Evolution of the vertebrate motor system — from forebrain to spinal cord
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Abstract
A comparison of the vertebrate motor systems of the oldest group of now living vertebrates (lamprey) with that of mammals shows that there are striking similarities not only in the basic organization but also with regard to synaptic properties, transmitters and neuronal properties. The lamprey dorsal pallium (cortex) has a motor, a visual and a somatosensory area, and the basal ganglia, including the dopamine system, are organized in a virtually identical way in the lamprey and rodents. This also applies to the midbrain, brainstem and spinal cord. However, during evolution additional capabilities such as systems for the control of foreleg/arms, hands and fingers have evolved. The findings suggest that when the evolutionary lineages of mammals and lamprey became separate around 500 million years ago, the blueprint of the vertebrate motor system had already evolved.

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Introduction
My focus here will be on the evolution of the vertebrate motor system and the changes that occur within the vertebrate phylum. The precursors are the protostomes, such as Ciona intestinalis, that in its larval stage swims with lateral undulations and has a branched spinal cord with a limited number of neurons (80–100) [1], and the cephalochordates (Amphioxus) have a well-developed spinal cord and a brain vesicle but not an actual brain [2–4]. The latter swim with lateral undulations in spirals and does not stabilize the dorsal side up orientation in contrast to vertebrates. These two species differ very significant from cyclostomes (lamprey), which represents the oldest group of extant vertebrates. The lamprey has a fully developed CNS, which includes a small forebrain, with all its components, as well as midbrain, brainstem and spinal cord [5–7]. The cerebellum is, however, vestigial in lampreys. All other groups of vertebrates have a cerebellum, as well as all other parts of the brain, and in addition of course a variety of specializations.

The midbrain—brainstem—spinal cord in all vertebrates contains the different neuronal networks that are used for the execution and coordination of standard movements, such as locomotion, postural adjustments, eye and orienting movements and oral motor programs. These parts of the nervous system are thus specialized for the execution of movement, and the different motor programs can actually be performed without the involvement of the forebrain. However, to recruit motor programs in the context of being adapted to the demands of the surrounding world, the involvement of the forebrain is required. It is responsible for interpreting the surrounding world and determining which action to take, that is, which motor program should be called into action. Selection of behaviour, motor learning and cognitive processing are tasks for the forebrain to solve. In this review, I will first discuss the forebrain, and then the networks responsible for the execution of movements in an evolutionary perspective, and mainly compare two extremes, the lamprey representing the oldest group and the newcomers, the mammals.

The forebrain — an evolutionary perspective
What is common between circuits in the forebrain of the lamprey and mammals, after a detailed comparison, indicates that they had evolved when the lamprey lineage separated from that leading to tetrapods, including mammals. Until recently, the lamprey pallium (cortex) was considered mainly olfactory, but it has now turned out that it actually has the main parts present in mammals, sensory and motor parts of the cortex (pallium). In addition, the basal ganglia, dopamine system and habenula are similar between the lamprey and mammals.
Pallium/cortex
In the lamprey, the dorsal pallium, the area which later will become the neocortex, comprises three main areas. The first processes visual information from different parts of the retina and is arranged in a retinotopic fashion (as in the mammalian V1). In reptiles, there is a visual representation in the dorsal cortex and the related telencephalic dorsal ventricular ridge, but only the latter is retinotopic [8,9]. The second corresponds to a somatosensory representation and finally a separate motor area [7,10,11] (Figure 1g). Stimulation of the latter area elicits eye and orienting movements, oral movements or locomotion (Figure 1a–e). This motor area contains neurons that project to different motor centres, such as the midbrain (tectum/superior colliculus), tegmentum, reticulospinal neurons and rostral spinal cord, and in addition, there are projections to the striatum and thalamus (Figure 1f). This corresponds to the efferent projection pattern of mammalian pyramidal tract projections in the motor areas, such as M1. There are also

Figure 1

The lamprey motor pallium. (a) Dorsal schematic view of the lamprey brain showing the distribution of electrical stimulation sites, which evoked different motor responses. (b), (c), (d), (e) Heat maps representing the threshold current needed to evoke different motor behaviours. Note that the excitability decreases from the caudal to the rostral pallial pole. (f) Schematic of a transverse section of the lamprey pallium indicating the efferent targets of pallial projection neurons (PT-type). (g) Summarizing schematic of the lamprey dorsal pallium, showing the retinotopic visual area, somatosensory and motor areas. (h) Transverse section of lamprey forebrain with the dorsal pallium and the visual, somatosensory and motor areas (beige), and in mauve the piriform olfactory area in the ventral part of the pallium.
olfactory projections to a primordial piriform cortex in the ventral part of pallium [12] (Figure 1h) as in mammals.

