Genetically identified spinal interneurons integrating tactile afferents for motor control

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Bui TV, Stifani N, Panek I, Farah C. Genetically identified spinal interneurons integrating tactile afferents for motor control. J Neurophysiol 114: 3050 –3063, 2015. First published October 7, 2015; doi:10.1152/jn.00522.2015.—Our movements are shaped by our perception of the world as communicated by our senses. Perception of sensory information has been largely attributed to cortical activity. However, a prior level of sensory processing occurs in the spinal cord. Indeed, sensory inputs directly project to many spinal circuits, some of which communicate with motor circuits within the spinal cord. Therefore, the processing of sensory information for the purpose of ensuring proper movements is distributed between spinal and supraspinal circuits. The mechanisms underlying the integration of sensory information for motor control at the level of the spinal cord have yet to be fully described. Recent research has led to the characterization of spinal neuron populations that share common molecular identities. Identification of molecular markers that define specific populations of spinal neurons is a prerequisite to the application of genetic techniques devised to both delineate the function of these spinal neurons and their connectivity. This strategy has been used in the study of spinal neurons that receive tactile inputs from sensory neurons innervating the skin. As a result, the circuits that include these spinal neurons have been revealed to play important roles in specific aspects of motor function. We describe these genetically identified spinal neurons that integrate tactile information and the contribution of these studies to our understanding of how tactile information shapes motor output. Furthermore, we describe future opportunities that these circuits present for shedding light on the neural mechanisms of tactile processing.

tactile information; spinal cord; sensorimotor integration; genetically identified spinal neurons

THE NEURAL CONTROL OF MOTOR activity is a product of signals arising from three main sources: supraspinal centers, spinal networks, and peripheral sensory afferents. In most general terms, supraspinal centers generate motor commands and select appropriate sequences of motor activity; spinal networks translate descending motor commands into muscle activity. Sensory information conveys important information about the external world (exteroceptive) and about the internal self (interoceptive) to central networks. Whereas basic motor activity can be generated by spinal networks, with or without motor commands from supraspinal networks, the achievement of high complexity, range, accuracy, and fluency of movement within changing and challenging environments is impossible without sensory information (Acevedo and Diaz-Rios 2013; Akay et al. 2014). Sensory information is vital to ensuring appropriate motor execution by evaluating and adjusting motor commands during ongoing motor activity.

Sensory information can be arranged into functional groups or modalities, such as sight, hearing, balance, taste, smell, temperature, nociception, proprioception, and touch. Proprioception contributes to the control of movement by communicating muscle properties and body position. Tactile information is also integral to the control of movement, as it guides movements by providing information about physical features of the external world. This occurs via a process where tactile stimuli are detected and transduced by specialized mechanoreceptors in the skin [for review, see Abraira and Ginty (2013)] and transmitted via afferent fibers from the periphery to the
central nervous system (CNS). These signals enter the spinal cord and are directed to the sensory areas of the brain via brain stem nuclei and the thalamus. At the cortical level, tactile information is processed, organized, and interpreted, which in turn, is used to guide behaviors by adjusting descending motor commands. In parallel to the perception of tactile signals generated at the cortical level, tactile signals are also integrated at the level of the spinal cord. That is, in addition to sending projections that travel rostrally up the dorsal column, cutaneous afferents project collaterals that branch out within the spinal cord and terminate onto spinal interneurons (INs) (Brown et al. 1981). Thus the spinal cord serves as a site of active integration of tactile information, putatively for the purpose of shaping tactile perception and/or sensorimotor integration.

With regards to the perception of touch stimuli, little is known about how it is influenced by integration of tactile information at the level of the spinal cord. However, it has been established that movement itself can both stimulate sensory receptors and suppress cutaneous sensation (Prochazka 1989). Indeed, the perceived intensity of cutaneous stimulation is reduced during movement (Duysens et al. 1995; Milne et al. 1988). This may be a result of suppressed sensory transmission at the level of the spinal cord, as suggested by experiments in monkeys where cutaneous sensory-evoked potentials recorded in the spinal cord were reduced during active hand movement (Seki and Fetz 2012). Hence, spinal networks likely contribute to the final tactile perception.

The involvement of tactile information in shaping motor control through spinal circuitry is much more established than its role in tactile perception (briefly reviewed in Panek et al. (2014)). In humans, motor reflexes can be evoked by electrical stimulation of cutaneous afferents applied through surface or ring electrodes. The early components of these reflexes were revealed to be mediated by spinal circuits rather than through long ascending and descending pathways connecting the brain and the spinal cord (Jenner and Stephens 1982). These circuits denote a strong coupling of low-threshold mechanoreceptors (LTMRs) to both hand and leg motoneurons (Fallon et al. 2005; McNulty et al. 1999). As described below, these observations are part of a growing body of work demonstrating integration of tactile information by spinal circuits involved in motor control. However, the precise outcome of this integration in actually sculpting motor activity has not been well understood. Recent studies have started to shed light on spinal circuits processing tactile signal and their role in motor function (Bourane et al. 2015; Bui et al. 2013; Fink et al. 2014). In this review, we provide an overview of the spinal circuits that have been shown to be involved in sensorimotor integration of tactile information. Furthermore, we discuss the properties of these spinal circuits, including their location, connectivity, and interactions, with spinal motor circuits. We focus on spinal INs that have been identified recently using molecular and genetic studies and that have been ascribed to sensorimotor integration. The study of these INs has added to our understanding of how tactile information can shape motor activity through spinal circuitry. Finally, we outline potential avenues for research using genetically identified spinal neurons to address outstanding questions.

