THE MOTOR INFRASTRUCTURE: FROM ION CHANNELS TO NEURONAL NETWORKS

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The vertebrate motor system is equipped with a number of neuronal networks that underlie different patterns of behaviour, from simple protective reflexes to complex movements. The current challenge is to understand the intrinsic function of these networks: that is, the cellular basis of motor behaviour. In one vertebrate model system, the lamprey, it has been possible to make the connection between different subtypes of ion channels and transmitters and their roles at the cellular and network levels. It is therefore possible to link the role of certain genes or molecules to motor behaviour in this system.

The motor system is the only available external output channel of the brain, or as formulated by Sherrington[1], "To move things is all mankind can do … whether whispering, or felling a forest." Various networks at different levels of the nervous system coordinate different motor patterns, be they eye or hand movements or those that underlie respiration, locomotion and posture. Together, these networks provide a 'motor infrastructure' that can be used by the nervous system[2] to generate the elegant movements of a ballet dancer or the demanding postural control of a tight-rope walker. Some networks are present at birth, whereas others mature during development to be modified and perfected through learning.

This review considers the conceptual framework that is used to understand the generation of motor behaviour. I focus first on the neural bases for execution of movement, from basic to more complex aspects. From a discussion of the general principles that underlie motor behaviour, I move on to address, in some detail, the motor system of a lower vertebrate, the lamprey. Owing to its relative simplicity, compared with mammals, it has been possible to describe not only the different networks that are present in the lamprey, but also the intrinsic function of these networks in terms of interacting neurons, transmitters and ion channels, and to provide a detailed computational model based on experimentally derived facts from the molecular (gene) level to that of networks and motor behaviour. Direct and indirect evidence indicate that the knowledge obtained in lower vertebrate models such as the lamprey also applies to higher vertebrates. In analogy, the lamprey can be considered a vertebrate prototype[3] — a Ford Model T, if primates are equated with the most recent Ferrari. Although the latter is more advanced, the same general control principles apply. At the same time, it must be acknowledged that moving from water, where gravity is not a large problem, to land has added significant challenges to the nervous system. Evolution has progressively favoured the development of fins and later legs to develop efficient locomotion over ground and in the air.

Movements are performed in relation to the surrounding world, which requires a fast interpretation of the location of objects and the entire terrain. Consider, for instance, a bat moving rapidly in the dark through a dense forest, or our own ability to catch a ball that is thrown at us at high speed. Although this is an important aspect of movement control, this type of sensorimotor processing will have to await another review, as the space available is limited.

General control structure

Neural networks that coordinate movements. Both vertebrates and invertebrates have a common type of neural control structure for the generation of different

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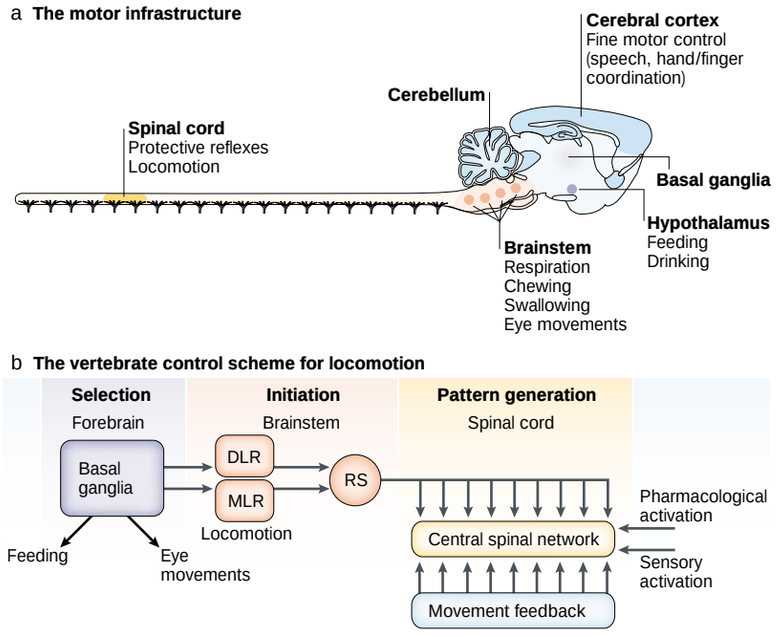

Figure 1 | **The motor infrastructure. a** | Location of different networks (central pattern generators, CPGs) that coordinate different motor patterns in vertebrates. The spinal cord contains the CPGs for locomotion and protective reflexes: the brainstem, those for breathing, chewing, swallowing and saccadic eye movements; and the hypothalamus, centres that regulate eating and drinking. These areas can coordinate the activation of different CPGs in a behaviourally relevant order. For instance, if the fluid intake area is activated, an animal will look for water, walk towards it, position itself and start drinking. The cerebral cortex is important in particular for fine motor coordination involving hands and fingers and for speech. **b** | General control strategy for vertebrate locomotion. Locomotion is initiated by activity in reticulospinal neurons (RS) of the brainstem locomotor centre, which produces the locomotor pattern in close interaction with sensory feedback. With increased activation of the locomotor centre, the speed of locomotion increases and interlimb coordination can change (from a walk to a gallop, for example). The basal ganglia exert a tonic inhibitory influence on motor centres that is released when a motor pattern is selected. Experimentally, locomotion can also be elicited pharmacologically by administration of excitatory amino-acid agonists and by sensory input. DLR, diencephalic locomotor area; MLR, mesopontine locomotor area.

patterns of motor behaviour, despite the fundamental differences in anatomical organization between their neural systems. Movements are generated by dedicated networks of nerve cells (FIG. 1a) that contain the information that is necessary to activate different motor neurons in the appropriate sequence and intensity to generate motor patterns[2,4]. Such networks are referred to as CENTRAL PATTERN GENERATORS (CPGs). The most basic CPGs coordinate protective reflexes, swallowing or coughing. At the next level are those that generate rhythmic movements[5]. Some, such as respiratory CPGs, are active throughout life, but are modulated with changing metabolic demands[5]. Others, such as locomotor CPGs, are inactive at rest, but can be turned on by signals from command centres[6–9]. Sensory input that is generated by ongoing movements can help to regulate the duration of different phases of the movement.

Another level of complexity is added when one considers SACCADIC EYE MOVEMENTS, which are generated from the superior colliculus. This structure contains a topological map, and the location of activity within each microregion determines the specific direction and amplitude of the saccade[10,11]. The collicular saccade map can be considered as a modular CPG organization. An eye movement is usually followed by a reorientation of the head and body to face the target. The generation of reaching movements might follow a similar logic. Another class of motor patterns[13,14] are used to express species-specific, innate emotions (in man, for example, crying, smiling or laughter).

For each category of movement, there is an innate machinery, which can be adapted and perfected by experience. In addition, this machinery can be used to learn new, skilled tasks, such as the sequence of motor patterns required to play a musical instrument. The learning of such sequences of motor patterns is referred to as motor or procedural memory.

This motor infrastructure allows various adaptable and flexible movements, the combination of motor programs and the ability to learn new patterns of coordination[14,15]. Together, these represent the entire motor repertoire of an individual or species[2,7,16]. Most of these motor patterns, such as locomotion, speech or gaze, are voluntary — they can be recruited and modified at will[17]. The use of the word 'voluntary' in the context of motor control should therefore not be restricted, as it often is, to aspects such as arm–hand coordination. This common subdivision creates a false dichotomy.

Sensory contribution to movement control. An important aspect of motor control is correction, whether for errors or for unexpected perturbations (such as obstacles). Sensory signals can aid the control of movement in several ways, but in general, sensory feedback systems are used for slow movements, which allow time for the feedback to operate. In contrast to engineering systems, conduction times in biological systems are often long in comparison to the time needed to execute a given movement. The relative importance of the conduction delays differs in different species, for example between a fruitfly and a giraffe. When time allows, as during respiration[5] and slower forms of locomotion[18–21], feedback systems can help to regulate the duration of different phases of a movement controlled by a CPG and can also contribute to the degree of muscle activation. When movements are faster, though, sensory feedback may be insufficient. Consider a tall person with long conduction delays from the foot to the spinal cord. Add the central processing time, efferent conduction time to the muscle and finally the neuromechanical lag. The time lag to onset of change in mechanical muscle response can be 0.1 to 0.2 seconds, which is substantial if one considers the need for fast corrective responses during rapid movements such as downhill skiing. This is why nervous systems are designed to use predictions[22] of necessary changes whenever possible, rather than making corrections after a perturbation has occurred. Immediate compensation for obstacles or other perturbations can only rely on muscle and tendon stiffness[23] — many species have 'springy' legs that can momentarily absorb perturbations. Sensory input is also used in a non-feedback mode, when a movement or a component of a motor pattern is initiated. The sensory information before the movement starts is crucial for

CENTRAL PATTERN GENERATOR
A neural circuit that produces patterns of behaviour independently of sensory input, for instance the pattern of activity in different motor neurons that results in respiration or locomotion.

SACCADIC EYE MOVEMENTS
A rapid eye movement (with speeds of up to 800 degrees per second) that brings the point of maximal visual acuity — the fovea — to the image of interest.

Box 1 | Invertebrate model systems

The crustacean stomatogastric system — which is responsible for chewing food at the gastric level — has been analysed in great detail[132–134]. It comprises two subsystems in the same ganglion, the gastric mill system (14 neurons) and the pyloric system (12 neurons), with a small network in the oesophageal ganglion that can be coordinated with the two other systems to propel food forward. These three networks can work together or individually, and have separate functions. The motor pattern generation of the gastric mill and pyloric networks have been identified in terms of synaptic interaction, electric coupling, pacemaker properties, subtypes of ion channels and presynaptic modulation. Peptidergic and aminergic modulation tune the network to allow changes in the phase relations between different neurons or muscles. It is assumed that the different patterns of muscle activity match the needs of the gastric mill system for chewing different foods. The leech heartbeat is similarly controlled by a small network of which the cellular basis of the output pattern is understood[135].

Locomotion has been studied in several invertebrate systems. In the leech, swimming and crawling have been analysed and for each a significant part of the neuronal network and the role of sensory feedback are understood[136]. The locomotion of two molluscs, *Tritonia* and *Clione limacina,* has also been analysed. *Clione* is a small, free-swimming mollusc with paired wings that flap as it swims through the water. The motor pattern is produced by a network of paired neurons that generate alternating rhythmic contractions of the antagonistic muscle groups. The general properties of these neurons are adapted to the motor pattern, and the system for controlling body orientation (posture) has been deduced[137]. *Tritonia* generates a brief bout of escape swimming using a network with three phases of motor pattern[134]. Locomotor systems in insects and crustaceans have also been intensely studied. Although the possible roles of different sensory systems have been addressed with success, less knowledge is available about the mode of operation or cellular properties of the CPGs.

What conclusions can be drawn from these studies in terms of general mechanisms used to generate motor activity?

- Groups of neurons with antagonistic functions are connected through reciprocal inhibition.
- Neurons with a similar function often mutually excite each other, or are connected by gap junctions.
- Inducible plateau potentials or pacemaker properties of network neurons are common.
- Burst termination can be induced by frequency adaptation of action potentials and progressive activity-dependent activation of specific membrane currents such as Ca^{2+}-dependent K^+ channels.
- Post-inhibitory rebound can be important for triggering burst onset. It is generated by low-voltage-activated Ca^{2+} channels, and the hyperpolarization-activated current I_H.
- Aminergic, peptidergic and metabotropic receptors modulate intrinsic pre- or postsynaptic ion channels. Fine tuning of ion channel subtypes (Ca^{2+}, K^+) can modify both cellular and network properties.
- Some networks can operate separately, or be combined into concerted action.

deciding, for instance, how locomotion will be initiated from a standing position (depending on asymmetries in the position of the two feet), or from one phase of a task to the next, as in the sequence of formants in speech.

Intrinsic function of neuronal networks

The knowledge of the general control structure of motor systems in terms of CPGs, sensory feedback and command systems for initiation of movements originated in parallel from invertebrate and vertebrate studies by investigators using various techniques and experimental models[5,8,24–27]. The next level to be addressed, the intrinsic mode of operation of these neuronal systems, is more difficult — it requires knowledge of which neurons comprise a network, their synaptic interactions (including transmitters and receptors), membrane properties (palette of ion channels) and so forth. In mammals, the large number of neurons and general complexity of the nervous system cause great problems to investigators. To simplify the situation, lower vertebrate and invertebrate model systems have been developed (BOX 1). However, mammalian models, in particular neonatal mouse and rat *in vitro* preparations, now also provide important new information[28–32].

