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Brainstem Circuits for Locomotion

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Abstract

Locomotion is a universal motor behavior that is expressed as the output of many integrated brain functions. Locomotion is organized at several levels of the nervous system, with brainstem circuits acting as the gate between brain areas regulating innate, emotional, or motivational locomotion and executive spinal circuits. Here we review recent advances on brainstem circuits involved in controlling locomotion. We describe how delineated command circuits govern the start, speed, stop, and steering of locomotion. We also discuss how these pathways interface between executive circuits in the spinal cord and diverse brain areas important for context-specific selection of locomotion. A recurrent theme is the need to establish a functional connectome to and from brainstem command circuits. Finally, we point to unresolved issues concerning the integrated function of locomotor control.

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INTRODUCTION

Locomotion is a fundamental motor behavior common to most animals and humans. It is used episodically in many of life's daily activities. Behavior is expressed through locomotion as an innate response to fear or hunger, a cognitive desire to move toward a goal, or an emotional urge to explore the environment, perhaps in search of a mate.

Seamless locomotion requires integrated action of motor circuits located at multiple levels of the nervous system. The execution of locomotion, which involves selection of specific muscles that are activated for exact periods of time with precise coordination, is in large part accomplished by activity in neuronal networks of the spinal cord itself. Spinal circuitries for locomotor execution have been studied for many years in phylogenetically diverse vertebrate models, allowing detailed insight as to their organization, and are extensively reviewed elsewhere (Goulding 2009; Grillner & El Manira 2020; Grillner & Jessell 2009; Kiehn 2006, 2016). Planning of locomotion takes place in supraspinal structures, including cortical motor areas and the basal ganglia. Immediate central control over spinal circuits, however, is located in the brainstem, which exerts control over the initiation, speed, termination, and direction of locomotor bouts. Brainstem circuits have traditionally been difficult to dissect due to their heterogeneous composition and borderless structures. However, critical advances in the organization of brainstem circuits are now emerging (Ruder & Arber 2019). The route to understanding these circuits has been paved by electrophysiological, molecular genetic, network, and behavioral approaches, which together link specific neuronal populations to distinct aspects of behavior.

In this review, we focus on brainstem circuits involved in controlling locomotion in mammals, with emphasis on recent advances in this area. We discuss how dedicated command circuits implement initiation, stop, and steering of locomotion and how these command circuits may interact with executive circuits in the spinal cord. We also address how brainstem locomotor circuits may be selected in different behavioral contexts and demonstrate how the clear delineation of the command circuits provides entry points for functional bottom-up analysis of higher brain functions that use locomotion as an output. Throughout the review, we point to the importance of establishing functional links of connectivity. We also point to unresolved issues about the integrated function of brain, brainstem, and spinal cord networks that control locomotion.

DESCENDING COMMAND FUNCTIONS FOR LOCOMOTION

Midbrain Nuclei Mediate Start and Speed of Locomotion and Selection of Gaits

A key function of locomotor control is the initiation or start of locomotion. Executive locomotor networks in the spinal cord are able to produce and maintain a locomotor output consisting of coordinated muscle activity when appropriately activated by unpatterned excitation. In the isolated spinal cord, this can be obtained by applying neuroactive substances directly to the cord (Grillner 2003, Harris-Warrick 2011, Kiehn 2006, Schmidt & Jordan 2000). In the intact animal, this excitatory command or start signal to spinal locomotor networks originates in supraspinal regions. Research to define this or these command regions has evolved over time, starting with seminal studies by Shik, Severin, and Orlovskiĭ (Shik et al. 1966), who discovered that an area in or around the cuneiform nucleus (CnF) in the midbrain initiates locomotion when electrically stimulated. Stimulation evoked different gaits, with walking at low stimulation intensity, trot at slightly higher intensity, and gallop at the highest stimulation intensity. The authors named this midbrain area the mesencephalic locomotor region (MLR). Since then, the presence of a functional MLR has been demonstrated in a variety of vertebrate species, including fish, birds, and legged mammals (Grillner et al. 1997, Jordan 1998, Ryczko & Dubuc 2013).

After these early studies, the nature and anatomical location of MLR remained a matter of debate. In addition to CnF, the pedunculopontine nucleus (PPN) was implicated as a major component of MLR. Many studies, including those in cats (Amemiya & Yamaguchi 1984; Mori et al. 1989; Opris et al. 2019; Shefchyk & Jordan 1985; Shefchyk et al. 1984; Sirota & Shik 1973; Takakusaki et al. 2003, 2016), monkeys (Eidelberg et al. 1981), guinea pigs (Marlinsky & Voitenko 1991), lamprey (Dubuc et al. 2008, Sirota et al. 2000), and rats (Brudzynski et al. 1986, Coles et al. 1989), showed that electrical stimulation or chemical activation of CnF was effective in initiating locomotion. Therefore, the CnF was suggested to be the main component of MLR as CnF exhibited the lowest threshold for initiating locomotion. In contrast, other studies using electrical or chemical stimulation indicated that the PPN in cats (Garcia-Rill et al. 1981) or the caudal PPN in rats (Brudzynski & Wang 1996, Garcia-Rill et al. 1985, Milner & Mogenson 1988, Skinner & Garcia-Rill 1984, Virmani et al. 2019) was the main component of MLR, and especially the large cholinergic neurons in caudal PPN. While electrical and chemical stimulation experiments pointed to the sufficiency of CnF and/or PPN for locomotor initiation, lesions aimed at establishing the necessity for locomotor initiation of these regions provided unclear and conflicting results (see Jordan 1998, Ryczko & Dubuc 2013, Winn 2006). In some studies, lesions of the PPN or the CnF did not affect spontaneous locomotion (Allen et al. 1996, Inglis et al. 1994), while in other studies, similar lesions of PPN caused reduced locomotor activity (Aziz et al. 1998, Brudzynski & Mogenson 1985) or gait disturbances (Karachi et al. 2010). So, after decades of research, studies to functionally define MLR pointed to two different regions in the brainstem: CnF and PPN.

CnF and PPN are extended structures situated close to each other in the midbrain and contain neurons with excitatory long-range projections that are glutamatergic in CnF and both glutamatergic and cholinergic in PPN. Excitatory populations in both CnF and PPN are also intermingled with local and long-range projecting inhibitory interneurons (Mena-Segovia & Bolam 2017, Ryczko & Dubuc 2013). Electrical or chemical stimulation experiments or broad lesion studies were therefore unable to distinguish the contribution from the various neuronal populations present in these areas and also exhibited low fidelity in terms of localization. In very recent experiments, these issues have been tackled using cell type– and location-specific targeting in the two regions of the mouse brainstem. Optogenetic activation has unambiguously shown that activation of glutamatergic neurons—expressing the vesicular glutamate transporter Vglut2—in CnF can

