● PERSPECTIVE

Anatomical changes in the somatosensory system after large sensory loss predict strategies to promote functional recovery after spinal cord injury

Among cases of spinal cord injury are injuries involving the dorsal column in the cervical spinal cord that interrupt the major cutaneous afferents from the hand to the cuneate nucleus (Cu) in the brainstem. Deprivation of touch and proprioceptive inputs consequently impair skilled hand use. Although dexterous hand use can be significantly restored in some patients after months of recovery, some patients never fully recover from the injury. Patients also may develop painful and nonpainful phantom sensations (Moore et al., 2000). Such differences in recovery are often attributed, in part, to differences in the level and extent of the injury. However, specific relationships between individual injuries and indicators of recovery require intensive study. Due to

the similarities of the nervous system in humans and non-human primates, research in monkeys greatly advances the understanding of relationships between injury and plasticity in human brains that contribute to functional recoveries.

Previous research has revealed that appropriate reactivation of primary somatosensory cortex, with neuronal responsiveness to touch restored with nearly normal somatotopic organization, is associated with functional improvement after the spinal cord injury (see Qi et al., 2014 for review). Activation in cortex is a marker of neural function that can be tested in human and nonhuman primates, along with measures of sensorimotor functional recovery. Here we review the contributions to the cortical reorganization after injuries in the somatosensory system by reviewing recent anatomical research in monkeys with controlled injuries. We focus on spinal cord injury models of sensory loss *via* dorsal column lesions (DCL), while other types of spinal cord injury models including loss of sensory and motor functions are beyond the scope of this perspective (Darian-Smith et al., 2014). As in patients with spinal cord injury, DCL may be incomplete or complete, which affects anatomical and functional changes involved in recovery and maladaptive plasticity. This review focuses on neuronal connections within somatosensory cortex in monkeys with incomplete and complete DCL that primarily affect touch and proprioceptive sensation from one
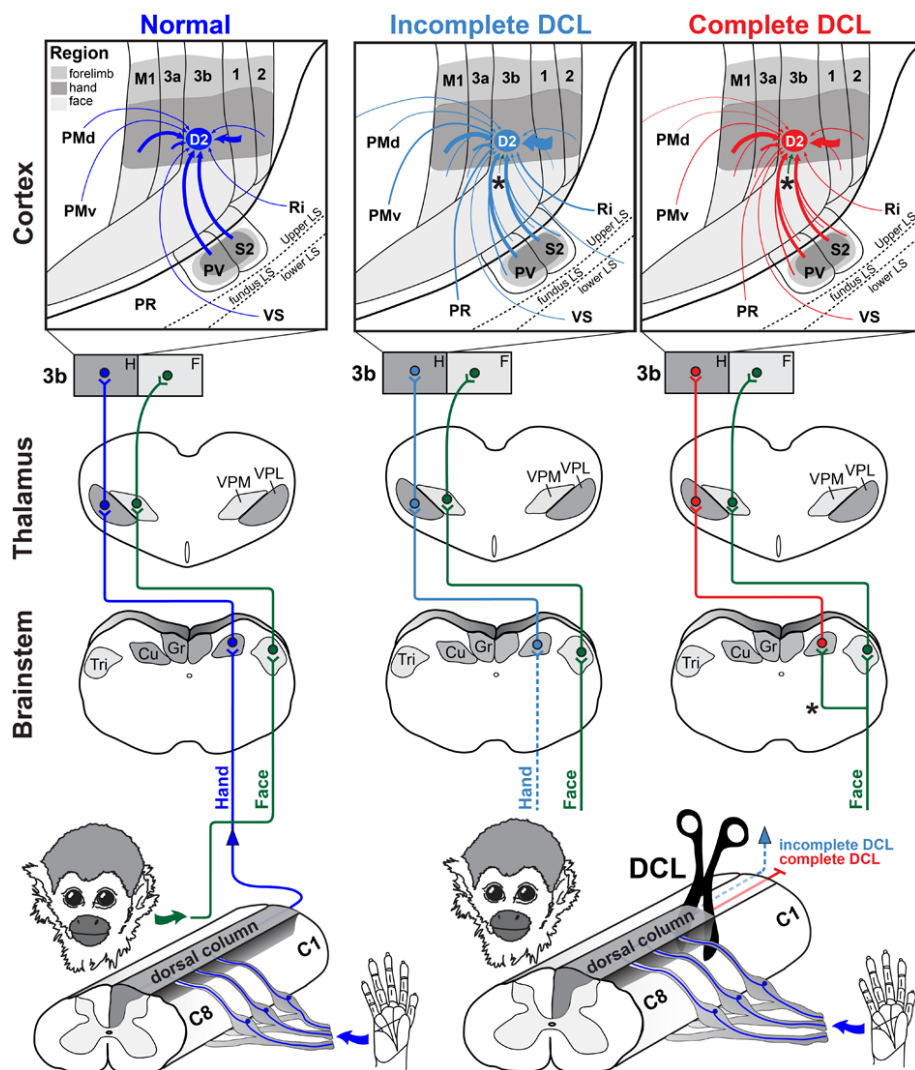

