Connecting Circuits for Supraspinal Control of Locomotion.

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Abstract

Locomotion is regulated by distributed circuits and achieved by the concerted activation of body musculature. While the basic properties of executive circuits in the spinal cord are fairly well understood, the precise mechanisms by which the brain impacts locomotion are much less clear. This Review discusses recent work unraveling the cellular identity, connectivity, and function of supraspinal circuits. We focus on their involvement in the regulation of the different phases of locomotion and their interaction with spinal circuits. Dedicated neuronal populations in the brainstem carry locomotor instructions, including initiation, speed, and termination. To align locomotion with behavioral needs, brainstem output structures are recruited by midbrain and forebrain circuits that compute and infer volitional, innate, and context-dependent locomotor properties. We conclude that the emerging logic of supraspinal circuit organization helps to understand how locomotor programs from exploration to hunting and escape are regulated by the brain.

Introduction

Locomotion is the undoubtedly most universal and conserved form of movement of the virtually endless variety of behaviors that animal and human bodies perform. Understanding the mechanisms within the nervous system involved in controlling its planning and execution has been a long-standing scientific quest. Early studies have advanced the field by delineating regions in the nervous system linked to the control of locomotion through performing lesion experiments, pharmacological interventions, electrical stimulations, and neuronal recordings. This body of work provided first important insights into how the nervous system controls locomotion, including the identification of key regions distributed throughout the nervous system, which will provide the organizational anchor points for this Review.

Recent technological advances have revolutionized neuroscience and, in parallel, also strongly influenced research on the control of movement. These novel insights have transformed the way we think about the control of locomotion. It is now clear that defined neuronal cell types, characterized by various means including molecular, developmental, and/or distinct synaptic input-output organization, are embedded into specifically wired neuronal circuits to implement many different aspects of locomotor function. Such work has been pioneered in the spinal cord and reviewed extensively (Alaynick et al., 2011, Arber, 2012, Goulding, 2009, Grillner and Jessell, 2009, Kiehn, 2016), allowing us here to only briefly summarize this work with an emphasis on some of the most recent relevant studies. On the other hand, the elucidation of specific supraspinal circuit architecture and organization using these emerging technologies has only just begun. We will highlight and synthesize predominantly a selection of this most recent literature on supraspinal control of locomotion. Our emphasis will be on circuit- and cell-type-

level insight and how identified neuronal populations integrate into the complex locomotion-controlling circuitry of the nervous system. We refer readers to previously published review articles for historic coverage of this topic. To set the stage for this Review, we will first briefly dissect the behavioral process of locomotion into temporal and regulatory categories. We will return to these definitions throughout the Review with the goal of identifying circuit-level solutions for controlling and adjusting locomotion according to behavioral needs.

Dividing Locomotion into Temporal and Regulatory Behavioral Categories

Three temporally separate behavioral phases accompany locomotion (Figure 1A). Initiation and termination are the two boundary events defining a locomotor episode. Transition from a stationary period or another motor behavior to a locomotor episode can entail different circuit-level events to begin this full-body action. It can be caused by a sensory stimulus, such as a fearful encounter with a predator leading to an escape response, but also often occurs in the absence of obvious external triggers. Such initiations can be linked to internal needs, including hunger and thirst, but can also be caused by planning or cognitive decisions leading to exploration. In analogy, termination of locomotion can occur for a variety of reasons depending on behavioral context, ranging from immediate stopping with a freezing response to more gradual termination due to arrival at a food source or encountering an interesting object.

The time frames flanked by initiation and termination encompass the locomotor episode itself (Figure 1B). Each episode can be described by a set of behavioral attributes, patterns, or categories. One important attribute during ongoing locomotion is speed. Locomotor behavior

ranges from low-speed exploration to high-speed escape running. Speed can also fluctuate within a given locomotor episode by virtue of acceleration and deceleration. Second, during locomotion, quadrupedal animals move their limbs in coordinated and stereotype patterns called gaits (Bellardita and Kiehn, 2015, Halbertsma, 1983, Lemieux et al., 2016). Behavioral studies in different species provide evidence that gait selection occurs linked to different speed ranges. Notably, during low-speed exploratory locomotion, many quadrupedal animals alternate paired fore- and hindlimbs, respectively, and exhibit synchrony in diagonal fore- and hindlimbs. In contrast, high-speed escape running goes hand in hand with bound gait selection. These observations suggest that a given gait likely represents the optimal biomechanical solution for the chosen speed range. Another behavioral attribute during locomotion is its directionality. Animals only rarely locomote along the shortest straight trajectory, and they, as well as humans, also have the ability to locomote backward using the same muscles in different configurations, likely controlled and mediated by different networks (Choi and Bastian, 2007, Wang et al., 2011). This Review will focus mainly on quadrupedal locomotion although similar principles likely apply to bipedal locomotion, swimming, and flight.

Diversity and Specificity in Spinal Circuits for Execution of Locomotion

The spinal cord harbors neuronal circuits required for the execution of locomotion. Skeletal muscles receive their commands for contraction from spinal motor neurons that are grouped into topographically arranged motor pools according to the innervated muscles (Romanes, 1951). Understanding the behavioral phenomenon of locomotion can therefore essentially be paraphrased into the question of how the temporally stereotypically patterned muscle activation

inherent to locomotion is achieved through regulation of synaptic inputs to motor pools. Although many of these inputs arise from spinal neurons, the locomotor program requires supraspinal or sensory sources located outside the spinal cord for initiation, maintenance, and adjustment. In fact, complete spinal transection in mammals leads to permanent paralysis of body parts innervated by segments below injury (Dietz, 2010, Shik and Orlovsky, 1976). In the absence of supraspinal input, spinal circuits can still be recruited for basic locomotion by either sensory feedback activation or application of neurochemical substances (Forssberg et al., 1980, Miller and van der Meché, 1976). These observations were extensively leveraged in reduced in vitro preparations, in which neonatal spinal cords are stimulated electrically or pharmacologically to delineate the function of broad spinal interneuron classes defined by genetics. It is now clear that the different spinal subpopulations are organized into specific circuit modules and contribute differentially to locomotion. These spinal networks—also referred to as central pattern generators (CPGs)—can generate locomotor pattern and rhythm upon extrinsic synaptic input through microcircuits encompassing interneuron subtypes and motor neurons (Alaynick et al., 2011, Arber, 2012, Goulding, 2009, Grillner and Jessell, 2009, Kiehn, 2016).

Spinal neurons are derived from different, transcriptionally defined dorso-ventral progenitor domains during development, with several classes implicated in the regulation of important aspects of locomotion, including interlimb coordination, speed, and rhythmicity, work that is reviewed extensively elsewhere (Arber, 2012, Goulding, 2009, Jessell, 2000, Kiehn, 2016). While the existence of diversity beyond single progenitor domain origin was already apparent early on (Alaynick et al., 2011), a key open question has been the extent to which neurons diversify in the spinal cord to support generation of locomotor and other movement output of the body. It is also essential to resolve how a given population of spinal neurons defined by

developmental and/or transcriptional entry points aligns to the functional attributes observed during in vivo locomotion. Recent work reviewed below has begun to shed light on these aspects of spinal neuron diversification, focusing on dorso-ventral and rostro-caudal axis, as well as the organization and connectivity of spinal neurons into circuits beyond local microcircuits (Figures 2A–2D).

In adult zebrafish, motor neurons of the slow, intermediate, and fast subtypes are recruited progressively with increasing swimming speed (Ampatzis et al., 2013). Intriguingly, separate and speed-dependent modules also exist within the V2a spinal neuron population (Figure 2A). These V2a subpopulations exhibit preferential connectivity to corresponding motor neuron subtypes, and neurons within the same V2a submodule are interconnected but only rarely connect across submodules (Ampatzis et al., 2014). This study thus defines specific V2a neuron ensembles in the spinal cord aligned with locomotor speed to match behavioral need. In mice, execution of quadrupedal locomotion at higher speeds is accompanied by gait changes with limb coordination changing from alternating to synchronous patterns (Bellardita and Kiehn, 2015, Lemieux et al., 2016), raising the question of how speed and gait phenomena are linked and whether they are mediated, at least in part, by spinal circuits. Developmental ablation of V2a neurons leads to deficits in hindlimb coordination exclusively at higher speeds in adult mice (Crone et al., 2009). These findings suggest that V2a neurons also exhibit speed-dependent roles in mice, but it is currently unclear whether functional subdivisions for V2a neurons similar to zebrafish exist. In addition, V0 spinal neurons subdivide into predominantly excitatory V0v (marked by Evx1) and mostly inhibitory V0d (marked by Pax7) subtypes, and these two classes exhibit distinct roles in maintenance of gait parameters adequately aligned with increasing speed during quadrupedal locomotion (Talpalar et al., 2013) (Figure 2A), phenotypes not discernable by studying V0

neurons as an entity. Locomotor parameters are also shaped by central processing of sensory feedback (Rossignol et al., 2006, Windhorst, 2007). Recent work identified an inhibitory spinal interneuron class characterized by the expression of RORβ orphan nuclear receptor (Koch et al., 2017) (Figure 2B). This population might gate proprioceptive information during the swing phase of the step cycle, acting by virtue of presynaptic inhibition of myelinated sensory and likely proprioceptive afferents. In the absence of these neurons, mice exhibit a peculiar duck-gait locomotor phenotype.

Gene expression analysis and computational methods are potent catalyzers to systematically unravel cellular diversity in many systems, and they have also been applied in the spinal cord (Bikoff et al., 2016, Hayashi et al., 2018, Sweeney et al., 2018). Focusing on V0-V2 spinal neuron distribution along the rostro-caudal axis, different patterns and gene expression profiles were observed comparing cervical, thoracic, and lumbar levels (Francius et al., 2013). A more recent study dissected V2a neuron diversity in mice, demonstrating that the expression of one of its canonical markers Chx10 shows postnatal rostro-caudal expression differences (Hayashi et al., 2018) (Figure 2C). Notably, V2a type II neurons are characterized by low Chx10 expression, preferential residence at cervical segments, and establishment of ascending axons to supraspinal targets. In contrast, the V2a type I cohort maintains Chx10 expression and is present at both lumbar and cervical levels (Figure 2C). What might be the mechanisms by which spinal neurons diversify along the rostro-caudal axis? It is well established that rostro-caudal identity in motor neurons is driven by differential developmental expression of Hox transcription factors (Philippidou and Dasen, 2013). Evidence now supports the idea that this principle extends to other spinal neurons, in which V1 spinal neuron diversification along the rostro-caudal axis can

be regulated by Hox transcription factors independent of segmental motor neurons (Sweeney et al., 2018).