In this review, I highlight the lamprey nervous system, which is the only adult vertebrate nervous system in which the cellular bases of locomotor control are well understood. The swimming coordination that underlies locomotion in the developing frog (embryo/tadpole) has also been well analysed[33–36], and comparisons with this and other systems are made when appropriate.

Neuronal networks: a lamprey perspective

The vertebrate nervous system is organized in a similar way throughout vertebrate phylogeny, although the level of complexity increases. From lamprey to man, the forebrain, brainstem and spinal cord have the same general features, including basal ganglia, hypothalamic nuclei, cranial nerves and descending motor systems. Although different areas of pallium (the forerunner of cortex) are present in lower vertebrates, there is no layered cerebral cortex and in the lamprey only a vestigial cerebellum. Lampreys are jawless vertebrates known as cyclostomes that are more 'primitive' than fish. They have changed comparatively little during evolution, and became separated from the main vertebrate line 450 million years ago. The lamprey central nervous system (CNS) can be regarded as a vertebrate prototype, with the experimental advantages that it has fewer neurons than higher vertebrates and that it can be maintained *in vitro*. The motor pattern that underlies locomotion or respiration can be maintained in the isolated nervous system for several days[37] (FIG. 2).

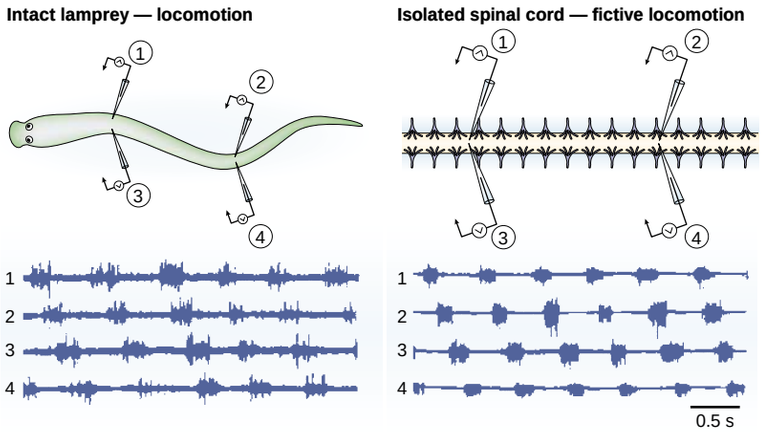

Figure 2 | **Similarities of locomotor pattern generation in an intact lamprey and an isolated spinal cord.** The bilateral segmental electromyogram activity in two segments along the spinal cord of the intact lamprey is shown on the left. Activity alternates between segments 1 and 3, and 2 and 4, and there is an intersegmental lag between 1 and 2, and 3 and 4. To the right, the corresponding activity recorded from the isolated spinal cord of the lamprey is shown[112]. Locomotor coordination can be generated by the isolated spinal cord in the same way as the intact behaving lamprey.

Conserved command areas for CPGs. Different command systems control the level of activity of CPGs. In the lamprey, as in other vertebrates (FIGS 1b and 3), locomotion can be initiated by stimulation of a DIENCEPHALIC and a MESOPONTINE LOCOMOTOR REGION (DLR and MLR, respectively)[24,25,38,39]. From cyclostomes to mammals, the MLR is found in an area that contains cholinergic and glutamatergic neurons. The DLR corresponds to groups of neurons with descending connections that make up the VENTRAL THALAMUS in the lamprey and zona incerta in mammals. These two areas project independently and monosynaptically to reticulospinal neurons in the middle and posterior reticulospinal nuclei, which in turn activate the spinal CPGs that generate locomotor activity. Both pathways are glutamatergic and project bilaterally. From the MLR there is also a monosynaptic cholinergic projection that acts on nicotinic receptors on reticulospinal neurons[10]. The reticulospinal neurons (RS in FIG. 3) can respond with plateau depolarizations that result from activation of NMDA (*N*-methyl-D-aspartate) receptors and Ca^{2+}-activated cation channels[40]. The level of activation of the locomotor regions determines the drive to the spinal locomotor CPGs and therefore the speed of locomotion (FIG. 1b).

Locomotor pattern generation by spinal CPGs. In all classes of vertebrates, the spinal cord contains the basic networks that coordinate locomotor activity, be it swimming, flying or walking[7–9,24,41]. In the lamprey spinal cord, alternating left–right locomotor activity is produced in each segment along the spinal cord with a frequency ranging from 0.1 to 8–10 Hz during normal swimming (FIG. 2, left). Locomotor activity can be produced not only by brainstem stimulation but also in the isolated spinal cord by superfusion of glutamate agonists to replace the supraspinal drive[37] (FIG. 2, right). Normally, a stable burst frequency can occur across the full frequency range. A longitudinal hemisection, which isolates the left and right hemicords from each other, results in marked acceleration of this burst activity, but each hemicord can still produce both fast and slow bursting under different conditions[42]. This finding is in contrast to previous studies[43], probably because of differences in time of observation and in resolution. Bursting in the hemicord can also be elicited by electrical stimulation of the spinal cord, which activates reticulospinal fibres. Remarkably, locomotor burst activity can be elicited even when only one hemisegment is intact. Moreover, in the hemicord bursting remains when glycinergic synaptic transmission is blocked, indicating that ipsilateral excitatory interneurons can drive bursting[44].

A lesion of the crossed glycinergic fibres between the hemicords results in a speeding up of the burst rate, showing that crossed inhibitory fibres both slow down the rhythm and ensure that the two sides alternate. Similarly, a pharmacologically induced partial blockade of glycinergic transmission with strychnine causes the frequency to speed up and finally to change to a burst

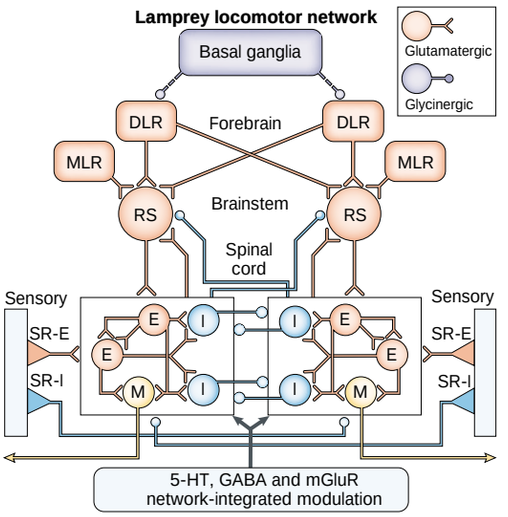

Figure 3 | **Locomotor network of the lamprey.** Schematic representation of the forebrain, brainstem and spinal components of the core neural circuitry that generates rhythmic locomotor activity. All neuron symbols denote populations rather than single cells. The reticulospinal (RS) glutamatergic neurons excite all classes of spinal interneurons and motor neurons. The excitatory interneurons (E) excite all types of spinal neurons — the inhibitory glycinergic interneurons (I) that cross the midline to inhibit all neuron types on the contralateral side, and motor neurons (M). The stretch receptor neurons are of two types; excitatory (SR-E), which excite ipsilateral neurons, and inhibitory (SR-I), which cross the midline to inhibit contralateral neurons. RS neurons receive excitatory synaptic input from the diencephalic and mesopontine locomotor regions (DLR and MLR, respectively), which receive input from the basal ganglia as well as visual and olfactory input. Metabotropic receptors are also activated during locomotion and are an integral part of the network (5-HT (5-hydroxytryptamine, serotonin), GABA (γ-aminobutyric acid) and mGluR (metabotropic glutamate receptor)). Dashed lines, indirect connections.

DIENCEPHALIC LOCOMOTOR REGION
Area corresponding to ventral thalamus, which contains neurons that project to reticulospinal neurons, and that thereby can activate the spinal locomotor networks.

MESOPONTINE LOCOMOTOR REGION
Area located at the border between mesencephalon and pons (mesopontine), which contains neurons that project to reticulospinal neurons, and thereby can activate the spinal locomotor networks. This area is often referred to as the mesencephalic locomotor region.

VENTRAL THALAMUS
Nucleus in diencephalon that sends axonal glutamatergic projections to reticulospinal neurons, thereby eliciting locomotor activity. Ventral thalamus should not be confused with the dorsal thalamus, which projects to pallium (corresponding to cortex) as in mammals.

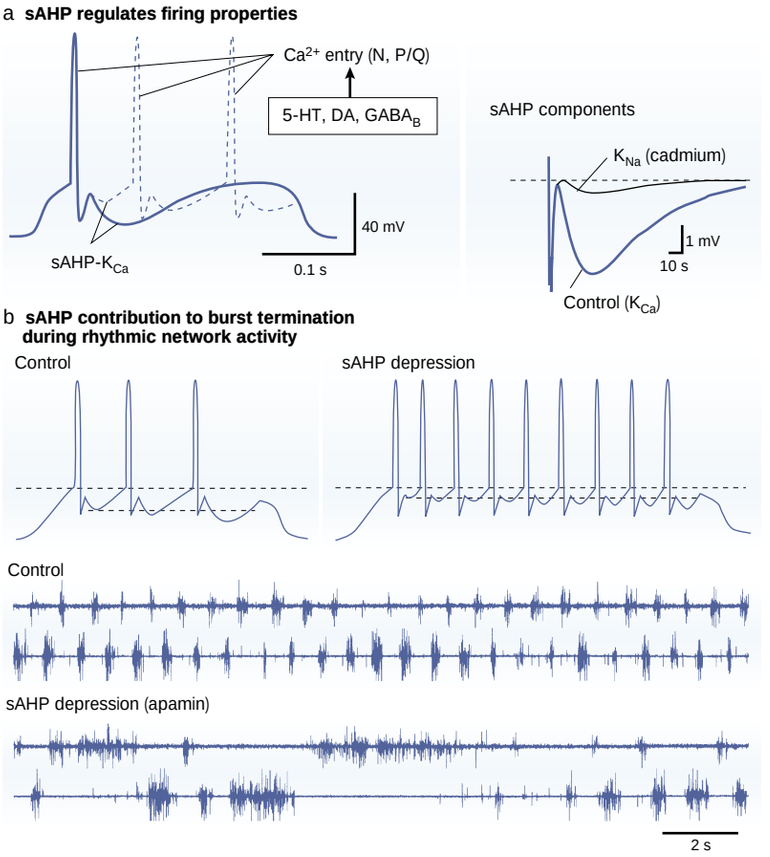

Figure 4 | **The roles of the slow afterhyperpolarization (sAHP) and K_{Ca} channels at the single cell and network level. a** | Drawing of an action potential with the slow (sAHP) and fast afterhyperpolarization, and the effect on the firing pattern of reducing the sAHP (blue dashed line). During the action potential, Ca^{2+} enters through N and P/Q channels, which triggers the opening of K_{Ca} channels. Activation of 5-HT (5-hydroxytryptamine, serotonin), dopamine (DA) and $GABA_B$ (γ-aminobutyric acid B) receptors reduces Ca^{2+} entry and causes a decrease in the sAHP, which alters frequency regulation and adaptation. A small component of the sAHP remains after a blockade of Ca^{2+} channels with cadmium (right). This component is due to K_{Na} channels[66,67]. **b** | Frequency adaptation in a control situation and when the sAHP is reduced. The upper dashed line indicates spike threshold and the lower indicates the level of the first sAHP. The effect of a partial blockade of K_{Ca} with apamin on the motor pattern is shown. Particularly at slow rates of motor activity, the rhythm can break down entirely. Modified, with permission, from REF. 65 © (1994) American Physiological Society.

pattern in which both sides are active simultaneously[44–46]. The fact that the coordination shifts from alternation to in-phase indicates that the crossed excitatory interneurons[47] provide sufficient mutual excitation between the CPGs to produce in-phase coordination.

The burst-generating machinery in a single hemisegment relies on ipsilateral excitatory interneurons (E in FIG. 3), which excite each other within the excitatory interneuron population[48–50]. The excitatory interneurons are glutamatergic and activate postsynaptic AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and NMDA receptors. They monosynaptically excite not only excitatory interneurons, but also ipsilateral motor neurons and crossed glycinergic inhibitory neurons (I in FIG. 3) that inhibit contralateral neurons[47,48]. There are two types of crossed inhibitory neurons: larger neurons with a long descending axon, and smaller interneurons with much shorter axons[51]. The latter provide larger unitary inhibitory postsynaptic potentials (IPSPs) than the former[50]. There are also some small ipsilateral glycinergic interneurons that are co-activated with motor neurons, probably by excitatory interneurons, and that provide monosynaptic inhibition to motor neurons and crossed inhibitory interneurons[50,52]. In addition, the rostral part of the spinal cord contains a few large glycinergic 'lateral interneurons' with fast-conducting, long ipsilateral axons, which probably subserve mainly a propriospinal function. Burst activity can continue during a glycinergic blockade, and in the hemicord a blockade does not have a significant effect on the burst frequency. So ipsilateral glycinergic neurons are not required for burst generation to occur, although whether they contribute to burst termination under some conditions is unknown.

