Published in final edited form as:

Exp Neurol. 2008 February ; 209(2): 407–416.

Cortical and subcortical plasticity in the brains of humans, primates, and rats after damage to sensory afferents in the dorsal columns of the spinal cord

Jon H. Kaas¹, Hui-Xin Qi¹, Mark Burish^{2,3}, Omar Gharbawie¹, Stephen M. Onifer⁴, and James M. Massey^{5,6,7}

¹Department of Psychology, Vanderbilt University, Lexington, Kentucky, 40536-0509, USA

²M.D./Ph.D. Program, Vanderbilt University School of Medicine, Lexington, Kentucky, 40536-0509, USA

³Neuroscience Graduate Program, Vanderbilt University, Lexington, Kentucky, 40536-0509, USA

⁴Spinal Cord and Brain Injury Research Center, University of Kentucky College of Medicine, Lexington, Kentucky, 40536-0509, USA

⁵M.D./Ph.D. Program, University of Louisville School of Medicine, Lexington, Kentucky, 40536-0509, USA

⁶Department of Anatomical Sciences and Neurobiology, University of Louisville School of Medicine, Lexington, Kentucky, 40536-0509, USA

⁷Kentucky Spinal Cord Injury Research Center, University of Louisville School of Medicine, Lexington, Kentucky, 40536-0509, USA

Abstract

The failure of injured axons to regenerate following spinal cord injury deprives brain neurons of their normal sources of activation. These injuries also result in the reorganization of affected areas of the central nervous system that is thought to drive both the ensuing recovery of function and the formation of maladaptive neuronal circuitry. Better understanding of the physiological consequences of novel synaptic connections produced by injury and the mechanisms that control their formation are important to the development of new successful strategies for the treatment of patients with spinal cord injuries. Here we discuss the anatomical, physiological and behavioral changes that take place in response to injury-induced plasticity after damage to the dorsal column pathway in rats and monkeys. Complete section of the dorsal columns of the spinal cord at a high cervical level in monkeys and rats interrupts the ascending axon branches of low threshold mechanoreceptor afferents subserving the forelimb and the rest of the lower body. Such lesions render the corresponding part of the somatotopic representation of primary somatosensory cortex totally unresponsive to tactile stimuli. There are also behavioral consequences of the sensory loss, including an impaired use of the hand/forelimb in manipulating small objects. In monkeys, if some of the afferents from the hand remain intact after dorsal column lesions, these remaining afferents extensively reactivate portions of somatosensory cortex formerly representing the hand. This functional reorganization develops over a postoperative period of one month, during which hand use rapidly improves. These recoveries appear to be mediated, at least in part, by the sprouting of preserved afferents within the cuneate

Correspondence to: Jon H. Kaas, Department of Psychology, Vanderbilt University, 111 21st Ave. S., Nashville, TN 37203, jon.h.kaas@vanderbilt.edu, Tele: 615-322-6029, Fax: 615-343-8449.

Prepared for a special issue of *Experimental Neurology*: Rehabilitation after Spinal Cord Injury

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

nucleus of the dorsal column-trigeminal complex. In rats, such functional collateral sprouting has been promoted by the post-lesion digestion of the perineuronal net in the cuneate nucleus. Thus, this and other therapeutic strategies have the potential of enhancing sensorimotor recoveries after spinal cord injuries in humans.

Introduction

The dorsal (posterior) columns of the spinal cord consist mainly of sensory afferents that subserve the cutaneous sensations of touch, pressure, flutter, and vibration (Whitsel et al., 1972; see Fig 1). Complete section of this pathway at a high level of the cervical spinal cord deactivates much of primary somatosensory cortex, and probably a number of other areas of somatosensory cortex as well. Such lesions abolish or greatly impair the ability to discriminate tactile textures, touch frequencies, and directions of moving tactile stimuli (see Mountcastle, 2005 for review). There are also impairments of motor control, most likely as a result of the loss of sensory feedback. Nevertheless, the ability to localize somatosensory stimuli survives, and locomotive behavior can appear to be quite normal. These and other functions remain after dorsal column sections likely because axon tracts ascending in the ventral and dorsolateral quadrants of the spinal cord, which provide sensory and proprioceptive feedback, are spared.

Confusion between functional recovery and compensation has complicated the characterization of sensory and motor deficits from dorsal column sections. The magnitudes of these deficits were not fully apparent until a series of carefully controlled studies on monkeys with dorsal column lesions were completed by Vierck and co-workers (e.g., Vierck, 1998). In contrast, earlier studies were often difficult to interpret because lesions were incomplete or included other parts of the spinal cord. As a result, Wall (1970) once argued that most sensory abilities were left intact after dorsal column lesions. Others concluded that the loss of sensory abilities was severe (Mountcastle and Darian-Smith, 1968; Nathan et al., 1986). Part of the reason for these differing conclusions was that the importance of a few remaining afferents in incompletely sectioned dorsal columns was not fully appreciated. For example, Schwartz and co-workers (1972), in a study of dorsal column section in monkeys, concluded that such lesions left the “discrimination of subtle tactile differences in textures, form, pattern and hardness unchanged or only slightly affected”. However, the authors skeptically allowed the alternative interpretation that “very few residual fibers may mediate these complex discriminations”. Here we review more recent findings in humans, monkeys, and rats showing that a few remaining dorsal column fibers may be very important in mediating recovery of functions. Furthermore, there is evidence that therapies that promote the survival, sprouting, or regeneration, of even a few such fibers are effective promoting recovery in animal models and may be of value to human spinal cord injuries.

Dorsal column section in humans

The functions of the dorsal columns in humans are understood in part from the types of impairments that follow degenerative diseases that target the dorsal columns, such as neurosyphilis (tabes dorsalis), Friedreich’s ataxia, and subacute combined degeneration (Harrison and Braunwald, 2001). Patients with these diseases show clinical deficits in two-point discrimination, vibratory sense, and proprioception, suggesting that the dorsal columns in humans are functionally similar to those of monkeys. It must be noted, however, that in all three diseases other areas such as the dorsal roots or the lateral spinal tracts may also be involved (Harrison and Braunwald, 2001; Hotson, 1981; Hughes et al., 1968; Srikanth et al., 2002). In this review, we focus on injury involving the dorsal columns as opposed to dorsal column disease, as the damage caused by such injuries is more often similar to that induced in experimental studies in monkeys and rats.

