Central pattern generators and the control of rhythmic movements

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Central pattern generators are neuronal circuits that when activated can produce rhythmic motor patterns such as walking, breathing, flying, and swimming in the absence of sensory or descending inputs that carry specific timing information. General principles of the organization of these circuits and their control by higher brain centers have come from the study of smaller circuits found in invertebrates. Recent work on vertebrates highlights the importance of neuromodulatory control pathways in enabling spinal cord and brain stem circuits to generate meaningful motor patterns. Because rhythmic motor patterns are easily quantified and studied, central pattern generators will provide important testing grounds for understanding the effects of numerous genetic mutations on behavior. Moreover, further understanding of the modulation of spinal cord circuitry used in rhythmic behaviors should facilitate the development of new treatments to enhance recovery after spinal cord damage.

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Introduction

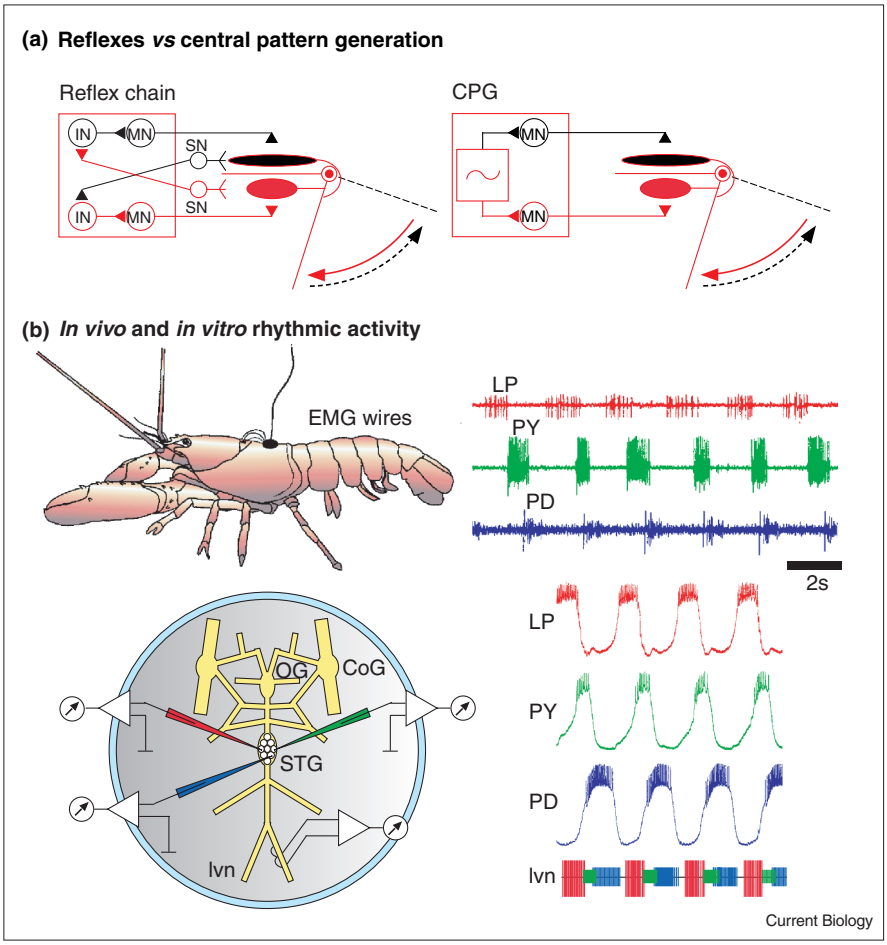
Biologists often take for granted the rapidity at which new information is acquired. It is humbling, therefore, to reread the papers of the first systems neuroscientists, and to discover among them the first articulation of many of the basic concepts that we still struggle to elucidate today. Almost ninety years ago, Brown [1] suggested that the alternate flexion and extension of leg muscles in walking could be produced by rhythmic central circuits in which the antagonistic muscles were driven by neurons that inhibited each other. Nonetheless, the spinal reflex has dominated a century of textbooks, and many biologists labor under the misconception that rhythmic movements are produced by reflex activation, rather than by central circuits. This review is not intended to supplant or replace the many outstanding and detailed reviews of the organization of the neural control of rhythmic movements in both invertebrates and vertebrates [2–6]. Rather, here our purpose is to provide a roadmap to the general principles underlying pattern generation. We hope that this review will be helpful to those looking for neural circuits with easily quantifiable outputs with which to evaluate the role of genes in neuronal function.

Fictive motor patterns show that rhythmic movements can be generated in the absence of sensory input

How does one show the existence of central circuits capable of the production of rhythmic movements? For many years early neuroscientists debated whether rhythmic movements were produced by chains of reflexes or central oscillators (Figure 1a). The first direct experiments designed to address this question were attempts to cut all sensory feedback to the central nervous system. This is obviously a difficult task, and some of the earliest successful experiments of this kind were carried out by Wilson and colleagues [7–9], who showed that a deafferented locust could generate rhythmic flight motor patterns in response to non-rhythmic stimulation of the nerve cord.

