Sensory Feedback Control of Locomotor Pattern Generation in Cats and Mice

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Abstract—Traditionally, research aimed at the understanding of the sensory control of terrestrial mammalian locomotion has focused on cats as the animal model. But advances in molecular genetics and new methods to record movement in small animals have moved mice into the forefront of locomotor research. In this review article, I will first give an overview of what is known about sensory feedback control of locomotion, mainly emerged from experiments performed on cats. This overview will not be an exhaustive overview, but will rather aim to give a broad picture of what has been learned about the sensory control of locomotion using cats as the animal model. I will then give a brief summary of how the mouse is adding to these insights.
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Key words: locomotion, walking, sensory feedback, cat, mouse.

LOCOMOTION AND THE SPINAL CIRCUITRY

Locomotion is defined as the movement from one place to another and is a basic behavior required for animal survival. The control of terrestrial locomotion depends on the temporal and phasic coordination of limb muscle activities, driven in large part by stereotypic and individualized patterns of flexor and extensor muscle activity at the hip, knee, and ankle joints (locomotor pattern) (Engberg and Lundberg, 1969; Grillner, 1981; Rossignol, 1996). How these patterned activities of multiple muscles are achieved has been one focus of neuroscience research and many insights have been gained for over a century. However, some core questions remain unresolved. For example, what is the precise role of somatosensory feedback in the generation of the locomotor pattern? One view was that locomotion is a result of sequential activation of reflexes, where the outcome of one reflex would activate the next reflex response, termed the reflex chain hypothesis (Sherrington, 1910). Later, it was shown that in the complete absence of somatosensory feedback, a network of interconnected interneurons located within the spinal cord (central pattern generator; CPG) can generate rhythmic motor activities that, to a certain degree, resembles the locomotor pattern (Brown, 1911; Stuart and Hultborn, 2008). Currently, it is generally accepted that the locomotor pattern emerges through the integrated action of the CPG in the spinal cord and the somatosensory feedback, however, the aspects of the locomotor pattern that are controlled by sensory feedback is still obscure. This article will summarize the main ideas that have emerged using the cat as the animal model in the last century and the emergence of the mouse model that now providing unprecedented insight into the neuronal mechanisms of locomotion.

During walking, each step is divided into two phases: the stance and the swing phases. During the stance phase, the foot is on the ground, moves backward with respect to the body during forward walking, and the leg provides body support and propulsion. At the end of the stance phase, when the leg is extended, the foot lifts off the ground and moves forward to be placed back on the ground to start the next stance phase. At a joint level, each joint has a characteristic angular movement profile during the swing and stance phases (Fig. 1A). The rhythmic and coordinated leg movements during walking are generated by patterned contractions of several dozen flexor and extensor muscles that move hip, knee, and ankle joints (Engberg and Lundberg, 1969; Grillner, 1981; Prochazka et al., 1989; Rossignol, 1996) (Fig. 1B). This patterned activity of muscles, the locomotor pattern, underlies the rhythmic and coordinated stepping movements of the hip, knee, and ankle joints of the mammalian leg.

Studies, mainly performed on cat hind legs, have revealed that during locomotion, extensor and flexor muscles controlling hip, knee, and ankle joints display distinct on- and offset timing, as well as a pronounced alternation in flexor–extensor phasing that accompanies the biomechanical transition of the hindlimb from stance to swing or swing to stance (Engberg and Lundberg,