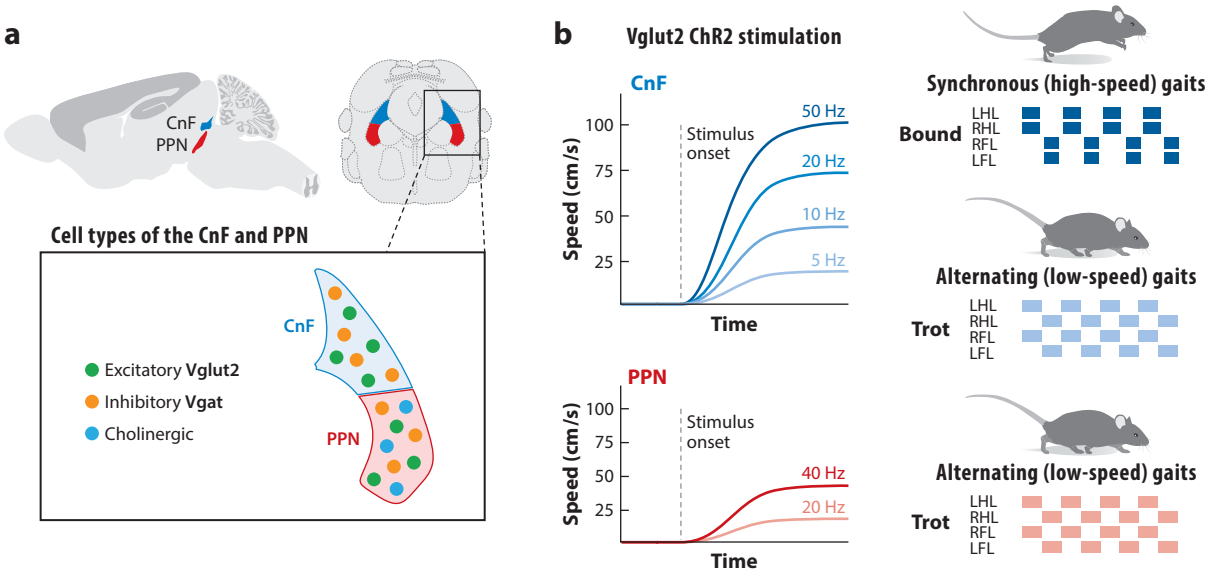


Figure 1

The MLR, composed of glutamatergic neurons in the CnF and the caudal PPN, controls initiation of locomotion and diverse aspects of speed and gait. (*a*) Anatomical localization of the MLR, composed of CnF (*blue*) and PPN (*red*), in the midbrain of the mouse in sagittal and transverse sections. The two structures are found lateral to the periaqueductal gray, ventral to the superior and inferior colliculi, and dorsal to the pontine reticular nucleus, oral part. Glutamatergic (Vglut2) and GABAergic (Vgat) neurons are intermingled in the CnF and PPN, with cholinergic neurons also present in the PPN. (*b*) Speed and gait profiles after optogenetic stimulation of CnF- or PPN-Vglut2 neurons. Stimulation of CnF-Vglut2 neurons results in the expression of the entire range of speeds and gaits observed in spontaneously moving mice. Lower stimulation frequencies elicit slow locomotor speeds and the alternating gaits walk and trot. Higher stimulation frequencies evoke faster locomotor speeds and the synchronous gaits gallop and bound. In contrast, stimulation of PPN-Vglut2 neurons only elicits slow speeds and the alternating gaits walk and trot, even at high stimulation frequencies (Caggiano et al. 2018). On the right, examples of a synchronous high-speed gait (bound) and an alternating gait (trot) are shown as step diagrams. Filled boxes represent the stance phase, and open spaces represent the swing phase. Trot is characterized by alternation around the girdle and simultaneous activity in the diagonal forelimbs and hindlimbs. Bound is characterized by synchronous activity around the girdle and alternation between the forelimbs and hindlimbs. Abbreviations: CnF, cuneiform nucleus; LFL, left forelimb; LHL, left hindlimb; MLR, mesencephalic locomotor region; PPN, pedunculopontine nucleus; RFL, right forelimb; RHL, right hindlimb.

initiate locomotion with short latencies from rest and modulates the speed of ongoing locomotion in mice (Caggiano et al. 2018, Dautan et al. 2021, Josset et al. 2018, Roseberry et al. 2016, van der Zouwen et al. 2021) (**Figure 1**). CnF-Vglut2 neurons allow acquisition of the full range of locomotor speeds and gaits, with expression of low-speed alternating gaits like walk and trot at lower stimulation frequencies and high-speed gaits like gallop and bound at higher stimulation frequencies (Caggiano et al. 2018). Optogenetic stimulation of PPN-Vglut2 neurons in caudal PPN also initiates locomotion in mice and rats (Caggiano et al. 2018, Carvalho et al. 2020, Lee et al. 2014, Masini & Kiehn 2022). In contrast to CnF, PPN activation only causes expression of slow alternating locomotor gaits (Caggiano et al. 2018) (**Figure 1**). Caggiano et al. (2018) also showed that the glutamatergic neurons in the CnF are necessary to initiate high-speed gaits—gallop and bound—independently of PPN-Vglut2 neurons. The firing of CnF-Vglut2 and PPN-Vglut2 neurons is related to locomotor speed (Caggiano et al. 2018, Roseberry et al. 2016), suggesting that neuronal activity codes frequency of the locomotor rhythm. Other studies have been unable to demonstrate locomotor initiation by stimulation of PPN-Vglut2 neurons (Dautan et al. 2021, Josset et al. 2018), instead showing that stimulation of these neurons in nonmoving animals elicited phasic muscle

activity (Josset et al. 2018) or tonic muscle activity (Dautan et al. 2021). The outcome discrepancies between studies may reflect different targeting approaches and/or stimulus paradigms leading to activation of different subpopulations of PPN-Vglut2 neurons. Indeed, subpopulations of glutamatergic neurons in PPN, stratified by their distinct axonal projections to the basal ganglia, the spinal cord, or medulla, are intermingled and exhibit neuronal activity related to diverse body actions, including rearing, body extension, and locomotion (Ferreira-Pinto et al. 2021). Optogenetic stimulation of PPN-Vglut2 neurons with selective projections to substantia nigra pars reticulata elicits antikinetic modulation of movement (Ferreira-Pinto et al. 2021). Moreover, the locomotor-promoting effect of PPN-Vglut2 neurons is restricted to the caudal PPN (Caggiano et al. 2018, Masini & Kiehn 2022), and, similar to what has been observed from electrical stimulation in rostral PPN (Takakusaki et al. 2003, 2016), glutamatergic neurons in the rostral PPN control whole-body motor arrest (Carvalho et al. 2020, Goñi-Erro et al. 2020). Therefore, targeting PPN-Vglut2 neurons broadly will lead to variable effects with locomotor promotion in caudal PPN and movement arrest in rostral PPN.

The role of cholinergic PPN neurons in locomotor initiation has also been addressed directly in recent rodent studies. Activation of cholinergic PPN neurons may have no effect (Josset et al. 2018, Kroeger et al. 2017), decrease (Caggiano et al. 2018), or slightly increase the speed of ongoing locomotion (Roseberry et al. 2016, Xiao et al. 2016). These experiments strongly suggest that cholinergic PPN neurons in mammals are not an essential part of the locomotor command, as was originally suggested, although their activity may modulate ongoing locomotion possibly via ascending connections (Mena-Segovia & Bolam 2017).

In summary, cell type–specific studies have provided important insight into the functional identity of the MLR in mammals by showing that speed-dependent locomotor control resides in glutamatergic neurons in both PPN and CnF. These two separate start command pathways encode speeds of locomotion in complementary ways. Caudal PPN-Vglut2 neurons support exploratory locomotion, while CnF-Vglut2 neurons are necessary for high-speed locomotion characteristic of escape responses (Caggiano et al. 2018). Dual channels for locomotor initiation are reflected by distinct input connectivity to CnF- and PPN-Vglut2 neurons. PPN-Vglut2 neurons receive strong input from the basal ganglia, including from the substantia nigra pars reticulata (SNr) and compacta (SNc) and the subthalamic nucleus (STN), from cortical areas and several brainstem regions that convey sensorimotor information, including the colliculi (Caggiano et al. 2018, Dautan et al. 2021, Mena-Segovia & Bolam 2017, Roseberry et al. 2016, Ryczko & Dubuc 2013). In contrast, input to CnF-Vglut2 neurons is more restricted, with weak input from SNr but strong inputs from the periaqueductal gray and the superior colliculus (SC), which are both associated with escape behavior (Caggiano et al. 2018, Dautan et al. 2021).

