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Towards a connectome of descending commands controlling locomotion

Sandeep Sharma, Linda H Kim and Patrick J Whelan

Understanding the neural basis for locomotion is of critical importance since it subserves many behaviours necessary for survival. The spinal cord contains all the elements required to produce the basic locomotor pattern. These elements which compose the central pattern generator for locomotion are activated and sculpted by descending inputs from the brainstem, subcortical and cortical structures. In this review, we examine the aspects of descending control of spinal cord circuits, focusing on the spinal cord, brainstem, and the diencephalon–hypothalamus. In this short review, we discuss recent data and consider opportunities for incorporating connectomics and optogenetic advances to continue the progress in deciphering the descending locomotor connectome.

Address
Hotchkiss Brain Institute, Comparative Biology and Experimental Medicine, Faculty of Veterinary Medicine, University of Calgary, Calgary, Alberta, T2N 4N1, Canada

Corresponding author: Whelan, Patrick J (whelan@ucalgary.ca)

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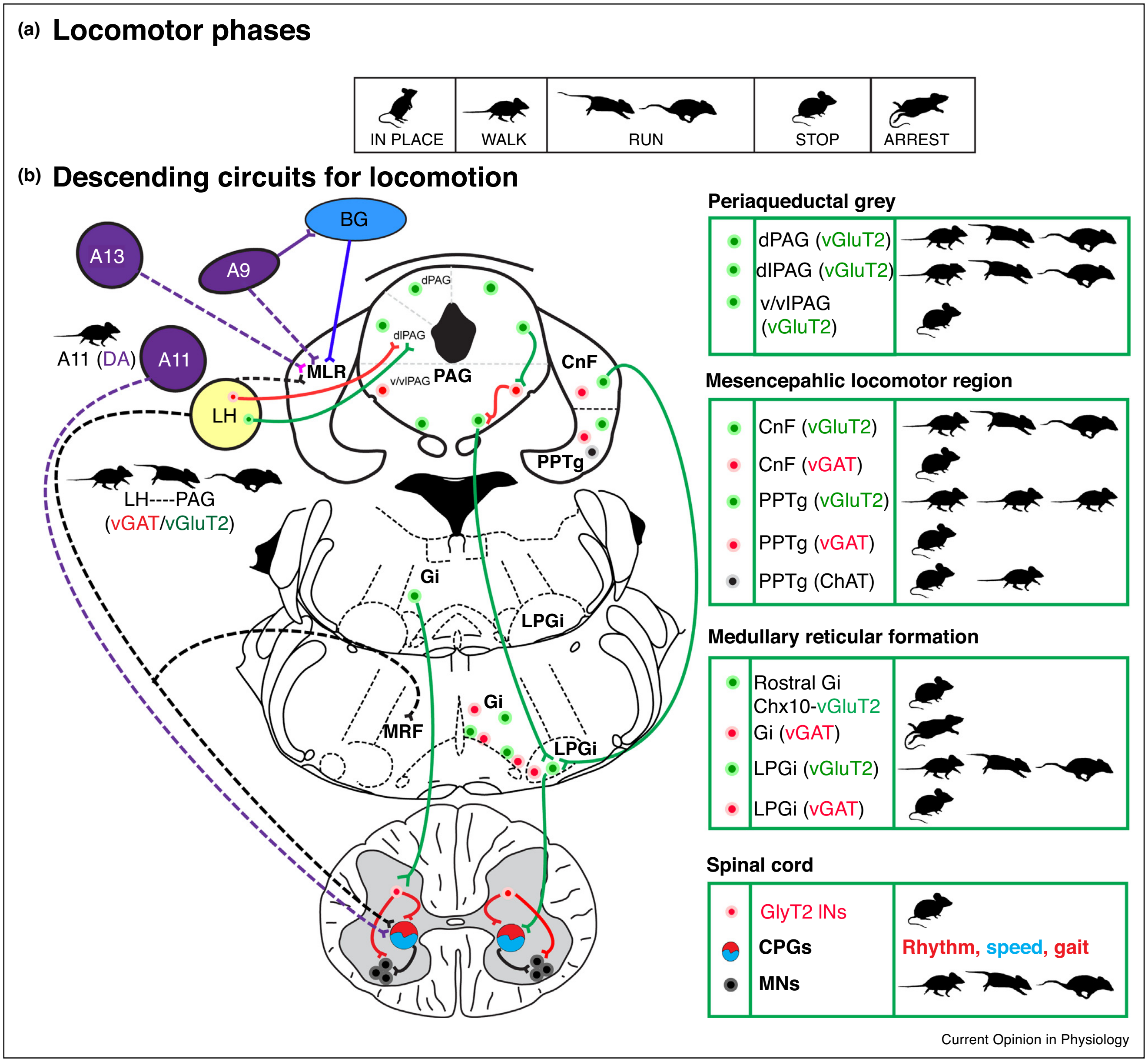
Introduction

