Plasticity and Recovery After Dorsal Column Spinal Cord Injury in Nonhuman Primates

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ABSTRACT: Here, we review recent work on plasticity and recovery after dorsal column spinal cord injury in nonhuman primates. Plasticity in the adult central nervous system has been established and studied for the past several decades; however, capacities and limits of plasticity are still under investigation. Studies of plasticity include assessing multiple measures before and after injury in animal models. Such studies are particularly important for improving recovery after injury in patients. In summarizing work by our research team and others, we suggest how the findings from plasticity studies in nonhuman primate models may affect therapeutic interventions for conditions involving sensory loss due to spinal cord injury.

KEYWORDS: monkey, somatosensory, spinal cord

Introduction

In this study, we review multiple measures to assess plasticity including recovery of hand use, brain reactivation, and anatomical changes, specifically in nonhuman primates with partial injuries to the spinal cord dorsal column (DC) somatosensory pathway. Spinal cord injury in patients typically affects both sensory and motor functions, but DC spinal cord injuries in nonhuman primates are used to investigate the somatosensory system in particular. Within this context, we seek to simplify and clarify the current state of knowledge, regarding cortical reorganization and plasticity after partial sensory loss due to spinal cord injury. Brain plasticity in the adult central nervous system continues to be investigated for potential means to promote repair and recovery. Many plasticity studies use animal models of spinal cord injury for foundational and translational research. Spinal cord injuries are common, and recoveries are limited. Nevertheless, the return of some function is typical, particularly if the injury is not classified as complete. Even after accounting for clinical assessments of injury severity, recovery prognosis is complex and difficult to predict precisely. Better ways to predict and to promote recoveries are important goals that motivate the study of animal models of spinal cord injury. Similarities between human and nonhuman primates further motivate the use of monkeys in studies of injury recovery.[1] While rodent models of spinal cord injury may be more common than nonhuman primate models, this review focuses on the role of plasticity in the somatosensory system of nonhuman primates. As reviewed by Kaas et al,[2] one anatomical difference is that in rodents, the spinal cord DCs contain the ascending somatosensory pathways along with descending corticospinal motor pathways. In primates, the DCs contain ascending somatosensory pathways, while the descending corticospinal motor pathways are contained in the lateral columns. Therefore, DC injuries produce different effects in primates and rodents.[2] Here, we do not discuss further the roles of different animal models of spinal cord injury and treatment, but such topics are examined by others.[3,4]

First, in this review, we introduce the injury model, and we outline how injuries can be assessed in order to link characteristics of individual injuries to outcome measures. Then, we discuss results of multiple measures that are used to assess recovery, including use of the impaired limb; neuronal reactivation, particularly in somatosensory cortex; and compensations or changes in anatomical connections. Evaluating such measures provide information about relationships between functional plasticity, sites, and types of plasticity underlying recovery, and factors that predict individual differences in recovery trajectories. This review concentrates on subsets of data gained from experimentally induced dorsal column lesions (DCLs) and survival times within the first weeks to months after injury during which time the brain reactivates and new connections may form. Additional changes occur in populations that lack input over many

months and years, including axon withdrawal[5] and atrophy.[6] The additional types of functional and maladaptive plasticity that occur after longer survival times are not discussed in detail here.[2,7,8] Our research, and that of others reviewed here, includes approaches to study relationships between behavioral recovery, lesion extent, brain reactivation, neuronal response properties, and anatomical changes. Such studies are particularly important for guiding treatments and predicting recovery after injury in patients. Interventions to promote plasticity may enhance functional recovery, but further research is needed to understand how to avoid abnormal undesirable changes.[9–11]

A Model of Plasticity After Sensory Loss

One model used to study plasticity and recovery after injury is a DCL model of spinal cord injury in which the ascending tactile inputs are disrupted from one hand while other inputs and descending pathways are largely intact. Pathways affected by a DCL in a squirrel monkey are shown in Figure 1. Afferents from the hand enter the cervical spinal cord through the dorsal roots, and one branch ascends in the DC pathway to terminate in the ipsilateral cuneate nucleus. Another branch of the primary afferents terminates in the dorsal horn to form synapses with second-order neurons in the spinal cord, which then are part of second-order pathways to the ipsilateral cuneate nucleus. In addition, dorsal horn neurons project to the contralateral spinal cord to form the spinothalamic pathway for pain, temperature, and tactile input. Lesions that cut the DC pathway at a mid-cervical level deactivate the cuneate nucleus by removing the direct primary afferent inputs and parts of the projections of the second-order spinal cord neurons from the hand for fine touch and proprioception, while leaving other input pathways largely intact. From the cuneate nucleus, any surviving tactile inputs representing the hand reach the somatosensory thalamus ventroposterior lateral nucleus (VPL). Spinothalamic inputs also reach VPL. Tactile inputs from VPL reach Brodmann's area 3b (primary somatosensory cortex). Rostral to area 3b, Brodmann's area 3a receives primarily proprioceptive information from another division of the thalamus (the ventroposterior superior nucleus) and is connected with area 3b. Area 3b is connected with the area on its caudal border, Brodmann's area 1, which contains a higher order representation of touch. Area 2 is a more complex higher order somatosensory area caudal to area 1. Within the primary ascending pathway for tactile information, the sensory surfaces are represented in a somatotopic organization that generally follows the same patterns in individuals of the same species. As previously summarized, for example, by Jain et al,[12] the consistent general organization of the representation across individuals in a species allow reasonable estimates of plastic reorganization by comparing monkeys with and without lesion injuries, even when the organization of the system is unknown for the specific individual before the injury.
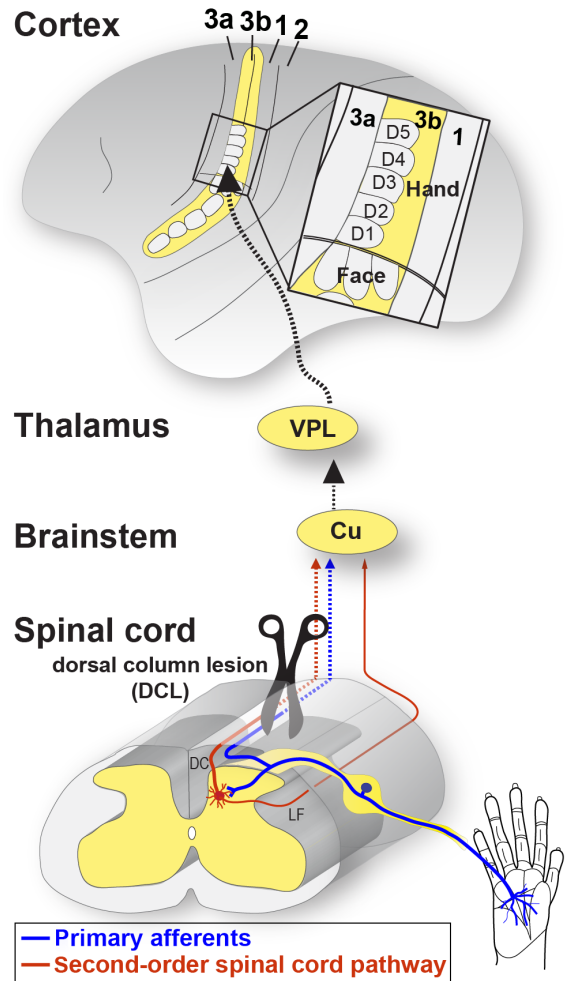