By far the most compelling argument that a piece of the nervous system is intrinsically able to generate a rhythmic motor pattern is to remove it from the animal and place it in a dish filled with physiological saline (Figure 1b). Under these conditions there are no sensory pathways remaining, and no timing information available from the environment. Today, many preparations have been shown to generate what are called **fictive motor patterns**, motor patterns that would drive muscle movement if the muscles were present. The absence of rhythmic activity in an isolated part of the

Figure 1



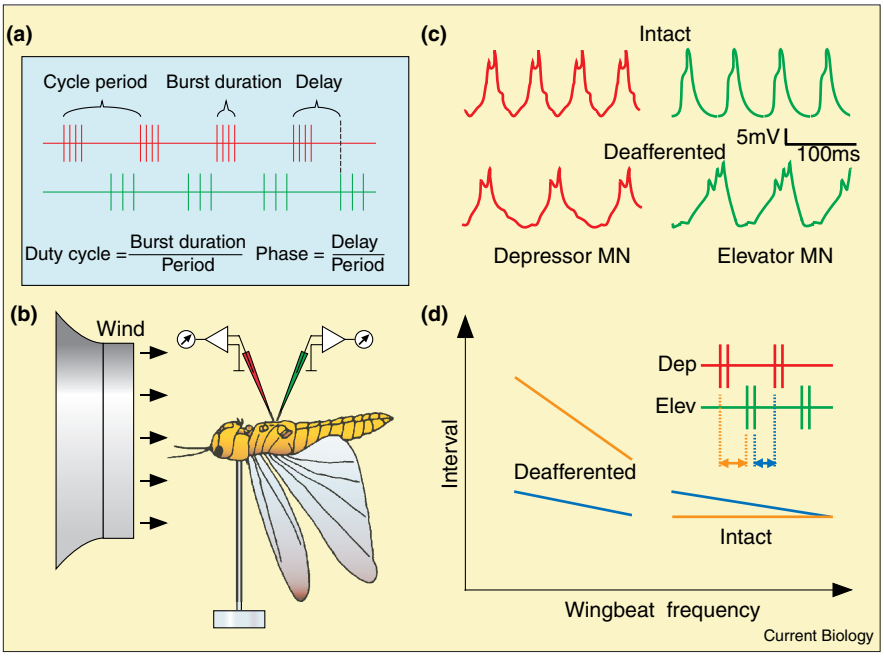
Central pattern generators. **(a)** Early work suggested two hypotheses for the generation of rhythmic and alternating movements. In the reflex chain model (left) sensory neurons innervating a muscle fire and excite interneurons that activate motor neurons to the antagonist muscle. Right, in a central pattern generator (CPG) model a central circuit generates rhythmic patterns of activity in the motor neurons to antagonist muscles. **(b)** Fictive motor patterns resemble those recorded *in vivo*. Top left, picture of a lobster with electromyographic recording (EMG) wires implanted to measure stomach motor patterns in the behaving animal. Top right, EMG recordings showing that triphasic motor pattern generated by the LP, PY, and PD neurons. Modified from [34]. Bottom left, *in vitro* preparation, showing the dissected stomatogastric nervous system in a saline-filled dish with extracellular recording electrodes on the motor nerves and intracellular recordings from the somata of the stomatogastric ganglion motor neurons. Bottom right, unpublished recordings by V. Thirumalai made *in vitro* from the stomatogastric ganglion of the lobster, *Homarus americanus*. The top three traces are simultaneous intracellular recordings from the somata of the LP, PY, and PD neurons, and the bottom trace is an extracellular recording from the motor nerve that carries the axons of these neurons. Note the similarity of the *in vivo* recordings and the fictive motor patterns produced *in vitro* in the absence of sensory inputs. STG, stomatogastric ganglion; OG, esophageal ganglion; CoG, commissural ganglion; lvn, lateral ventricular nerve.

nervous system does not imply the absence of a central pattern generator. Central pattern generators are capable of producing rhythmic activity without receiving extrinsic phasic timing information, but as discussed below, neuromodulators, supplied by descending pathways, are often required to activate central pattern generating circuits. In fact, many fictive preparations used to study the organization and mechanisms underlying motor pattern generation require activation by bath application of one or more of the neuromodulators found in descending pathways [10–13].

Caution is required in studying fictive motor patterns, especially those activated by addition of exogenous neuromodulators. In many cases, preparations placed *in vitro* clearly generate rhythms. But it is not always straightforward to demonstrate that an *in vitro* rhythm is actually the one responsible for a given behavior. For example, great success has been made in obtaining robust rhythms from slices of the vertebrate respiratory centers [14,15]. However, animals breathe, cough, gasp, sigh and even vomit using many of the same muscles, albeit in somewhat different sequences. This has caused some controversy and confusion in the respiratory rhythm field, as determining which behavior is best attributed to the rhythms seen in slices under different conditions is not always straightforward. This task is made even more complex if the same neurons are involved in several different pattern generating circuits [16].

