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REVIEW

*Now and Then***Locomotor pattern generation and descending control: a historical perspective****Réjean Dubuc,^{1,2} Jean-Marie Cabelguen,^{3†} and  Dimitri Ryczko^{4,5,6,7}**

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Abstract

The ability to generate and control locomotor movements depends on complex interactions between many areas of the nervous system, the musculoskeletal system, and the environment. How the nervous system manages to accomplish this task has been the subject of investigation for more than a century. In vertebrates, locomotion is generated by neural networks located in the spinal cord referred to as central pattern generators. Descending inputs from the brain stem initiate, maintain, and stop locomotion as well as control speed and direction. Sensory inputs adapt locomotor programs to the environmental conditions. This review presents a comparative and historical overview of some of the neural mechanisms underlying the control of locomotion in vertebrates. We have put an emphasis on spinal mechanisms and descending control.

brain stem; central pattern generator; locomotion; spinal cord

INTRODUCTION

Locomotion is one of the most fundamental behaviors. It allows animals to move in their environment for different purposes such as social interactions, food seeking, reproducing, or escaping from predators. The neural mechanisms underlying locomotion have been examined in several animal species for more than a century. Because locomotion is a rhythmical motor activity, early neuroscientists used this easily identifiable output to design correlative and causal experiments to understand how the brain and spinal cord control behavior. This visionary idea is still used to this day by neuroscientists, who are now deciphering the genetically defined cell types controlling locomotion. Interestingly, the organization of the neural networks controlling locomotion is very similar in different vertebrate species (Fig. 1; for review see Ref. 1). Although not covered here, these networks share common principles with those described in invertebrates, which also generate standardized rhythmic

and patterned motor activities in many circumstances (for review see Refs. 2, 3).

In the absence of sensory inputs and supraspinal structures, the neural networks located in the spinal cord can independently generate the rhythmic pattern of muscle contractions responsible for locomotion (Fig. 1). There was an intense debate in the 1970s relative to the complexity of the neural activity that is programmed centrally. Some suggested that the central program consists of a simple alternate activity between a flexor and an extensor component without the complex timing seen in different flexor muscles and different extensor muscles during natural locomotion. On the other hand, it was suggested that a central program produces detailed and complex muscle synergies as seen during natural locomotion (Refs. 4–8; reviewed in Ref. 9). Graham Brown (10, 11) had provided the first evidence that the locomotor rhythm and pattern were generated centrally, whereas Sherrington (12) proposed that locomotor movements resulted from a series of



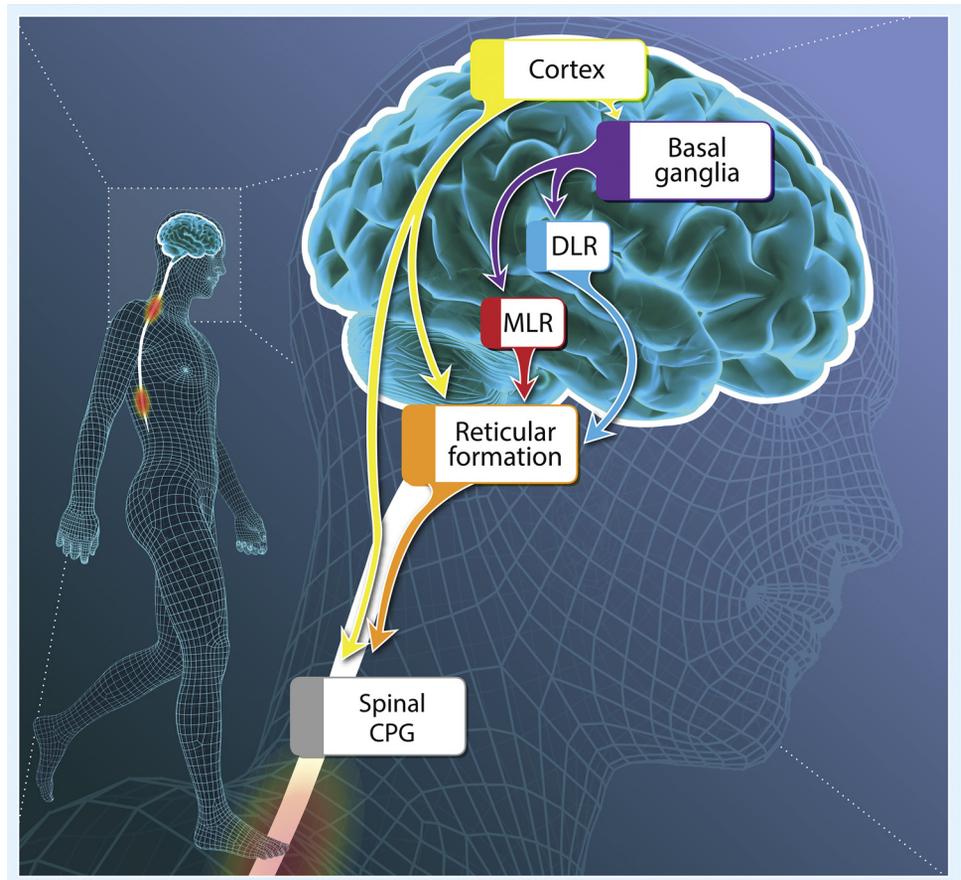
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Figure 1. Schematic representation of the main supraspinal structures involved in the control of locomotion in vertebrates. The reticular formation contains the reticulospinal command neurons for locomotion initiation, speed control, steering, and locomotor termination. These command neurons are under control of the mesencephalic locomotor region (MLR) and of the less known diencephalic locomotor region (DLR). The basal ganglia send tonic inhibition to the locomotor centers, and such inhibition is temporarily decreased during locomotion initiation. The motor cortex can provide inputs at all levels of the circuitry described above. CPG, central pattern generator.



sensory reflexes. After removing the descending and sensory inputs, Sten Grillner and colleagues (5, 6, 13) showed that the spinal locomotor networks could still generate an elaborate complex sequence of muscle activations that was remarkably similar to that seen during locomotion in natural conditions. Consequently, the spinal neural networks generating this detailed locomotor pattern were named central pattern generators (CPGs; Refs. 5, 6, 14), as previously proposed from studies performed in invertebrates (3, 16, 17).

While the roles of spinal cord in the control of locomotion were being clarified in the 1960s and 1970s, researchers were acquiring new information on the role of supraspinal structures. A group of Russian scientists headed by Grigori Orlovsky discovered in cats that a specific area of the brain stem, the mesencephalic locomotor region (MLR), plays a crucial role in controlling the locomotor output (18). Stereotyped locomotor movements can be induced in response to electrical or chemical stimulation of the MLR. Similar findings were later obtained in several species (reviewed in Ref. 19 and more recently in Refs. 20–23). The strength of the MLR stimulation determines the speed, the gait (e.g., walk/trot/gallop in cat; Ref. 18), and the locomotor mode (e.g., stepping and swimming in salamander; Ref. 24). In recent years significant progress was made in our understanding of the roles of spinal and supraspinal structures in the control of locomotion, and some of the key findings are summarized below.

SPINAL MECHANISMS RESPONSIBLE FOR THE GENERATION OF LOCOMOTOR RHYTHM

A Century of CPG Models

In lower vertebrates that use their axial body parts to swim, a conceptual organization of the CPG was inherited from the “half-center CPG model” proposed by Graham Brown (11), which was further supported by Lundberg (7, 8). According to this model, rhythmic left-right alternated activity can be generated in each spinal segment by two hemisegments interconnected by mutual inhibition, and removal of mutual inhibition abolishes the rhythm (Fig. 2A). This view is supported by some studies in which acute surgical destruction of commissural connections was done (33, 34). However, the vast majority of other studies in lamprey and other vertebrates are in accordance with another conceptual organization proposed by Sten Grillner and referred to as the “unit burst generator” CPG model (Fig. 2B) (25). According to this model, the hemisegmental networks are able to produce rhythmic activity in isolation from one another, i.e., independently of mutual inhibition. In lamprey and amphibians a single spinal hemisegment carefully isolated surgically can generate rhythmic activity when tonically stimulated pharmacologically or electrically (Refs. 35–45, for review see Ref. 46; see also Ref. 47). The exact anatomical boundaries of these oscillatory centers are unresolved. Some authors proposed that the swimming CPG in larval zebrafish could also

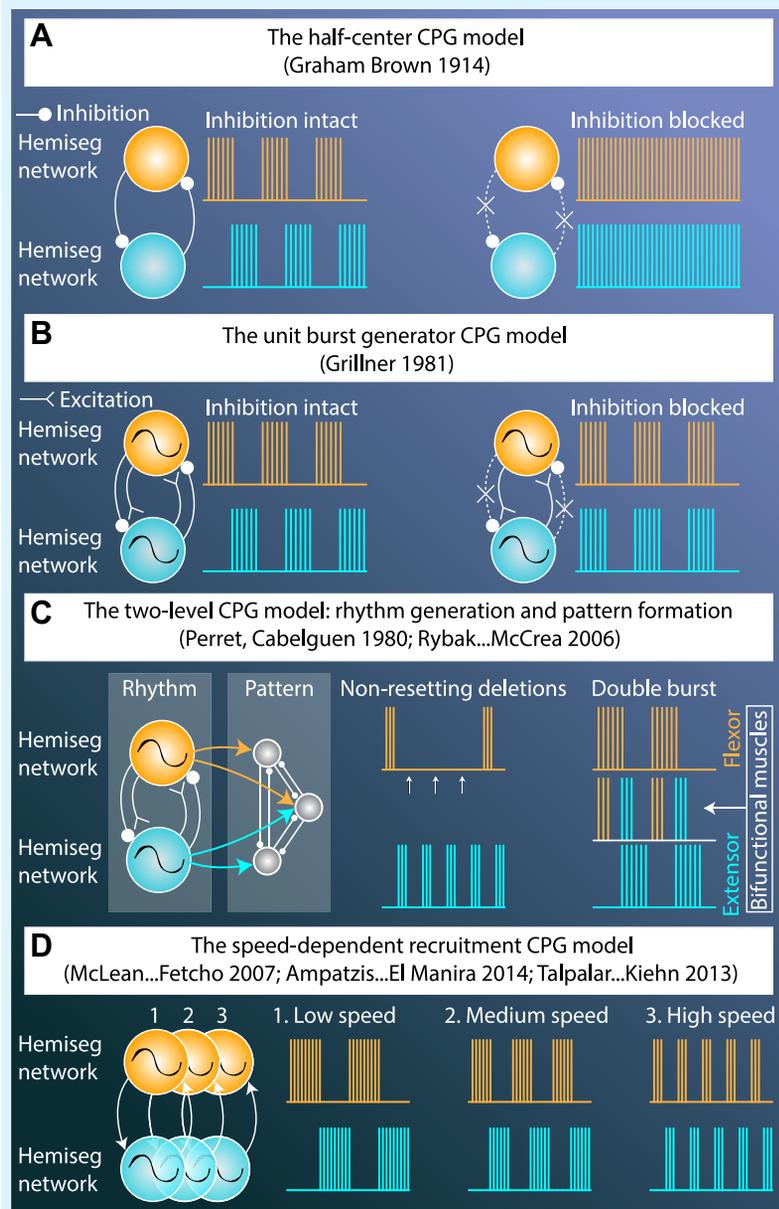


Figure 2. Main conceptual models of central pattern generators (CPGs) for locomotion over the last century. **A:** the “half-center CPG model.” In this model proposed by Graham Brown in 1914 (11), and further supported by Lundberg (9), mutual inhibition between two hemisegments of the CPG (i.e., either flexor or extensor within a limb controller or left and right hemisegments in the body axis controller) is necessary for the rhythm to be generated. A prediction from this model is that isolated hemisegments cannot oscillate. Flexible coordination of multiple segments is limited with this model. **B:** the “unit burst generator CPG model.” In this model proposed by Grillner in 1981 (25), each unit burst generator controls a group of close synergists (flexors or extensors, left or right axial muscles) at a given joint (hip/knee/ankle/digits or vertebra). Mutual inhibition between two hemisegments of the CPG is not necessary for the rhythm to be generated. A prediction from this model is that isolated hemisegments can oscillate. The bursting units at different joints can be combined in different ways, depending on afferent/descending inputs onto their connectivity, to generate the various limb or axial motor patterns associated with the different locomotor gaits. **C:** the “two-level CPG model.” In this model proposed by Perret and Cabelguen in 1980 (26; see also Ref. 27), and supported by Rybak et al. in 2006 (28), two layers of neurons can independently generate the rhythm and the pattern. This model explains the nonresetting deletions and the double burst recorded in bifunctional muscles and in their motoneurons. It provides a relevant framework to integrate descending and sensory inputs on different network components, thereby allowing high reconfigurability of the coordination. **D:** the emerging “speed-dependent recruitment CPG model.” This model was proposed by McLean et al. in 2007 (29) and further supported by the teams of El Manira (30, 31) and Kiehn (32). In this model, different layers of interneurons are recruited as a function of speed. Some components of the network can be added or derecruited as a function of speed.

consist of an unsegmented, “continuous” network of rhythmogenic microcircuits (48, 49).

In quadrupeds, the neural circuits controlling each limb appear to be distributed, and therefore the unit burst generator CPG model has been proposed to account for the complexity and flexibility of the limb locomotor pattern (Refs. 25, 50, 51; see also Refs. 52–54). The neural networks generating locomotor movements of forelimbs and hindlimbs are in the cervical and lower thoracic/lumbar regions of the spinal cord (55–61). Spinal sections and pharmacological manipulations further show that these rhythmogenic regions consist of neural networks distributed on the left and right sides, which independently control each limb and are linked by commissural connections coordinating the limbs at different locomotor speeds (62–64). This model could be improved to account for spontaneous deletions of motoneuron activity (65) and the phasic gating of reflex pathways during locomotion (66).