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E-mail address: turgay.akay@dal.ca
Abbreviations: CPG, central pattern generator; GTOs, Golgi tendon organs.
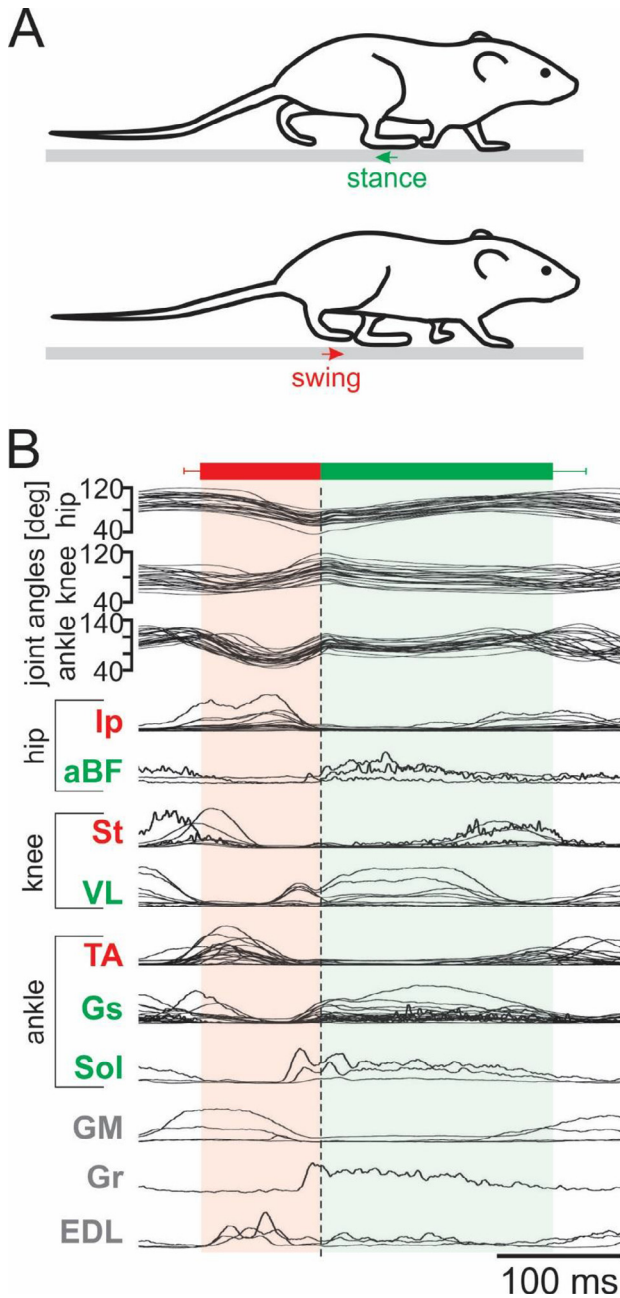
Fig. 1. The locomotor pattern during intact walking. **(A)** A single step cycle is divided into a stance (top) and a swing (bottom) phase. The green and red arrows indicate the movement of the foot relative to the body during stance and swing, respectively. Notice that during stance phase, the foot is stationary relative to the ground. **(B)** Angular movement of the three leg joints together with the EMG activity patterns of multiple muscles. The joint angle traces are averages from 25 wild type mice. The EMG traces are averages from these 25 mice with 4–6 EMG recording electrodes implanted into different combinations of muscles. The horizontal red and green bars are average swing and stance durations, respectively. Error bars indicate standard deviations. During swing (red background) and stance (green background) phases, individual joints move in a characteristic way. These joints are controlled by multiple flexor and extensor muscles that express a complex onset/offset pattern relative to each other. Flexors: Ip – Iliopsoas, St – Semitendinosus, TA – Tibialis anterior. Extensors: aBF – anterior Biceps femoris, Vastus lateralis, Gs – Gastrocnemius, Sol – Soleus. Others: GM – Gluteus maximus (abductor), Gr – Gracilis (adductor), EDL – Extensor digitorum longus (ankle flexor/paw dorsiflexor).

1969; Grillner, 1981; Rossignol, 1996; Stuart and Hultborn, 2008; Grillner and El Manira, 2020). Research conducted for over a century has provided evidence that core aspects of locomotion are imposed through the action of a network of spinal interneurons, the CPG (Brown, 1911; Jordan et al., 1979; Grillner, 1981; Lundberg, 1981). Further evidence from other investigations also indicates that sensory feedback impinges onto CPG networks and is required for the functional locomotor pattern to accommodate changes in task and terrain (Grillner and Rossignol, 1978; Duysens and Pearson, 1980; Hiebert et al., 1996; Lam and Pearson, 2001, 2002; McVea et al., 2005).