Properties of Spinal Circuits Processing Tactile Information

Location. The most likely location of spinal INs processing tactile information for motor control can be estimated based on the topographical distribution of the central terminals of LTMRs within the spinal cord. The spinal cord is composed of INs located in Rexed laminae I–VIII and X and motoneurons located in laminae IX (Rexed 1952, 1954). Whereas nociceptive sensory neurons predominantly contact spinal INs in the most superficial laminae (I and II) of the dorsal horn, tracing studies of myelinated cutaneous afferents have described the most dense labeling of terminals to be found in laminae III–V of the spinal cord in rodents (Levinsson et al. 2002; Molander and Grant 1986; Panneton et al. 2005), cats (Brown et al. 1981), and primates (Florence et al. 1991). Consistent with this distribution of tactile afferents within the spinal cord, electrophysiological recordings of touch-evoked sensory inputs to spinal neurons in laminae III–V have been reported in primates (Wagman and Price 1969), rats (Woolf and King 1989), hamsters (Schneider 2005), and cats (Koerber et al. 1990; Sahai et al. 2006), amongst others. Some of these laminae III–V spinal neurons receiving sensory inputs from LTMRs have been identified as premotor INs [i.e., neurons projecting directly to motoneurons (Egger and Wall 1971; Hongo et al. 1989a, b)], whereas some have been observed in more ventral laminae VI and/or VII (Edgley and Jankowska 1987; Moschovakis et al. 1992; Stepfen et al. 2010). This anatomical specificity reflects functional differences that are embedded in the spinal network connectivity.

Shaping specific forms of motor activity. Whereas the precise connectivity between tactile afferents and spinal neurons has not been fully characterized, tactile information has been shown to be particularly important for several motor functions, such as the control of grip strength (Jenner and Stephens 1982; Johansson and Flanagan 2009). During hand grasp, activation of tactile afferents increases hand muscle contraction (Collins et al. 1999; Johansson et al. 1987). Local anesthesia of the fingers or hands precludes human subjects from performing gripping tasks accurately (Augurelle et al. 2003; Johansson and Westling 1984). Furthermore, this deficit could not be compensated by consciously attempting to increase grip strength. Tactile afferents are also involved with locomotor function at the level of the spinal cord. Activation of LTMRs can evoke sets of stereotyped limb reflexes [e.g., tripping perturbations; see Drew and Rossignol (1987); Forsberg et al. (1977); Quevedo et al. (2005a)], as well as modulate the timing (Duysens and Pearson 1976) and levels of muscle activation during locomotion (Duysens and Loeb 1980; Loeb et al. 1987). These reflexes have been suggested to be involved in fine-tuning the timing of locomotor activity (MacKay-Lyons 2002), as well as stabilizing gait in the wake of unexpected perturbations (Bunday and Bronstein 2009; Choi et al. 2013; Zehr et al. 1998). These results underline the importance of the recruitment of spinal circuits by tactile afferents to perform precise motor functions.

Gating of sensory integration at the level of the spinal cord by motor circuits. As alluded earlier, the relationship between tactile inputs and spinal motor circuits is not strictly unidirectional, where sensory inflow adjusts motor activity through spinal circuitry. Rather, it is bidirectional; there is ample evidence that sensory transmission to the spinal cord from
LTMRs is, in turn, modulated by motor activity. For instance, motor reflexes evoked by tactile input are phasically modulated during locomotion in cats (Degtyarenko et al. 1998; Forsssberg et al. 1977; Quevedo et al. 2005a, b) and in humans (Baken et al. 2005; Van Wezel et al. 1997; van Wezel et al. 2000; Zehr et al. 1997, 1998). Cutaneous reflexes also seem to be modulated by the type of activity during which they are evoked, as observed in humans, for example, during different gaits (Duyssens et al. 1993; Hoogkamer et al. 2012), fine vs. coarse hand movements (Evans et al. 1989), and different limb or hand postures (Garnett and Stephens 1981; Gibbs et al. 1995).

The modulation of cutaneous reflexes by motor activity may be due to gating of sensory transmission, which seems to occur at many levels of the CNS, including at the level of the spinal cord (Seki and Fetz 2012). However, there is also evidence suggesting that modulation of spinal INs integrating tactile information for motor control may contribute to gating of cutaneous reflexes (Burke et al. 2001; Quevedo et al. 2005a).

It is not clear whether the bidirectional interactions between tactile inputs and motor networks are mediated strictly by spinal circuits or whether they rely on supraspinal control. Indeed, motor control involves hierarchical circuits spanning both spinal and supraspinal networks that enable motor adaptation and motor learning (Kawato et al. 1987). Likewise, sensorimotor integration is distributed across the CNS hierarchy. The distance of a sensorimotor circuit to the musculoskeletal system (spinal circuits being closer, supraspinal circuits being farther) introduces a relative delay to when sensory information influences motor activity (Shadmehr et al. 2010). Therefore, the understanding of at which levels of the CNS sensorimotor interactions occur is important to uncover the roles of these widely distributed sensorimotor circuits. In spite of the truly heroic efforts in earlier decades to demonstrate the presence of spinal circuits integrating tactile afferents, ascribing detailed motor roles to particular groups of spinal INs has been a difficult goal to achieve. The advent of recent genetic approaches to studying spinal neurons has enabled combinations of electrophysiological, cell labeling, and behavioral testing techniques that have provided strong evidence that spinal circuits integrating tactile information play crucial roles in ensuring proper motor control (Bourane et al. 2015; Bui et al. 2013). These genetic approaches are based on the insight that during development, populations of neurons emerge from common progenitor pools that arise from the interaction of inductive signals released by structures, such as the roof plate, floor plate, and notochord (Jessell 2000; Stifani 2014). These signals promote the activation of many transcription factors involved in a diverse set of developmental processes, such as cell cycle progression and exit, cell migration, axon guidance, and establishment of neurotransmitter phenotype, to name a few. Each progenitor pool will express a unique combinatorial set of transcription factors (Fig. 1F). The partitioning of spinal neurons into genetically identified populations has been particularly successful (Alaynick et al. 2011; Francius and Clotman 2014; Lu et al. 2015; Stifani 2014). Herein, we describe those populations of genetically identified spinal neurons that have been determined to integrate tactile afferents for the purpose of shaping motor activity and the fundamental insights that the study of these neurons has provided.