Studies based on optogenetics in newborn mice revealed that rhythm generation in hindlimb spinal segments is mediated by multiple subpopulations of excitatory interneurons able to generate the rhythm on each side independently, or flexor and extensor activity independently, as predicted by the unit burst generator CPG model (Ref. 54; reviewed in Ref. 67). Within the segments controlling a single hindlimb, a minimal neural circuit sufficient to generate reciprocal inhibition between flexor and extensor bursts has been identified in newborn mice (68, 266). It comprises two classes of genetically defined inhibitory interneurons: V1 neurons (69) and V2b neurons (70). Some of these neurons could correspond to the Renshaw cells and reciprocal Ia inhibitory interneurons previously defined in the cat (71–74). The latter interneurons were found to be rhythmically active during MLR-induced fictive locomotion in the cat (75).

Beyond Flexion and Extension: Bifunctional Muscles Reflect the Complexity of CPG Organization

During fictive locomotion, the limb motor pattern has been shown to be more complex than a simple synchronous activation of all flexor motoneurons alternating with a synchronous activation of all extensor motoneurons in cats (Ref. 6; for review see Refs. 76, 77) and in neonatal rodent preparations (78). The nerves of some hindlimb or forelimb muscles (“monofunctional muscles”) discharge simply as flexors or extensors with one single burst of activity per cycle, whereas the nerves to other muscles (“bifunctional muscles”) display more complex and versatile discharge patterns, including double bursts, during each locomotor cycle (Fig. 2C) (6, 26, 79–84). The different fictive patterns displayed by nerves of hindlimb bifunctional muscles have been related to different gaits (e.g., walk/gallop, forward/backward walking). Therefore, each limb CPG can generate the complex and detailed pattern of activation of the different limb muscles seen during different gaits, indicating that each limb controller is more complex than a simple neural network producing synchronous activation of all flexor muscles alternating with synchronous activation of all extensor muscles (half-center CPG model; see Refs. 7, 8). The complexity of the CPG output was well illustrated by recordings of motoneurons of bifunctional muscles, which display complex membrane potential oscillations during fictive locomotion (26, 84, 85). These complex oscillations result from a mixture of excitatory and inhibitory synaptic inputs from the limb CPGs during both the flexor and extensor phases of the fictive step cycle (83, 84). Changing the balance between flexor and extensor synaptic influences through descending or afferent inputs appears to be a simple and subtle way to shift the motor pattern expressed by bifunctional muscles according to demand (26).

The Emergence of a Two-Level CPG Model

The idea that the CPG controlling limb movements can be subdivided into two functionally independent, but hierarchically connected, subcomponents (two-level CPG model) was suggested on the basis of the variations of the fictive locomotor pattern in the thalamic cat (all brain tissue removed above the thalamus), occurring spontaneously or consecutively to exteroceptive limb stimulation (Refs. 26, 86, 87; Fig. 2C). In this conceptual model, a first component (“rhythm generator” or “clock”) sets the locomotor rhythm and acts on a second component (“pattern-formation network”) that produces the individual pattern of activity within the cycle. Interestingly, specific location of interneurons responsible for rhythm generation or pattern formation was characterized in the lumbar spinal cord of neonatal mice (88). Several findings suggest that some of the interneurons comprising reflex pathways like those activated by flexor reflex afferents belong to the pattern-formation network (79, 87). Studies on the rhythmic modulation of reflex responses during fictive locomotion have provided indirect evidence that proprioceptive and cutaneous inputs control differentially the two subcomponents of the limb CPG (for review see Ref. 66). Whether the two-level CPG concept applies to the axial locomotor circuitry (e.g., in zebrafish, tadpole, or lamprey) is unclear. In zebrafish for instance, the

subpopulations of segmental V2a interneurons are necessary and sufficient to generate locomotor activity (see for review Ref. 1).

A computational model of the hindlimb CPG based on a two-level CPG organization (Fig. 2C) and incorporating afferent signals was shown to reproduce the patterns of activity of hindlimb flexors and extensors and most of the effects of proprioceptive inputs during stepping (89). Genetically identified neuronal types of the hindlimb CPG were recently added to the model (90–93). In the future, these modeling studies will likely include models of muscles that exhibit complex and variable locomotor patterns (cf. Ref. 94). The flexibility of the locomotor patterns displayed by bifunctional limb muscles strongly suggests that these muscles play a crucial role in the adaptation of limb movements to changing environment and goal. This implies that they are the main targets of peripheral and supraspinal inputs (see Ref. 66 for in-depth review). Importantly, the unit burst generator CPG model can also account for complex motor patterns as summarized in Ref. 95.

SUPRASPINAL STRUCTURES CONTROLLING LOCOMOTION

Overview

Locomotion is controlled through the activation of an ensemble of supraspinal regions playing different roles (Fig. 1). A significant part of these regions are connected in a linear fashion from forebrain to lower hindbrain. There is now growing evidence that supraspinal structures play a crucial role in starting, maintaining, and stopping locomotion. These structures can also integrate sensory inputs to adapt locomotor behavior according to both internal and external environmental conditions. Steering and speed control result from the interplay of supraspinal and spinal neural mechanisms.

The role of forebrain structures in the control of locomotion is not fully resolved. It has been suggested that the posterior parietal cortex contributes to planning locomotion by providing an estimate of the position of an animal with respect to objects in its path. In contrast, motor cortex would contribute primarily to the execution of gait modifications by modulating the activity of groups of synergistic muscles active at different times during the gait cycle (Refs. 96–98; for review see Refs. 99, 100). In addition, the basal ganglia send descending projections to the brain stem for controlling locomotion (Refs. 101–103; for review see Ref. 20). These are believed to play a crucial role in the selection of locomotor behaviors (Refs. 104–106; see also Ref. 107).

The MLR: an Emerging Target for Parkinson’s Disease and Spinal Cord Injury

A striking feature of the supraspinal control of locomotion is the presence of locomotor centers specifically dedicated to initiating and controlling locomotion (for review see Refs. 76, 104, 108–114). As indicated above, one such region is the MLR. Its existence has been confirmed in several vertebrate species (for review see Refs. 19, 104, 112, 114, 115; for more recent review see Refs. 20–23, 116). Stimulation of the MLR induces swimming in fishes and lampreys, flying in birds,

and walking in tetrapods. The MLR controls locomotion not by projecting directly to the spinal cord but via projections to reticulospinal (RS) neurons in the pons and medulla, which, in turn, project to the spinal cord (104, 117–125). In lamprey, MLR neurons provide glutamatergic and nicotinic inputs to reticulospinal neurons (126, 127). An important aspect is that the MLR provides bilateral inputs on downstream reticulospinal neurons while inducing locomotion (128). The MLR also sends cholinergic input to a group of muscarinoceptive interneurons that in turn provide glutamatergic input to reticulospinal neurons (129). Recent studies in mice uncovered the genetic identity of MLR neurons and their role in the control of locomotor movements in vivo (Refs. 102, 124, 130–134; for review see Refs. 20, 22, 23). Interestingly, some MLR neurons encode aspects of behavior beyond locomotion (for review see Ref. 116). Some neurons projecting to the respiratory centers increase respiratory activity in lamprey (135) and mice (136). Some neurons projecting to the spinal cord control rearing, and others projecting to basal ganglia output station encode forelimb movements (137).

The MLR plays a role in locomotor control in humans. Damage to the MLR produces marked locomotor deficits (Refs. 138, 139, reviewed in Ref. 140). Functional MRI revealed that the MLR is active during mental imagery of walking and running in healthy volunteers (141). Deep brain stimulation is now carried out in the MLR as a target to improve locomotor function in patients with Parkinson's disease (Refs. 142–150; for review see Refs. 23, 151) as well as in patients suffering from other gait disorders such as primary progressive freezing of gait (152, 153) or progressive supranuclear palsy (154). In Parkinson's disease, deep brain stimulation of the MLR led to conflicting results that may result from the diversity of genetically defined MLR cell types, as uncovered in recent rodent studies (for review see Ref. 23). Some MLR cells induce locomotion, whereas others stop it. Therefore, selective stimulation of a subset of glutamatergic neurons in subparts of the MLR (cuneiform nucleus and caudal pedunculopontine nucleus) is needed to improve locomotor function in rodent models of Parkinson's disease (155, 156). Overall, the recent increase in interest for the MLR in the clinical field stresses an urgent need for understanding its function.

In rats with a partial spinal cord lesion, electrical stimulation of the MLR was shown to improve locomotor function (157, 158). Recently, optogenetic stimulation of glutamatergic neurons of the cuneiform nucleus, the dorsal part of the MLR, was shown to improve locomotor recovery after spinal cord injury in mice (159). The activity of these MLR neurons appears to be necessary for recovery (159). These studies will likely motivate the use of MLR stimulation to improve locomotor function in spinal cord-injured patients.

The inputs and outputs of the MLR have been identified in several animal species. The basal ganglia involved in the selection of motor programs project to the MLR. The organization of the basal ganglia is highly conserved throughout the vertebrate phylum, including lampreys (160). It has been demonstrated that the MLR of lampreys receives direct dopaminergic and glutamatergic inputs from a brain region homologous to the substantia nigra compacta (161, 268). This projection was confirmed in salamanders and rats (162). In addition, a direct dopaminergic projection from the zona

incerta to the MLR has been identified in mice (163). The MLR is thus under descending dopaminergic and glutamatergic control. In lamprey, the dopaminergic component amplifies the glutamatergic component through the activation of D1 receptors, resulting in faster locomotor movements (140, 161). In mammals, the specific contribution of these two neurotransmitter systems remains to be established. The hypothalamus also projects to the MLR (110, 164), with additional direct projections to reticulospinal cells (164).

Other locomotor centers have been reported, although in a less detailed manner. The diencephalic locomotor region (DLR), which sends input to reticulospinal neurons, was shown to initiate and control locomotion in lamprey (165, 166) (Fig. 1). In mammals the DLR region likely corresponds to the subthalamic locomotor region (167, 168). In those experiments, it is unclear whether the subthalamic nucleus was stimulated or the closely located zona incerta, whose stimulation is also associated with locomotor activity and postural adjustments (169–172) and which is known to send projections to the MLR, including dopaminergic ones (163). The subthalamic nucleus sends direct and indirect projections to the MLR (for review see Ref. 19) and is therefore also an interesting substrate to control locomotor activity. The inputs and outputs of the DLR have been better documented in the lamprey than in other vertebrate species. Stimulation of the DLR elicits monosynaptic excitatory postsynaptic potentials, polysynaptic excitatory postsynaptic potentials, and inhibitory postsynaptic potentials in hindbrain reticulospinal neurons. Stimulation of the DLR was shown to induce rhythmic firing of reticulospinal neurons as well as rhythmic bursts of discharge in spinal ventral roots (165). Injection of GABA agonists in the DLR inhibits locomotion, whereas GABA antagonists facilitate the induction of locomotion, indicating that GABAergic projections provide tonic inhibition of the DLR that once turned off can release locomotion (166). It was shown by the same authors that populations of GABAergic neurons in the pallidum and striatum project to the DLR.

Another locomotor center is the cerebellar locomotor region, which was shown to send input to reticulospinal neurons and to elicit locomotion in cats (173). In zebrafish, neurons of the medial longitudinal fasciculus (nMLF) also play an important role in locomotor initiation, speed, and bout duration, through direct projections to spinal locomotor circuits (174).

Reticulospinal Neurons: Vertebrate Equivalent of Invertebrate “Command Neurons”?

The spinal CPGs receive powerful inputs from reticulospinal cells, and since the early studies of Orlovsky and his group (175, 176) it has been recognized that these supraspinal neurons play a crucial role in the descending control of locomotion. Lamprey reticulospinal cells are functionally heterogeneous, including excitatory and inhibitory neurons (177). Since the early studies by Carl Rovainen on the physiology of lamprey reticulospinal neurons (178, 179), major advances have been made in understanding the contribution of these neurons to the descending control of locomotion. Reticulospinal neurons resemble command neurons described in invertebrates (180,

181). They project directly to locomotor CPG neurons in the spinal cord and in turn receive inputs from several sensory modalities to adapt their activity in response to conditions prevailing in the external and internal environments (Ref. 182 in lamprey, Ref. 174 in zebrafish). Specific populations of lamprey reticulospinal cells initiate, maintain, or stop locomotion (126, 183–185). Other reticulospinal populations control locomotor speed, adjust posture, or produce forward versus backward swimming (186–189). Studies on the mammalian reticulospinal system have recently established the presence and role of genetically defined excitatory and inhibitory reticulospinal cells (124, 190, 191).

In recent years, the role of reticular glutamatergic V2a neurons has been examined in zebrafish and mice. In the zebrafish, glutamatergic V2a neurons in the hindbrain were identified by their expression of the transcription factor Chx10 (192). They project to the spinal cord, and their optogenetic activation elicits locomotion, whereas their inactivation stops it (192). Recordings of these neurons revealed that they are rhythmically active during swimming (192). In contrast, in mice the group of Ole Kiehn showed that V2a neurons located at the ponto-medullary border acted as stop neurons. They halt locomotion when optogenetically activated on both sides, whereas they decrease the occurrence of spontaneous stopping when their synaptic output is blocked (193). Activation of some brainstem V2a neurons was observed during stops in vivo by calcium imaging in mice (194). Unilateral activation of V2a neurons induces ipsilateral turns in vivo in mice (195, 196). Virus injections in mice revealed that V2a reticulospinal neurons projecting to the cervical and lumbar segments differentially control head turns or decrease in locomotor speed, respectively (196). The activity of brainstem V2a neurons that control turning maneuvers is controlled by direct inputs from superior colliculus (195). Whether similar V2a reticular neurons were recorded in zebrafish and mice is not fully resolved. In zebrafish, V2a reticular neurons receive input from the MLR (125). In mice, some V2a neurons receive inputs from the MLR according to calcium imaging experiments, and they express the early response gene *c-fos* after a long bout of locomotor activity (122). However, a monosynaptic tracing study showed that V2a reticular neurons do not receive input from the MLR in mice, so the extent to which the MLR controls V2a neurons in mammals is not fully resolved (195).