Most work aimed at understanding neuronal diversity in the spinal cord has focused on local circuit mechanisms. Yet, precise interactions of distributed spinal microcircuits along the length of the spinal cord is essential for locomotion, especially in quadrupedal animals in which distant limbs must be coordinated to enable locomotion. While neuronal mechanisms involved in left-right coordination of hindlimbs are mostly driven by segmental spinal neurons and fairly well understood (Kiehn, 2016), much less is known about circuit mechanisms for fore- and hindlimb coordination. A recent study demonstrated that long projection neurons interconnecting the cervical and lumbar spinal cord are important in coordinating fore- and hindlimb patterns during high-speed locomotion as well as for maintenance of postural stability (Figure 2C) (Ruder et al., 2016). The characterized long projection neurons are composed of a major excitatory and a minor inhibitory population derived from distinct developmental origin, each establishing specific projection patterns (Figure 2C). Furthermore, long descending projection neurons receive synaptic inputs from many centers in the brain engaged in the regulation of locomotion and thus provide a neuronal substrate for integration and broadcasting of supraspinal information throughout the circuitry of spinal cord to coordinate locomotion.

Together, these findings demonstrate that important parameters of subtype identity for spinal neurons during early development arise by transcriptional programs intersecting along the dorso-ventral and rostro-caudal axis. These interactions, as well as usage of emergent spinal networks, likely dictate the ultimate connectivity of neurons into specific circuit modules as well as their function. Recent work demonstrates that the diversity of spinal neurons is higher than originally

anticipated, foreshadowing the likely existence of microcircuits endowed with dedicated functions in the execution of locomotion. One big challenge is to unravel how such spinal microcircuits process input from descending pathways and sensory feedback circuits. Clearly, how long-range supraspinal inputs trigger the engagement of specific spinal microcircuit modules is instrumental for the execution of motor programs driving any form of body movement, including locomotion (Figure 2D). We will now focus on supraspinal locomotion-regulatory signals in the brain and how they are conveyed to executive circuits in the spinal cord.

Dissection of Brainstem Circuits Regulating Locomotor Execution

Classical work performed in cats has mapped regions in the brain whose electrical stimulation elicits coordinated locomotion (Mori et al., 1989, Shik and Orlovsky, 1976, Shik et al., 1966). Several prominent regions were identified in the diencephalon, midbrain, and ventral to the cerebellum. We will focus here on the mesencephalic locomotor region (MLR) in the midbrain due to recent progress in its characterization. Electrical stimulation of the MLR in cats elicits coordinated locomotion at a wide range of speeds and gaits scaling with applied stimulation frequency (Shik and Orlovsky, 1976). Still today, this functionally defined site is considered a key region in the supraspinal orchestration of locomotion. According to a unifying model based on many studies, the MLR integrates inputs from numerous brain regions and regulates locomotion in a context-adequate manner (Jordan, 1998, Ryczko and Dubuc, 2013) (Figure 3A). It accesses executive spinal circuits mostly by recruiting neurons residing in the reticular formation of the caudal brainstem acting as intermediaries to transmit locomotor signals to the spinal cord. Supporting such a model, MLR stimulation in conjunction with cooling the ventral

medulla to attenuate synaptic transmission blunts transfer of the locomotor signal and its execution to the spinal cord (Shefchyk et al., 1984). This work suggests the existence of neurons in the reticular formation with a key role in the locomotor process. Homologous regions in the brainstem of several vertebrate species, including humans, have been identified (Grillner et al., 1997, Le Ray et al., 2011). These findings suggest that the concept of an MLR region and associated downstream structures in the brainstem are evolutionarily conserved throughout the vertebrate lineage, although some connectivity differences likely exist, perhaps also reflecting the adaptation of neuronal circuits to support bipedalism (Alam et al., 2011). We will now briefly summarize historic entry points and debates in the field about how brainstem circuits between the MLR and the reticular formation affect locomotion and describe the most recent studies beginning to resolve the circuit mechanisms underlying these processes.

Historical Perspective and Open Questions on MLR Organization and Function

Since the first description of the MLR following a functional definition, many studies have sought to pinpoint the exact location of the locomotion-promoting site and its neuronal identity in numerous animal models. Original studies in cats reported that the anatomical substrate of the MLR corresponds to the cuneiform nucleus (CnF) and its vicinity (Shik and Orlovsky, 1976). Interestingly, CnF stimulation in both rats and cats generates a type of locomotion that resembles aversive, escaping behavior with high-speed running at synchronous gaits and explosive jumps (Depoortere et al., 1990, Mori et al., 1989). Given the findings that the CnF also modulates nociception, cardiovascular, and respiratory responses (Ryczko and Dubuc, 2013), it was proposed that the CnF supports defensive forms of locomotion (Jordan, 1998). Electrical

mapping of the MLR in rats demonstrated that locomotion could be elicited by stimulation of both the CnF and the pedunculopontine nucleus (PPN) (Skinner and Garcia-Rill, 1984), but the region with the shortest latency was mapped to the caudal part of the PPN, coinciding with a distinct cholinergic cell cluster and its vicinity (Garcia-Rill et al., 1987). Given the absence of explosive behaviors elicited by PPN stimulation and the selective connectivity of the basal ganglia (BG) with the PPN (Martinez-Gonzalez et al., 2011), it was proposed that the PPN might mediate exploratory locomotor behaviors driven and actively selected by the BG, while the CnF mediates defensive locomotion, for example, in the context of an urgent need to escape from dangerous contexts (Jordan, 1998). Another layer of complexity emerges from the fact that electrical stimulations along a dorso-ventral axis encompassing the CnF and PPN region can elicit variable responses ranging from opposing changes in muscle tone and posture to locomotion-promotion ones (Figure 3B) (Takakusaki et al., 2016).

Together, these experiments suggest that locomotion and posture controlling functional attributes in the MLR cannot be fully explained by neuronal position alone. While the literature consistently supports a role for the CnF as locomotion-promoting site, the PPN and adjacent regions might be composed of closely located or even intermingled populations of locomotion-promoting and opposing posture-regulating neurons. In addition, PPN neurons also contact numerous rostral brain regions (Martinez-Gonzalez et al., 2011), making it challenging to dissociate direct effects on locomotion through descending pathways from indirect effects through ascending interactions. Thus, studies using electrical stimulation or pharmacology cannot disentangle the complexity of these circuits. Work described below and mostly carried out in mice makes use of viral and genetic tools to elucidate the cellular and functional identity within the MLR, with a focus on its descending circuits.

Neuronal and Functional Diversity in the Mouse MLR

To consolidate results of experiments performed in other species in mice, electrical mapping of the mouse MLR revealed that the effective stimulation sites to elicit locomotion span over a rostro-caudally and dorso-ventrally broad region, including the PPN, CnF, pre-CnF, and the adjacent mesencephalic reticular formation (Roseberry et al., 2016). These regions contain intermingled glutamatergic, GABAergic, and, exclusively in the case of the PPN, cholinergic neurons (Martinez-Gonzalez et al., 2011) (Figure 3C). The most advanced insight on control of locomotion emerged from studying glutamatergic MLR neurons marked by the expression of the vesicular glutamate transporter vGlut2 (Caggiano et al., 2018, Josset et al., 2018, Lee et al., 2014, Roseberry et al., 2016), which will be the main focus here. All four studies demonstrate that optogenetic activation of glutamatergic neurons in the broad MLR region in mice recapitulates short latency initiation of locomotion with a stimulus intensity-to-speed correlation analogous to electrical stimulation experiments. Furthermore, optogenetic stimulation triggered during ongoing locomotion increases speed by shortening the duration of hindlimb extensor muscle activation during stance and anticipating the next swing phase (Josset et al., 2018, Roseberry et al., 2016). Single-unit neuronal recording experiments in vivo revealed that general vGlut2-MLR neurons correlate with locomotor state with a fraction of neurons also tracking locomotor speed (Caggiano et al., 2018, Roseberry et al., 2016). Optogenetic stimulation experiments were also carried out for other MLR populations. While the experimental outcome for stimulating cholinergic PPN neurons was somewhat contradictory across studies (Caggiano et al., 2018, Dautan et al., 2016, Josset et al., 2018, Roseberry et al., 2016, Xiao et al., 2016), it is nevertheless

clear that they likely exhibit a modulatory rather than a driver role in locomotion. This seems to be at least partially mediated by direct regulation of dopaminergic neuronal activity in the substantia nigra compacta (SNc), the ventral tegmental area (VTA) (Dautan et al., 2016, Xiao et al., 2016), and possibly other ascending and descending targets (Mena-Segovia and Bolam, 2017, Moehle et al., 2017). In contrast, GABAergic neurons influence locomotion negatively through both local and distant circuit mechanisms (Caggiano et al., 2018, Roseberry et al., 2016). Taken together, these results demonstrate that glutamatergic MLR neurons constitute the neuroanatomical basis for the functionally described short-latency locomotion-promoting MLR site in the midbrain.

A long-lasting quest concerns the possible functional subdivision of regions residing within the MLR boundaries. While studies in mice consistently find that optogenetic stimulation of CnF-vGlut2 neurons can elicit locomotion, analogous evidence for PPN-vGlut2 neurons is variable (Caggiano et al., 2018, Josset et al., 2018). One study puts forward a model in which the PPN controls low-speed locomotion while the CnF regulates high-speed locomotion (Caggiano et al., 2018) (Figure 3C). In support, optogenetic activation of PPN-vGlut2 neurons induces low-speed, long-latency locomotion with alternating gaits, while CnF-vGlut2 neuron activation generates short-latency locomotion with speed scaling according to stimulation intensity and aligned with the selection of speed-appropriate gait types. Single-unit recordings from PPN and CnF neurons during locomotion on a head-fixed treadmill also revealed differences in firing properties aligned with speed. Moreover, glutamatergic PPN neurons integrate inputs from a wide variety of brain structures contributing to action selection and voluntary movements including BG, while CnF neurons receive preferential input from structures implicated in escaping behavior, including the periaqueductal gray (PAG) and the inferior colliculus. The second study demonstrates that

stimulation of either PPN or CnF glutamatergic neurons elicits short-latency electromyography responses in both ankle flexor and extensor muscles, with the strongest responses in the ankle flexor (Josset et al., 2018). This study further compared the effects of stimulation at rest to during ongoing locomotion. Glutamatergic CnF neuron stimulation at rest increased postural muscle tone before eliciting locomotion and shortened the extensor bursts to accelerate locomotion with transition to gaits typical for high-speed during ongoing locomotion. In contrast, stimulation of PPN-vGlut2 neurons at rest elicited phasic muscle activity but no locomotion, but surprisingly, either stimulation or silencing of these neurons during locomotion slowed down locomotor rhythm rather than speeding it up. It is not straightforward to reconcile the results of these two studies on PPN-vGlut2 neurons, but one possibility is that subtle differences in neuronal targeting locations within the PPN area and/or currently unidentified cell-type diversity provide explanations.

Overall, recent studies support the existence of at least two midbrain circuits, spatially segregated between the PPN and CnF regions, embedded within specific input-output matrices providing differential control over circuitry regulating the scale from low-speed to high-speed locomotion (Figure 3C). It is likely that these populations are recruited in a context-dependent manner, shaped by emotional valence, internal homeostatic needs, and sensory perception, ultimately producing forms of locomotion with speed and gait needed for the respective context. These programs must include the full range of possible locomotor forms from quiet actively selected exploration to urgent, reflexive, escaping behavior from imminent dangers.

