



Published in final edited form as:

Curr Opin Physiol. 2021 February ; 19: 187–193. doi:10.1016/j.cophys.2020.10.007.

Converging integration between ascending proprioceptive inputs and the corticospinal tract motor circuit underlying skilled movement control

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Abstract

Converging interactions between ascending proprioceptive afferents and descending corticospinal tract projections are critical in the modulation and coordination of skilled motor behaviors. Fundamental to these processes are the functional inputs and the mechanisms of integration in the brain and spinal cord between proprioceptive and corticospinal tract information. In this review, we first highlight key connections between corticospinal tract motor circuit and spinal interneurons that receive proprioceptive inputs. We will also address corticospinal tract access to the presynaptic inhibitory system in the spinal cord and its role in modulating proprioceptive stimuli. Lastly, we will focus on the corticospinal neuron influences on the dorsal column nuclei complex, an integration hub for processing ascending somatosensory information.

Keywords

corticospinal neurons; proprioceptive sensory neurons; spinal cord; motor cortex

1. Introduction

The coordination of peripheral muscle activation for movement control is predicated upon the interplay between proprioceptive sensory feedback information (e.g. muscle activity and body position) and motor output [1, 2]. Descending motor commands from supraspinal structures exert an additional level of integration onto proprioceptive afferent inputs for the appropriate execution of motor function [3, 4]. Much progress has been made on how proprioceptive and descending motor inputs influence one another during movement control

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The authors have no competing interests to declare.

at various levels of the brain and spinal cord and remains a central topic of interest in neuroscience.

The corticospinal tract (CST) system which originates in layer V sensorimotor cortex, is a multifunctional pathway that controls skilled and voluntary limb movement, but also mediates sensory functions including the modulation of proprioceptive inputs [3–6]. In primates, cats and rodents, CST axon projections from primary somatosensory cortex (S1) and primary motor cortex (M1), terminate in the dorsal and ventral spinal cord respectively, accessing the different spinal interneuron and select motoneuron populations [7–12]. Importantly, proprioceptive information (i.e. sensory-motor reflex circuits) which is processed in the dorsal spinal cord and a major source for presynaptic inhibition, is also likely modulated by descending CST projections during active movements [3, 13, 14]. In addition, corticospinal axon collaterals innervate the brainstem dorsal column nuclei (DCN) complex, an integration and distribution hub for ascending mechanosensory inputs which includes proprioception [15, 16].

The understanding that sensory and descending motor functions are not separate and that integration between the two is fundamental to movement control has been well established in the motor control field for many decades. However, what has changed in recent years is that we are now elucidating the underlying circuitry mediating these essential control functions with remarkable specificity. Here we review the converging interactions between proprioceptive inputs (i.e. mechanosensory neurons connected to muscles, tendons and joints) and descending CST projections in the modulation and coordination of movement control. First, we address the organization and functional connectivity between proprioceptive and sensorimotor CST circuits at the spinal interneuron level. We will also review the role of CST influences on the presynaptic inhibitory system in modulating proprioceptive information. Furthermore, we will look at the dorsal column nuclei (DCN) complex, an integration processing center for ascending proprioceptive and descending sensorimotor inputs.

2. Interneuron spinal network integration of the proprioceptive sensory-motor circuit and sensorimotor CST system

In primates including humans, the CST system operates through direct monosynaptic cortico-motoneuronal connections between CST axons and motoneurons, to facilitate skilled movements of the hands and fingers [3, 4, 6, 17–19]. Additionally, indirect cortico-motoneuronal connections, via segmental and propriospinal interneurons in the spinal cord (i.e. intermediate zone and dorsal horn), as observed in most mammalian species including non-primates, are also fundamentally critical for distal movements, as well as other aspects of skilled motor control [6, 20]. The diversity of spinal interneurons enables the integration of converging CST motor output and proprioceptive sensory afferents, thus contributing to the broad array of skilled motor behaviors [21]. Studies in the primate and cat using classical anatomical and electrophysiological techniques has laid the foundation for circuit analysis in the spinal cord on the interactions between sensory and descending inputs [4, 13, 22]. The advent of powerful cellular and molecular tools in the rodent however, has provided many

new insights on the organization and function between proprioceptive and sensorimotor CST circuits at the interneuron spinal level in facilitating movement control.