In lamprey, three different populations of reticulospinal cells were identified according to their activity pattern during locomotion. Start cells are transiently active at the beginning of the locomotor bout, maintain cells are active throughout the locomotor bout, and stop cells are transiently active at the beginning and the end of a locomotor episode (185). The activity pattern of the latter cell group was present not only when locomotion was elicited by MLR stimulation but also during sensory-evoked or spontaneous locomotion (185). Pharmacological activation of these cells was shown to stop ongoing locomotion, whereas their inactivation impaired the termination process (185). Like what was reported in mice, the lamprey stop cells are predominantly located in an area homologous to the caudal pons of mammals. Interestingly, in lamprey these stop cells receive input from the MLR, confirming that the MLR has direct access to a stopping mechanism (183, 184).

Inhibitory reticulospinal cells have also been shown to stop ongoing locomotion in the *Xenopus* tadpole (197) and in mice (124). In *Xenopus*, these cells are activated by sensory inputs (197). In mice, optogenetic activation of inhibitory neurons in various reticular nuclei of the caudal brain stem stops movement (124).

A study in lamprey has shown that reticulospinal neurons not only play a role in activating the spinal neurons responsible for generating locomotion but also activate interneurons involved in phase-dependent modulation of reflexes or reflex reversal. These observations demonstrate that descending inputs from the brain stem also control the flux of sensory information reaching spinal interneurons involved in generating locomotion (198).

■ CONTROLLING THE SPEED OF LOCOMOTION: SPINAL AND SUPRASPINAL CONTRIBUTIONS

Speed-Dependent Networks

In vertebrate swimmers, the neural mechanisms responsible for controlling locomotor speed involve both supraspinal and spinal structures. The MLR has been shown to act like a gas pedal by controlling the power of locomotor output (Ref. 199; for review see Ref. 161). In every animal species where the MLR was identified, increasing the stimulation strength of this region linearly increased the locomotor output, indicating that the MLR controls the speed of locomotion by modulating the excitatory drive onto reticulospinal neurons that in turn directly activate spinal CPG neurons (e.g., lamprey: Ref. 126, salamander: Refs. 24, 123, mouse: Refs. 124, 130–132, 134, 155, 190, 191, zebrafish: Ref. 125, reviewed in Refs. 20, 22, 23).

The spinal mechanisms underlying locomotor speed control were also recently investigated. A first series of studies in larval zebrafish revealed that different layers of motoneurons and interneurons neurons are recruited as a function of swimming speed (29, 200) (Fig. 2D). In adult zebrafish, double patch-clamp experiments during locomotor activity revealed that separate classes of ipsilaterally projecting glutamatergic V2a interneurons selectively activate slow, intermediate, and fast motoneuronal pools (31, 201). Interestingly, speed-dependent activity was also observed in commissural excitatory VO_v interneurons in adult zebrafish (202). In adult zebrafish, inhibitory commissural interneurons were also shown to be recruited in a speed-dependent manner (203). Axial motoneurons themselves contribute to the generation of the swimming rhythm by acting on premotor CPG interneurons through electrical coupling (Ref. 204; see however Ref. 205 in lamprey). These separate neural modules allow for the increase of swimming speed by sequentially adding slow, intermediate, and fast microcircuits likely through the activation of descending inputs from the brain stem motor command centers. Although the organization of the descending excitatory drive to these different subclasses of neurons remains unknown, reticulospinal cells receiving a direct input from the MLR are good candidates. In adult zebrafish, brain stem glutamatergic neurons with axons in the medial longitudinal fasciculus were found to be important in the control of speed-related spinal modules (174).

In tetrapods, a modular reciprocal organization of premotor inhibitory and excitatory networks has been suggested for the hindlimb CPG in the neonatal mouse (32, 206). Whether the modules can be further subdivided into specific subunits driving slow, intermediate, and fast motoneuron pools (as indicated above) remains to be determined. An additional complexity is the high variability in the motor unit composition between limb muscles in the adult stage (207).

Asymmetric Control of Stance and Swing Phases and Forelimb-Hindlimb CPG Differences

In adult tetrapods, a change in stepping speed is accomplished by varying the duration of the stance phase, while the swing phase remains relatively invariant (reviewed in Ref. 76). This extensor/flexor asymmetry is an inbuilt property of the limb CPG as shown by electrophysiological recordings in decerebrate/spinal cats and optogenetics in *in vitro* isolated spinal cords of neonatal mice (54, 208). This suggests that the bursting capabilities of rhythm-generating flexor circuits are stronger than those of the rhythm-generating extensor circuits (cf. Refs. 93, 209). Simulations of the mammalian CPG revealed that the flexor burst can be kept constant, whereas the duration of the extensor burst could vary by 10-fold when the excitatory drive to the extensor part of the network was changed (95). However, descending signals from the brain stem (e.g., indirect inputs from the MLR) and proprioceptive signals can contribute to produce the different modes of phase-cycle period changes observed during locomotion (208, 210).

Quadrupeds commonly switch between gaits or between locomotor modes as they change their speed of locomotion (211). For example, in salamanders ground locomotor speed increases by switching from walking to trotting (i.e., change in gait) and in water by switching from trotting to swimming (i.e., change in locomotor mode) (212–215). Studies using selective ablation of genetically identified commissural interneurons in neonate rodents suggest a gait-dependent organization of the commissural neuron population at the pelvic girdle (see Ref. 67 for review). Data in neonatal mice suggest that a group of inhibitory interneurons ensures hindlimb alternation during slow walking frequencies, whereas a distinct group of excitatory interneurons is recruited at higher frequencies to maintain left-right hindlimb alternation (32).

It is likely that forelimb and hindlimb CPGs are organized differently. An early study suggested that the commissural connections between forelimb CPGs are less flexible than those between hindlimb CPGs. The coordination pattern between forelimb CPGs is always a left-right alternation during spontaneous fictive locomotion in the cat (216). In contrast, several fictive coordination patterns between hindlimb CPGs have been reported, each one corresponding to a specific gait (walk, trot, or gallop) (6, 56, 216, 217). Furthermore, forelimb-axial coupling appears to be stronger than the hindlimb-axial coupling during fictive locomotion in salamanders (215). Differences between the intrinsic frequencies of the forelimb and hindlimb CPGs have also been reported (Refs. 55, 80, 217; see Ref. 61, however). Taken together, these

functional differences between the cervical and pelvic girdle CPGs are likely related to the observation that the hindlimbs are more involved in gait changes than the forelimbs (218).

Switches in Coordination during Fictive Locomotion: What Do They Tell Us?

Spontaneous abrupt switches between fictive gaits have been observed in thalamic, decerebrate, and high spinal-paralyzed cats, thus revealing that spinal motor circuits are sufficient to govern gait changes (216, 217, 219). Switches between rostrocaudal waves and caudorostral waves were also reported during fictive locomotion in lampreys (39, 40) and salamanders (215, 220). The central pathways and the mechanisms underlying fictive gait switches are not fully understood. Simulations of the lamprey locomotor circuitry showed that switches in coordination between rostro-caudal and caudo-rostral waves can easily be accounted for (267). The mechanism proposed is the trailing oscillator hypothesis, according to which the oscillator of higher excitability leads the oscillator chain (39, 40). The rostral oscillator leads the chain during rostrocaudal traveling waves (forward swimming), and the caudal oscillator leads the chain during caudorostral traveling waves (backward swimming) (39, 40, 267). Similarly, in a modeling study of the salamander locomotor circuitry (221) local uncontrolled fluctuations of the tonic pharmacological drive evoked by glutamatergic agonists in the bath could play a role in the status of saturation of forelimb versus hindlimb oscillatory centers, and this would in turn influence the propagation direction of the traveling wave in the axial circuit. Several findings suggest that propriospinal neurons connecting the lumbar and cervical enlargements could also be involved, but the relative strength of ascending and descending influences seems to depend on the preparation used (55, 58, 59, 80, 216). A study using genetic tools has revealed a complex functional organization of the propriospinal pathways in mice (222). The ascending tracts (e.g., the ventral spinocerebellar tract) that give off collaterals at more rostral spinal segmental levels and exhibit rhythmic activity during fictive locomotion could contribute to intergirdle coordination (76). It is likely that the central interactions between the forelimb and hindlimb networks are functionally separated, in accordance with the different functional modules described within each limb CPG (223). This modular design increases the dynamics of the interlimb coordinating network by increasing its number of degrees of freedom. A model of interlimb coordination considering part of this modular organization replicates the speed-dependent expression of locomotor gaits and transitions between them as observed *in vivo* (224).

The switch between two hindlimb fictive gaits is always complete within one or two cycles (216). This supports the view that switch from one fictive hindlimb gait to another results from a transition from one motor program to another (225). However, other mechanisms can be involved during real locomotion. Indeed, several observations in vertebrates suggest that the movement-related inputs from the limbs can couple or decouple the fore- and hindlimbs during real locomotion (225–232). In line with this, spinal cats can walk forward or backward depending on the direction of the treadmill (233). Inputs from supraspinal structures also likely

play a critical role in intergirdle coordination switches during real locomotion (234–237). This could explain why both gradual and abrupt switches between gaits are observed in intact animals (238), whereas only abrupt switches are observed during fictive locomotion (216, 219).

In conclusion, the central coordination of the four limbs can be viewed as resulting from the interactions between forelimb and hindlimb CPGs with several different preferred modes of coupling. However, the forelimb and hindlimb CPGs sometimes may be uncoupled and run freely in various fictive preparations (59, 80, 217) and in split-belt experiments in cats (239). This emphasizes the important role of the movement-related afferent feedback in interlimb coordination.

Coordination between Limb and Axial CPGs during Locomotion

It should be stressed here that in searching for the central mechanisms underlying interlimb coordination it is necessary to include the network controlling the body axis. During locomotion in cats and humans, there are two bursts of EMG activity in lower back muscles for each step cycle (Refs. 240–242; for review Ref. 243). During alternate stepping in high decerebrate cats the back muscles have two bursts of activity per step cycle, but during gallop the back muscle activity is a single burst of ~200-ms duration that starts some 75 ms before the onset of activity in the quadriceps (242).

Interestingly, during pharmacologically induced fictive locomotion in the high spinal cat (lesion at the upper cervical level) the muscle nerves innervating the lumbar back muscles display a variety of rhythmic patterns corresponding to the different gaits observed in freely moving animals (219). Systematic investigations of the different motor patterns produced by in vitro isolated spinal cords of several lower vertebrates have revealed a high degree of flexibility in the intersegmental coordination pattern, i.e., in the operating mode of the CPG controlling the body axis (39, 40, 215, 244). Intersegmental phase lags range from positive values (i.e., backward-propagating motor waves) to negative values (i.e., forward-propagating motor waves). Importantly, each fictive axial motor pattern is characterized by a distinct combination of intersegmental phase lags and cycle durations (215, 244). The flexibility in the fictive axial motor pattern has been related to the diversity of locomotor modes observed in vivo (Refs. 39, 40, 215, 221, 244; see also Ref. 245).

The mechanisms of axial motor pattern selection (i.e., switch between locomotor modes) remain to be identified. Studies in lower vertebrates have demonstrated that some spinal neurons (multifunctional neurons) are shared by several rhythmic axial motor patterns whereas others (specialized neurons) are dedicated to a specific pattern (Ref. 246; for review see Ref. 247). As an example, a core of neurons producing left-right alternation is used during forward and backward swimming in larval zebrafish, whereas separate groups of neurons are recruited to produce the intersegmental coordination pattern specific of each swimming mode (248).

Some findings in lamprey, larval zebrafish, and *Xenopus* tadpole further suggest that tonic inputs from distinct brain

stem nuclei and sensory inputs from specific areas of the body (e.g., head/tail) play a critical role in switching between axial locomotor modes (249–251). This suggests that each type of sensory or descending input activates a specialized spinal network dedicated to producing just one behavior. An alternative view is that a single spinal network is sufficient to produce multiple rhythmic motor patterns through its reconfiguration induced by descending and afferent inputs (252).

Modeling and robotics experiments suggest that in salamanders a single spinal network controlling the axial musculature generates traveling waves during swimming but is made to generate standing waves when under the influence of limb controllers during walking (253). One possible mechanism for locomotor mode transition might be a gating process by which the MLR drive would not be transmitted from reticulospinal neurons to the limb controllers when it exceeds a certain threshold. Another possibility would be a spinal mechanism by which the limb oscillators, but not the axial ones, would have a limited capability to oscillate at high frequency (“saturation”) (253).

The intrinsic frequency of the limb CPGs is lower than that of the axial CPG in adult salamanders (253), *Xenopus* at metamorphic climax (“froglet”, Ref. 254) and newborn rats (Ref. 255; see Ref. 256, however). The difference in the intrinsic frequencies of limb and axial oscillators in salamanders provides an explanation for the abrupt increase of frequency during the switch from stepping to swimming when limb oscillators saturate (253). A similar mechanism might explain the abrupt transition between slow and fast swimming in zebrafish (257, 258). In froglet, the coupling of the axial and the hindlimb CPGs for swimming appears to be under aminergic control to set the swimming mode (“tail based” or “limb based”) to the demands of the animal (254).

A neurobiological study in salamander suggests that the central coupling between the limbs and the axial CPGs is mainly local, i.e., it involves a coupling of limb oscillators to the nearest axial oscillators, as opposed to a coupling to large parts of the axial CPG (215). A numerical simulation has suggested that this configuration of the locomotor network is able to generate several of the various locomotor modes and gaits (swimming, forward and backward land stepping, forward aquatic stepping) expressed by salamanders, as well as transition between them, when under control of only two drives, which can be provided by the brain stem or by sensory feedback (259). Further experiments are needed to elucidate the mechanisms involved.