Complete and isolated injury to the dorsal columns is exceedingly rare in humans. However, studies of incomplete dorsal column injuries and of extensive spinal cord injuries are available, and can provide insight into the extent of functional recovery after their injury. For example, spinal myelotomies limited to the dorsal columns have been developed as a palliative treatment for abdominal pain syndromes (Nauta et al., 1997). For the treatment, a needle or forceps are typically used to make a lesion 5–6 mm deep and 1–2 mm wide in the medial-most portion of the dorsal columns (Hong and Andren-Sandberg, 2007). The objective is to sever some of the afferents for visceral pain that ascend in the most medial portion of the dorsal column but at the same time spare more lateral ascending afferents pertaining to classical sensations of fine touch, vibration, and proprioception (Al-Chaer et al., 1999; Al-Chaer et al., 1996). Post-operatively, pain is relieved in most cases, but there have been reports of consequential neurological deficits. These deficits were usually only transient ataxia or paresthesias of the leg (Becker et al., 1999; Kim and Kwon, 2000; Papo and Luongo, 1976), suggesting that medial proprioceptive and tactile afferents had been injured and that recovery generally occurred in the setting of incomplete injury.

Larger dorsal column lesions, which involve additional pathways, have been extensively reviewed by Nathan and colleagues (Nathan et al., 1986). Patients with injuries that included the dorsal columns had deficits in the perception of fine touch and vibration as well as proprioceptive impairments. Light touch and pressure senses were generally not lost, and the deficits were primarily related to temporal and spatial discrimination (Nathan et al., 1986). In many cases functional recovery occurred over time, perhaps because the dorsal columns were incompletely damaged. For a loss of light touch and pressure sense, an additional pathway had to be cut in the anterolateral spinal cord, presumably the anterolateral spinothalamic tract. Injury of the anterolateral spinal cord alone did not affect tactile ability or proprioception, but resulted in the loss of warmth, cold, and pain sensations that were spared by dorsal column lesions.

Phantom sensations have also been reported in patients with spinal cord injuries. Referred sensations, such as touching the arm to elicit phantom sensations in the chest, have been correlated through functional MRI to an expanded activation of the arm representations in somatosensory cortex (Moore et al., 2000). Comparable functional reorganizations following spinal cord injuries have been seen in both somatosensory cortex and thalamus (see Wall et al., 2002), but the brainstem has not been well studied. These phantom sensations appear to be similar to those of patients with amputated limbs (Ramachandran, 1993), and likely involve similar mechanisms, including axonal sprouting in the brainstem.

Functional reorganization, however, may not always be detrimental, especially when the lesion is incomplete and surviving afferents remain. One patient who sustained a high cervical spinal cord injury with near complete loss of sensory and motor function for more than five years, underwent intense rehabilitation therapy and developed a modest amount of recovery. This recovery was associated with cortical activation visible with functional MRI (Corbetta et al., 2002). Thus, sustained physical activity after spinal cord injury over the course of years appears to drive the neuroplasticity of surviving axons.

Dorsal column section in monkeys

In monkeys, complete section of the dorsal columns at a high cervical level resulted in a reluctance to use the deprived forelimb in reaching for food and a persistent lack of skilled use of the digits (Glendinning et al., 1992; Kaas, 2002). The impairments in motor control appeared to be largely or completely related to deficits in somatosensory processing, although some alterations in the functional organization of motor cortex after dorsal column lesions may have contributed to the defective hand use (see below). Nevertheless, after one to three months of

recovery, the deprived hand participated in less skilled actions such as those used to support a food item that is too large to manipulate with one hand. Also, dorsal column lesions did not significantly impair locomotion and climbing, which do not appear to depend on cortical levels of sensory guidance.

Complete section of the dorsal columns at a high cervical level interrupts the ascending branches of afferents from not only the forelimb but also from the rest of the body below the forelimb. Consequently, dorsal column lesions extensively deactivated portions of the forelimb, trunk, and hindlimb representations in areas 3b and 1 of somatosensory cortex (Jain et al., 1997). However, with longer recovery times (6-8 months), other sources of afferent information came to activate neurons in the deprived cortex. For example, afferents remaining from the arm activated neurons throughout the formerly deprived hand cortex in areas 3b and 1 (Jain et al., 1997; and unpublished experiments). Also, afferents from the chin reactivated not only the former hand representations, but also the more medial representational territories of the trunk and hindlimb. The extensive reactivations depended on the sprouting of afferents to new locations in the trigeminal-dorsal column complex in the brainstem (Jain et al., 2000b). New connections may have developed at thalamic and cortical levels as well. What confusing messages newly formed chin afferents provided to the extensively reactivated cortex remains uncertain, but in humans with arm amputations, touch on the face or arm stump triggered phantom sensations of touch on the missing limb (e.g., Ramachandran and Hirstein, 1998). Thus, the reactivation of hand cortex by inputs from the face appears to contribute to phantom sensations, rather than to functional recovery.

Incomplete spinal cord injuries also produce severe impairments in hand use and sensory abilities. Recovery is generally more rapid however (weeks) as compared to that from complete spinal cord section. This type of behavioral recovery has been studied more fully after section of some, but not all, of the dorsal roots of the peripheral nerves subserving the hand (Darian-Smith, 2004; Darian-Smith and Ciferri, 2005; Darian-Smith and Ciferri, 2006). In these monkeys, the deprived portions of the cuneate nucleus and primary somatosensory cortex (area 3b) were initially unresponsive when investigated with recording microelectrodes, and skilled reaching was impaired. Recovery of skilled hand use coincided with the reactivation of deprived somatosensory cortex by the preserved, but previously ineffective, afferents from the hand. The nature of the recovery depended on which skin surfaces the preserved afferents subserved, with those from distal glabrous digits 1-3 being the most useful. Nevertheless, it is unclear if the reactivation of the normal cortical territories of the preserved afferents alone allowed the recovery, or if the expanded cortical representations of these afferents also contributed. Additionally, this recovery may have limits: when the extent of these lesions was increased, both somatosensory cortex reactivation and functional recovery remained incomplete even after months of recovery (Darian-Smith and Ciferri, 2005; Darian-Smith and Ciferri, 2006).

In a similar manner, incomplete dorsal column sections that spared some of the ascending axons from afferents of the hand were followed by extensive reactivation of somatosensory hand cortex (Jain et al., 1997; see Fig 2). This reactivation depended in part on the sprouting of preserved forelimb afferents within the cuneate nucleus of the dorsal column nuclei. Consequently, cuneate neurons were reactivated (Jain et al., 2000a), which in turn activated more neurons in the contralateral ventroposterior nucleus (Jain et al., 2000b, 2001). There, additional sprouting of axons and the further spread of activation may have occurred. Surprisingly, portions of the hand or foot cortical representations were reactivated by preserved afferents from the hand or foot within the first month of recovery, and could still subsequently be activated by inputs from the face (Jain et al., 1997; 2000a). Thus, cortical neurons may become responsive to both inputs from the hand and from the face. The perceptual

consequences of such confusing patterns of cortical activation are unclear, but sensation from both the hand and the face may occur when the hand is touched.