A recent study by Ueno and colleagues [7**], generated a detailed connectivity map between CST neurons in sensory and motor cortex and various spinal interneuron populations, using numerous tracing and viral techniques, as well as, several Cre-reporter lines. One of the major interneuron groups connected to CST axons from motor cortex is the premotor excitatory propriospinal V2a Chx10 interneurons which synapse onto motoneurons and receive proprioceptive-sensory inputs via feedforward disynaptic inhibition (Figure 1A) [23]. Notably, neuronal silencing of Chx10+ interneurons showed that these interneurons contribute to the execution of skilled reaching during a pellet retrieval task, suggesting that Chx10+ interneurons relay commands from CST neurons to motoneurons [7**]. These propriospinal V2a+ neurons which also receive direct and indirect supraspinal input, are involved in an internal copy of rapid feedback circuit critical for precise skilled reaching (Figure 1A) [23]. Moreover, connectivity mapping revealed CST connections from sensory and motor cortex onto Atoh1+ and Isl1+ interneurons located in laminae IV and V, which receive proprioceptive sensory inputs from group-1 afferents (Figure 1B) [24*]. Atoh1+ interneurons which target the cerebellum, have been shown to be involved in fine motor coordination of the hindlimb [25], whereas Isl1+ interneurons, form excitatory synapses onto motoneurons, and are critical for integrating crucial sensory feedback for paw grip (Figure 1B) [26].

The innervation of CST neurons onto these interneurons populations raises important questions on how these spinal networks engage proprioceptive afferent and descending sensorimotor CST information to control various skilled movements. In a similar region of the spinal cord as Atoh1+ and Isl1+, a study by Levine and colleagues [24*], characterized a population of motor synergy encoder (MSE) spinal neurons critical for voluntary and reflexive movement patterns. They identified a heterogeneous population of excitatory and inhibitory Tcfap2 β + and Satb1/2+ premotor interneurons located in the medial deep dorsal horn, which receive focal inputs from proprioceptive afferents and CST neurons (Figure 1C). The authors proposed that these interneurons, which are a major source of monosynaptic input to motoneurons, may possibly encode the motoneuron activation patterns for motor synergy programs. A more recent paper by Paixão and colleagues [27] showed that Zic2 neurons which integrate sensory feedback information and are required for corrective motor movements, also receive direct monosynaptic CST inputs from layer V motor cortex.

Another class of spinal neurons involved in sensorimotor integration are the dorsal spinocerebellar (dSC) neurons, located in the thoracic and lumbar nucleus and are known as Clarkes column (Figure 1D) [28*]. Clarkes column dSC neurons are a convergent target for proprioceptive sensory and descending cortical information, which relay proprioceptive information to the cerebellum for integrating and anticipating peripherally derived feedback. CST also neurons exert control over Clarkes column dSC neurons by direct excitatory and/or indirect inhibitory inputs (i.e. glycinergic and GABAergic interneurons), with the capacity to transfer predictive commands, as well as, modulate proprioceptive input for fine motor control (Figure 1D, D') [28].

Renshaw cells [29] located in the ventral horn, are another class of spinal inhibitory interneurons which receive recurrent collaterals from alpha motoneurons (Figure 1E) [30]. The Renshaw cells which release glycine or GABA, project back to alpha motoneurons and provide inhibitory feedback (called recurrent inhibition) thus limiting motoneuron output. Studies in human have shown that CST neurons suppress Renshaw cells resulting in facilitation of reflex muscle responses [31]. Moreover it was shown in mouse that Renshaw cells receive putative direct connections from CST axons [32], as well as proprioceptive inputs (Figure 1E) [33]. Thus, direct CST and proprioceptive access of Renshaw cells, may offer another source of integration where specific spinal motor pools are potentially subject to inhibitory control.