CONCLUSIONS

Studies in different animal models have yielded important advances in our understanding of the control of locomotion. Whereas mammalian studies have traditionally provided important information at the system level, studies in lamprey and *Xenopus* tadpole, with their simpler nervous systems, have additionally elucidated many of the cellular and synaptic mechanisms underlying locomotion thanks to electrophysiological, anatomical, and imaging experiments. More recently, optogenetic techniques used in zebrafish and in mice now pave the way for characterizing the role of genetically identified neurons. With a powerful set of genetic tools in development, the salamander is now becoming an

attractive model to understand the development of limb controllers and their interaction with axial networks, as well as their control by the brain and sensory feedback, before and after regeneration of the nervous system (260). From a historical perspective, the complementary approaches from all these preparations undoubtedly contribute to increase the speed at which neuroscientists can reach a better understanding of the neural control of locomotion. Although not explored here, muscle anatomy, muscle dynamics, and sensory feedback also contribute in addition to the CPGs to the production of different gaits (261–263). Because of the complexity of the interactions between these components, a global approach combining neurosciences, modeling, and genetics is needed to understand locomotion (260, 264, 265).

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

D.R. prepared figures; R.D. and J.-M.C. drafted manuscript; R.D., J.-M.C., and D.R. edited and revised manuscript; R.D. and D.R. approved final version of manuscript.

REFERENCES

1. Grillner S, El Manira A. Current principles of motor control, with special reference to vertebrate locomotion. *Physiol Rev* 100: 271–320, 2020. doi:10.1152/physrev.00015.2019.
2. Pearson KG. Common principles of motor control in vertebrates and invertebrates. *Annu Rev Neurosci* 16: 265–297, 1993. doi:10.1146/annurev.ne.16.030193.001405.
3. Selverston AI. Invertebrate central pattern generator circuits. *Philos Trans R Soc Lond B Biol Sci* 365: 2329–2345, 2010. doi:10.1098/rstb.2009.0270.
4. Engberg I, Lundberg A. An electromyographic analysis of muscular activity in the hindlimb of the cat during unrestrained locomotion. *Acta Physiol Scand* 75: 614–630, 1969. doi:10.1111/j.1748-1716.1969.tb04415.x.
5. Grillner S, Zangger P. How detailed is the central pattern generation for locomotion? *Brain Res* 88: 367–371, 1975. doi:10.1016/0006-8993(75)90401-1.
6. Grillner S, Zangger P. On the central generation of locomotion in the low spinal cat. *Exp Brain Res* 34: 241–261, 1979. doi:10.1007/BF00235671.
7. Jankowska E, Jukes MG, Lund S, Lundberg A. The effect of DOPA on the spinal cord. 5. Reciprocal organization of pathways transmitting excitatory action to alpha motoneurons of flexors and extensors. *Acta Physiol Scand* 70: 369–388, 1967. doi:10.1111/j.1748-1716.1967.tb03636.x.
8. Jankowska E, Jukes MG, Lund S, Lundberg A. The effect of DOPA on the spinal cord. 6. Half-centre organization of interneurons transmitting effects from the flexor reflex afferents. *Acta Physiol Scand* 70: 389–402, 1967. doi:10.1111/j.1748-1716.1967.tb03637.x.
9. Stuart DG, Hultborn H. Thomas Graham Brown (1882–1965), Anders Lundberg (1920–), and the neural control of stepping. *Brain Res Rev* 59: 74–95, 2008. doi:10.1016/j.brainresrev.2008.06.001.
10. Graham Brown T. The intrinsic factors in the act of progression in mammals. *Proc R Soc Lond B Biol Sci* 84: 308–319, 1911. doi:10.1098/rspb.1911.0077.
11. Graham Brown T. On the nature of the fundamental activity of the nervous centres: together with an analysis of the conditioning of rhythmic activity in progression, and a theory of the evolution of function in the nervous system. *J Physiol* 48: 18–46, 1914. doi:10.1113/jphysiol.1914.sp001646.
12. Sherrington CS. Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. *J Physiol* 40: 28–121, 1910. doi:10.1113/jphysiol.1910.sp001362.
13. Grillner S, Zangger P. The effect of dorsal root transection on the efferent motor pattern in the cat's hindlimb during locomotion. *Acta Physiol Scand* 120: 393–405, 1984. doi:10.1111/j.1748-1716.1984.tb07400.x.
14. Grillner S. Locomotion in vertebrates: central mechanisms and reflex interaction. *Physiol Rev* 55: 247–304, 1975. doi:10.1152/physrev.1975.55.2.247.
15. Stevenson PA, Kutsch W. A reconsideration of the central pattern generator concept for locust flight. *J Comp Physiol A* 161: 115–129, 1987. doi:10.1007/BF00609460.
16. Wilson DM. The central nervous control of flight in a locust. *J Exp Biol* 38: 471–490, 1961. doi:10.1242/jeb.38.2.471.
17. Shik ML, Severin FV, Orlovskii GN. Control of walking and running by means of electric stimulation of the midbrain. *Biofizika* 11: 659–666, 1966.
18. Ryczko D, Dubuc R. The multifunctional mesencephalic locomotor region. *Curr Pharm Des* 19: 4448–4470, 2013. doi:10.2174/1381612811319240011.
19. Arber S, Costa RM. Networking brainstem and basal ganglia circuits for movement. *Nat Rev Neurosci* 23: 342–360, 2022. doi:10.1038/s41583-022-00581-w.
20. Ferreira-Pinto MJ, Ruder L, Capelli P, Arber S. Connecting circuits for supraspinal control of locomotion. *Neuron* 100: 361–374, 2018. doi:10.1016/j.neuron.2018.09.015.
21. Leiras R, Cregg JM, Kiehn O. Brainstem circuits for locomotion. *Annu Rev Neurosci* 45: 63–85, 2022. doi:10.1146/annurev-neuro-082321-025137.
22. Ryczko D. The mesencephalic locomotor region: multiple cell types, multiple behavioral roles, and multiple implications for disease. *Neuroscientist* 2022: 10738584221139136, 2022. doi:10.1177/10738584221139136.
23. Cabelguen JM, Bourcier-Lucas C, Dubuc R. Bimodal locomotion elicited by electrical stimulation of the midbrain in the salamander *Notophthalmus viridescens*. *J Neurosci* 23: 2434–2439, 2003. doi:10.1523/JNEUROSCI.23-06-02434.2003.

25. **Grillner S.** Control of locomotion in bipeds, tetrapods, and fish. In: *Handbook of Physiology, The Nervous System*. Bethesda, MD: American Physiological Society, 1981, p. 1179–1236. doi:10.1002/cphy.cp010226.
26. **Perret C, Cabelguen JM.** Main characteristics of the hindlimb locomotor cycle in the decorticate cat with special reference to bifunctional muscles. *Brain Res* 187: 333–352, 1980. doi:10.1016/0006-8993(80)90207-3.
27. **Perret C, Cabelguen JM, Orsal D.** *Stance and Motion: Facts and Concepts: 3rd Soviet-French Roundtable Meeting on Neurobiology*. New York: Plenum Press, 1989.
28. **Rybak IA, Shevtsova NA, Lafreniere-Roula M, McCrear DA.** Modelling spinal circuitry involved in locomotor pattern generation: insights from deletions during fictive locomotion. *J Physiol* 577: 617–639, 2006. doi:10.1113/jphysiol.2006.118703.
29. **McLean DL, Fan J, Higashijima S, Hale ME, Fetcho JR.** A topographic map of recruitment in spinal cord. *Nature* 446: 71–75, 2007. doi:10.1038/nature05588.
30. **Gabriel JP, Ausborn J, Ampatzis K, Mahmood R, Eklöf-Ljunggren E, El Manira A.** Principles governing recruitment of motoneurons during swimming in zebrafish. *Nat Neurosci* 14: 93–99, 2011. doi:10.1038/nn.2704.
31. **Ampatzis K, Song J, Ausborn J, El Manira A.** Separate microcircuit modules of distinct V2a interneurons and motoneurons control the speed of locomotion. *Neuron* 83: 934–943, 2014. doi:10.1016/j.neuron.2014.07.018.
32. **Talpalal AE, Bouvier J, Borgius L, Fortin G, Pierani A, Kiehn O.** Dual-mode operation of neuronal networks involved in left-right alternation. *Nature* 500: 85–88, 2013. doi:10.1038/nature12286.
33. **Jackson AW, Horinek DF, Boyd MR, McClellan AD.** Disruption of left-right reciprocal coupling in the spinal cord of larval lamprey abolishes brain-initiated locomotor activity. *J Neurophysiol* 94: 2031–2044, 2005 [Erratum in *J Neurophysiol* 94: 3658, 2005]. doi:10.1152/jn.00039.2005.
34. **Messina JA, St Paul A, Hargis S, Thompson WE, McClellan AD.** Elimination of left-right reciprocal coupling in the adult lamprey spinal cord abolishes the generation of locomotor activity. *Front Neural Circuits* 11: 89, 2017. doi:10.3389/fncir.2017.00089.
35. **Kahn JA, Roberts A.** Experiments on the central pattern generator for swimming in amphibian embryos. *Philos Trans R Soc Lond B Biol Sci* 296: 229–243, 1982. doi:10.1098/rstb.1982.0004.
36. **Kahn JA, Roberts A.** The central nervous origin of the swimming motor pattern in embryos of *Xenopus laevis*. *J Exp Biol* 99: 185–196, 1982. doi:10.1242/jeb.99.1.185.
37. **Kahn JA, Roberts A.** The neuromuscular basis of rhythmic struggling movements in embryos of *Xenopus laevis*. *J Exp Biol* 99: 197–205, 1982. doi:10.1242/jeb.99.1.197.
38. **Soffe SR.** Roles of glycinergic inhibition and N-methyl-D-aspartate receptor mediated excitation in the locomotor rhythmicity of one half of the *Xenopus* embryo central nervous system. *Eur J Neurosci* 1: 561–571, 1989. doi:10.1111/j.1460-9568.1989.tb00363.x.
39. **Matsushima T, Grillner S.** Local serotonergic modulation of calcium-dependent potassium channels controls intersegmental coordination in the lamprey spinal cord. *J Neurophysiol* 67: 1683–1690, 1992. doi:10.1152/jn.1992.67.6.1683.
40. **Matsushima T, Grillner S.** Neural mechanisms of intersegmental coordination in lamprey: local excitability changes modify the phase coupling along the spinal cord. *J Neurophysiol* 67: 373–388, 1992. doi:10.1152/jn.1992.67.2.373.
41. **Cangiano L, Grillner S.** Fast and slow locomotor burst generation in the hemispinal cord of the lamprey. *J Neurophysiol* 89: 2931–2942, 2003. doi:10.1152/jn.01100.2002.
42. **Cangiano L, Grillner S.** Mechanisms of rhythm generation in a spinal locomotor network deprived of crossed connections: the lamprey hemicord. *J Neurosci* 25: 923–935, 2005. doi:10.1523/JNEUROSCI.2301-04.2005.
43. **Ryczko D, Charrier V, Ijspeert A, Cabelguen JM.** Segmental oscillators in axial motor circuits of the salamander: distribution and bursting mechanisms. *J Neurophysiol* 104: 2677–2692, 2010. doi:10.1152/jn.00479.2010.
44. **Cangiano L, Hill RH, Grillner S.** The hemisegmental locomotor network revisited. *Neuroscience* 210: 33–37, 2012. doi:10.1016/j.neuroscience.2012.03.007.
45. **Charrier V, Cabelguen JM.** Fictive rhythmic motor patterns produced by the tail spinal cord in salamanders. *Neuroscience* 255: 191–202, 2013. doi:10.1016/j.neuroscience.2013.10.020.
46. **Mullins OJ, Hackett JT, Buchanan JT, Friesen WO.** Neuronal control of swimming behavior: comparison of vertebrate and invertebrate model systems. *Prog Neurobiol* 93: 244–269, 2011. doi:10.1016/j.pneurobio.2010.11.001.
47. **Cangiano L, Grillner S.** Commentary: Elimination of left-right reciprocal coupling in the adult lamprey spinal cord abolishes the generation of locomotor activity. *Front Neural Circuits* 12: 34, 2018. doi:10.3389/fncir.2018.00034.
48. **Wiggin TD, Peck JH, Masino MA.** Coordination of fictive motor activity in the larval zebrafish is generated by non-segmental mechanisms. *PLoS One* 9: e109117, 2014. doi:10.1371/journal.pone.0109117.
49. **Wolf E, Soffe SR, Roberts A.** Longitudinal neuronal organization and coordination in a simple vertebrate: a continuous, semi-quantitative computer model of the central pattern generator for swimming in young frog tadpoles. *J Comput Neurosci* 27: 291–308, 2009. doi:10.1007/s10827-009-0143-9.
50. **Grillner S.** Biological pattern generation: the cellular and computational logic of networks in motion. *Neuron* 52: 751–766, 2006. doi:10.1016/j.neuron.2006.11.008.
51. **Grillner S.** Neuronal networks in motion from ion channels to behaviour. *An R Acad Nac Med (Madr)* 123: 297–298, 2006.
52. **Cheng J, Stein RB, Jovanović K, Yoshida K, Bennett DJ, Han Y.** Identification, localization, and modulation of neural networks for walking in the mudpuppy (*Necturus maculatus*) spinal cord. *J Neurosci* 18: 4295–4304, 1998. doi:10.1523/JNEUROSCI.18-11-04295.1998.
53. **Currie SN.** Fictive hindlimb motor patterns evoked by AMPA and NMDA in turtle spinal cord-hindlimb nerve preparations. *J Physiol (Paris)* 93: 199–211, 1999. doi:10.1016/S0928-4257(99)80152-1.
54. **Hägglund M, Dougherty KJ, Borgius L, Itohara S, Iwasato T, Kiehn O.** Optogenetic dissection reveals multiple rhythmogenic modules underlying locomotion. *Proc Natl Acad Sci USA* 110: 11589–11594, 2013. doi:10.1073/pnas.1304365110.
55. **Ballion B, Morin D, Viala D.** Forelimb locomotor generators and quadrupedal locomotion in the neonatal rat. *Eur J Neurosci* 14: 1727–1738, 2001. doi:10.1046/j.0953-816x.2001.01794.x.
56. **Cabelguen JM, Orsal D, Perret C, Zattara M.** Central pattern generation of forelimb and hindlimb locomotor activities in the cat. *Adv Physiol Sci* 1: 199–211, 1980.
57. **Frigon A, Thibaudier Y, Hurteau MF.** Modulation of forelimb and hindlimb muscle activity during quadrupedal tied-belt and split-belt locomotion in intact cats. *Neuroscience* 290: 266–278, 2015. doi:10.1016/j.neuroscience.2014.12.084.
58. **Juvin L, Le Gal JP, Simmers J, Morin D.** Cervicolumbar coordination in mammalian quadrupedal locomotion: role of spinal thoracic circuitry and limb sensory inputs. *J Neurosci* 32: 953–965, 2012. doi:10.1523/JNEUROSCI.4640-11.2012.
59. **Viala D, Vidal C.** Evidence for distinct spinal locomotion generators supplying respectively fore-and hindlimbs in the rabbit. *Brain Res* 155: 182–186, 1978. doi:10.1016/0006-8993(78)90322-0.
60. **Yamaguchi T.** The central pattern generator for forelimb locomotion in the cat. *Prog Brain Res* 143: 115–122, 2004. doi:10.1016/S0079-6123(03)43011-2.
61. **Zangger P.** The effect of 4-aminopyridine on the spinal locomotor rhythm induced by L-DOPA. *Brain Res* 215: 211–223, 1981. doi:10.1016/0006-8993(81)90503-5.
62. **Kiehn O.** Locomotor circuits in the mammalian spinal cord. *Annu Rev Neurosci* 29: 279–306, 2006. doi:10.1146/annurev.neuro.29.051605.112910.
63. **Quinlan KA, Kiehn O.** Segmental, synaptic actions of commissural interneurons in the mouse spinal cord. *J Neurosci* 27: 6521–6530, 2007. doi:10.1523/JNEUROSCI.1618-07.2007.
64. **Samara RF, Currie SN.** Crossed commissural pathways in the spinal hindlimb enlargement are not necessary for right left hindlimb alternation during turtle swimming. *J Neurophysiol* 98: 2223–2231, 2007. doi:10.1152/jn.00722.2007.
65. **Lafreniere-Roula M, McCrear DA.** Deletions of rhythmic motoneuron activity during fictive locomotion and scratch provide clues to the organization of the mammalian central pattern generator. *J Neurophysiol* 94: 1120–1132, 2005. doi:10.1152/jn.00216.2005.