Insight about somatosensory cortex reactivation after denervation has also been gained from monkeys that lost an arm due to injury. Deprived neurons in the ventroposterior nucleus were reactivated by preserved afferents from the upper arm stump and the face (Florence et al, 2000). The relay from the ventroposterior nucleus to somatosensory cortex activated neurons in the hand region of area 3b, where the growth of intrinsic horizontal connections may have further spread the information from the few preserved afferents subserving cutaneous receptors of the hand (Florence et al., 1998).

While the effects of dorsal column sections on cortical somatosensory areas have focused on areas 3b and 1, other cortical areas such as area 2, the second somatosensory area (S2), and the parietal ventral area (PV), depend on areas 3b and 1 for activation. In addition, the cortical outputs of these somatosensory areas are to motor and premotor areas of the frontal lobe, as well as to posterior parietal cortical areas that project to these motor areas (Kaas, 2004). It is therefore conceivable that the initial pattern of deactivation and the subsequent pattern of reactivation with areas 3b and 1, have a huge impact on the nature of all somatosensory cortical processing. Furthermore, it is also possible that the impaired hand use observed after dorsal column lesion reflects motor cortex dysfunction related to the disruption of its sensory inputs from the same somatosensory cortical areas.

Do dorsal column lesions alter the functional output of motor cortex?

Our efforts to assess the possibility that the loss of sensory information alters the functional organization of motor cortex are ongoing and incomplete. Electrical stimulation of primary motor cortex in macaque monkeys with long-standing dorsal column lesions, showed that movements of body parts can be evoked at normal levels of stimulating current from sites throughout motor cortex (Qi, Collins, Jain, and Kaas, unpublished studies). In addition, the topographic organization of the representational territories between the elbow and the face were approximately normal. Thus, all parts of stimulated motor cortex, including those with reduced or abnormal sensory guidance, remained functional. Nevertheless, some stimulation sites produced combinations of movements of different digits and the wrist that were not seen in normal monkeys. Changes in the movement patterns evoked from motor cortex with abnormal sensory inputs may contribute to the dysfunctional hand use of monkeys with dorsal column lesions.

Dorsal column section in rats

The organization of the dorsal columns is fundamentally different in rats than in primates because it includes both ascending sensory axons and descending motor axons (Fig 1). As in primates, the primary sensory afferents that project to the cuneate and gracilis nuclei occupy the dorsal portion of the dorsal columns. In addition, corticospinal fibers from motor cortex cross the brainstem midline at the caudal end of the medulla and in large part traverse along the base of the dorsal columns filling the region between the grey matter and the sensory tracts. Smaller portions of the corticospinal fibers form separate funiculi that descend in the lateral and ventral spinal cord. Thus, complete section of the dorsal columns alone results in both a sensory loss and a motor loss in rats.

The consequences of neonatal complete dorsal column section on the responsiveness of somatosensory cortex have been studied in rats. At the age of three postnatal days, rats received extensive spinal cord injury at cervical levels 3-4, including the dorsal columns of both sides (Jain et al., 2003). The injury interrupted ascending afferents from the hindlimb, lower body, and most of the forelimb. Only afferents from the head and a few from the upper arm remained

intact. The somatosensory cortex was explored with recording microelectrodes 6-8 months later and the trunk, hindlimb, and forelimb portions of primary somatosensory cortex (S1) were almost completely unresponsive to tactile stimuli. A few recording sites in forelimb cortex were responsive to stimuli on the upper arm and neck, indicating that surviving afferents from these skin territories had expanded their normal focus of cortical activation in S1 to include parts of the forelimb representation. The anatomical substrates for this partial reactivation of forelimb cortex are unknown, but possibly moderate amounts of sprouting of afferents from the upper arm and neck occurred in the cuneate nucleus so that they became capable of activating neurons normally responsive to forelimb afferents. New connections at thalamic and cortical levels could have developed as well. Nevertheless, the reactivation of deprived portions of S1 was quite limited in these developing rats.

Similar results were obtained from adult rats following extensive dorsal column lesions. Transection of the upper cervical dorsal columns abolished evoked potentials to tactile forelimb stimulation in both the ipsilateral cuneate nucleus and the contralateral forelimb somatosensory cortex (Onifer et al., 2005; Massey et al., 2006). In other studies, section of afferents from the hindlimb and lower body in the thoracic dorsal columns selectively and completely deactivated corresponding areas of contralateral hindlimb somatosensory cortex (see Fig 2; Jain et al., 1995; Schlag et al., 2001). Deactivated portions of the cortex formerly representing the hindlimb and lower trunk failed to recover responsiveness to any body region over a post-surgical recovery period of three months (Jain et al., 1995). In addition, the few preserved hindlimb primary afferents in rats with incomplete dorsal column sections failed to expand activation beyond their normal anatomical boundaries. Thus, at least over a three-month recovery period, intact afferents from the hindlimb, forelimb and face appear to be unable to form widespread new connections and thereby activate the deprived hindlimb and trunk cortex. Overall, the results suggest that rats have limited ability to form new connections in the ascending dorsal column system. The reorganization that does occur is insufficient to substantially reactivate deprived portions of the somatosensory system.

Behaviorally, dorsal column lesions in rats produce observable impairments of motor function. Like primates, rats will reach for and grasp small food items in their digits. This dexterity appears to be subject to the integrity of both the ascending sensory axons in the dorsal columns and the descending motor pathways of neocortical origin (Castro, 1972; Whishaw et al., 1991; Whishaw et al., 1993). Although the intricacies of reaching impairments reported after dorsal column section vary somewhat, a constellation of deficits has been consistently described (Ballermann et al., 2001; McKenna and Whishaw, 1999; Saling et al., 1992; Schrimsher and Reier, 1993). First, dorsal column section produced a transient decline in reaching success scores, but preoperative levels were approached within one-to-two weeks of injury. Second, there were postural and limb kinematic aberrations, suggesting that the restored success scores could be attributed to chronic impairments masked by compensatory strategies. Third, elbow aiming during limb transport was impaired, resulting in a number of misdirected reaches. Nevertheless, the limb transport trajectory was spared, suggesting that is a ballistic action that does not necessitate sensory feedback. Fourth, the sequence of digit flexion, limb withdrawal, and paw inspection that succeeded a misguided reach implied that rats with dorsal column sections were unaware of their failures to retrieve the food target. This impairment also occurred on probe trials in which a food target was not presented but the rat reached anyway and inspected its paw for food. In contrast, control animals palpated the shelf on probe trials as if searching for the food pellet. Somatosensory feedback is therefore central to limb aiming and for modulating the actions associated with grasping and withdrawing the forelimb to present food to the mouth. This feedback does not recover after long-standing dorsal column injury resulting in chronic impairments.