An excellent and provocative talk by Wolpert suggests that the brain's function is to generate adaptive movements [1]. Part of the reason for a large amount of brain real estate to be devoted to movement is that animals must be able to locomote to find new sources of food, move away from threats, explore novel environments, and reproduce. The goal of these movements is different yet ultimately, they converge on pools of motoneurons to produce output that is often similar. Key areas include the prefrontal cortex, motor cortex, basal ganglia, brainstem, hypothalamus and spinal cord. It is known that parallel circuits exist to produce locomotor activity and that diverse regions work together. For example, circuits underlying appetitive behaviours can be linked to reward circuits that together motivate an animal to move toward certain food sources [2,3]. Yet dedicated circuits must exist since exploratory locomotor behaviour is qualitatively different from escape responses from a predator. Within motor systems research optogenetic and chemogenetic tools [3,4] have allowed testing of necessity and sufficiency of locomotor circuits that are projection and neurotransmitter-specific. These advances coupled with tools that allow us to record from selected populations continue to drive our understanding of locomotor systems. This short review will examine the descending control of locomotion and will focus on recent advances in the field (Figure 1).

Spinal cord

The spinal cord is the final integration for descending commands and is capable of producing a remarkably sophisticated repertoire of locomotor behaviours. Benefiting from transcriptional genetic approaches to identify classes of interneurons, researchers have deciphered circuits that when manipulated can produce or modulate locomotion [4]. These circuits represent opportunities for investigating the convergence of descending commands in controlling locomotion. For example, the Shox2-non-V2a neuron population is one which is identified with rhythm generation [5], while the V3 class is associated with gait transitions and rhythm stability [6]. A full overview of this exciting topic has been recently published [3]. Descending monoaminergic populations contribute to locomotor activity by acting directly on the networks. Serotonergic systems appear to be critical, are recruited by mesencephalic locomotor region (MLR) stimulation, and can act on spinal central pattern generator (CPG) networks [7,8]. Other monoamines also contribute, including dopamine and noradrenaline [9]. Motoneurons, once thought to be not part of the CPG, show an ability, through recurrent collateral non-cholinergic projections, to control rhythm frequency [10••]. A recent work suggests that at least a portion of these recurrent collaterals project onto the V3 interneuron system forming a set of bidirectional layered microcircuits [11•]. This is a fundamental finding in terms of the descending control of locomotion since motoneurons receive wide-ranging inputs from monoaminergic, glutamatergic, peptidergic, and GABAergic descending projections. Dopamine, for example, operating through D_2 receptor systems, can decrease the efficacy of recurrent collateral feedback from motoneurons affecting CPG circuits [12]. Positive feedback circuits need to be carefully controlled or they can lead to instability so it is a puzzle as to why they exist within the spinal cord [13]. Indeed,

Figure 1



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Descending circuits for the control of locomotion.

(a) A schematic describing different locomotor phases. Walking and running are signature locomotor gaits which are speed-dependent. The stopping of locomotion may be replaced by in place activity which consists of grooming, rearing and head-turning. Alternatively, stopping may be accompanied by behavioural arrest which is defined as immobility that is not passive and includes postural muscle tonus [30].

(b) Summary of locomotor circuits and descending inputs with an emphasis on optogenetic cell-type and circuit-specific approaches (solid lines). Advances in our knowledge of cell-type specific control of locomotion have been highlighted in the tables. The dotted lines show possible modulation of descending locomotor circuits by recently reported parallel descending dopaminergic inputs (A9 and A13) to the mesencephalic locomotor region and known long-range projections of A11 to the spinal cord. There is a possibility for a potential role for the lateral hypothalamic descending inputs in the modulation of locomotor commands at various levels such as MLR, MRF, and spinal cord.

positive feedback in the spinal cord motor system can be high, and it appears that the length–tension properties of muscle provide a mechanism to control instability [14]. Controlling positive recurrent feedback from motoneurons onto the rhythm generating kernel could provide additional mechanisms for reinforcing rhythm frequency. It is interesting to speculate that recurrent feedback microcircuits from motoneuron pools could be rapidly recruited to drive fast and selective alterations in network activity.