66. **Rossignol S, Dubuc R, Gossard JP.** Dynamic sensorimotor interactions in locomotion. *Physiol Rev* 86: 89–154, 2006. doi:10.1152/physrev.00028.2005.
67. **Kiehn O.** Decoding the organization of spinal circuits that control locomotion. *Nat Rev Neurosci* 17: 224–238, 2016. doi:10.1038/nrn.2016.9.
68. **Talpalar AE, Endo T, Löw P, Borgius L, Hägglund M, Dougherty KJ, Ryge J, Hnasko TS, Kiehn O.** Identification of minimal neuronal networks involved in flexor-extensor alternation in the mammalian spinal cord. *Neuron* 71: 1071–1084, 2011. doi:10.1016/j.neuron.2011.07.011.
69. **Higashijima S, Masino MA, Mandel G, Fetcho JR.** Engrailed-1 expression marks a primitive class of inhibitory spinal interneuron. *J Neurosci* 24: 5827–5839, 2004. doi:10.1523/JNEUROSCI.5342-03.2004.
70. **Zhou Y, Yamamoto M, Engel JD.** GATA2 is required for the generation of V2 interneurons. *Development* 127: 3829–3838, 2000. doi:10.1242/dev.127.17.3829.
71. **Curtis DR, Eccles RM.** The excitation of Renshaw cells by pharmacological agents applied electrophoretically. *J Physiol* 141: 435–445, 1958. doi:10.1113/jphysiol.1958.sp005987.
72. **Engberg I, Lundberg A, Ryall RW.** Reticulospinal inhibition of transmission in reflex pathways. *J Physiol* 194: 201–223, 1968. doi:10.1113/jphysiol.1968.sp008402.
73. **Hultborn H, Jankowska E, Lindström S.** Recurrent inhibition of interneurons monosynaptically activated from group Ia afferents. *J Physiol* 215: 613–636, 1971. doi:10.1113/jphysiol.1971.sp009488.
74. **Hultborn H, Santini M.** Supraspinal control of monosynaptically activated group Ia interneurons in the ventral horn. *Acta Physiol Scand* 84: 142–144, 1972. doi:10.1111/j.1748-1716.1972.tb05164.x.
75. **Pratt CA, Jordan LM.** Ia inhibitory interneurons and Renshaw cells as contributors to the spinal mechanisms of fictive locomotion. *J Neurophysiol* 57: 56–71, 1987. doi:10.1152/jn.1987.57.1.56.
76. **Orlovsky GN, Deliagina TG, Grillner S.** *Neural Control of Locomotion, from Mollusc to Man.* New York: Oxford University Press, 1999.
77. **Rossignol S.** Neural control of stereotypic limb movements. In: *Handbook of Physiology Exercise, Regulation and Integration of Multiple Systems* edited by Rowel LB, Sheperd JT. Bethesda, MD: American Physiological Society, 1996, p. 173–215.
78. **Nishimaru H, Kudo N.** Formation of the central pattern generator for locomotion in the rat and mouse. *Brain Res Bull* 53: 661–669, 2000. doi:10.1016/S0361-9230(00)00399-3.
79. **Burke RE, Degtyarenko AM, Simon ES.** Patterns of locomotor drive to motoneurons and last-order interneurons: clues to the structure of the CPG. *J Neurophysiol* 86: 447–462, 2001. doi:10.1152/jn.2001.86.1.447.
80. **Cabelguen JM, Orsal D, Perret C, Zattara M.** Central pattern of forelimb and hindlimb locomotor activities in the cat. In: *Regulatory Functions of the CNS: Motion and Organisation Principles, Advances in Physiological Sciences*, edited by Szentagothai J, Palkovits M, Hamori J. Budapest: Pergamon Press/Akademiai Kiado, 1981, p. 199–211.
81. **Gödderz W, Illert M, Yamaguchi T.** Efferent pattern of fictive locomotion in the cat forelimb: with special reference to radial motor nuclei. *Eur J Neurosci* 2: 663–671, 1990. doi:10.1111/j.1460-9568.1990.tb00456.x.
82. **Iles JF, Nicolopoulos-Stourmaras S.** Fictive locomotion in the adult decerebrate rat. *Exp Brain Res* 109: 393–398, 1996. doi:10.1007/BF00229623.
83. **Orsal D, Perret C, Cabelguen JM.** Evidence of rhythmic inhibitory synaptic influences in hindlimb motoneurons during fictive locomotion in the thalamic cat. *Exp Brain Res* 64: 217–224, 1986. doi:10.1016/S0079-6123(08)63416-0.
84. **Perret C.** Synaptic influences contributing to the pattern of limb motoneuron activity during fictive locomotion in the cat. In: *Neurobiology of Vertebrate Locomotion*, edited by Grillner S, Stein PS, Stuart DG, Forsberg H, Herman RM. London: Macmillan, 1986, p. 173–184.
85. **Fleshman JW, Lev-Tov A, Burke RE.** Peripheral and central control of flexor digitorum longus and flexor hallucis longus motoneurons: the synaptic basis of functional diversity. *Exp Brain Res* 54: 133–149, 1984. doi:10.1007/BF00235825.
86. **Perret C.** Centrally generated pattern of motoneuron activity during locomotion in the cat. In: *Neural Origin of Rhythmic Movements*, edited by Roberts A, Roberts B. London: Society for Experimental Biology, 1983, p. 405–422.
87. **Perret C, Cabelguen JM, Orsal D.** Analysis of the pattern of activity in “knee flexor” motoneurons during locomotion in the cat. In: *Stance and Motion: Facts and Concepts*, edited by Gurfinkel VS, Ioffe ME, Massion J, Roll JP. New York: Plenum Press, 1988, p. 133–141.
88. **Griener A, Dyck J, Gosgnach S.** Regional distribution of putative rhythm-generating and pattern-forming components of the mammalian locomotor CPG. *Neuroscience* 250: 644–650, 2013. doi:10.1016/j.neuroscience.2013.07.070.
89. **McCrea DA, Rybak IA.** Organization of mammalian locomotor rhythm and pattern generation. *Brain Res Rev* 57: 134–146, 2008. doi:10.1016/j.brainresrev.2007.08.006.
90. **Danner SM, Zhang H, Shevtsova NA, Borowska-Fielding J, Deska-Gauthier D, Rybak IA, Zhang Y.** Spinal V3 interneurons and left-right coordination in mammalian locomotion. *Front Cell Neurosci* 13: 516, 2019. doi:10.3389/fncel.2019.00516.
91. **Rybak IA, Dougherty KJ, Shevtsova NA.** Organization of the mammalian locomotor CPG: review of computational model and circuit architectures based on genetically identified spinal interneurons. *eNeuro* 2: ENEURO.0069-15.2015, 2015. doi:10.1523/ENEURO.0069-15.2015.
92. **Zhang H, Shevtsova NA, Deska-Gauthier D, Mackay C, Dougherty KJ, Danner SM, Zhang Y, Rybak IA.** The role of V3 neurons in speed-dependent interlimb coordination during locomotion in mice. *Elife* 11: e73424, 2022. doi:10.7554/eLife.73424.
93. **Zhong G, Shevtsova NA, Rybak IA, Harris-Warrick RM.** Neuronal activity in the isolated mouse spinal cord during spontaneous deletions in fictive locomotion: insights into locomotor central pattern generator organization. *J Physiol* 1590: 4735–4759, 2012. doi:10.7554/eLife.73424.
94. **Markin SN, Lemay MA, Prilutsky BI, Rybak IA.** Motoneuronal and muscle synergies involved in cat hindlimb control during fictive and real locomotion: a comparison study. *J Neurophysiol* 107: 2057–2071, 2012. doi:10.1152/jn.00865.2011.
95. **Grillner S, Kozlov A.** The CPGs for limbed locomotion—facts and fiction. *Int J Mol Sci* 22: 5882, 2021. doi:10.3390/ijms22115882.
96. **Beloozerova IN, Sirota MG.** The role of the motor cortex in the control of accuracy of locomotor movements in the cat. *J Physiol* 461: 1–25, 1993. doi:10.1113/jphysiol.1993.sp019498.
97. **Beloozerova IN, Sirota MG.** The role of the motor cortex in the control of vigour of locomotor movements in the cat. *J Physiol* 461: 27–46, 1993. doi:10.1113/jphysiol.1993.sp019499.
98. **Bretzner F, Drew T.** Contribution of the motor cortex to the structure and the timing of hindlimb locomotion in the cat: a microstimulation study. *J Neurophysiol* 94: 657–672, 2005. doi:10.1152/jn.01245.2004.
99. **Drew T, Andujar JE, Lajoie K, Yakovenko S.** Cortical mechanisms involved in visuomotor coordination during precision walking. *Brain Res Rev* 57: 199–211, 2008. doi:10.1016/j.brainresrev.2007.07.017.
100. **Drew T, Marigold DS.** Taking the next step: cortical contributions to the control of locomotion. *Curr Opin Neurobiol* 33: 25–33, 2015. doi:10.1016/j.conb.2015.01.011.
101. **McElvain LE, Chen Y, Moore JD, Brigidi GS, Bloodgood BL, Lim BK, Costa RM, Kleinfeld D.** Specific populations of basal ganglia output neurons target distinct brain stem areas while collateralizing throughout the diencephalon. *Neuron* 109: 1721–1738.e4, 2021. doi:10.1016/j.neuron.2021.03.017.
102. **Roseberry TK, Lee AM, Lalive AL, Wilbrecht L, Bonci A, Kreitzer AC.** Cell-type-specific control of brainstem locomotor circuits by basal ganglia. *Cell* 164: 526–537, 2016. doi:10.1016/j.cell.2015.12.037.
103. **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 USA* 110: E3670–E3679, 2013. doi:10.1073/pnas.1314815110.
104. **Grillner S, Georopoulos AP, Jordan LM.** Selection and initiation of motor behavior. In: *Neurons, Networks, and Motor Behavior*, edited by Stein PS, Grillner S, Selverston AI, Stuart DG. Cambridge, MA: The MIT Press, 1997, p. 3–19.