MLR-induced locomotion is preserved after precollicular transection, supporting a model in which locomotion-promoting effects are conveyed via caudal projections. Yet, an interesting

additional aspect to consider in the equation of MLR function is that glutamatergic MLR neurons also provide input to rostral brain structures (Figure 3D). The PPN establishes connections with most BG nuclei as well as dopaminergic neurons in the VTA and SNc, the thalamus, and the basal forebrain (Martinez-Gonzalez et al., 2011). These findings implicate the MLR not only in behavioral execution, but also put it in a position to influence rostral computations involved in motor program selection or reinforcement such as cortical processing. The role of rostral projections by glutamatergic MLR neurons remains mostly unexplored, with some notable exceptions. Stimulation of glutamatergic MLR projections to the basal forebrain increases the gain of visual responses and generates gamma oscillations in the primary visual cortex (Lee et al., 2014), reproducing the previously described effects of spontaneous locomotion in cortical processing (Niell and Stryker, 2010). Interestingly, cortical effects were seen even at stimulation strengths below the threshold to induce locomotion by MLR neuron stimulation, demonstrating that the cortical changes and the production of the locomotor behavior are dissociable. Additionally, projections of PPN-vGlut2 neurons to the VTA target dopaminergic neurons and promote behavioral reinforcement (Yoo et al., 2017), presumably by promoting dopamine release in the nucleus accumbens and activating reward-processing circuits. By demonstrating that MLR glutamatergic neurons not only convey descending signals for motor execution, but also send ascending projections to multiple brain regions that influence cortical processing and motivation/behavioral reinforcement, these studies suggest that the complexity of the MLR goes far beyond neurotransmitter identity and might also depend on target specificity, models to be explored in the future.

Identification of Lower Brainstem Cell Types Conveying Locomotor Speed Signals

The functional linkage between brain locomotor centers (most notably MLR) and executive circuits in the spinal cord has long been proposed to involve neurons in the lower brainstem reticular formation (Orlovsky et al., 1999). This model is based on experiments including regional injections of pharmacological substances and/or inactivation approaches using tissue cooling methods in conjunction with electrical microstimulation in several species including cats, rats, and lampreys that have been extensively reviewed (Brownstone and Chopek, 2018, Mori, 1989, Orlovsky et al., 1999, Ryczko and Dubuc, 2013, Takakusaki et al., 2016). However, despite strong evidence supporting such a model, the precise identity of neurons in the reticular formation acting as intermediaries between MLR and the spinal cord was long unclear. Unlike in the midbrain, within the caudal brainstem reticular formation, electrical stimulation experiments produced variable results with no clear consensual sites able to elicit full-body locomotion (Drew and Rossignol, 1990, Kinjo et al., 1990, Ross and Sinnamon, 1984), and it had been argued that neuronal cell-type diversity might be the underlying reason for this failure of identification (Orlovsky et al., 1999).

Several studies in mice employing genetics and viruses intersectionally have addressed the identity of neurons in the caudal brainstem involved in regulation of locomotor speed (Bouvier et al., 2015, Capelli et al., 2017, Giber et al., 2015). These studies identify brainstem neurons with locomotion-promoting and/or locomotion-attenuating functional properties and jointly demonstrate that criteria other than simply location are often needed to unravel functional cellular identities in the brainstem.

Within the caudal medulla, the two broad regions magnocellular nucleus (Mc) and gigantocellular nucleus (Gi) have been shown to contain neurons with connections to both cervical and lumbar motor neurons (Esposito et al., 2014). These neurons are thus in a position to influence spinal locomotor circuits throughout their rostro-caudal extent as might be expected for descending neurons targeting locomotor circuits. To map the precise location and neurotransmitter identity of these neurons in the adult, retrograde tracing from the spinal cord demonstrated that all three Mc subdomains (LPGi, lateral paragigantocellular nucleus; GiA, gigantocellular nucleus alpha; and GiV, gigantocellular nucleus ventral) and the more dorsally located Gi contain intermingled excitatory and inhibitory neurons (Capelli et al., 2017) (Figure 4A). Optogenetic activation of neurons confined to any of these four regions indiscriminate of neurotransmitter identity did not lead to changes in locomotor behavior (Figure 4A). Strikingly, however, selective stimulation of vGlut2 neurons located in LPGi, but not in any of the other three studied subdomains, induced short-latency locomotion from rest and increased speed of ongoing locomotion (Capelli et al., 2017). Elimination of LPGi-vGlut2 neurons selectively impaired high-speed locomotion but left exploratory low-speed locomotion unperturbed (Figure 4B). Given these functional studies on the role of LPGi-vGlut2 neurons in natural locomotion, and mapping experiments defining the descending synaptic outputs of CnF-vGlut2 neurons (Caggiano et al., 2018), it is likely that high-speed locomotor signals reach these caudal brainstem neurons from CnF-vGlut2 neurons. Indeed, locomotion-promoting signals from the MLR can be significantly attenuated by selective ablation of LPGi-vGlut2 neurons (Figure 4C), and optogenetic stimulation of MLR-vGlut2 axon terminals in the caudal medulla can also elicit locomotion (Capelli et al., 2017). Together, these findings demonstrate that, at least in part, descending locomotion-promoting signals from the MLR reach spinal circuits by recruiting LPGi-vGlut2 neurons in the caudal brainstem. Yet, the findings also demonstrate the need to

search for additional neuronal populations that transmit signals for low-speed exploratory locomotion to the spinal cord. Such a network might be more distributed over several populations given its importance for survival, and/or perhaps an even finer dissection of cell types will be required to unravel identity of brainstem neurons involved in exploratory locomotion. Of note, some MLR neurons have been described to project directly to the spinal cord (Liang et al., 2012), but possible functional implications have not been tested.

The search for dissecting cell types according to a locomotion-attenuating activity in the lower brainstem has already provided more insight. Using developmental ontogeny as an entry point to stratify neurons, a study dissected the role of brainstem neurons expressing the transcription factor Chx10 in excitatory neurons (Bouvier et al., 2015). Optogenetic activation of Chx10 neurons in specific domains of the rostral medulla and caudal pons, but not the caudal medulla, attenuated ongoing locomotion (Figure 4D). Neuronal silencing by selective expression of a tetanus toxin variant led to behavioral hyperactivity with increased locomotion in an open field assay and a decreased ability to halt locomotion in a reward task. The study also demonstrates that the characterized excitatory Chx10 neurons connect to glycinergic spinal neurons that are likely mediators to execute behavioral arrest (Bouvier et al., 2015) (Figure 4D). There are also inhibitory brainstem neurons that can induce behavioral arrest (Capelli et al., 2017, Giber et al., 2015). Within the caudal medulla, separate optogenetic stimulation of each of four studied populations induced short-latency behavioral arrest during ongoing locomotion, ranging from simple stopping behavior to full-body collapse reminiscent of atonia (Capelli et al., 2017) (Figure 4A), suggesting that different populations are involved in dissimilar forms of behavioral arrest. Interestingly, glycinergic LPGi neurons connect to motor neurons, whereas intermingled LPGi-vGlut2 neurons needed for high-speed locomotion target mostly spinal neurons in intermediate

lamina where rhythm- and pattern-generating interneurons of the CPG reside, suggesting that functionally opposing brainstem populations act through different downstream circuits. Lastly, glycinergic neurons in the pontine reticular formation project to the intralaminar thalamic nucleus and optogenetic stimulation of their axon terminals induces behavioral arrest (Giber et al., 2015) (Figure 4E), indicating that also ascending brainstem pathways can indirectly impact locomotion controlling pathways.

The concept of brainstem neurons in the reticular formation acting as intermediaries to coordinate spinal locomotion is evolutionarily conserved. Lamprey serves as a successful model organism to dissect circuitry regulating locomotion that recapitulates many of the organizational principles seen in mammals (Grillner, 2003, Ryczko and Dubuc, 2013). A recent calcium imaging study analyzed neurons in the reticular formation during MLR stimulation (Juvin et al., 2016) and identified three types of reticulospinal neurons based on their response properties (Figure 4F). One neuronal population maintained firing activity throughout the duration of MLR stimulation (i.e., maintain cells), a second exhibited a firing burst at the onset of MLR stimulation (i.e., start cells), and a third showed a two-phasic activity profile with a burst at the onset and another one at offset of MLR stimulation coinciding with the stop of swimming (i.e., stop cells). Because stop cells exhibited a spatially slightly segregated location from the other two cell types, the authors carried out local pharmacological gain- and loss-of-function experiments and found that while stop cell region activation terminated ongoing swimming, inactivation prolonged swimming (Juvin et al., 2016). Upstream drivers responsible for the different neuronal activity phases of the identified stop, maintain, and start cells are currently unknown. Lower organisms also have highly developed circuits to mediate rapid escape behavior and one well-understood brainstem cell type is the Mauthner cell extensively studied in fish and amphibia (Gahtan and Baier, 2004,

Hale et al., 2016). The activation of a single Mauthner cell by mostly unilateral sensory information rapidly induces turning behavior away from dangerous stimuli. Thus, studies in evolutionarily less developed species underscore the fact that functionally diverse cell types tuned to different locomotor parameters exist within the reticular formation and are embedded in specific circuits to process relevant inputs and transmit their output to spinal circuits for execution.

Upstream Circuitry Supporting Locomotor Behavior from Exploration to Escape

One key question is how an animal selects the appropriate locomotor behavior, as well as its vigor, aligned with environmental constraints and needs. As summarized in work above, an important contributor to determine the vigor of a locomotor behavior in its execution phase from low-speed exploration to high-speed escape behavior is the recruitment of specific and distinct circuit elements within the broader MLR area. Conceptual division of locomotion into three categories has been proposed to be computed by different forebrain regions, reflecting the contexts in which locomotion is performed (Sinnamon, 1993). The described categories and structures would be exploratory locomotion (i.e., actively selected by volition and through the BG), primary appetitive locomotion (i.e., promoted by the lateral hypothalamus), and primary defensive locomotion (regulated by the medial hypothalamus and the PAG). These rostral regions would signal through selected MLR-reticulo-spinal networks to orchestrate behavioral execution (Jordan, 1998). Recent studies have addressed these concepts and dissected cell-type identity of the more rostral brain structures involved in context-specific forms of locomotion. We will

discuss the organization and function of these upstream structures with the goal to explain how appropriate locomotor vigor along a continuous scale can be implemented to regulate locomotion.

Supraspinal Regulation of Locomotion through Basal Ganglia Circuits

The BG are interconnected brain structures that are involved in motor program selection (Albin et al., 1989, Chakravarthy et al., 2010, DeLong, 1990). The different components of the BG motor loop are connected in an interactive network that integrates and processes information from the cortex and thalamus. In such a model, the combined computations of these BG-thalamo-cortical circuits influence the activity of brainstem motor circuits to select the movement to be executed in a volitional context (Hikosaka et al., 2000). BG activity is also modulated at several levels by dopaminergic neurons residing in the midbrain VTA and SNc, providing crucial signals for motivation and movement initiation and vigor, respectively (Cohen et al., 2012, da Silva et al., 2018, Howe and Dombeck, 2016) (Figure 5A).

