

Nervous mechanisms of locomotion in different directions

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Locomotion, that is active propulsive movement of the body in space, is a vital motor function. Intensive studies of the main, for the majority of living beings, form of locomotion, forward locomotion, have revealed essential features of the organization and operation of underlying neural mechanisms. However, animals and humans are capable to locomote not only forward but also in other directions in relation to the body axis, for example backward, sideways, and so on. Single steps in different directions are also used for postural corrections during locomotion and during standing. Recent studies of mechanisms underlying control of locomotion in different directions have greatly expanded our knowledge about locomotor system and can contribute to improvement of rehabilitation strategies aimed at restoration of locomotion and balance control in patients. This review outlines recent advances in the studies of locomotion in different directions in lower and higher vertebrates, with special attention given to the neuronal locomotor mechanisms.

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Introduction

Locomotion is an evolutionary old basic motor function. Neural mechanisms for control of the main form of locomotion, forward locomotion, have been studied in different species from simple animals to humans [1]. These studies revealed basic principles in the organization and operation of these mechanisms common for phylogenetically remote species.

Most vertebrates can locomote not only forward but also in other directions. Thus, lower vertebrates exhibiting

axial locomotion can swim backward [2,3], and legged higher vertebrates can walk in any direction in relation to the body axis [4,5,6^{*}]. These forms of locomotion are usually generated in the context of avoidance behavior (called ‘escape’ in the lamprey and ‘struggling’ in the zebrafish and *Xenopus* tadpole). Also, single steps in different directions are used for postural corrections during locomotion [7,8] and during standing [9^{*},10,11].

This review outlines recent progress in understanding the neural mechanisms underlying control of locomotion in different directions in lower and higher vertebrates.

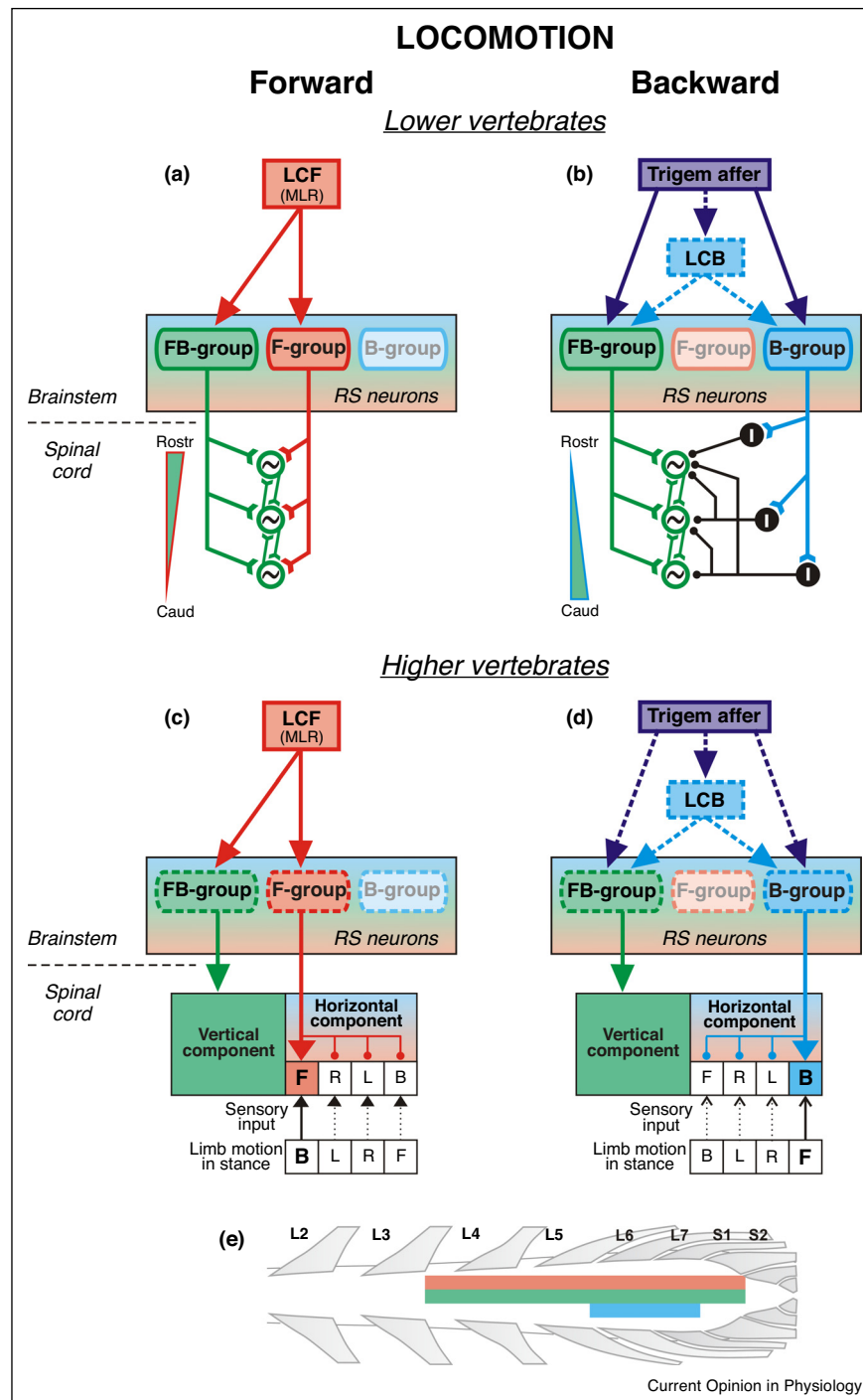
Forward and backward locomotor movements