Figure 1. Schematic diagram of primary ascending somatosensory pathways in a squirrel monkey illustrates how lesions in the DC of the spinal cord disrupt the tactile input reaching the cortex. Primary afferents from the hand are shown in blue, with one branch ascending in the DC pathway to terminate in the ipsilateral brainstem cuneate nucleus (Cu). The other branch terminates in the dorsal horn of the spinal cord and forms synapses with second-order neurons (red). Second-order terminals reach the ipsilateral Cu via the DC pathway, or the lateral funiculus (LF) dorsolateral pathway, or other pathways. Projections to the contralateral spinal cord from the spinothalamic pathway are not shown. DC lesion at a mid-cervical level is indicated by scissors, and dashed lines mark the disrupted pathways of sensory inputs from the (right) hand, from spinal cord to brainstem, to thalamus, to cortex. From the (right) Cu representing the hand, inputs reach the contralateral (left) VPL of the thalamus, and projections from VPL reach the (left) cortex. The schematic depicts the left hemisphere of cortex of squirrel monkeys, with Brodmann's area 3b highlighted and surrounding somatosensory areas indicated (areas 3a, 1, and 2). The inset enlarges the boxed region of 3b to show the general organization of the hand representation with digits 1–5 (D1–5) represented from lateral to medial, and the face represented lateral to the hand.

Injury assessments. Studies in animal models provide the ability for detailed investigations of the injury extent that can be used to correlate with measures of plasticity and functional recoveries. As reviewed by Darian-Smith,[6] relating an individual's injury to the behavioral consequences with specificity requires detailed reconstructions of the lesion.

Historically, lack of information about the lesions resulted in discrepancies in the literature regarding the function of the spinal cord DCs, but careful examinations can provide individualized information and lead to improved predictions for outcomes based on injury. Typically, histological sections are studied to reconstruct the regions damaged by the experimental injury (Fig. 2A). Additionally, the pattern and intensity of labeling after transganglionic tracer injections into both of the hands can provide quantitative estimates of the lesion's effects.[7,13] As the example in Figure 2 shows, primary afferents take up anatomical tracers that are injected into the skin of the hand, and the terminal branches result in foci of label in the spinal cord and in the brainstem cuneate nuclei. The size (area) of the labeled foci and the strength of the staining (intensity) can be compared between matched regions on the sides with and without spinal cord lesions. This represents a step toward making better assessments and ability to link specific lesion characteristics with resulting plasticity and recovery. These detailed evaluations do not specifically show primary and secondary injury stages. However, imaging methods may aid in examining broad changes over time.

Chen et al[14] used quantitative magnetic resonance imaging (MRI) at 9.4 T to track changes in the spinal cord before and after DCLs in squirrel monkeys. Detailed histological assessments can be conducted at selected times after lesions, guided by the imaging results. Diffusion tensor imaging (DTI)
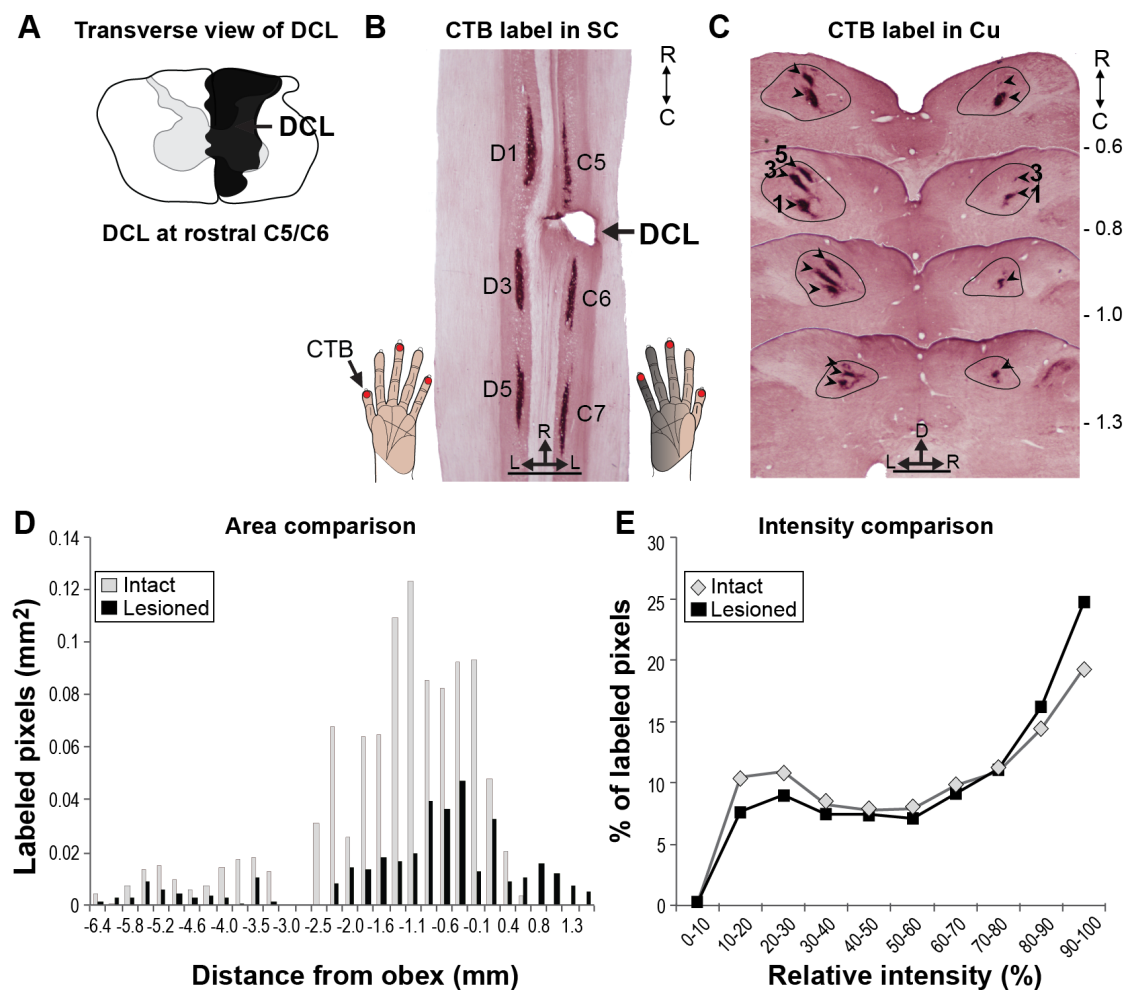