The lamprey cortex/pallium is three-layered with a molecular layer, containing few neurons, an inner and outer cellular layer with altogether 22% GABA interneurons and the remainder being glutamatergic cells. The latter include thalamorecipient cells, the pyramidal tract projections-type neurons mentioned previously, and neurons that project to the contralateral pallium and the striatum, intratelencephalic neurons. Single-cell RNA-seq has not yet been performed on the lamprey forebrain, but it can be noted that in the dorsal cortex of the turtle, the GABA interneurons appear to be conserved when compared with the mouse [13,14]. The situation is less clear with the glutamatergic neurons, and in mice, there is a large variety [15]. There are thus visual, somatosensory and motor areas present in the lamprey that represent essential building blocks of the mammalian neocortex, as well as the basic cellular types of the cortical circuitry. The number of neurons in the neocortex has increased dramatically during evolution from lamprey to mouse and man. This will, of course, allow, for a more elaborate processing and interpretation of the surrounding world, but the essential ‘Bauplan’ was developed already very early in vertebrate evolution.

**Basal ganglia and the dopamine system**

The lamprey basal ganglia are organized in a very similar way to that of mammals (Figure 2a and b) with regard to cell types, transmitters, neuropeptides and connectivity [6,16]. It contains all parts of what is usually called the direct pathway involving the striatal projection neurons expressing D1-receptors that project to the spontaneously active basal ganglia output neurons in the substantia nigra, *pars reticulata* (SNr) (Figure 2a). This pathway promotes movement initiation because it

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**Figure 2**

The lamprey basal ganglia. (a), (b) Detailed similarity between the different characteristic elements of the basal ganglia in the lamprey and mammals. (c) Shows the connectivity of the substantia nigra, *pars compacta* (SNC), and it applies to both rodents and lamprey. Note, the SNC targets in the basal ganglia and the downstream motor centres and the common input from the tectum, lateral habenula (LHb), pedunculopontine nucleus (PPN) and cortex/pallium. (d) Describes the connectivity from the striatum to the medial habenula, the interpeduncular nucleus (IPN) and periaqueductal grey. Striosomes control dopamine neurons in the SNC directly, and also via a separate route to the habenula-projecting part of globus pallidus (GPh) and further to the lateral habenula and dopamine neurons mainly via inhibitory interneurons.
inhibits the inhibitory SNr neurons, which project to different brainstem motor centres eliciting, for example, locomotion or saccadic eye movements. The basal ganglia also have all components of the indirect pathway with striatal projection neurons expressing D2 receptors, the net effect of which is to enhance the inhibitory output from the SNr and hence terminate ongoing motor actions. With regard to the striatal interneurons, cholinergic and fast-spiking interneurons have been identified in the lamprey [17,18] but whether some of the newly identified mammalian interneurons [19,20] are present is still unknown. The mammalian arypepallidal ‘stop-cells’ [21–23] have not been identified in the lamprey. Evidence is accumulating that the striatum is subdivided into a number of discrete modules connected to specific compartments of SNr that, in turn, control individual motor programs (e.g. a type of eye movement). During vertebrate evolution, the number of such modules has increased with a gradually more varied movement repertoire [6], but the basic design of each module has remained virtually the same.

With regard to the dopamine system, the lamprey substantia nigra, pars compacta (SNc), has virtually the same input and output structures as in rodents and the same type of dopamine receptors (Figure 2c) [24–26]. The diagram in Figure 2c actually applies to both rodents and lamprey. Dopamine denervation gives similar hypokinetiic symptoms in both groups [27]. The SNc neurons are activated by salient visual (or other senses) stimuli. These effects are conveyed via the tectum/superior colliculus in both the lamprey and rodents [24,28]. In rodents, practically every episode of locomotion is preceded by a burst of dopamine activity [29,30], which then facilitates direct pathway neurons in the striatum. Dopamine can trigger activity in the striatal modules that already have elevated excitability because of input from the cortex/thalamus and lead to action.