A chronic sensory impairment was also evident when rats with dorsal column sections attempted haptic discrimination. Control rats presented with a smooth food item and a textured but otherwise identical non-food item, consistently averted their grasp when a non-food item was palpated, and directed their reach towards the food item and retrieved it instead (Ballermann et al., 2001). In contrast, dorsal column sectioned rats grasped and retrieved either item at chance levels. Skilled and overground locomotion were also chronically disrupted by dorsal column section. The impairments included increased numbers of footfalls (Webb and Muir, 2003) and an asymmetric gait characterized by impaired braking with the ipsilateral-to-lesion forelimb and reduced weight support with the ipsilateral-to-lesion hindlimb (Webb and Muir, 2003; Kanagal and Muir, 2007). This suggests that in contrast to monkeys, some of the locomotor deficits seen in rats were due to interruption of descending motor fibers traveling in the dorsal columns.

Some sensory impairments were more transient when measured on other tests of sensory discrimination. For example, when a small adhesive paper was applied to the distal forelimbs of control rats, it was immediately removed with the mouth. In contrast, orientations to the adhesive paper on the ipsilateral-to-lesion forelimb were delayed or the stimulus was neglected all together during the first two weeks of dorsal column lesion. Orientation times returned to normal by four weeks (Ballermann et al., 2001; Onifer et al., 2005).

In summary, rats with dorsal column lesions had chronic deficits on tasks requiring action, such as reaching for food, skilled and overground locomotion (Ballermann et al., 2001; McKenna and Whishaw, 1999; Kanagal and Muir, 2007). These deficits were not exacerbated with additional sensory input loss as in dorsal hemisection (Onifer et al., 2005) or deafferentation of the dorsal root (Saling et al., 1992). In contrast, dorsal column lesions produced transient impairments on tasks of sensory discrimination such as the adhesive dot removal task, as normal behavior recovered within a few weeks of injury (Ballermann et al., 2001; Onifer et al., 2005). Such a dichotomy suggests that dorsal column afferent fibers provide unique sensory inputs central to some behaviors, whereas some sensory discriminations can be mediated by alternate sensory pathways (Ballermann et al., 2001; McKenna and Whishaw, 1999).

Improving functional recovery by promoting axon growth

The mechanisms that limit somatosensory plasticity in the dorsal column pathway following injury are not completely understood. An increasing amount of recent work has centered on the extracellular matrix that surrounds denervated target neurons. In the normal adult nervous system, chondroitin sulfate proteoglycans are widely distributed and form much of the extracellular matrix that surrounds neurons (Celio and Blumcke, 1994; Celio et al., 1998; Celio, 1999; Yamaguchi, 2000; Viapiano and Matthews, 2006; Galtrey and Fawcett, 2007). These heterogeneous molecules form a significant component of specialized structures called perineuronal nets first described over one hundred years ago by Golgi (1893; 1898). Evidence from both adult and developing rats has suggested that an important function of this specialized extracellular matrix is to regulate synaptic plasticity. For example, the expression of chondroitin sulfate proteoglycans associated with perineuronal nets has been shown to coincide with the end of the developmental critical period plasticity (Guimaraes et al., 1990; Kalb and Hockfield, 1990a; 1990b; Lander et al., 1997; Pizzorusso et al., 2002). This expression appeared to be activity-dependent in the visual cortex, the spinal cord, and the somatosensory cortex (Kalb and Hockfield, 1988; 1990a; b; 1992; Lander et al., 1997; Pizzorusso et al., 2002; McRae et al., 2007) and was delayed in the absence of normal activity (Kalb and Hockfield, 1990a,b; Lander et al., 1997; Pizzorusso et al., 2002; McRae et al., 2007). In adult rats, chondroitin sulfate proteoglycans appeared to be richly deposited within the perineuronal

nets that surround both secondary dorsal column neurons and potential relay neurons in the thalamus (Vitellaro-Zuccarello et al, 2001; Massey et al, 2006; 2007).

After spinal cord injury, glial activation and increased chondroitin sulfate proteoglycans expression were evident at the injury site, and their denervated secondary dorsal column relay neurons (McKeon et al., 1995; Asher et al., 2000; Jones et al., 2002a,b; Jones et al., 2003; Tang et al., 2003; Silver and Miller, 2004; Koshinaga and Whittemore, 1995; Massey et al, 2007). Regenerating adult dorsal root ganglion neurons that were able to extend their processes for long distances through degenerating dorsal column fiber tracts but did not penetrate spinal cord lesion sites containing high concentrations of chondroitin sulfate proteoglycans (Davies et al., 1999). Thus, this increased expression appeared to prevent significant sprouting of preserved axons to the denervated neurons. Application of chondroitinase ABC at the injury site promoted regenerative sprouting of both endogenous corticospinal and sensory dorsal column axons after spinal cord injury, resulting in functional recovery (Bradbury et al., 2002). Several other studies have shown that the treatment enhanced axonal regeneration through areas of decreased chondroitin sulfate proteoglycans expression and demonstrated subsequent functional recoveries (Yick et al., 2000; Bradbury et al., 2002; Yick et al., 2003; Chau et al., 2004; Davies et al., 2004; Yick et al., 2004; Fouad et al., 2005; Caggiano et al., 2005; Steinmetz et al, 2005; Houle et al., 2006). Increased plasticity following chondroitinase treatment is likely also an important component of the recovery observed in many of these studies and may significantly augment reinnervation by regenerating injured axons. Sugar moieties digested with chondroitinase ABC on endogenous and newly expressed chondroitin sulfate proteoglycans resulted in the collapse of much of the perineuronal nets (Bruckner et al., 1998; Pizzorusso et al., 2002; Massey et al., 2006). Regenerating axons of adult dorsal root ganglion neurons microtransplanted into the dorsal columns of spinal cord injured adult rats were unable to enter chondroitin sulfate proteoglycan-rich denervated dorsal column nuclei without chondroitinase ABC application or increased neurotrophin expression (Massey et al, 2007). This treatment promoted collateral sprouting of preserved primary afferents that resulted in reactivation of denervated cuneate neurons demonstrated by recording microelectrodes (Massey et al, 2006). The treatment was also effective in promoting collateral sprouting of corticospinal and sensory axons deafferented by either peripheral nerve injury or dorsal rhizotomies (Barritt et al, 2006; Galtrey et al, 2007). In addition to improved functional recovery, the studies showed that there was no increase in nociception, suggesting that the treatment might have selectively promoted the sprouting of proprioceptive and low threshold mechanoreceptive axons.