DIFFERENT TYPES OF SENSORY FEEDBACK REGULATE DIFFERENT ASPECTS OF STEPPING DURING LOCOMOTION – A CAT PERSPECTIVE

In general, peripheral afferents that provide somatosensory feedback to the locomotor CPG can be classified as exteroceptors and proprioceptors, depending on the source of the stimuli. The exteroceptive sensory feedback provides the locomotor CPG with information regarding stimuli coming from outside of the body. These signals are carried by different types of cutaneous afferents that innervate the skin of the body and respond to different kinds of skin deformations. There is a large number of cutaneous afferent types signaling a wide range of different aspects of tactile stimuli at the skin (Abraira and Ginty, 2013; Gatto et al., 2019). This review will be limited to non-nociceptive cutaneous afferents. These cutaneous afferents are mechanosensitive afferents that signal contact of the skin with external objects and can be activated with the injection of relatively lower current intensity (low-threshold). The proprioceptive sensory feedback provides information regarding the posture and movement of the animal's own body. This review will mainly focus on the role of two classes of proprioceptive sensory feedback on locomotor behavior. The first feedback is transmitted by the group Ia and II afferent fibers that carry information from the muscle spindles (Ruffini, 1898; Houk and Henneman, 1967; Windhorst, 2007, 2008). These group Ia and II afferents respond mostly to dynamic (group Ia) or static (group II) components of a muscle stretch and consequently signal angular joint movement or position, respectively. The second type of proprioceptive sensory feedback comes from the group Ib afferents carrying information from the Golgi tendon organs (GTOs) (Ruffini, 1898; Houk and Henneman, 1967; Windhorst, 2007). The GTOs are located at the myotendinous junctions and are sensitive to force. Furthermore, joint receptors also play a role in the detection of angular position (Burgess and Clark, 1969; Burke et al., 1988), but whether or not they play any role during locomotion is not clear.

WHAT IS THE ROLE OF CUTANEOUS FEEDBACK DURING LOCOMOTION?

Does low-threshold cutaneous sensory feedback information play any role during locomotor behavior? It

has been shown that electrical stimulation of cutaneous afferents from the plantar surface of the paw in decerebrate cats reduces ongoing flexor muscle activity and prematurely switches activity from flexor to extensor muscles, or augments ongoing extensor activity depending on the timing of stimulation (Duysens and Pearson, 1976). Similarly, when the cutaneous afferents from the dorsal surface (dorsum) of the paw are stimulated during the stance phase in spinalized cats, there is a strengthening of ongoing extensor muscle activity. Interestingly, when the dorsum stimulation occurs during the swing phase, it elicits a sequence of movements that lifts the foot higher up during the swing phase caused by activating distal flexor muscles (Forssberg et al., 1975, 1977). The latter reflex reaction resembles the response when the distal part of the leg of a cat collides with an obstacle during normal swing movement during walking, a reflex that is referred to as the "stumbling corrective reaction" (Forssberg, 1979). These results suggest that cutaneous feedback has at least a modulatory influence on locomotor behavior.

Is cutaneous feedback necessary for locomotor behavior? Research conducted more than a century ago suggested that removal of cutaneous feedback does not cause significant changes in locomotion, leading to the conclusion that cutaneous feedback has no major role in locomotion (Sherrington, 1910). Recent research confirmed these results by showing that surgical removal of cutaneous feedback from both hind legs in otherwise intact cats led to only minor changes during level walking (Bouyer and Rossignol, 2003a). However, these authors showed that more visible changes occurred during inclined walking and walking on a horizontal ladder, which in large part, though not completely, recovered in a matter of weeks following cutaneous ablation (Bouyer and Rossignol, 2003b). A recent study that silenced cutaneous feedback using a local anesthetic showed that cats could walk on a split-treadmill with left and right legs walking at different speeds, but stability is affected (Park et al., 2019). The importance of cutaneous feedback for locomotion became more obvious when the cats were spinalized either before or after the loss of cutaneous feedback (Bouyer and Rossignol, 2003b); in these spinalized cats, silencing cutaneous feedback led to significant misplacement of the paw after the swing phase and loss of weight-bearing during stance. These observations suggest that cutaneous feedback is essential for the fine-control of locomotion and it helps during recovery following injury, but its loss can be compensated for, perhaps by supraspinal centers connected to the spinal circuitry.

WHAT IS THE ROLE OF PROPRIOCEPTIVE FEEDBACK DURING LOCOMOTION?

Apart from cutaneous feedback that signals exteroceptive information, proprioceptive feedback has also been shown to be important in controlling locomotion, as it has been shown that rhythmic proprioceptive signaling can entrain the locomotor pattern in spinalized or in decerebrate cats (Pearson et al., 1992; Kriellaars et al., 1994). Furthermore, two different aspects of the locomo-

tor activity are controlled by the proprioceptive feedback: First, proprioceptive feedback controls the strength of muscle activation during walking. Second, proprioceptive sensory feedback controls the transitions form the stance to swing phases. Below, I summarize these two aspects of proprioceptive control of locomotion.