\textbf{dI3 INs}

dI3 INs represent one of six identified, early born, dorsally derived populations of INs (dI1–dI6) of the spinal cord (Fig. 1B). These neurons were described initially following the analysis of transcription factors active in the spinal dorsal horn during development, in particular, through the assessment of the effects of gene knockouts on expression patterns of transcription factors (Gross et al. 2002; Muller et al. 2005; Nakada et al. 2004; Wine-Lee et al. 2004). As a result, the dI3 IN population is well characterized by the expression of Brn3a/b, Tlx3, Gsh1/2, and Ascl1, amongst other transcription factors in progenitor and/or postmitotic cells derived from this population (Mizuguchi et al. 2006; Zou et al. 2012). More importantly, they are characterized further by the expression of Isl1, a LIM homeodomain transcription factor that is also expressed in motoneurons but uniquely found in dI3 INs amongst neurons of the dorsal spinal cord (Liem et al. 1997; Pfaff et al. 1996). This exclusive expression of Isl1 amongst dorsal neurons has enabled the application of genetic, electrophysiological, and immunohistochemical methods to characterize dI3 INs and to determine their role in motor control (Bui et al. 2013; Goetz et al. 2015; Pivetta et al. 2014; Stepien et al. 2010).

Conditional expression of yellow fluorescent protein by Isl1 has been used to determine that dI3 INs are primarily located in laminae V–VII at similar densities in cervical and lumbar spinal segments (Bui et al. 2013). Cell labeling and in situ hybridization for vesicular glutamate transporter 2 (vGluT2) mRNA showed that dI3 INs are predominantly glutamatergic with ipsilateral projections (Bui et al. 2013). Retrograde tracing of synaptic inputs to motoneurons using modified rabies virus demonstrated that dI3 INs directly contact motoneurons in the spinal cord (Goetz et al. 2015; Stepien et al. 2010). They are therefore part of a large group of “last-order” spinal INs that control motor activity through direct excitation of motoneurons (Brownstone and Bui 2010).

Of these last-order spinal INs, dI3 INs belong to the subset that receives sensory inputs. Indeed, vGluT1 labeling revealed that dI3 INs receive primary afferent input (Alvarez et al. 2004). A large portion of these vGluT1-immunoreactive afferents were characterized by an absence of expression of parvalbumin, suggesting that much of the sensory input to dI3 INs is not proprioceptive in nature but may rather originate from cutaneous afferents (Bui et al. 2013). Transgenic mice (named dI3OFF)—in which dI3 IN neurotransmission was genetically silenced through conditional ablation of vGluT2, a protein used by these INs for glutamatergic synaptic transmission—were used to define further the nature of the cutaneous afferents that project to dI3 INs (Bui et al. 2013). In control mice, in vivo or in vitro stimulation of the sural nerve, which predominantly carries cutaneous information (Peyronnard and Charron 1982), resulted in strong motor reflexes. The early components of this reflex exhibited latencies characteristic of a disynaptic pathway. Concurrently, recordings of dorsal root potential demonstrated that the reflex was generated by stimulation of low-threshold myelinated fibers corresponding to low-threshold myelinated Aβ-LTMRs. This reflex response was completely absent in dI3OFF mice, suggesting that dI3 INs are involved in a disynaptic microcircuit linking cutaneous afferents (conveying touch) with motoneurons (Figs. 1B and 2) (Bui et al. 2013).
To determine the functional role of the tactile sensorimotor circuit mediated by dI3 INs, motor function of the dI3OFF mice was tested in a number of behavioral tests. dI3OFF mice demonstrated greater difficulty with the ladder test and displayed an increase in missteps compared with control littermates (Bui et al. 2013). Even so, the most striking deficit was an inability to mediate grip strength in the face of increasing loads—their own weight—during the wire hang test (Bui et al. 2013). Both of these handicaps resulted from the silencing of dI3 INs. Whereas the above experiments did not identify exact types of LTMRs con-
tacting dI3 INs, it is possible to exclude a major contribution from Merkel cells, as experiments in which Merkel cells were eliminated from mice did not result in any deficits in grasping, as tested by the wire hang test (Maricich et al. 2012). The genetic silencing studies and the previous immunohistochemical and electrophysiological experiments lead us to believe that dI3 INs integrate cutaneous information necessary for motor behaviors. The most evident involvement of this circuitry is in grasping; however, their full involvement in other motor behaviors has not been fully determined.