Collectively, these studies suggest that the normal expression of chondroitin sulfate proteoglycans within the perineuronal nets, alone or in combination with increased expression by activated glia following dorsal column injury, creates a potent barrier that limits axonal access to denervated neurons within subcortical structures and likely contributes to the chronic deactivation of somatosensory cortex and the limited functional recovery in rats. Thus, the selective manipulation of chondroitinase (Steinmetz et al., 2005; Massey et al., 2006, 2007; Barritt et al, 2006; Galtrey et al, 2007), perhaps in combination with other treatments such as Nogo antibodies that neutralize the axon growth inhibitor, that have also been shown to promote plasticity (Schwab et al., 1993; Buffo et al., 2000; Raineteau et al., 2002; Schwab, 2004; Freund et al. 2006), may have therapeutic potential for spinal cord injuries.

Apparent differences in plasticity between rats and monkeys

Dorsal column injuries appear to have different neurophysiological and behavioral consequences in monkeys and rats that were reviewed earlier in this report. This dichotomy may represent underappreciated interspecies differences related to the anatomical organization of the dorsal columns as well as differences in the spontaneous response to denervating injuries.

Reparative strategies effective in rats may therefore require modification when applied to primate models of spinal cord injury. In pilot studies, chondroitin sulfate proteoglycans associated with perineuronal nets were present in the dorsal column nuclei of squirrel monkeys and were similar to those found in adult rats (see Fig 3; see Hausen et al., 1996; Adams et al., 2001 for perineuronal nets in humans). In addition, denervation of the cuneate nuclei of non-human primates resulted in the formation of an astrogliotic scar that persisted for years following the injury (Woods et al, 2000), suggesting that reactive changes following injury in these animals may be similar to those found in rats. Thus, the effects of manipulating chondroitin sulfate proteoglycans on collateral sprouting or regeneration should be explored to more depth in primates. Promoting collateral sprouting by application of chondroitinase ABC may allow the opportunity to study the recovery of skilled hand use in primates after dorsal column section. At the same time, restricting maladaptive sprouting that causes phantom sensations is an issue that should be addressed.

Conclusions

In humans, monkeys, and rats, damage to the ascending afferents in the dorsal columns of the spinal cord can be followed by considerable recovery of lost sensorimotor abilities. This spontaneous recovery appears to depend on the sprouting of preserved afferents and their enhanced role in activating neurons throughout the somatosensory system. Treatments that promote the formation of new connections in the somatosensory system after dorsal column lesions are under study, and they have the potential to both decrease the time required and augment the extent of the reorganization resulting from physical therapy in humans.

References

- Al-Chaer ED, Lawand NB, Westlund KN, Willis WD. Pelvic visceral input into the nucleus gracilis is largely mediated by the postsynaptic dorsal column pathway. *J Neurophysiol* 1996;76:2675–2690. [PubMed: 8899637]
- Al-Chaer ED, Feng Y, Willis WD. Comparative study of viscerosomatic input onto postsynaptic dorsal column and spinothalamic tract neurons in the primate. *J Neurophysiol* 1999;82:1876–1882. [PubMed: 10515976]
- Adams I, Brauer K, Arélin C, Härtig W, Fine A, Mäder M, Arendt T, Brückner G. Perineuronal nets in the Rhesus monkey and human basal forebrain including basal ganglia. *Neurosci* 2001;108:285–298.
- Asher RA, Morgenstern DA, Fidler PS, Adcock KH, Oohira A, Braistead JE, Levine JM, Margolis RU, Rogers JH, Fawcett JW. Neurocan is upregulated in injured brain and in cytokine-treated astrocytes. *J Neurosci* 2000;20:2427–2438. [PubMed: 10729323]
- Ballermann M, McKenna J, Whishaw IQ. A grasp-related deficit in tactile discrimination following dorsal column lesion in the rat. *Brain Res Bull* 2001;54:237–242. [PubMed: 11275414]
- Barritt AW, Davies M, Marchand F, Hartley R, Grist J, Yip P, McMahon SB, Bradbury EJ. Chondroitinase ABC promotes sprouting of intact and injured spinal systems after spinal cord injury. *J Neurosci* 2006;26:10856–10857. [PubMed: 17050723]
- Becker R, Sure U, Bertalanffy H. Punctate midline myelotomy. A new approach in the management of visceral pain. *Acta Neurochir (Wien)* 1999;141:881–883. [PubMed: 10536726]
- Bradbury EJ, Moon LD, Popat RJ, King VR, Bennett GS, Patel PN, Fawcett JW, McMahon SB. Chondroitinase ABC promotes functional recovery after spinal cord injury. *Nature* 2002;416:636–640. [PubMed: 11948352]
- Bruckner G, Bringmann A, Hartig W, Koppe G, Delpech B, Brauer K. Acute and long-lasting changes in extracellular-matrix chondroitin-sulphate proteoglycans induced by injection of chondroitinase ABC in the adult rat brain. *Exp Brain Res* 1998;121:300–310. [PubMed: 9746136]
- Buffo A, Zagrebelsky M, Huber AB, Skerra A, Schwab ME. Application of neutralizing antibodies against N1-35/250 myelin-associated neurite growth inhibitory proteins to the adult rat cerebellum induces sprouting of purkinje cell axons. *J Neurosci* 2000;20:2275–2286. [PubMed: 10704503]