It has been established that muscle activity strength is adjusted to environmental and behavioral requirements, as demonstrated with electromyogram (EMG) recordings in cats locomoting at different speeds (Pierotti et al., 1989; Smith et al., 1993), across locomotor gaits (Smith et al., 1993), and walking upslope (Pierotti et al., 1989; Carlson-Kuhta et al., 1998), or downslope (Smith et al., 1998). This evidence indicated that proprioceptive feedback is important for the regulation of muscle activity strength (Hiebert and Pearson, 1999). Later experiments supported the idea that proprioceptive feedback from group Ib afferents from the GTOs provides the source for this sensory regulation of muscle activity (Donelan and Pearson, 2004a,b; Donelan et al., 2009; Hatz et al., 2012), with a more minor contribution from the muscle spindles through the group II afferents (Hatz et al., 2012). Together, these studies suggested that group Ib feedback from the GTOs regulates muscle activity strength during locomotion at different environments and speeds in cats, but the importance of feedback from muscle spindles remained obscure.

When animals locomote, the transition from stance to swing phase is controlled by proprioceptive sensory feedback that signals the body's position or motion. More specifically, two critical proprioceptive signals have been shown to play a role in the initiation of the transition from stance to swing. First, the hip joint needs to extend to a specific position that is signaled by muscle spindles from the hip flexor muscles to start a swing phase (Grillner and Rossignol, 1978; Hiebert et al., 1996). Second, the loading of extensor muscles, signaled by GTOs, prevents the initiation of the swing phase (Duysens and Pearson, 1980). It has been suggested that the unloading of the extensor muscles during the progression of the stance phase is a necessary sensory signal that contributes to the transition from stance to swing phase. Furthermore, feedback signaling the angular position of the hip joint of the hind leg has been shown to play a role at the end of the swing phase (Lam and Pearson, 2001; McVea et al., 2005). Thus, while intrinsic networks in the spinal cord are able to initiate transition of activities in flexor and extensor muscles that could correspond to swing and stance phase, these transitions seem to be controlled by proprioceptive sensory feedback during natural walking.

Is sensory feedback required for the relative timing of on- and offsets of individual muscle activities relative to the rhythmic and coordinated leg movement (locomotor pattern) during walking? As discussed above, sensory feedback is important for the generation of intact locomotion, but it is not clear that it is necessary for the generation of the locomotor pattern. It is possible that the locomotor pattern could be achieved by the CPG in the absence of sensory feedback, implying that the locomotor pattern in an animal would be preserved

following the ablation of sensory feedback (Grillner, 1981). Alternatively, in the absence of sensory feedback, the CPG would only generate a flexor–extensor alternation where all flexor and extensor MN pools would be active during the flexor or extensor phases, respectively (Lundberg, 1981). This implies that the locomotor pattern observed in the intact animal is a result of the interaction between the sensory feedback and the CPG. Experiments were performed on walking cats with sensory feedback removed either by surgical (Grillner and Zangger, 1979, 1984) or pharmacological methods (Jordan et al., 1979; Pearson and Rossignol, 1991) to differentiate between these two possibilities. Nevertheless, it has not been possible to obtain persuasive evidence that the CPG can produce locomotor pattern as it occurs during intact walking. The output generated by the CPG is not a simple flexor–extensor alternation but a more complex pattern that is unstable (Grillner and Zangger, 1979, 1984) and to only some extent, resembles the normal locomotor pattern (Pearson and Rossignol, 1991; Markin et al., 2012). From these observations, it follows that some aspects of the coordinated activation of multiple muscles can be achieved by the CPG alone, but sensory feedback is necessary to achieve the actual pattern that occurs during intact locomotion.

COMBINATION OF MOLECULAR GENETICS AND IN VIVO PHYSIOLOGY – A MOUSE PERSPECTIVE

With advances in molecular genetics and developmental biology, mice have become a critical animal model for understanding neuronal mechanisms of locomotion. Mice have only relatively recently become a model system for locomotor experiments and consequently, there are far fewer studies on locomotion than those in the cat. However, some observations in mice have already confirmed and extended work in the cat. Below, I will summarize recent findings that have provided new insights into sensory control of locomotion.

WHAT IS THE ROLE OF CUTANEOUS FEEDBACK DURING LOCOMOTION?