Despite its complex organization, the BG motor loop has been classically divided into two major pathways, diverging at the level of the striatum, the major BG input structure (Figure 5A). Two classes of GABAergic striatal spiny projection neurons (SPNs) stratify by distinct projection patterns and by differential expression of dopamine receptors D1 and D2 (Albin et al., 1989, Kreitzer and Malenka, 2008). D1-SPNs are the origin of the direct pathway and project to the main and inhibitory BG output structures, the internal globus pallidus (GPi, in rodents mostly referred to as entopeduncular nucleus) and the substantia nigra reticulata (SNr). D2-SPNs form the indirect pathway with the external globus pallidus (GPe) and the subthalamic nucleus (STN)

as intermediate targets. However, the view of BG circuits being two parallel pathways independently influencing BG output structures is clearly too simplistic and the two pathways are interconnected at different levels (Cazorla et al., 2014, Mallet et al., 2012, Taverna et al., 2008).

Functionally, the classical model regarded the direct and indirect pathways as prokinetic and antikinetic, respectively (Albin et al., 1989, DeLong, 1990). This notion was supported by optogenetic experiments showing that D1-SPN activation throughout a broad striatal region enhances movement and D2-SPN activation produces bradykinesia (Kravitz et al., 2010). However, recent evidence monitoring neuronal activity of striatal subpopulations during natural behaviors points to a more complex involvement of BG circuitry in movement regulation. Endogenous neuronal activity of the two striatal subpopulations demonstrated that both D1- and D2-SPNs are active during movement initiation and execution (Barbera et al., 2016, Cui et al., 2013, Jin et al., 2014, Klaus et al., 2017, Parker et al., 2018, Tecuapetla et al., 2014). In addition, the activity of each neuronal population is necessary for the proper execution of an intended movement (Tecuapetla et al., 2014, Tecuapetla et al., 2016) and sufficient to bidirectionally modulate the speed of ongoing movement without affecting action selection (Yttri and Dudman, 2016). It is therefore likely that dedicated neuronal ensemble activity within the striatum, composed of D1- and D2-SPNs, is involved in movement orchestration. Such SPN ensembles could be viewed as the functional units of the striatum contributing to the selection of concrete forms of movement such as locomotion. In agreement with this model, D1 or D2 functional ensembles coherently active during locomotion are spatially closer and more correlated to each other than neurons engaged in other forms of movement (Figure 5B) (Barbera et al., 2016, Klaus et al., 2017, Parker et al., 2018), suggesting that different actions likely recruit mostly distinct subpopulations of SPNs.

When focusing on descending motor pathway function, understanding how BG link to locomotor output circuitry is an important question. Optogenetic stimulation of D1- or D2-SPNs elicits opposing neuronal activity changes in glutamatergic MLR neurons (Figure 5C) (Roseberry et al., 2016). Furthermore, initiation of head-fixed treadmill locomotion upon bilateral stimulation of dorso-medial striatal D1-SPNs correlates with and depends on glutamatergic MLR neuron activity, whereas analogous experiments with D2-SPNs stop ongoing locomotion by decreasing the firing rate of glutamatergic MLR neurons (Roseberry et al., 2016). The involved anatomical link between D1 and D2 striatal neurons and glutamatergic MLR neurons has not been directly addressed, but it is thought that the SNr, the most prominent BG output structure in rodents (Alam et al., 2011, Hikosaka et al., 2000), provides tonic inhibitory control to MLR neurons (Garcia-Rill et al., 1985, Mori, 1987, Noda and Oka, 1984). Indeed, glutamatergic MLR neurons receive inhibitory input from GABAergic SNr neurons (Roseberry et al., 2016) that mostly target the PPN (Caggiano et al., 2018). In addition, individual SNr neurons are modulated by the activity of D1- and D2 SPNs (Figure 5D) (Freeze et al., 2013, Kravitz et al., 2010, Tecuapetla et al., 2016). Interestingly, optogenetic activation of either D1- or D2-SPNs produces heterogeneous responses in the SNr, with some neurons being excited and others inhibited by activation of each pathway. However, only SNr neurons suppressed by D1-SPN activation predict locomotion initiation, while D2-SPN-induced movement arrest was most strongly correlated with the activity of excited SNr neurons (Freeze et al., 2013). These activity changes in locomotion-related SNr neurons are probably transmitted downstream to glutamatergic MLR neurons, which influence locomotion. Although it is unknown whether locomotion-predictive SNr neurons are preferentially connected to locomotion-promoting neurons in the MLR, this is certainly an interesting possibility.

While these results support the idea that the BG output nucleus SNr constitutes a gate for movement, they also underscore the complexity of intrinsic SNr and BG organization, where likely neuronal subpopulations specialize in the regulation of different aspects of movement. In addition to the SNr, the MLR also receives input from other BG structures, such as the GPi, the striatum, and the STN (Caggiano et al., 2018, Roseberry et al., 2016), but the functional significance of SNr-bypassing circuits remains unaddressed.

BG circuits are also influenced by neuromodulators, most notably dopamine. The essential role of dopamine is most strikingly revealed in Parkinson's patients, whose dopamine-depleted state is associated with akinesia and bradykinesia (Albin et al., 1989, Dauer and Przedborski, 2003, DeLong, 1990) and for whom dopamine replacement therapy provides the main intervention to alleviate symptoms. Early work suggested that dopamine might act as a modulator of striatal and cortical firing by activating striatal D1-SPNs and repressing D2-SPNs. However, augmenting or lowering dopamine signaling does not alter striatal and cortical firing rates similarly across the board but rather influences individual neurons differentially (Costa et al., 2006). Following the same striatal neurons using calcium imaging across different dopaminergic states in a mouse model demonstrated that D1-SPNs and D2-SPNs respond differently to altered dopamine levels (Parker et al., 2018). Interestingly, movement-related activity of D2-SPNs in the dopamine-depleted state became less spatially biased and less correlated to movement on- and offset, whereas D1-SPNs showed analogous response pattern changes in the hyper-dopaminergic state (Parker et al., 2018). To more clearly resolve the temporal and behavioral role of SNc dopamine signaling in the regulation of locomotion and movement in general, several recent studies used high spatial precision at the level of single neurons or axons (da Silva et al., 2018, Dodson et al.,

2016, Howe and Dombeck, 2016, Parker et al., 2018). Notably, movement-related dopaminergic SNc neurons do not only signal by slow tonic activity, but also display phasic bursting activity shortly before the onset of locomotion or other self-paced movements (Figure 5E). These observations suggest that locomotion-related dopamine signals can act at fast sub-second timescales, an activity pattern affected in a mouse model of Parkinson's disease (Dodson et al., 2016).

Calcium imaging of individual midbrain dopaminergic axons in the striatum revealed that locomotor- and reward-related signals were largely found in different axons, suggesting spatial and functional segregation (Howe and Dombeck, 2016). Supporting a role of dopaminergic SNc neurons in movement initiation, but not maintenance, their optogenetic stimulation increases the probability for movement initiation, whereas optogenetic inhibition only affects resting, but not moving, animals by decreasing the probability of movement initiation (da Silva et al., 2018). Interestingly, the SNc dopamine signal is not specific for a certain type of movement such as locomotion but rather represents a more general "go" signal and encodes the vigor of an upcoming movement (da Silva et al., 2018, Howe and Dombeck, 2016) (Figure 5E). Therefore, dopamine might provide a general motivational signal that modulates activity throughout the BG network, influencing the initiation of context-adequate movements with desired vigor. Such context-dependent modulation by dopamine could help to explain the heterogeneity of movement-related activity patterns observed in different SPN classes. Furthermore, in the specific case of locomotion, BG-imposed vigor needs to be translated into the desired speed of body translocation mediated by downstream brainstem centers, where speed-encoding neurons reside and receive input from BG output structures (Caggiano et al., 2018, Roseberry et al., 2016). It is also interesting to reflect on the fact that initiation of locomotion requires the

simultaneous suppression of competing limb-dependent movements (such as grooming, scratching, or reaching) through precise orchestration of activity between BG-thalamo-cortical circuits and brainstem centers. Although important questions remain to be addressed pertaining to how brainstem centers are regulated by dopaminergic signals influencing action initiation and vigor, these combined recent results call for an updated view on the role of dopaminergic SNc neurons and BG pathways in locomotion and movement in general.

How Circuits for Behavioral Needs and Contexts Interface with Action Programs

While BG are essential for the smooth execution of planned movements, including exploratory or goal-directed locomotion, locomotion can also be strongly shaped by emotional valence of a behavioral context as well as internal physiological needs. These internal and external cues can lead to abrupt changes of locomotor states, overriding ongoing plans and the complex information processing they entail. Escaping and hunting are examples of such behaviors classified as primary defensive and appetitive motivational locomotor forms (Sinnamon, 1993). We will discuss selected examples of circuits influencing defensive (escaping and freezing) and predatory (hunting) actions to illustrate this point, with a focus on their locomotor components. Brain structures implicated in these behaviors and mentioned here are hypothalamic nuclei, the central amygdala (CeA), and the superior colliculus. A frequent pattern of these upstream structures is the convergence of some of their outputs to the PAG, an intermediary midbrain structure between regions encoding internal and external states and locomotor executive centers in the brainstem (Figure 6A). It is important to note that the nervous system output accompanying innate responses goes well beyond the locomotion aspects discussed here, including other motor

outputs (such as capture, biting, tail rattling, stretch posture, and actions related to internal needs, including hunger, fear, social, and sexual behavior) as well as autonomic responses (Fadok et al., 2018, Stuber and Wise, 2016).

Exposure to threatening situations, such as predators, induces a state of increased anxiety and fear. Two opposing reactive responses affecting locomotor states are flight, a high-speed form of locomotion intended to escape from a threat, and freezing, a sudden arrest of body movement intended to avoid detection. Freezing is produced by activation of glutamatergic lateral and ventrolateral PAG (l/vlPAG) neurons with connections to medullary premotor neurons, while flight is mediated by activation of glutamatergic neurons in the dorso-lateral PAG (dlPAG) (Figure 6B) (Tovote et al., 2016). Also, excitatory neurons in a more dorsal region of the PAG (dPAG) can control escape behavior and its vigor by receiving processed visual information about looming stimuli from superior collicular neurons (Evans et al., 2018). The target regions that mediate escaping responses of d/dlPAG circuits have not yet been described, but glutamatergic CnF and/or LPGi neurons might be direct or indirect targets, since both receive input from more dorsal regions of the PAG and control high-speed locomotion (Caggiano et al., 2018, Capelli et al., 2017). Lastly, defensive behavior can be elicited by neurons in the superior colliculus marked by parvalbumin, whose axons bypass PAG circuitry altogether, inducing escape followed by freezing through outputs to the parabigeminal nucleus and immediate freezing via the lateral posterior thalamic nucleus (LPTN) (Figure 6C) (Shang et al., 2018).