The core of the lamprey locomotor network therefore consists of ipsilateral glutamatergic neurons and glycinergic neurons with contralateral axons[46–48] (FIG. 3). The descending reticulospinal axons (RS in FIG. 3) drive the network by activating AMPA and NMDA receptors on excitatory interneurons, crossed inhibitory interneurons and motor neurons[53]. NMDA receptors are particularly important owing to their voltage dependence, which contributes to plateau-like depolarizations that are important for slow bursting. All the evidence indicates that spinal locomotor networks in other adult and developing vertebrates are also built on a core of glycine and glutamate neurons[21,28,36,54–57].

In addition, there is evidence that tadpole and lamprey motor neuron collaterals can provide recurrent excitation to other motor neurons and to excitatory interneurons[58,59]. In the tadpole, locomotor episodes are prolonged when cholinergic activity is potentiated[60]. Network activity also continues when $GABA_A$ (γ-aminobutyric acid A) receptors are blocked, but the rate of bursting increases, indicating that GABA interneurons contribute to slowing down the motor activity[61–64].

Ion channels in the locomotor CPG. The behaviour of a neuron is determined by the ion channels that are expressed in its cell membrane, and by transmitter-activated receptors. In spinal neurons, frequency regulation and SPIKE-FREQUENCY ADAPTATION (FIG. 4a,b) are determined primarily by the slow afterhyperpolarization (sAHP) that follows an action potential, which is mainly (80%) due to Ca^{2+}-dependent K^+ channels (K_{Ca}) of the SK3 type, and to a lesser degree to Na^+dependent K^+ channels (K_{Na}; FIG. 4a)[65–67]. K_{Ca} channels are activated by Ca^{2+} entry through N and P/Q channels (FIG. 4a) during the action potential[68]. A partial blockade of K_{Ca} with apamin markedly reduces the sAHP, and reduces spike frequency adaptation. The latter affects burst termination and causes longer bursts and a slowing of the burst rate, which in addition often becomes irregular and can break down altogether (FIG. 4b). K_{Ca} channels are particularly important for the CPG activity at slow burst rates. Similarly, transmitters[69,70] that reduce the sAHP by acting on Ca^{2+} channel subtypes (FIG. 4a) slow the burst rate.

SPIKE-FREQUENCY ADAPTATION
A decrease in the rate of action potentials fired by a neuron under prolonged depolarization.

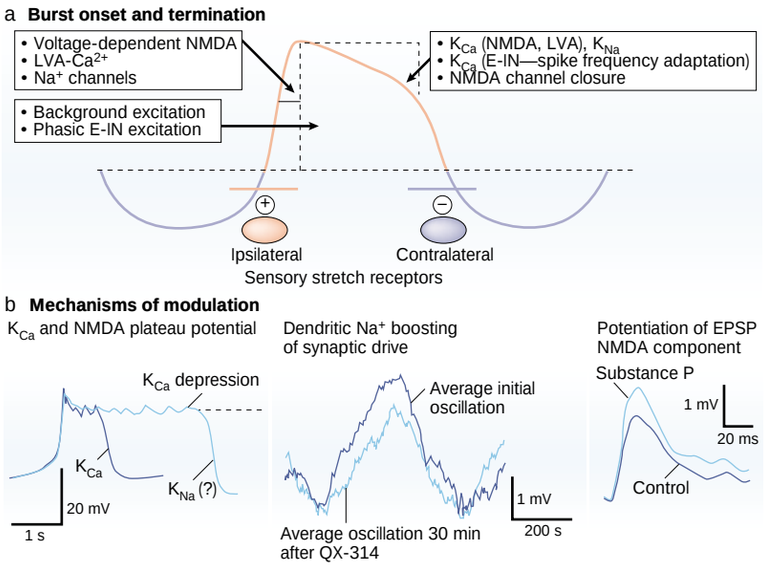

Figure 5 | **Factors controlling burst onset and termination. a** | Several factors contribute to the initiation, maintenance and termination of the depolarizing phase. In addition to conventional synaptic, voltage-dependent NMDA (*N*-methyl-D-aspartate) receptors, low-voltage-activated Ca^{2+} channels (LVA-Ca^{2+}) and Na^+ channels might be activated. Ca^{2+} enters the cell through these channels, activates K_{Ca} channels, and initiates a progressive hyperpolarization leading to closure of the NMDA channels. The initiation of depolarization is facilitated by activation of ipsilateral excitatory stretch receptors, whereas its termination is partially a result of activation of contralateral inhibitory stretch receptors. E-IN, excitatory interneuron. Dashed line indicates the resting membrane potential. Modified, with permission, from REF. 72 © (2001) Cambridge Univ. Press. **b** | Mechanism of modulation in neurons of the locomotor network. The left panel shows NMDA-induced plateau potentials that depend on the interaction between voltage-dependent NMDA receptors and voltage-dependent K^+ channels. Modified, with permission, from REF. 72 © (2001) Cambridge Univ. Press. Ca^{2+} entry during the NMDA plateau activates K_{Ca} channels and terminates the plateau. If K_{Ca} channels are blocked the plateau terminates later, or the termination is blocked altogether as when Ba^{2+} (dashed line) is substituted for Ca^{2+} (REF. 79). In the middle panel, the synaptic drive potentials that occur intracellularly in neurons that do not fire action potentials are amplified by activation of Na^+ channels. If Na^+ channels are blocked by intracellular injection of QX-314, the amplitude of the synaptic potential is reduced by 20%. Modified, with permission, from REF. 77 © (2002) American Physiological Society. The current carried by NMDA channels is markedly enhanced by tachykinins such as substance P and metabotropic glutamate receptors (mGluR1)[101]. The right panel shows a reticulospinal excitatory postsynaptic potential (EPSP) that is facilitated by substance P. The facilitation is limited to the NMDA component, whereas AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and gap junction components are not affected[101].

N- and P/Q-type Ca^{2+} channels are also responsible for triggering exocytosis[71] in synapses of lampreys and other species. A partial blockade of these channels will markedly disturb rhythmic activity. They are therefore an ideal and frequent target for presynaptic modulation. A selective blockade of L channels, on the other hand, has little or no effect on the burst pattern[72,73]. Finally, low-voltage-activated (LVA) Ca^{2+} channels are responsible for generating post-inhibitory rebound and can contribute to the generation of a stable burst pattern[61,74].

Two types of voltage-gated K^+ channel affect the repolarization of the action potential in these spinal lamprey neurons: the delayed rectifier type and a very fast-activating type of Kv3.4 channel. The latter is important for maintaining the action potential at a constant duration, at both the soma and axon-terminal level[75,76]. In both cases, the duration of the action potential determines the Ca^{2+} entry and thereby the amplitude of the sAHP and the efficacy of synaptic transmission. If the fast K^+ current is selectively blocked, the efficacy of synaptic transmission varies greatly with the presynaptic frequency of action potentials and so becomes unpredictable. A blockade of this fast K^+ current leads to marked changes in locomotor burst frequency and regularity.

Active dendritic properties. The excitatory synapses that are activated in a neuron when the network is active will, locally at the postsynaptic site in a dendrite, produce a certain excitatory current and a corresponding membrane depolarization. The effect that this will exert at the soma or initial segment level depends on the attenuation of the synaptic signal that occurs along the dendrite. Several mechanisms can amplify or boost the synaptic signal (FIG. 5a). One factor is subthreshold and asynchronous activation of dendritic Na^+ channels, which may be of the inactivating rather than persistent type[77] (FIG. 5b, middle panel). Na^+ channels can be selectively blocked by QX-314 at low concentrations. When injected into single neurons during locomotor network activity, QX-314 reduced the synaptic drive potential from the CPG by around 20%, indicating that this is the amplification factor provided by dendritic Na^+ channels under these conditions (FIG. 5b).

Other factors that boost the synaptic drive are LVA Ca^{2+} channels, which provide a postinhibitory rebound[70,78] that facilitates depolarization directly after the inhibitory phase and thereby the phase transition. The voltage-dependent properties of NMDA channels, which are directly activated by glutamate, provide another type of direct amplification, when the membrane potential is close to the spike threshold (FIG. 5a).

The voltage-dependent properties of NMDA receptors also confer plateau properties on the neurons under certain conditions[79] (FIG. 5b, left panel). A brief synaptic excitation can therefore elicit a long-lasting depolarization. This depolarization results from activation of voltage-dependent NMDA channels that interact with ion channels intrinsic to the cell (FIG. 5b). K_{Ca} channels that are activated by the Ca^{2+} entry through NMDA channels, and possibly also K_{Na} channels, contribute to the termination of the plateau[67,72,80]. The plateau properties are important in particular to maintain long-lasting bursts and a slow, regular locomotor activity. Plateau potentials can also be elicited by activation of low-threshold L-type Ca^{2+} channels, as shown in the turtle and in mammals[81].

Presynaptic modulation of synaptic efficacy. The terminals of network interneurons (excitatory and inhibitory) and sensory cells conveying touch and pressure sensations are subject to phasic presynaptic modulation of synaptic efficacy during each locomotor cycle[82–84]. This is due to a phasic activation of presynaptic $GABA_A$ and $GABA_B$ receptors, which allows phasic adaptation of synaptic efficacy in the locomotor network. This means that, at the sensory level, there is a phase-dependent gating of synaptic transmission. Such a CPG-induced gating of sensory signals has also been described in mammals and invertebrates[82]. The modulation originates from segmental interneurons; bipolar GABA neurons terminate on sensory afferents, whereas the larger GABA

Table 1 | Spinal modulation — G-protein-coupled receptors

	Presynaptic	HVA_{Ca}	LVA_{Ca}	K_{Ca}	K^+	NMDA	Network	References
$GABA_B$	I	↓	↓	(↓)			↓	61,62,70,78,84
$mGluR_I$	0	0	0		↓	↑	↑	82,96–98
$mGluR_{II—III}$	I	0	0				↓	71
$5\text{-}HT_{1A}$	I	↓		(↓)			↓	69,89,92–94,99,102
D2	I	↓	↓	(↓)			↓	69,72
TK	F	↑↓		↓	↓	↑	↑	49,85,101,105
NPY	I						0	86,72
Som.		0	0	0	↑		↓	86,72
NT		0	0	0			↑	86,72

Metabotropic amino acid, aminergic and peptidergic G-protein-mediated modulation of ion channel, synaptic, cellular and network activity in the lamprey spinal cord. Presynaptic actions can be targeted to sensory afferents, excitatory or inhibitory interneurons and descending reticulospinal axons. Different transmitters have selective actions on different cellular targets (I indicates presynaptic inhibition and F, facilitation; 0 indicates no known effect). Sometimes the effects are cell-type specific. The locomotor network is modulated phasically in each cycle by sensory afferents and interneurons. The modulation of high-voltage-activated calcium channels (HVA_{Ca}), low-voltage-activated calcium channels (LVA_{Ca}), K_{Ca}, K^+ and NMDA (*N*-methyl-D-aspartate) channels is indicated with a downward arrow for depression and an upward arrow for facilitation. HVA_{Ca} includes N, P/Q and L-type calcium channels; K^+ indicates subtypes of K^+ channels. Finally, the effects on the network level have been studied on the background of locomotor activity (arrows relate to locomotion burst frequency) and in related modelling experiments. 5-HT, 5-hydroxytryptamine (serotonin) receptor; D_2, type 2 dopamine receptor; mGluR, metabotropic glutamate receptor; NPY, neuropeptide Y; NT, neurotensin; Som., somatostatin; TK, tachykinin.

neurons probably mediate the presynaptic modulation of locomotor interneurons. The presynaptic modulation is in most cases produced by a reduction in Ca^{2+} entry, through direct or indirect actions on presynaptic Ca^{2+} channels.

Various metabotropic modulators (5-HT (5-hydroxytryptamine, serotonin), dopamine, glutamate, GABA, neuropeptide Y and tachykinins) also depress or facilitate synaptic efficacy at a presynaptic level[49,82,85,86] (TABLE 1). These effects can be synapse-specific.