A critical element in motor learning is that each attempt to perform a movement should be evaluated, as to whether it is better or worse than the preceding attempt. This serves as the basis for reinforcement learning. The striatum has a ‘matrix’ compartment that is concerned with movement control, while around 20% is referred to as the striosomal compartment with input primarily from the limbic system [31,32]. The striosomes contain GABAergic projection neurons that directly inhibit the dopamine neurons in SNc (Figure 2d) [31]. Strisomes also acts on the dopamine neurons through another pathway via an excitatory relay (GPh; see Figure 2d) that, in turn, controls the level of activity in the lateral habenula that mainly activates an inhibitory relay [33] that inhibits dopamine neurons. This entire circuit for evaluation, first demonstrated in the lamprey [34,35], is now established in the mouse [36,37]. The striosomal projections via the habenula and directly to the dopamine neurons will thus determine whether an action will lead to an enhanced ‘reward’ dopamine burst or a pause as a negative sign. The phasic changes in dopamine activity will determine if an action will be promoted as reinforcement learning or conversely will receive less support through a reduced dopamine activity. In both the lamprey and rodents, the striosome compartment of the striatum is involved both directly and through the GPh and habenula in the evaluation of an action — a critical factor in motor learning.

The execution of movement — evolutionary perspective

The transition from swimming to tetrapod walking

One basic behaviour is locomotion. Cyclostomes swim like an eel with undulatory movements coordinated by the spinal cord itself. They have no appendages, and therefore have to rely fully on movements of the trunk for forwards or backward swimming or navigation. There is only a medial motor column present in the spinal cord that activates the different segments in the appropriate sequence (Figure 3). As the pectoral and anal fins develop later in evolution in elasmobranchs (sharks and rays), a lateral motor column emerged 420 million years ago to control the appendages that later became the
tetrapod limb [38]. In fact, the pelvic fins can produce alternating movements that can move the ray forward if it rests on the bottom of the sea. Already at this stage, the spinal cord has developed the characteristic combination of transcription factors for motoneurons and the subtypes of interneurons that is present in mammals [38–40].

Animals that swim with lateral undulations, such as the lamprey, most fish and salamanders, generate alternation at the segmental level. Essentially, there are on each side of the spinal cord, a group of excitatory neurons that drive the motoneurons on the same side, and then inhibitory commissural neurons that ensure left—right alternating activity as found in both the lamprey and frog larval tadpole [41]. This type of coordination has been detailed in the adult zebrafish [42–44] in which the slow, intermediate and fast motoneurons receive input from three different subtypes of excitatory interneurons of the V2a subtype (central pattern generator network, CPG). In slow locomotion, the slow subgroup of interneurons that mutually excite each other, drives the locomotor activity. With more excitatory supraspinal drive, the intermediate group of interneurons is recruited, and they also receive input from the slow subtype of interneurons. A combination of the membrane properties of the interneurons and motoneurons and their connectivity determine the rhythmic burst generation. In addition, a novel sensory receptor [45] located at the edge of the spinal cord and connected to the wall of the vertebrate canal sense lateral movements in each swim-cycle. It is integrated into the segmental CPG. The segmental network can, through experiments in the zebrafish, be regarded as understood at a detailed level.

The next stage of the evolution of tetrapod locomotion is the condition in which the limbs not only propel the animal but also support the body against the action of gravity. In this case, the CPG needs to provide four different phases of the movement (support, lift up, flexion phase and then touch down). The transition between a swimming CPG with simple left—right alternation and the more complex situation that adds alternation between flexors and extensors on the same side, as during walking, has been studied in the frog tadpole. It initially swims with left—right alternation before developing limb buds for walking. In a transition phase, the pure swimming pattern occurs together with brief bouts of flexor—extensor alternation [46,47]. The walking and swimming patterns thus coexist. These data can be taken to indicate that the swimming CPG is further subdivided, at this stage, into two circuits at this stage that produces ipsilateral flexor—extensor alternation. As shown by Jung et al. [38], the molecular machinery for developing both motoneurons and interneurons for ipsilateral alternation, as in the limb CPG, is available already in elasmobranchs.