Lower Brainstem Nuclei Integrate Start and Speed Commands

The locomotor start signals from MLR (CnF/PPN) do not act directly on executive circuits in the spinal cord. Instead, MLR start neurons connect to reticulospinal neurons that provide the final command signal to locomotor networks in the spinal cord (**Figure 2**). The exact identity of these reticulospinal neurons has been the focus of much research. Anatomical tracing and electrical/chemical activation experiments in the brainstem suggested that neurons in the medullary reticular formation (MRF), including neurons in the reticular gigantocellular nucleus (Gi) and the reticular magnocellular nucleus (Mc), may mediate the final locomotor command from the electrically defined MLR (Brownstone & Chopek 2018; Dubuc et al. 2008; Garcia-Rill et al. 1985; McClellan & Grillner 1984; Mori et al. 1978; Noga et al. 1988, 1991; Takakusaki et al. 2003). Two main transmitter-defined neuronal groups located in these areas were suggested to be

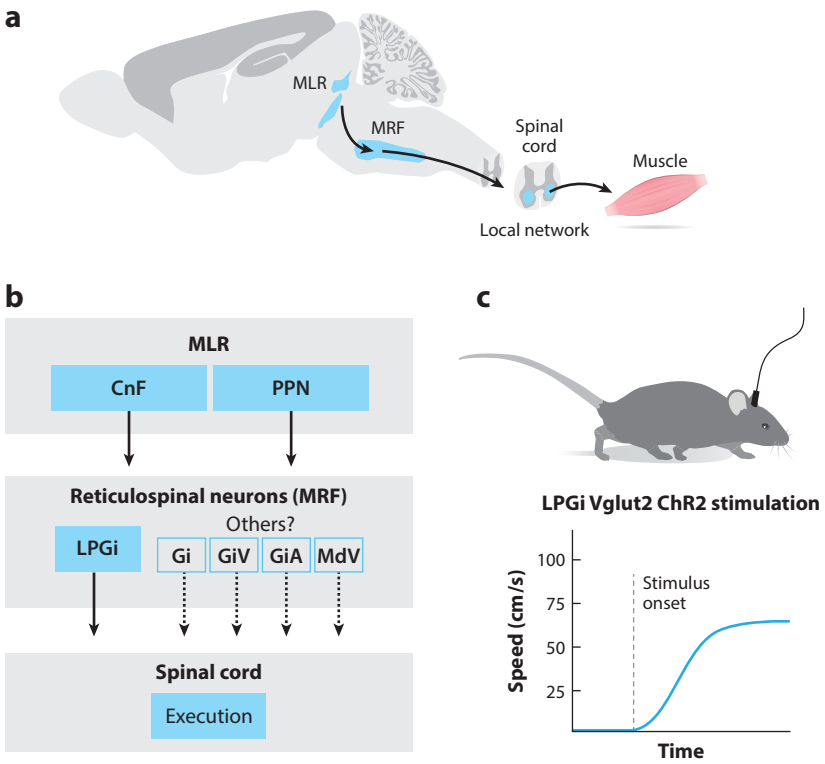


Figure 2

Mesencephalic locomotor region (MLR) connections with reticulospinal targets. (*a*) Schematic view of MLR activation of neurons in the medullary reticular formation (MRF) with reticulospinal axons that descend to executive locomotor networks in the spinal cord through the ventrolateral funiculus. (*b*) As a primary target of the MLR, the lateral paragigantocellular nucleus (LPGi) receives convergent input from cuneiform nucleus (CnF)- and pedunculopontine nucleus (PPN)-Vglut2 neurons. Both CnF- and PPN-Vglut2 neurons project to other MRF regions, including the reticular gigantocellular nucleus (Gi), the ventral part (GiV), the alpha part (GiA), and the medullary reticular formation ventral part (MdV). This MLR-MRF connectivity matrix indicates that, in addition to LPGi-Vglut2 neurons, other descending locomotor pathways mediate CnF and PPN locomotor initiation. (*c*) Optogenetic stimulation of Vglut2-postive neurons in the LPGi initiates locomotion (Capelli et al. 2017).

involved: serotonergic and glutamatergic (Jordan et al. 2008). The evidence for the existence of a serotonergic pathway is derived from experiments in rodents that have shown that 5-HT reliably evokes locomotor activity in the isolated spinal cord (Schmidt & Jordan 2000) and that electrical stimulation of the parapyramidal nucleus, which contains serotonergic neurons, can initiate locomotion (Liu & Jordan 2005). The evidence for a glutamatergic descending pathway came from experiments in several different vertebrates showing that locomotion can be initiated by glutamatergic agonists applied to the cord, which demonstrated that CnF-evoked locomotion is transmitted through large-diameter descending reticulospinal neurons and that CnF-evoked locomotion can be blocked by preventing glutamatergic receptor activation in the spinal cord (Douglas et al. 1993, Grillner et al. 1997, Jordan et al. 2008). However, because the locomotor rhythm-generating circuitries in the spinal cord themselves are glutamatergic, pharmacological perturbation only provides indirect evidence of the existence of a descending glutamatergic signal. Early optogenetic experiments confirmed the glutamatergic nature of the reticulospinal command, demonstrating

that broad optogenetic stimulation of brainstem glutamatergic neurons could initiate locomotor-like activity in isolated brainstem–spinal cord preparations (Hägglund et al. 2010). These studies have been taken a step further by focusing on the cell type–specific function of neurons in subdomains of Mc—which is composed of the alpha part of the gigantocellular nucleus (GiA) and the ventral part of the gigantocellular nucleus (GiV)—in the lateral paragigantocellular nucleus (LPGi) and in Gi itself (Capelli et al. 2017). Optogenetic stimulation of glutamatergic LPGi neurons, but not of glutamatergic GiA, GiV, or Gi neurons, caused initiation of forward-directed locomotion in freely moving mice (**Figure 2**). Lemieux & Bretzner (2019) also showed that broad stimulation of glutamatergic neurons in Gi could not initiate locomotion. Optogenetic activation of inhibitory neurons in GiA, GiV, or Gi disrupted or arrested locomotion (Capelli et al. 2017). These experiments point to LPGi as an important functional reticulospinal locomotor command node regulating the expression of high-speed locomotion. This notion is supported by observation of strong input projections from locomotor-promoting CnF neurons to LGPi (Caggiano et al. 2018, Capelli et al. 2017) and by experiments demonstrating that LPGi-Vglut2 neuron ablation attenuates the effect of CnF-Vglut2-induced locomotion (Capelli et al. 2017). Nonetheless, CnF-Vglut2 neurons also project to GiA and GiV, and locomotor-promoting PPN-Vglut2 neurons have projections to diverse MRF nuclei, including LPGi, Gi, GiA, GiV, and medullary reticular formation ventral part (Caggiano et al. 2018, Dautan et al. 2021). Therefore, it is likely that descending glutamatergic locomotor pathways have several origins in the brainstem reticular formation, forming parallel pathways corresponding to the diverse descending projection patterns from CnF and PPN to brainstem nuclei (**Figure 2**). Future experiments may address this issue by mapping the pathways in a behavioral context directly linked to the two MLR (CnF/PPN) regions. Linking of MLR regions to modulatory pathways, for example, serotonergic (Jordan et al. 2008) or acetylcholinergic (Dubuc et al. 2008), will also be of interest.