Mathematical modelling of CPGs. Although knowledge of interneuron connectivity, types of synaptic transmission and membrane properties is required for an understanding of CPGs, it is not in itself sufficient. The many interactive processes on the subcellular, cellular and network levels are dynamic and complex. Computational methods are therefore required to test whether tentative explanations derived by intuition can account for experimental findings. Biophysically realistic models of both the lamprey and the frog embryo systems have been developed[33,35,37,87–90]. In the models of the lamprey network, populations of neurons have been simulated. Each neuron is modelled with Na^+, K^+, Ca^{2+} and K_{Ca} channel subtypes, and in most cases with three dendritic, one somatic and one initial segment compartment. Simulated neurons mimic their biological counterparts in terms of some aspects, such as the size and shape of the action potential and the dynamic relation between depolarizing current and frequency of action potentials (FIG. 6a). Within each pool of neurons there is some variability in terms of input resistance of different neurons, again simulating the distribution that is found experimentally. This distribution has turned out to be important for providing stable network activity[89,90].

Next, populations of model excitatory and inhibitory interneurons were synaptically connected into a network as established experimentally, with excitatory postsynaptic potentials (EPSPs) mediated by a conductance increase to cations (Na^+ and K^+), and IPSPs to Cl^- ions. The voltage dependence of NMDA receptors has also been simulated[87,91]. The segmental network, with populations of excitatory interneurons and crossed inhibitory interneurons, can generate alternating phases of activity, if supplementary excitatory drive is provided by simulated reticulospinal neurons[89,90] (FIG. 6b). So, a network configuration with modelled neurons that simulate their natural counterparts can produce alternating burst activity that would result in swimming. Moreover, if the reticulospinal drive is varied, the burst frequency changes within the biological range. At lower rates of swimming, NMDA receptors are particularly important for maintaining lasting bursts of activity. These simulations show that the available experimental data can account for the intrinsic function of the segmental network. Simulations of this type are an indispensable analytical tool, in which one can test the contributions of different components such as ion channel subtypes, and go back and forth between modelling and biological experiments.

Intrinsic modulator systems. The core of the CPG, which regulates the basic burst activity, consists of glutamatergic and glycinergic interneurons acting through ligand-gated ion channels. However, G-protein-mediated systems are also integrated into the normal operation of the locomotor network.

In the lamprey spinal cord, 5-HT neurons that also contain dopamine are located below the central canal, and form a dense bilateral plexus of varicosities into which network interneurons extend their dendrites[69]. The 5-HT neurons are active during fictive locomotion[92,93], and contribute to the burst pattern through activation of $5\text{-}HT_{1A}$ receptors on interneurons and motor neurons. Blocking these receptors causes the burst pattern to speed up and often to become less regular. Although 5-HT neurons show a phasic burst pattern during locomotor activity, 5-HT acts through slow, G-protein-mediated modulation of the sAHP and

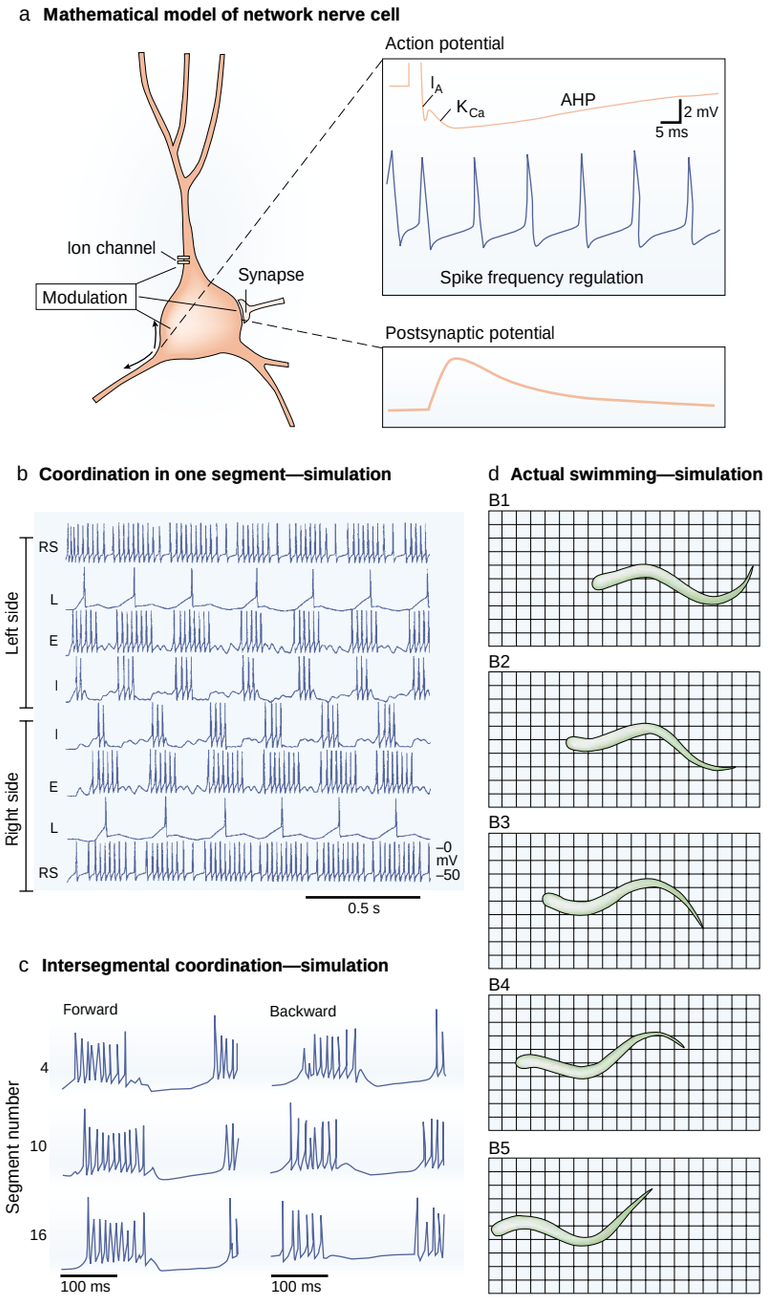

Figure 6 | **Modelling the lamprey locomotor network. a** | Neurons of the network were simulated in a realistic fashion, with the different voltage-dependent ion channels (Na^+, K^+ (I_A), Ca^{2+}), Ca^{2+}-dependent K^+ channels (K_{Ca}) and ligand-gated channels (AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid)/kainate, NMDA (*N*-methyl-D-aspartate), glycine). Action potentials with an early and late afterhyperpolarization (AHP) and spike frequency adaptation can be simulated, together with postsynaptic potentials in different compartments. Modulation of spike-generating, ion channel and synaptic properties can also be simulated. **b** | Simulation of the segmental network using a pool of excitatory (E), inhibitory (I) and lateral (L) interneurons. The activity is driven by excitatory reticulospinal neurons (RS). Activity on the left and right sides alternates. **c** | Pattern of intersegmental coordination, produced by a simulated network of 60 segments. This circuitry produces a rostro-caudal phase lag along the simulated spinal cord, and this lag can be reversed if the excitability is increased in the caudal end, which results in backward locomotion. **d** | Simulation of swimming movements using a neuromechanical model. Frames (B1–B5) show steady-state swimming at 4 Hz, resulting from tonic excitation of the network, with the model lamprey moving forwards at a speed of 0.73 m s^{-1}. Time interval between frames is 50 ms. Modified, with permission, from REF. 156 © (1995) Elsevier Science.

synaptic efficacy. The 5-HT system is therefore an integral part of the locomotor network, which fine-tunes neuronal properties[49,69,92,94]. Dopamine has a complementary action to that of 5-HT. 5-HT seems to promote a regular locomotor pattern in all vertebrates studied, although in some species this modulation depends mainly on descending projections[34,36,57,95].

The GABA system in the spinal cord is also active during network activity, although locomotor activity continues when GABA receptors are blocked[46,61–63,84]. Both $GABA_A$ and $GABA_B$ receptors are activated during locomotor network activity, and a blockade of either causes the burst pattern to speed up. The mechanisms of this action include presynaptic depression of interneuronal synaptic transmission (as discussed earlier), and an action of $GABA_B$ receptors on Ca^{2+} channels that indirectly affects the sAHP[70]. The GABA system can therefore also be regarded as an integral part of the locomotor system in the lamprey, and it has a similar action in the frog tadpole after hatching[64,70].

Glutamate also has a modulatory effect, acting through metabotropic glutamate receptors (mGluRs) at presynaptic (type II and III) and postsynaptic sites (type I, mGluR1 and 5)[96–98]. Postsynaptic mGluRs are activated during fictive locomotion, and mGluR1 speeds up locomotor activity (a subtype-specific blockade slows activity). mGluR1 acts by potentiating NMDA receptors and blocking a LEAK CURRENT[98]. The mGluRs are therefore also an integral part of the locomotor network that contributes to the level of activity.

Mode of action of modulators

As we have seen above, some modulator systems, like the 5-HT/dopamine or GABA systems, are intrinsic to the central network operations. The same modulator systems, and other, extrinsic systems, can also be activated, for example by descending brainstem fibres, to separately adapt the locomotor networks to different external demands, modulating the locomotor network from the outside when needed. By contrast, the 'intrinsic' modulation described above is turned on whenever the CPG is active. TABLE 1 summarizes the actions of different metabotropic receptors on different ion-channel subtypes and at the presynaptic level. By understanding the transmitter-induced effects exerted on certain target molecules at the cellular and network levels, we can make the link from gene products to network activity and motor behaviour. Below, the mode of action of the different modulator systems is summarized in terms of cellular target mechanisms.

Modulation of sAHP modifies burst frequency. By reducing the Ca^{2+} current though N and P/Q channels (FIG. 4a), the 5-HT, dopamine and GABA systems indirectly decrease the current through apamin-sensitive K_{Ca} channels, and thereby reduce the amplitude of the sAHP. This reduction in the sAHP decreases sAHP summation and thereby reduces frequency adaptation, which in turn delays burst termination[68–70,72,89,99,100]. A delay in burst termination prolongs the cycle duration and thereby reduces the burst frequency.

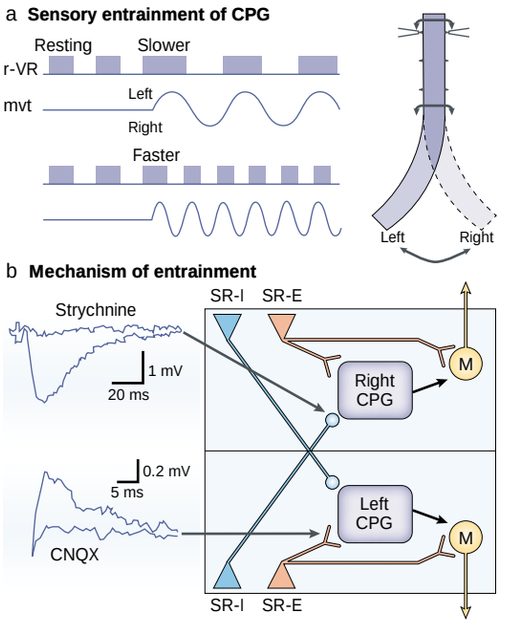

Figure 7 | **Effects on the central pattern generator (CPG) of sensory input from stretch receptors activated during the movement. a** | The locomotor activity from one ventral root (r-VR) under resting conditions, and when a slower and a faster movement than the rest rate is superimposed. The CPG activity is entrained in both cases. The experimental situation is illustrated to the right: the caudal part of the spinal cord resting on the notochord is moved back and forth, simulating locomotor movement. **b** | The underlying neural organization of stretch receptor neurons and the CPG that allows sensory control is shown. The crossed inhibitory stretch receptors (SR-Is) are glycinergic and inhibit the CPG neurons of the contralateral side (the inhibitory postsynaptic potential (IPSP) is blocked by strychnine), and the ipsilateral glutamatergic stretch receptors activate ipsilateral CPG neurons. The CPG in turn has motor neurons (M, yellow) as its output stage. CNQX, AMPA (α-amino-3-hydroxy -5-methyl-4-isoxazole propionic acid) receptor antagonist; SR-E, excitatory stretch receptors. Modified, with permission, from REF. 156 © (1995) Elsevier Science.