In general, backward locomotion could be considered as reversed forward locomotion. Thus, in low vertebrates during backward swimming the waves of periodic lateral body flexion propagate in a caudo-rostral direction, while in a rostro-caudal — during forward locomotion [2,3]. In higher vertebrates and humans during stance and during swing phases of backward locomotion, a limb moves in directions opposite to those during forward stepping [4,5]. Although in both lower and higher vertebrates the muscle activity patterns of forward and backward locomotion differ, analysis of these patterns in higher vertebrates and humans revealed similar basic flexor-extensor synergies [6^{*},12,13]. This led to a suggestion that there are some common direction-independent neuronal mechanisms contributing to generation of both forward and backward locomotion.

Organization of spinal networks

In both lower and higher vertebrates, the neuronal mechanisms generating locomotion in different directions reside in the spinal cord [14–17]. The axial locomotor rhythm is generated by a chain of coupled segmental oscillators (Figure 1a,b; [18–20]). Each oscillator generates rhythmically alternating bursts of activity in the right and left hemisegments. Recording of individual spinal interneurons during forward and backward swimming in the tadpole and larval zebrafish, revealed a group of excitatory interneurons with activity modulated in locomotor rhythm during swimming in both directions [3,21,22]. This suggests the presence of a core rhythmogenic kernel that is active independently of the particular direction of locomotion. In the tadpole, these neurons exhibit mutual excitation [22] and form two subpopulations preferentially active during forward and backward swimming, respectively [21]. Differences in biophysical properties of these subpopulations may explain differences in parameters of forward and backward rhythms [21,23^{*}].

Figure 1



Hypothetical neural mechanisms for the control of locomotion in different directions. (a–d) Hypothetical models of the spinal locomotor network and of the descending commands controlling forward (a, c) and backward (b, d) locomotion in lower (a, b) and higher (c, d) vertebrates. (a, b) The spinal locomotor network in lower vertebrates consists of segmental oscillators (green circles) that excite one another and thus form a chain, along which the waves of activity propagate. (a) Elicitation of forward swimming. The MLR, which is a locomotor center for forward locomotion (LCF), activates reticulospinal (RS) neurons of FB-group and F-group. FB-group activates the chain of oscillators generating the swim rhythm. F-group stabilizes an intrinsic rostro-caudal gradient of excitability of oscillators or creates this gradient (green ramp with red outline). As a result, the waves of activity propagate in the caudal direction. (b) Elicitation of backward swimming. Trigeminal afferents activate RS neurons of FB-group and B-group (possibly, through the locomotor center for backward locomotion, LCB). FB-group activates the chain of oscillators generating the swim rhythm. At the same time, neurons of B-group activate inhibitory neurons (I) that invert the gradient of excitability (green ramp with blue outline). This results in the caudo-rostral propagation of locomotor waves. (c, d) Spinal cord of higher vertebrates contains two principal

Two models have been proposed to explain the change in the direction of locomotor waves. The trailing-oscillator model with symmetrical intersegmental connections [24] suggests that the direction of propagation of locomotor waves is determined by a gradient of excitability of individual oscillators along the chain. In isolated lamprey spinal cord this gradient is rostral-caudal. In the tadpole, ascending glycinergic inhibitory interneurons are involved in the locomotor wave reversal [25,26] and presumably inverse this gradient (*I* in Figure 1b) [27]. Such inhibitory interneurons (active only during backward locomotion) have been found in the zebrafish [3]. A model with asymmetrical intersegmental connections explains the reverse of the wave propagation from rostral-caudal to caudal-rostral by switching from activation of the descending coupling to activation of the ascending one [28].