A key determinant regarding the contribution of neuromodulators to locomotor function is the underlying state of the network. Work on invertebrate stomatogastric ganglia circuits using modelling shows that the effects of a neuromodulator are dependent on its position relative to the parameter space [15]. Practically, this means that neuromodulators have the greatest effects at the boundary between two stable states [16]. This was tested in the mouse spinal cord where the effects of dopamine and 5-HT were found to produce fundamentally different effects depending on the excitability of the underlying network [17]. This is a factor that should be considered when elements of the network are manipulated, since if the perturbation changes the excitability of the network then this may allow the network to enter a new state. That said the rhythmic pattern produced by spinal cord networks once established is quite robust and can be reliably evoked by diverse means, including by descending command circuits. We suspect that spinal networks may enter unstable states when descending inputs are compromised such as following stroke or spinal cord injury. Under these circumstances remaining descending inputs may cause unpredictable effects since the network has moved to a lower-conductance state [18].

Brainstem

Historically, locomotion has been studied in the context of initiation, speed control, and gait transitions [19]. The brainstem provides a set of locomotor-evoking nuclei where integration of signals from cortical, hypothalamic, and diencephalic areas occurs. The Mesencephalic Locomotor Region (MLR) consists of several nuclei that affect locomotion and appears to be largely conserved across species [20]. The original studies mapped the cuneiform nucleus (CnF) as an important anatomical and functional substrate of MLR responsible for high-speed locomotion suggesting its role in defensive behaviour [21–24]. In contrast, the activation of the pedunculopontine tegmental nucleus (PPTg) produces locomotor behaviour that is slower and exploratory in nature [24].

With the advent of optogenetic tools, it is now possible to investigate neuronal and functional diversity in the brainstem locomotor circuits. Photostimulation of GABAergic neurons in the MLR suppresses locomotion. Conversely, activation of glutamatergic (vGluT2) neurons in MLR, and in particular CnF, leads to short-latency, locomotion bouts with bounding or galloping gaits [25••,26••,27••]. The CnF projects to caudal brainstem locomotor areas such as the medullary reticular formation (MRF), and directly to the spinal cord [28]. While the direct spinal cord projection has not been tested using intersectional viral approaches, photostimulation of CnF vGlut2 neurons does evoke short-latency EMG responses in flexor and extensor muscles suggesting that these spinal cord projections are functional [27••]. The CnF vGluT2 neurons likely also functionally connect with the vGluT2 neurons of the lateral paragigantocellular nucleus (LPGi) in MRF since ablation of these LPGi vGluT2 neurons abolishes locomotion at higher speeds but not the low-speed exploratory locomotion [29••]. The results from photostimulation of PPTg vGluT2 neurons are mixed and variable across different studies.

Stopping and arresting of locomotion is a critical element when faced with a threat or simply to engage in non-locomotor activities [30]. But stopping is a complex activity since deceleration has to be fluidly merged with activation of postural systems. A recent work indicates that Chx10-identified vGluT neurons in the rostral medulla project to glycinergic and glutamatergic neurons within lamina VII of the spinal cord to suppress locomotion [31••]. The activation of inhibitory vGAT neurons in different subdivisions of MRF leads to a range of behaviours from a termination of ongoing locomotion to complete muscle atonia [29••].

Diencephalic/hypothalamic inputs

Orchestration of natural and adaptive movements to initiate, modulate or terminate locomotion requires complex interaction between brainstem locomotor circuits, cortex and the diencephalic–hypothalamic regions. Within the diencephalon and hypothalamus, dopamine is one of the transmitters that is now considered to have multiple motor roles. The canonical dopamine motor pathway is centred on the nigrostriatal circuit [32]. Classically dopamine's role in motor control was thought to be largely indirect acting through ascending striatal projections, which in turn led to downstream effects on brainstem and cortical motor circuits [25••,33]. There has been renewed interest in the role of other dopamine pathways in movement control [9] that is conserved from basal vertebrates to mammals [34]. For example, the A11 region located in the posterior diencephalon around the third ventricle contains a small cluster of dopaminergic neurons that when optogenetically activated produces an increase in motor activity, that seems to be exploratory in nature [35]. The A11 is interesting as it is one of the major dopaminergic inputs to the spinal cord, with a small input from the A10 area also being recognised [36–38]. Axons descend through the dorsolateral funiculus and close to the central canal sending collaterals to all segments of the spinal cord [39,40]. The A11 receives inputs from several areas of the brain including the suprachiasmatic nucleus, bed nucleus of striata, infralimbic cortex and parabrachial nucleus [41,42]. The A13 dopamine nucleus located in the medial zona incerta is contiguous with the A11 but the neuronal size is distinctly smaller [43•]. The targets for the A13 are primarily the cuneiform nucleus with moderate projections to the PPTg suggesting that it may play a role in escape-like behaviour. Projections to the MRF and the spinal cord are sparse and there are no clear connections to the dorsal striatum, indicating a separate parallel pathway for dopaminergic neurons onto motor circuits.

Combined with data showing that the dopaminergic neurons of the substantia nigra compacta project onto the MLR [44,45••], it is clear that multiple dopamine motor pathways exist.

