving Beyond ITN-NO-316639, Human Brain Project, and the Karolinska Institutet’s Research Funds.

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