Functional organization of networks generating stepping in different directions was studied by analyzing locomotor movements evoked by direct unspecific activation of these networks by epidural stimulation of the spinal cord in the decerebrate cat [29**]. It was demonstrated that during stimulation of certain sites, the direction of locomotion is determined by the direction of the treadmill belt motion, and on immobile surface or in the air, in-place stepping is observed, suggesting that the locomotor system includes two principal mechanisms (Figure 1c,d). One mechanism generates the vertical component of step (VC, limb elevation and lowering), and the other generates the horizontal component (HC, limb transfer from one extreme point to the other). The latter includes networks generating the horizontal component of step in different directions. These circuits receive sensory input signaling limb motion in stance; reaching an extreme position triggers the limb lifting and transfer in the opposite direction. One can suggest that VC-mechanism contains rhythm-generating while HC-mechanism — pattern formation networks.

Analysis of kinematics and EMG patterns of single corrective steps in different directions generated in response to postural disturbances during standing, revealed their similarity with those of locomotor steps in the corresponding direction [9*]. It was proposed that a corrective step is

generated by the same (VC and HC) mechanisms, which generate locomotor steps in corresponding direction, but they are activated by sensory information caused by postural disturbance and signaling deviation of the limb in relation to the trunk. This hypothesis is supported by finding that training locomotion in different directions improves balance control in spinal cord injured and stroke subjects [17,30,31].

Mapping the efficacy of epidural stimulation of different sites of the lumbosacral enlargement to evoke forward and backward locomotion combined with c-Fos immunostaining [32*] led to a suggestion that networks generating the VC of steps and the HC for forward stepping are distributed throughout the whole lumbosacral enlargement, while the network generating the HC for backward stepping is confined to a zone from caudal L5 to L7 (Figure 1e). Recording of the same individual spinal interneurons in L5–L6 during both forward and backward locomotion, revealed neurons with activity phase in the locomotor cycle independent of the locomotion direction and those modulated during forward or during backward locomotion only, presumably belonging to the VC and corresponding HC networks, respectively [33].

Though the basic principles of organization of axial and legged locomotor networks are similar, their neuronal compositions are different. In the zebrafish, spinal glutamatergic V2a interneurons are necessary and sufficient for the locomotor rhythm generation [34]. In contrast, in mice, glutamatergic non-V2a spinal interneurons contribute to generation of locomotor rhythm [35,36*], while V2a interneurons are involved in interlimb coordination [37]. In the zebrafish, an increase in the locomotor speed is associated with recruitment of new modules of locomotor network containing excitatory (V0v) commissural interneurons [38]. By contrast, in mice, inhibitory V0d interneurons determine the left–right limb alternation at low frequencies characteristic for slow forward walking, while excitatory V0v interneurons — at higher frequencies characteristic for both fast forward and backward locomotion [39–41]. These findings suggest that though some populations of genetically identified spinal interneurons are elements of both axial and legged locomotor

(Figure 1 Legend Continued) mechanisms, one generating the vertical component of step (limb elevation and lowering), and the other generating the horizontal component (limb transfer from one extreme point to the other). The latter includes networks generating the horizontal component of step in different directions (for simplicity, only the networks generating steps in four directions — F, forward; B, backward; R, rightward; L, leftward are shown). These networks receive sensory input signaling the limb motion during stance. (c) Elicitation of forward stepping. The MLR activates specific populations of RS neurons (presumably, FB-group and F-group). FB-group activates a network generating the vertical component of step. At the same time, neurons of F-group activate a network generating the horizontal component for forward stepping. Sensory input signaling that the limb reached the extreme caudal position during stance (B) assists in initiation of the forward swing. (d) Elicitation of backward stepping. Trigeminal afferents presumably activate RS neurons of FB-group and B-group (possibly, through LCB). FB-group activates a network generating the vertical component of step. At the same time, neurons of B-group activate a network generating the horizontal component for backward stepping. Sensory input signaling that the limb reached the extreme rostral position in stance (F), assists in initiation of the backward swing. (e) Rostro-caudal distribution in the lumbosacral enlargement of networks generating vertical component of the steps, horizontal component for forward steps, and horizontal component for backward steps, are shown schematically by thick green, red and blue lines, respectively.

networks, they have different specific functional role in generation of locomotion. Most likely, the legged locomotor network cannot be considered as axial network updated with some new populations of neurons, and thus the axial network does not represent the core of the legged one.