The situation is clearly more complex than simple PAG input-output transmission since intra-PAG circuitry is involved in guiding appropriate behavioral responses. Notably, GABAergic l/vlPAG interneurons locally inhibit freeze-neurons and can act as a switch to ensure that the

execution of flight and freezing motor programs are mutually exclusive (Tovote et al., 2016). In support, freezing information is transmitted by long-range inhibitory projections from the CeA that decrease the activity of GABAergic l/vlPAG interneurons with consequent disinhibition of l/vlPAG freeze-neurons. On the other hand, dlPAG flight-neurons contact and likely excite GABAergic l/vlPAG interneurons, thus silencing l/vlPAG freeze-neurons (Tovote et al., 2016). Additionally, glutamatergic lateral hypothalamus (LH) flight-neurons (Li et al., 2018) could also connect to the GABAergic l/vlPAG interneurons and silence the l/vlPAG freeze-neurons, similar to the excitatory dlPAG flight-neurons. Lastly, neurons in the dorsomedial and central parts of the ventromedial hypothalamus (VMHdm/c) tailor their function according to environmental cues, with a population defined by the expression of Steroidogenic factor 1 (SF1) promoting the expression of either freezing or escaping responses depending on the magnitude of their activation and whether or not a shelter is present (Figure 6D) (Wang et al., 2015). Whereas flight responses are transmitted via projections to the AHN, freezing responses pass via descending projections to the dPAG, suggesting that SF1-expressing VMHdm/c neurons might even be further divisible.

The PAG is also a central player in the regulation of predatory hunting, for which prey pursuit requires suppression of glutamatergic l/vlPAG neurons (Figure 6D) (Han et al., 2017, Li et al., 2018). Individual GABAergic CeA neurons encode pursuit, capture, and consumption during predatory hunting, and CeA pursuit-phase locomotor signals are conveyed to the l/vlPAG (Han et al., 2017). Predation-encoding GABAergic neurons projecting to l/vlPAG were also identified in the LH (Li et al., 2018). But whereas optogenetic stimulation of l/vlPAG-projecting CeA neurons elicited only prey pursuit (Han et al., 2017), the analogous experiment with LH neurons additionally induced prey capture and consumption and even led to conspecific attacks (Li et al.,

2018), suggesting only partially overlapping information coding for these two populations. Evidence is still insufficient to conclude whether the glutamatergic l/vlPAG neurons inhibited during predation are the same neurons active during freezing (Han et al., 2017, Li et al., 2018, Tovote et al., 2016) and what the precise downstream targets receiving their output signals are. Although data suggest that the predatory signal is conveyed to the MLR, it will be important to clarify which MLR subpopulations are targeted by these glutamatergic l/vlPAG neurons suppressed during predatory hunting (Figure 6D). Glutamatergic MLR neurons seem unlikely candidates, as they are active during locomotion and receive most of their PAG input from dorsal domains (Caggiano et al., 2018, Roseberry et al., 2016). Instead, GABAergic MLR neurons might be candidates as they receive direct input from the PAG and exert local inhibitory effects on glutamatergic neurons (Roseberry et al., 2016).

In summary, innate forms of locomotion involve many neuronal subpopulations located in the mid- and forebrain (Figures 6B–6D). The LH segregates neurons involved in predatory and escaping locomotion, while the CeA promotes both hunting and freezing. Several appetitive and defensive locomotion motives are also present in the PAG as a key intermediary structure. Revealing the detailed functional links between escape and predation-related PAG neurons and connected output brainstem neurons will contribute to understanding whether these functionally distinct channels extend into downstream circuits or whether they align with the described speed-related populations distributed between PPN for exploration and CnF for fast locomotion.

Outlook

Supraspinal circuits involved in the control of locomotion are distributed over many brain areas, making their comprehensive understanding a challenging task. Yet it has become clear that for many behavioral choices linked to locomotion, neuronal populations encoding and responsible for the implementation of specific functional attributes of locomotion are embedded in complex circuitry and can be recruited by different encountered contexts. The networks described in this Review represent only a fraction of involved circuits, and as circuit dissection proceeds, connectivity matrices and functions will be understood better. Also other brain structures, including the cerebellum and the cortex, not described here contribute to shaping appropriate locomotor responses. Finally, another important question to consider will be how behavioral choice occurs at a more general level to select locomotion over the many other behaviors an animal can execute, for which supraspinal circuits are also responsible. Answers to all of these questions lie buried deep in the intricate circuitry of the brain.

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References

M. Alam, K. Schwabe, J.K. Krauss. The pedunculopontine nucleus area: critical evaluation of interspecies differences relevant for its use as a target for deep brain stimulation. Brain, 134 (2011), pp. 11-23

W.A. Alaynick, T.M. Jessell, S.L. Pfaff. SnapShot: spinal cord development. Cell, 146 (2011), pp. 178-178.e1

R.L. Albin, A.B. Young, J.B. Penney. The functional anatomy of basal ganglia disorders. Trends Neurosci., 12 (1989), pp. 366-375

K. Ampatzis, J. Song, J. Ausborn, A. El Manira. Pattern of innervation and recruitment of different classes of motoneurons in adult zebrafish. J. Neurosci., 33 (2013), pp. 10875-10886

K. Ampatzis, J. Song, J. Ausborn, A. El Manira. Separate microcircuit modules of distinct v2a interneurons and motoneurons control the speed of locomotion. Neuron, 83 (2014), pp. 934-943

S. Arber. Motor circuits in action: specification, connectivity, and function. Neuron, 74 (2012), pp. 975-989

G. Barbera, B. Liang, L. Zhang, C.R. Gerfen, E. Culurciello, R. Chen, Y. Li, D.T. Lin. Spatially compact neural clusters in the dorsal striatum encode locomotion relevant information. Neuron, 92 (2016), pp. 202-213

C. Bellardita, O. Kiehn. Phenotypic characterization of speed-associated gait changes in mice reveals modular organization of locomotor networks. Curr. Biol., 25 (2015), pp. 1426-1436

J.B. Bikoff, M.I. Gabitto, A.F. Rivard, E. Drobac, T.A. Machado, A. Miri, S. Brenner-Morton, E. Famojure, C. Diaz, F.J. Alvarez, et al. Spinal inhibitory interneuron diversity delineates variant motor microcircuits. Cell, 165 (2016), pp. 207-219

J. Bouvier, V. Caggiano, R. Leiras, V. Caldeira, C. Bellardita, K. Balueva, A. Fuchs, O. Kiehn. Descending command neurons in the brainstem that halt locomotion. Cell, 163 (2015), pp. 1191-1203

R.M. Brownstone, J.W. Chopek. Reticulospinal systems for tuning motor commands. Front. Neural Circuits, 12 (2018), p. 30

V. Caggiano, R. Leiras, H. Goñi-Erro, D. Masini, C. Bellardita, J. Bouvier, V. Caldeira, G. Fisone, O. Kiehn. Midbrain circuits that set locomotor speed and gait selection. Nature, 553 (2018), pp. 455-460

P. Capelli, C. Pivetta, M.S. Esposito, S. Arber. Locomotor speed control circuits in the caudal brainstem. Nature, 551 (2017), pp. 373-377

M. Cazorla, F.D. de Carvalho, M.O. Chohan, M. Shegda, N. Chuhma, S. Rayport, S.E. Ahmari, H. Moore, C. Kellendonk. Dopamine D2 receptors regulate the anatomical and functional balance of basal ganglia circuitry. Neuron, 81 (2014), pp. 153-164

V.S. Chakravarthy, D. Joseph, R.S. Bapi. What do the basal ganglia do? A modeling perspective. Biol. Cybern., 103 (2010), pp. 237-253

J.T. Choi, A.J. Bastian. Adaptation reveals independent control networks for human walking. Nat. Neurosci., 10 (2007), pp. 1055-1062

J.Y. Cohen, S. Haesler, L. Vong, B.B. Lowell, N. Uchida. Neuron-type-specific signals for reward and punishment in the ventral tegmental area. Nature, 482 (2012), pp. 85-88

R.M. Costa, S.-C. Lin, T.D. Sotnikova, M. Cyr, R.R. Gainetdinov, M.G. Caron, M.A.L. Nicolelis. Rapid alterations in corticostriatal ensemble coordination during acute dopamine-dependent motor dysfunction. Neuron, 52 (2006), pp. 359-369

S.A. Crone, G. Zhong, R. Harris-Warrick, K. Sharma. In mice lacking V2a interneurons, gait depends on speed of locomotion. J. Neurosci., 29 (2009), pp. 7098-7109

G. Cui, S.B. Jun, X. Jin, M.D. Pham, S.S. Vogel, D.M. Lovinger, R.M. Costa. Concurrent activation of striatal direct and indirect pathways during action initiation. Nature, 494 (2013), pp. 238-242

J.A. da Silva, F. Tecuapetla, V. Paixão, R.M. Costa. Dopamine neuron activity before action initiation gates and invigorates future movements. Nature, 554 (2018), pp. 244-248

W. Dauer, S. Przedborski. Parkinson's disease: mechanisms and models. Neuron, 39 (2003), pp. 889-909

D. Dautan, A.S. Souza, I. Huerta-Ocampo, M. Valencia, M. Assous, I.B. Witten, K. Deisseroth, J.M. Tepper, J.P. Bolam, T.V. Gerdjikov, J. Mena-Segovia. Segregated cholinergic transmission modulates dopamine neurons integrated in distinct functional circuits. Nat. Neurosci., 19 (2016), pp. 1025-1033

M.R. DeLong. Primate models of movement disorders of basal ganglia origin. Trends Neurosci., 13 (1990), pp. 281-285

R. Depoortere, G. Sandner, G. Di Scala. Aversion induced by electrical stimulation of the mesencephalic locomotor region in the intact and freely moving rat. Physiol. Behav., 47 (1990), pp. 561-567

V. Dietz. Behavior of spinal neurons deprived of supraspinal input. Nat. Rev. Neurol., 6 (2010), pp. 167-174

P.D. Dodson, J.K. Dreyer, K.A. Jennings, E.C.J. Syed, R. Wade-Martins, S.J. Cragg, J.P. Bolam, P.J. Magill. Representation of spontaneous movement by dopaminergic neurons is cell-type selective and disrupted in parkinsonism. Proc. Natl. Acad. Sci. USA, 113 (2016), pp. E2180-E2188

T. Drew, S. Rossignol. Functional organization within the medullary reticular formation of intact unanesthetized cat. I. Movements evoked by microstimulation. J. Neurophysiol., 64 (1990), pp. 767-781

M.S. Esposito, P. Capelli, S. Arber. Brainstem nucleus MdV mediates skilled forelimb motor tasks. Nature, 508 (2014), pp. 351-356

D.A. Evans, A.V. Stempel, R. Vale, S. Ruehle, Y. Lefler, T. Branco. A synaptic threshold mechanism for computing escape decisions. Nature, 558 (2018), pp. 590-594

J.P. Fadok, M. Markovic, P. Tovote, A. Lüthi. New perspectives on central amygdala function. Curr. Opin. Neurobiol., 49 (2018), pp. 141-147

H. Forssberg, S. Grillner, J. Halbertsma, S. Rossignol. The locomotion of the low spinal cat. II. Interlimb coordination. Acta Physiol. Scand., 108 (1980), pp. 283-295

C. Francius, A. Harris, V. Rucchin, T.J. Hendricks, F.J. Stam, M. Barber, D. Kurek, F.G. Grosveld, A. Pierani, M. Goulding, F. Clotman. Identification of multiple subsets of ventral interneurons and differential distribution along the rostrocaudal axis of the developing spinal cord. PLoS ONE, 8 (2013), p. e70325