The cellular composition of the mouse limb CPG has been examined over the last decade but is not yet fully understood. One subgroup of electrically coupled interneurons expressing Shox2 is thought to play an important role in burst generation [48]. In addition, HB9 and V2a interneurons and the inhibitory V2b and V1 interneurons may play a role in this context [49–52].

Coordination between the left and the right limb can take the form of alternation as in walk and trot or be active largely in phase as in a gallop. Commisural interneurons are responsible for this coordination, and deletion of one subtype, V0d interneurons, leads to a loss of walking. The deletion of V0v leads instead to loss of trot, and finally, when both are deleted, alternation is lost altogether, and the mouse can only gallop [53]. The three different types of locomotion are thus served by three different patterns of commissural interneuron activity. Propriospinal neurons also play a major role [54] in the coordination between fore- and hindlimbs.

The transition from whole-body locomotor commands to the fine forelimb control
Locomotion can be initiated from an area referred to as the mesencephalic locomotor region (MLR) in all vertebrates investigated, thus an evolutionarily conserved area [41,55–57]. In the lamprey, cholinergic and glutamatergic neurons drive the reticulospinal neurons, which in turn activate the spinal CPGs [56,57]. In mammals, the identity of the subtypes of neurons affected by the MLR stimulation was for a long time unclear. However, with a combination of virus technology and optogenetics, it could be shown that the cuneiform pathway activated a small area, the lateral paragigantocellular nucleus, that in turn activates the CPGs in the spinal cord [58–61]. Neurons in the pedunculopontine nucleus also contribute but to a lesser degree [58].

In addition to supporting the body during locomotion and standing, the forelimbs contribute to steering and eventually to grasping and securing external objects. Mammals such as rodents, cats and primates can grasp objects with their paw/hand and even perform fine manipulations, such as pealing the hull off a piece of seed [62,63]. In rodents, it has now been possible to identify a subpopulation of neurons in the lateral rostral medulla concerned with reaching out for an object, grasping or handling a small object like a seed. These commands are only concerned with one limb [63,64]. In primates, the corticospinal system allows for the control of individual finger movements and allow us to master playing the piano [65]. Thus, in contrast to the MLR/lateral paragigantocellular nucleus inducing whole-body movements, these areas in the rostral medulla are concerned with specific parts of an integrated movement and represent a type of control not available in phylogenetically older groups of vertebrates.
Eye and orienting movements towards points in the surrounding space

The superior colliculus/tectum in the midbrain is a structure that has evolved to generate eye or orienting movements of the head towards a salient stimulus in the surrounding space. Vision, but also other senses, convey information that is represented as a map of the surrounding space located in the superficial layers of the superior colliculus/tectum. Stimuli from a given point in space elicit neuronal activity in one location of the map. Aligned with this spatial map, in the deeper layers of tectum/superior colliculus lies a motor map from which eye movements to the same point of the surrounding space can be elicited [66,67]. The neurons in the motor map also elicit orienting movements of the head and body. A separate set of neurons generates movement in the opposite direction helps to avoid collision with an object, an important function, for instance, during navigation in a complex terrain [68–72]. The superior colliculus/tectum neurons in the motor map also receive inhibitory input from the basal ganglia that can prevent, for instance, saccadic eye movements. Conversely, excitatory input from the cortex can facilitate eye movements to a given point in space (e.g. from the frontal eye field).

The superior colliculus/tectum is well-developed in the lamprey, as is the input from the basal ganglia and cortex/pallium [68–73], an arrangement present in all vertebrates [67]. It is likely that there is a more refined sensory processing in the superficial layer with input from different classes of retinal ganglion cells in zebrafish and mammals [74]. The superior colliculus/tectum thus provides another example of an essential part of the motor system that emerged early in vertebrate evolution and has retained its basic features.