105. Grillner S, Wallén P, Saitoh K, Kozlov A, Robertson B. Neural bases of goal-directed locomotion in vertebrates—an overview. *Brain Res Rev* 57: 2–12, 2008. doi:10.1016/j.brainresrev.2007.06.027.
106. Grillner S, Robertson B, Kotaleski JH. Basal ganglia—a motion perspective. *Compr Physiol* 10: 1241–1275, 2020. doi:10.1002/cphy.c190045.
107. Grillner S, Thompson WS. Basal ganglia reign through downstream control of motor centers in midbrain and brain stem while updating cortex with efference copy information. *Neuron* 109: 1587–1589, 2021. doi:10.1016/j.neuron.2021.04.015.
108. Armstrong DM. Supraspinal contributions to the initiation and control of locomotion in the cat. *Prog Neurobiol* 26: 273–361, 1986. doi:10.1016/0301-0082(86)90021-3.
109. Jordan LM. Brainstem control of locomotion. In: *Neurobiology of Vertebrate Locomotion*, edited by Grillner S, Stein PS, Stuart D, Forssberg H, Herman RM. London: MacMillan, 1986, p. 21–37.
110. Jordan LM. Initiation of locomotion in mammals. *Ann NY Acad Sci* 860: 83–93, 1998. doi:10.1111/j.1749-6632.1998.tb09040.x.
111. Grillner S, Dubuc R. Control of locomotion in vertebrates: spinal and supraspinal mechanisms. *Adv Neurol* 47: 425–453, 1988.
112. Whelan PJ. Control of locomotion in the decerebrate cat. *Prog Neurobiol* 49: 481–515, 1996. doi:10.1016/0301-0082(96)00028-7.
113. Dubuc R, Brocard F, Antri M, Fénelon K, Gariépy JF, Smetana R, Ménard A, Le Ray D, Viana Di Prisco G, Pearlstein E, Sirota MG, Derjean D, St-Pierre M, Zielinski B, Auclair F, Veilleux D. Initiation of locomotion in lampreys. *Brain Res Rev* 57: 172–182, 2008. doi:10.1016/j.brainresrev.2007.07.016.
114. Dubuc R. Locomotor regions in the midbrain (MLR) and diencephalon (DLR). In: *Encyclopedia of Neuroscience*, edited by Binder MD, Hirokawa N, Windhorst U. Berlin: Springer-Verlag, 2009, p. 2168–2171.
115. Le Ray D, Juvin L, Ryczko D, Dubuc R. Supraspinal control of locomotion: the mesencephalic locomotor region. *Prog Brain Res* 188: 51–70, 2011. doi:10.1016/B978-0-444-53825-3.00009-7.
116. Noga BR, Whelan PJ. The mesencephalic locomotor region: beyond locomotor control. *Front Neural Circuits* 16: 884785, 2022. doi:10.3389/fncir.2022.884785.
117. Garcia-Rill E, Skinner RD, Gilmore SA, Owings R. Connections of the mesencephalic locomotor region (MLR). II Afferents and efferents. *Brain Res Bull* 10: 63–71, 1983. doi:10.1016/0361-9230(83)90076-X.
118. Garcia-Rill E, Skinner RD, Conrad C, Mosley D, Campbell C. Projections of the mesencephalic locomotor region in the rat. *Brain Res Bull* 17: 33–40, 1986. doi:10.1016/0361-9230(86)90158-9.
119. Steeves JD, Jordan LM. Autoradiographic demonstration of the projections from the mesencephalic locomotor region. *Brain Res* 307: 263–276, 1984. doi:10.1016/0006-8993(84)90480-3.
120. Garcia-Rill E, Skinner RD. The mesencephalic locomotor region. I. Activation of a medullary projection site. *Brain Res* 411: 1–12, 1987. doi:10.1016/0006-8993(87)90675-5.
121. Garcia-Rill E, Skinner RD. The mesencephalic locomotor region. II. Projections to reticulospinal neurons. *Brain Res* 411: 13–20, 1987. doi:10.1016/0006-8993(87)90676-7.
122. Bretzner F, Brownstone RM. Lhx3-Chx10 reticulospinal neurons in locomotor circuits. *J Neurosci* 33: 14681–14692, 2013. doi:10.1523/JNEUROSCI.5231-12.2013.
123. 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* 524: 1361–1383, 2016. doi:10.1002/cne.23911.
124. Capelli P, Pivetta C, Soledad Esposito M, Arber S. Locomotor speed control circuits in the caudal brainstem. *Nature* 551: 373–377, 2017. doi:10.1038/nature24064.
125. Carbo-Tano M, Lapoix M, Jia X, Auclair F, Dubuc R, Wyart C. Functional coupling of the mesencephalic locomotor region and V2a reticulospinal neurons driving forward locomotion (Preprint). *bioRxiv* 2022.04.01.486703, 2022. doi:10.1101/2022.04.01.486703.
126. Brocard F, Dubuc R. Differential contribution of reticulospinal cells to the control of locomotion induced by the mesencephalic locomotor region. *J Neurophysiol* 90: 1714–1727, 2003. doi:10.1152/jn.00202.2003.
127. Le Ray D, Brocard F, Bourcier-Lucas C, Auclair F, Lafaille P, Dubuc R. Nicotinic activation of reticulospinal cells involved in the control of swimming in lampreys. *Eur J Neurosci* 17: 137–148, 2003. doi:10.1046/j.1460-9568.2003.02417.x.
128. Brocard F, Ryczko D, Fénelon K, Hatem R, Gonzales D, Auclair F, Dubuc R. The transformation of a unilateral locomotor command into a symmetrical bilateral activation in the brainstem. *J Neurosci* 30: 523–533, 2010. doi:10.1523/JNEUROSCI.3433-09.2010.
129. Smetana R, Juvin L, Dubuc R, Alford S. A parallel cholinergic brainstem pathway for enhancing locomotor drive. *Nat Neurosci* 13: 731–738, 2010. doi:10.1038/nn.2548.
130. Caggiano V, Leiras R, Goñi-Erro H, Masini D, Ballardita C, Bouvier J, Caldeira V, Fisone G, Kiehn O. Midbrain circuits that set locomotor speed and gait selection. *Nature* 553: 455–460, 2018. doi:10.1038/nature25448.
131. Dautan D, Kovács A, Bayasgalan T, Diaz-Acevedo MA, Pal B, Mena-Segovia J. Modulation of motor behavior by the mesencephalic locomotor region. *Cell Rep* 36: 109594, 2021. doi:10.1016/j.celrep.2021.109594.
132. Josset N, Roussel M, Lemieux M, Lafrance-Zoubga D, Rastqar A, Bretzner F. Distinct contributions of mesencephalic locomotor region nuclei to locomotor control in the freely behaving mouse. *Curr Biol* 28: 884–901.e3, 2018. doi:10.1016/j.cub.2018.02.007.
133. Lee AM, Hoy JL, Bonci A, Wilbrecht L, Stryker MP, Niell CM. Identification of a brainstem circuit regulating visual cortical state in parallel with locomotion. *Neuron* 83: 455–466, 2014. doi:10.1016/j.neuron.2014.06.031.
134. van der Zouwen CI, Boutin J, Fougère M, Flaive A, Vivancos M, Santuz A, Akay T, Sarret P, Ryczko D. Freely behaving mice can brake and turn during optogenetic stimulation of the mesencephalic locomotor region. *Front Neural Circuits* 15: 639900, 2021. doi:10.3389/fncir.2021.639900.
135. Gariépy JF, Missaghi K, Chevallier S, Chartré S, Robert M, Auclair F, Lund JP, Dubuc R. Specific neural substrate linking respiration to locomotion. *Proc Natl Acad Sci USA* 109: E84–E92, 2012 [Erratum in *Proc Natl Acad Sci USA* 109: 5133, 2012]. doi:10.1073/pnas.1113002109.
136. Hérent C, Diem S, Fortin G, Bouvier J. Upregulation of breathing rate during running exercise by central locomotor circuits (Preprint). *bioRxiv* 2021.07.28.453983, 2021. doi:10.1101/2021.07.28.453983.
137. Ferreira-Pinto MJ, Kanodia H, Falasconi A, Sigrist M, Esposito MS, Arber S. Functional diversity for body actions in the mesencephalic locomotor region. *Cell* 184: 4564–4578.e18, 2021. doi:10.1016/j.cell.2021.07.002.
138. Bhidayasiri R, Hathout G, Cohen SN, Tourtellotte WW. Midbrain ataxia: possible role of the pedunculopontine nucleus in human locomotion. *Cerebrovasc Dis* 16: 95–96, 2003. doi:10.1159/000070123.
139. Masdeu JC, Alampur U, Cavaliere R, Tavoulares G. Astasia and gait failure with damage of the pontomesencephalic locomotor region. *Ann Neurol* 35: 619–621, 1994. doi:10.1002/ana.410350517.
140. Ryczko D, Dubuc R. Dopamine and the brainstem locomotor networks: from lamprey to human. *Front Neurosci* 11: 295, 2017. doi:10.3389/fnins.2017.00295.
141. Jahn K, Deutschländer A, Stephan T, Kalla R, Wiesmann M, Strupp M, Brandt T. Imaging human supraspinal locomotor centers in brainstem and cerebellum. *Neuroimage* 39: 786–792, 2008. doi:10.1016/j.neuroimage.2007.09.047.
142. Ferraye MU, Debù B, Fraix V, Goetz L, Ardouin C, Yelnik J, Henry-Lagrange C, Seigneuret E, Piallat B, Krack P, Le Bas JF, Benabid AL, Chabardès S, Pollak P. Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease. *Brain* 133: 205–214, 2010. doi:10.1093/brain/awp229.
143. Khan S, Mooney L, Plaha P, Javed S, White P, Whone AL, Gill SS. Outcomes from stimulation of the caudal zona incerta and pedunculopontine nucleus in patients with Parkinson's disease. *Br J Neurosurg* 25: 273–280, 2011. doi:10.3109/02688697.2010.544790.
144. Mazzone P, Lozano A, Stanzione P, Galati S, Scarnati E, Peppe A, Stefani A. Implantation of human pedunculopontine nucleus: a safe and clinically relevant target in Parkinson's disease. *Neuroreport* 16: 1877–1881, 2005. doi:10.1097/01.wnr.0000187629.38010.12.
145. Moro E, Hamani C, Poon YY, Al-Khairallah T, Dostrovsky JO, Hutchison WD, Lozano AM. Unilateral pedunculopontine stimulation improves falls in Parkinson's disease. *Brain* 133: 215–224, 2010. doi:10.1093/brain/awp261.