The lateral hypothalamus (LH) is an area associated with a variety of goal-directed actions, including locomotor initiation, whose role has been re-examined using optogenetic and chemogenetic approaches. Within the LH, the orexin neurons (OXs) are of interest, OXs are hypothesised to be important for goal-directed motor behaviours such as reward acquisition (e.g. food), and escape responses. Recordings from OXergic areas in the LH show that spike activity is highest during exploratory locomotion such as foraging and eating [46]. Work on the cat has shown that LH stimulation depolarises lumbar motoneurons through OX release in the spinal cord [47] and recent data in the mouse show that OX can directly activate spinal networks [48]. Locomotor activity is also increased following intracerebroventricular administration of OX, a behaviour that was reversed by administering an OX receptor antagonist. In addition to OXergic neurons, contributions from other neurotransmitter types for goal-directed locomotor behaviour have recently gained traction. Orexin-driven increase in locomotor activity is partly mediated by increased activity of glutamic acid decarboxylase (GAD65)-expressing inhibitory LH neurons [49]. When chemogenetically activated, these inhibitory cells promote locomotor activity whereas chemogenetic silencing suppresses locomotion. Combining projection-type and cell-type specific optogenetic manipulations, PAG-projecting GABAergic and glutamatergic LH neurons can separately drive predatory attacks and evasion from predictive danger, respectively [50]. A challenge for the field will be integrating these diencephalic and hypothalamic microcircuits with downstream locomotor circuits for the execution of behaviourally relevant locomotion.

Integration of sensor and actuator tools to further dissect descending locomotor command systems

There has been an increase in the number of tools to allow selective activation and inactivation of neural circuits which led to a richer understanding of the selection of locomotor synergies and the control of stop and start. What then are the opportunities for further investigation? First, we need a better understanding of the motor connectome, and the advent of tissue clearing technologies has paved the way for this to occur [51]. Second, we need to understand the plasticity of this connectome during development and following injury, to provide new therapeutic approaches for recovery of function [52]. Third, a richer understanding of cortical activation of subcortical motor structures would help us understand how subcortical structures promote goal-directed locomotion. Fourth, we need to capitalise and build high-throughput devices to capture the full spectrum of motor behaviour occurring both in and out of the lab, encompassing hardware and machine learning solutions [53–55].

The next wave in our understanding will occur when we get the ability to examine the activity of neuronal ensembles involved in motor control [56]. Especially for understanding skilled avoidance of obstacles we need to examine population activity of identified neurons during the acquisition of behaviour. This is possible using mini-cameras [57] but ultimately, we need to be able to move beyond the use of calcium transients and record using voltage sensors from populations of cells [58]. Reading in complex arrays of activity will provide clues to the recruitment pattern of neurons that project to particular descending targets or the spinal cord. These patterns could be recorded and then a temporally and precise photostimulation of identified cells could occur. There are indications that this technology is at hand. Using holographic 2-photon imaging, along with driving of somatic soCoChR, neurons can be targeted in slice tissue for photostimulation [59]. Voltage sensors recording subthreshold activity patterns through 2-photon equipped mini-cameras will provide the ability to record subthreshold activation of the network. In combination with targeted photostimulation of neurons, this provides an exciting opportunity to examine state-dependent changes in connectivity of cortical and subcortical motor control areas during the execution of motor tasks. The devil is in the details of course [60] but there are clear indications that we are getting closer to this reality. This will then augment the current strategy of large-scale synchronous recruitment of neurons within a network. Another technological advance will be the integration of information from diverse fields. Within this space, we see investigators focused on the spinal cord and brainstem locomotion, collaborating with those in other fields of neuroscience, including appetitive, reward, and anxiety. These fields often include locomotor activity as a read-out, and increased collaboration between motor researchers would yield new work on contextual control of locomotion. Yet the sheer volume of data has made it difficult for motor researchers to identify these opportunities especially since locomotion data can be tucked away within papers whose prime objective is not to understand the motor connectome. This job will be made easier as machine learning approaches, storage of data associated with primary work, and data analytics converge to identify new collaborative possibilities [61,62].

Concluding remarks

Our understanding of the descending control of locomotion has been enriched with the use of tools that provide the ability to target descending circuits. In the case of dopamine, for example, several parallel pathways have been identified that contribute to locomotor control. Moreover, centres have been identified that contribute to fine motor control and locomotion. As we look forward there will be a new slate of tools making population recordings more feasible and data more accessible. And we will start to examine the effects of perturbation of motor areas on a wider catalogue of behaviours compared to the restricted tests that we have performed in the past. The expected richer datasets will need to be to collated using techniques for large data analytics, which will be facilitated by requirements from journals to deposit data upon publication of work.

Conflict of interest statement

Nothing declared.

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