Concluding remarks

The last few years have shown that all essential building blocks of the forebrain, including the ‘cortex’, the basal ganglia and the dopamine system are present in the lamprey, an animal that belongs to the oldest group of now living vertebrates. This also applies to the midbrain and brainstem–spinal cord. The similarities are not limited to the overall organization but include the detailed design with synaptic properties, transmitters, neuropeptides and expression of ion channels (see Figure 2b). The inference is that these structures had already evolved when the lamprey lineage separated from that leading to mammals, some 500 million years ago. During evolution, new functions have been added with the development of limbs and separate control of the forelimbs allowing independent hand and finger movements, language and cognitive functions, but the essential ‘Bauplan’ of the vertebrate nervous system evolved very early in vertebrate evolution. Given the remarkable and detailed similarities between the lamprey brain and that of mammals, convergent evolution cannot possibly account for these findings. Contrary to our initial belief the basic design of the vertebrate brain dates back to the dawn of vertebrate evolution.

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Conflict of interest statement

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References

1. Zega G, Thordyke MC, Brown ER: Development of swimming behaviour in the larva of the ascidian Ciona intestinalis. J Exp Biol 2006, 209:3405–3412.
2. Arendt D: Elementary nervous systems. Philos Trans R Soc Lond B Biol Sci 2021, 376:20200347.
3. Horie R, Hazbun A, Chen K, Cao C, Levine M, Horie T: Shared evolutionary origin of vertebrate neural crest and cranial placodes. Nature 2018, 560:228–232.
4. Lacalli T: Amphioxus, motion detection, and the evolutionary origin of the vertebrate retinotectal map. Evodevo 2018, 9:6.
5. Grillner S: Biological pattern generation: the cellular and computational logic of networks in motion. Neuron 2006, 52:751–766.
6. Grillner S, Robertson B: The basal ganglia over 500 million years. Curr Biol 2016, 26:R1086–R1100.
7. Suryanarayana SM, Pérez-Fernández J, Robertson B, Grillner S: The evolutionary origin of visual and somatosensory representation in the vertebrate pallium. Nat Ecol Evol 2020, 4:639–651.
8. Fournier J, Muller CM, Schneider I, Laurent G: Spatial information in a non-retinotopic visual cortex. Neuron 2018, 97:164–180. e167.
9. Manger PR, Slutsy DA, Molnar Z: Visual subdivisions of the dorsal ventricular ridge of the iguana (Iguana iguana) as determined by electrophysiologic mapping. J Comp Neurol 2002, 453:226–246.
10. Ocaña FM, Suryanarayana SM, Saitoh K, Kardamakis AA, Capantini L, Robertson B, Grillner S: The lamprey pallium provides a blueprint of the mammalian motor projections from cortex. Curr Biol 2015, 25:413–423.
11. Suryanarayana SM, Robertson B, Wallén P, Grillner S: The lamprey pallium provides a blueprint of the mammalian layered cortex. Curr Biol 2017, 27:3264–3277. e3265.
12. Suryanarayana SM, Pérez-Fernández J, Robertson B, Grillner S: Olfaction in lamprey pallium revisited: dual projections of mitral and tufted cells. Cell Rep 2021, 34:108596.
Huang ZJ, Paul A: The diversity of GABAergic neurons and neural communication elements. Nat Rev Neurosci 2019, 20: 563–572.

13. Tosches MA, Yamawaki TM, Naumann RK, Jacobi AA, Tushov G, Laurent G: Evolution of pallium, hippocampus, and cortical cell types revealed by single-cell transcriptomics in reptiles. Science 2018, 360:881–888.

15. Tasic B, Yao Z, Graybuck LT, Smith KA, Nguyen TN, Stephenson Jones M, Samuelsson E, Ericsson J, Robertson B, Grillner S: Evolutionary conservation of the basal ganglia as a common vertebrate mechanism for action selection. Curr Biol 2011, 21:1081–1091.

16. Ericsson J, Stephenson Jones M, Kardamakis A, Robertson B, Silberberg G, Grillner S: Evolutionarily conserved differences in pallial and thalamic short-term synaptic plasticity in striatum. J Physiol 2013, 591:859–874.

18. Ericsson J, Stephenson Jones M, Pérez-Fernández J, Robertson B, Silberberg G, Grillner S: Dopamine differentially modulates the excitability of striatal neurons of the direct and indirect pathways in lamprey. J Neurosci 2013, 33:8045–8054.

