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Claire Wyart

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Title

Taking a big step towards understanding locomotion

Authors list

Claire Wyart¹

Affiliations

1. Sorbonne Universités, UPMC Univ Paris 06, Inserm, CNRS, AP-HP, Institut du Cerveau et de la Moelle épinière (ICM) - Hôpital Pitié-Salpêtrière, Boulevard de l'hôpital, F-75013, Paris, France.

***Correspondence:**

claire.wyart@icm-institute.org (C. Wyart).

Keywords

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Abstract

Locomotion is generated by intrinsically oscillating circuits in the spinal cord that are modulated by information from the brain and periphery. In their 1987 publication, Buchanan and Grillner provided evidence for excitatory spinal neurons receiving inputs from descending commands and sensory afferents, and synapsing onto motoneurons and commissural inhibitory interneurons. These findings established one of the first circuit models for central pattern generators incorporating excitatory interneurons' role in the rhythm-production mechanism.

Main text

In the 1980s, after multiple decades of a heated debate that inflamed the field of circuits underlying locomotion, a consensus seems to finally emerge [1]. At its core, the debate focused on the locus of the minimal neural circuit required for generating the rhythmic pattern controlling locomotion. Some researchers had argued that the oscillatory activity of motoneurons driving muscle contractions during locomotion relied on the recruitment of mechanosensory feedback at each cycle. Others defended the idea that locomotion was primarily generated centrally, i.e. in the spinal cord, as shown by evidence from multiple species of rhythmic activity of motor neurons induced in the absence of sensory feedback. Eventually, the field came to an agreement that locomotion is generated centrally in the spinal cord, by circuits referred to as central pattern generators (CPGs) [1,2]. Experiments of electrical stimulations had indicated that spinal CPGs could be triggered by descending commands from the brain to initiate or stop locomotion, and were modulated by sensory feedback associated with stimulation of skin afferents in particular [3,4]. One of the open questions that remained, however, pertained to the precise roles of excitatory and inhibitory spinal interneurons; despite indirect evidence for their importance in locomotion control, in the early 1980s, the overall neuronal organization of spinal CPGs, and the specific contribution of different interneuron types to their operation were mostly unknown.

Investigations in simple aquatic animals with undulating locomotion have been instrumental to tackle this question. In parallel to the *in vivo* xenopus tadpole spinal cord preparation [5], the investigation of cellular mechanisms underlying fictive locomotion in the lamprey spinal cord *in vitro* was a game changer [6]. When the lamprey spinal cord is isolated *in vitro*, despite an apparent “slow down” of the rhythm, application of agonists of glutamatergic receptors induces ‘fictive’ locomotion in which the properties of the oscillatory activity of motoneurons strikingly resembled those of innate locomotion [7]. Moreover, the *in vitro* lamprey spinal cord preparation could be kept functional over long time periods, and enabled single and double intracellular recordings of neurons combined with multiple extracellular recordings of the ventral nerve root. It also allowed application of a ‘split bath’

methodology to perform local manipulation using pharmacology, as well as mechanical manipulation of the spinal cord to mimic locomotor entrainment. The lamprey spinal cord preparation offered seemingly endless possibilities for novel experiments. In this preparation, previous evidence had shown that inhibitory premotor neurons were providing inhibition to motoneurons – inhibition that was out of phase with the ipsilateral ventral nerve root at each locomotor cycle. Interestingly, in 1986, evidence for in-phase *excitation* onto motor neurons had also been reported [8], but the precise nature of the excitatory drive onto motoneurons, and its specific roles in the overall circuit organization remained unclear.

By carefully performing double intracellular recordings of interneurons and motor neurons combined with ventral nerve root recordings, James Buchanan and Sten Grillner isolated excitatory interneurons in the spinal cord projecting mono-synaptically onto motoneurons and receiving indirect inputs from skin afferents and descending pathways from the brainstem [9]. By simultaneously recording these excitatory premotor interneurons with lateral inhibitory interneurons, the authors showed that some excitatory premotor interneurons projected onto inhibitory commissural interneurons involved in left / right alternation.

Altogether, based on these double intracellular recordings, Buchanan and Grillner proposed an elegant schematic of how a relatively simple circuit map – constituted of reciprocal excitation and inhibition between interneurons, which together with commissural inhibitory interneurons project onto motor neurons – could lead to rhythmic activity patterns in motoneurons with left / right alternation. Consequently to this CPG schematic drawn from the lamprey spinal cord, a similar overall circuit organization has been identified by Alan Roberts, Wang-Chang Li and collaborators who elaborated a comprehensive circuit map after performing hundreds of double intracellular recording *in vivo* in the *Xenopus* spinal cord (reviewed in [10]).

Subsequently, studies led by the groups of Tom Jessell, Martyn Goulding and many other teams working in the mouse, chick and zebrafish, harnessed the power of genetic approaches and revealed that the vertebrate spinal cord is organized in about a dozen of progenitor domains, each expressing a specific cascade of transcription factors [11, 12]. Electrophysiological recordings from genetically-identified neurons have suggested multiple links between Buchanan and Grillner's schematic model of spinal cord organization and interneurons originating from each progenitor domain [13, 14]. These joint discoveries – of a map for central pattern generators, and a topographic organization of spinal interneurons based on a cascade of transcription factors – were some of the breakthroughs that led to the nomination of Thomas Jessell and Sten Grillner as co-recipients, along with Pasko Rakic, of the inaugural Kavli prize for Neuroscience in 2008.

The general architecture of central pattern generators as drawn by Buchanan and Grillner largely stood the test of time. Innovative approaches, for instance single cell RNAseq combined with electrophysiological characterization of single class of interneurons, continue to reveal an astonishing and unexpected level of molecular and physiological diversity among interneurons, even those originating from a single progenitor domain (e.g. [15], exemplifying the idea for spinal inhibitory interneurons from the V1 domain, which express the transcription factor engrailed). Clarifying the relevance of such molecular and physiological diversity to the intrinsic functions of central pattern generators remains a major quest for future research.

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