There is currently very limited data on what the role of cutaneous feedback is during unperturbed mouse locomotion that could be comparable to the insights gained on cat walking. It has been shown that in the absence of genetically identified groups of interneurons, the dI3 interneurons that mediate specific cutaneous reflex responses, only minor changes in walking were observed (Bui et al., 2013, 2016). However, these studies also showed that the walking behavior did not recover after spinal cord transection in mice with dI3 interneurons silenced to the same extent as observed in wild type mice (Bui et al., 2016). This observation supports the results from cat experiments suggesting that loss of cutaneous feedback in intact cats causes minor changes (Bouyer and Rossignol, 2003a), but in spinal cats causes major deficits (Bouyer and Rossignol, 2003b).

As shown in cats (Forssberg et al., 1975, 1977) when an obstacle hits the dorsum of the mouse hind paw during swing, a stumbling corrective reaction is elicited that involves activation of distal flexor muscles that pull the leg higher to clear the obstacle (Mayer and Akay, 2018). This stumbling corrective reaction can also be elicited with electrical activation of afferents that normally signal an obstacle if stimulation occurs during the swing but not during stance phase. Furthermore, genetically distinct groups of interneurons have been identified that seem to be part of the network controlling corrective responses after slips during beam walking (Bourane et al., 2015; Paixao et al., 2019). At this point, we do not know whether these interneurons are involved in the stumbling corrective reactions during mouse walking.

In short, there is no data originating from experiments on mice that would support the conclusions drawn from cat studies that cutaneous feedback has a minor role in normal locomotion, but its importance is more visible during locomotion on challenging surfaces or after spinal cord injury (Bouyer and Rossignol, 2003a,b). However, mechanical perturbation of the swing movement during mouse walking initiates a well-defined response (Mayer and Akay, 2018), the stumbling corrective reaction, described in cats almost half a century ago (Forssberg et al., 1975, 1977). The challenge and the opportunity for the future is to combine molecular genetic techniques that isolate different classes of interneurons (Bui et al., 2013; Bourane et al., 2015; Abraira et al., 2017; Paixao et al., 2019) with electrophysiology and motion analysis to understand the discrete components of the spinal network that controls the stumbling corrective reaction.

WHAT IS THE ROLE OF PROPRIOCEPTIVE FEEDBACK DURING LOCOMOTION?

Removal of proprioceptive feedback in mice, including the feedback from muscle spindles and the Golgi tendon organs, has a profound effect on the locomotor pattern, expressed as ataxia (Akay et al., 2014; Takeoka and Arber, 2019). However, if proprioceptive feedback is removed only from the muscle spindles with feedback from the Golgi tendon organs left intact, as in the *Egr3* knockout (*Egr3-KO*) mice, a milder form of ataxia is observed when animals walk on a treadmill at constant speed (Akay et al., 2014). This mild ataxia was shown to be associated with compromised precision of foot placement following a swing movement. In addition to ataxia, it has also been shown that in the absence of muscle spindles, mice are more susceptible to external perturbations (Santuz et al., 2019). The mild ataxia observed during walking becomes more obvious when *Egr3-KO* mice swim, likely to the fact that intact GTO feedback is reduced during swimming because of diminished gravitational influence due to the buoyancy of the water (Gruner and Altman, 1980). Together, these results support the idea that proprioceptive sensory feedback is necessary to generate a functional locomotor pattern. Apart from the ataxia that was observed in the absence of proprioceptive feedback from muscles, it has also been shown that proprioceptive feedback from muscles is important for locomotor recovery following spinal cord injury (Takeoka et al., 2014). The results from research per-

formed on mice, therefore, strongly suggest that normal locomotor activity and recovery after injury require proprioceptive feedback.

From previous work in cats, it has been shown that proprioceptive feedback plays a role in the regulation of EMG activity strength in the muscles (amplitude modulation) but it is not clear what the specific role feedback from muscle spindles play in modulating amplitude (Donelan and Pearson, 2004a,b; Donelan et al., 2009). In a recent investigation in mice, it was shown that muscle spindle feedback plays an important role in the regulation of the speed-dependent amplitude modulation in extensor muscles (Mayer et al., 2018). Furthermore, it has been demonstrated that muscle spindle feedback from the ankle extensor muscles specifically is the source of this feedback. This finding is in accordance with the previous observations in cats that stimulation of muscle afferents from ankle extensors specifically enhances extensor activity during locomotor activity (Guertin et al., 1995; McCrea, 2001). These mouse studies, therefore, show that muscle spindle feedback does play a role in activity amplitude modulation and define ankle extensor muscles as the source of this feedback.