146. **Peppe A, Pierantozzi M, Chiavalon C, Marchetti F, Caltagirone C, Musico M, Stanzione P, Stefani A.** Deep brain stimulation of the pedunculopontine tegmentum and subthalamic nucleus: effects on gait in Parkinson's disease. *Gait Posture* 32: 512–518, 2010. doi:10.1016/j.gaitpost.2010.07.012.
147. **Plaha P, Gill SS.** Bilateral deep brain stimulation of the pedunculopontine nucleus for Parkinson's disease. *Neuroreport* 16: 1883–1887, 2005. doi:10.1097/01.wnr.0000187637.20771.a0.
148. **Schrader C, Seehaus F, Capelle HH, Windhagen A, Windhagen H, Krauss JK.** Effects of pedunculopontine area and pallidal DBS on gait ignition in Parkinson's disease. *Brain Stimul* 6: 856–859, 2013. doi:10.1016/j.brs.2013.05.005.
149. **Stefani A, Lozano AM, Peppe A, Stanzione P, Galati S, Tropepi D, Pierantozzi M, Brusa L, Scarnati E, Mazzone P.** Bilateral deep brain stimulation of the pedunculopontine and subthalamic nuclei in severe Parkinson's disease. *Brain* 130: 1596–1607, 2007. doi:10.1093/brain/awl346.
150. **Thevathasan W, Coyne TJ, Hyam JA, Kerr G, Jenkinson N, Aziz TZ, Silburn PA.** Pedunculopontine nucleus stimulation improves gait freezing in Parkinson's disease. *Neurosurgery* 69: 1248–1253, 2011. doi:10.1227/NEU.0b013e31822b6f71.
151. **Mazzone P, Sposato S, Insola A, Scarnati E.** The deep brain stimulation of the pedunculopontine tegmental nucleus: towards a new stereotactic neurosurgery. *J Neural Transm (Vienna)* 118: 1431–1451, 2011. doi:10.1007/s00702-011-0593-x.
152. **Ostrem JL, Christine CW, Glass GA, Schrock LE, Starr PA.** Pedunculopontine nucleus deep brain stimulation in a patient with primary progressive freezing gait disorder. *Stereotact Funct Neurosurg* 88: 51–55, 2010. doi:10.1159/000268742.
153. **Wilcox RA, Cole MH, Wong D, Coyne T, Silburn P, Kerr G.** Pedunculopontine nucleus deep brain stimulation produces sustained improvement in primary progressive freezing of gait. *J Neurol Neurosurg Psychiatry* 82: 1256–1259, 2011. doi:10.1136/jnnp.2010.213462.
154. **Hazrati LN, Wong JC, Hamani C, Lozano AM, Poon YY, Dostrovsky JO, Hutchison WD, Zadikoff C, Moro E.** Clinicopathological study in progressive supranuclear palsy with pedunculopontine stimulation. *Mov Disord* 27: 1304–1307, 2012. doi:10.1002/mds.25123.
155. **Fougère M, van der Zouwen CI, Boutin J, Neszvecsko K, Sarret P, Ryczko D.** Optogenetic stimulation of glutamatergic neurons in the cuneiform nucleus controls locomotion in a mouse model of Parkinson's disease. *Proc Natl Acad Sci USA* 118: e2110934118, 2021. doi:10.1073/pnas.2110934118.
156. **Masini D, Kiehn O.** Targeted activation of midbrain neurons restores locomotor function in mouse models of parkinsonism. *Nat Commun* 13: 504, 2022. doi:10.1038/s41467-022-28075-4.
157. **Bachmann LC, Matis A, Lindau NT, Felder P, Gullo M, Schwab ME.** Deep brain stimulation of the midbrain locomotor region improves paretic hindlimb function after spinal cord injury in rats. *Sci Transl Med* 5: 208ra146, 2013. doi:10.1126/scitranslmed.3005972.
158. **Hofer AS, Scheuber MI, Sartori AM, Good N, Stalder SA, Hammer N, Fricke K, Schalbetter SM, Engmann AK, Weber RZ, Rust R, Schneider MP, Russi N, Favre G, Schwab ME.** Stimulation of the cuneiform nucleus enables training and boosts recovery after spinal cord injury. *Brain* 145: 3681–3697, 2022. doi:10.1093/brain/awac184.
159. **Roussel M, Lafrance-Zoubga D, Josset N, Lemieux M, Bretzner F.** Functional contribution of mesencephalic locomotor region nuclei to locomotor recovery after spinal cord injury. *Cell Rep Med* 4: 100946, 2023. doi:10.1016/j.xcrm.2023.100946.
160. **Grillner S, Robertson B.** The basal ganglia over 500 million years. *Curr Biol* 26: R1088–R1100, 2016. doi:10.1016/j.cub.2016.06.041.
161. **Ryczko D, Grätsch S, Auclair F, Dubé C, Bergeron S, Alpert MH, Cone JJ, Roitman MF, Alford S, Dubuc R.** Forebrain dopamine neurons project down to a brainstem region controlling locomotion. *Proc Natl Acad Sci USA* 110: E3235–E3242, 2013. doi:10.1073/pnas.1301125110.
162. **Ryczko D, Cone JJ, Alpert MH, Goetz L, Auclair F, Dubé C, Parent M, Roitman MF, Alford S, Dubuc R.** A descending dopamine pathway conserved from basal vertebrates to mammals. *Proc Natl Acad Sci USA* 113: E2440–E2449, 2016. doi:10.1073/pnas.1600684113.
163. **Sharma S, Kim LH, Mayr KA, Elliott DA, Whelan PJ.** Parallel descending dopaminergic connectivity of A13 cells to the brainstem locomotor centers. *Sci Rep* 8: 7972, 2018. doi:10.1038/s41598-018-25908-5.
164. **Sinnamon HM.** Preoptic and hypothalamic neurons and the initiation of locomotion in the anesthetized rat. *Prog Neurobiol* 41: 323–344, 1993. doi:10.1016/0301-0082(93)90003-B.
165. **El Manira A, Pombal MA, Grillner S.** Diencephalic projection to reticulospinal neurons involved in the initiation of locomotion in adult lampreys *Lampetra fluviatilis*. *J Comp Neurol* 389: 603–616, 1997. doi:10.1002/(SICI)1096-9861(19971229)389:4<603::AID-CNE5>3.0.CO;2-4.
166. **Ménard A, Grillner S.** Diencephalic locomotor region in the lamprey—afferents and efferent control. *J Neurophysiol* 100: 1343–1353, 2008. doi:10.1152/jn.01128.2007.
167. **Milner KL, Mogenson GJ.** Electrical and chemical activation of the mesencephalic and subthalamic locomotor regions in freely moving rats. *Brain Res* 452: 273–285, 1988. doi:10.1016/0006-8993(88)90031-5.
168. **Parker SM, Sinnamon HM.** Forward locomotion elicited by electrical stimulation in the diencephalon and mesencephalon of the awake rat. *Physiol Behav* 31: 581–587, 1983.
169. **Mogenson GJ, Swanson LW, Wu M.** Evidence that projections from substantia innominata to zona incerta and mesencephalic locomotor region contribute to locomotor activity. *Brain Res* 334: 65–76, 1985. doi:10.1016/0006-8993(85)90568-2.
170. **Périer C, Tremblay L, Féger J, Hirsch EC.** Behavioral consequences of bicuculline injection in the subthalamic nucleus and the zona incerta in rat. *J Neurosci* 22: 8711–8719, 2002. doi:10.1523/JNEUROSCI.22-19-08711.2002.
171. **Supko DE, Uretsky NJ, Wallace LJ.** Activation of AMPA/kainic acid glutamate receptors in the zona incerta stimulates locomotor activity. *Brain Res* 564: 159–163, 1991. doi:10.1016/0006-8993(91)91367-A.
172. **Supko DE, Uretsky NJ, Wallace LJ.** AMPA/kainic acid glutamate receptor antagonism in the zona incerta dorsal to the subthalamic nucleus inhibits amphetamine-induced stereotypy but not locomotor activity. *Brain Res* 576: 89–96, 1992. doi:10.1016/0006-8993(92)90612-D.
173. **Mori S, Matsui T, Kuze B, Asanome M, Nakajima K, Matsuyama K.** Cerebellar-induced locomotion: reticulospinal control of spinal rhythm generating mechanism in cats. *Ann NY Acad Sci* 860: 94–105, 1998. doi:10.1111/j.1749-6632.1998.tb09041.x.
174. **Berg EM, Mrowka L, Bertuzzi M, Madrid D, Picton LD, El Manira A.** Brainstem circuits encoding start, speed, and duration of swimming in adult zebrafish. *Neuron* 111: 372–386.e4, 2023. doi:10.1016/j.neuron.2022.10.034.
175. **Orlovsky GN.** Work of the reticulo-spinal neurones during locomotion. *Biofizika* 4: 728–737, 1970.
176. **Orlovsky GN.** The effect of different descending systems on flexor and extensor activity during locomotion. *Brain Res* 40: 359–371, 1972. doi:10.1016/0006-8993(72)90139-4.
177. **Buchanan JT, Brodin L, Dale N, Grillner S.** Reticulospinal neurones activate excitatory amino acid receptors. *Brain Res* 408: 321–325, 1987. doi:10.1016/0006-8993(87)90397-0.
178. **Rovainen CM.** Physiological and anatomical studies on large neurons of central nervous system of the sea lamprey (*Petromyzon marinus*). I. Müller and Mauthner cells. *J Neurophysiol* 30: 1000–1023, 1967. doi:10.1152/jn.1967.30.5.1000.
179. **Rovainen CM.** Synaptic interactions of reticulospinal neurons and nerve cells in the spinal cord of the sea lamprey. *J Comp Neurol* 154: 207–223, 1974. doi:10.1002/cne.901540207.
180. **Frost WN, Katz PS.** Single neuron control over a complex motor program. *Proc Natl Acad Sci USA* 93: 422–426, 1996. doi:10.1073/pnas.93.1.422.
181. **Puhl JG, Masino MA, Mesce KA.** Necessary, sufficient and permissive: a single locomotor command neuron important for intersegmental coordination. *J Neurosci* 32: 17646–17657, 2012. doi:10.1523/JNEUROSCI.2249-12.2012.
182. **Ohta Y, Grillner S.** Monosynaptic excitatory amino acid transmission from the posterior rhombencephalic reticular nucleus to spinal neurons involved in the control of locomotion in lamprey. *J Neurophysiol* 62: 1079–1089, 1989. doi:10.1152/jn.1989.62.5.1079.
183. **Grätsch S, Auclair F, Demers O, Auguste E, Hanna A, Büschges A, Dubuc R.** A brainstem neural substrate for stopping locomotion. *J Neurosci* 39: 1044–1057, 2019. doi:10.1523/JNEUROSCI.1992-18.2018.

184. Grätsch S, Büschges A, Dubuc R. Descending control of locomotor circuits. *Curr Opin Physiol* 8: 94–98, 2019. doi:10.1016/j.cophys.2019.01.007.
185. Juvin L, Grätsch S, Trillaud-Doppia E, Gariépy JF, Büschges A, Dubuc R. A specific population of reticulospinal neurons controls the termination of locomotion. *Cell Rep* 15: 2377–2386, 2016. doi:10.1016/j.celrep.2016.05.029.
186. Deliagina TG, Zelenin PV, Fagerstedt P, Grillner S, Orlovsky GN. Activity of reticulospinal neurons during locomotion in the freely behaving lamprey. *J Neurophysiol* 83: 853–863, 2000. doi:10.1152/jn.2000.83.2.853.
187. Shaw AC, Jackson AW, Holmes T, Thurman S, Davis GR, McClellan AD. Descending brain neurons in larval lamprey: spinal projection patterns and initiation of locomotion. *Exp Neurol* 224: 527–541, 2010. doi:10.1016/j.expneurol.2010.05.016.
188. Di Prisco GV, Pearlstein E, Robitaille R, Dubuc R. Role of sensory-evoked NMDA plateau potentials in the initiation of locomotion. *Science* 278: 1122–1125, 1997. doi:10.1126/science.278.5340.1122.
189. Zelenin PV. Reticulospinal neurons controlling forward and backward swimming in the lamprey. *J Neurophysiol* 105: 1361–1371, 2011. doi:10.1152/jn.00887.2010.
190. Hägglund M, Borgius L, Dougherty KJ, Kiehn O. Activation of groups of excitatory neurons in the mammalian spinal cord or hindbrain evokes locomotion. *Nat Neurosci* 13: 246–252, 2010. doi:10.1038/nn.2482.
191. Hsu LJ, Bertho M, Kiehn O. Deconstructing the modular organization and real-time dynamics of mammalian spinal locomotor networks. *Nat Commun* 14: 873, 2023. doi:10.1038/s41467-023-36587-w.
192. Kimura Y, Satou C, Fujioka S, Shoji W, Umeda K, Ishizuka T, Yawo H, Higashijima S. Hindbrain V2a neurons in the excitation of spinal locomotor circuits during zebrafish swimming. *Curr Biol* 23: 843–849, 2013. doi:10.1016/j.cub.2013.03.066.
193. Bouvier J, Caggiano V, Leiras R, Caldeira V, Bellardita C, Balueva K, Fuchs A, Kiehn O. Descending command neurons in the brainstem that halt locomotion. *Cell* 163: 1191–1203, 2015. doi:10.1016/j.cell.2015.10.074.
194. Schwenkgrub J, Harrell ER, Bathellier B, Bouvier J. Deep imaging in the brainstem reveals functional heterogeneity in V2a neurons controlling locomotion. *Sci Adv* 6: eabc6309, 2020. doi:10.1126/sciadv.abc6309.
195. Cregg JM, Leiras R, Montalant A, Wanken P, Wickersham IR, Kiehn O. Brainstem neurons that command mammalian locomotor asymmetries. *Nat Neurosci* 23: 730–740, 2020. doi:10.1038/s41593-020-0633-7.
196. 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* 30: 4665–4681.e6, 2020. doi:10.1016/j.cub.2020.09.014.
197. Perrins R, Walford A, Roberts A. Sensory activation and role of inhibitory reticulospinal neurons that stop swimming in hatchling frog tadpoles. *J Neurosci* 22: 4229–4240, 2002. doi:10.1523/JNEUROSCI.22-10-04229.2002.
198. Hsu LJ, Zelenin PV, Orlovsky GN, Deliagina TG. Supraspinal control of spinal reflex responses to body bending during different behaviours in lampreys. *J Physiol* 595: 883–900, 2017. doi:10.1113/JP272714.
199. Sirota MG, Di Prisco GV, Dubuc R. Stimulation of the mesencephalic locomotor region elicits controlled swimming in semi-intact lampreys. *Eur J Neurosci* 12: 4081–4092, 2000. doi:10.1046/j.1460-9568.2000.00301.x.
200. McLean DL, Masino MA, Koh IY, Lindquist WB, Fetcho JR. Continuous shifts in the active set of spinal interneurons during changes in locomotor speed. *Nat Neurosci* 11: 1419–1429, 2008. doi:10.1038/nn.2225.
201. Song J, Pallucchi 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. *Neuron* 105: 1048–1061.e4, 2020. doi:10.1016/j.neuron.2019.12.030.
202. Björnfors ER, El Manira A. Functional diversity of excitatory commissural interneurons in adult zebrafish. *Elife* 5: e18579, 2016. doi:10.7554/eLife.18579.
203. Picton LD, Björnfors ER, Fontanel P, Pallucchi I, Bertuzzi M, El Manira A. Developmental switch in the function of inhibitory commissural V0d interneurons in zebrafish. *Curr Biol* 32: 3515–3528.e4, 2022. doi:10.1016/j.cub.2022.06.059.
204. Song J, Ampatzis K, Björnfors ER, El Manira A. Motor neurons control locomotor circuit function retrogradely via gap junctions. *Nature* 529: 399–402, 2016. doi:10.1038/nature16497.
205. Wallén P, Lansner A. Do the motoneurons constitute a part of the spinal network generating the swimming rhythm in the lamprey? *J Exp Biol* 113: 493–497, 1984. doi:10.1242/jeb.113.1.493.
206. Endo T, Kiehn O. Asymmetric operation of the locomotor central pattern generator in the neonatal mouse spinal cord. *J Neurophysiol* 100: 3043–3054, 2008. doi:10.1152/jn.90729.2008.
207. Burke RE. Revisiting the notion of ‘motor unit types’. *Prog Brain Res* 123: 167–175, 1999.
208. Frigon A, Gossard JP. Asymmetric control of cycle period by the spinal locomotor rhythm generator in the adult cat. *J Physiol* 587: 4617–4628, 2009. doi:10.1113/jphysiol.2009.176669.
209. Duysens J, Pearson KG. The role of cutaneous afferents from the distal hindlimb in the regulation of the step cycle of thalamic cats. *Exp Brain Res* 24: 245–255, 1976. doi:10.1007/BF00235013.
210. Yakovenko S, McCrea DA, Stecina K, Prochazka A. Control of locomotor cycle durations. *J Neurophysiol* 94: 1057–1065, 2005. doi:10.1152/jn.00991.2004.
211. Hildebrand C. Growth of myelinated lumbosacral ventral root fibers in kittens after early postnatal dorsal rhizotomy, dorsal rhizotomy and spinal cord hemisection, or sciatic neurectomy. *Exp Neurol* 53: 189–213, 1976. doi:10.1016/0014-4886(76)90292-2.
212. Frolich LM, Biewener AA. Kinematic and electromyographic analysis of the functional role of the body axis during terrestrial and aquatic locomotion in the salamander *Ambystoma tigrinum*. *J Exp Biol* 162: 107–130, 1992. doi:10.1242/jeb.162.1.107.
213. Ashley-Ross M. Hindlimb kinematics during terrestrial locomotion in a salamander (*Dicamptodon tenebrosus*). *J Exp Biol* 193: 255–283, 1994. doi:10.1242/jeb.193.1.255.
214. Ashley-Ross M. Metamorphic and speed effects on hindlimb kinematics during speed effects on locomotion in the salamander *Dicamptodon tenebrosus*. *J Exp Biol* 193: 285–305, 1994. doi:10.1242/jeb.193.1.285.
215. Ryczko D, Knüsel J, Crespi A, Lamarque S, Mathou A, Ijspeert AJ, Cabelguen JM. Flexibility of the axial central pattern generator network for locomotion in the salamander. *J Neurophysiol* 113: 1921–1940, 2015. doi:10.1152/jn.00894.2014.
216. Orsal D, Cabelguen JM, Perret C. Interlimb coordination during fictive locomotion in the thalamic cat. *Exp Brain Res* 82: 536–546, 1990. doi:10.1007/BF00228795.
217. Rossignol S, Saltiel P, Perreault MC, Drew T, Pearson KG, Bélanger M. Intralimb and interlimb coordination in the cat during real and fictive rhythmic motor programs. *Neurosciences* 5: 67–75, 1993. doi:10.1016/S1044-5765(05)80026-0.
218. Maes L, Abourachid A. Gait transitions and modular organization of mammal locomotion. *J Exp Biol* 216: 2257–2265, 2013. doi:10.1242/jeb.082149.
219. Koehler WJ, Schomburg ED, Steffens H. Phasic modulation of trunk muscle efferents during fictive spinal locomotion in cats. *J Physiol* 353: 187–197, 1984. doi:10.1113/jphysiol.1984.sp015331.
220. Delvolvé I, Branchereau P, Dubuc R, Cabelguen JM. Fictive rhythmic motor pattern induced by NMDA in an in vitro brain stem-spinal cord preparation from an adult urodele. *J Neurophysiol* 82: 1074–1077, 1999. doi:10.1152/jn.1999.82.2.1074.
221. Knüsel J, Crespi A, Cabelguen JM, Ijspeert AJ, Ryczko D. Reproducing five motor behaviors in a salamander robot with virtual muscles and a distributed CPG controller regulated by drive signals and proprioceptive feedback. *Front Neurobot* 14: 604426, 2020. doi:10.3389/fnbot.2020.604426.
222. Ruder L, Takeoka A, Arber S. Long-distance descending spinal neurons ensure quadrupedal locomotor stability. *Neuron* 92: 1063–1078, 2016. doi:10.1016/j.neuron.2016.10.032.
223. Bellardita C, Kiehn O. Phenotypic characterization of speed-associated gait changes in mice reveals modular organization of locomotor networks. *Curr Biol* 25: 1426–1436, 2015. doi:10.1016/j.cub.2015.04.005.