Supraspinal control

In all studied vertebrates, forward locomotion can be elicited and the speed of progression controlled from mesencephalic locomotor region (MLR), which represents a command center for forward locomotion only [29^{••},42]. Its activation leads to formation of reticulospinal commands, which selectively activate a part of spinal locomotor networks necessary for generation of forward locomotion (Figure 1a,c). Recent study in mice demonstrated that activation of glutamatergic neurons of MLR located in both the cuneiform (CnF) and the pedunculopontine nucleus evokes slow, alternating-gait locomotion, whereas activation of those in the CnF — high-speed synchronous-gait locomotion [43[•]]. One can hypothesize that some other forms of locomotion (e.g. backward and sideward) also have their command centers.

In both lower and higher vertebrates, backward locomotion can be initiated by continuous stimulation of the skin mechanoreceptors of the head [2,3,15,41]. Signals from these receptors are transmitted by specific populations of trigeminal nerve afferents [2].

In the lamprey and tadpole, reticulospinal neurons active exclusively during forward (F-group) or during backward locomotion (B-group), or active both during forward and backward locomotion (FB-group), were revealed [21,27]. It was suggested that the FB-group activates segmental oscillators during forward and during backward swimming (Figure 1a,b; [27]). In the framework of the trailing-oscillator model with symmetrical intersegmental connections [24], activation of FB-group alone (due to intrinsic rostro-caudal gradient of excitability in the chain of segmental oscillators) evokes forward swimming. The F-group can contribute to stabilization or (in the framework of the model with asymmetrical intersegmental connections [28]) creation of the rostro-caudal gradient of excitability. The B-group inverts the excitability gradient in the chain of segmental oscillators presumably through the ascending inhibitory interneurons (*I* in Figure 1b), and thus, co-activation of B-group and FB-group results in backward swimming. One may hypothesize that in higher vertebrates, signals from MLR and skin mechanoreceptors activate VC mechanism via FB-group of reticulospinal neurons, and specific HC circuits determining forward and backward direction of locomotion via F-population and B-population of reticulospinal neurons, respectively (Figure 1c,d).

Besides populations of reticulospinal neurons contributing to activation of locomotion [44^{••},45,46^{••}], reticulospinal neurons terminating forward locomotion were found in both lower and higher vertebrates [44^{••},47,48,49^{••}]. In lampreys and tadpoles, glutamatergic and GABA-ergic reticulospinal neurons terminate forward locomotion, respectively. It was demonstrated that in tadpoles they do not stop backward locomotion. In mice, glutamatergic V2a reticulospinal neurons in the rostral medulla terminate forward locomotion through inhibition of interneurons of the rhythm-generating network [49^{••}]. One can expect that they stop locomotion in other directions as well.

While supraspinal control of forward locomotion in higher vertebrates was studied in a considerable detail [1], only activity of corticospinal neurons was investigated during locomotion in different directions [50]. In intact cat, activity of almost all corticospinal neurons is phasically modulated in the rhythm of stepping during both forward and backward locomotion. However, the modulation pattern is direction-dependent. It is caused by inputs only from locomotor mechanisms of the projection girdle when this girdle is leading, and from locomotor mechanisms of both girdles when this girdle is trailing. This suggests flexibility of functional roles of individual corticospinal neurons during different forms of locomotion. Involvement of motor cortex in control of both backward and forward locomotion was also demonstrated in humans [51].

Sensory feedback

In lower vertebrates, a specific movement-related sensory feedback can be provided by intraspinal mechanoreceptors (stretch receptor neurons (SRNs) in the lamprey [52] and cerebrospinal fluid contacting neurons (CSF-cNs) in zebrafish [53]), while in higher vertebrates — by proprioceptors and cutaneous afferents [54].

