

# Network Modularity: Back to the Future in Motor Control

Optogenetic analysis has revealed the existence of multiple rhythm-generating neural networks that drive leg motoneuron pools in the lumbar spinal cord of rodents. These findings extend the concept of a modular neural network organization for locomotion from invertebrates and lower vertebrates to mammals.

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Locomotor movements of animals and of ourselves appear so automatic that we generally take their generation for granted. During walking, the stance and swing phase of a leg alternate with each other, with leg stance pushing the body in the direction of movement and leg swing ensuring return of the leg for the next stance. In order to make all the segments of a leg step, about three dozen muscles have to be activated in a coordinated fashion in a mammal, and more than a dozen muscles in an insect leg. For more than a century neuroscientists have striven to unravel the organization and operation of the neural networks responsible. The first groundbreaking insights into the organization were made in 1911 when Brown [1] showed that the lumbar spinal cord of the cat is able to generate rhythmic motor activity in leg muscles without sensory feedback and without contribution of the brain. Since then, the unresolved question has been how those neural networks in the mammalian spinal cord that drive and coordinate three dozen muscles per leg are organized. A new study by Hägglund *et al.* [2] provides data to resolve this issue: the authors took an optogenetic approach to probe in a series of compelling experiments the organizational layout of the mouse hindlimb locomotor network.

Hägglund *et al.* [2] used a conditional approach that allowed them to target glutamatergic interneurons in the neonatal mouse spinal cord [3]. They were able to depolarize and activate glutamatergic neurons in a spatially and temporally very precise way by using a light-activated rhodopsin channel that was introduced specifically into the glutamatergic interneurons [4]. In a series of experiments, the authors made use of this technique to sequentially activate neural networks in the spinal cord that

drive different motoneuron pools of hind leg muscles by shining blue light at 473nm wavelength on defined areas of the spinal cord (Figure 1).

First, the authors showed that light-induced activation of glutamatergic interneurons of the lumbar spinal cord evokes locomotor-like alternating activity in flexor–extensor motoneuron pools with appropriate left–right coordination

(Figure 1A). The activation of glutamatergic interneurons was shown to be both necessary and sufficient to induce fictive locomotor-like activity in flexor and extensor motoneuron pools of the mouse hindlimb locomotor networks (Figure 1A).

Hägglund *et al.* [2] then restricted the area of light-induced activation of glutamatergic interneurons to different sides and different areas of the lumbar spinal cord. They show unilateral activation of locomotor networks in the spinal cord by restricting the light stimulation to one side (Figure 1B). Flexor and extensor networks could be activated individually by restricting the area of light stimulation to the rostral or caudal lumbar cord, respectively. They found this not only for flexor and extensor networks in general, but also for the activation of

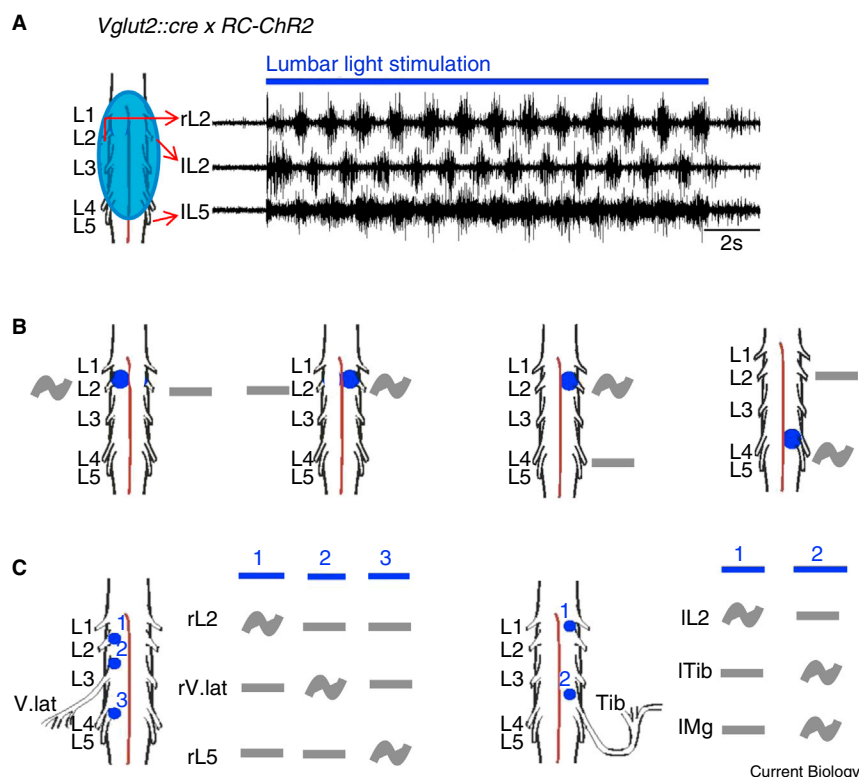


Figure 1. The mouse hindlimb locomotor network shows a modular organization with multiple rhythmogenic flexor and extensor modules.

(A) Stimulating the ventral surface of the lumbar spinal cord of *Vglut2::Cre; RC-ChR2* mice with blue light evokes locomotor-like activity with direct onset and well-tuned flexor–extensor and left–right coordination. (B) Stimulating a unilateral spot in *Vglut2::Cre; RC-ChR2* mice elicits unilateral locomotor-like activity on left and right sides consecutively. Activating glutamatergic neurons in a restricted area at the rostral or caudal lumbar spinal cord can evoke locomotor-like activity exclusively in the flexor network or extensor network, respectively. Grey sinewaves denote rhythmic activity elicited, grey lines denote inactivity. (C) Small spot stimulation shows that flexor-related vastus lateralis and tibialis anterior motoneuron pools can be independently activated.

closely related motoneuron pools that fire in the same phase and reside next to each other in the spinal cord. Finally, by locally restricted light stimulation flexor-related vastus lateralis and tibialis anterior motoneuron pool activity could be activated independently (Figure 1C), indicating the existence of individual neural networks driving each of the muscles.