**Related Orphan Receptor INs**

To identify putative populations of spinal neurons that process tactile information for motor control, Del Barrio and colleagues (2013) performed a preliminary transcription factor screening to probe the molecular identities of INs in laminae III–V, which are predominantly innervated by LTMRs that transduce cutaneous mechanosensory information. From this screen, INs expressing the protein retinoic acid receptor-related orphan receptor α (RORα) were targeted and studied further using transgenic methods (Bourane et al. 2015). The RORα IN population is characterized by its expression of RORα, MafA, c-Maf, and Lmx1b, amongst other transcription factors, where the latter can mark excitatory INs in the dorsal spinal horn (Ding et al. 2004). To confirm the excitatory nature of these cells, in situ hybridization for vGlut2 mRNA revealed that RORα INs are predominantly glutamatergic.

The mapping of RORα INs demonstrated that they are mostly located between inner lamina II (III) and lamina III. RORα INs are primarily innervated by LTMRs and receive little to no nociceptive input. The combination of recent advances in recombinant rabies virus techniques to label genetically identified neurons (Weible et al. 2010) and identification of molecular markers for LTMRs (Li et al. 2011; Luo et al. 2009) allowed for characterization of the sources of sensory input to RORα INs. Interestingly, these INs were demonstrated to be innervated by Meissner corpuscles in glabrous skin and Merkel cells, D-hair terminals, and transverse lanceolate endings in hairy skin (Bourane et al. 2015). Furthermore, putative evidence suggests the implication of Ruffini endings as sensory input; however, the full extent of the innervation of RORα INs by LTMRs innervating this class of sensory receptors requires...
further investigation. These anatomical experiments were substantiated further by whole cell recording of these neurons, which demonstrated the presence of monosynaptic excitatory potentials mostly in response to electric recruitment of low-threshold myelinated Aβ and high-threshold myelinated Aδ fibers (Bourane et al. 2015).

To determine whether RORα INs play a role in motor control, projections to spinal neurons involved in motor activity were sought (Bourane et al. 2015). Indeed, spinal RORα INs were found to project directly on motoneurons in the lumbar spinal cord. Furthermore, contacts were found on V0 cholinergic (V0c) neurons, which are known to modulate the excitability of motoneurons, suggesting perhaps that RORα INs possess the ability to modulate motor output through the intermediary of V0c neurons (Zagoraiou et al. 2009). Additionally, RORα INs were found to be innervated by corticospinal tract neurons in motor cortex and by lateral vestibulospinal tract (LVST) neurons. LVST neurons are known to originate in the pons and project downwards to the spinal cord carrying information about posture and balance (Markham 1987). Collectively, these results demonstrate that RORα INs are spinal neurons that are implicated in integrating tactile inputs to shape motor activity (Fig. 1C).

To study the specific role of RORα INs in motor control, ablation of RORα INs in the caudal spinal cord was achieved by inducing selective expression of the diphtheria toxin receptor in RORα INs and subsequent treatment with diphtheria toxin (Bourane et al. 2015). The resulting mice were subjected to a battery of sensory tests. Most interestingly, these mice displayed an impairment in sensing dynamic and static light touch on the plantar surface of the foot. Nonetheless, the RORα IN-ablated mice showed no difference in pain sensation, suggesting that RORα INs mainly contribute to light-touch perception without compromising responsiveness to other sensory modalities. RORα IN-ablated mice did not show any significant locomotor differences to control littersmates when tested on a treadmill or on a horizontal ladder. However, when fine motor control during locomotion was accessed by the raised beam test (Crawley 2008), a significant increase in hindlimb missteps was reported. These results suggest that RORα INs mediate cutaneous sensory information for use in motor commands involved in corrective foot movements.

The ablation and tracing studies showed that RORα INs integrate cutaneous sensory information from LTMRs with descending cortical inputs into motor commands for corrective foot movements; however, the mechanisms by which these neurons integrate this descending cortical input have yet to be studied.

**dl1 INs**

Defined by expression of Atoh1 (formerly Math1), dl1 INs are also a population of dorsally derived neurons that migrate ventrally to be positioned in the deep dorsal horn of the spinal cord (Bermingham et al. 2001). These neurons form three distinct spinocerebellar tracts (SCTs), by which sensory feedback is relayed to the cerebellum. In more rostral spinal cord segments (cervico-thoracic), dl1 INs form the rostral SCT (rSCT), whereas in more caudal spinal cord segments (thoracolumbar-sacral), dl1 INs are found in two clusters that form the dorsal SCT (dSCT) and the ventral SCT (vSCT) (Miesegaes et al. 2009) (Fig. 1E). The SCTs convey sensory information from muscle afferents and to a lesser degree, from LTMRs to the cerebellum (Edgley and Jankowska 1988; Randic et al. 1981), a region important for correcting movements and for motor learning (Brownstone et al. 2015; Kawato et al. 1987). Therefore, these neurons are involved with sensorimotor integration at supraspinal levels. There is less information about their interaction with motor circuitry at the spinal cord level; however, neurons of the dSCT are contacted by corticospinal inputs, suggesting that the sensory feedback that they relay is shaped by descending motor commands (Hantman and Jessell 2010).