19. Johansson Y, Silberberg G: The functional organization of cortical and thalamic inputs onto five types of striatal neurons is determined by source and target cell identities. Cell Rep 2020, 30:1178–1194, e1173.

20. Muñoz-Manchado AB, Bengtsson Gonzales C, Zeisel A, Munguba H, Bekhouche B, Skene GN, Lönnberg P, Ryge J, Harris KD, Linnarsson S, et al.: Diversity of interneurons in the dorsal striatum revealed by single-cell RNA sequencing and PatchSeq. Cell Rep 2018, 24:2170–2190. e2177.

21. Aristieta A, Barresi M, Azizpour Lindi S, Barrière G, Courtand G, de la Crome B, Guilmans L, Gauthier S, Fioramonti S, Baufreton J, et al.: A disynaptic circuit in the globus pallidus controls locomotion inhibition. Curr Biol 2021, 31:707–721. e707.

22. Ketzel M, Silberberg G: Differential synaptic input to external globus pallidus neuronal subpopulations in vivo. Neuron 2021, 109:516–529. e514.

23. Mallet N, Micklem BR, Henry P, Brown MT, Williams C, Bolam JP, Nakamura KC, Magli PJ: Dichtomatus organization of the external globus pallidus. Neuron 2012, 74:1075–1086.

24. Pérez-Fernández J, Kardamakis AA, Suzuki DG, Robertson B, Grillner S: Direct dopaminergic projections from the SNC modulate visuomotor transformation in the lamprey tectum. Neuron 2017, 96:910–924. e915.

25. Pérez-Fernández J, Stephenson Jones M, Suryanarayana SM, Robertson B, Grillner S: Evolutionarily conserved organization of the dopaminergic system in lamprey: SNC/VTa afferent and efferent connectivity and D2 receptor expression. J Comp Neurol 2014, 522:3775–3794.

26. Robertzen B, Kardamakis A, Capantini L, Pérez-Fernández J, Suryanarayana SM, Wallén P, Stephenson Jones M, Grillner S: The lamprey blueprint of the mammalian nervous system. Prog Brain Res 2014, 212:337–349.

27. Thompson RH, Ménard A, Pombal M, Grillner S: Forebrain dopamine depletion impairs motor behavior in lamprey. Eur J Neurosci 2008, 27:1452–1460.

28. Dommett E, Coizet V, Blaha CD, Martindale J, Lefebvre V, Walton N, Mayhew JE, Overton PG, Redgrave P: How visual stimuli activate dopaminergic neurons at short latency. Science 2005, 307:1476–1479.

29. da Silva JA, Tecuapetla F, Paixão V, Costa RM: Dopamine neuron activity before action initiation gates and invigorates future movements. Nature 2018, 554:244–248.

30. Klaus A, Alves da Silva J, Costa RM: What, if, and when to move: basal ganglia circuits and self-paced action initiation. Annu Rev Neurosci 2019, 42:469–483.

31. Crittenden JR, Tillberg PW, Riad MH, Shima Y, Gerfen CR, Curry J, Housman DE, Nelson SB, Boydén ES, Graybiel AM: Striosome-dendron bouquets highlight a unique striatonical circuit targeting dopamine-containing neurons. Proc Natl Acad Sci U S A 2016, 113:11316–11323.

32. Grillner S, Robertson B, Kotaleski JH: Basal ganglia-A motion perspective. Compr Physiol 2020, 10:1241–1275.

33. Hikosaka O: The habenula: from stress evasion to value-based decision-making. Nat Rev Neurosci 2010, 11:503–513.

34. Stephenson Jones M, Flores O, Robertson B, Grillner S: Evolutionary conservation of the habenular nuclei and their circuitry controlling the dopamine and 5-hydroxytryptophan (5-HT) systems. Proc Natl Acad Sci U S A 2012, 109:E164–E173.

35. Stephenson Jones M, Kardamakis AA, Robertson B, Grillner S: Independent circuits in the basal ganglia for the evaluation and selection of actions. Proc Natl Acad Sci U S A 2013, 110: E3670–E3679.

36. Lazaridis I, Tzortz O, Weglage M, Mäntt A, Xuan Y, Parent M, Johansson Y, Fuzik J, Fürth D, Fenno LE, et al.: A hypothalamus-habenula circuit controls aversion. Mol Psychiatry 2019, 24:1351–1368.