How closely do fictive motor patterns resemble those generated in the intact animal during movement? The answer to this question is partly in the eye of the beholder. Often there is surprisingly good correspondence between *in vivo* and *in vitro* motor patterns. For example, in the crustacean stomatogastric nervous system electromyographic recordings of the muscles of the pylorus in freely behaving animals show triphasic motor patterns similar to the fictive motor patterns seen in the isolated nervous system

Figure 2



Sensory input can alter the properties of a centrally generated motor pattern. **(a)** Measures used to quantify rhythmic motor patterns include the cycle period, burst duration, duty cycle, and phase of firing of an individual element, as illustrated and defined here. **(b)** Preparation used to study insect flight. A locust is attached to a stick and placed in a wind tunnel while intracellular recordings are made from the thoracic ganglia. **(c)** Recordings from the depressor motor neuron (red) and elevator motor neuron (green) in the intact (top) and deafferented (bottom) showing the frequency drops after deafferentation. **(d)** Plots of the interval between onset of depressor and elevator bursts as a function of wingbeat frequency for both the intact and deafferented preparations. (b–d) modified from [17,139].

(Figure 1b). However, detailed quantitative comparisons of the period of the rhythm, duty cycle, or phase relationships among the elements in a pattern (Figure 2a) often reveal differences between *in vivo* and fictive motor patterns. For example, there are significant differences between the motor patterns produced by intact and deafferented flying locusts [17] (Figure 2b–d).

Presumably some behaviors require cycle-by-cycle corrections of the movement during behavior while other behaviors depend less on sensory input. Therefore, the proper evaluation of the importance of sensory input during centrally generated behavior necessitates comparing cycle frequency, the phase relationships of the elements of the rhythm (Figure 2a), the regularity of the rhythm [18], and, if the motor patterns are produced episodically [19], the length of the episodes and the intervals between them.

Intrinsic properties of central pattern generating neurons

Studies of central pattern generating networks in both invertebrates and vertebrates have shown that the intrinsic membrane properties of the neurons (Figure 3a) that form central pattern generators are crucial for understanding the mechanisms of motor pattern generation [3]. Some neurons fire bursts of action potentials, either endogenously or in the presence of neuromodulatory substances [20,21]. When neurons are strongly oscillatory they can provide important timing inputs for circuits. However, when neurons are strongly oscillatory it can be quite difficult to entrain or reset their activity except within a small frequency range, and strong, intrinsically oscillatory neurons are relatively rarely found in circuits. Some neurons are bistable, and generate plateau potentials [22–26] that can be triggered by a depolarizing pulse, and terminated by a hyperpolarizing pulse. Plateau neurons can act as intrinsic 'memories' of their last synaptic input, and also can produce a discharge pattern that long outlasts their excitatory drive [24–26].

Many of the synaptic interactions in central pattern generating circuits are inhibitory. Indeed, many pattern generating neurons fire on rebound from inhibition, and it is this postinhibitory rebound that is crucial for the timing of their firing [3,27–29]. Another common feature of many neurons is spike-frequency adaptation, a decrease in the frequency of firing during a constant depolarization. Other neurons show different kinds of dynamics, all of which will play a role in governing how neurons in circuits will respond to a particular pattern of synaptic inputs.

Mechanisms underlying motor pattern production

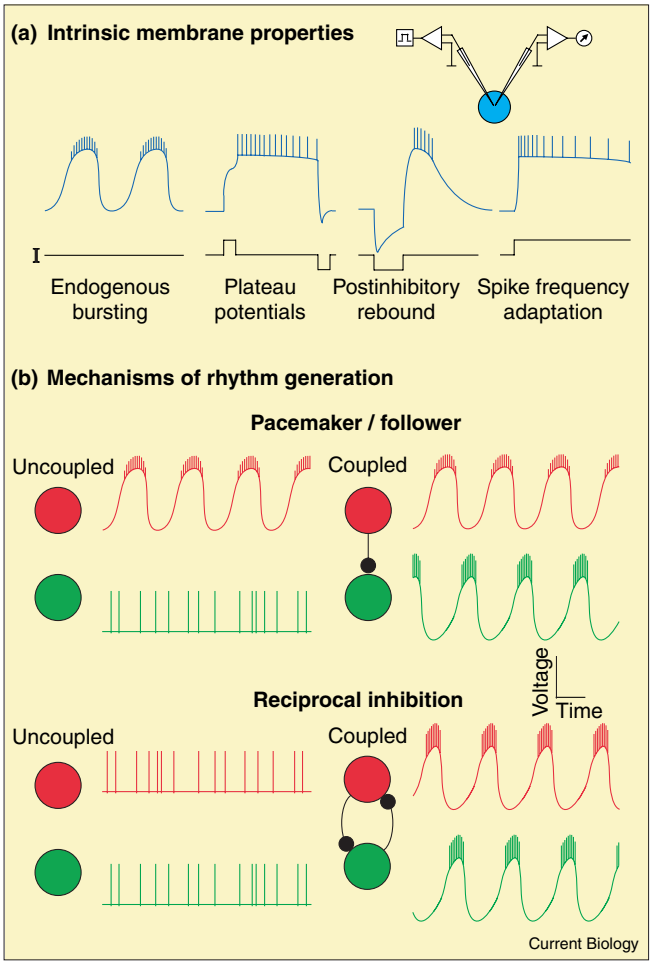
The dynamics of all networks depend on the ongoing interplay between the intrinsic properties of the neurons that make up networks and the strength, time course, and time-dependent properties of the synapses among them [4,30]. As in other networks, frequency and phasing of central pattern generating networks depend on intrinsic and synaptic properties.