B.S. Freeze, A.V. Kravitz, N. Hammack, J.D. Berke, A.C. Kreitzer. Control of basal ganglia output by direct and indirect pathway projection neurons. J. Neurosci., 33 (2013), pp. 18531-18539

E. Gahtan, H. Baier. Of lasers, mutants, and see-through brains: functional neuroanatomy in zebrafish. J. Neurobiol., 59 (2004), pp. 147-161

E. Garcia-Rill, R.D. Skinner, J.A. Fitzgerald. Chemical activation of the mesencephalic locomotor region. Brain Res., 330 (1985), pp. 43-54

E. Garcia-Rill, C.R. Houser, R.D. Skinner, W. Smith, D.J. Woodward. Locomotion-inducing sites in the vicinity of the pedunculopontine nucleus. Brain Res. Bull., 18 (1987), pp. 731-738

K. Giber, M.A. Diana, V. Plattner, G.P. Dugué, H. Bokor, C.V. Rousseau, Z. Maglóczky, L. Havas, B. Hangya, H. Wildner, et al. A subcortical inhibitory signal for behavioral arrest in the thalamus. Nat. Neurosci., 18 (2015), pp. 562-568

M. Goulding. Circuits controlling vertebrate locomotion: moving in a new direction. Nat. Rev. Neurosci., 10 (2009), pp. 507-518

S. Grillner. The motor infrastructure: from ion channels to neuronal networks. Nat. Rev. Neurosci., 4 (2003), pp. 573-586

S. Grillner, T.M. Jessell. Measured motion: searching for simplicity in spinal locomotor networks. Curr. Opin. Neurobiol., 19 (2009), pp. 572-586

S. Grillner, A.P. Georgopoulos, L.M. Jordan. Selection and initiation of motor behavior. P.S.G. Stein, S. Grillner, A.I. Selverston, D.G. Stuart (Eds.). Neurons, Networks, and Motor Behavior, The MIT Press (1997), pp. 3-19

J.M. Halbertsma. The stride cycle of the cat: the modelling of locomotion by computerized analysis of automatic recordings. Acta Physiol. Scand. Suppl., 521 (1983), pp. 1-75

M.E. Hale, H.R. Katz, M.Y. Peek, R.T. Fremont. Neural circuits that drive startle behavior, with a focus on the Mauthner cells and spiral fiber neurons of fishes. J. Neurogenet., 30 (2016), pp. 89-100

W. Han, L.A. Tellez, M.J. Rangel Jr., S.C. Motta, X. Zhang, I.O. Perez, N.S. Canteras, S.J. Shammah-Lagnado, A.N. van den Pol, I.E. de Araujo. Integrated control of predatory hunting by the central nucleus of the amygdala. Cell, 168 (2017), pp. 311-324.e18

M. Hayashi, C.A. Hinckley, S.P. Driscoll, N.J. Moore, A.J. Levine, K.L. Hilde, K. Sharma, S.L. Pfaff. Graded arrays of spinal and supraspinal V2a interneuron subtypes underlie forelimb and hindlimb motor control. Neuron, 97 (2018), pp. 869-884.e5

O. Hikosaka, Y. Takikawa, R. Kawagoe. Role of the basal ganglia in the control of purposive saccadic eye movements. Physiol. Rev., 80 (2000), pp. 953-978

M.W. Howe, D.A. Dombeck. Rapid signalling in distinct dopaminergic axons during locomotion and reward. Nature, 535 (2016), pp. 505-510

T.M. Jessell. Neuronal specification in the spinal cord: inductive signals and transcriptional codes. Nat. Rev. Genet., 1 (2000), pp. 20-29

X. Jin, F. Tecuapetla, R.M. Costa. Basal ganglia subcircuits distinctively encode the parsing and concatenation of action sequences. Nat. Neurosci., 17 (2014), pp. 423-430

L.M. Jordan. Initiation of locomotion in mammals. Ann. N Y Acad. Sci., 860 (1998), pp. 83-93

N. Josset, M. Roussel, M. Lemieux, D. Lafrance-Zoubga, A. Rastqar, F. Bretzner. Distinct contributions of mesencephalic locomotor region nuclei to locomotor control in the freely behaving mouse. Curr. Biol., 28 (2018), pp. 884-901.e3

L. Juvin, S. Grätsch, E. Trillaud-Doppia, J.F. Gariépy, A. Büschges, R. Dubuc. A specific population of reticulospinal neurons controls the termination of locomotion. Cell Rep., 15 (2016), pp. 2377-2386

O. Kiehn. Decoding the organization of spinal circuits that control locomotion. Nat. Rev. Neurosci., 17

N. Kinjo, Y. Atsuta, M. Webber, R. Kyle, R.D. Skinner, E. Garcia-Rill. Medioventral medulla-induced locomotion. Brain Res. Bull., 24 (1990), pp. 509-516

A. Klaus, G.J. Martins, V.B. Paixao, P. Zhou, L. Paninski, R.M. Costa. The spatiotemporal organization of the striatum encodes action space. Neuron, 95 (2017), pp. 1117-1180

S.C. Koch, M.G. Del Barrio, A. Dalet, G. Gatto, T. Günther, J. Zhang, B. Seidler, D. Saur, R. Schüle, M. Goulding. RORβ spinal interneurons gate sensory transmission during locomotion to secure a fluid walking gait. Neuron, 96 (2017), pp. 1419-1431.e5

A.V. Kravitz, B.S. Freeze, P.R. Parker, K. Kay, M.T. Thwin, K. Deisseroth, A.C. Kreitzer. Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry. Nature, 466 (2010), pp. 622-626

A.C. Kreitzer, R.C. Malenka. Striatal plasticity and basal ganglia circuit function. Neuron, 60 (2008), pp. 543-554

D. Le Ray, L. Juvin, D. Ryczko, R. Dubuc. Chapter 4-Supraspinal control of locomotion: the mesencephalic locomotor region. Prog. Brain Res., 188 (2011), pp. 51-70

A.M. Lee, J.L. Hoy, A. Bonci, L. Wilbrecht, M.P. Stryker, C.M. Niell. Identification of a brainstem circuit regulating visual cortical state in parallel with locomotion. Neuron, 83 (2014), pp. 455-466

M. Lemieux, N. Josset, M. Roussel, S. Couraud, F. Bretzner. Speed-dependent modulation of the locomotor behavior in adult mice reveals attractor and transitional gaits. Front. Neurosci., 10 (2016), p. 42

Y. Li, J. Zeng, J. Zhang, C. Yue, W. Zhong, Z. Liu, Q. Feng, M. Luo. Hypothalamic circuits for predation and evasion. Neuron, 97 (2018), pp. 911-924.e5

H. Liang, G. Paxinos, C. Watson. Spinal projections from the presumptive midbrain locomotor region in the mouse. Brain Struct. Funct., 217 (2012), pp. 211-219

N. Mallet, B.R. Micklem, P. Henny, M.T. Brown, C. Williams, J.P. Bolam, K.C. Nakamura, P.J. Magill. Dichotomous organization of the external globus pallidus. Neuron, 74 (2012), pp. 1075-1086

C. Martinez-Gonzalez, J.P. Bolam, J. Mena-Segovia. Topographical organization of the pedunculopontine nucleus. Front. Neuroanat., 5 (2011), p. 22

J. Mena-Segovia, J.P. Bolam. Rethinking the pedunculopontine nucleus: from cellular organization to function. Neuron, 94 (2017), pp. 7-18

S. Miller, F.G.A. van der Meché. Coordinated stepping of all four limbs in the high spinal cat. Brain Res., 109 (1976), pp. 395-398

M.S. Moehle, T. Pancani, N. Byun, S.E. Yohn, G.H. Wilson 3rd, J.W. Dickerson, D.H. Remke, Z. Xiang, C.M. Niswender, J. Wess, et al. Cholinergic projections to the substantia nigra pars reticulata inhibit dopamine modulation of basal ganglia through the M4 muscarinic receptor. Neuron, 96 (2017), pp. 1358-1372.e4

S. Mori. Integration of posture and locomotion in acute decerebrate cats and in awake, freely moving cats. Prog. Neurobiol., 28 (1987), pp. 161-195

S. Mori. Contribution of postural muscle tone to full expression of posture and locomotor movements: multi-faceted analyses of its setting brainstem-spinal cord mechanisms in the cat. Jpn. J. Physiol., 39 (1989), pp. 785-809

S. Mori, T. Sakamoto, Y. Ohta, K. Takakusaki, K. Matsuyama. Site-specific postural and locomotor changes evoked in awake, freely moving intact cats by stimulating the brainstem. Brain Res., 505 (1989), pp. 66-74

C.M. Niell, M.P. Stryker. Modulation of visual responses by behavioral state in mouse visual cortex. Neuron, 65 (2010), pp. 472-479

T. Noda, H. Oka. Nigral inputs to the pedunculopontine region: intracellular analysis. Brain Res., 322 (1984), pp. 332-336

G.N. Orlovsky, T.G. Deliagina, S. Grillner. Neuronal Control of Locomotion: From Mollusc to Man, Oxford University Press (1999)

J.G. Parker, J.D. Marshall, B. Ahanonu, Y.W. Wu, T.H. Kim, B.F. Grewe, Y. Zhang, J.Z. Li, J.B. Ding, M.D. Ehlers, M.J. Schnitzer. Diametric neural ensemble dynamics in parkinsonian and dyskinetic states. Nature, 557 (2018), pp. 177-182

P. Philippidou, J.S. Dasen. Hox genes: choreographers in neural development, architects of circuit organization. Neuron, 80 (2013), pp. 12-34

G.J. Romanes. The motor cell columns of the lumbo-sacral spinal cord of the cat. J. Comp. Neurol., 94 (1951), pp. 313-363

T.K. Roseberry, A.M. Lee, A.L. Lalive, L. Wilbrecht, A. Bonci, A.C. Kreitzer. Cell-type-specific control of brainstem locomotor circuits by basal ganglia. Cell, 164 (2016), pp. 526-537

G.S. Ross, H.M. Sinnamon. Forelimb and hindlimb stepping by the anesthetized rat elicited by electrical stimulation of the pons and medulla. Physiol. Behav., 33 (1984), pp. 201-208

S. Rossignol, R. Dubuc, J.P. Gossard. Dynamic sensorimotor interactions in locomotion. Physiol. Rev., 86 (2006), pp. 89-154

L. Ruder, A. Takeoka, S. Arber. Long-distance descending spinal neurons ensure quadrupedal locomotor stability. Neuron, 92 (2016), pp. 1063-1078

D. Ryczko, R. Dubuc. The multifunctional mesencephalic locomotor region. Curr. Pharm. Des., 19 (2013), pp. 4448-4470

C. Shang, Z. Chen, A. Liu, Y. Li, J. Zhang, B. Qu, F. Yan, Y. Zhang, W. Liu, Z. Liu, et al. Divergent midbrain circuits orchestrate escape and freezing responses to looming stimuli in mice. Nat. Commun., 9 (2018), p. 1232

S.J. Shefchyk, R.M. Jell, L.M. Jordan. Reversible cooling of the brainstem reveals areas required for mesencephalic locomotor region evoked treadmill locomotion. Exp. Brain Res., 56 (1984), pp. 257-262