NMDA current increases burst frequency. Both tachykinins and mGluR1 activation cause an enhanced NMDA current (FIG. 5b). Tachykinins achieve this by phosphorylating NMDA channels through protein kinase C (PKC)[98,101], leading to a potentiation of the NMDA component in glutamatergic synapses (FIG. 5b, right). This leads to increased Ca^{2+} entry through NMDA receptors, and thereby to activation of K_{Ca} channels and early burst termination, which increases the frequency of bursting.

Modulation of IPSPs affects burst frequency. In a train of IPSPs, the amplitude of the individual IPSPs decreases. The degree of depression is markedly affected by modulators. Tachykinins cause the IPSP amplitude to decline more rapidly, whereas 5-HT causes the amplitude to remain higher than in untreated neurons[49]. A reduction in the crossed inhibition results in an increase in bursting frequency — as found with tachykinins[101] — and potentiation of this inhibition probably contributes to the slowing of the burst rate that results from application of 5-HT[69,102]. In the tadpole, both noradrenaline and nitric oxide can modulate the burst frequency by potentiating inhibition in the locomotor network[96,103].

mGluR1 depresses a leak current. mGluR1 activation reduces a leak current that is probably carried by K^+. This reduction leads to depolarization of the neuron, which contributes to an increase in burst frequency[98]. The effect of mGluR1 activation on network activity is reduced by cannabinoid receptor antagonists. During locomotion, a blockade of cannabinoid receptors results in a slowing of the burst frequency, which can be explained at least partially by a cannabinoid-induced reduction in the crossed inhibition[96].

ATP and adenosine in the tadpole. In the tadpole, ATP has an important role. Tadpoles swim in bouts of a few seconds. At the beginning of each bout, ATP is released and exerts an excitatory effect on the network through P2X receptors. During the swimming bout, the ATP is converted to adenosine, which instead has a depressant action on the network through P2Y receptor subtypes acting on K^+ channels. This action contributes to the control of bout duration[36,90,104]. The role of ATP and adenosine in other locomotor networks remains to be explored.

Peptidergic modulation and plasticity. Detailed studies have been carried out on the effect of tachykinins and in particular substance P on synaptic transmission, cellular properties and network activity. Some of the midline 5-HT/dopamine neurons[69] also express tachykinins[105]. A brief (10 min) application of tachykinins to the network causes a lasting (24 h) and pronounced enhancement of the locomotor burst rate[69,101]. Administration of D_2 receptor antagonists produces a similar lasting increase in the burst rate, and this is blocked by co-administration of tachykinin antagonists. This indirect effect of the D_2 receptor antagonist indicates that endogenous release of tachykinins can produce a similar lasting increase in locomotor activity during a constant excitatory drive. This long-lasting effect is elicited by three consecutive mechanisms, the first of which involves potentiation of NMDA receptors caused by PKC activation. After about an hour, this is followed by a protein-synthesis-dependent phase that relies on pre-existing RNA. The last phase starts at around 10–15 hours and depends on synthesis of new RNA[85,101,106]. The effects of neuropeptide Y, neurotensin and somatostatin are summarized in TABLE 1.

Feedback action on the CPG

Sensory feedback to the CPG is a prominent part of the control system for vertebrate locomotion, but only in the lamprey is it understood how sensory input affects the neurons of the CPG. Stretch receptors at the lateral margin of the spinal cord sense the lateral bending movements that occur during each swim cycle[107]. As the muscle fibres in one hemisegment contract, the stretch receptors on the contralateral side are extended. These stretch receptor neurons are of two types.

LEAK CURRENT
Ionic current produced by ion channels that are open at resting membrane potential. They are usually voltage insensitive and often permeable to K^+.

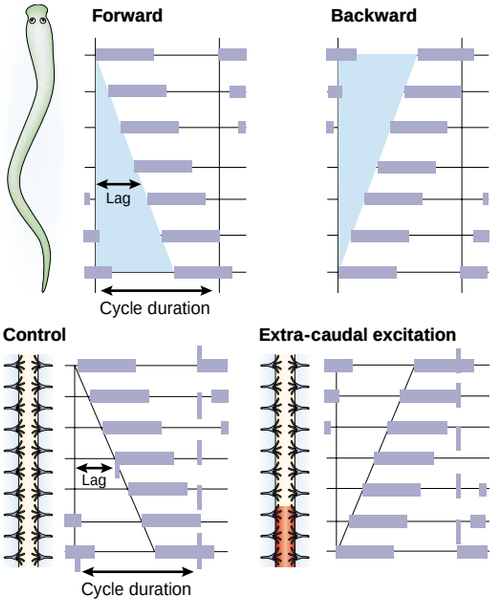

Figure 8 | **Intersegmental coordination in the lamprey.** The lamprey swims by producing a mechanical wave that is transmitted along the body. As illustrated during forward locomotion, there is a lag between consecutive segments in the spinal cord. This lag is always a certain proportion of the cycle duration (a constant phase lag). It can be reversed into a wave that is propagated from tail to head, as during backward locomotion. In the isolated spinal cord (bottom panel) a rostro-caudal phase lag can also be produced, so the ability to generate a constant phase lag is inherent to the spinal cord. The pattern can be reversed if extra excitation is added to the caudal spinal cord (right). The segments of the caudal part have higher excitability and generate a high rate that can entrain the more rostral segmental networks. The rostral segments have a lower inherent burst rate and are therefore entrained but with a certain lag[74].

Inhibitory glycinergic stretch receptors (SR-I in FIGS 3 and 7) inhibit the CPG interneurons on the actively contracting (contralateral) side, and help to terminate the activity of this CPG. Excitatory glutamatergic stretch receptors (SR-E in FIGS 3 and 7) provide excitation to the ipsilateral CPG neurons, which are activated as the activity of the contralateral CPG terminates[108]. This sensory input therefore provides a sensory overlay of the CPG. The input is so strong that rhythmic activation of the stretch receptor neurons by alternating locomotor-like movements will faithfully entrain the locomotor rhythm generated by the CPG (FIG. 7). This will also occur when the superimposed movements are faster or slower than the control burst frequency (see REF. 37). The stretch receptors receive phasic inhibition and excitation from the CPG during the locomotor cycle. The unloading of the stretch receptor neurons during ipsilateral muscle contraction is partially compensated for by an additional excitatory input from the CPG during this phase[109]. This arrangement is similar to the co-activation of muscle spindles through activation of γ-motor neurons during muscle contraction in mammals (α/γ-linkage during locomotion, see REF. 8).

Intersegmental coordination

So far we have focused on segmental pattern generation and paid little attention to the intersegmental coordination that is needed for locomotion. The lamprey swims like an eel, with an undulatory wave that passes along the body and pushes the animal forwards through the water. This is achieved by a lag between the activation of consecutive segments along the body (FIG. 8). The faster the wave is propagated backwards, the faster the animal will move forwards through the water. The lag between consecutive segments decreases with increasing speed in a characteristic fashion so that it is always a certain proportion of the cycle duration, whether it is 5 s or 0.1 s. This arrangement has the advantage that the phase lag between the most rostral and the most caudal segments will always be constant, usually around 100% of cycle duration in most species. Such a phase lag was first described in the dogfish and later in other species including lamprey[110–112]. This is the standard coordination during swimming, but the phase lag can be reversed to allow backward swimming when the fish is caught in a blind alley. A change in phase lag can be induced by sensory stimuli in the spinal dogfish or lamprey, and this pattern of coordination is therefore not dependent on supraspinal control.

Each hemisegment has the potential to generate locomotor CPG activity through its excitatory interneurons. The interneurons in one segment also extend their axons over a few rostral and a greater number of caudal segments. Also, in the isolated spinal cord, the rostral segments lead with a constant rostro-caudal phase lag (FIG. 8). If the excitability of the caudal spinal cord is enhanced experimentally by local application of glutamate agonists, the caudal segments instead become the leading segments and the phase lag is reversed into a caudo-rostral lag[74]. The simplest explanation for the intersegmental phase lag is that under normal conditions the rostral segments entrain more caudal segments that have the tendency to be active at a slower rate, but if additional excitatory input reaches the caudal segments (FIG. 8), they will instead become the fastest and entrain more rostral segments (see also 'Virtual lamprey' section). The intersegmental coordination has also been analysed through modelling in different contexts[113–115].

Steering and body orientation

Symmetrical bilateral activation of the reticulospinal neurons in the middle and posterior rhombencephalic reticular nucleus generates forwards locomotor activity. If there is a bias towards greater activation on one side, this results in longer ventral root bursts on this side, and consequently the direction of locomotion will deviate towards this side. Such asymmetric reticulospinal activation occurs during left–right turning in the lamprey[74,116,117]. Vertical deviations are probably achieved by reticular neurons that preferentially activate ventral or dorsal myotome neurons.

All vertebrates maintain a characteristic body configuration during locomotion, usually with the dorsal side up, as in the lamprey. Rotation of the head is achieved predominantly by a vestibular input acting through interneurons on contralateral reticulospinal neurons.

Box 2 | Potential for rehabilitation after spinal cord injury

In all classes of vertebrates, including primates, the spinal cord can generate stereotypic locomotor movements even when it has no connections to the brainstem[9,41,54,57,138–140]. After a low, thoracic spinal cord transection, amphibians, reptiles, birds and mammals can produce walking movements of the hindlimbs that are coordinated by the lumbosacral spinal cord. This was first shown in spinal cats[138], which can perform walking movements on a treadmill, and within a certain range can adapt to its speed. The kinematic details of the joint movements, and the detailed pattern of muscle activity, were the same as in the intact cat. Directly after a spinal cord lesion in the adult cat, pharmacological activation by noradrenergic agonists is required to induce walking movements[141]. Later, chronically spinal cats can be made to walk but only if they are 'trained' on a treadmill every day[142]. The neural substrate for walking is therefore present in the feline spinal cord directly after the lesion, but without transmitter agonists, repeated locomotor training is required[139,140]. In addition to the central network, there is a sensory overlay from receptors signalling the load on the limb during the support phase and the rostrocaudal position of the limb at the level of the hip[18–20,140,142]. The treadmill training produces the appropriate 'compound' sensory signal throughout the step cycle. The most likely explanation for the importance of training is use-dependent facilitation of the synapses that are activated during locomotion. Chronically spinal animals that are trained to stand but not to walk will achieve efficient standing, at the expense of walking[143,144]. So, the effect is directed towards the specific pattern of coordination that is trained.

Could patients that had a spinal cord lesion that had bound them to a wheelchair, sometimes for years, be trained to walk again with a similar training programme to that used for chronic spinal rats and cats? Several laboratories have explored this possibility by training patients with incomplete spinal cord lesions on a treadmill[140,145–155], initially supporting the body weight with a harness. The two limbs are manually moved forward by physical therapists to be placed on the moving treadmill belt, and brought backwards by the belt, to be moved forward again by the therapist along the same trajectory that the limb would normally move during the swing phase. This will produce a similar type of sensory input as would occur during normal locomotion. With training over several weeks, a proportion of patients regained the ability not only to walk on the treadmill, but also to walk over ground, initially with a walker and later even with a cane. These results indicate that use-dependent facilitation of the spinal circuitry can make the spinal cord operational again in humans. In these cases the spinal cord lesion cannot be complete, and a certain number of axons from the brainstem must remain intact. In the case of patients with a complete spinal cord lesion, a spinal locomotor automatism can be demonstrated, but the patient will be unable to control it actively. It therefore seems that a proportion of the patients that are confined to a wheelchair, but have the cervical cord intact, can regain a locomotor control that is sufficient to walk for limited distances, such as to a car, given intensive initial treadmill training. Once the patients have started to walk, they will maintain this ability by practicing every day.

When the vestibular input is symmetrical on the left and right, reticulospinal neurons are activated symmetrically. A deviation of the head towards the left or right will produce asymmetric activation of the reticulospinal neurons, which will produce an automatic correction of body orientation[118,119]. An asymmetric light stimulus applied to one eye will lead to a bias in the body position, so that the dorsum of the body becomes oriented towards the light source (dorsal light response)[120].

The vestibular input is the main source for postural control for fish and also for the orientation of the head in higher vertebrates, in which the correction of body position also depends on input from the limbs.

