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Editorial overview: Motor control systems of the spinal cord and hindbrain

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The foundations of modern neurophysiology were laid over a century ago by scientists such as Charles Sherrington [1] and his protégé Graham Brown [2], who studied motor control systems of the spinal cord. Later, John Eccles *et al.*, conducted the first intracellular recordings of mammalian central nervous system neurons, spinal motor neurons [3]. Such pioneering studies of motor control systems have, for over a century, led to some of the most fundamental advances in our understanding of neural function. As highlighted by the diverse articles in this issue, compiled by leading scientists from around the world, the impact of studies focused on motor control systems of the spinal cord and hindbrain has not diminished. In fact, it has expanded with the application of innovative technologies such as transcriptomic analyses, optogenetics, population calcium imaging and connectivity mapping using trans-synaptic viruses. Research into motor control systems is today at the forefront of advances in neuroscience and physiology and promises to contribute to the development of new treatments, not only for devastating disorders and injuries afflicting motor control systems, but also dysfunctions that arise in other areas of the nervous system. The convergence of efforts from teams working in the midbrain, hindbrain and spinal cord to decipher vertebrate motor circuits, and the pathophysiology that afflicts them, is what prompted the current review series featured in *Current Opinion in Physiology*.

In order to understand neural circuit function, it is imperative that the cellular components of a given circuit are fully characterised. Several articles in this issue are devoted to recent advances in our understanding of the diversity of neuronal subtypes that combine to form functional spinal motor circuits. Articles by Bikoff, as well as Dobrott et al., discuss genetic approaches for the dissection of interneuron diversity, including recent single cell transcriptomic analyses, which have been pioneered in the spinal cord. Deska-Gauthier and Zhang, and Dougherty and Ha, focus on efforts to identify subtypes of spinal interneurons that are fundamental for the control of locomotion. Manuel and Zytnicki consider molecular and physiological markers for subdividing the final common pathway formed by motor neurons.

Motor neurons and premotor interneurons of the spinal cord are organised to sustain different modes of locomotion including varying speeds. Falgairolle and O'Donovan discuss emerging data in support of feedback regulation of locomotor circuits by motor neurons themselves, countering a mere output role for the final common pathway. Björnfors et al. review a recent body of work revealing diversity in the properties and connectivity of premotor interneurons, specifically of V2a and V0 interneurons, which is critical for

University of California in Berkeley with Profs. Noam Sobel and Ehud Isacoff. Her lab investigates the role of mechanosensory feedback in the control of posture and locomotion, and its contribution to the development of the body axis and spine morphogenesis. Dr Wyart's research focused in particular on an ancestral interoceptive sensory pathway linking the cerebrospinal fluid to motor circuits in vertebrates.

controlling the speed and coordination of locomotion. Jay and McLean formulate an original comparison between the properties of commissural excitatory neurons in invertebrates and vertebrates. The authors propose that a comparison between species enables testable predictions to elucidate general principles of locomotor network organisation. Finally, Deliagina et al. advocate the investigation of circuits underlying all forms of locomotion. They discuss evidence of shared rhythm-generating circuits, but also distinct circuits for the control of locomotion in different directions.

Beyond the identification of neuronal subtypes, deciphering circuit function requires characterisation of the intrinsic properties and synaptic connectivity of constituent neurons. In this issue, Brocard focuses on the intrinsic properties of spinal neurons, highlighting newly discovered roles for ion channels and other membrane proteins such as sodium pumps in determining the output of spinal locomotor control circuits. Synaptic connectivity within spinal motor networks is addressed by Berg et al. who emphasise the role of balanced excitation-inhibition, and by Quilgars and Bertrand who discuss activity-dependent synaptic plasticity within spinal motor circuits.