Recent studies demonstrated that in the lamprey, the spinal reflex to body bending during forward swimming mediated by SRNs observed during forward locomotion is reversed during backward locomotion [55[•]]. This reflex reversal is aimed at reinforcement of the movements generated in each of these behaviors. It assists in initiation of contralateral bending during forward swimming and augments the body undulations amplitude during backward locomotion. A population of reticulospinal neurons transmitting commands causing modification of unilateral spinal networks processing signals from SRNs, which lead to the reflex reversal, has been revealed. They are activated by trigeminal nerve stimulation causing backward swimming and presumably belong to B-group. It was found that in the zebrafish CSF-cNs increase speed of forward locomotion [53], however, their role in control of backward swimming is unknown.

It was shown that in higher vertebrates, modulation of the efficacy of the soleus H-reflex during locomotor cycle, as

well as cutaneous afferents reflex effects, which are characterized by a 'reversal of actions' that depends on the step cycle phase, are similar during backward and forward locomotion [56,57], suggesting that phase-dependent changes of these reflexes most likely caused by a locomotor network common for forward and backward locomotion.

A critical point in the step cycle is onset of the swing phase. It was suggested that the swing onset in any direction is determined by the afferents signaling a critical limb deviation in the stance phase [29[•],54]. One can expect that supraspinal command determining the direction of stepping, selects and activates a specific spinal network in HC-mechanism for processing this information (Figure 1c,d).

Conclusions

The rhythm-generating part of locomotor networks, as well as neuronal mechanisms underlying left-right coordination are common and contribute to generation of locomotion in any direction. By contrast, networks determining direction of locomotion are different and specific for each direction. They contain neuronal mechanisms for specific processing of movement-related sensory feedback. A detailed analysis of these networks (including clarification of functional roles of genetically identified populations of neurons) and their interaction, is one of the major lines of future studies. Evidence of shared neuronal networks for locomotor and corrective steps in different directions provides a basis for rehabilitation strategies employing walking in different directions aimed at improvement of both locomotion and balance control in patients. Such strategies showed promising results [17,30,31]. Determining specific functions of genetically identified populations of neurons and subsequent well-controlled precisely targeted activation/inactivation of relevant populations will undoubtedly boost these efforts.

Conflict of interest statement

Nothing declared.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Orlovsky GN, Deliagina TG, Grillner S: *Neuronal Control of Locomotion. From Mollusc to Man*. New York: Oxford UP; 1999.
2. Islam SS, Zelenin PV: **Modifications of locomotor pattern underlying escape behavior in the lamprey**. *J Neurophysiol* 2008, **99**:297-307.
3. Liao JC, Fetcho JR: **Shared versus specialized glycinergic spinal interneurons in axial motor circuits of larval zebrafish**. *J Neurosci* 2008, **28**:12982-12992.
4. Buford JA, Zernicke RF, Smith JL: **Adaptive control for backward quadrupedal walking. I. Posture and hindlimb kinematics**. *J Neurophysiol* 1990, **64**:745-755.
5. Thorstensson A: **How is the normal locomotor program modified to produce backward walking**. *Exp Brain Res* 1986, **61**:664-668.
6. Zelik KE, La Scaleia V, Ivanenko YP, Lacquaniti F: **Can modular strategies simplify neural control of multidirectional human locomotion?** *J Neurophysiol* 2014, **111**:1686-1702.
- In this paper, the EMG patterns during forward, backward, sideward and in place walking in humans, are analyzed to reveal shared across locomotor behaviors muscle synergies. The functional significance of the revealed synergies and modules is thoroughly discussed.
7. Karayannidou A, Zelenin PV, Orlovsky GN, Sirota MG, Beloozerova IN, Deliagina TG: **Maintenance of lateral stability during standing and walking in the cat**. *J Neurophysiol* 2009, **101**:8-19.
8. Musienko PE, Deliagina TG, Gerasimenko YP, Orlovsky GN, Zelenin PV: **Limb and trunk mechanisms for balance control during locomotion in quadrupeds**. *J Neurosci* 2014, **34**:5704-5716.
9. Hsu LJ, Zelenin PV, Lyalka VF, Vemula MG, Orlovsky GN, Deliagina TG: **Neural mechanisms of single corrective steps evoked in the standing rabbit**. *Neuroscience* 2017, **347**:85-102.
- In this study, postural corrections, which include single corrective steps in different directions, have been analyzed in intact and decerebrate rabbits. It was demonstrated that a corrective step is generated by a mechanism activated by sensory signal from the displaced limb, and that integrity of the highest levels of CNS is not necessary for their generation. Results of this study allowed to propose that a single corrective step in a particular direction is generated by the same locomotor system that generates sequential stepping in the corresponding direction.
10. Chvatal SA, Torres-Oviedo G, Safavynia SA, Ting LH: **Common muscle synergies for control of center of mass and force in nonstepping and stepping postural behaviors**. *J Neurophysiol* 2011, **106**:999-1015.
11. Lee P-Y, Gadareh K, Bronstein AM: **Forward-backward postural protective stepping responses in young and elderly adults**. *Hum Mov Sci* 2014, **34**:137-146.
12. Pratt CA, Buford JA, Smith JL: **Adaptive control for backward quadrupedal walking V. Mutable activation of bifunctional thigh muscles**. *J Neurophysiol* 1996, **75**:832-842.
13. Jansen K, De Groote F, Massaad F, Meyns P, Duysens J, Jonkers I: **Similar muscles contribute to horizontal and vertical acceleration of center of mass in forward and backward walking: implications for neural control**. *J Neurophysiol* 2012, **107**:3385-3396.
14. Hsu L-J, Orlovsky GN, Zelenin PV: **Different forms of locomotion in the spinal lamprey**. *Eur J Neurosci* 2014, **39**:2037-2049.
15. Soffe SR: **Triggering and gating of motor responses by sensory stimulation: behavioural selection in *Xenopus* embryos**. *Proc R Soc Lond B Biol Sci* 1991, **246**:197-203.
16. Courtine G, Gerasimenko Y, van den Brand R, Yew A, Musienko P, Zhong H, Song B, Ao Y, Ichiyama RM, Lavrov I et al.: **Transformation of nonfunctional spinal circuits into functional states after the loss of brain input**. *Nat Neurosci* 2009, **12**:1333-1342.
17. Shah PK, Gerasimenko Y, Shyu A, Lavrov I, Zhong H, Roy RR, Edgerton VR: **Variability in step training enhances locomotor recovery after spinal cord injury**. *Eur J Neurosci* 2012, **36**:2054-2062.
18. Grillner S: **Neurobiological bases of rhythmic motor acts in vertebrates**. *Science* 1985, **228**:143-149.
19. Sigvardt KA, Williams TL: **Effects of local oscillator frequency on intersegmental coordination in the lamprey locomotor CPG: theory and experiment**. *J Neurophysiol* 1996, **76**:4094-4103.