**Key Insights and Open Questions**

Much work has been dedicated in the past to revealing the presence of spinal neurons that integrate tactile input and in the process, sculpt ongoing motor activity. The recent studies of genetically defined spinal INs that we have described (summarized in Fig. 1) build on the work of the past decades and serve...
Identification of Other Spinal Populations/Subpopulations that Integrate Tactile Information

A long-standing question in neuroscience is how to classify populations of neurons (DeFelipe et al. 2013). Classes of neurons can be defined based on single or combinations of intrinsic properties, such as protein expression, morphology, anatomical location, neurotransmitter phenotypes, synaptic inputs, and/or outputs. Alternatively, neurons can be classified along functional lines, such as firing behavior and involvement with certain neuronal or physiological forms of activity. Needless to say, the classification of neurons is an ongoing, fluid exercise that is necessary for the proper study of neural systems. For the immediate purpose of discussing classes of spinal neurons involved with the integration of tactile information for motor control, it is necessary to highlight that each of the canonical populations of genetically identified spinal INs (dI1–dI6; dIL,A-B; V0–V3) and motoneurons is likely to consist of many subpopulations of neurons that are differentiated along molecular and/or functional lines. For instance, the V2 population of ipsilaterally projecting ventral neurons, which are characterized by Lhx3 expression, has been parsed out to consist of V2a, V2b, and V2c, based on Chx10, Gata2, and Sox1 expression (Al-Mosawi et al. 2007; Lundfeld et al. 2007; Panayi et al. 2010; Zhou et al. 2000). These neurons are also distinguished by different neurotransmitter phenotypes and likely, functional roles as well (Crone et al. 2008; Zhong et al. 2007; Panayi et al. 2010; Zhou et al. 2000). Not surprisingly, there is some degree of functional heterogeneity within each subpopulation (Dougherty et al. 2013). Clearly, the identification of the functional roles of spinal neurons from common progenitor pools is only the starting step to understanding fully the roles of spinal circuits in processing tactile information. The identification of subpopulations within these cardinal cell populations, based on molecular, anatomical, and functional properties, will refine the classification further. With the consideration that spinal INs receiving both proprioceptive and cutaneous afferents have

Table 1. Molecular markers expressed by spinal interneurons involved in sensorimotor integration of tactile information

| Common Name                   | Approved Name | UniProt ID | References                        |
|-------------------------------|---------------|------------|-----------------------------------|
| Ascl1                         | Achaete-scute | P50553     | dI3 IN, dl4 IN: Mizuguchi et al. (2006) |
| BarH1                         | BarH-like     | Q9BZE3     | dI1 IN: Bermingham et al. (2001)   |
| Brn3a                         | POU class 4   | Q01851     | dI1 IN, dI3 IN: Zou et al. (2012)   |
| Brn3b                         | POU class 2   | Q12837     | dI3 IN: Zou et al. (2012)          |
| Cbhn2                         | Cerebellin 2  | Q8IU8      | dI1 IN: Miesegaes et al. (2009)    |
| c-Maf                         | v-maf Avian   | Q75444     | RORα IN: Bourane et al. (2015)     |
| Drg11                         | Dorsal root   | A6NNA5     | dI3 IN: Rebelo et al. (2010)       |
| Enkephalin                    | Prodynorphin  | P01213     | dI4 IN: Betley et al. (2009)       |
| Gad2                          | Glutamate     | Q05329     | dI4 IN: Betley et al. (2009)       |
| GlyT2                         | Solute carrier| Q9Y345     | dI4 IN: Betley et al. (2009)       |
| Gsh1                          | GS homeobox 1 | Q0H8S2     | dI4 IN: Mizuguchi et al. (2006)    |
| Gsh2                          | GS homeobox 2 | Q9BZM3     | dI3 IN, dI4 IN: Mizuguchi et al. (2006) |
| Isl1                          | ISL LIM homebox 1 | P61371 | dI3 IN: Liem et al. (1997); Pfaff et al. (1996) |
| Lhx1                          | LIM homebox 1 | P48742     | dI4 IN: Pillai et al. (2007)       |
| Lhx2                          | LIM homebox 2 | P50458     | dI1 IN: Bermingham et al. (2001)   |
| Lhx5                          | LIM homebox 5 | Q9HC21     | dI4 IN: Pillai et al. (2007)       |
| Lhx9                          | LIM homebox 9 | Q9NQ69     | dI1 IN: Bermingham et al. (2001)   |
| Lmx1b                         | LIM homebox   | Q06063     | RORα IN: Bourane et al. (2015)     |
| Math1                         | Atonal homolog| Q92858     | dI1 IN: Bermingham et al. (2001)   |
| NPY                           | Neuropeptide Y| P01303     | dI4 IN: Betley et al. (2009)       |
| Pax2                          | Paired box 2  | Q02962     | dI4 IN: Glasgow et al. (2005)      |
| Ptf1a                         | Pancreas      | Q7RTS3     | dI4 IN: Glasgow et al. (2005)      |
| RORα                          | RAR-related   | P35598     | RORα IN: Del Barrio et al. (2013)  |
| Smarca2                       | SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a, member 2 | P51531 | dI1 IN: Miesegaes et al. (2009) |
| Tag-1                         | Contactin 2   | Q02246     | dI1 IN: Miesegaes et al. (2009)    |
| Tlx3                          | T cell        | O43711     | dI3 IN: Cheng et al. (2005); Mizuguchi et al. (2006) |
| vGlut2                        | Solute carrier| Q9P2U8     | dI3 IN: Bui et al. (2013); RORα IN: Bourane et al. (2015) |

bHLH, basic helix-loop-helix; IN, interneuron; RORα, retinoic acid receptor (RAR)-related orphan receptor α; SWI/SNF, switch/sucrose nonfermentable. Sources: http://www.genenames.org/ and http://www.uniprot.org/.
long been identified in deep dorsal horn and intermediate laminae of the spinal cord (Edgley and Jankowska 1987; Moschovakis et al. 1992), it would not be altogether surprising if subpopulations of ventrally derived spinal neurons were found to integrate tactile information for motor control. A prime candidate for ventrally derived spinal neurons integrating tactile information is a subpopulation of the V3 IN population, which consists of commissural INs, involved in maintaining locomotor stability (Zhang et al. 2008), found to migrate during development and to be ultimately positioned in the deep dorsal horn (Blacklaws et al. 2015; Borowska et al. 2013).