3. Presynaptic inhibitory influences on the proprioceptive sensory-motor circuit and the CST spinal circuitry

The anatomical origins of CST projections from somatosensory cortex to the spinal cord dorsal horn are likely involved in the modulation of proprioceptive inputs generated by movement control through presynaptic inhibitory mechanisms [3, 13, 14, 22, 34]. The dorsal horn, an important region of presynaptic inhibition, has been shown to possess a diverse array of inhibitory interneurons populations that receive inputs from the CST [35, 36]. One class of inhibitory interneurons that are connected to CST circuits are the GABAergic interneurons, termed GABApre, which modulate the proprioceptive sensory-motor reflex circuit (Figure 1F, 1F') [7**, 37, 38*]. Last-order GABAergic interneurons form presynaptic inhibitory synapses on proprioceptive afferent terminals and produce what is known as primary afferent depolarization (PAD), modulating proprioceptive control and shaping motoneuron responses [13, 22, 39–41].

A study by Fink and colleagues [42] showed that these GABApre interneurons play an important role in smooth execution of skilled forelimb movement by activating PAD and resulting in presynaptic inhibition of proprioceptive feedback in the spinal cord (Figure 1E, 1E'). This presynaptic inhibitory system with PAD interneurons can be evoked by proprioceptive and local inputs, but can also be recruited by the CST following stimulation of sensorimotor cortex, suggesting a crucial role for appropriate skilled motor control [22, 43–45]. Furthermore, CST axons can depress PAD, switching off presynaptic inhibition via inhibitory interneurons which inactivate first-order PAD interneurons, thus enhancing Ia afferents (Figure 1F) [46, 47].

It has also been shown that glutamate retrograde signals serve to regulate the inhibitory/excitatory signaling across the proprioceptive sensory-motor reflex circuit [48]. The CST system, which is glutamatergic, can release glutamate (i.e. VGlut1 and/or VGlut2) and regulate GABApre interneurons [19, 49, 50]. Additionally, CST axons could exert presynaptic inhibition on Clarke's column dSC neurons by the recruitment of GABApre interneurons [28*]. Corticospinal tract access to the presynaptic inhibitory system therefore enables an additional level of sensorimotor integration by selectively controlling proprioceptive information, sculpting motor neuron output and thus facilitating proper control of motor movement.

4. The dorsal column nuclei complex: an integration hub for processing ascending proprioceptive and descending sensorimotor CST information.

In addition to sensorimotor processing during active movement at the spinal cord level, the brainstem dorsal column nuclei complex (DCN-complex) provides further integration between the corticospinal (CS) neurons and proprioceptive inputs (Figure 2A) [15, 16]. The DCN complex which is recognized as a relay processing center for diverse ascending mechanosensory information, send projection targets throughout the brain and spinal cord, and also receive descending modulatory inputs from the CS neurons in sensorimotor cortex [51–53]. Previous work in primates and cat have shown that CS neurons originating in lamina V of primary motor cortex [(M1); area 4] and area 3a, send projecting axons to cervical spinal cord, as well as collaterals towards the proprioceptive-dominated regions of the rostral and ventral portion of the DCN (Figure 2A) [51, 54–59]. These parallel CST influences onto cervical neuron populations and the DCN level suggest an important role for skilled forelimb movement control [15]. Indeed, lesion experiments of the DCN in monkeys revealed deficits in skilled forelimb performance with limited defects in hindlimb function [60].

Corticospinal inputs from sensorimotor cortex onto the DCN-complex also induce both direct excitatory (i.e. glutamatergic) effects, and indirect post inhibitory effects (i.e. GABAergic), via inhibitory INs within the DCN-complex (Figure 2B) [61–63]. For example, in cat, ascending proprioceptive input processed in the DCN and relayed to the thalamus, are modulated by cortical feedback from area 3a and M1 [64*]. Descending CST collaterals exert an excitatory influence directly onto DCN neurons that process relevant muscular inputs (i.e. the same joint), and at the same time will activate GABA/glycine INs, thus inhibiting DCN cells that receive non-relevant muscle inputs (i.e. from different joints) (Figure 2B) [64*]. This suggests that inputs from sensorimotor cortex to the DCN complex plays an important role in “selecting” the relevant and non-relevant ascending proprioceptive information during active movements. This relatively ubiquitous gating mechanism is also observed in other sensory systems, such as in layer 6 corticothalamic cells, which regulate sensory processing by modulating thalamic neuron activity [65]. For an extensive review on the DCN complex, see Loutit, Vickery & Potas, 2020 [16].