M.L. Shik, G.N. Orlovsky. Neurophysiology of locomotor automatism. Physiol. Rev., 56 (1976), pp. 465-501

M.L. Shik, F.V. Severin, G.N. Orlovskiĭ. [Control of walking and running by means of electric stimulation of the midbrain]. Biofizika, 11 (1966), pp. 659-666

H.M. Sinnamon. Preoptic and hypothalamic neurons and the initiation of locomotion in the anesthetized rat. Prog. Neurobiol., 41 (1993), pp. 323-344

R.D. Skinner, E. Garcia-Rill. The mesencephalic locomotor region (MLR) in the rat. Brain Res., 323 (1984), pp. 385-389

G.D. Stuber, R.A. Wise. Lateral hypothalamic circuits for feeding and reward. Nat. Neurosci., 19 (2016), pp. 198-205

L.B. Sweeney, J.B. Bikoff, M.I. Gabitto, S. Brenner-Morton, M. Baek, J.H. Yang, E.G. Tabak, J.S. Dasen, C.R. Kintner, T.M. Jessell. Origin and segmental diversity of spinal inhibitory interneurons. Neuron, 97 (2018), pp. 341-355.e3

K. Takakusaki, R. Chiba, T. Nozu, T. Okumura. Brainstem control of locomotion and muscle tone with special reference to the role of the mesopontine tegmentum and medullary reticulospinal systems. J Neural Transm (Vienna), 123 (2016), pp. 695-729

A.E. Talpalar, J. Bouvier, L. Borgius, G. Fortin, A. Pierani, O. Kiehn. Dual-mode operation of neuronal networks involved in left-right alternation. Nature, 500 (2013), pp. 85-88

S. Taverna, E. Ilijic, D.J. Surmeier. Recurrent collateral connections of striatal medium spiny neurons are disrupted in models of Parkinson's disease. J. Neurosci., 28 (2008), pp. 5504-5512

F. Tecuapetla, S. Matias, G.P. Dugue, Z.F. Mainen, R.M. Costa. Balanced activity in basal ganglia projection pathways is critical for contraversive movements. Nat. Commun., 5 (2014), p. 4315

F. Tecuapetla, X. Jin, S.Q. Lima, R.M. Costa. Complementary contributions of striatal projection pathways to action initiation and execution. Cell, 166 (2016), pp. 703-715

P. Tovote, M.S. Esposito, P. Botta, F. Chaudun, J.P. Fadok, M. Markovic, S.B. Wolff, C. Ramakrishnan, L. Fenno, K. Deisseroth, et al. Midbrain circuits for defensive behavior. Nature, 534 (2016), pp. 206-212

F. Wang, J. Zhu, H. Zhu, Q. Zhang, Z. Lin, H. Hu. Bidirectional control of social hierarchy by synaptic efficacy in medial prefrontal cortex. Science, 334 (2011), pp. 693-697

L. Wang, I.Z. Chen, D. Lin. Collateral pathways from the ventromedial hypothalamus mediate defensive behaviors. Neuron, 85 (2015), pp. 1344-1358

U. Windhorst. Muscle proprioceptive feedback and spinal networks. Brain Res. Bull., 73 (2007), pp. 155-202

C. Xiao, J.R. Cho, C. Zhou, J.B. Treweek, K. Chan, S.L. McKinney, B. Yang, V. Gradinaru. Cholinergic mesopontine signals govern locomotion and reward through dissociable midbrain pathways. Neuron, 90 (2016), pp. 333-347

J.H. Yoo, V. Zell, J. Wu, C. Punta, N. Ramajayam, X. Shen, L. Faget, V. Lilascharoen, B.K. Lim, T.S. Hnasko. Activation of pedunculopontine glutamate neurons is reinforcing. J. Neurosci., 37 (2017), pp. 38-46

E.A. Yttri, J.T. Dudman. Opponent and bidirectional control of movement velocity in the basal ganglia. Nature, 533 (2016), pp. 402-406

Figures

Figure 1. Temporal and Regulatory Categories of Locomotion

(A) Division of the locomotor process in three behavioral phases (initiation, locomotion, and termination).

(B) A locomotor episode can range from low-speed exploration to high-speed escaping, during which different locomotor speeds align with alternating or synchronous gait patterns, and can have different directions of the chosen trajectory (illustrated by three example mice; (1) low-speed exploration, (2) backward walking, and (3) high-speed locomotion).

Figure 2. Diversity and Specificity in Spinal Circuits for Execution of Locomotion

(A) Summary diagram of spinal circuits in zebrafish (left) and mice (right) implicated in the regulation of speed-linked locomotor parameters.

(B) Schematic summary of the role of RORβ-expressing spinal GABAergic neurons in sensory gating through presynaptic inhibition and influence on behavior.

(C) Rostro-caudal organization of spinal circuits based on Chx10-expression levels, Hox transcription factor expression (left), or the organization of descending projections from the cervical to the lumbar spinal cord and their influence on fore- and hindlimb coordination during locomotion (right).

(D) Proposed model of how supraspinal commands may signal locomotor parameters, including speed, gait, latency, or direction, to spinal executive microcircuits that in turn regulate locomotor output

Figure 3. Functional and Cellular Diversity of the Mouse MLR

(A) MLR processes contextual information and its descending pathways signal to caudal brainstem neurons to influence locomotor output.

(B) Summary diagram of historical electrical site-mapping experiments in the cat CnF and PPN to define locations influencing locomotion (see Takakusaki et al., 2016, for review).

(C) Schematic diagram summarizing recent findings on the role of mouse MLR-vGlut2 neurons subdivided by location within CnF (cuneiform nucleus) and PPN (pedunculopontine nucleus). Both CnF and PPN also contain vGAT neurons, but only PPN contains cholinergic neurons.

(D) Summary diagram of PPN-vGlut2 neuron projections to ascending targets and known implicated functions.

Figure 4. Brainstem Cell Types Regulating Locomotion

(A) Subdivision of ventral medulla into four regions (LPGi, lateral paragigantocellular nucleus; GiA, gigantocellular nucleus alpha; GiV, gigantocellular nucleus ventral; Gi, gigantocellular nucleus) all containing intermingled neurotransmitter (NT)-stratified (vGlut2/vGAT) neurons (7N demarcates facial motor nucleus). Table (right) summarizes behavioral findings from optogenetic activation experiments of different neuronal subpopulations.

(B and C) Ablation of LPGi-vGlut2 neurons impairs high-speed locomotion (B) and attenuates speed of locomotion induced by optogenetic stimulation of MLR-vGlut2 neurons (C).

(D) vGlut2 neurons expressing the transcription factor Chx10 in the rostral gigantocellular nucleus (Gi) implicated in halting by signaling through locomotion-inhibiting circuits in the spinal cord.

(E) Glycinergic neurons in the pontine reticular formation project ascendingly to the intralaminar nucleus of the thalamus (IL) to attenuate locomotion.

(F) Summary of firing properties of three populations of neurons in the lamprey reticular formation implicated in locomotor control.

Figure 5. Basal Ganglia Circuit Control of Locomotion

(A) Schematic diagram of the main feedforward connectivity by indirect (D2) and direct (D1) striatal spiny projection neurons (SPNs) within the basal ganglia, as well as their dopaminergic inputs.

(B) D1- and D2-SPNs containing striatal functional ensembles exhibit a proximity-biased spatial distribution, according to different behaviors (e.g., locomotion or rearing). Summary of their neuronal activity patterns is depicted on the right.

(C and D) Recording of MLR-vGlut2 (C) or SNr-inhibitory (D) neurons upon optogenetic stimulation of D1- or D2-SPNs. Note that not all SNr neurons are predictive of locomotor behavior, likely a reflection of further neuronal diversity yet to be identified.

(E) SNc-derived dopamine signaling to the dorsal striatum before movement initiation (e.g., locomotion) determines the vigor of the future executed action.

Figure 6. Circuits for Behavioral Need and Context Influencing Locomotion

(A) Periaqueductal gray (PAG) and associated structures are central in processing information about danger and needs in order to then signal through brainstem circuits to adjust locomotor state as part of numerous defensive and appetitive behaviors.

(B–D) Summary of functionally known (solid) and inferred (dashed) circuit organization for the PAG (B), superior colliculus (C), and forebrain circuits implicated in defensive and hunting behaviors (D). Neurons shown in boxes implies that there might be multiple neuronal subpopulations processing the shown inputs.

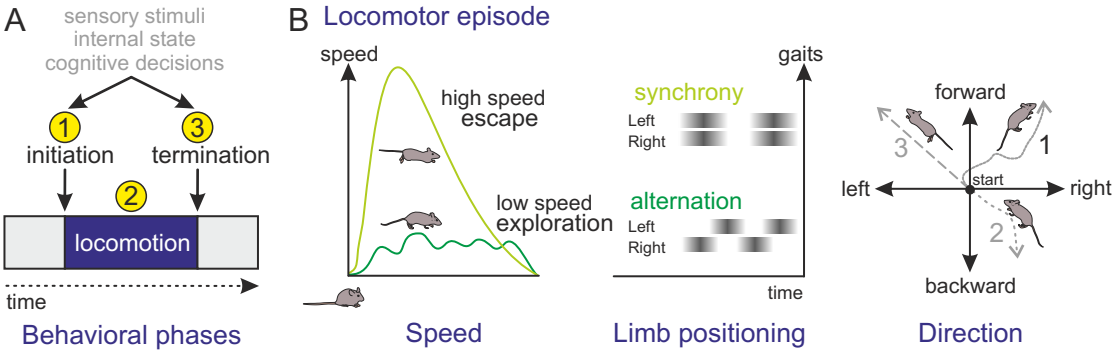

Figure 1. Temporal and regulatory categories of locomotion

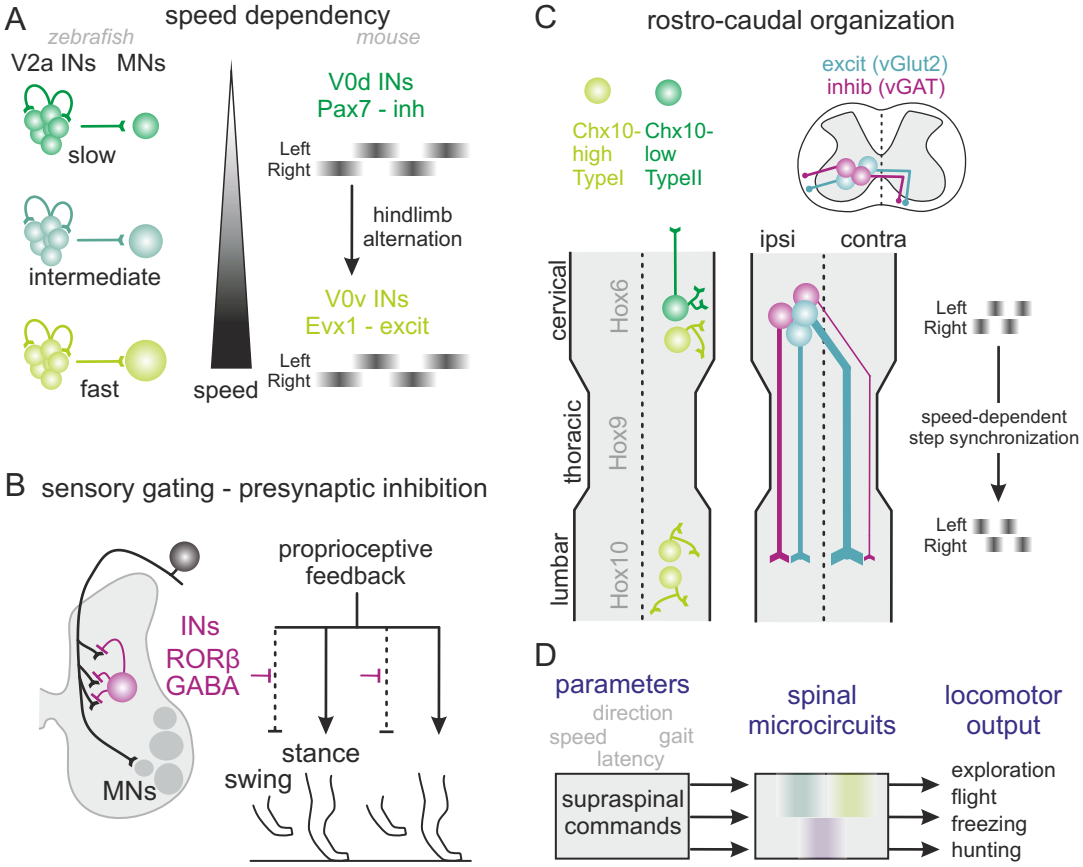

Figure 2. Diversity and specificity in spinal circuits for execution of locomotion