37. Stephenson Jones M, Yu K, Ahrens S, Tucciarone JM, van Huijsteene AN, Meija LA, Penzo MA, Tai LH, Wilbrecht L, Li B: A basal ganglia circuit for evaluating action outcomes. Nature 2016, 539:289–293.

38. Jung H, Baek M, D’Elia KP, Boisvert C, Currie PD, Tay BH, Venkatesh B, Brown SM, Heguy A, Schoppik D, et al.: The ancient origins of neural substrates for land walking. Cell 2018, 172:667–682, e615.

39. Catela C, Shin MM, Dasen JS: Assembly and function of spinal circuits for motor control. Annu Rev Cell Dev Biol 2015, 31:669–698.

40. D’Elia KP, Dasen JS: Development, functional organization, and evolution of vertebrate axial motor circuits. Neural Dev 2018, 13:10.

41. Grillner S, El Manira A: Current principles of motor control, with special reference to vertebrate locomotion. Physiol Rev 2020, 100:271–320.

42. Song J, Ampatzis K, Björnors ER, El Manira A: Motor neurons control locomotor circuit function retrogradely via gap junctions. Nature 2016, 529:399–402.

43. Song J, Dahlberg E, El Manira A: V2a interneuron diversity tailors spinal circuit function to control the vigor of locomotor movements. Nat Commun 2018, 9:3370.

44. Song J, Pallucchini I, Ausborn J, Ampatzis K, Bertuzzi M, Fontanel P, Picton LD, El Manira A: Multiple rhythm-generating circuits act in tandem with pacemaker properties to control the start and speed of locomotion. Neurouron 2020, 105: 1048–1061. e1044.

45. Picton LD, Bertuzzi M, Pallucchini I, Fontanel P, Dahlberg E, Björnors ER, Iacovellio F, Shearing PR, El Manira A: A spinal organ of proprioception for integrated motor action feedback. Neurouron 2021, 109:1188–1201.

46. Combes D, Merrywest SD, Simmers J, Sillar KT: Developmental segregation of spinal networks driving axial- and hindlimb-based locomotion in metamorphosing Xenopus laevis. J Physiol 2004, 559:17–24.

47. Rauschen A, Le Ray D, Cabriol-Pol MJ, Sillar KT, Simmers J, Combes D: Development and neuromodulation of spinal locomotor networks in the metamorphosing frog. J Physiol Paris 2006, 100:317–327.

48. Ha NT, Dougherty KJ: Spinal Shox2 interneuron interconnectivity related to function and development. Elife 2018, 7.

49. Bikoff JB, Gabitto MI, Rivard AF, Drobac E, Machado TA, Mira A, Brenner-Morton S, Famojere E, Diaz C, Alvarez FJ, et al.: Spinal inhibitory interneuron diversity delineates variant motor microcircuits. Cell 2016, 162:207–219.
50. Gabitto MI, Pakman A, Bikoff JB, Abbott LF, Jessell TM, Paninski L: Bayesian sparse regression analysis documents the diversity of spinal inhibitory interneurons. *Cell* 2016, 165:220–233.

51. Sweeney LB, Bikoff JB, Gabitto MI, Brenner-Morton S, Baek M, Yang JH, Tabak EG, Dassen JS, Kintner CR, Jessell TM: Origin and segmental diversity of spinal inhibitory interneurons. *Neuron* 2018, 97:341–355. e343.

52. Zhang J, Lanuza GM, Britz O, Wang Z, Siembab VC, Zhang Y, Velasquez T, Alvarez FJ, Frank E, Goulding M: V1 and v2b interneurons secure the alternating flexor-extensor motor activity mice require for limbed locomotion. *Neuron* 2014, 82: 138–150.

53. Talpalar AE, Bouvier J, Borgius L, Fortin G, Pierani A, Kiehn O: Dual-mode operation of neuronal networks involved in left-right alternation. *Nature* 2013, 500:85–88.

54. Ruder L, Takeoka A, Arber S: Long-distance descending spinal neurons ensure quadrupedal locomotor stability. *Neuron* 2016, 92:1063–1078.