Figure 2. Example of histological assessment of the lesion extent with quantified estimates of differences between the sides of the spinal cord and brainstem for a squirrel monkey. (**A**) Projection of the DCL extent into a coronal plane between segments C5 and C6 created by reconstructing sections cut in a horizontal plane. (**B**) Horizontal section showing the lesion on left side of the spinal cord and axon terminal labeling from injections of cholera toxin subunit B (CTB) tracer into digits 1, 3, 5 of both hands. The labeled foci corresponding to the digits (D1, 3, 5) and cervical spinal cord levels (C5–C7) are indicated in the photomicrograph on the left and right, respectively. Red dots on the hand schematics indicate tracer injection sites. Gray shading gradient illustrates estimated deprivation of sensory input zones due to the lesion, which affected digit 5 inputs most and digit 1 inputs least. (**C**) Coronal sections through the brainstem with the cuneate nucleus (Cu) outlined on both sides show CTB label in the digit representations (1, 3, 5). Numbers to the right refer to distance from the obex (mm). (**D**) The combined size of the areas of the CTB-labeled foci (pixels, mm^2) are graphed for the Cu on the intact (gray) and lesioned (black) sides. The x-axis shows the distance of the section from the obex (mm). Statistical comparisons for paired samples indicate that the distribution of CTB label is reduced on the lesioned side ($P < 0.001$). (**E**) The relative intensity percentage of the labeled pixels indicates that even though the area of the labeled foci are reduced on the lesioned side, label intensity was not different from the labeling on the intact side ($P = 0.496$). Adapted from Liao et al.[7]

may also be useful for evaluating the characteristics and extent of spinal cord damage in patients. Structural changes and atrophy in the sensory and motor systems identified using MRI have been associated with measures of sensory and motor outcomes in patients with cervical spinal cord injury.[15] Similarly, in patients with cervical spinal cord injury, particularly those without metal spinal implants, Kim et al[16] found that DTI parameters can correlate with clinical measurements and outcomes. More comprehensive evaluations of the relationships between the physical injury and individual outcomes are challenging and require further investigation.[17] Practical concerns currently limit the use of imaging methods in broad populations of spinal cord injury patients. Therefore, detailed studies often require animal subjects prior to and in conjunction with clinical studies in samples of patients. Together, such studies seek to better understand and predict individual recoveries and response to rehabilitation and other treatment interventions.

Assessments of impairment recovery. Assessments of impairment and recovery of functions are vital clinically, and nonhuman primate studies incorporate assessments to evaluate the initial deficits and recovery progress over time.

Before histological assessments of the injury extent are made in animal subjects, measures of performance on experimental tasks provide benchmarks of recovery. In our typical experiments, monkeys are trained to perform a task to reach for a food item from wells of varying sizes using one hand. The trajectory of the movements can be tracked, and the number of attempts and successful performance can be recorded as references for impairment and recovery after DCLs. Such measures are then compared to those taken over time after the lesions. Figure 3 illustrates an example of tracking movement trajectories at times before and after lesions. While these illustrations are not quantified, measures obtained from movement trajectory analysis, such as distance or speed, can be more easily compared.