20. Tunstall MJ, Roberts A: **Longitudinal coordination of motor output during swimming in *Xenopus* embryos.** *Proc R Soc Lond B Biol Sci* 1991, **244**:27-32.
 21. Li W-C, Sautois B, Roberts A, Soffe SR: **Reconfiguration of a vertebrate motor network: specific neuron recruitment and context-dependent synaptic plasticity.** *J Neurosci* 2007, **27**:12267-12276.
 22. Li W-C, Roberts A, Soffe SR: **Locomotor rhythm maintenance: electrical coupling among premotor excitatory interneurons in the brainstem and spinal cord of young *Xenopus* tadpoles.** *J Physiol* 2009, **587**:1677-1693.
 23. Borisjuk R, Merrison-Hort R, Soffe SR, Koutsikou S, Li W-C: **To swim or not to swim: a population-level model of *Xenopus* tadpole decision making and locomotor behavior.** *BioSystems* 2017, **161**:3-14.
- The authors incorporate all previous experimental data in one model that simulates integration of different sensory signals resulting in choice of behavior (to locomote forward or backward or to halt) in the tadpole. This model is one of the most advanced and detailed among all vertebrate species.
24. Matsushima T, Grillner S: **Neural mechanisms of intersegmental coordination in lamprey: local excitability changes modify the phase coupling along the spinal cord.** *J Neurophysiol* 1992, **67**:373-388.
 25. Green CS, Soffe SR: **Roles of ascending inhibition during two rhythmic motor patterns in *Xenopus* tadpoles.** *J Neurophysiol* 1998, **79**:2316-2328.
 26. Issberner JP, Sillar KT: **The contribution of the NMDA receptor glycine site to rhythm generation during fictive swimming in *Xenopus laevis* tadpoles.** *Eur J Neurosci* 2007, **26**:2556-2564.
 27. Zelenin PV: **Reticulospinal neurons controlling forward and backward swimming in the lamprey.** *J Neurophysiol* 2011, **105**:1361-1371.
 28. Kopell N, Ermentrout GB: **Coupled oscillators and the design of central pattern generators.** *Math Biosci* 1988, **89**:14-23.
 29. Musienko PE, Zelenin PV, Lyalka VF, Gerasimenko YP, Orlovsky GN, Deliagina TG: **Spinal and supraspinal control of the direction of stepping during locomotion.** *J Neurosci* 2012, **32**:17442-17453.
- In this study, locomotor movements evoked by stimulation of the mesencephalic locomotor region (MLR) and by epidural stimulation of the spinal cord and performed on the treadmill moving in different directions, as well as on the immobile surface or in the air, were compared. Results of this study allowed to formulate the functional model of the locomotor system generating stepping in different directions. It was also demonstrated that the MLR is a command center for forward locomotion only.
30. Rose DK, DeMark L, Fox EJ, Clark DJ, Wludyka P: **A backward walking training program to improve balance and mobility in acute stroke: a pilot randomized controlled trial.** *J Neurol Phys Ther* 2018, **42**:12-21.
 31. Foster H, DeMark L, Spigel PM, Rose DK, Fox EJ: **The effects of backward walking training on balance and mobility in an individual with chronic incomplete spinal cord injury: a case report.** *Physiother Theory Pract* 2016, **32**:536-545.
 32. Merkulyeva N, Veshchitskii A, Gorsky O, Pavlova N, Zelenin PV, Gerasimenko Y, Deliagina TG, Musienko P: **Distribution of spinal neuronal networks controlling forward and backward locomotion.** *J Neurosci* 2018, **38**:4695-4707.
- In this study, first, efficacy of epidural stimulation of different spinal segments to evoke forward and backward locomotion was tested. Second, by using c-Fos immunostaining, the distributions of spinal neuronal networks controlling forward and backward locomotion were compared. Results indicate that the neuronal networks responsible for forward locomotion are distributed broadly in the lumbosacral spinal cord, while the network determining backward direction of stepping is distributed from caudal part of L5 to caudal part of L7.
33. Zelenin PV, Musienko PE, Gorsky OV, Lyalka VF, Merkulyeva N, Gerasimenko YP, Orlovsky GN, Deliagina TG: **Activity of individual spinal neurons during forward and backward locomotion.** *Soc Neurosci Abstr* 2016, **535**:02.