LIMITATION OF EXPERIMENTS WITH SENSORY ABLATION

The traditional way of investigating the role of feedback from different sensory systems in the locomotor behavior has been to eliminate sensory feedback using surgical, pharmacological or genetic methods and measure the outcome on locomotion. One limitation with this approach is that the nervous system, when deprived of a specific sensory information, is capable of adapting to the sensory loss. This has been demonstrated for example for loss of vision and audition (Voss et al., 2010) or for loss of proprioception (Cole and Sedgwick, 1992). In each case, sensory information from other modalities was able to compensate for the loss of a particular sensory modality. Therefore, the results in which a certain type of somatosensory sensation is removed have to be interpreted with caution. Furthermore, adaptation can also occur by secondary changes within the premotor neuronal network within the central nervous system due to sensory loss. For example, when proprioceptive afferents are killed by selective diphtheria toxin light chain A expression during embryonic development in a mutant mouse, the mice are severely affected (Akay et al., 2014). However, when the same afferent neurons are selectively killed by systemic diphtheria toxin injection in mutant mice in which these afferents express the receptor for the diphtheria toxin, the effect is milder (Takeoka and Arber, 2019). One possible explanation for this discrepancy is changes within the premotor network due to loss of proprioception during embryonic development when the premotor network is still under development (Tripodi et al., 2011). Therefore, when deafferentation experiments are conducted, adaptation must be considered by focusing on acute removal of sensory feedback and avoiding long delays until recordings to avoid adaptation.

CATS OR MICE?

There is no doubt that the emergence of the mouse as an animal model has provided new insights into the sensory control of locomotion that would have not been possible in classical model systems. Does this make research performed on cats redundant? I personally believe strongly that the mouse cannot replace cats as an animal model, but rather these two models complement each other for at least four reasons: (1) The large size of the cat allows the implantation of larger numbers of electrodes, enabling a more complete picture of the locomotor pattern (Krouchev et al., 2006; Hurteau et al., 2018). On the other hand, while the smaller size of the mouse limits the number of recording sites, the use of neural circuit manipulation through genetics provides enormous opportunities to gain insights into neuronal networks (Akay et al., 2006a, 2014; Mayer and Akay, 2018; Mayer et al., 2018; Santuz et al., 2019). (2) Cats can be easily trained to perform more complex locomotor tasks, such as walking on split-belt treadmills with different legs moving with different speeds (Cruse and Warnecke, 1992; Akay et al., 2006b; Park et al., 2019) or walking on pegways (Donelan et al., 2009; Hatz et al., 2012). These experiments, although possible, are significantly harder to do with mice (Darmohray et al., 2019). (3) The tall posture and longer legs of the cat lead to a higher location of the center of mass than in mice, making the cat mechanically less stable to lateral perturbations during locomotion (Bolton and Misiaszek, 2009). (4) The inertia of the mouse limb is too small to significantly affect limb dynamics, whereas effects of the larger inertia of the cat limb on limb dynamics are more similar to humans (Wisleder et al., 1990; Zernicke et al., 1991). Somatosensory feedback is critical for the control of complex dynamics of multisegmented limbs with large inertia (Sainburg et al., 1995; Hooper et al., 2009; Hooper, 2012). Thus, a higher center of mass and larger leg inertia makes cat locomotion more comparable to human walking, and therefore more relevant for comparative studies to aid the understanding of human locomotion in the clinical context. Ideally, the most efficient way to understand neuronal control of locomotion in mammals is to conduct parallel and complementary research in cats and mice, rather than replacing one with the other.

The development of the mouse as an animal model has added important insights to our understanding of the sensory control of locomotion. The contribution of Dr. Thomas M. Jessell to these advancements is enormous (Arber et al., 2019). In terms of understanding the sensorimotor control of mammalian locomotion, his contributions laid the foundation for developmental genetics that allowed the identification of interneurons of the spinal CPG based on transcriptional codes (Tanabe and Jessell, 1996; Ericson et al., 1997; Briscoe et al., 2000; Jessell, 2000). Moreover, he was an endless innovator in the development of new *in vivo* methodologies to record motor behavior (Akay et al., 2014; Azim et al., 2014; Murray et al., 2018). This combination of neural and behavioral access promises new unprecedented insights into the neuronal control of movement and can be considered as one of many legacies of Dr. Jessell to the field.

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