Functional impairments in spinal cord injury patients are correlated with assessments of the spinal cord damage or atrophy,[18] and as expected, the extent of the spinal cord injury correlates with initial impairments after experimentally induced DCLs.[19] Monkeys with more severe injuries require more testing days before using the impaired hand when task behavior is assessed post-lesion.
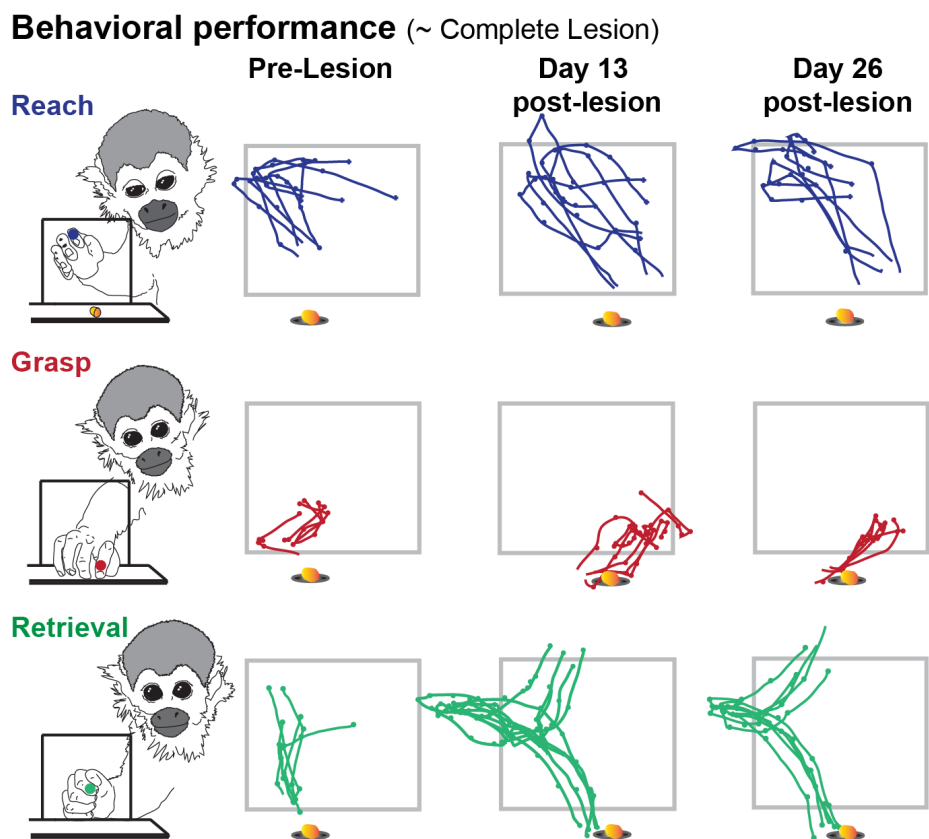
Figure 3. Hand movement trajectories reflect impairment after DCL and signs of recovery over time. Five successful trials are traced in each panel in relation to the opening through which the monkey reached (box) to retrieve a sugar pellet from a testing well. Video recordings were analyzed frame by frame following a reference point (knuckle of distal digit 2), depicted on schematic drawings (left). Dots and connecting lines illustrate the trajectory (from top to bottom panels) as the monkey reaches the hand toward the pellet (blue), grasps the pellet (red), and retrieves the pellet toward the mouth (green). Data from one case are shown (from left to right panels) before (pre-lesion) and at times after a nearly complete DC lesion (day 13 post-lesion, day 26 post-lesion). Visual comparisons of the movement trajectories (along with quantitative measures of distance, speed, etc.) indicate that impairments found soon after injury (day 13) can recover over time (day 26). Adapted from Qi et al.[20]

When cases are ranked based on early measures of task performance, the impairments in hand use are strongly correlated with the quantified estimates of the proportion of axons affected by the spinal cord injury.[19,20] Notably, in experimental nonhuman primate models with unilateral DCLs, task-specific functional recovery of hand use occurs over time to return to nearly normal levels in all but the most severe injuries. Conversely, the structural recovery at the level of the lesion is extremely limited and typically involves secondary injury or stabilization, without spontaneous regrowth of lesioned axons.[21,22] Thus, the strong relationship between the injury and the task-related hand use weakens over increasing recovery times, which suggests that plasticity at various levels in the somatosensory system compensates for unrepaired damage in the spinal cord.

Measures of task-specific recovery are correlated with measures of brain reactivation, and these relationships are under study in nonhuman primate models.[19,20,23,24] After incomplete unilateral DCLs, hand use recovers naturally/spontaneously without intervention. Evidence suggests that activity-dependent plasticity processes may be invoked by task performance. Even without sensory loss depriving the brain of normal inputs, Xerri et al[25] reported that task performance or skill learning can result in cortical reorganization and plasticity in area 3b. Exercise or rehabilitative therapy after spinal cord injury is linked to cortical reorganization in animal models and in patients.[10,26,27] Tactile stimulation paradigms may also affect cortical plasticity along with sensorimotor functions and tactile perception,[28] but the effects may be subtle and dependent on multiple factors.[29] As reviewed by Sandrow-Feinberg and Houlé,[30] behavioral task training or exercise used as a form of rehabilitation helps restore or improve impaired functions and is additionally linked to neuroregeneration and neuroprotection. Overall, multiple methods to assess injuries indicate that with greater severity of spinal cord damage, greater functional impairments and abnormal cortical activation are expected. However, strategies to promote functional plasticity and discourage maladaptive plasticity require further investigation for useful interventions.

Nervous system reactivation. Several types of studies track the reactivation of the nervous system at different times following injury. We briefly review noninvasive studies of neural activity after spinal cord injury (patients) and DCLs (nonhuman primates), and invasive studies after lesions in monkeys, focusing on cortical regions and the spinal cord. While the types of information acquired from noninvasive and invasive studies can differ, common goals of such studies include relating properties of neural function to impairment and recovery outcomes. Many types of noninvasive and invasive methods are available to assess the nervous system, and here, we focus on results from the techniques most commonly used in nonhuman primate models of spinal cord injury: noninvasive MRI and invasive neurophysiology.

Information from MRI. Imaging methods may be used to investigate the injury in the spinal cord, and functional MRI (fMRI) may be useful for tracking functional changes in the brain, and recently in the spinal cord in humans[31,32] and monkeys.[14,33] Resting-state fMRI has shown alterations in spontaneous neuronal activity in several brain regions and the spinal cord in monkeys with spinal cord injury.[14,34]

Figure 4 provides examples of brain activations summarized from fMRI experiments for a monkey with a nearly complete DCL and for a monkey with an incomplete DCL. Both incomplete and complete lesion cases show abnormal activity four weeks post-lesion. Surprisingly, after a complete lesion of the DC pathway, primary somatosensory cortex was activated in response to tactile stimulation on the impaired hand, although activity patterns were abnormal. After eight weeks, activation patterns appear to more closely resemble normal, particularly in the incomplete lesion case. Though these visualizations are not quantifications, measures from such images can be quantified and compared to track signatures of recovery.

Such noninvasive imaging methods can provide clinical tools to track structural and functional changes in patients with spinal cord injury.[18,35] fMRI of somatosensory cortex in subjects with spinal cord injury reveals evidence of plasticity and reorganization similar to findings in nonhuman primates after extensive DCLs, including abnormal activation in the territory representing the face that occurs after stimulating the median nerve, which innervates the hand.[36] But fMRI studies in patients after spinal cord injury have not supported consistent relationships between cortical reorganization, chronic pain, and recovery.[37] Evidence suggests that maladaptive plasticity possibly underlying phantom sensations can be revealed when touching the face causes activation in hand territory of somatosensory cortex; however, studies in patients with deafferentation differ in assessing links between cortical reorganization and phantom sensations,[8,38] and Makin et al[39,40] suggested that no single link explains the development of phantom pain and the changes in cortical activation after injury.