The work on spinal RORα INs is a prime example of the need for studying subpopulations as well. It is not clear whether these neurons form a subpopulation of neurons that arise from a common progenitor domain or whether they consist of neurons from several progenitor domains. The latter would reveal that functional roles may be distributed amongst spinal neurons originating from a broad distribution of progenitor pools. A precedent for the distribution of functional roles amongst neurons arising from different progenitor pools was demonstrated when the spinal neurons responsible for reciprocal inhibition mediated by 1a afferents were found to arise from both V1 and V2b populations (Siembab et al. 2010; Zhang et al. 2014). The screening for genes commonly expressed in spinal lamina III–V, where sensory neurons innervating mechanoreceptors are most abundantly found, has revealed a number of candidate proteins that may mark other classes of functionally related spinal neurons that integrate tactile information and shape motor activity (Del Barrio et al. 2013). It would not be altogether surprising to discover that neurons belonging to the dI1, dI3, and dI4 IN populations consist of several subpopulations, as is already suggested for dI1 INs, based on anatomical location and ascending tract formation (Miesegaes et al. 2009). The dissection of these canonical populations of sensorimotor INs is a crucial step to understanding further the integration of tactile information for motor control.

**Connecting Spinal Circuits for Sensorimotor Integration of Tactile Information**

It is clear that dI3 INs and RORα INs both use tactile information but play distinct roles in motor control. For instance, when dI3 INs were silenced, mice showed deficits on the ladder test as well as in controlling grip strength (Bui et al. 2013), whereas ablation of caudal populations of RORα INs did not impact performance on the ladder test but resulted in impairments on the raised beam test (Bourane et al. 2015). However, this does not preclude the possibility that to serve their respective motor functions, these two populations of neurons interact. Along the same lines, dI4 INs may be linked to dI3 INs and RORα INs through presynaptic inhibition of cutaneous afferents to the two groups of excitatory neurons.

In addition to studying the interactions between genetically identified spinal INs involved in sensorimotor integration of tactile inputs, their interactions with other spinal neurons involved in complementary aspects of motor function must be determined. For example, whereas dI3 INs have been implicated with controlling grip strength, they do not seem to be critical for other aspects of hand control, such as skilled reach (unpublished observation). On the other hand, the V2a population of spinal neurons has been shown to be intimately involved with skilled reaching (Azim et al. 2014b). A subset of dI4 INs is also involved in ensuring smooth hand trajectory (Fink et al. 2014). Evidently, dI3 INs, dI4 INs, and V2a INs seem to operate concurrently to achieve proper hand control (Azim et al. 2014a). Therefore, as the individual contributions of genetically identified spinal INs to motor control and to sensorimotor integration of tactile inputs are revealed, the mutual connectivity between spinal neurons has to be mapped to understand fully how tactile information truly tailors motor output across the spectrum of possible motor activities.

**Connecting Spinal Circuits with Supraspinal Circuits for Sensorimotor Integration of Tactile Information**

Whereas spinal circuits involved in sensorimotor integration are able to operate in isolation without supraspinal input (e.g., tendon reflex), cortical and subcortical regions of the brain, as well as the cerebellum, are involved with motor processes, such as motor planning, motor learning, and motor adaptation. In addition, several regions of the brain stem are involved in the control of motor activity, such as locomotion (Grillner and Shik 1973) and hand function (Soteropoulos et al. 2012), through direct recruitment of spinal circuitry. Therefore, spinal circuits are likely to operate in conjunction with descending inputs from supraspinal areas. Indeed, cortical stimulation has been shown to modulate hindlimb cutaneous reflexes (Bretzner and Drew 2005). Similarly, cutaneous reflexes may modulate corticospinal efficacy through ascending reflex pathways (Christensen et al. 1999). RORα INs have been shown to receive supraspinal inputs from motor cortex and the cerebellum, the latter through the intermediary of projections originating from the lateral vestibular nuclei (Bourane et al. 2015). In addition, they project to ascending postsynaptic dorsal column neurons that may link these neurons with the cerebellum (Bourane et al. 2015). We also expect dI3 INs to receive supraspinal inputs based on clinical observations. For instance, dI3 INs mediate a palmar grasp reflex at early postnatal stages (Bui et al. 2013) that resembles a postnatal grasp reflex in humans. This reflex disappears in time (Mestre and Lang 2010), in parallel with the maturation of descending pathways to the spinal cord (Clarac et al. 2004). In addition, abnormal grasp reflexes in human patients have often been associated with frontal cerebral lesions (Mestre and Lang 2010), perhaps due to loss of supraspinal regulation of dI3 INs or of an analogous population in humans. Supraspinal regions may also be targeted by dI3 INs, as revealed by their innervation of the lateral reticular nucleus, a precerebellar nuclei (Pivetta et al. 2014). Therefore, the sources of supraspinal inputs to these neurons will be an active area of investigation. In addition, the role of these supraspinal projections in shaping sensorimotor integration of tactile information at the level of the spinal cord will be important. A prominent role for supraspinal projections may be the gating of sensory information during motor activity (see above). Therefore, how supraspinal inputs influence the gating of tactile information at the spinal level and during which forms of motor activity may be answered through the study of supraspinal projections to genetically identified spinal neurons.
Alternatively, spinal circuits may also influence the processing of tactile information by supraspinal regions dedicated to somatosensation, as demonstrated by findings that dI1 INs, dI3 INs, and RORα INs are part of ascending pathways from the spinal cord to the brain. Postsynaptic dorsal column neurons contacted by RORα INs send ascending projections that may ultimately be relayed to somatosensory cortex. Indeed, mice lacking RORα INs showed delays in detecting an irritant taped to their paws (Bourane et al. 2015). In addition to shaping somatosensation, spinal circuits may shape the motor strategies used to probe the external world. Indeed, perception and action are often processes that overlap (Hsiao et al. 2011). Classically, the relationship between sensory and motor systems has been viewed as sensory circuits informing motor systems. However, motor systems can shape sensory processing. For example, by changing whisking strategies, an animal can change the rate of tactile sensory inflow (Saig et al. 2012). By virtue of their access to motor circuits, both dI3 INs and RORα INs may influence tactile perception by shaping motor processes involved with sensing the external world. Therefore, the mutual interactions between spinal and supraspinal circuits must be investigated to understand further the processes by which tactile information shapes motor activity, and spinal circuits shape somatosensation and the motor strategies used to acquire sensory information.