Why are central pattern generators rhythmic, and what controls the phasing of each of the elements of the rhythm? There are two general mechanisms for rhythm production: some networks are driven by pacemaker neurons and some rhythms emerge as a consequence of synaptic connections among neurons that are not themselves intrinsically rhythmic (Figure 3b). In a pacemaker driven network, a neuron or several neurons act as a core oscillator, driving neurons that are not themselves bursting, into a rhythmic motor pattern. The pyloric rhythm of the crustacean stomatogastric ganglion [21,31–33] and the vertebrate respiratory rhythms [14] are pacemaker driven. Both of these rhythms are continuously active in the animal [15,34,35], suggesting that pacemakers may be commonly found in rhythmic networks that act continuously.

Figure 3b also illustrates the simplest emergent rhythm, often termed a 'half-center oscillator.' In this network two neurons reciprocally inhibit each other. Although when isolated these neurons do not fire in bursts, when coupled they produce alternating patterns of activity. These networks were first suggested by Brown [1] to explain alternation of extension and flexion phases in cat locomotion, and have subsequently been studied extensively both theoretically [36–42] and experimentally [43–51]. Crucial to understanding the dynamics of alternation in half-centers is understanding why each neuron makes its transitions between activated and inhibited states. These transitions can occur via a number of mechanisms: for example if the neurons show spike-frequency adaptation (Figure 3a), the active neuron may slow down or stop firing, thus releasing the other neuron from inhibition [36,38]. Alternatively, the inhibited neuron may escape from the inhibition due to its intrinsic membrane properties, cross its spike threshold, and in turn inhibit the first neuron [36,38]. Reciprocal inhibition is a core feature in almost all known central pattern generating networks, and has been intensively studied as a pattern generating mechanism in leech heartbeat [45–49], swimming in the mollusc *Clione* [50,51] and in the spinal cord of amphibian tadpoles [52–54] and the lamprey [55,56].

The connectivity diagrams for a number of central pattern generating networks are becoming known. Although all of them contain circuit 'building blocks' like reciprocal inhibition, the details of each are different [3,5]. Understanding the specific dynamics of each network requires determining the pattern of connectivity, and the intrinsic properties of the constituent neurons. This approach has been most successfully carried out in small invertebrate networks, where the identification of the neurons is relatively straightforward, and has been more difficult in vertebrate preparations where identification of neurons and paired intracellular recordings necessary for the determination of connectivity are more technically difficult.