As reviewed by Huber et al,[35] multimodal MRI techniques allow quantification of structural and functional reorganization of the spine and brain in patients with spinal cord injury and in animal models. But continued study is needed to understand the pathophysiological mechanisms behind these structural and functional neural changes and the relationships to clinical recovery outcomes. Still, such noninvasive methods allow human subjects to be studied readily and enable longitudinal studies to be performed within the same individuals.

Information from neurophysiology. While the results are broadly similar to those using noninvasive methods, invasive neurophysiological methods can provide better temporal and spatial resolution when examining neural activation and reorganization reflecting plasticity. A method from the earliest neurophysiological studies, which remains a useful
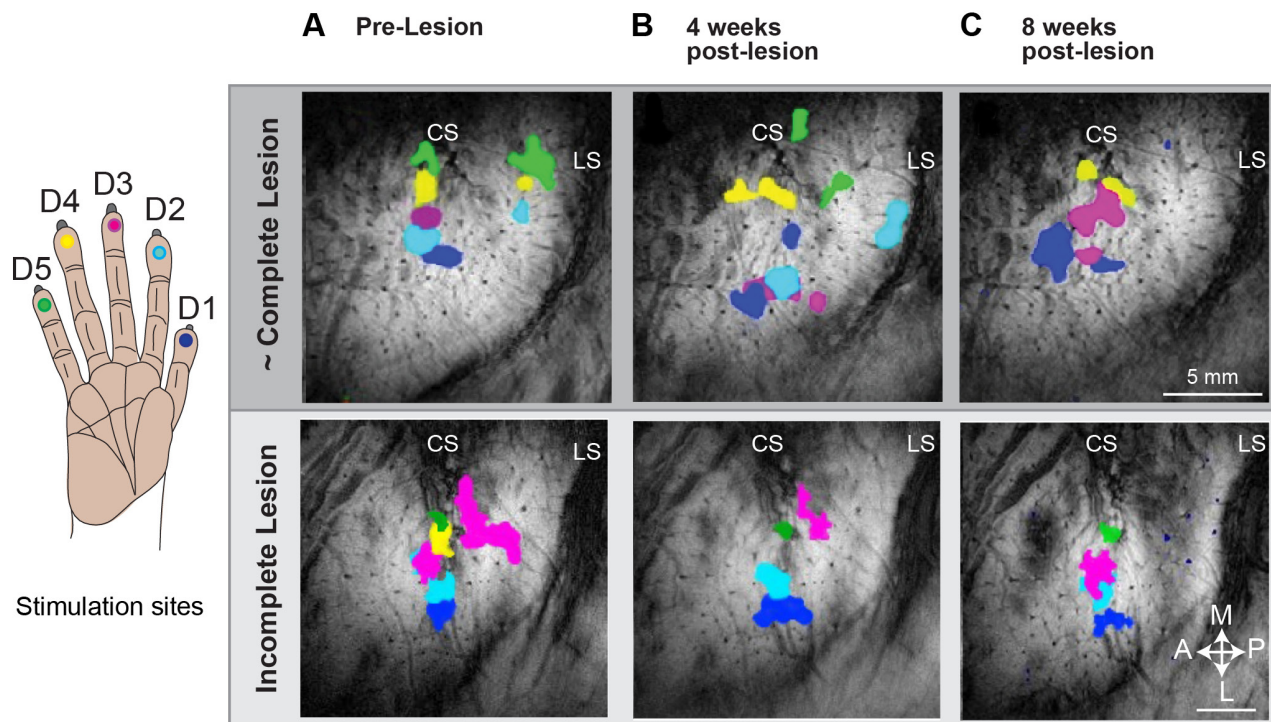
Figure 4. Longitudinal mapping of fMRI activation to vibrotactile stimulation on digits 1–5 (D1–5) before and at times after unilateral DCL in a squirrel monkey with a nearly complete lesion (dark gray shaded panel) and a squirrel monkey with an incomplete lesion (light gray shaded panel). Dots on the hand schematic (left) indicate individual sites for tactile stimulation and are color coded to correspond to the activation in cortex when that digit location was stimulated. (**A**) Before the lesion (pre-lesion), the composite (superimposed) activation evoked from stimulating the digits individually is relatively orderly in area 3b, located near the central sulcus (CS). Additional foci of activation between the CS and lateral sulcus (LS) occur in the vicinity of areas 1 and 2, but fMRI activation in these regions is inconsistent under anesthesia. (**B**) After four weeks post-lesion, activation foci are more disorganized and the centers are shifted away from the normal locations in 3b. (**C**) After eight weeks post-lesion, the centers of activation foci shift closer to pre-lesion locations, but activations are not found representing every digit. Scale bar for both panels is 5 mm. Adapted from Chen et al[68] and Qi et al.[69]

tool, involves microelectrode recordings of neural activity to map sensory responsiveness and evaluate plasticity and brain reorganization.[13,41,42]

Another type of study uses implanted microelectrode arrays to examine neuron properties in more detail. Qi et al[19] used implanted arrays rather than single microelectrodes to isolate neuronal signals for longer periods to calculate properties of responses to various tactile stimulation parameters. As Figure 5 illustrates, when a case was examined months after an incomplete lesion, somatotopic organization was largely normal. Notably, the possible expansions of the territories devoted to digits 1 and 2 correlate well with the injury extent, as a majority of the inputs from digits 1 and 2 were spared by the incomplete lesion in that case. After severe DC pathway disruption from nearly complete lesions, more regions of area 3b were disorganized and more neurons were weakly responsive or unresponsive to tactile stimulation. In spite of the cortical map changes, the neurons in the example cases (Fig. 5B) recovered the ability to fire action potentials such that when the neurons were responsive to stimuli, the firing rates were indistinguishable from normal monkeys.[19]

Experiments examining neuron properties would be especially informative with the ability to record from the same neurons before injury, during recovery periods, and after recovery from impairments. Technical challenges using arrays implanted over long periods limit such experiments currently.[43–46] Although the techniques to record neuronal activity are not perfect, they offer promising clinical applications. A retrospective analysis by Barrese et al[43] of long-term array recordings in macaque monkeys, using arrays similar to those approved for use in humans (Blackrock Microsystems), suggested specific targets to improve the use of such arrays for future research and clinical purposes.