Neural Coding

One of the many achievements of Steven Hsiao (Hsiao and Yau 2008) in the field of tactile perception was the discovery of neural codes for the perception of object features, such as texture, size, and shape. Whereas much focus has been paid to the role of the somatosensory cortex in this process, recent studies in humans provide evidence that sensory neurons innervating glabrous skin of the hand can perform higher-order feature detection, such as edge detection (Pruszynski and Johansson 2014). In light of this, we propose that spinal neurons receiving inputs from cutaneous receptors may further process features detected by sensory neurons for the purpose of motor control.

Indeed, spinal neurons have characteristics that hint at their capability to detect object features. For instance, the response of dorsal spinal neurons to tactile stimuli applied to the skin has been shown to depend on the nature of the stimuli and the receptive field. Responses can be graded (Fitzgerald 1985; King et al. 1990; Schneider 2005), excitatory, inhibitory, or a mixture of both (Hillman and Wall 1969; Kato et al. 2011; Kolmodin and Skoglund 1960; Woolf and King 1989), subthreshold or suprathreshold (Woolf and King 1989), and short or sustained (De Koninck and Henry 1994; Schneider 2005). The wide ranges of response patterns of spinal neurons are a reflection of the range of activation patterns of LTMRs (Abraira and Ginty 2013; Johansson and Flanagan 2009), as well as heterogeneity in intrinsic properties of spinal neurons (Ku and Schneider 2011).

Recordings of genetically identified spinal neurons can further establish whether detection of features of objects can occur at the spinal level. We know that dI3 INs have a number of ionic currents that alter the latency and the duration of their response to sensory inputs (Bui et al. 2013). As well, both dI3 INs and RORα INs receive inputs from multiple sources of sensory information. In fact, they also exhibit a number of different firing responses to electrical stimulation of sensory afferents (Bourane et al. 2015; Bui et al. 2013). To determine fully whether these neurons are capable of detecting object features, studies detailing the receptive fields of individual INs and their response to different forms of tactile stimuli, as well as the integration of stimuli applied to multiple sites on the skin, various tactile receptors, or other sensory modalities, need to be undertaken.

Another important aspect of feature detection and sensory processing, in general, is the representation of sensory information at different neural layers as information flows centrally through the nervous system. Studies of other sensory systems, such as the visual, olfactory, and electrosensory systems, suggest the involvement of common mechanisms of sensory information processing that may apply to sensorimotor integration of tactile information within the spinal cord as well (Babadi and Sompolinsky 2014). First, sensory processing is characterized by an expansion of sensory representations, whereby as sensory information travels centrally, it is processed by an increasing number of neurons. A second commonly observed mechanism of sensory processing is sparse representation, whereby as sensory information travels centrally, it only projects to a subset of downstream neurons (Bui and Brownstone 2015), despite the larger number of downstream neurons devoted to the processing of sensory information (see expansion). These two mechanisms are illustrated in the fly olfactory system, where ~150 projection neurons, relaying signals from olfactory receptor neurons, project to 2,500 Kenyon cells in the fly mushroom body (Turner et al. 2008). However, as a consequence of limited convergence of inputs from projection neurons to Kenyon cells, each individual Kenyon cell responds only to a small sample of possible odors captured by olfactory receptor neurons. In the context of the flow of tactile information from the skin to spinal circuits, an expansion of tactile signals conducted by sensory neurons in exclusive parallel fibers would imply a projection of these signals to a wide array of spinal neurons. These sensory fibers account for specific sensory modalities but additionally, for their intensity and spatiotemporal distribution. The requirement for sparseness would dictate that the tactile signals relayed to the spinal cord would converge toward a network of spinal INs composed of nonoverlapping and/or partially overlapping populations. The study of genetically identified spinal neurons involved in sensorimotor integration could reveal whether there is expansion and sparseness in the representation of tactile information at the spinal level. Finally, to shape motor control through an integration of tactile information, these spinal INs must project a set of instructive motor commands. We suggest that these motor commands diverge to activate spinal circuits or motor modules dedicated to specific aspects of motor control (Giszter and Hart 2013). The activity of a single or multiple motor modules generates a coordinated motor response to the tactile stimuli (Fig. 3).

Concluding Remarks

Most of the studies of genetically identified spinal INs were performed in mice, testing the cutaneous afferents either on hairy or glabrous skins. Therefore, caution should be exercised in attempting to generalize these finding to
other species. However, many of the transcription factors and molecular markers studied are phylogenetically conserved and expressed in spinal neurons (e.g., Isl1 in chicks and in zebrafish) (Avraham et al. 2010; Uemura et al. 2005), leading us to believe that there are some universal mechanisms of tactile integration at the spinal level that are shared among various species, perhaps also including humans. However, before insights into tactile sensorimotor integration at the spinal level gleaned from studies of animal models can be confidently related to our understanding of human function, it is instructive to consider the directions taken in human studies and how the studies using animal models can complement or supplement the former.