Locomotor Stop

An essential component of locomotor control is the ability to terminate a locomotor bout. Goal-directed locomotor stops impart finalization of the step cycle and a postural readjustment that promotes performance of subsequent behavioral output. Cortical areas and the basal ganglia are thought to be involved in termination of ongoing movements (Roseberry & Kreitzer 2017, Wessel & Aron 2017). However, specific brainstem mechanisms that generate a locomotor stop are not well understood. Locomotion can be suppressed momentarily by short-lasting activation of GABAergic neurons of the CnF or PPN (Caggiano et al. 2018, Roseberry et al. 2016), the two structures that encompass the MLR. This MLR-mediated locomotor arrest is thought to reflect the suppression of an initiation or speed command rather than an active locomotor stop per se. Nonetheless, recent experiments have defined active stop mechanisms in the brainstem. Bilateral optogenetic stimulation of glutamatergic Chx10-positive neurons in Gi halts ongoing locomotion (Bouvier et al. 2015) (**Figure 3**). This locomotor arrest is executed as a canonical stop, where the animal finalizes the step cycle and adopts a stereotypic sitting posture with the hindlimb position about the girdle coming to rest at a perpendicular position relative to the body axis. Recordings of locomotor-like activity in in vitro spinal cord preparations demonstrated that bilateral stimulation of Chx10 Gi neurons arrests spinal locomotor activity on both sides of the lumbar spinal cord (Bouvier et al. 2015). Expression of the canonical stop is observed spontaneously during open field exploration and is reduced after eliminating synaptic transmission in Chx10 Gi neurons (Bouvier et al. 2015). Chx10 Gi neurons are active during locomotor activity (Bretzner & Brownstone 2013), and calcium imaging has shown that a proportion of Chx10 Gi neurons are active during spontaneous locomotor stops (Schwenkgrub et al. 2020), confirming an active role in mediating the

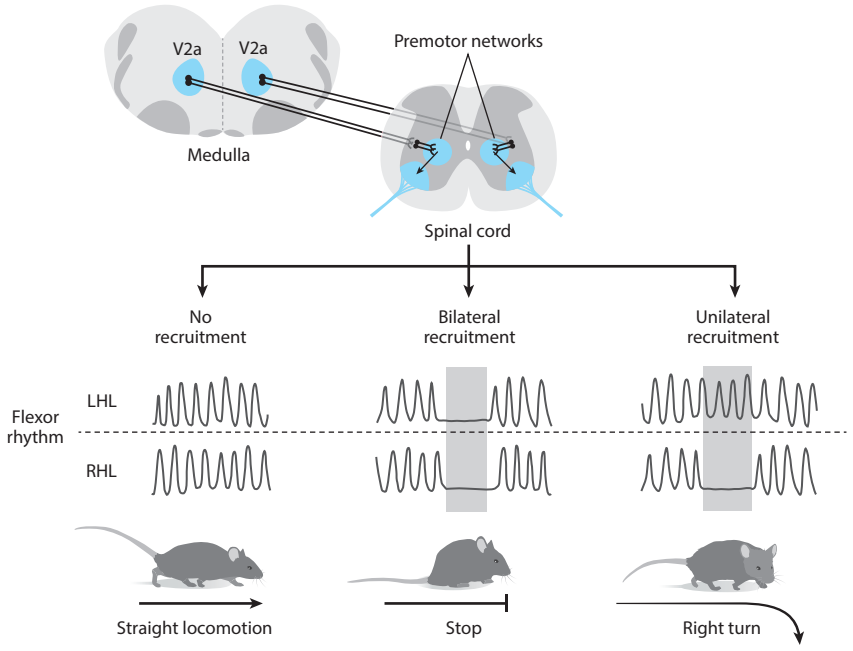


Figure 3

Stop and asymmetric locomotion mediated by Chx10 reticular Gi neurons in the mouse brainstem. Excitatory Chx10 Gi neurons project to locomotor networks in the spinal cord. When Chx10 Gi neurons are bilaterally recruited, mice perform a canonical stop where the animal adopts a resting position with the hindlimb position about the girdle in a perpendicular orientation relative to the body axis (*middle*). Chx10 Gi neurons mediate their effect by inhibiting locomotor rhythm (Bouvier et al. 2015). When Chx10 Gi neurons are recruited unilaterally, mice perform a turn toward the side of recruitment (*right*). This asymmetric recruitment causes turning by reducing flexor rhythm and step length on the side of recruitment (Cregg et al. 2020). Abbreviations: Gi, gigantocellular nucleus, LHL, left hindlimb; RHL, right hindlimb.

stop. Neurons with the ability to stop locomotion are a general feature of the vertebrate nervous system and found in evolutionary old animals like the lamprey (Grätsch et al. 2019, Juvin et al. 2016). Together, these experiments point to a brainstem pathway that acts to cause an intentional stop of locomotion, which is appropriately incorporated into the locomotor behavior.

Locomotor Asymmetries

Initial experiments on the MLR (CnF) revealed that unilateral stimulation evokes bilateral, full-bodied locomotion with no directional bias (Shik et al. 1966). This finding was confirmed in many later studies, including those employing cell type–specific stimulation of CnF and PPN (Caggiano et al. 2018, Josset et al. 2018, Musienko et al. 2012, Roseberry et al. 2016, Ryczko & Dubuc 2013). This finding demonstrates that symmetry is a property of circuits that initiate locomotion and control its speed. Neurons of CnF and PPN exhibit anatomical and functional signatures of symmetry, including bilateral projection and recruitment of putative reticulospinal targets in the medulla (Brocard et al. 2010, Caggiano et al. 2018, Capelli et al. 2017, Ryczko & Dubuc 2013). Moreover, symmetry is reinforced at the level of reticulospinal projections (Brocard et al. 2010, Capelli et al. 2017), including those of LPGi, which project bilaterally to the spinal cord (Capelli et al. 2017).

The observation that many of the descending locomotor-related systems identified to date exhibit functional symmetry (Brownstone & Chopek 2018, Capelli et al. 2017, Ferreira-Pinto

et al. 2018) prompted a search for pathways with the capacity to regulate spinal networks unilaterally. Chx10 Gi neurons represented candidates for this function because Chx10 neurons are ipsilaterally projecting, at least within the spinal cord (Al-Mosawie et al. 2007, Lundfald et al. 2007). Indeed, Chx10 Gi neurons exhibit predominant ipsilateral projection to the spinal cord, where they arborize and synapse within the ipsilateral gray matter (Cregg et al. 2020, Usseglio et al. 2020). Unilateral stimulation of Chx10 Gi neurons in freely moving mice caused ipsilaterally biased locomotor bouts, that is, turning, whereas unilateral inhibition of Chx10 Gi neurons biased locomotion toward the contralateral side (Cregg et al. 2020). Mice cannot compensate for dysfunction of Chx10 Gi neurons (Cregg et al. 2020), indicating that this population is obligatory for control over locomotor direction.