- Caggiano AO, Zimmer MP, Ganguly A, Blight AR, Gruskin EA. Chondroitinase ABCI improves locomotion and bladder function following contusion injury of the rat spinal cord. *J Neurotrauma* 2005;22:226–239. [PubMed: 15716629]
- Castro AJ. The effects of cortical ablations on digital usage in the rat. *Brain Res* 1972;37:173–185. [PubMed: 5061111]
- Celio MR. Evolution of the concept of “extracellular matrix” in the brain. *J Hist Neurosci* 1999;8:186–190. [PubMed: 11624300]
- Celio MR, Blumcke I. Perineuronal nets—a specialized form of extracellular matrix in the adult nervous system. *Brain Res Brain Res Rev* 1994;19:128–145. [PubMed: 8167657]
- Celio MR, Spreafico R, De Biasi S, Vitellaro-Zuccarello L. Perineuronal nets: past and present. *Trends Neurosci* 1998;21:510–515. [PubMed: 9881847]
- Chau CH, Shum DK, Li H, Pei J, Lui YY, Wirthlin L, Chan YS, Xu XM. Chondroitinase ABC enhances axonal regrowth through Schwann cell-seeded guidance channels after spinal cord injury. *FASEB J* 2004;18:194–196. [PubMed: 14630702]
- Corbetta M, Burton H, Sinclair RJ, Conturo TE, Akbudak E, McDonald JW. Functional reorganization and stability of somatosensory-motor cortical topography in a tetraplegic subject with late recovery. *Proc Natl Acad Sci U S A* 2002;99:17066–17071. [PubMed: 12477938]
- Darian-Smith C. Primary afferent terminal sprouting after a cervical dorsal rootlet section in the macaque monkey. *J Comp Neurol* 2004;470:134–150. [PubMed: 14750157]
- Darian-Smith C, Ciferri MM. Loss and recovery of voluntary hand movements in the macaque following a cervical dorsal rhizotomy. *J Comp Neurol* 2005;491:27–45. [PubMed: 16127695]
- Darian-Smith C, Ciferri MM. Cuneate nucleus reorganization following cervical dorsal rhizotomy in the macaque monkey: its role in the recovery of manual dexterity. *J Comp Neuro* 2006;498:552–565.
- Davies JE, Tang X, Denning JW, Archibald SJ, Davies SJ. Decorin suppresses neurocan, brevicin, phosphacan and NG2 expression and promotes axon growth across adult rat spinal cord injuries. *Eur J Neurosci* 2004;19:1226–1242. [PubMed: 15016081]
- Davies SJ, Goucher DR, Doller C, Silver J. Robust regeneration of adult sensory axons in degenerating white matter of the adult rat spinal cord. *J Neurosci* 1999;19:5810–5822. [PubMed: 10407022]
- Florence SL, Taub HB, Kaas JH. Large-scale sprouting of cortical connections after peripheral injury in adult macaque monkeys. *Science* 1998;282:1117–1121. [PubMed: 9804549]
- Florence SL, Hackett TA, Strata F. Thalamic and cortical contributions to neural plasticity after limb amputation. *J Neurophysiol* 2000;83:3154–3159. [PubMed: 10805710]
- Fouad K, Schnell L, Bunge MB, Schwab ME, Liebscher T, Pearce DD. Combining Schwann cell bridges and olfactory-ensheathing glia grafts with chondroitinase promotes locomotor recovery after complete transection of the spinal cord. *J Neurosci* 2005;25:1169–1178. [PubMed: 15689553]
- Freund P, Schmidlin E, Wannier T, Bolch J, Mir A, Schwab ME, Rouiller EM. Nogo-A-specific antibody treatment enhances sprouting and functional recovery after cervical lesions in adult primates. *Nat Med* 2006;12:790–792. [PubMed: 16819551]
- Galtrey CM, Fawcett JW. The role of chondroitin sulfate proteoglycans in regeneration and plasticity in the central nervous system. *Brain Research Reviews* 2007;54:1–18. [PubMed: 17222456]
- Galtrey CM, Asher RA, Nothias F, Fawcett JW. Promoting plasticity in the spinal cord with chondroitinase improves functional recovery after peripheral nerve repair. *Brain* 2007;130:926–939. [PubMed: 17255150]
- Glendinning DS, Cooper BY, Vierck CJ, Leonard CM. Altered precision grasping in stump-tail macaques after fasciculus cuneatus lesions. *Somatosens and Mot Res* 1992;9:61–73. [PubMed: 1595322]
- Golgi, C. Rendiconti della Reale Accademia Del Lincei. 1893. Intorno all’origine del quarto nervo cerebrale e una questione isto-fisiologica che a questo argomento si collega; p. 433–450.
- Golgi, C. Bolletino della Società medico-chirurgica di Pavia. 1898. Intorno all’struttura delle cellule nervose; p. 1–14.
- Guimaraes A, Zaremba S, Hockfield S. Molecular and morphological changes in the cat lateral geniculate nucleus and visual cortex induced by visual deprivation are revealed by monoclonal antibodies Cat-304 and Cat-301. *J Neurosci* 1990;10:3014–3024. [PubMed: 1697900]
- Harrison, TR.; Braunwald, E. *Harrison’s Principles of Internal Medicine*. McGraw-Hill; New York: 2001.

- Hausen D, Brückner G, Drlicak M, Hürtig W, Brauer K, Bigl V. Pyramidal cells ensheathed by perineuronal nets in human motor and somatosensory cortex. *NeuroReport* 1996;7:1725–1729. [PubMed: 8905652]
- Hong D, Andren-Sandberg A. Punctate midline myelotomy: a minimally invasive procedure for the treatment of pain in inextirpable abdominal and pelvic cancer. *J Pain Symptom Manage* 2007;33:99–109. [PubMed: 17196911]
- Hotson JR. Modern neurosyphilis: A partially treated chronic meningitis. *West J Med* 1981;135:191–200. [PubMed: 7340118]
- Houle JD, Tom VJ, Mayes D, Wagoner G, Phillips N, Silver J. Combining an autologous peripheral nervous system “bridge” and matrix modification by chondroitinase allows robust, functional regeneration beyond a hemisection lesion of the adult rat spinal cord. *J Neurosci* 2006;26:7405–7415. [PubMed: 16837588]
- Hughes JT, Brownell B, Hewer RL. The peripheral sensory pathway in Friedreich’s ataxia. An examination by light and electron microscopy of the posterior nerve roots, posterior root ganglia, and peripheral sensory nerves in cases of Friedreich’s ataxia. *Brain* 1968;91:803–818. [PubMed: 4178703]
- Jain N, Catania KC, Kaas JH. Deactivation and reactivation of somatosensory cortex after dorsal spinal cord injury. *Nature* 1997;386:495–498. [PubMed: 9087408]
- Jain N, Diener PS, Coq JO, Kaas JH. Patterned activity via spinal dorsal quadrant inputs is necessary for the formation of organized somatosensory maps. *J Neurosci* 2003;23:10321–10330. [PubMed: 14614091]
- Jain N, Florence SL, Kaas JH. Limits on plasticity in somatosensory cortex of adult rats: Hindlimb cortex is not reactivated after dorsal column section. *J Neurophysiol* 1995;73:1537–1546. [PubMed: 7643165]
- Jain N, Florence SL, Qi H-X, Kaas JH. Growth of new brain stem connections in adult monkeys with massive sensory loss. *Proc Natl Acad Sci USA* 2000a;97:5546–5550. [PubMed: 10779564]
- Jain N, Qi H-X, Kaas JH. Large-scale reorganization in the somatosensory cortex and thalamus after dorsal column lesions in macaque monkeys. *Soc Neurosci Abstr* 2000b;26:1462.
- Jain N, Qi H-X, Kaas JH. Long-term chronic multichannel recordings from sensorimotor cortex and thalamus of primates. *Prog Brain Res* 2001;130:64–72. [PubMed: 11480289]2001
- Jones LL, Margolis RU, Tuszynski MH. The chondroitin sulfate proteoglycans neurocan, brevican, phosphacan, and versican are differentially regulated following spinal cord injury. *Exp Neurol* 2003;182:399–411. [PubMed: 12895450]
- Jones LL, Tuszynski MH. Spinal cord injury elicits expression of keratan sulfate proteoglycans by macrophages, reactive microglia, and oligodendrocyte progenitors. *J Neurosci* 2002a;22:4611–4624. [PubMed: 12040068]
- Jones LL, Yamaguchi Y, Stallcup WB, Tuszynski MH. NG2 is a major chondroitin sulfate proteoglycan produced after spinal cord injury and is expressed by macrophages and oligodendrocyte progenitors. *J Neurosci* 2002b;22:2792–2803. [PubMed: 11923444]
- Kaas JH. Sensory loss and cortical reorganization in mature primates. *Prog Brain Res* 2002;138:167–176. [PubMed: 12432769]
- Kaas JH. Evolution of the large, complex sensorimotor systems of anthropoid primates. *Internat J Comp Psych* 2004;17:34–52.
- Kalb RG, Hockfield S. Molecular evidence for early activity-dependent development of hamster motor neurons. *J Neurosci* 1988;8:2350–2360. [PubMed: 3249230]
- Kalb RG, Hockfield S. Induction of a neuronal proteoglycan by the NMDA receptor in the developing spinal cord. *Science* 1990a;250:294–296. [PubMed: 2145629]
- Kalb RG, Hockfield S. Large diameter primary afferent input is required for expression of the Cat-301 proteoglycan on the surface of motor neurons. *Neuroscience* 1990b;34:391–401. [PubMed: 2333149]
- Kalb RG, Hockfield S. Activity-dependent development of spinal cord motor neurons. *Brain Res Brain Res Rev* 1992;17:283–289. [PubMed: 1467812]
- Kanagal SG, Muir GD. Bilateral dorsal funicular lesions alter sensorimotor behaviour in rats. *Exp Neurol* 2007in press