From invasive and noninvasive assessments of cortical reorganization and neuron properties, relationships of nervous system functional reactivation and functional task performance can be examined. However, anatomical features after injury should also be considered as key factors involved in the manifestations of impairment and recovery.

Anatomical connections after injury. Neuronal connections in the somatosensory system are topographically organized with inputs from parts of the body surface projecting to corresponding representations at every level in the system. Changes in the neuronal connections in the somatosensory system, including axonal sprouting and withdrawal, or the dynamics in synaptic strengths and circuit balance, are
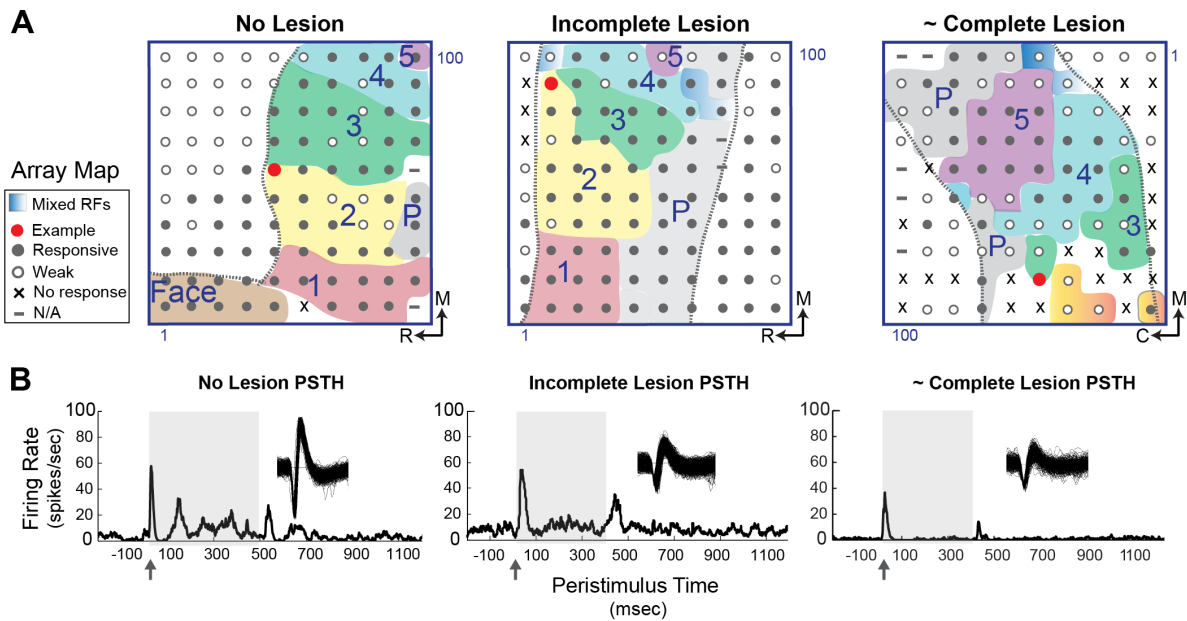
Figure 5. Neuron response properties and somatotopic representations in area 3b after task-specific recovery from DCLs show similarities to normal. (**A**) Area 3b somatotopic organization based on receptive field mapping from multielectrode arrays (Blackrock Microsystems) for a normal monkey (left), a monkey with an incomplete lesion (middle), and a monkey with a nearly complete lesion (right). Dashed lines indicate estimated borders of area 3b based on receptive fields and histological reconstructions of flattened cortex sections. Representations of the dorsal hand are not specified, but receptive fields representing multiple hand or arm locations are indicated with gradient shading (Mixed receptive fields [RFs]). Expected somatotopic organization is found after task-specific recovery from an incomplete lesion (middle) at C6 that preserved many of the afferents from digits 1 and 2. Digits 1 and 2 appear to be represented in more territory than digits 3–5, and responsive regions include mixed RFs. After task-specific recovery from a nearly complete lesion (right) at C4, more regions of area 3b were unresponsive to touch on the hand (X) or weakly responsive (open circles), but reactivated cortex was largely somatotopically organized. (**B**) Peristimulus time histograms (PSTH) of example neuronal activity in (contralateral) area 3b indicates responsiveness to tactile stimulation on digit 3 in cases without lesion (left), with incomplete lesion (middle), and nearly complete lesion (right). A red dot on each map in (**A**) marks the electrode location from which an example neuron in (**B**) was recorded. In (**B**), gray arrows mark the stimulus onset, and gray shading indicates stimulus duration in each trial (500 ms in the case with no lesion, 400 ms in the cases with lesions). Modified from Reed et al[70] and Qi et al.[19,69]

relevant substrates for functional recovery.[5] Although anatomical studies illustrating the altered connections in shorter recovery times (<5 months) are limited, comparisons of results from studies in subjects with longer recovery periods (>6 months) to normal cases can be used to predict the capacity for structural plasticity after injuries. New connections emerging at levels of the spinal cord, brainstem, thalamus, or cortex could contribute to functional reactivations.