Although the final motor output governing behaviours such as locomotion is ultimately conveyed by spinal neurons, a range of descending inputs from hindbrain sources are required for the generation of appropriate motor behaviours. The mesencephalic locomotor region (MLR) is a functionally defined area of the midbrain identified by Shik *et al.* [4] that is associated with the initiation and control of locomotor movements in vertebrate species. Grätsch et al. highlight similarities in the organisation, inputs, outputs and function of this structure between lamprey and mammals. The authors describe recent findings regarding 'stop cells' whose activation is sufficient to arrest locomotion. Ritson and Li also address the question of how locomotion stops, discussing the potential roles of integrated sensory cues, descending commands from higher brain areas and internal mechanisms within the spinal cord.

Neuromodulation is a common feature of all motor systems. Fougère et al. review the ascending and descending dopaminergic control of brainstem locomotor circuits, emphasizing the dopaminergic innervation of the MLR that degenerates in a monkey model of Parkinson's disease. Sharma et al. also address the neuromodulatory roles of dopamine via multiple motor pathways and highlight how optogenetic tools have recently enabled the investigation of distinct types of neurons, characterised by different neurotransmitter phenotypes (glutamatergic, cholinergic and GABAergic) in the mouse MLR.

Although there are obvious differences between reticulospinal systems among vertebrate species, the motor field can learn a lot in terms of developmental origin and organisation by comparing species. B. Lau et al. introduce the structure and function of the MLR in normal and parkinsonian primates, comparing the anatomy and organisation found in primates to recent studies investigating homologous circuits in mice using optogenetics. Perrault and Giorgi present the molecular and anatomical diversity of reticulospinal systems in mammals and discuss the need for a better understanding of their developmental origins in order to elucidate their function. In another review, J. Lau et al. report how the transparent zebrafish larva has emerged as an excellent genetic model organism for investigating the function of reticulospinal neurons whose activity can be recorded while the animal actively locomotes.

Sensory feedback is critical to shape active locomotion and adapt movement to the surrounding environment. Witts and Murray discuss emerging evidence that vestibulospinal tract neurons, which receive multimodal sensory input, contribute to the generation of appropriate locomotor patterns. Koch reviews recent studies of the mammalian spinal cord that have revealed motor task-selective sensorimotor interneurons. Azim and Seki discuss how sensory feedback signals can be modulated so that their influence on motor circuits is tuned to suit behavioural demands. Henderson et al. introduce diverse mechanosensory neurons from either proprioceptive or interoceptive pathways in the zebrafish spinal cord, where their connectivity and contributions to the initiation or patterning of active locomotion can be investigated in an entire, intact animal. Shang et al. present an overview of how diverse sensory inputs, including vision, proprioception, and information about internal states, converge onto motor systems to modulate locomotion and posture.

One of the main translational goals regarding the investigation of spinal circuits is the improvement of recovery after spinal cord injury. Dickson et al. discuss evidence that the functional recovery of sensorimotor circuits following spinal cord injury may be best facilitated by combining plasticity enhancing treatments with rehabilitation interventions. Sławińska and Jordan highlight the potential benefits of targeting plasticity of the serotonergic system for functional recovery following spinal cord injury.

Although it could be the subject of an entire issue itself, one review in this issue addresses the role of the cerebellum in motor control. Narayanan and Thirumalai review recent findings on the cerebellum, focusing on granule cells, Purkinje neurons and the cells of the deep cerebellar nuclei. They discuss interactions with cortex and basal ganglia that contribute to motor planning and motor learning.

Taken together, the excellent reviews in this issue on motor control systems of the spinal cord and hindbrain highlight a new era for motor control research, with the interests of teams studying nuclei of the telencephalon, diencephalon, and mesencephalon converging with those who have classically investigated motor circuits of the spinal cord. This new era is exemplified by parallel and interconnected research aiming to decipher the connectivity, recruitment and impact of motor circuits across the spinal cord and hindbrain. Such research will provide major advances in our understanding of motor control and, as the history of motor control research has demonstrated, will also reveal principles of neural function that are applicable more broadly in the field of neuroscience.

Conflict of interest statement

Nothing declared.

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