Unilateral activation of Chx10 Gi neurons causes ipsilateral contraction of muscles that rotate the head about the yaw axis (Cregg et al. 2020, Usseglio et al. 2020) and axial muscles that bend the trunk (Cregg et al. 2020) but no forward movement when the animal is at rest. Therefore, although axial circuits adjust posture as it relates to head or trunk orientation, locomotor direction is ultimately mediated via the limbs (Gruntman et al. 2007). While strong unilateral optogenetic activation may initiate a bilateral locomotor stop and axial bend toward the ipsilateral side (Usseglio et al. 2020), more modest optogenetic activation caused locomotor turning accompanied by a reduction in speed without a stop (Cregg et al. 2020) (**Figure 3**). Chemogenetic stimulation of Chx10 Gi neurons also biased ipsilaterally turning without a stop (Cregg et al. 2020). These findings implicated a unilateral brake mechanism for turning. In vitro experiments in brainstem–spinal cord preparations allowed parsing of this mechanism as it directly engages lumbar locomotor circuits; unilateral Chx10 Gi stimulation reduced flexor-related and promoted extensor-related locomotor activity on the ipsilateral side (Cregg et al. 2020). While aquatic vertebrates primarily use axial mechanisms to control locomotor direction (Fagerstedt et al. 2001, Grillner et al. 2007, Huang et al. 2013, Thiele et al. 2014), these data indicate that mammals have evolved a brake mechanism for reducing stride length on the inside of the turn, creating a steering moment about the yaw axis. This unilateral brake mechanism seems to account for turning at higher speeds of locomotion (van der Zouwen et al. 2021), where mice brake and turn to avoid a barrier during CnF-Vglut2-induced increases in locomotor speed.

Although turning is perhaps an obvious example of locomotor asymmetries, it is thought that parallel systems can adjust individual steps (e.g., left or right) in relation to an ongoing locomotor rhythm. Such asymmetric commands are thought to be critical for online adjustments related to obstacle avoidance (Dyson et al. 2014, Schepens & Drew 2006, Warren et al. 2021) and for cerebellar adaptation (Darmohray et al. 2019), although it is unknown what descending circuits may accommodate these functions. Additionally, while Chx10 Gi neurons control rotation of the body about the yaw axis (Cregg et al. 2020), the descending neurons that control body rotation about the pitch and roll axes are not known (Masullo et al. 2019).

COMMAND EXECUTION BY SPINAL LOCOMOTOR NETWORKS

While brainstem circuits generate the commands for start, speed, stop, and turn, spinal locomotor circuits receive and convert these descending signals into coordinated locomotion. How this conversion takes place and which neurons of the spinal circuitry receive these brainstem commands are not well understood. Spinal locomotor networks are composed of inhibitory and excitatory interneurons with a modular organization that generates the main characteristics of locomotion: rhythm and left-right coordination in nonlimbed animals with additional flexor-extensor coordination in limbed animals (Dougherty & Ha 2019; Goulding 2009; Grillner & El Manira 2020; Kiehn 2006, 2016; Rancic & Gosgnach 2021).

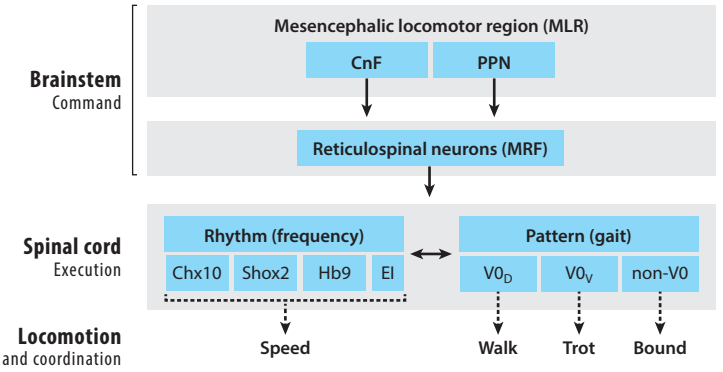


Figure 4

Circuitry integrating locomotor command in the spinal cord. Proposed neuronal targets in the spinal cord for the brainstem locomotor command. Excitatory rhythm-generating interneurons of diverse types in the zebrafish (Chx10 V2a neurons), mouse (Shox2, Hb9, or unidentified excitatory interneurons), or lamprey and tadpole (EI) may convert the descending signal into a rhythm controlling speed. In the mouse spinal cord, commissural neurons ($V0_V$ and $V0_D$) enable alternating gaits (walk and trot) at different speeds of locomotion. These cells might be sequentially activated in parallel to the signal controlling speed, securing the expression of appropriate gait coordination at increasing speeds. At the highest speeds, non-V0 activity secures synchronous gaits (gallop and bound). Abbreviations: CnF, cuneiform nucleus; MLR, mesencephalic locomotor region; MRF, medullary reticular formation; PPN, pedunculopontine nucleus.

Excitatory spinal interneurons compose the locomotor rhythm-generating kernel (Dougherty & Ha 2019; Goulding 2009; Grillner & El Manira 2020; Kiehn 2006, 2016; Rancic & Gosgnach 2021), which in turn activates left-right and flexor-extensor coordinating circuits as well as motor neurons. Rhythm-generating excitatory circuits are an obvious target for transforming the descending locomotor start and speed signal into coordinated locomotion. Yet, few studies have demonstrated such connections to putative rhythm-generating neurons. In the lamprey, the activity of medullary reticulospinal neurons monosynaptically excites rhythmically active excitatory spinal neurons (Ohta & Grillner 1989). Similarly, monosynaptic connections from excitatory hindbrain neurons to rhythmically active spinal excitatory neurons have been found in the tadpole (Li et al. 2006). In the cat, stimulation of the CnF activates spinal neurons (presumably via reticulospinal intermediates), which contribute to locomotion (Edgley et al. 1988). Based on such studies, connections from MLR to excitatory reticulospinal neurons onto spinal rhythm-generating neurons have been proposed in several models of vertebrate locomotor networks (Ausborn et al. 2019, Grillner 2003, Roberts et al. 2010). However, such connections have not been confirmed functionally. This hypothesis should be possible to test experimentally because, in mice and zebrafish, excitatory spinal interneurons expressing the transcription factors Chx10 (V2a interneurons), Shox2, and/or Hb9 contribute to the rhythm-generating population (Caldeira et al. 2017, Crone et al. 2008, Dougherty et al. 2013, Eklöf Ljunggren et al. 2014, Song et al. 2020) (**Figure 4**). These molecular markers enable experimental access to putative rhythm-generating populations, allowing tests for functional connectivity with speed-related excitatory reticulospinal inputs. Further questions about how rhythm is established and how speed is coded—for example, by recruitment of different excitatory rhythm-generating neurons as observed in zebrafish swimming (McLean et al. 2008, Song et al. 2020) or increased firing of the same population of excitatory neurons—should also be possible to answer.