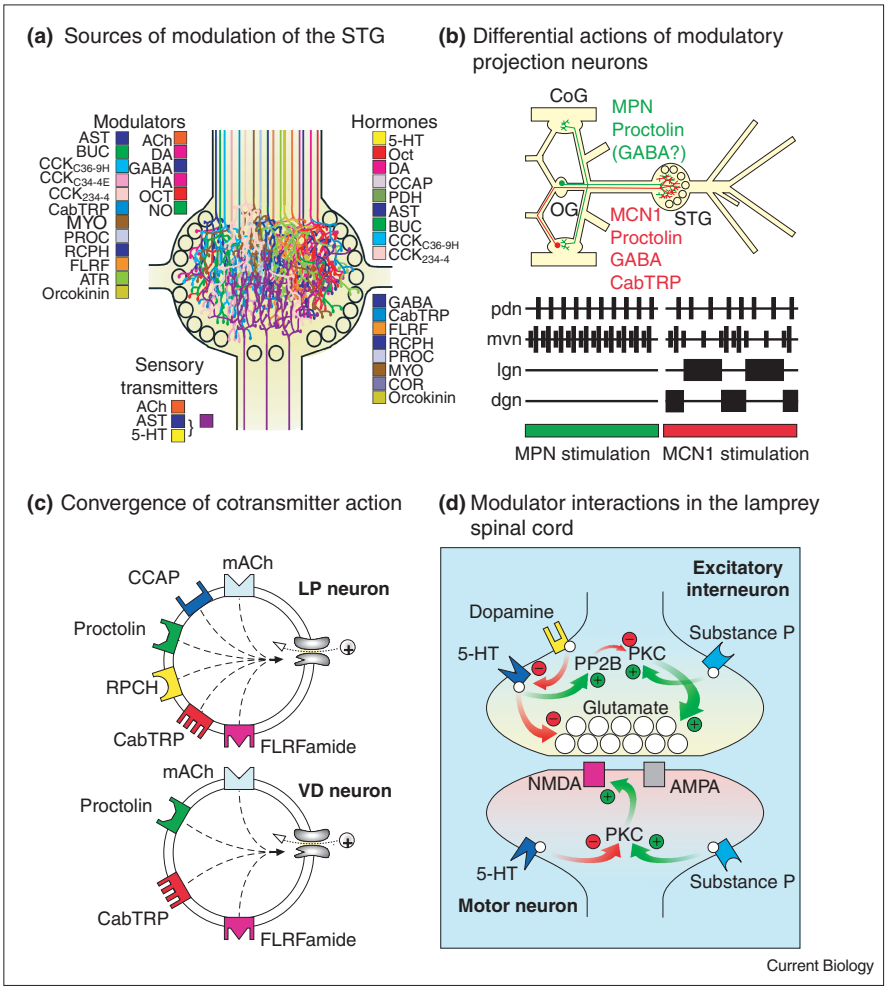
Figure 3



Cellular mechanisms underlying pattern generation. **(a)** Neurons have different intrinsic properties. Some neurons fire bursts of action potentials endogenously (panel 1). In some neurons depolarizing current pulses trigger plateau potentials that outlast the duration of the depolarization but that can be terminated by hyperpolarizing current pulses (panel 2). Some neurons respond to inhibition with rebound firing (panel 3), and others show spike frequency adaptation (panel 4). **(b)** Rhythms can be generated by endogenous bursters, or can be an emergent property of synaptic coupling between non-bursting neurons. In pacemaker driven networks a pacemaker neuron or neuron (red) can synaptically drive an antagonist (green) to fire in alternation. The simplest example of a network oscillator is one formed between two neurons that fire non-rhythmically in isolation, but fire in alternating bursts as a consequence of reciprocal inhibition.

In most systems, the actual central pattern generator consists of a circuit of pre-motor interneurons that drives motor neurons. However, in some preparations motor neurons themselves are part of the central pattern generator [57–59] or make direct connections to the central pattern generator [60]. Even when motor neurons are thought not to participate in the generation of the rhythm, the intrinsic membrane properties of the motor neurons can play a

Figure 4



Modulation of motor pattern generators. **(a)** The stomatogastric ganglion receives modulatory input from a large number of neuropeptides, amines, and amino acids. These are found in input projection neurons, in sensory neurons, and as hormones. Abbreviations: ACh (acetylcholine) AST (allatostatin), BUC (buccalin), CCK (cholycystokinin), CabTRP (*Cancer borealis* tachykinin-related peptide), MYO (myomodulin), PROC (proctolin), RPCH (red pigment concentrating hormone), FLRF (extended FLRFamide peptides-TNRNFLRFamide and SDRNFLRFamide), ATR (allatotropin), CCAP (crustacean cardioactive peptide), COR (corazonin), DA (dopamine), GABA (γ-aminobutyric acid), HA(histamine), OCT (octopamine), NO (Nitric oxide), 5-HT (serotonin). This Figure summarizes work from many published figures, with original citations found in [65,140,141]. **(b)** Stimulation of different proctolin-containing neurons evokes different motor patterns. MPN (green) (modulatory proctolin-containing neuron) contains proctolin and GABA evokes a strong pyloric rhythm but not a gastric mill rhythm. MPN may release GABA but not proctolin in the commissural ganglia (CoG) [77]. MCN1 (modulatory commissural neuron 1) contains proctolin, GABA, and CabTRP and elicits a gastric mill rhythm [67,80]. Modified from [67]. **(c)** The LP and VD neurons both show receptors to multiple modulators. In each neuron, multiple modulators converge to activate a single modulatory current [81,82]. Abbreviations as in (a). Modified from [81]. **(d)** The nerve terminals of lamprey spinal cord excitatory interneurons are multiply-modulated by several substances that via different second messenger pathways increase or decrease the release of glutamate. The same substances act both pre- and postsynaptically. Substance P acts through protein kinase C (PKC) to potentiate both transmitter release in the presynaptic interneuron and NMDA receptors in the postsynaptic motor neuron. 5-HT inhibits glutamatergic transmission both directly and by inhibition of PKC-mediated facilitatory effects of Substance P. The presynaptic effect is mediated by protein phosphatase 2B (PP2B). Presynaptic 5-HT effects can in turn be inhibited by dopaminergic modulation. See [73] for details.

significant role in shaping the resulting motor pattern [25,61–63].

Neuromodulators activate, modify and terminate central pattern generators

Some central pattern generating circuits operate continuously. Others are activated to perform specific behavioral tasks, such as those governing walking, flying and swimming. As we learn more about the neural and hormonal control of central pattern generators, we see that they receive multiple and parallel inputs so that they can be activated in a number of different fashions. A great deal is known about the modulatory control of the crustacean stomatogastric nervous system. The stomatogastric ganglion receives neuromodulation from three sources (Figure 4a): descending fibers from higher centers; fibers ascending from peripheral sensory neurons; and hormones liberated from neurosecretory structures [4,64,65]. Several important principles can be drawn from this single circuit: the same substances are frequently found in neural pathways and as circulating hormones; multiple substances are part of the control pathways for a single target network; and understanding the pattern of colocalization and release of multiple modulatory substances in identified neurons [66] will be crucial to understanding how central pattern generating networks, and other neural circuits, are modulated [67].