5. Conclusion

Converging influences between proprioceptive inputs and descending corticospinal tract projections are critical for skilled movement control. Proprioceptive feedback relayed to the spinal cord, the brainstem DCN complex and cortical motor centers, can engage the CST system through interneuron populations for feedforward processing of proprioceptive stimuli during active movements. At the spinal cord level, CST connection patterns onto excitatory and inhibitory interneuron populations in the dorsal horn modulate proprioceptive feedback signals at the local circuit level, as well as ascending projections to cortex for the coordination of skilled movements. CST regulation of PAD through GABApre interneurons also serves to selectively control for desired or disruptive proprioceptive sensory input. Furthermore, descending CST axon collaterals from M1 and 3a on the DCN complex, can

discriminate between appropriate proprioceptive stimuli, by inhibiting non-relevant DCN cells and by selectively enhancing relevant DCN cells via cortical feedback. Thus, regulation of proprioceptive feedback is fundamental to sensorimotor processing where the diversity of integration at various levels of the central nervous system enables a wide repertoire of skilled motor behaviors. The gradual enhancement of powerful genetic tools and the exceptional engineering of targeted silencing or activation of neuron cell types, will pave the way for future insights in the converging integration of proprioceptive and descending motor pathways underlying skilled movement control.

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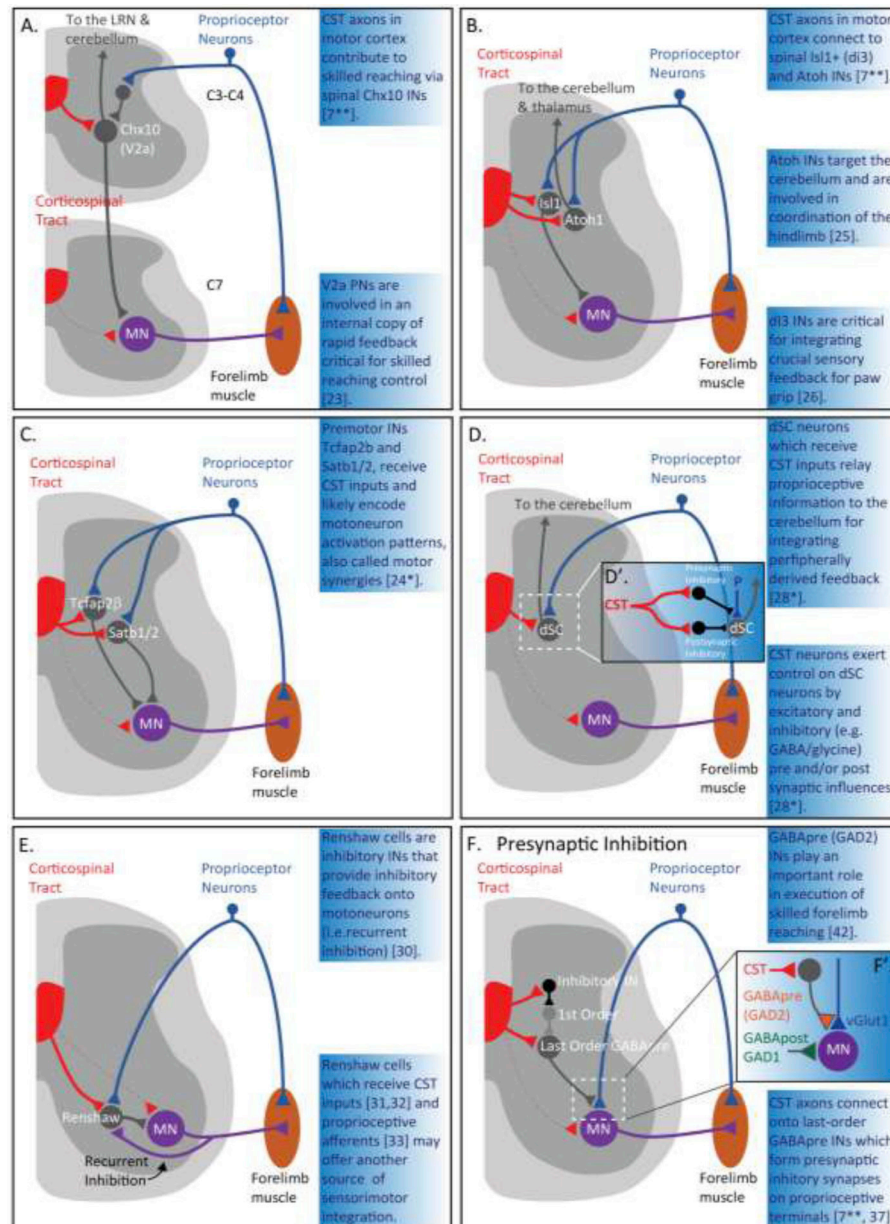