Virtual lamprey

We have discussed how to reproduce segmental motor pattern generation using mathematical modelling (FIG. 6). The same type of analysis has also been applied to intersegmental coordination and steering[90,121–123]. Similar models as for the segmental network have been used, but they have taken into consideration that the axons of both excitatory and inhibitory crossed interneurons have ascending and descending axons that extend over a limited number of segments. It is possible to model the entire network with populations of neurons and to show that the rostrocaudal phase lag can be produced by the simulated network (FIG. 6c). Moreover, the direction of the wave can be reversed, as in backward swimming. The network can be made to produce a phase lag in the normal frequency range of the biological system. We subsequently simulated a neuromechanical model (FIG. 6d), which simulates swimming through water at different speeds, and with maintained body configuration[88,121]. These models can also simulate turning movements and swimming backwards. So, to a first approximation we have created a 'virtual lamprey' built on detailed information from the biological system. The solutions used for describing the lamprey system have recently also been applied to newt swimming[124], and the tadpole has been modelled with neuronal populations[33,125].

Higher level control

A fundamental question is how different patterns of behaviour are selected and initiated in the CNS. Indirect evidence indicates that the basal ganglia are important in the context of locomotion. The lamprey striatum contains the same cell types as the primate striatum, with GABA-mediated medium spiny cells and interneurons and the same type of input from thalamus, pallium and dopamine neurons in the brain stem[126,127]. The basic neuronal design is therefore conserved. In the lamprey, the basal ganglia project to the DLR[128] (FIGS 1b and 3), but it is not known whether the basal ganglia also project to the MLR (as in mammals[129]). Activation of the ventral striatum (nucleus accumbens) in rodents, elicited by local injection of dopamine or glutamate agonists, leads to the initiation of locomotion channelled through the MLR[130]. Conversely, lesions of the dopamine input to the striatum lead to characteristic deficits in locomotor initiation and exertion in humans (for example, in Parkinson's disease) and lamprey[131]. It seems likely that the basal ganglia can contribute to the initiation of locomotion through disinhibition of either of the two locomotor regions. It has been proposed that the two locomotor regions are activated in different behavioural contexts, such as foraging and aggressive behaviour, respectively[38].

Concluding remarks

This review outlines the general organization of the motor system, including central networks, CPGs and sensory control, which I have referred to as the motor infrastructure. I have focused on one example from the lamprey — the motor system that underlies locomotion, extending from the brainstem command systems — and have detailed the different mechanisms involved in the intrinsic function of the motor pattern generator networks. The effects of modulation of specific ion channel subtypes have been analysed and it is understood how

this affects the neuronal activity at the cellular, network and behavioural levels. In these cases it is now possible to make the link between the chain of events that extend from genes/molecules to behaviour. The way in which the network operates using mathematical models has subsequently been shown, beginning at the segmental level. Finally, intersegmental coordination, steering and the control of body orientation during movements have been discussed.

How do the results from the lamprey CNS compare with those from other vertebrates? Many aspects of the organization of basic motor function are similar throughout evolution, although additional mechanisms have been added. The overall organization of the vertebrate locomotor system is conserved, including diencephalic and mesencephalic locomotor regions that control the activity of spinal CPGs. Sensory regulation of the locomotor CPG is also present in all adult systems investigated. All vertebrate locomotor CPGs seem to be built from a core of glutamate and glycine interneurons that provide the basic motor pattern. From the left–right alternation of the lamprey, the CPG output has become more complex with the development of legs. In different tetrapods and bipeds, the efferent locomotor pattern remains surprisingly similar, indicating that understanding one limb CPG would provide crucial information for other species. The activity of spinal CPGs is modulated by various monoamines and metabotropic GABA and glutamate receptors that act pre- or postsynaptically, often with synapse- and cell-specific effects. These effects are exerted at both a pre-and postsynaptic level and they seem to be similar in the different model systems studied (lampreys, amphibian tadpoles, neonatal rodents and cats).

The challenges now are to reach an understanding of the intrinsic function of mammalian CPGs, and to explore the more complex mechanisms of selection and initiation of goal-directed motor behaviour in different animal models. Understanding the conservation of CPGs through evolution also has important clinical implications for humans with spinal injuries (BOX 2). The lamprey model has provided important insights into the intrinsic functions of its locomotor control system. Evolution has probably acted on these networks to adapt them to the control of appendages. In the future, genomic analyses will also be important in this context. The zebrafish genome should complement the information from the lamprey, and the comparison between zebrafish (with fins) and the mouse should provide important insights into the modifications made when changing from an aquatic to a terrestrial life. The animal models in which both genetic and experimental information are available will probably be at an advantage, but soon this might apply to many species.

1. Eccles, J. C. & Gibson, W. C. *Sherrington: His Life and Thought* (Berlin, Springer, 1979).
2. Grillner, S. in *Fundamental Neuroscience* (eds. Zigmond, M. J., Bloom, F. E., Landis, S. C., Roberts, J. L. & Squire, L. R.) 755–767 (Academic, San Diego, 2002).
   A general review of the motor system, from simple to complex.
3. Nieuwenhuys, R., Donkelaar, H. J. & Nicholson, C. *The Central Nervous System of Vertebrates* Vol. 1 (Springer, Berlin, 1998).
4. Delcomyn, F. Motor activity during searching and walking movements of cockroach legs. *J. Exp. Biol.* **133**, 111–120 (1987).
5. von Euler, C. The contribution of sensory inputs to the pattern generation of breathing. *Can. J. Physiol. Pharmacol.* **59**, 700–706 (1981).
6. Grillner, S. Neural networks for vertebrate locomotion. *Sci. Am.* **274**, 64–69 (1996).
7. Grillner, S. Neurobiological bases of rhythmic motor acts in vertebrates. *Science* **228**, 143–149 (1985).
8. Grillner, S. in *Handbook of Physiology, Section 1. The Nervous System II. Motor Control* (ed. Brooks, V. B.) 1179–1236 (American Physiological Society, Waverly, Maryland, 1981).
9. Grillner, S. Locomotion in vertebrates: central mechanisms and reflex interaction. *Physiol. Rev.* **55**, 247–304 (1975).
10. Isa, T. Intrinsic processing in the mammalian superior colliculus. *Curr. Opin. Neurobiol.* **12**, 668–677 (2002).
    A brief review of the network underlying saccade generation.
11. Sparks, D. L. The brainstem control of saccadic eye movements. *Nature Rev. Neurosci.* **3**, 952–964 (2002).
12. Darwin, C. *The Expression of the Emotions in Man and Animals* (Univ. Chicago Press (1965), Chicago and London, 1872).
    The classic description of innate motor patterns.
13. Russell, J. & Bullock, M. Multidimensional scaling of emotional facial expressions: similarity from preschoolers to adults. *J. Pers. Soc. Psychol.* **48**, 1290–1298 (1985).
14. Ito, M. The molecular organization of cerebellar long-term depression. *Nature Rev. Neurosci.* **3**, 896–902 (2002).
15. Jog, M. S., Kubota, Y., Connolly, C. I., Hillegaart, V. & Graybiel, A. M. Building neural representations of habits. *Science* **286**, 1745–1749 (1999).
16. Grillner, S. Recombination of motor pattern generators. Simple neuronal networks combine to produce complex versatile motor patterns. *Curr. Biol.* **1**, 231–233 (1991).
17. Grillner, S. & Wallén, P. in *Brain Mechanisms for the Integration of Posture and Movement* (eds Mori, S., Stuart, D. G. & Wiesendanger, M.) (Elsevier, Amsterdam, in the press).
18. Duysens, J. & Pearson, K. G. Inhibition of flexor burst generation by loading ankle extensor muscles in walking cats. *Brain Res.* **187**, 321–332 (1980).
19. Grillner, S. & Rossignol, S. On the initiation of the swing phase of locomotion in chronic spinal cats. *Brain Res.* **146**, 269–277 (1978).
20. Lam, T. & Pearson, K. G. The role of proprioceptive feedback in the regulation and adaptation of locomotor activity. *Adv. Exp. Med. Biol.* **508**, 343–355 (2002).
21. Stein, R. B., Misiaszek, J. E. & Pearson, K. G. Functional role of muscle reflexes for force generation in the decerebrate walking cat. *J. Physiol. (Lond.)* **525**, 781–791 (2000).
22. Massion, J. Postural control system. *Curr. Opin. Neurobiol.* **4**, 877–887 (1994).
23. Grillner, S. The role of muscle stiffness in meeting the changing postural and locomotor requirements for force development by the ankle extensors. *Acta Physiol. Scand.* **86**, 92–108 (1972).
24. Orlovsky, G. N., Deliagina, T. G. & Grillner, S. *Neuronal Control of Locomotion. From Mollusc to Man* (Oxford Univ. Press, New York, 1999).
    A comparative review of locomotor control systems throughout the animal kingdom.
25. Shik, M. L. & Orlovsky, G. N. Neurophysiology of locomotor automatism. *Physiol. Rev.* **56**, 465–501 (1976).
26. von Holst, E. Über relative Koordination bei Saugern und beim Menschen. *Pfluegers Archiv.* **240**, 44–49 (1938).
27. Wiersma, C. A. G. & Ikeda, K. Interneurons commanding swimmeret movements in the crayfish, *Procambarus clarkii* (Girard). *Comp. Biochem. Physiol.* **12**, 509–525 (1964).
28. Kiehn, O. & Kjaerulff, O. Distribution of central pattern generators for rhythmic motor outputs in the spinal cord of limbed vertebrates. *Ann. NY Acad. Sci.* **860**, 110–129 (1998).
29. Butt, S. J., Harris-Warrick, R. M. & Kiehn, O. Firing properties of identified interneuron populations in the mammalian hindlimb central pattern generator. *J. Neurosci.* **22**, 9961–9971 (2002).
    An analysis of interneurons in the rodent locomotor network.
30. Kiehn, O. & Tresch, M. C. Gap junctions and motor behavior. *Trends Neurosci.* **25**, 108–115 (2002).
31. Vinay, L., Brocard, F. & Clarac, F. Differential maturation of motoneurons innervating ankle flexor and extensor muscles in the neonatal rat. *Eur. J. Neurosci.* **12**, 4562–4566 (2000).
32. Pflieger, J. F., Clarac, F. & Vinay, L. Postural modifications and neuronal excitability changes induced by a short-term serotonin depletion during neonatal development in the rat. *J. Neurosci.* **22**, 5108–5117 (2002).
    A study of developmental changes in the network that controls locomotion.
33. Roberts, A., Tunstall, M. J. & Wolf, E. Properties of networks controlling locomotion and significance of voltage dependency of NMDA channels: stimulation study of rhythm generation sustained by positive feedback. *J. Neurophysiol.* **73**, 485–495 (1995).
34. Sillar, K. T., Woolston, A. M. & Wedderburn, J. F. Involvement of brainstem serotonergic interneurons in the development of a vertebrate spinal locomotor circuit.*Proc. R. Soc. Lond. B.* **259**, 65–70 (1995).
35. Tunstall, M. J., Roberts, A. & Soffe, S. R. Modelling intersegmental coordination of neuronal oscillators: synaptic mechanisms for uni-directional coupling during swimming in *Xenopus* tadpoles. *J. Comput. Neurosci.* **13**, 143–158 (2002).
36. Dale, N. & Kuenzi, F. M. Ion channels and the control of swimming in the *Xenopus* embryo. *Prog. Neurobiol.* **53**, 729–756 (1997).
    A review of the intrinsic function of the locomotor network in the developing amphibian nervous system.
37. Grillner, S. & Wallen, P. Cellular bases of a vertebrate locomotor system — steering, intersegmental and segmental co-ordination and sensory control. *Brain Res. Rev.* **40**, 95–106 (2002).
38. Grillner, S., Georgopoulos, A. P. & Jordan, L. in *Neurons, Networks and Motor Behavior* (eds Stein, P. S. G., Grillner, S., Selverston, A. I. & Stuart, D. G.) 3–19 (MIT Press, Cambridge, Massachusetts,1997).
    A discussion of the different supraspinal systems that contribute to vertebrate locomotor control.
39. Sirota, M. G., Di Prisco, G. V. & Dubuc, R. Stimulation of the mesencephalic locomotor region elicits controlled swimming in semi-intact lampreys. *Eur. J. Neurosci.* **12**, 4081–4092 (2000).
40. Di Prisco, G. V., Pearlstein, E., Le Ray, D., Robitaille, R. & Dubuc, R. A cellular mechanism for the transformation of a sensory input into a motor command. *J. Neurosci.* **20**, 8169–8176 (2000).
    A study of the role of plateau potentials in the reticulospinal neurons that mediate locomotor drive.