Speed-dependent gait changes, observed by activating either CnF or PPN with increasing frequencies, are implemented via diverse network activity in the spinal cord. The different alternating

(walk and trot) and synchronous (gallop or bound) gaits are organized by left-right coordinating locomotor circuits composed of populations of excitatory and inhibitory commissural neurons (CNs) (Butt & Kiehn 2003, Jankowska 2008, Kiehn 2016, Quinlan & Kiehn 2007). Experiments in mice have demonstrated that left-right alternation during locomotion depends on functional crossed inhibition produced directly by inhibitory CNs or indirectly by excitatory CNs acting on inhibitory neurons on the other side of the cord (Kiehn 2006, 2016). This dual inhibitory system is enabled by *Dbx1*-derived V0 CNs (Lanuza et al. 2004, Talpalar et al. 2013). Full ablation of V0 interneurons results in complete loss of left-right alternation at all speeds of locomotion. The inhibitory dorsal class of V0 interneurons ($V0_D$) controls alternating locomotion at low speeds of locomotion. The excitatory ventral class of V0 interneurons ($V0_V$), which composes the remaining half of V0 interneurons, controls alternation during higher speeds of locomotion (Talpalar et al. 2013). In the absence of $V0_V$ CNs, mutant mice do not exhibit trot, while with ablation of both $V0_V$ and $V0_D$ CNs, mice can only bound (Bellardita & Kiehn 2015). This dual system thus serves a speed-dependent role in coordinating alternating gaits, walk and trot, and allows the expression of synchronous gaits when suppressed. CN organization enables pattern control that is separate and distinct from locomotor rhythm, which indicates that CnF/PPN- and reticulospinal-mediated locomotor commands target V0 CNs to generate gait switching between walk, trot, and bound (**Figure 4**). MRF-spinal CN connections are well known, but their relationship to subgroups of CNs has not been studied (Jankowska et al. 2003, Matsuyama et al. 2004, Ohta & Grillner 1989, Szokol et al. 2011). A recent modeling study has advanced hypotheses for how speed and gait changes can be implemented by spinal circuits (Ausborn et al. 2019). In this model, PPN, CnF, and LPGi neurons have access to two discrete lines controlling speed and gait, respectively. Speed is implemented via access to rhythm-generating neurons, whereas gait expression is implemented via access to $V0_V$ and $V0_D$ CNs and propriospinal forelimb-hindlimb connecting neurons (Ausborn et al. 2019). These hypotheses will be important to investigate as descending speed command circuitry is resolved in greater detail.

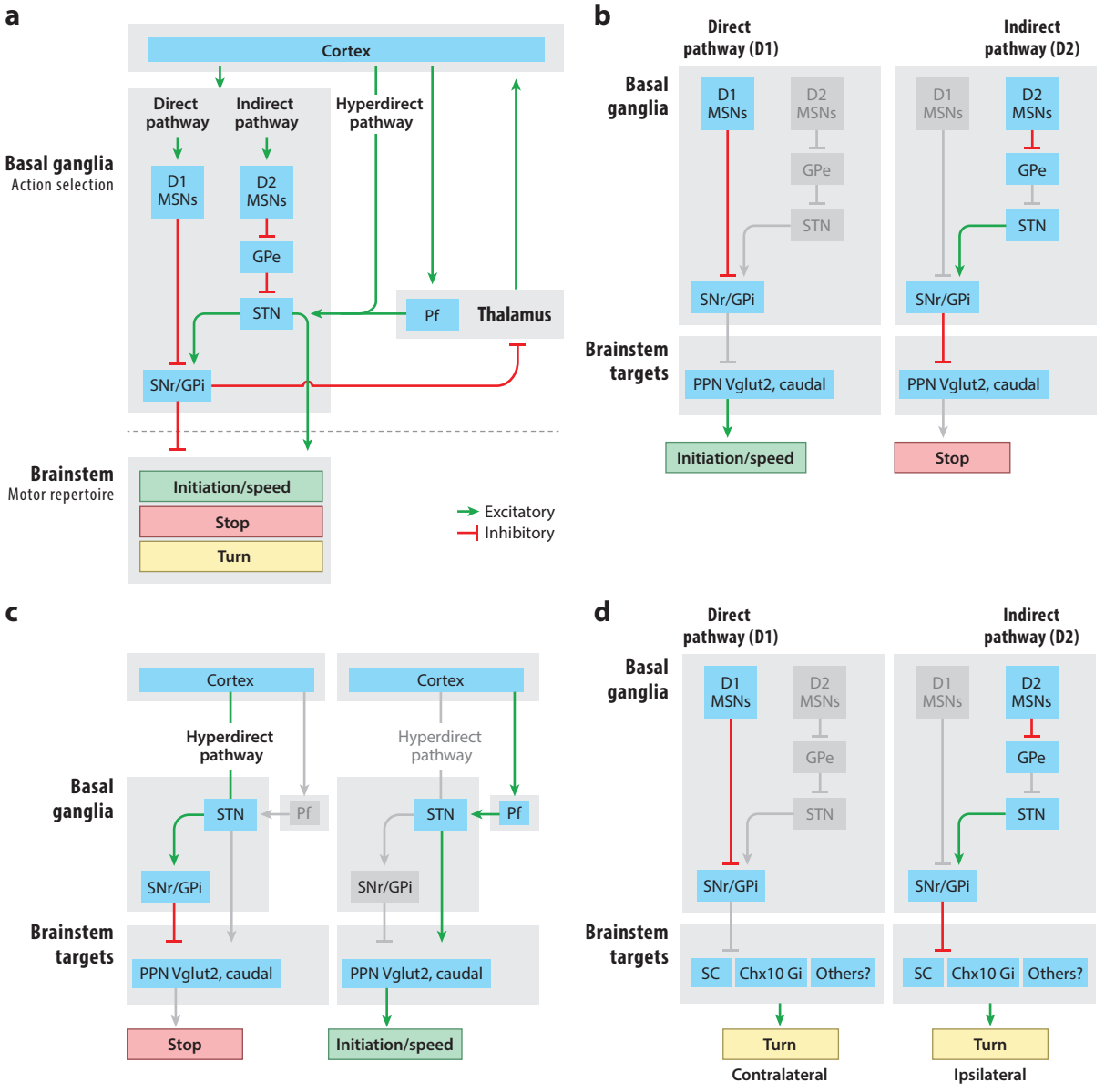
Chx10 Gi-mediated locomotor stops arise via a direct effect on spinal interneurons. The available evidence suggests that the primary effect is on those neurons governing rhythm generation (Bouvier et al. 2015). Since the Chx10 Gi descending signal is excitatory, the obvious mechanism for a stop is the recruitment of spinal inhibitory neurons—either directly or indirectly via local excitatory neurons—which in turn inhibits rhythm-generating circuits (Bouvier et al. 2015). For turning, Chx10 Gi neurons have an asymmetric effect on rhythm generation, leading to decreased step length on the inside of the turn made possible by reducing flexor bursting and enhancing extensor bursting (Cregg et al. 2020). These data would suggest that the line of action is primarily on the flexor rhythm-generating circuits.

BEHAVIORAL SELECTION OF DESCENDING COMMAND FUNCTIONS

In the first sections of this review, we described brainstem circuits involved in the direct control of locomotor initiation, speed, stop, and turn, with some valence linked to the integrated system. Essentially, every context-dependent locomotor behavior—including navigation, foraging, escaping predators, and exploring the environment—must interface with these systems. Delineated brainstem circuits form parallel descending pathways acting on spinal motor circuits, and the repertoire of these pathways can act to support a broad range of behaviors. These command pathways act as nodes that link a clear motor output to context-dependent behavioral states and higher brain functions. To understand how this happens, we examine how different nodes are connected to diverse upstream brain areas and how this connectivity may lead to recruitment in diverse behavioral tasks.