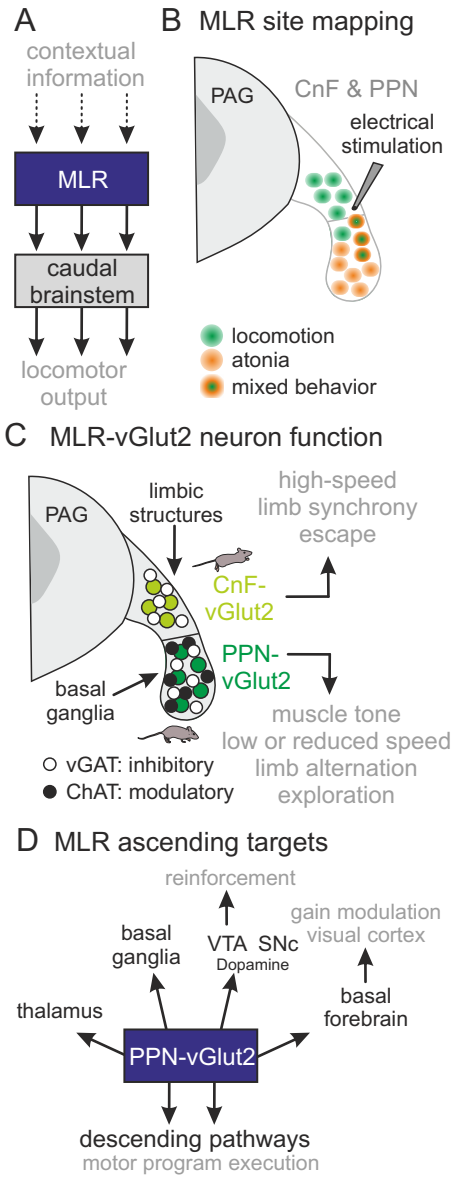

Figure 3. Functional and cellular diversity of the mouse MLR

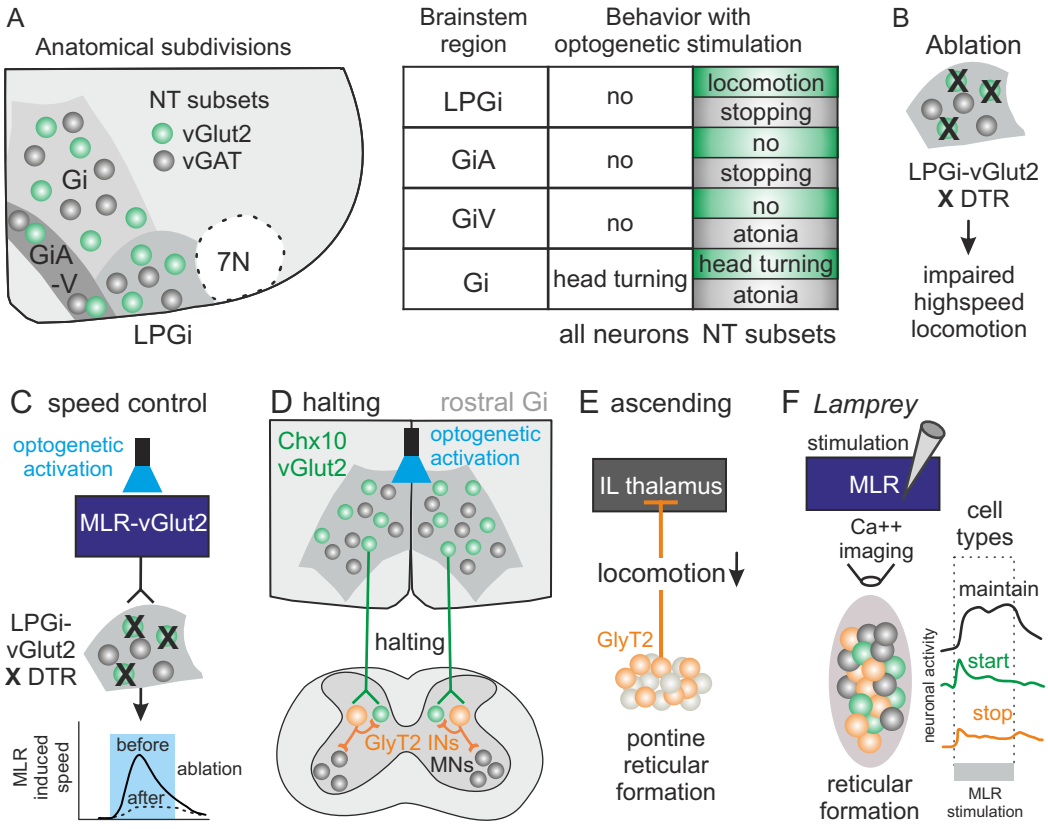

Figure 4. Brainstem cell types regulating locomotion

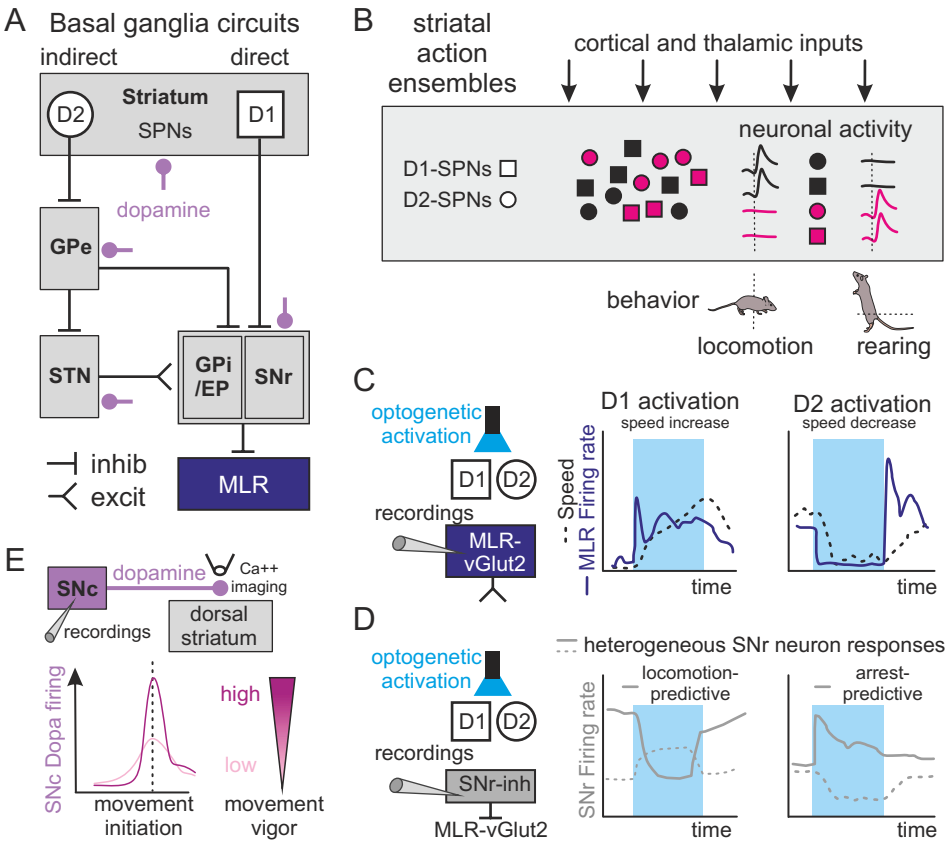

Figure 5. Basal ganglia circuit impact on locomotion

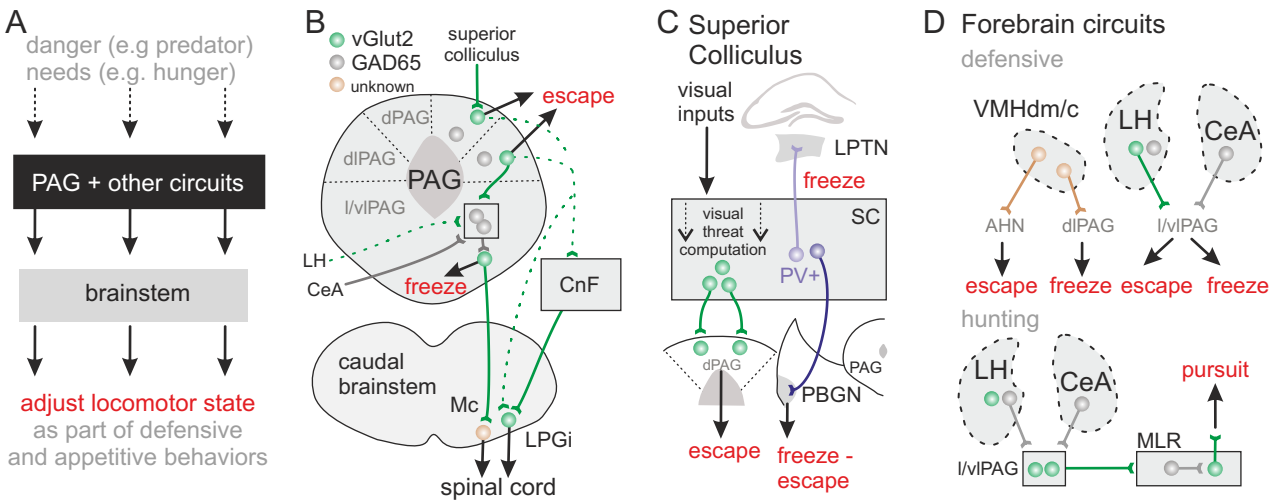

Figure 6. Circuits for behavioral need and context influencing locomotion