Kiehn and coworkers [2] showed conclusively that the rhythm-generating networks for the mammalian locomotor system are organized in a modular fashion. The authors provided convincing support for the so-called ‘unit-burst-generator’ (UBG) hypothesis (Figure 2). According to the UBG concept, which has been around for more than 30 years, on each side of the spinal cord individual neural networks exist that can generate rhythmic motor activity for the motoneuron pools independently [5–7]. Coordination of the different UBGs to generate a functional movement sequence was hypothesized to be controlled in a task-dependent manner (Figure 2A). At the time Grillner formulated this hypothesis, it was based on the conclusion that in the cat spinal cord only a flexible network organization could account for the observed variability in motor outputs and movements generated. Now, more than 30 years later, Hägglund *et al.* [2] have finally provided evidence that indeed modules of rhythm-generating networks can be activated in individual hemisegments of the mouse lumbar spinal cord. These networks selectively drive motoneuron pools supplying individual leg muscles.

Importantly, Hägglund *et al.* [2] did not find support in their experiments for the currently favored hypothesis, the so-called ‘half-center model’ for mammalian walking (Figure 2B). The half-center model hypothesizes that on each side of the spinal cord neural networks reside for generating alternating activity between all stance and swing motoneuron pools (for example, [8,9]). Capability for generating rhythmic locomotor activity was thought to depend on mutual inhibition between network components driving the antagonistic sets of motoneurons — flexor and extensor motoneurons. The new work of Hägglund *et al.* [2] represents a significant step forward in clarifying the basic layout for motor pattern

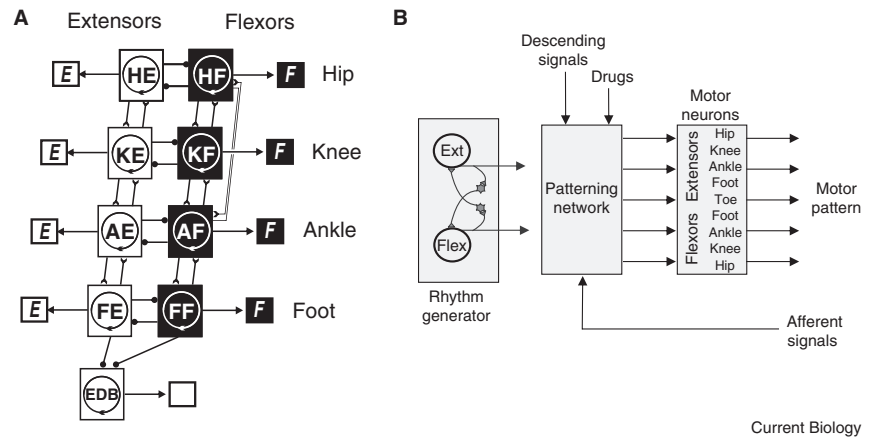


Figure 2. Schematic representation of the two contemporary models on network organization and interaction for walking pattern generation.

(A) Schematic representation of the ‘unit-burst-generator’ (UBG) concept formulated by Grillner [5,6]. Each synergist muscle group is assumed to be driven by its own rhythm-generating network (box with circle). The individual units controlling functional antagonistic motoneurons of one joint are connected with each other by mutual inhibition as well as with the other UBGs in various ways. Arrows denote influences; circles denote synaptic inhibitory interaction; open triangles denote synaptic excitatory interactions (adapted with permission from [6]). (B) Schematic description of a locomotor pattern generator. The basic rhythmic pattern is produced by mutually inhibiting flexor and extensor half-centers. The interneurons of these half-centers drive the motor neurons through an intermediate system of interneurons (patterning network) that control the timing of activation of different classes of motor neurons. Descending signals, drugs, or afferent signals can modify the temporal motor activity pattern by altering the functioning of interneurons in the patterning network. Please note that while in the UBG-concept multiple rhythm-generating networks exist that generate the motor pattern in coordination with each other (A), there is only one such rhythm-generating network assumed to drive pattern generation in the half-center concept (B). (Adapted with permission from [16].)

generation in the mammalian spinal cord.

How do the new findings on the mammalian spinal cord compare to pattern generation for walking in other vertebrates? A particularly fascinating aspect is that the new results [2] closely resemble the findings of Cheng *et al.* [10] on the organization of spinal locomotor networks in a lower vertebrate anuran species. Cheng *et al.* [10] showed in their study, by means of specific lesions, that individual UBG networks in the neighboring segments of the mudpuppy cranial spinal cord control the activity of elbow flexor and extensor muscles. This was the first time that the UBG-hypothesis was explicitly supported by experimental findings in a walking vertebrate. Indications of a modular structure of limb controlling spinal rhythm-generating networks were also reported for the chick embryo [11], and for the turtle spinal cord [12], although evidence for their hemisegmental organization was lacking. Finally, in invertebrates a modular organization of neural networks controlling segmented

appendages for walking with one rhythm-generating module in each hemiganglion per leg segment was reported (for example, [13]).

Taken together with previous insights into the network organization for walking in non-mammalian vertebrates and invertebrates, the findings of Hägglund *et al.* [2] push for the notion that modularity of neural networks appears to be a significant conserved control feature of the leg muscle control systems across animal kingdom (see also [14]). The next important steps will be to unravel those mechanisms that underlie task-specific coordination between the individual modules (for example, [15]). This could eventually lead to an understanding of what it takes to step, scratch, point, climb and grip with the same limb, being it a leg or an arm, of an animal or a human.

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