1. *Spinal cord*: At the spinal cord level, there is no evidence for spontaneous recovery to return the tissue to its pre-injury state. Yet, when the DC injury is incomplete and spares some axons, surviving primary afferents and second-order spinal cord projections are able to project to the cuneate nucleus. Most of the afferents of second-order tactile neurons in the dorsal horn that course in the DCs may be preserved as well, but others may join the DCs above the lesions, or travel outside the lesion in the dorsolateral fiber tracts.[47] New inputs from the spinothalamic pathway for noxious, temperature, and some tactile sensations may also expand into the deafferented somatosensory territory at the level of thalamus. Another source of tactile and pressure inputs

identified in cats may come from the spinocervical pathways that travel outside the DC.[48]

2. *Brainstem*: Anatomical plasticity in the brainstem largely determines how the cortex is reactivated.[49] After incomplete lesions, surviving DC inputs to the cuneate nucleus likely sprout to reactivate more of the cuneate nucleus neurons that would be relayed to cortex. With extensive or complete lesions, large-scale axonal sprouting into the cuneate nucleus that originates from representations other than the hand (such as the face from the trigeminal nucleus) can occur after more than six months.[7,50] The effects of this large-scale brainstem plasticity are associated with abnormal representations in primary somatosensory cortex that appear to involve maladaptive cortical reactivation and possibly phantom sensations.[8] The role of the brainstem has also been demonstrated by delivering the enzyme chondroitinase ABC treatment near the cuneate nucleus to encourage the sprouting of surviving spinal cord inputs, which was reflected in primary somatosensory cortex as expansion of representations that were spared from the DCL.[51]

3. *Thalamus*: Thalamic nuclei, including VPL, can undergo large-scale topographic reorganization over months to

years after spinal cord injury. As reported by Jain et al,[52] approximately two years after DCLs in macaque monkeys, VP was reorganized with inputs representing the face inputs intruding into the hand region. However, the thalamocortical connections did not differ from normal. Reactivation and plasticity of the hand representation in the cortex that occurs soon after injury may be related to changes in synaptic strengths within single axon arbors, as Garraghty et al[53] showed that thalamocortical axons terminating in the cortex can branch widely in normal New World monkeys. But the normal branching of thalamocortical axons has not been found to underlie the intrusion of inputs across regional borders (eg, between the face and hand territories) in cortex. Although there is no evidence of altered anatomical inputs or projections of VP in primates,[7,54] these pre-existing connections may convey new inputs from the brainstem or spinal cord to the cortex.

4. *Cortex*: The connections of the deafferented hand cortex in area 3b to other cortical somatosensory areas 1 and 3a after DCLs[7,54] mostly resemble the normal pattern.[55–59] However, modest changes are noticeable. In monkeys with less severe injuries, connections between hand representations of the somatosensory areas are more widespread. In monkeys with complete/severe injuries, the intrinsic connections of area 3b could even expand across the regional border (eg, the hand/face border). Liao et al[7] found some evidence of expanded connections at the cortical level after long-standing (>10 months) DCLs, but changes were not as extensive as sprouting in the cortex of face inputs into the hand territory years after therapeutic forelimb amputations.[60,61] While such newly formed connections between the hand representations in different areas may facilitate the reactivation of hand responses, the axonal sprouting across the regional borders, such as between the hand and face, may convey maladaptive inputs and phantom sensations.

Continued anatomical studies of the effects of spinal cord lesions on regions within and beyond the primary somatosensory ascending pathway are required to identify sources of plasticity and potential targets for treatments. Future studies are needed to address the roles of feedback pathways on plasticity, as well as to understand the effects of therapeutic interventions across multiple levels of the sensorimotor systems.

Correlations and Treatment Implications

Relating multiple measures in primate models of injury can help to guide treatments to encourage appropriate/desirable plasticity, discourage dysfunctional plasticity, and better tailor treatments based on individual differences. Without successful treatments, the spinal cord injury does not spontaneously recover to the pre-injury structure and function. Yet, even though the somatosensory system and spinal cord do not

show full recovery to normal pre-injury states, partial functional recoveries can be measured after DCLs. These spontaneous recoveries must be related to central nervous system plasticity. Figure 6 is a summary of the associations between neurophysiological, behavioral, and anatomical measures of the effects of incomplete DCLs in relation to plasticity and recovery. Because studies have shown that immediately after lesion, neurons in area 3b are deactivated, the somatotopic organization and nearly normal response properties found months after the lesion represent neuroplasticity. Initially, the reactivation of area 3b (and subcortical structures) must occur through fast-occurring mechanisms like disinhibition to reveal modulating inputs that become driving inputs and relatively quick synaptic weighting. Only after long recovery times can new axon collaterals from surviving neurons grow into territories deprived of normal inputs.[2,50,62] After complete or nearly complete lesions, cortical responsiveness may occur via alternative pathways for information to reach cortex other than by the DC pathway.

One strategy employed using nonhuman primate models of injury involves relating specific measures within each individual subject prior to assessing average results from groups of subjects. For example, with detailed lesion reconstruction, Darian-Smith and Ciferri[63] correlated maps of neural activity representing the hand in primary somatosensory cortex with the extent of digit use after cutting inputs to the spinal cord DCs (with a dorsal rhizotomy). Similar correlations have been made after reconstructing DCLs to correlate the lesion extents with cortical activity maps,[13] the behavioral outcome,[20] or the anatomical connections.[7] Investigations that integrate multiple types of measures seek to better translate between non-primate and primate studies[64] and provide more complete assessments to better translate findings from nonhuman primate models of spinal cord injury into treatments for human patients.[65]

Links between observable measures in nonhuman primates, such as behavioral task performance, with functional measures of brain plasticity are particularly useful for applying predictions of recovery prognosis and treatment efficacy. As depicted in Figure 6, functional recoveries can be revealed through a variety of measures after incomplete DCLs, even when the lesioned pathway does not recover. When hand use nearly recovers to pre-injury levels, neuronal activity in deprived area 3b tends to be nearly normal (as tracked with noninvasive imaging and investigated with microelectrodes), but the original anatomical pathways are not restored. Instead, new connections drive neuron activity and the brain reorganizes in ways that likely underlie the recovery of hand use.