Action Selection via Basal Ganglia Circuits

The planning of goal-directed locomotion is thought to arise at motor cortical areas (Drew & Marigold 2015, Grillner & El Manira 2020, Svoboda & Li 2018). Besides direct connections to brainstem command circuits, motor cortical areas connect to the brainstem via the basal ganglia. There is ample evidence that the basal ganglia are involved in planning and execution of motor acts by complex integration of activity in the classical direct and indirect striatal pathways. Activity in the striatal direct pathway causes inhibition of basal ganglia output neurons, for example, in the SNr or internal globus pallidus (GPi) [entopeduncular nucleus (EP) in nonprimates] (**Figure 5*a***).



(*Caption appears on following page*)

Figure 5 (*Figure appears on preceding page*)

Action selection of start, stop, or turn from basal ganglia. (*a*) Simplified schematic of basal ganglia motor circuitries. The direct pathway is composed of striatal GABAergic dopamine receptor 1 medium spiny neurons (D1 MSNs), which act on GABAergic substantia nigra pars reticulata (SNr) or internal globus pallidus [GPi; entopeduncular nucleus (EP) in nonprimates] neurons connected to brainstem motor circuits or thalamic motor areas projecting back to cortex. The indirect pathway is composed of striatal GABAergic dopamine receptor 2 (D2) MSNs, which act on GABAergic external globus pallidus (GPe) neurons that inhibit the excitatory subthalamic nucleus (STN). The hyperdirect and cortical-parafascicular thalamic nucleus (Pf) pathways project to STN. Dopaminergic substantia nigra pars compacta projections to striatum and brainstem targets, including the pedunculopontine nucleus (PPN), are not shown. (*b*) Opposing effects on locomotion by activation of striatal D1 MSNs (initiation) or D2 MSNs (stop), possibly mediated by decreased or increased SNr-inhibition of PPN-Vglut2 neurons, respectively (see Roseberry et al. 2016). (*c*) Opposing effects on locomotion from activation of STN by the hyperdirect (stop) and the Pf pathway (initiation) through SNr inhibition of PPN-Vglut2 neurons or direct activation of PPN-Vglut2 neurons, respectively (see Adam et al. 2020, Nambu 2004, Watson et al. 2021). (*d*) Opposing effects on turning by activation of striatal D1 MSNs or D2 MSNs (see Kravitz et al. 2010). Turning is proposed to be controlled by SNr inhibition of brainstem motor circuits, possibly including Chx10 Gi neurons, the superior colliculus (SC), or other unknown brainstem targets.

Activity in the striatal indirect pathway has an opposing effect by increasing activity in the excitatory STN, which activates SNr and GPi/EP. Direct pathway activity causes disinhibition of motor targets and results in movement promotion, whereas indirect pathway activity inhibits motor targets and suppresses movement. These actions may arise through either the SNr-brainstem or pallidal-thalamic-cortical pathway (Klaus et al. 2019) (**Figure 5*a***).

This general model of basal ganglia action selection has led to the suggestion that direct pathway-mediated decreases of tonic SNr activity cause disinhibition of MLR, thereby promoting initiation of locomotion, while indirect pathway activity inhibits locomotion (Garcia-Rill 1986; Grillner & Robertson 2015; Jordan 1998; Kim et al. 2017; Takakusaki et al. 2004, 2016). Experiments using optogenetic manipulations have lent support to this model; bilateral stimulation of striatal direct (D1R) or indirect (D2R) pathway medium spiny neurons promotes or suppresses locomotion, respectively (Kravitz et al. 2010, Roseberry et al. 2016) (**Figure 5*b***). This raises the question, which part of MLR is primarily involved? Takakusaki et al. (2003) showed that electrical stimulation of the ventral SNr has a powerful modulatory effect on locomotion induced by electrical stimulation of the CnF/dorsal PPN in cats and proposed that SNr primarily modulates CnF activity (Takakusaki et al. 2003). However, while SNr neurons have abundant direct connections to PPN (McElvain et al. 2021, Mena-Segovia & Bolam 2017, Ryczko & Dubuc 2013) and strong projections to PPN-Vglut2 neurons (Caggiano et al. 2018, Ferreira-Pinto et al. 2021, Roseberry et al. 2016), there is only weak innervation of CnF-Vglut2 neurons (Caggiano et al. 2018, Roseberry et al. 2016). Priority access to locomotor-initiating PPN neurons from SNr suggests that locomotor initiation via direct pathway activity is mediated by disinhibition of PPN-Vglut2 neurons rather than of CnF-Vglut2 neurons (**Figure 5*b***).

Parallel basal ganglia pathways may assist in the recruitment of PPN neurons to support goal-directed locomotion. Through an evolutionarily conserved pathway, dopaminergic SNc neurons have collateral axons to PPN that may facilitate the activity of PPN neurons (Rolland et al. 2009, Ryczko & Dubuc 2013, Ryczko et al. 2016). The increased burst firing of dopaminergic SNc neurons at movement onset (Klaus et al. 2019) may therefore have a dual action on PPN activity: disinhibition through the direct pathway and simultaneous direct activation of PPN neurons. The dynamics of this modulation with respect to PPN-Vglut2 recruitment needs to be worked out in greater detail. Presently, there are limited data on basal ganglia neuronal activity with respect to locomotion (Fobbs et al. 2020, Mullie et al. 2020, Robbe 2018, Schwarz et al. 1984, Shi et al. 2004). Experiments with recordings of basal ganglia cell activity during different locomotor speeds or contexts together with targeted activation and inactivation experiments of the output pathways are necessary for understanding how action is selected. Such experiments should also enable definition of the network and cellular mechanism(s) for disinhibition at the level of PPN.

Locomotion can be modulated through changes in STN activity that act via SNr (and GPi/EP) (**Figure 5*a***). Selective ablation of Vglut2 STN neurons causes hyperlocomotion and decreased latency to initiation of movement (Schweizer et al. 2014). In contrast, bilateral optogenetic stimulation of STN neurons inhibits ongoing locomotion (Guillaumin et al. 2021, Parolari et al. 2021). These results fit within the standard model of basal ganglia, where it is well accepted that Parkinsonian-related changes lead to increases in STN activity causing general movement inhibition, and ablation of STN in this situation can normalize movement deficits (DeLong 1990, Klaus et al. 2019). In addition to being regulated by external globus pallidus activity, STN may also be influenced directly through excitatory input from cortical areas—the hyperdirect pathway (Nambu 2004) (**Figure 5*a*,*c***). Mounting evidence has shown that the hyperdirect pathway may be recruited in no-go motor tasks (Wessel & Aron 2017). Premotor cortex–STN neurons can also be recruited during visually guided locomotion to execute a learned motor stop (Adam et al. 2020), possibly acting through SNr to inhibit PPN-induced locomotion. Glutamatergic locomotor-promoting PPN neurons also receive direct input from STN neurons (Caggiano et al. 2018, Roseberry et al. 2016), which would imply a locomotor-promoting effect upon STN activation (**Figure 5*a*,*c***). Such a locomotor-promoting effect has recently been discovered for thalamic projections from the parafascicular nucleus to STN (Watson et al. 2021) (**Figure 5*a*,*c***). The opposing effect on locomotion by STN-SNr-PPN and STN-PPN pathways implies that these pathways can be recruited to stop or initiate locomotion in specific behavioral contexts.

Steering can be evoked via unilateral stimulation of striatal medium spiny neurons (Kravitz et al. 2010), and locomotor direction can be read out from population activity within the striatum (Tecuapetla et al. 2014). Furthermore, unilateral stimulation of SNr or STN induces turning (Guillaumin et al. 2021, Parolari et al. 2021, Rizzi & Tan 2019). Since unilateral MLR stimulation leads to symmetric forward locomotion, steering must be mediated through parallel basal ganglia output pathways, with possible connections to Chx10 Gi neurons, SC, or other brainstem targets (**Figure 5*d***).