41. Fedirchuk, B., Nielsen, J., Petersen, N. & Hultborn, H. Pharmacologically evoked fictive motor patterns in the acutely spinalized marmoset monkey (*Callithrix jacchus*). *Exp. Brain Res.* **122**, 351–361 (1998).
42. Cangiano, L. & Grillner, S. Fast and slow locomotor burst generation in the hemi–spinal cord of the lamprey. *J. Neurophysiol.* 22 Jan 2003 (DOI 10.1152/jn.01100.2002). **A demonstration of locomotor burst generation in hemisegments, and without inhibition.**
43. Buchanan, J. T. Commissural interneurons in rhythm generation and intersegmental coupling in the lamprey spinal cord. *J. Neurophysiol.* **81**, 2037–2045 (1999).
44. Cangiano, L. & Grillner, S. Fast and slow locomotor burst generation in the hemi-spinal cord of the lamprey. *Soc. Neurosci. Abstr.* **28**, 65.10 (2002).
45. Cohen, A. H. & Harris-Warrick, R. M. Strychnine eliminates alternating motor output during fictive locomotion in the lamprey. *Brain Res.* **293**, 164–167 (1984).
46. Grillner, S. & Wallen, P. Does the central pattern generator for locomotion in lamprey depend on glycine inhibition? *Acta Physiol. Scand.* **110**, 103–105 (1980).
47. Buchanan, J. T. Identification of interneurons with contralateral, caudal axons in the lamprey spinal cord: synaptic interactions and morphology. *J. Neurophysiol.* **47**, 961–975 (1982).
48. Buchanan, J. T. & Grillner, S. Newly identified 'glutamate interneurons' and their role in locomotion in the lamprey spinal cord. *Science* **236**, 312–314 (1987). **The original description of spinal locomotor connectivity.**
49. Parker, D. & Grillner, S. Activity-dependent metaplasticity of inhibitory and excitatory synaptic transmission in the lamprey spinal cord locomotor network. *J. Neurosci.* **19**, 1647–1656 (1999).
50. Parker, D. & Grillner, S. The activity-dependent plasticity of segmental and intersegmental synaptic connections in the lamprey spinal cord. *Eur. J. Neurosci.* **12**, 2135–2146 (2000).
51. Ohta, Y., Dubuc, R. & Grillner, S. A new population of neurons with crossed axons in the lamprey spinal cord. *Brain Res.* **564**, 143–148 (1991).
52. Buchanan, J. T. & Grillner, S. A new class of small inhibitory interneurones in the lamprey spinal cord. *Brain Res.* **438**, 404–407 (1988).
53 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).
54. Stein, P. S. Central pattern generators and interphyletic awareness. *Prog. Brain Res.* **123**, 259–271 (1999).
55. O'Donovan, M. J., Wenner, P., Chub, N., Tabak, J. & Rinzel, J. Mechanisms of spontaneous activity in the developing spinal cord and their relevance to locomotion. *Ann. NY Acad. Sci.* **860**, 130–141 (1998).
56. Drapeau, P. *et al.* Development of the locomotor network in zebrafish. *Prog. Neurobiol.* **68**, 85–111 (2002). **A review of recent studies of the developing zebrafish locomotor system.**
57. Rossignol, S. *et al.* Pharmacological activation and modulation of the central pattern generator for locomotion in the cat. *Ann. NY Acad. Sci.* **860**, 346–359 (1998).
58. Perrins, R. & Roberts, A. Cholinergic and electrical synapses between synergistic spinal motoneurones in the *Xenopus laevis* embryo. *J. Physiol. (Lond.)* **485**, 135–144 (1995).
59. Placas, P. G. & Buchanan, J. T. Endogenous release of acetylcholine modulates the locomotor network of the lamprey spinal cord. *Soc. Neurosci. Abstr.* **28**, 270.10 (2002).
60. Perrins, R. & Roberts, A. Cholinergic contribution to excitation in a spinal locomotor central pattern generator in *Xenopus* embryos. *J. Neurophysiol.* **73**, 1013–1019 (1995).
61. Tegner, J. & Grillner, S. Interactive effects of the GABABergic modulation of calcium channels and calcium-dependent potassium channels in lamprey. *J. Neurophysiol.* **81**, 1318–1329 (1999).
62. Tegner, J., Matsushima, T., El Manira, A. & Grillner, S. The spinal GABA system modulates burst frequency and intersegmental coordination in the lamprey: differential effects of GABAA and GABAB receptors. *J. Neurophysiol.* **69**, 647–657 (1993).
63. Schmitt, D. E., Hill, R. H. & Grillner, S. A $GABA_A$ activation contributes to the locomotor pattern generation by slowing the locomotor rhythm in lamprey. *Soc. Neurosci. Abstr.* **28**, 65.7 (2002).
64. Reith, C. A. & Sillar, K. T. Development and role of $GABA_A$ receptor-mediated synaptic potentials during swimming in postembryonic *Xenopus laevis* tadpoles. *J. Neurophysiol.* **82**, 3175–3187 (1999).
65. El Manira, A., Tegner, J. & Grillner, S. Calcium-dependent potassium channels play a critical role for burst termination in the locomotor network in lamprey. *J. Neurophysiol.* **72**, 1852–1861 (1994). **A description of the role of calcium-dependent potassium channels in the locomotor network.**
66. Cangiano, L., Wallen, P. & Grillner, S. Role of apamin-sensitive K_{Ca} channels for reticulospinal synaptic transmission to motoneuron and for the afterhyperpolarization. *J. Neurophysiol.* **88**, 289–299 (2002).
67. Wallén, P., Hess, D., El Manira, A. & Grillner, S. A slow non-Ca^{2+}-dependent afterhyperpolarization in lamprey neurons. *Soc. Neurosci. Abstr.* **28**, 46.9 (2002).
68. Wikstrom, M. A. & El Manira, A. Calcium influx through N- and P/Q-type channels activate apamin-sensitive calcium-dependent potassium channels generating the late afterhyperpolarization in lamprey spinal neurons. *Eur. J. Neurosci.* **10**, 1528–1532 (1998).
69. Schotland, J. *et al.* Control of lamprey locomotor neurons by colocalized monoamine transmitters. *Nature* **374**, 266–268 (1995).
70. Matsushima, T., Tegner, J., Hill, R. H. & Grillner, S. GABAB receptor activation causes a depression of low- and high-voltage-activated Ca^{2+} currents, postinhibitory rebound, and postspike afterhyperpolarization in lamprey neurons. *J. Neurophysiol.* **70**, 2606–2619 (1993).
71. Krieger, P., Buschges, A. & El Manira, A. Calcium channels involved in synaptic transmission from reticulospinal axons in lamprey. *J. Neurophysiol.* **81**, 1699–1705 (1999).
72. Grillner, S., Wallen, P., Hill, R., Cangiano, L. & El Manira, A. Ion channels of importance for the locomotor pattern generation in the lamprey brainstem-spinal cord. *J. Physiol. (Lond.)* **533**, 23–30 (2001). **A review of ion channels that are important for pattern generation in the lamprey.**
73. Buschges, A., Wikstrom, M. A., Grillner, S. & El Manira, A. Roles of high-voltage-activated calcium channel subtypes in a vertebrate spinal locomotor network. *J. Neurophysiol.* **84**, 2758–2766 (2000).
74. 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**, 373–88 (1992).
75. Lamotte d'Incamps, B., Hess, D. & El Manira, A. A-type potassium current limits synaptic transmission by normalizing presynaptic spike waveform and calcium influx. *Soc. Neurosci. Abstr.* **27**, 384.8 (2001).
76. Hess, D. & El Manira, A. Characterization of a high-voltage-activated IA current with a role in spike timing and locomotor pattern generation. *Proc. Natl Acad. Sci. USA* **98**, 5276–5281 (2001). **A study on the role of Kv3.4-like channels in locomotor pattern generation.**
77. Hu, G. Y., Biro, Z., Hill, R. H. & Grillner, S. Intracellular QX-314 causes depression of membrane potential oscillations in lamprey spinal neurons during fictive locomotion. *J. Neurophysiol.* **87**, 2676–2683 (2002). **A demonstration of the potentiation of locomotor drive synaptic potentials by soma-dendritic Na^+ channels.**
78. Tegner, J., Hellgren-Kotaleski, J., Lansner, A. & Grillner, S. Low-voltage-activated calcium channels in the lamprey locomotor network: simulation and experiment. *J. Neurophysiol.* **77**, 1795–1812 (1997).
79. Wallen, P. & Grillner, S. *N*-methyl-D-aspartate receptor-induced, inherent oscillatory activity in neurons active during fictive locomotion in the lamprey. *J. Neurosci.* **7**, 2745–2755 (1987).
80. Bacskai, B. J., Wallen, P., Lev-Ram, V., Grillner, S. & Tsien, R. Y. Activity-related calcium dynamics in lamprey motoneurons as revealed by video-rate confocal microscopy. *Neuron* **14**, 19–28 (1995).
81. Guertin, P. A. & Hounsgaard, J. NMDA-induced intrinsic voltage oscillations depend on L-type calcium channels in spinal motoneurons of adult turtles. *J. Neurophysiol.* **80**, 3380–3382 (1998).
82. El Manira, A., Parker, D., Krieger, P., Wikstrom, M. & Grillner, S. in *Presynaptic Inhibition and Neural Control* (eds Rudomin, P., Romo, R. & Mendell, L.) 329–348 (Oxford Univ. Press, 1998). **An overview of presynaptic modulation in various transmitter systems.**
83. El Manira, A., Tegner, J. & Grillner, S. Locomotor-related presynaptic modulation of primary afferents in the lamprey. *Eur. J. Neurosci.* **9**, 696–705 (1997).
84. Alford, S., Christenson, J. & Grillner, S. Presynaptic $GABA_A$ and $GABA_B$ receptor-mediated phasic modulation in axons of spinal motor interneurons. *Eur. J. Neurosci.* **3**, 107–117 (1991).
85. Parker, D. & Grillner, S. Long-lasting substance-P-mediated modulation of NMDA-induced rhythmic activity in the lamprey locomotor network involves separate RNA- and protein-synthesis-dependent stages. *Eur. J. Neurosci.* **11**, 1515–1522 (1999).
86. Parker, D. Presynaptic and interactive peptidergic modulation of reticulospinal synaptic inputs in the lamprey. *J. Neurophysiol.* **83**, 2497–2507 (2000).
87. Ekeberg, O. *et al.* A computer based model for realistic simulations of neural networks. I. The single neuron and synaptic interaction. *Biol. Cybern.* **65**, 81–90 (1991).
88. Ekeberg, Ö., Lansner, A. & Grillner, S. The neural control of fish swimming studied through numerical simulations. *Adapt. Behav.* **3**, 363–384 (1995).
89. Hellgren, J., Grillner, S. & Lansner, A. Computer simulation of the segmental neural network generating locomotion in lamprey by using populations of network interneurons. *Biol. Cybern.* **68**, 1–13 (1992).
90. Kozlov, A. K. *et al.* Mechanisms for lateral turns in lamprey in response to descending unilateral commands: a modeling study. *Biol. Cybern.* **86**, 1–14 (2002).
91. Brodin, L. *et al.* Computer simulations of *N*-methyl-D-aspartate receptor-induced membrane properties in a neuron model. *J. Neurophysiol.* **66**, 473–484 (1991).
92. Zhang, W. & Grillner, S. The spinal 5-HT system contributes to the generation of fictive locomotion in lamprey. *Brain Res.* **879**, 188–192 (2000).
93. Svensson, E., Grillner, S., Kristensson, K. & Hill, R. H. Midline modulator neurons are rhythmically active during fictive locomotion in the lamprey spinal cord. *Soc. Neurosci. Abstr.* **28**, 65.9 (2002).
94. Wikstrom, M., Hill, R., Hellgren, J. & Grillner, S. The action of 5-HT on calcium-dependent potassium channels and on the spinal locomotor network in lamprey is mediated by 5-HT1A-like receptors. *Brain Res.* **678**, 191–199 (1995).
95. Schmidt, B. J. & Jordan, L. M. The role of serotonin in reflex modulation and locomotor rhythm production in the mammalian spinal cord. *Brain Res. Bull.* **53**, 689–710 (2000).
96. Kettunen, P., Hallén, K. & El Manira, A. Release of endogenous cannabinoids by group I mGluR activation modulates the locomotor rhythm in the lamprey. *Soc. Neurosci. Abstr.* **28**, 167.5 (2002).
97. Krieger, P., Hellgren-Kotaleski, J., Kettunen, P. & El Manira, A. J. Interaction between metabotropic and ionotropic glutamate receptors regulates neuronal network activity. *J. Neurosci.* **20**, 5382–5391 (2000). **An elegant study of the contribution of metabotropic glutamate receptors to cell and network activity.**
98. Hess, D., Kettunen, P., Krieger, P. & El Manira, A. Pharmacology and mechanisms of group I mGluR-mediated effects in lamprey spinal cord neurons. *Soc. Neurosci. Abstr.* **27**, 705.5 (2001).
99. Wallen, P. *et al.* Effects of 5-hydroxytryptamine on the afterhyperpolarization, spike frequency regulation, and oscillatory membrane properties in lamprey spinal cord neurons. *J. Neurophysiol.* **61**, 759–768 (1989).
100. Svensson, E., Dewael, Y., Hill, R. H. & Grillner, S. 5-HT inhibits N-type calcium channels in lamprey spinal neurons. *Soc. Neurosci. Abstr.* **27**, 934.14 (2001).
101. Parker, D., Zhang, W. & Grillner, S. Substance P modulates NMDA responses and causes long-term protein synthesis-dependent modulation of the lamprey locomotor network. *J. Neurosci.* **18**, 4800–4813 (1998). **A demonstration of the long-lasting (24 h) effects that brief (10 min) applications of tachykinins can exert on the locomotor network.**
102. Harris-Warrick, R. M. & Cohen, A. H. Serotonin modulates the central pattern generator for locomotion in the isolated lamprey spinal cord. *J. Exp. Biol.* **116**, 27–46 (1985).
103. McLean, D. L. & Sillar, K. T. Nitric oxide selectively tunes inhibitory synapses to modulate vertebrate locomotion. *J. Neurosci.* **22**, 4175–4184 (2002). **A study of the role of nitric oxide in the control of the tadpole locomotor network.**
104. Dale, N. & Gilday, D. Regulation of rhythmic movements by purinergic neurotransmitters in frog embryos. *Nature* **383**, 259–263 (1996).
105. Van Dongen, P. A. *et al.* Immunohistochemical and chromatographic studies of peptides with tachykinin-like immunoreactivity in the central nervous system of the lamprey. *Peptides* **7**, 297–313 (1986).
106. Dale, N. & Kuenzi, F. Ionic currents, transmitters and models of motor pattern generators. *Curr. Opin. Neurobiol.* **7**, 790–796 (1997).
107. Grillner, S., Williams, T. & Lagerback, P. A. The edge cell, a possible intraspinal mechanoreceptor. *Science* **223**, 500–503 (1984).
108. Di Prisco, G. V., Wallen, P. & Grillner, S. Synaptic effects of intraspinal stretch receptor neurons mediating movement-related feedback during locomotion. *Brain Res.* **530**, 161–166 (1990).
109. Vinay, L., Barthe, J. Y. & Grillner, S. Central modulation of stretch receptor neurons during fictive locomotion in lamprey. *J. Neurophysiol.* **76**, 1224–1235 (1996).