Repairing spinal cord damage is an important treatment goal to recover the most normal function possible, and many avenues are being pursued.[66,67] When axons are damaged after injury, affected neuron cell bodies have the potential to regrow axons to appropriate targets with interventions. Another treatment approach does not emphasize structural
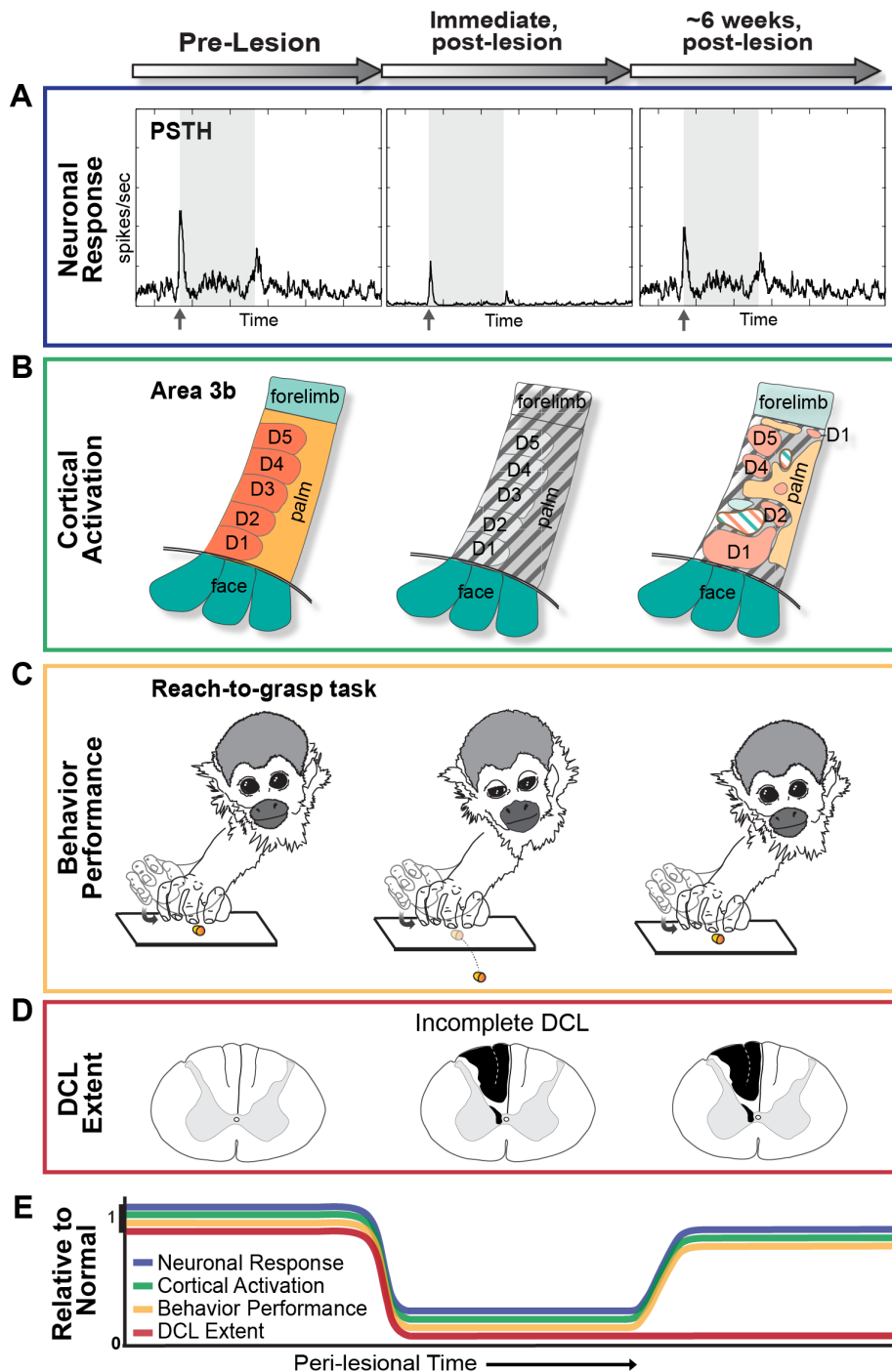
Figure 6. Summary of differences before and after incomplete DCLs for different measures reflecting plasticity. All panels show schematics representing measures without lesions (pre-lesion, left), shortly after incomplete lesion (immediate, post-lesion, middle), and several weeks after incomplete lesion (~6 weeks, post-lesion, right). (**A**) Representative neuronal activities are shown to indicate decreased responsiveness shortly after lesion and recovery to near-normal levels over time. Conventions follow Figure 5. (**B**) Schematics of area 3b cortical activation (which may be measured with imaging, electrophysiology, or other methods) depict inactivation immediately after the lesion deprives the cortex of normal driving activity (gray hatching). The extent of cortical reactivation can vary based on characteristics of the lesion and other factors; however, when the lesion is incomplete responsiveness can return, but may be weaker (light shading). Representations may also show abnormal organization or represent multiple receptive fields, including for the face and forelimb (multicolored hatching). (**C**) Graphics of the movement to reach (gray) and grasp (black) a sugar pellet from a well depict impairment of performance on the reach-to-grasp task shortly after lesion and recovery of performance over time. (**D**) Drawings of coronal sections of cervical spinal cord before and after lesion (black) depict lack of spontaneous improvement of the lesion over several weeks. (**E**) Simplified schematic summarizes differences in measures relative to normal over time before and after incomplete lesion. Lines correspond to the color of the boxes shown for each of the panels (**A**–**D**). Lines would overlap, but are separated for visualization, as indicated by the black bar on the y-axis at 1 representing normal levels. The spinal cord does not heal structurally after a DC lesion (red); however, functional improvements can be measured that indicate plasticity outside of the DCs underlies recovery to near-normal levels several weeks after incomplete DCL.

spinal cord repair, but instead focuses on encouraging the survival and plasticity of neurons that have been spared from injury.[2,27,30,51] Such studies probe the types of changes that occur and the extent and sources of plasticity, in order to target ways to promote the powerful mechanisms of recovery. Treatment strategies also seek to avoid maladaptive plasticity while strengthening use-dependent functional plasticity. As reviewed here, when injuries are incomplete and spare even a small portion of the neurons from damage, these surviving neurons can sprout axon collaterals and provide input to deprived areas, reducing axon withdrawal and eventual atrophy within the system. When more system-level measures are examined and combined with genetic and molecular-level studies, predictions and prognosis of individual cases may improve exponentially, and better customized treatments may be soon within reach.

Author Contributions

Wrote the first draft of the manuscript: JLR. Contributed to the writing of the manuscript: C-CL, H-XQ and JHK. Agreed with manuscript results and conclusions: JLR, C-CL, H-XQ and JHK. Jointly developed the structure and arguments for the paper: JLR, C-CL, H-XQ and JHK. Made critical revisions and approved the final version: JLR, C-CL, H-XQ and JHK. All the authors reviewed and approved the final manuscript.

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