It has been known for quite a while that modulators alter both synaptic strength and intrinsic membrane properties, and by so doing, can modulate the motor patterns produced

by a given circuit in terms of frequency and phasing of the units [4,68,69]. Indeed, applications of exogenous neuromodulators have been remarkably useful in untangling the fundamental mechanisms of pattern generation in a large number of preparations [10,61,70–75]. The most detailed studies of cotransmission in identified projection neurons to a central pattern generator are those of a set of proctolin containing neurons in the crab stomatogastric nervous system [67] (Figure 4b). The modulatory proctolin neurons (MPN) contain proctolin and GABA, and strongly activate the pyloric rhythm of the stomatogastric ganglion through the action of proctolin [67,76], but appear to release GABA but not proctolin in the other neural network target of these neurons, the commissural ganglia [77]. The modulatory commissural neuron 1 (MCN1) contains proctolin, GABA, and another neuropeptide, *Cancer borealis* tachykinin-related peptide (CabTRP), and elicits a gastric mill rhythm [67,78–80]. An additional proctolin-containing projection neuron, modulatory projection neuron 7 (MCN7) contains proctolin, but not GABA or CabTRP, and also elicits different motor patterns from the stomatogastric ganglion [80].

Why do different proctolin-containing neurons evoke different motor patterns from the same neuronal circuit? One possibility is that they contain different cotransmitters that have different actions. A second possibility is that the proctolin may diffuse some distance from its site of release, but it may still have a fairly restricted spatial action. Interestingly, proctolin and CabTRP are two of a number of neuropeptides that converge onto the same membrane current in stomatogastric ganglion target neurons (Figure 4c) [81,82]. However, each stomatogastric ganglion neuron has a different mix of receptors to these substances (Figure 4c) [81,82]. Therefore some of the differential actions of the proctolin-containing neurons can be attributed to their different cotransmitters. Some of the differences must also come from differential spatial release profiles, as pharmacological blockade of CabTRP receptors does not completely convert the actions ofMCN1 to those of MPN [83].

Much less detail is known about the modulatory control of central pattern generating circuits in vertebrates, although it is clear that they are also influenced by a number of different neurotransmitters and neuromodulators [11,73,84,85]. Many of these factors may be colocalized [73,86], and may interact on central pattern generating circuitry or on the synapses between pattern generating interneurons and the motor neurons whose activity they control [73]. Indeed, it is important to remember that modulation can occur at the level of the central pattern generating circuit itself, on the motor neurons directly, or on the terminals that bring the rhythmic drive to the motor neurons.

Such interactions take place both in higher order supraspinal networks and in the spinal cord [87], where sources of modulation are both brainstem neurons that descend into the spinal cord, as well as propriospinal interneurons and afferents. Svensson *et al.* [73] show interactions between substance P, dopamine and 5-HT on fictive swimming in the lamprey spinal cord (Figure 4d). These modulators are colocalized in some propriospinal interneurons. The authors use the interneuron to motor neuron synapse to explore presynaptic and postsynaptic interactions that they argue may reflect cellular mechanisms of modulation of glutamatergic transmission in the central pattern generating networks. 5-HT inhibits transmitter release on the presynaptic side both directly and by shutting off substance P-evoked facilitation of the glutamatergic synapse. This 5-HT action in turn can be inhibited by dopamine. This type of 'metamodulation' or modulation of modulatory processes, may be commonly found in the future as more investigators start to look at the actions of multiple neurotransmitters on the same neurons and synapses.