Defensive Locomotor Behavior

Modulation of locomotion is fundamental for executing defensive behavior. In its most basic form, defensive behavior has two motor outcomes—freezing or flight. The choice between these two exclusive behaviors depends on the context, leading to an optimal decision whether to escape from an aversive or threatening stimulus or to immobilize to reduce the risk of being seen. Both motor behaviors are active responses where locomotion either is increased dramatically or abruptly comes to a halt. The neuronal circuits that control defensive behavior therefore, by necessity, converge on brainstem locomotor pathways.

The amygdala plays an essential role in defensive behavior (Ciocchi et al. 2010, Fadok et al. 2017, Herry & Johansen 2014, Tovote et al. 2015). Recent work has connected central fear circuits in amygdala with brainstem motor circuits (Tovote et al. 2016). This work identifies inhibitory circuits in the central amygdala (CEA) that cause freezing by disinhibition of excitatory neurons in the ventrolateral periaqueductal gray (vlPAG). Excitatory neurons in the vlPAG in turn project to reticulospinal neurons in the Mc. The freezing pathway also receives input from circuits in the dorsolateral periaqueductal gray (dlPAG) mediating flight. The dlPAG flight circuit inhibits the vlPAG freezing pathway, securing exclusive expression of flight behavior. The mutually exclusive expression of freezing and escape is also represented at the level of CEA, where distinct inhibitory populations promote either flight or freezing (Fadok et al. 2017). These inhibitory circuits are reciprocally connected, suggesting that selection of behavioral responses is a result of competitive interactions between two defined populations of inhibitory neurons (Fadok et al.

2017). How exactly the Mc signal is integrated in spinal motor circuits in order to elicit the phenotypic freezing response is still an open question that will require functional analysis of Mc projections to identified spinal neurons. Another question that needs clarification is how active locomotor movements are terminated to allow the expression of freezing. Locomotion could be terminated via a stop command relayed to spinal executive circuits or by blocking the locomotor speed command at the level of CnF/PPN. PPN and CnF-Vglut2 neurons both receive inputs from CEA (Caggiano et al. 2018, Roseberry et al. 2016), and GABAergic CEA neurons connect monosynaptically to MLR neurons (Roseberry et al. 2019). This pathway might, therefore, be activated in parallel to the freezing pathway to terminate ongoing locomotion in defensive behavior (Roseberry et al. 2019). Behavioral and network analyses have also demonstrated that basolateral amygdala neurons projecting to the CEA can drive momentary locomotor arrests in an experience-dependent manner when animals familiarize themselves with a novel environment (Botta et al. 2020). This locomotor arrest is likely mediated by CEA inhibition of MLR neurons (Botta et al. 2020). CEA-MLR circuits may therefore initiate halt of locomotion by suppressing the locomotor drive both as part of a defense response and also in nondefensive behaviors (Botta et al. 2020, Roseberry et al. 2019).

The defensive flight or escape behavior is triggered by visual input to the optic tectum or SC (Branco & Redgrave 2020, Isa et al. 2021). Classical stimulation experiments and lesion studies in rodents have shown that the medial SC receives input from the upper visual field and that this area of SC mediates the escape response (Dean et al. 1988, 1989), as also confirmed in recent optogenetic stimulation experiments (Isa et al. 2020). The medial SC has strong direct projections to CnF (Dean et al. 1988, 1989; Isa et al. 2020), with specific projections to CnF-Vglut2 neurons (Caggiano et al. 2018, Roseberry et al. 2016). Moreover, medial SC projects to dlPAG (Dean et al. 1988, 1989; Isa et al. 2020), which has long been implicated in flight responses (Assareh et al. 2016, Branco & Redgrave 2020, Deng et al. 2016). Using a mouse model for escape, Evans et al. (2018) showed that glutamatergic dlPAG neurons are monosynaptically activated from the medial SC through a synaptic threshold mechanism that only allows strong stimuli to cause threat-evoked escape (Evans et al. 2018). The dlPAG also exhibits direct projections to CnF (Dampney et al. 2013, Dean et al. 1989), with specific connections to CnF-Vglut2 neurons (Caggiano et al. 2018). High-speed CnF-Vglut2 neurons thus receive both direct and indirect input from SC. Escape behavior also involves simultaneous acquisition of optimal paths toward shelter (Branco & Redgrave 2020), possibly recruiting steering neurons in the brainstem.

Recruitment of Locomotor Asymmetries

Locomotor asymmetries subserve two primary organismal functions: (*a*) orientation relative to salient environmental stimuli (e.g., visual or auditory) and (*b*) navigation toward a target based on an internal model or map. While these functions may be dissociable in both vertebrate and invertebrate species (Ferris et al. 2018, Packard & McGaugh 1992, Rayshubskiy et al. 2020), their necessity overlaps in certain behavioral contexts. Identification of Chx10 Gi neurons, which are required for locomotor asymmetries, allows an entry point for bottom-up dissection of such systems. Chx10 Gi neurons receive a number of unilateral projections from upstream nuclei (Cregg et al. 2020, Usseglio et al. 2020), including the ipsilateral zona incerta, the contralateral medial deep cerebellar nucleus, and the contralateral SC, among others. Of these, the contralateral lateral SC imparts directional commands via monosynaptic projection on Chx10 Gi neurons (Cregg et al. 2020). In rodents, the lateral SC receives input from the lower visual field (Dean et al. 1986, Isa et al. 2021, Zingg et al. 2017). Thus, the SC-Gi crossed projection appears to account for

modes of orientation relative to salient stimuli. Much less is known about how memory-guided navigation uses brainstem motor circuits to steer and move forward.

CONCLUDING REMARKS

Brainstem circuits play a central role in locomotor control. From an era where these circuits were studied with classical electrophysiological, anatomical, and pharmacological techniques, we are now in an era where a pallet of electrophysiological, molecular genetic, network, and behavioral approaches are routinely used to link aspects of behavior to designated neuronal brainstem populations. These studies have resolved issues about the organization of MLR, showing that it is composed of excitatory neurons in two nearby brainstem structures that control different aspects of the locomotor start and speed control. These studies have also designated some of the downstream circuits in the reticular formation that convey the MLR signal to the spinal cord and have predicted that others are involved. Parallel brainstem pathways involved in the stop and steering of locomotion have now been identified. How these command pathways orchestrate locomotor behavior through executive spinal circuits is not yet well understood. But with an understanding of the functional organization of the brainstem command signals, and key neuronal elements of spinal locomotor networks in vertebrates, it should now be possible to establish a functional connectome from the brainstem to the spinal cord. Such studies would be able to directly establish how locomotor rhythm is implemented in the cord and how gaits are controlled by the command signal. Perhaps the most significant aspect of delineating brainstem command pathways is that they serve as nodes that link distinct aspects of the motor output to context-dependent behavioral expression of locomotion. The clear behavioral organization of command pathways allows a bottom-up approach to probe higher brain functions—with locomotion as the vantage point. Building functional locomotor connectomes in this way will be an attractive theme in future research.

Insight into the functional organization of the brainstem command pathways is not only helping us to understand how animals and humans can move. This work also has important implications for understanding locomotor disorders, for example, locomotor impairment in Parkinson's disease, with a possibility for providing better treatments clinically.

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