224. **Danner SM, Wilshin SD, Shevtsova NA, Rybak IA.** Central control of interlimb coordination and speed-dependent gait expression in quadrupeds. *J Physiol* 594: 6947–6967, 2016. doi:10.1113/JP272787.
225. **Halbertsma J, Miller S, van der Meche FG.** Basic 'programs' for the phasing of flexion and extension movements of the limbs during locomotion. In: *Neural Control of Locomotion*, edited by Herman R, Grillner S, Stein P, Stuart D. New York: Plenum Press, 1976, p. 489–518.
226. **Forsberg H, Grillner S, Halbertsma J.** The locomotion of the low spinal cat. I. Coordination within a hindlimb. *Acta Physiol Scand* 108: 269–281, 1980. doi:10.1111/j.1748-1716.1980.tb06533.x.
227. **Forsberg H, Grillner S, Halbertsma J, Rossignol S.** The locomotion of the low spinal cat. II. Interlimb coordination. *Acta Physiol Scand* 108: 283–295, 1980. doi:10.1111/j.1748-1716.1980.tb06534.x.
228. **Bouyer LJ, Rossignol S.** Contribution of cutaneous inputs from the hindpaw to the control of locomotion. I. Intact cats. *J Neurophysiol* 90: 3625–3639, 2003. doi:10.1152/jn.00496.2003.
229. **Bouyer LJ, Rossignol S.** Contribution of cutaneous inputs from the hindpaw to the control of locomotion. II. Spinal cats. *J Neurophysiol* 90: 3640–3653, 2003. doi:10.1152/jn.00497.2003.
230. **Pearson KG.** Generating the walking gait: role of sensory feedback. *Prog Brain Res* 143: 123–129, 2004. doi:10.1016/S0079-6123(03)43012-4.
231. **Thibaudier Y, Hurteau MF, Telonio A, Frigon A.** Coordination between the fore- and hindlimbs is bidirectional, asymmetrically organized, and flexible during quadrupedal locomotion in the intact adult cat. *Neuroscience* 240: 13–26, 2013. doi:10.1016/j.neuroscience.2013.02.028.
232. **D'Angelo G, Thibaudier Y, Telonio A, Hurteau MF, Kuczynski V, Dambreville C, Frigon A.** Modulation of phase durations, phase variations, and temporal coordination of the four limbs during quadrupedal split-belt locomotion in intact adult cats. *J Neurophysiol* 112: 1825–1837, 2014. doi:10.1152/jn.00160.2014.
233. **Harnie J, Audet J, Klishko AN, Doelman A, Prilutsky BI, Frigon A.** The spinal control of backward locomotion. *J Neurosci* 41: 630–647, 2021. doi:10.1523/JNEUROSCI.0816-20.2020.
234. **Drew T, Dubuc R, Rossignol S.** Discharge patterns of reticulospinal and other reticular neurons in chronic, unrestrained cats walking on a treadmill. *J Neurophysiol* 55: 375–401, 1986. doi:10.1152/jn.1986.55.2.375.
235. **Drew T, Rossignol S.** Phase-dependent responses evoked in limb muscles by stimulation of medullary reticular formation during locomotion in thalamic cats. *J Neurophysiol* 52: 653–675, 1984. doi:10.1152/jn.1984.52.4.653.
236. **Lajoie K, Andujar JE, Pearson K, Drew T.** Neurons in area 5 of the posterior parietal cortex in the cat contribute to interlimb coordination during visually guided locomotion: a role in working memory. *J Neurophysiol* 103: 2234–2254, 2010. doi:10.1152/jn.01100.2009.
237. **Lavoie S, Drew T.** Discharge characteristics of neurons in the red nucleus during voluntary gait modifications: a comparison with the motor cortex. *J Neurophysiol* 88: 1791–1814, 2002. doi:10.1152/jn.2002.88.4.1791.
238. **English AW, Lennard PR.** Interlimb coordination during stepping in the cat: in-phase stepping and gait transitions. *Brain Res* 245: 353–364, 1982. doi:10.1016/0006-8993(82)90818-6.
239. **Thibaudier Y, Frigon A.** Spatiotemporal control of interlimb coordination during transverse split-belt locomotion with 1:1 or 2:1 coupling patterns in intact adult cats. *J Neurophysiol* 112: 2006–2018, 2014. doi:10.1152/jn.00236.2014.
240. **Carlson H, Halbertsma J, Zomlefer M.** Control of the trunk during walking in the cat. *Acta Physiol Scand* 105: 251–253, 1979. doi:10.1111/j.1748-1716.1979.tb06338.x.
241. **Thorstensson A, Carlson H, Zomlefer MR, Nilsson J.** Lumbar back muscle activity in relation to trunk movements during locomotion in man. *Acta Physiol Scand* 116: 13–20, 1982. doi:10.1111/j.1748-1716.1982.tb10593.x.
242. **Zomlefer MR, Provencher J, Blanchette G, Rossignol S.** Electromyographic study of lumbar back muscles during locomotion in acute high decerebrate and in low spinal cats. *Brain Res* 290: 249–260, 1984. doi:10.1016/0006-8993(84)90942-9.
243. **Cabelguen JM, Ijspeert A, Lamarque S, Ryczko D.** Axial dynamics during locomotion in vertebrates lesson from the salamander. *Prog Brain Res* 187: 149–162, 2010. doi:10.1016/B978-0-444-53613-6.00010-1.
244. **Green CS, Soffe SR.** Transitions between two different motor patterns in *Xenopus* embryos. *J Comp Physiol A* 178: 279–291, 1996. doi:10.1007/BF00188169.
245. **Hsu YW, Wang SD, Wang S, Morton G, Zariwala HA, de la Iglesia HO, Turner EE.** Role of the dorsal medial habenula in the regulation of voluntary activity, motor function, hedonic state, and primary reinforcement. *J Neurosci* 34: 11366–11384, 2014. doi:10.1523/JNEUROSCI.1861-14.2014.
246. **Hao ZZ, Spardy LE, Nguyen EB, Rubin JE, Berkowitz A.** Strong interactions between spinal cord networks for locomotion and scratching. *J Neurophysiol* 106: 1766–1781, 2011. doi:10.1152/jn.00460.2011.
247. **Berkowitz A, Roberts A, Soffe SR.** Roles for multifunctional and specialized spinal interneurons during motor pattern generation in tadpoles, zebrafish larvae, and turtles. *Front Behav Neurosci* 4: 36, 2010. doi:10.3389/fnbeh.2010.00036.
248. **Liao JC, Fetcho JR.** Shared versus specialized glycinergic spinal interneurons in axial motor circuits of larval zebrafish. *J Neurosci* 28: 12982–12992, 2008. doi:10.1523/JNEUROSCI.3330-08.2008.
249. **Budick SA, O'Malley DM.** Locomotor repertoire of the larval zebrafish: swimming, turning and prey capture. *J Exp Biol* 203: 2565–2579, 2000. doi:10.1242/jeb.203.17.2565.
250. **Hsu WC, Wang TM, Lu HL, Lu TW.** Anticipatory changes in control of swing foot and lower limb joints when walking onto a moving surface traveling at constant speed. *Gait Posture* 41: 185–191, 2015. doi:10.1016/j.gaitpost.2014.10.003.
251. **Roberts A, Li WC, Soffe SR.** How neurons generate behavior in a hatchling amphibian tadpole: an outline. *Front Behav Neurosci* 4: 16, 2010. doi:10.3389/fnbeh.2010.00016.
252. **Marder E, Bucher D, Schulz DJ, Taylor AL.** Invertebrate central pattern generation moves along. *Curr Biol* 15: R685–R699, 2005. doi:10.1016/j.cub.2005.08.022.
253. **Ijspeert AJ, Crespi A, Ryczko D, Cabelguen JM.** From swimming to walking with a salamander robot driven by a spinal cord model. *Science* 315: 1416–1420, 2007. doi:10.1126/science.1138353.
254. **Rauscent A, Einum J, Le Ray D, Simmers J, Combes D.** Opposing aminergic modulation of distinct spinal locomotor circuits and their functional coupling during amphibian metamorphosis. *J Neurosci* 29: 1163–1174, 2009. doi:10.1523/JNEUROSCI.5255-08.2009.
255. **Gabbay H, Delvolvé I, Lev-Tov A.** Pattern generation in caudal-lumbar and sacrococcygeal segments of the neonatal rat spinal cord. *J Neurophysiol* 88: 732–739, 2002. doi:10.1152/jn.2002.88.2.732.
256. **Falgairolle M, Cazalets JR.** Metachronal coupling between spinal neuronal networks during locomotor activity in newborn rat. *J Physiol* 580: 87–102, 2007. doi:10.1113/jphysiol.2006.115709.
257. **Green MH, Hale ME.** Activity of pectoral fin motoneurons during two swimming gaits in the larval zebrafish (*Danio rerio*) and localization of upstream circuit elements. *J Neurophysiol* 108: 3393–3402, 2012. doi:10.1152/jn.00623.2012.
258. **Thorsen DH, Cassidy JJ, Hale ME.** Swimming of larval zebrafish: fin-axis coordination and implications for function and neural control. *J Exp Biol* 207: 4175–4183, 2004. doi:10.1242/jeb.01285.
259. **Knüsel J, Bicanski A, Ryczko D, Cabelguen JM, Ijspeert AJ.** A salamander's flexible spinal network for locomotion, modeled at two levels of abstraction. *Integr Comp Biol* 53: 269–282, 2013. doi:10.1093/icb/ict067.
260. **Ryczko D, Simon A, Ijspeert AJ.** Walking with salamanders: from molecules to biorobotics. *Trends Neurosci* 43: 916–930, 2020. doi:10.1016/j.tins.2020.08.006.
261. **Biewener AA.** Locomotion as an emergent property of muscle contractile dynamics. *J Exp Biol* 219: 285–294, 2016. doi:10.1242/jeb.123935.
262. **Frigon A, Akay T, Prilutsky BI.** Control of mammalian locomotion by somatosensory feedback. *Compr Physiol* 12: 2877–2947, 2021. doi:10.1002/cphy.c210020.
263. **Thandiackal R, Melo K, Paez L, Herault J, Kano T, Akiyama K, Boyer F, Ryczko D, Ishiguro A, Ijspeert AJ.** Emergence of robust self-organized undulatory swimming based on local hydrodynamic force sensing. *Sci Robot* 6: eabf6354, 2021. doi:10.1126/scirobotics.abf6354.

264. **Ijspeert AJ.** Biorobotics: using robots to emulate and investigate agile locomotion. *Science* 346: 196–203, 2014. doi:[10.1126/science.1254486](https://doi.org/10.1126/science.1254486).
265. **Nishikawa K, Biewener AA, Aerts P, Ahn AN, Chiel HJ, Daley MA, Daniel TL, Full RJ, Hale ME, Hedrick TL, Lappin AK, Nichols TR, Quinn RD, Satterlie RA, Szymik B.** Neuromechanics: an integrative approach for understanding motor control. *Integr Comp Biol* 47: 16–54, 2007. doi:[10.1093/icb/icm024](https://doi.org/10.1093/icb/icm024).
266. **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* 82: 138–150, 2014. doi:[10.1016/j.neuron.2014.02.013](https://doi.org/10.1016/j.neuron.2014.02.013).
267. **Kozlov A, Huss M, Lansner A, Kotalleski JH, Grillner S.** Simple cellular and network control principles govern complex patterns of motor behavior. *Proc Natl Acad Sci USA* 106: 20027–20032, 2009. doi:[10.1073/pnas.0906722106](https://doi.org/10.1073/pnas.0906722106).
268. **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* 522: 3775–3794, 2014. doi:[10.1002/cne.23639](https://doi.org/10.1002/cne.23639).