- Kim YS, Kwon SJ. High thoracic midline dorsal column myelotomy for severe visceral pain due to advanced stomach cancer. *Neurosurgery* 2000;46:85–90. [PubMed: 10626939]
- Koshinaga M, Whittemore SR. The temporal and spatial activation of microglia in fiber tracts undergoing anterograde and retrograde degeneration following spinal cord lesion. *J Neurotrauma* 1995;12:209–222. [PubMed: 7629867]
- Lander C, Kind P, Maleski M, Hockfield S. A family of activity-dependent neuronal cell-surface chondroitin sulfate proteoglycans in cat visual cortex. *J Neurosci* 1997;17:1928–1939. [PubMed: 9045722]
- Massey JM, Bickford ME, Zhang YP, Giamarra B, Shields CB, Roisen FJ, Magnuson DSK, Onifer SM. Vesicular Glutamate Transporter 1 as an Anatomical Marker of Adult Rat Dorsal Column Axon Synapse Formation. *Journal of Rehabilitation Research and Development* 2003;40:45. [PubMed: 15074453]
- Massey JM, Amps J, Viapiano MS, Matthews RT, Wagoner MR, Whitaker CM, Alilain W, Yonkof AL, Khalyfa A, Cooper NGF, Silver J, Onifer SM. Increased chondroitin sulfate proteoglycan expression in denervated brainstem targets following spinal cord injury creates a barrier to axonal regeneration overcome by chondroitinase ABC and neurotrophin-3. *Exp. Neurol.* 2007;217:101–116. [PubMed: 17380300] Doi:10.1016/j.expneurol.2007.03.003
- Massey JM, Hubscher CH, Wagoner MR, Decker JA, Amps J, Silver J, Onifer SM. Chondroitinase ABC digestion of the perineuronal net promotes functional collateral sprouting in the cuneate nucleus after cervical spinal cord injury. *J Neurosci* 2006;26:4406–4414. [PubMed: 16624960]
- McKenna JE, Whishaw IQ. Complete compensation in skilled reaching success with associated impairments in limb synergies, after dorsal column lesion in the rat. *J Neurosci* 1999;19:1885–1894. [PubMed: 10024372]
- McKeon RJ, Hoke A, Silver J. Injury-induced proteoglycans inhibit the potential for laminin-mediated axon growth on astrocytic scars. *Exp. Neurol* 1995;136:32–43. [PubMed: 7589332]
- McRae PA, Rocco MM, Kelly G, Brumberg JC, Matthews RT. Sensory deprivation alters aggrecan and perineuronal net expression in the mouse barrel cortex. *J Neurosci* 2007;27:5405–5413. [PubMed: 17507562]
- Moore CI, Stern CE, Dunbar C, Kostyk SK, Gehi A, Corkin S. Referred phantom sensations and cortical reorganization after spinal cord injury in humans. *Proc Natl Acad Sci U S A* 2000;97:14703–14708. [PubMed: 11114177]
- Mountcastle, VB. *The Sensory Hand*. Harvard Univ Press; Cambridge, MA: 2005.
- Mountcastle, VB.; Darian-Smith, I. Neural mechanisms in somesthesia. In: Mountcastle, VB., editor. *Medical Physiology*. V. Mosby; St. Louis: 1968. p. 1372–1423.
- Nathan PW, Smith MC, Cook AW. Sensory effects in man of lesions of the posterior columns and of some other afferent pathways. *Brain* 1986;109:1003–1041. [PubMed: 3096488]
- Nauta HJ, Hewitt E, Westlund KN, Willis WD Jr. Surgical interruption of a midline dorsal column visceral pain pathway. Case report and review of the literature. *J Neurosurg* 1997;86:538–542. [PubMed: 9046313]
- Onifer SM, Zhang YP, Burke DA, Brooks DL, Decker JA, McClure NJ, Floyd AR, Hall JA, Proffitt BL, Shields CB, Magnuson DS. Adult rat forelimb dysfunction after dorsal cervical spinal cord injury. *Exp Neurol* 2005;192:25–38. [PubMed: 15698616]
- Papo I, Luongo A. High cervical commissural myelotomy in the treatment of pain. *J Neurol Neurosurg Psychiatry* 1976;39:705–710. [PubMed: 1069098]
- Pizzorusso T, Medini P, Berardi N, Chierzi S, Fawcett JW, Maffei L. Reactivation of ocular dominance plasticity in the adult visual cortex. *Science* 2002;298:1248–1251. [PubMed: 12424383]
- Raineteau O, Fouad K, Bareyre F, Schwab M. Reorganization of descending motor tracts in the rat spinal cord. *Eur J Neurosci* 2002;16:1761–1771. [PubMed: 12431229]
- Ramachandran VS. Behavioral and magnetoencephalographic correlates of plasticity in the adult human brain. *Proc Natl Acad Sci U S A* 1993;90:10413–10420. [PubMed: 8248123]
- Ramachandran VS, Hirstein W. The perception of phantom limbs. The D. O. Hebb lecture. *Brain* 1998;121:1603–1630. [PubMed: 9762952]
- Saling M, Sitarova T, Vejsada R, Hnik P. Reaching behavior in the rat: absence of forelimb peripheral input. *Physiol Behav* 1992;51:1151–1156. [PubMed: 1641415]