Figure 1. Spinal integration of the proprioceptive sensory-motor circuit and the sensorimotor corticospinal tract system. Connectivity of spinal circuitry between convergent corticospinal tract (CST) axons (red) and proprioceptive inputs (blue) onto spinal interneurons (gray) (A–E). Rodents form rare direct monosynaptic connections between CST axons (dotted red) and motoneurons (purple). (A) Connectivity of motor CST axons (red) onto propriospinal Chx10 (V2a) interneurons (gray) in cervical spinal cord levels 3 and 4 (C3–C4) [7**]. Propriospinal V2a interneurons relay information to the lateral reticulate nucleus (LRN) and cerebellum and are critical for skilled reaching [23].

(B) Connectivity of CST axons (red) from sensorimotor cortex to spinal *Isl1* and *Atoh* interneurons (gray) [7**]. *Atoh* interneurons target the cerebellum and thalamus and are involved in coordination of the hindlimb [25]. *dI3* interneurons are critical for integrating for integrating sensory feedback for paw grip [26].

(C) Connectivity of CST inputs (red) onto *Tcfap2 β* and *Sat1/2* premotor neurons (gray) located in laminae IV and V [24*]. These premotor neurons may encode for motoneuron activation for motor synergy programs [24*].

(D) Connectivity of CST inputs (red) onto dorsal spinocerebellar (dSC) neurons, known as Clarkes column dSC neurons (gray) [28*]. dSC neurons receive direct excitatory or indirect inhibitory (**D'**; see inset) inputs via inhibitory interneurons (e.g. GABA and glycine) [28*]. dSC relay proprioceptive information to the cerebellum for peripherally derived sensory feedback [28*].

(E) Connectivity of CST inputs (red) [31, 32] and proprioceptive afferents (blue) [33] onto Renshaw cells (gray) a class of spinal inhibitory interneurons that receive recurrent collaterals from alpha motoneurons (purple) [30]. Renshaw cells project back to alpha motoneurons and provide inhibitory feedback (i.e. GABA, glycine) and is called recurrent inhibition [30].

(F) Connectivity of CST inputs (red) onto last-order GABApre inhibitory interneurons (gray) which modulate the proprioceptive sensory-motor reflex circuit and produce primary afferent depolarization (PAD) [7**, 37, 38*]. (**F'**; see inset) Last order GABApre interneurons form axo-axonic synapses onto proprioceptive afferent terminals, expressing the GABA synthesizing enzyme GAD2 (also known as GAD65) [38*, 42]. GABApost interneurons which synapse directly on motoneurons, express GAD1 (also known as GAD67) [38*, 42]. (**F**) CST axons (red) can also depress PAD, by activating inhibitory interneurons (black), which in turn, inactivate first-order PAD interneurons (light gray), enhancing Ia afferents [46, 47].

dSC – dorsal spinocerebellar; LRN – lateral reticular nucleus; MN – motoneuron; IN – interneuron; PN – propriospinal; CST – corticospinal tract; P – proprioceptive neuron; GAD65/67 – glutamic acid decarboxylase; vGlut1 – vesicular glutamate transporter; GABA – gamma-aminobutyric acid.