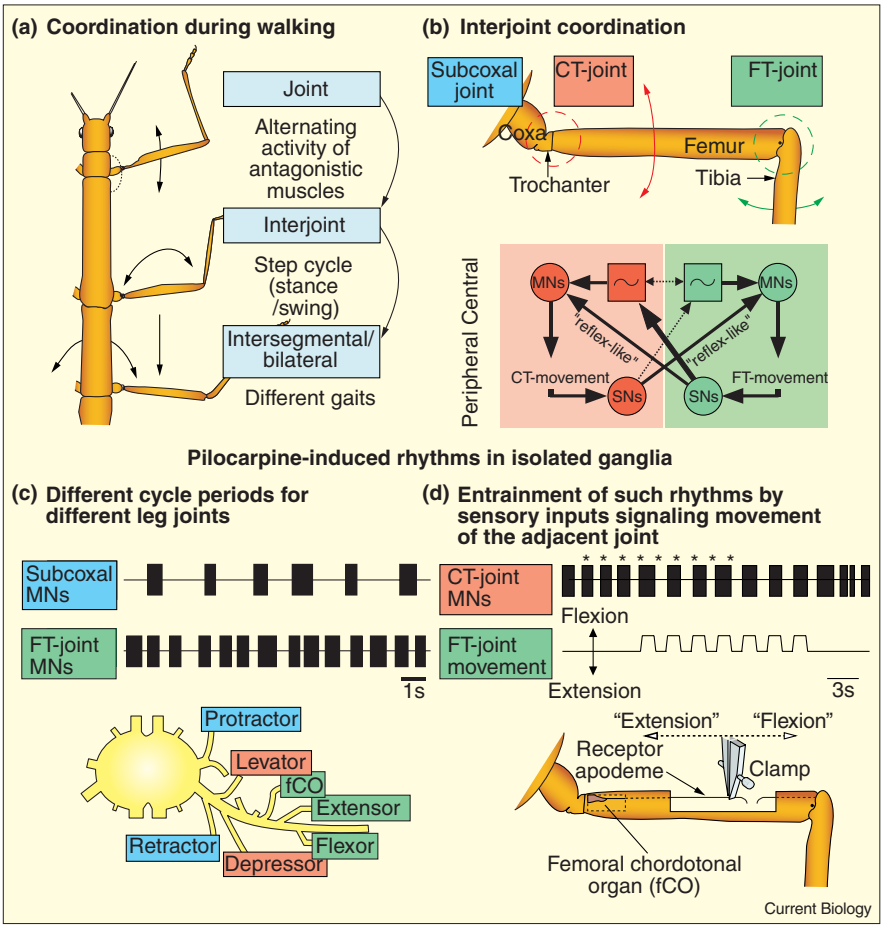
Coupling and coordination

How many central pattern generators are there in a given nervous system? All animals display a variety of different behaviors and most muscle groups are involved in many different movements. A given circuit of interconnected neurons can produce a whole range of different outputs with respect to frequency and phase relationships under the influence of different modulators. But that does not necessarily mean that different behavioral modes, such as different gaits in walking, are produced by a single circuit of central neurons in different modulatory states. Nor does it necessarily mean that there are discrete sets of neurons for every different mode of activity.

To what extent are complex organized movements produced by modulation of one neuronal ensemble, and to what extent are different central pattern generating networks coordinated or coupled? There is good evidence in the stomatogastric nervous system that individual neurons or groups of neurons may switch from one central pattern generating circuit to another [88–92]. Moreover, there is a considerable amount of circumstantial evidence from a variety of vertebrate preparations that argues that similar circuit reconfigurations involving many of the same neuronal elements may allow a large circuit to produce a number of related behaviors, such as breathing and gasping [16,93–102].

The simplest case of coordination occurs in animals that swim using multiple body segments. Animals such as leeches, lampreys and tadpoles swim by organizing left-right alternation in each segment, and by producing a wave of body contraction that propels the animal through the water [44,55,56,103]. In each of these animals a single or small subset of ganglia or spinal cord segments can produce fictive motor patterns that could organize the local

Figure 5



Stick insect walking: coordination and sensory input. **(a)** The control of movement occurs at numerous levels: the control of antagonistic muscles of a single joint, the coordinate regulation of multiple joints in a single step, and control of many legs to produce different gaits. **(b)** Interjoint coordination. The activity of motor neurons controlling two adjacent leg joints in the middle leg is coordinated by multiple interactions between sensory feedback, central rhythm generating networks, and reflex-like pathways. Modified from [113] and an unpublished figure from A. Büschges. **(c)** Pharmacologically induced rhythmicity in the isolated mesothoracic ganglion reveals a widely independent pattern generation for individual leg joints. Different motor neuron pools can readily be recorded from separate peripheral nerves. Modified from [115,117]. **(d)** Pilocarpine-induced rhythmic activity of motor neurons of one leg joint can be entrained by sensory feedback from adjacent joints. The receptor apodeme of the femoral chordotonal organ is moved to mimic flexion and extension of the femur-tibia joint. The ganglion is denervated except for the nerve carrying fCO afferents. Modified from [118].

swimming movements [104,105], and the output of these segmental oscillators must be coordinated by ascending and descending fibers [103,106,107]. In the absence of data to the contrary, it has often been assumed that coordinated behavior occurs as a result of coupling of similar oscillators, but recent work from the leech suggests that the segmental oscillators along the cord are in fact different [103,105]. Theoretical work has established that the relative strengths of the descending and ascending coupling pathways are crucial to segmental coordination [106,108–110]. Therefore, the details of the coordinating fiber system in each preparation must be laboriously established with combinations of anatomical and electrophysiological methods.

There are instances in which different joints and limbs or body segments may need to act independently, such as in walking and crawling during terrestrial locomotion [111]. As behaviors get more complex and involve multiple parts of the body, it has been suggested that coupling of central pattern generating circuits, or modules, may allow the production of many different motor outputs. In this organization, different segments, appendages or groups of antagonistic muscles along the body axis may each be driven by separate pattern generators, termed 'unit burst generators' by Grillner [6], which can be coupled in variable fashions. Consistent with this view are data from the mudpuppy in which separate oscillators control antagonists of the same joint [112].