Human studies are currently limited in terms of their access to spinal circuitry. However, compared with animal models, a greater range of sensorimotor tasks can be studied, and there is much greater access to peripheral sensory neurons that have frequently been recorded in human studies. The linkage between various tactile afferents and muscle activity in hands and feet (Fallon et al. 2005; McNulty et al. 1999) has been demonstrated. Furthermore, recordings of different cutaneous afferents during specific motor tasks have revealed complex patterns of activity. In particular, studies of hand grasp suggest that there is an intricate spatiotemporal pattern of activation of different types of tactile afferents distributed across the hand (Dimitriou and Edin 2008; Johansson and Flanagan 2009; Macefield et al. 1996). The ability to study these spatiotemporal patterns of sensory transmission during specific motor tasks in human and nonhuman primates is a powerful technique that remains relatively inaccessible in nonprimate animal models. These techniques enable the investigation of tactile integration at the spinal level during motor activity, motor learning, and motor adaptation. They provide a detailed understanding of the sensory signals used to inform certain movements, and they hint at certain central mechanisms (supraspinal and spinal) by which these signals are processed. However, current technical limitations prevent a better understanding of the neural mechanisms operating within the human CNS, by which complex patterns of tactile information shape motor control. To understand these phenomena further requires a dissection of the different neural circuitry within the periphery, the spinal cord, and supraspinal regions.

Therein lies the strengths of the animal model. The genetic identification of spinal neurons has spurred the application of genetic techniques to expand our understanding of how spinal circuitry controls movement. Of the many outcomes of this approach is the characterization of a number of spinal neuron populations that integrate tactile information and the identification of their role in shaping motor control as reviewed above. Each identified population of spinal INs presents further opportunities to probe mechanisms by which sensorimotor integration of tactile input occurs. Whereas this approach is conditioned by our ability to 1) identify and 2) manipulate defined neuronal populations, recent technical advances are meeting these challenges. Cellular RNA expression profiling, for example, has been used successfully to identify new neuronal populations (Del Barrio et al. 2013), whereas optogenetic and chemogenetic techniques, such as channelrhodopsins (Zhang and Oertner 2007) or designer receptors exclusively activated by designer drugs (DREADDs) (Coward et al. 1998; Lechner et al. 2002), offer exquisite approaches for the manipulation of genetically identified neurons. The greater popularization of advanced molecular techniques, such as intersectional genetics, virus-based mapping, and optogenetics, to name just a few, can lead to significant advances in manipulating and addressing the respective roles of spinal neuronal populations involved in processing tactile information. The integration of tactile information is complex and requires multiple circuits distributed within the spinal cord and supraspinal regions. Recent technological advances, such as two-photon in vivo and in operando recordings, combined with post hoc dimensionality reduction, will be invaluable tools in tackling the complexity of network activity in the spinal cord.

The greatest challenge in relating the findings from studies of genetically identified spinal neurons in animal models to our understanding of human function is in determining whether analogous, genetically defined spinal circuits are present in the human spinal cord. However, genetic techniques have already been applied in nonhuman primate models to dissect the spinal circuitry associated with hand function (Kinoshita et al. 2012). The importance of bridging the gap between our understanding of how tactile information shapes motor control through spinal circuitry in human and nonhuman animal models goes beyond understanding how sensorimotor control is implemented by the nervous system. In addition to applying genetic techniques for mechanistic studies, genetic identification of spinal neurons offers the potential for targeted control of spinal circuits for biomedical applications. As pointed out by Steven Hsiao (Hsiao et al. 2011) in a review detailing the use of sensory feedback for upper-limb prostheses, electrical and optical stimulation of the fibers associated with specific sensory

Fig. 3. Conceptual model of sensorimotor neural processing in the spinal cord. Proposed scheme in which sensory inputs from multiple modalities are conveyed in parallel to partially overlapping spinal IN populations. The converging sensory information is processed, and sets of instructive motor commands are generated. These commands diverge to motor modules that generate individual motor actions, which together, form the desired coordinated motor response. We propose that this anatomical and functional structure provides a biological framework to neuronal computations underlying spinal sensorimotor integration.
pathways will be required for optimal prostheses design. The potential involvement of tactile information in recovery of motor function following spinal cord injury is beginning to come to light (Bouyer and Rossignol 2003; Frigon et al. 2012; Hurteau et al. 2015; Slawinska et al. 2012). Moreover, as mentioned previously, the process of motor control encompasses a number of sensory modalities that are being studied, for the most part, in isolation. Better understanding of the circuitry implicated in the integration of tactile sensation is paramount to understanding the role of multimodal integration during movement (Kim et al. 2015).

Genetic identification of spinal circuits, along with sensory neurons (Abraira and Ginty 2013) and supraspinal circuitry, will therefore be critical in all of these endeavors.

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AUTHOR CONTRIBUTIONS

Author contributions: T.V.B. analyzed data; T.V.B. and N.S. interpreted results of experiments; T.V.B., N.S., I.P., and C.F. prepared figures; T.V.B., N.S., and C.F. drafted manuscript; T.V.B., N.S., I.P., and C.F. edited and revised manuscript; T.V.B., N.S., I.P., and C.F. approved final version of manuscript.

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