Figure 1 Summary diagram depicting how the extent of dorsal column lesion (DCL) in the cervical spinal cord altered the ascending inputs from the hand and face to the brainstem, thalamus, primary somatosensory area 3b, and the intracortical connections of the hand region in area 3b.

The hand pathway from normal, incomplete DCL, and complete DCL monkeys are in shown blue, light blue, and red, respectively, and the face pathway is shown in green. In the *cortex*, territories of the hand, forelimb, and face regions in the cortex are shown in dark to light gray, and the thickness of each line represents the relative density of the connection. Note, along with the existing connections from the hand region of areas 3a, 1, 2, and PV/S2 and other cortical areas as in normal monkeys, after long-term DCL the hand region in area 3b is additionally connected to the face region in area 3b (asterisks in Cortex). However, sprouting of the face inputs into the hand region of *brainstem* (cuneate nucleus, Cu) only appears in monkeys with the complete DCL (asterisks in Brainstem). The thalamocortical connections of the hand and face inputs remain somatotopically organized after the DCL. LS: Lateral sulcus; M1: primary motor cortex; PMd and PMv: premotor dorsal and ventral cortex; PR: parietal rostral; PV: parietal ventral; Ri: retroinsular cortex; S2: secondary somatosensory cortex.

hand (**Figure 1**). We also briefly review subcortical connections after such lesions. We suggest that treatment strategies and prognosis after spinal cord injury can be guided by investigating how injury-induced plasticity relates to indicators of cortical and sensorimotor function.