110. Grillner, S. On the generation of locomotion in the spinal dogfish. *Exp. Brain Res.* **20**, 459–470 (1974).
The original description of the intersegmental phase lag in fish swimming.
111. Grillner, S. & Kashin, S. in *Neural Control of Locomotion* Vol. 18 (eds Herman, R. M., Grillner, S., Stein, P. S. G. & Stuart, D. G.) 181–202 (Plenum, New York, 1976).
112. Wallen, P. & Williams, T. L. Fictive locomotion in the lamprey spinal cord *in vitro* compared with swimming in the intact and spinal animal. *J. Physiol. (Lond.)* **347**, 225–239 (1984).
113. McClellan, A. D. & Hagevik, A. Coordination of spinal locomotor activity in the lamprey: long-distance coupling of spinal oscillators. *Exp. Brain Res.* **126**, 93–108 (1999).
114. Cohen, A. H. *et al.* Modelling of intersegmental coordination in the lamprey central pattern generator for locomotion. *Trends Neurosci.* **15**, 434–438 (1992).
115. Jung, R., Kiemel, T. & Cohen, A. H. Dynamic behavior of a neural network model of locomotor control in the lamprey. *J. Neurophysiol.* **75**, 1074–1086 (1996).
116. Fagerstedt, P. & Ullen, F. Lateral turns in the lamprey. I. Patterns of motoneuron activity. *J. Neurophysiol.* **86**, 2246–2256 (2001).
117. Deliagina, T. G., Zelenin, P. V., Fagerstedt, P., Grillner, S. & Orlovsky, G. N. Activity of reticulospinal neurons during locomotion in the freely behaving lamprey. *J. Neurophysiol.* **83**, 853–863 (2000).
118. Deliagina, T. G. & Orlovsky, G. N. Comparative neurobiology of postural control. *Curr. Opin. Neurobiol.* **12**, 652–657 (2002).
A novel comparative analysis of the postural control system.
119. Deliagina, T. G., Orlovsky, G. N., Grillner, S. & Wallen, P. Vestibular control of swimming in lamprey. II. Characteristics of spatial sensitivity of reticulospinal neurons. *Exp. Brain Res.* **90**, 489–498 (1992).
120. Ullen, F., Deliagina, T. G., Orlovsky, G. N. & Grillner, S. Visual pathways for postural control and negative phototaxis in lamprey. *J. Neurophysiol.* **78**, 960–976 (1997).
121. Ekeberg, O. & Grillner, S. Simulations of neuromuscular control in lamprey swimming. *Phil. Trans. R Soc. Lond. B* **354**, 895–902 (1999).
A simulation of lamprey locomotor movements based on a biologically realistic network.
122. Kotaleski, J. H., Grillner, S. & Lansner, A. Neural mechanisms potentially contributing to the intersegmental phase lag in lamprey. I. Segmental oscillations dependent on reciprocal inhibition. *Biol. Cybern.* **81**, 317–330 (1999).
123. Kotaleski, J. H., Lansner, A. & Grillner, S. Neural mechanisms potentially contributing to the intersegmental phase lag in lamprey. II. Hemisegmental oscillations produced by mutually coupled excitatory neurons. *Biol. Cybern.* **81**, 299–315 (1999).
124. Bem, T., Cabelguen, J. M., Ekeberg, O. & Grillner, S. From swimming to walking: a single basic network for two different behaviors. *Biol. Cybern.* **88**, 79–90 (2003).
125. Dale, N. Coordinated motor activity in simulated spinal networks emerges from simple biologically plausible rules of connectivity. *J. Comput. Neurosci.* **14**, 55–70 (2003).
126. Pombal, M. A., El Manira, A. & Grillner, S. Afferents of the lamprey striatum with special reference to the dopaminergic system: a combined tracing and immunohistochemical study. *J. Comp. Neurol.* **386**, 71–91 (1997).
127. Pombal, M. A., El Manira, A. & Grillner, S. Organization of the lamprey striatum — transmitters and projections. *Brain Res.* **766**, 249–254 (1997).
128. El Manira, A., Pombal, M. A. & 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).
129. Swanson, L. W., Mogenson, G. J., Gerfen, C. R. & Robinson, P. Evidence for a projection from the lateral preoptic area and substantia innominata to the 'mesencephalic locomotor region' in the rat. *Brain Res.* **295**, 161–178 (1984).
130. Mogensen, G. J. in *Neurobiological Basis of Human Locomotion* (ed. Shimamura, M.) 33–44 (Japan Sci. Soc. Press, Tokyo, 1991).
A review of the locomotor activation from the nucleus accumbens through the mesopontine locomotor area to the spinal cord in rodents.
131. Grillner, S. *et al.* The intrinsic function of a motor system — from ion channels to networks and behavior. *Brain Res.* **886**, 224–236 (2000).
132. Nusbaum, M. P., Blitz, D. M., Swensen, A. M., Wood, D. & Marder, E. The roles of co-transmission in neural network modulation. *Trends Neurosci.* **24**, 146–154 (2001).
133. Selverston, A. What invertebrate circuits have taught us about the brain. *Brain Res. Bull.* **50**, 439–440 (1999).
134. Katz, P. S. & Harris-Warrick, R. M. The evolution of neuronal circuits underlying species-specific behavior. *Curr. Opin. Neurobiol.* **9**, 628–633 (1999).
135. Hill, A. A., Lu, J., Masino, M. A., Olsen, O. H. & Calabrese, R. L. A model of a segmental oscillator in the leech heartbeat neuronal network. *J. Comput. Neurosci.* **10**, 281–302 (2001).
136. Kristan, W. B. Jr, Eisenhart, F. J., Johnson, L. A. & French, K. A. Development of neuronal circuits and behaviors in the medicinal leech. *Brain Res. Bull.* **53**, 561–570 (2000).
137. Deliagina, T. G., Arshavsky, Y. I. & Orlovsky, G. N. Control of spatial orientation in a mollusc. *Nature* **393**,172–175 (1998).
138. Forssberg, H., Grillner, S. & Halbertsma, J. The locomotion of the low spinal cat. I. Coordination within a hindlimb. *Acta Physiol. Scand.* **108**, 269–281 (1980).
The first description of well coordinated locomotor movements and EMG pattern in a spinal animal.
139. Edgerton, V. R. *et al.* Retraining the injured spinal cord. *J. Physiol. (Lond.)* **533**, 15–22 (2001).
An elegant study that reveals the plasticity of the postural and locomotor systems in spinal animals.
140. Edgerton, V. R. & Roy, R. R. Paralysis recovery in humans and model systems. *Curr. Opin. Neurobiol.* **12**, 658–667 (2002).
141. Forssberg, H. & Grillner, S. The locomotion of the acute spinal cat injected with clonidine i.v. *Brain Res.* **50**, 184–186 (1973).
142. Rossignol, S. *et al.* The cat model of spinal injury. *Prog. Brain Res.* **137**, 151–168 (2002).
A review of the well studied cat model system for spinal injury.
143. Tillakaratne, N. J. *et al.* Use-dependent modulation of inhibitory capacity in the feline lumbar spinal cord. *J. Neurosci.* **22**, 3130–3143 (2002).
144. Orsal, D. *et al.* Locomotor recovery in chronic spinal rat: long-term pharmacological treatment or transplantation of embryonic neurons? *Prog. Brain Res.* **137**, 213–230 (2002).
A review of the effect of aminergic transplants in chronic spinal animals.
145. Barbeau, H., Fung, J., Leroux, A. & Ladouceur, M. A review of the adaptability and recovery of locomotion after spinal cord injury. *Prog. Brain Res.* **137**, 9–25 (2002).
146. Barbeau, H., Ladouceur, M., Norman, K. E., Pepin, A. & Leroux, A. Walking after spinal cord injury: evaluation, treatment, and functional recovery. *Arch. Phys. Med. Rehabil.* **80**, 225–235 (1999).
147. Behrman, A. L. & Harkema, S. J. Locomotor training after human spinal cord injury: a series of case studies. *Phys. Ther.* **80**, 688–700 (2000).
148. Dietz, V. Do human bipeds use quadrupedal coordination? *Trends Neurosci.* **25**, 462–467 (2002).
149. Dietz, V. Proprioception and locomotor disorders. *Nature Rev. Neurosci.* **3**, 781–790 (2002).
150. Dietz, V., Muller, R. & Colombo, G. Locomotor activity in spinal man: significance of afferent input from joint and load receptors. *Brain* **125**, 2626–2634 (2002).
151. Dietz, V., Wirz, M., Colombo, G. & Curt, A. Locomotor capacity and recovery of spinal cord function in paraplegic patients: a clinical and electrophysiological evaluation. *Electroencephalogr. Clin. Neurophysiol.* **109**, 140–153 (1998).
152. Duysens, J. Human gait as a step in evolution. *Brain* **125**, 2589–2590 (2002).
153. Harkema, S. J. Neural plasticity after human spinal cord injury: application of locomotor training to the rehabilitation of walking. *Neuroscientist* **7**, 455–468 (2001).
An evaluation of treadmill training for paralysed patients with spinal cord injury.
154. Wernig, A., Muller, S., Nanassy, A. & Cagol, E. Laufband therapy based on 'rules of spinal locomotion' is effective in spinal cord injured persons. *Eur. J. Neurosci.* **7**, 823–829 (1995).
An initial report of the beneficial effect of treadmill training on patients with spinal cord injury.
155. Wernig, A., Nanassy, A. & Muller, S. Maintenance of locomotor abilities following Laufband (treadmill) therapy in para- and tetraplegic persons: follow-up studies. *Spinal Cord* **36**, 744–749 (1998).
156. Grillner, S. *et al.* Neural networks that coordinate locomotion and body orientation. *Trends Neurosci.* **18**, 270–279 (1995).

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Online links

FURTHER INFORMATION
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