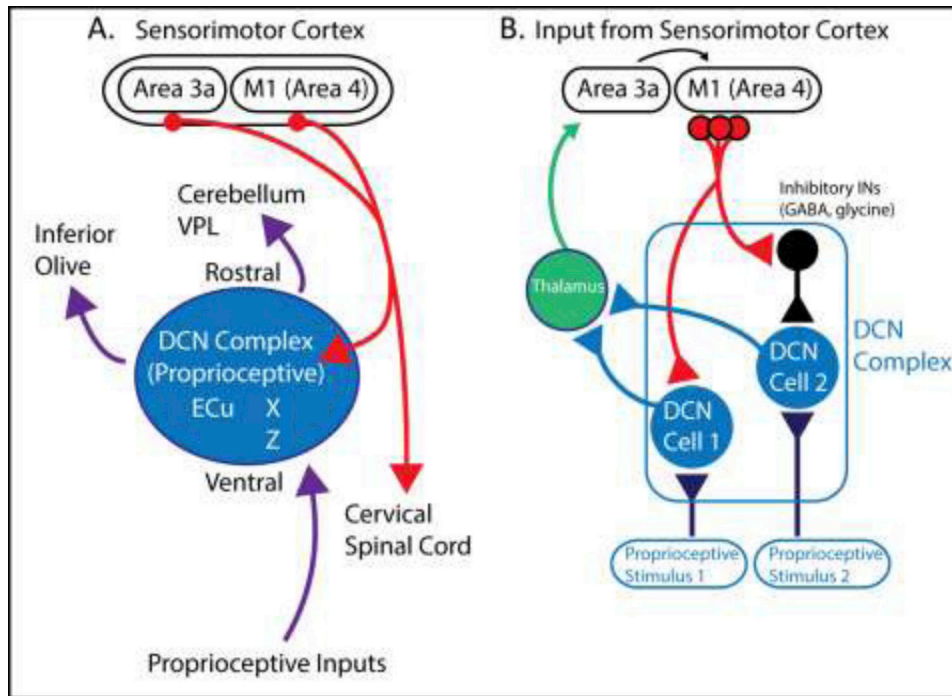


Figure 2.

The dorsal column nuclei complex: an integration center for processing ascending proprioceptive information and descending sensorimotor corticospinal inputs. **(A)** Schematic diagram showing corticospinal (CS) neurons (red) originating in M1 (area 4) and area 3a sending axon collaterals towards proprioceptive regions (rostral and ventral portion) of the dorsal column nuclei complex (DCN) (blue) as well as cervical spinal cord (see Figure 1) [51–59]. Furthermore, purple arrows shows proprioceptive inputs to the DCN complex (blue) and proprioceptive outputs to the cerebellum, inferior olive and ventral posterior lateral (VPL) nucleus of the thalamus.

(B) CS inputs (red) make both direct excitatory (i.e. glutamatergic) and/or indirect post inhibitory effects through inhibitory INs (i.e. GABA & glycine) (black) on DCN cells (blue) within the DCN complex [15, 16, 61–63]. CST inputs enhance relevant proprioceptive stimuli through excitatory interneurons and inhibit non-relevant proprioceptive stimuli via inhibitory interneurons [64*]. Furthermore, ascending proprioceptive information (dark blue) processed in the DCN, are relayed to thalamus (green), and modulated by cortical feedback from proprioceptive cortex (area 3a) and M1 (area 4).

VPL – ventral posterior lateral nucleus of the thalamus; X - nucleus X; Z – nucleus Z; ECu – External cuneate nuclei; DCN – dorsal column nuclei; M1 – primary motor cortex