55. Kiehn O: Decoding the organization of spinal circuits that control locomotion. *Nat Rev Neurosci* 2016, 17:224–238.

56. Ryczko D, Auclair F, Cabelguen JM, Dubuc R: The mesencephalic locomotor region sends a bilateral glutamatergic drive to hindbrain reticulospinal neurons in a tetrapod. *J Comp Neurol* 2016, 524:1361–1383.

57. Ryczko D, Grätzsch S, Schläger L, Kuyyalian A, Boukhatem Z, Garcia C, Auclair F, Büschges A, Dubuc R: Nigral glutamatergic neurons control the speed of locomotion. *J Neurosci* 2017, 37: 9759–9770.

58. Caggiano V, Leiras R, Goñi-Erro H, Masini D, Bellardita C, Bouvier J, Caldeira V, Fisone G, Kiehn O: Midbrain circuits that set locomotor speed and gait selection. *Nature* 2018, 553:455–460.

59. Capelli P, Pivetta C, Soledad Esposito M, Arber S: Locomotor speed control circuits in the caudal brainstem. *Nature* 2017, 551:373–377.

60. Josset N, Foussel M, Lemieux M, Lafrange-Zoubga D, Rastgar A, Bretzner F: Distinct contributions of mesencephalic locomotor region nuclei to locomotor control in the freely behaving mouse. *Curr Biol* 2018, 28:684–901. e883.

61. Usseglio G, Gatier E, Heuzé A, Hérent C, Bouvier J: Control of orienting movements and locomotion by projection-defined subsets of brainstem V2a neurons. *Curr Biol* 2020, 30: 4665–4681. e4666.

62. An X, Mohan H, Matho K, Kepescs A, Huang J: A cortical command circuit coordinates food handling and manipulation. *Neuroscience* 2019, 2019.

63. Ruder L, Schina R, Kanodia H, Valencia-Garcia S, Pivetta C, Arber S: A functional map for diverse forelimb actions within brainstem circuitry. *Nature* 2021, 590:445–450.

64. Ruder L, Arber S: Brainstem circuits controlling action diversification. *Annu Rev Neurosci* 2019, 42:485–504.

65. Lemon R: Recent advances in our understanding of the primate corticospinal system. *F1000Res* 2019, 8.

66. Basso MA, Bickford ME, Cang J: Unraveling circuits of visual perception and cognition through the superior colliculus. *Neuron* 2021, 109:918–937.

67. Isa T, Marquez-Legorreta E, Griller S, Scott E: The tectum/superior colliculus as the vertebrate solution for spatial sensory integration and action. *Curr Biol* 2021 (in press).

68. Kardamakis AA, Pérez-Fernández J, Griller S: Spatiotemporal interplay between multisensory excitation and recruited inhibition in the lamprey optic tectum. *Elife* 2016, 5.

69. Kardamakis AA, Saitoh K, Griller S: Tectal microcircuit generating visual selection commands on gaze-controlling neurons. *Proc Natl Acad Sci U S A* 2015, 112: E1956–E1965.

70. Masullo L, Mariotti L, Alexandre N, Freire-Pritchett P, Boulanger J, Tripodi M: Genetically defined functional modules for spatial orientation in the mouse superior colliculus. *Curr Biol* 2019, 29: 2892–2904. e2898.

71. Tokuoka K, Kasai M, Kobayashi K, Isa T: Anatomical and electrophysiological analysis of cholinergic inputs from the parabigeminal nucleus to the superficial superior colliculus. *J Neurophysiol* 2021, 124:1968–1985.

72. Wilson JJ, Alexandre N, Trentin C, Tripodi M: Three-dimensional representation of motor space in the mouse superior colliculus. *Curr Biol* 2018, 28:1744–1755. e1712.

73. Suzuki DG, Pérez-Fernández J, Wibble T, Kardamakis AA, Griller S: The role of the optic tectum for visually evoked orienting and evasive movements. *Proc Natl Acad Sci U S A* 2019, 116:15272–15281.

74. Förster D, Heimbrecht TO, Mears DS, Jordan L, Mokayes N, Baier H: Retinotectal circuitry of larval zebrafish is adapted to detection and pursuit of prey. *Elife* 2020, 9.