Cortical contributions to recovery from sensory loss: Notable similarities and differences exist in the organization of intracortical connections of the representations of the hand and face in primary somatosensory cortex area 3b between normal monkeys and monkeys with incomplete and complete DCL. In primates, neuronal responses in area 3b are somatotopically organized with representations of forelimb, hand, and face arranged in a medial to lateral sequence. Intracortical connections of area 3b are normally restricted to the regions that represent the same and/or adjacent body parts within 3b and to other cortical areas including areas 3a, 1, 2; as well as the premotor dorsal and ventral (PMd, PMv) cortex, secondary somatosensory (S2) cortex, parietal ventral (PV) cortex, ventral somatosensory (VS) cortex, and retroinsular (Ri) cortex (Burton and Fabri, 1995; Liao et al., 2013; **Figure 1**). However, neurons in the hand region in area 3b are immediately inactivated after DCL at cervical spinal levels (see Qi et al., 2014 for review). In monkeys with incomplete DCL, these deafferented area 3b neurons are reactivated in a nearly normal somatotopic organization after a period of recovery, accompanied by notable restored ability to perform tasks with the affected hand. However, after long recovery times in monkeys with nearly complete or complete DCL, neurons normally responsive to touch on the hand (or hand neurons) in area 3b could become responsive to touch on face and forearm, which may relate to phantom sensations in human patients. Results of recent anatomical studies (Chand and Jain, 2015 [macaque monkeys]; Liao et al., 2016 [squirrel monkeys]) indicate that the distribution of intracortical connections of hand and face neurons in area 3b closely resembles the pattern in normal monkeys, regardless of the extents of cortical reactivation after injuries (**Figure 1**). Liao et al. (2016) noted modest changes in intracortical connections, particularly the denser interconnections across the hand/face border, to the area 3b hand region in monkeys with incomplete and complete DCL. After incomplete DCL, neurons in the hand region of area 3b were extensively reactivated and recovered responsiveness to touch on hand. Labeled neurons from tracer injection in the area 3b hand region mostly overlapped the reactivated hand representations in area 3b, with few labeled neurons beyond the hand/face border in the 3b face region. In contrast, in a monkey with complete DCL, cortical reactivation in the area 3b hand region was only partial, and some hand neurons became responsive to touch with mismatched receptive fields in the hand and face, or face alone. The intrinsic connections of area 3b hand neurons included non-responsive cortex and the reorganized representations in the hand region, as well as the face region. The proportions of interconnections across the hand/face border in area 3b were greater with larger DCL extents (**Figure 1**). The modest expansion of pre-existing connections may promote cortical reactivation by integrating surviving inputs from the hand, hence promoting recovery of hand use in monkeys with incomplete DCL. However, the anatomical changes after long recovery times involving the small amount of inputs from the face region to the hand

region in area 3b may be maladaptive rather than substrates for functional recovery. We suggest that treatments promoting survival and growth of appropriate connections after injury may reduce maladaptive plasticity that may cause phantom sensations.

Detailed anatomical studies in animal models guide the understanding of individual differences in recovery trajectories by revealing relationships between areas in the spinal cord that are damaged and cortical reorganization. Although the pre-existing connections of area 3b are primarily preserved after injuries, the inputs integrated by these connections in 3b appear highly dependent on the available inputs from the periphery. For example, in normal monkeys, the intrinsic connections between representations of digits 2, 3, and 4 in area 3b are denser than to the representations of digits 1 and 5 (Liao et al., 2013). This connection pattern was maintained in one monkey with incomplete (61%) DCL at rostral C5 that spared inputs from digits 1-5. However, in one monkey with incomplete (65%) DCL at C5/C6 that spared inputs from digit 1 and a portion of digit 2, the digit 2 neurons in area 3b had obviously denser connections to the representation of digit 1 (Liao et al., 2016). In one monkey with a complete DCL, the new inputs from the face and remaining inputs from the hand in the area 3b hand region were integrated by the intrinsic connections, as evidenced by the overlap of connections in the territories that have receptive fields responding to both face and hand.

Subcortical contributions to recovery from sensory loss: Contributions to reorganization in the cortex also originate at subcortical levels and depend on the inputs available. The thalamocortical connections of the hand and face representations from the ventroposterior lateral nucleus (VPL) and ventroposterior medial nucleus (VPM) to the ipsilateral area 3b are somatotopically organized in normal monkeys. Two recent anatomical studies (Chand and Jain, 2015; Liao et al., 2016) found that even when neurons in the area 3b hand region became responsive to touch on face after DCL, these neurons remained connected to the neurons in the thalamus in normal locations in the hand representation, without connections from neurons in the forelimb region of VPL or the face region in VPM (**Figure 1**). These observations indicate that a notable anatomical outgrowth of thalamocortical connections does not play a major role in driving the cortical reorganization after DCL. This does not exclude the possibility that thalamocortical connections convey reorganized inputs from the brainstem through the deafferented VPL, as reported in forelimb-amputated rats (Li et al., 2014). However, the role of the thalamus in cortical reorganization and functional recoveries from DCL appears to be largely limited to relaying changes from the dorsal-column trigeminal complex to somatosensory cortex.