 34. Ljunggren EE, Haupt S, Ausborn J, Ampatzis K, El Manira A: **Optogenetic activation of excitatory premotor interneurons is sufficient to generate coordinated locomotor activity in larval zebrafish.** *J Neurosci* 2014, **34**:134-139.
 35. Dougherty KJ, Zagoraiou L, Satoh D, Rozani I, Doobar S, Arber S, Jessell TM, Kiehn O: **Locomotor rhythm generator linked to the output of spinal Shox2 excitatory interneurons.** *Neuron* 2013, **80**:920-933.
 36. Caldeira V, Dougherty KJ, Borgius L, Kiehn O: **Spinal Hb9::Cre-derived excitatory interneurons contribute to rhythm generation in the mouse.** *Sci Rep* 2017, **7**:41369.
- Results of this study indicate that spinal excitatory Hb9 INs represent a distinct population of neurons that participates in generation of the locomotor rhythm. This study and study [35] demonstrate that in the mouse the rhythm-generating network contains neurons with different genetic identities.
37. Crone SA, Quinlan KA, Zagoraiou L, Droho S, Restrepo CE, Lundfald L *et al.*: **Genetic ablation of V2a ipsilateral interneurons disrupts left-right locomotor coordination in mammalian spinal cord.** *Neuron* 2008, **60**:70-83.
 38. Björnfors R, El Manira A: **Functional diversity of excitatory commissural interneurons in adult zebrafish.** *eLife* 2016, **5**.
 39. Talpalar AE, Bouvire J, Borgius L, Fortin G, Pierani A, Kiehn O: **Dual-mode operation of networks involved in left-right alternation.** *Nature* 2013, **500**:85-88.
 40. Bellardita C, Kiehn O: **Phenotypic characterization of speed-associated gait changes in mice reveals modular organization of locomotor networks.** *Curr Biol* 2015, **25**:1426-1436.
 41. Vemula MDG, Lyalka VF, Talpalar AE, Kiehn O, Deliagina TG, Zelenin PV: **Role of V0 commissural interneurons in control of basic motor behaviors.** *Soc Neurosci Abstr* 2018, **151**:01.
 42. Sirota MG, Di Prisco GV, Dubuc R: **Stimulation of the mesencephalic locomotor region elicits controlled swimming in semi-intact lampreys.** *Eur J Neurosci* 2000, **12**:4081-4092.
 43. Caggiano V, Leiras R, Goñi-Errro H, Masini D, Bellardita C, Bouvier J, Caldeira V, Fisone G, Kiehn O: **Midbrain circuits that set locomotor speed and gait selection.** *Nature* 2018, **553**:455-460.
- With optogenetic methods, the authors demonstrate that glutamatergic neurons from different nuclei comprising the mesencephalic locomotor region play different functional roles. These results shed new light on the mechanisms of the gait control.
44. 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* 2016, **15**:2377-2386.
- In this study, three patterns of activity of reticulospinal neurons compatible with starting, maintaining, and stopping locomotion were revealed in the lamprey. Pharmacological activation and inactivation of reticulospinal neurons activated at the end of a locomotor bout showed that they determine locomotor offset. This result together with a similar result obtained in mice [49••] suggest an evolutionary conserved supraspinal system transmitting commands terminating locomotion.
45. 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* 2013, **23**:843-849.
 46. Capelli P, Pivetta C, Esposito MS, Arber S: **Locomotor speed control circuits in the caudal brainstem.** *Nature* 2017, **551**:373-377.
- By using optogenetic techniques, different functional roles of intermingled supraspinal neuronal subpopulations within the lateral paragonocellular nucleus were revealed. It was demonstrated that glutamatergic neurons are essential to support high-speed locomotion, while glycinergic neurons can induce different forms of behavioral arrest. This study complements the other studies in the mouse [43•,49••] related to functional roles of different populations of brainstem neurons in control of locomotion.
47. Perrins R, Walford A, Roberts A: **Sensory activation and role of inhibitory reticulospinal neurons that stop swimming in hatching frog tadpoles.** *J Neurosci* 2002, **22**:4229-4240.
 48. Li W-C, Perrins R, Walford A, Roberts A: **The neuronal targets for GABAergic reticulospinal inhibition that stops swimming in hatching frog tadpoles.** *J Comp Physiol A* 2003, **189**:29-37.