A thorough investigation of the coordination of control units has been carried out in the stick insect walking system [113]. In the stick insect, the segmental ganglia contain separate pattern generators for each leg joint in every hemisegment [114,115]. Motor output for walking thus requires coordination of activity between adjacent leg joints within one leg, between different legs on both sides of the body, and between different segments (Figure 5a). Coordination between different joints is achieved by an interplay of relatively weak central coupling and sensory feedback [115–118], the latter acting both *via* reflex-like pathways and directly onto central pattern generating elements (Figure 5b).

Both bilateral and intersegmental coordination can be seen in isolated preparations exhibiting pilocarpine-induced rhythmic activity in the stick insect [115] and the locust [119]. However, the coordination patterns only occasionally resemble closely those exhibited during step phase transitions in the intact animal. Figure 5c shows pilocarpine induced rhythmic activity in the isolated ganglion from a stick insect in which motor neurons supplying different leg joints in the intact animal burst independently at different cycle frequencies. The effects of afferent input on rhythmic activity generated by the isolated nervous system are seen in Figure 5d. Sensory input that would signal movement of one joint entrains the rhythmic drive to motor neurons of an adjacent leg joint [118]. This effect is not equally strong in both directions [116], and reflex-like pathways — both monosynaptic and polysynaptic — also play an important role in shaping motorneuron response in the adjacent joint, during both posture control and locomotion [116,117].

Genetics and central pattern generators

A number of investigators are starting to use genetic tools to attempt to understand the molecular and cellular mechanisms underlying the organization of vertebrate central pattern generators [120–122]. Locomotor rhythms pharmacologically activated with muscarinic agonists are easily recorded from *Drosophila* larvae [123]. Thus, in both mouse and flies, it is possible to study the effects of genetic manipulations on the activity of central pattern generating networks. Fictive motor patterns have many advantages for assessing the effects of genetic manipulations on the nervous system. Central pattern generators show robust rhythmic activity early during development, and function throughout the animal's life [87,124–126], allowing the investigation of a complex network phenotype at numerous developmental stages. The sterotyped outputs of central pattern generators are particularly easy to quantify (see Figure 3). And because they involve numerous cell types, ion channels and receptors, and numerous neurotransmitter and modulator systems, a variety of genes should influence their activity. Thus, these networks can be thought of as moderately complex for assessing the consequence of genetic manipulations: richer than a single neuron or single synapse, but far easier to interpret than complex cognitive behaviors such as learning.

Spinal cord recovery in animals and humans

Spinal cord injury in humans remains one of the most devastating neurological disorders. Much of the effort to produce functional recovery following spinal cord injury is spent trying to enhance regeneration and growth across the injured areas [127]. Some investigators are starting to exploit the uninjured circuitry below the lesions to produce some recovery of function. In principle, if there is undamaged central pattern generating circuitry below a lesion, it might be possible to produce patterned output from those regions if they are appropriately activated, either with neuromodulators, direct electrical stimulation or with sensory input [2,128–130]. A large body of work showing that isolated spinal cord preparations can generate rhythmic motor patterns when pharmacologically activated suggests that exogenous application of noradrenergic or dopaminergic agents might facilitate the production of rhythmic movements after spinal cord lesions [129,130]. A number of recent studies suggest that combining pharmacological activation of central pattern generating circuitry with treadmill training maximizes the outcomes of locomotor training [130].

One of the most exciting recent findings is that treadmill training, often coupled with weight support, profoundly enhances functional recovery following partial or complete spinal cord lesions [128,129,131–133]. Training over many weeks partially reverses changes in neurotransmitter and receptor concentrations that occur after spinal cord lesion [128]. Pearson [134] suggests that much of the functional recovery seen in treadmill-trained animals could be a consequence of alterations in the reflex pathways to the pattern generating interneurons in the spinal cord. This argues that phasically timed activation of sensory inputs to the spinal cord may help reconfigure the spinal networks to allow them to produce appropriately timed rhythmic movements. An extremely promising set of experiments showed that transplantation of embryonic raphe neurons into the lumbar spinal cord together with treadmill training enhanced locomotor recovery [129,130,135]. Presumably these neurons release serotonin, and provide an ongoing biological supply of neuromodulator to the spinal cord.

That the spinal cord shows functional recovery does not necessarily mean that the cells and circuits in the cord after treadmill training are identical to those before the lesion. Instead, one might imagine that a new network is formed, perhaps that can produce a behavior similar to the initial one, but by different mechanisms. This latter interpretation is consistent with recent studies in invertebrates that show that similar motor patterns can be produced by different mechanisms after removal of descending modulatory inputs [136–138]. And recent studies in humans also suggest that weight support and treadmill training, possibly supplemented with pharmacological and electrical stimulation, may prove to be extremely helpful in increasing the extent of functional recovery, particularly after partial spinal cord lesions [128].

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