The current body of research points to plasticity in the brainstem as the main subcortical contributor to cortical reorganization after sensory loss. Striking differences are well known between the distributions of axonal terminals from the hand and face in the brainstem in normal monkeys and monkeys with incomplete and complete DCL (**Figure 1**). In squirrel monkeys, Liao et al. (2016) found that responsiveness of area 3b hand neurons to touch on the face occurred only incomplete DCL cases with axonal sprouting from the trigeminal (Tri, face) nucleus to the Cu in the brainstem,

despite cortical connections across the hand/face border in cortex after both incomplete and complete DCL. The non-somatotopic activation from the face to the deafferented hand region only after severe injury suggests that remaining inputs from the hand prevent the intrusion of inputs from other body parts into the hand territory.

In macaque monkeys with nearly complete DCL, Kambi et al. (2014) examined the anatomical sources of inputs to the deafferented hand region in area 3b where neurons were newly responsive to touch on the face. They injected lidocaine as a neuronal blocker and found that responsiveness to the face within the area 3b hand region can only be inactivated when the lidocaine was injected into the brainstem Cu, not into the 3b face region. These results reveal that responsiveness to the face in the hand cortex originated from the Cu. Notably, in human patients, Moore et al. (2000) found fMRI activation related to phantom sensations in which nonadjacent regions in cortex were active. The authors suggest that subcortical plasticity rather than cortical reorganization likely leads to activation of nonadjacent cortical regions observed in relation to phantom sensations after spinal cord injury. Thus, current evidence supports the conclusion that the brainstem is the major subcortical station providing new activating inputs to parts of the deafferented cortex in monkeys with DCL.

Preserved first order spinal cord inputs and the second order spinal cord inputs to the brainstem provide the main route for information from the periphery to reach the cortex after injury. Liao et al. (2015) provided evidence for a possible role of the second-order spinal cord neurons in sending cutaneous inputs from the hand to the Cu through the spared dorsal column and lateral funiculus after DCL. We propose that the second-order spinal cord pathway contributes to useful cortical recovery after spinal cord injury, possibly through synaptogenesis and sprouting in the Cu over longer recovery times. It is widely accepted that treatments for axon survival and growth at the level of the spinal cord will benefit sensorimotor recovery. Cortical activation may be a useful indicator of inputs that reach the brain but need greater modulation through therapeutic interventions in order to express better functional output.

Implications and significance: Overall, review of anatomical plasticity within the somatosensory system after dorsal column spinal cord injuries indicates the importance of preserved inputs from the hand to prevent non-somatotopic responsiveness in cortex (area 3b) to other body parts, which may cause phantom sensations. Cortical activation and anatomical changes correlate with injury levels and extents, all of which are related to functional recovery. Anatomical studies reveal that large sensory loss stimulates axonal sprouting across the territories representing the hand and face in the cortex and brainstem. Investigations have not revealed such sprouting in the thalamus. Yet, because neuropathic pain after injury is related to neuronal activity in parts of thalamus, targeting appropriate sites and modalities (nonpainful versus painful sensations) is important for developing treatments. Damage sustained from injury shapes the recovery trajectory, and the brainstem appears to be a key location that determines the cortical reorganization after DCL. The types and sites of plasticity during recovery from spinal cord injury

suggest that therapeutic interventions promoting sprouting specifically within appropriate spinal cord and brainstem regions will be more effective for functional recovery than broadly promoting plasticity, which may encourage maladaptive axon sprouting from regions representing the face. Promoting the survival and growth of appropriate connections is a top priority in treating patients with sensory loss from spinal cord injuries; and further investigations in patients and animal models including anatomical and functional measures will aid in improving treatment strategies.

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