49. Bouvier J, Cagguano V, Leiras R, Caldeira V, Bellardita C,
 - Balueva K, Fuchs A, Kiehn O: **Descending command neurons in the brainstem that halt locomotion.** *Cell* 2015, **163**:1191-1203.
 The authors demonstrated that genetically identified population of reticulospinal neurons (V2a neurons) located in the rostral medulla transmit commands inhibiting spinal rhythm-generating networks and thus terminating locomotion.
50. Zelenin PV, Deliagina TG, Orlovsky GN, Karayannidou A, Stout EE, Sirota MG, Beloozerova IN: **Activity of motor cortex neurons during backward locomotion.** *J Neurophysiol* 2011, **105**:2698-2714.
51. Kurz MJ, Wilson TW, Arpin DJ: **Stride-time variability and sensorimotor cortical activation during walking.** *NeuroImage* 2012, **59**:1602-1607.
52. Grillner S, Williams T, Lagerbäck PA: **The edge cell, a possible intraspinal mechanoreceptor.** *Science* 1984, **223**:500-503.
53. Böhm UL, Prendergast A, Djenoune L, Nunes Figueiredo S, Gomez J, Stokes C, Kaiser S, Suster M, Kawakami K, Charpentier M *et al.*: **CSF-contacting neurons regulate locomotion by relaying mechanical stimuli to spinal circuits.** *Nat Commun* 2016, **7**:10866.
54. Rossignol S, Dubuc R, Gossard JP: **Dynamic sensorimotor interactions in locomotion.** *Physiol Rev* 2006, **86**:89-154.
55. Hsu LJ, Zelenin PV, Orlovsky GN, Deliagina TG: **Supraspinal control of spinal reflex responses to body bending during different behaviors in lampreys.** *J Physiol* 2017, **595**:883-900.

The present study has demonstrated that reflex response to body bending observed during forward swimming in lamprey is reversed during backward swimming, as well as during other forms of escape behavior. For the first time the neuronal mechanisms underlying reflex reversal in vertebrate animal have been characterized.
56. Ung RV, Imbeault MA, Ethier C, Brizzi L, Capaday C: **On the potential role of the corticospinal tract in the control and progressive adaptation of the soleus h-reflex during backward walking.** *J Neurophysiol* 2005, **94**:1133-1142.
57. Buford JA, Smith JL: **Adaptive control for backward quadrupedal walking. III. Stumbling corrective reactions and cutaneous reflex sensitivity.** *J Neurophysiol* 1993, **70**:1102-1114.