- Schlag MG, Hopf R, Redl H. Serial recording of sensory, corticomotor, and brainstem-derived motor evoked potentials in the rat. *Somatosens Mot Res* 2001;18:106–116. [PubMed: 11534774]
- Schrimsher GW, Reier PJ. Forelimb motor performance following dorsal column, dorsolateral funiculi, or ventrolateral funiculi lesions of the cervical spinal cord in the rat. *Exp Neurol* 1993;120:264–276. [PubMed: 8491282]
- Schwab ME. Nogo and axon regeneration. *Curr Opin Neurobiol* 2004;14:118–124. [PubMed: 15018947]
- Schwab ME, Kapfhammer JP, Bandtlow CE. Inhibitors of neurite growth. *Annu Rev Neurosci* 1993;16:565–595. [PubMed: 7681638]
- Silver J, Miller JH. Regeneration beyond the glial scar. *Nat Rev Neurosci* 2004;5:146–156. [PubMed: 14735117]
- Srikanth SG, Jayakumar PN, Vasudev MK, Taly AB, Chandrashekar HS. MRI in subacute combined degeneration of spinal cord: a case report and review of literature. *Neurol India* 2002;50:310–312. [PubMed: 12391459]
- Steinmetz MP, Horn KP, Tom VJ, Miller JH, Busch SA, Nair D, Silver DJ, Silver J. Chronic enhancement of the intrinsic growth capacity of sensory neurons combined with the degradation of inhibitory proteoglycans allows functional regeneration of sensory axons through the dorsal root entry zone in the mammalian spinal cord. *J Neurosci* 2005;25:8066–8076. [PubMed: 16135764]
- Tang X, Davies JE, Davies SJ. Changes in distribution, cell associations, and protein expression levels of NG2, neurocan, phosphacan, brevican, versican V2, and tenascin-C during acute to chronic maturation of spinal cord scar tissue. *J Neurosci Res* 2003;71:427–444. [PubMed: 12526031]
- Todd AJ, Hughes DI, Polgar E, Nagy GG, Mackie M, Ottersen OP, Maxwell DJ. The expression of vesicular glutamate transporters VGLUT1 and VGLUT2 in neurochemically defined axonal populations in the rat spinal cord with emphasis on the dorsal horn. *Eur J Neurosci* 2003;17:13–27. [PubMed: 12534965]
- Viapiano MS, Matthews RT. From barriers to bridges: chondroitin sulfate proteoglycans in neuropathology. *Trends Mol Med* 2006;12:488–496. [PubMed: 16962376]
- Vierck CJ. Impaired detection of repetitive stimulation following interruption of the dorsal spinal column in primates. *Somatosens Mot Res* 1998;15:157–163. [PubMed: 9730116]
- Vitellaro-Zuccarello L, Meroni A, Amadeo A, De Basi S. Chondroitin sulfate proteoglycans in the rat thalamus: expression during postnatal development and correlation with calcium-binding proteins in adults. *Cell Tissue Res* 2001;306:15–26. [PubMed: 11683176]
- Wall PD. The sensory and motor role of impulses traveling in the dorsal columns towards cerebral cortex. *Brain* 1970;93:505–524. [PubMed: 4990230]
- Wall JT, Xu J, Wang X. Human brain plasticity: an emerging view of the multiple substrates and mechanisms that cause cortical changes and related sensory dysfunctions after injuries of sensory inputs from the body. *Brain Res Brain Res Rev* 2002;39:181–215. [PubMed: 12423766]
- Webb AA, Muir GD. Unilateral dorsal column and rubrospinal tract injuries affect overground locomotion in the unrestrained rat. *Eur J Neurosci* 2003;18:412–422. [PubMed: 12887423]
- Whishaw IQ, Pellis SM, Gorny B, Kolb B, Tetzlaff W. Proximal and distal impairments in rat forelimb use in reaching follow unilateral pyramidal tract lesions. *Behav Brain Res* 1993;56:59–76. [PubMed: 7691077]
- Whishaw IQ, Pellis SM, Gorny BP, Pellis VC. The impairments in reaching and the movements of compensation in rats with motor cortex lesions: an endpoint, videorecording, and movement notation analysis. *Behav Brain Res* 1991;42:77–91. [PubMed: 2029348]
- Whitsel BL, Petrucelli LM, Ha H, Dreyer DA. The resorting of spinal afferents as antecedent to the body representation in the postcentral gyrus. *Brain Behav Evol* 1972;5:301–341.
- Woods TM, Cusick CG, Pons TP, Taub E, Jones EG. Progressive transneuronal changes in the brainstem and thalamus after long-term dorsal rhizotomies in adult macaque monkeys. *J. Neurosci* 2000;20:3884–3899. [PubMed: 10804228]
- Yamaguchi Y. Leticans: organizers of the brain extracellular matrix. *Cell Mol Life Sci* 2000;57:276–289. [PubMed: 10766023]
- Yick LW, Cheung PT, So KF, Wu W. Axonal regeneration of Clarke's neurons beyond the spinal cord injury scar after treatment with chondroitinase ABC. *Exp Neurol* 2003;182:160–168. [PubMed: 12821386]

- Yick LW, So KF, Cheung PT, Wu WT. Lithium chloride reinforces the regeneration-promoting effect of chondroitinase ABC on rubrospinal neurons after spinal cord injury. *J Neurotrauma* 2004;21:932–943. [PubMed: 15307905]
- Yick LW, Wu W, So KF, Yip HK, Shum DK. Chondroitinase ABC promotes axonal regeneration of Clarke's neurons after spinal cord injury. *NeuroReport* 2000;1:1063–1067. [PubMed: 10790883]

Figure 1. The dorsal column somatosensory pathway and comparative anatomy of rat and primate spinal cord

A) Low threshold mechanoreceptor afferents transmit somatosensory information directly to secondary and motor neurons in the spinal cord and to thalamic relay neurons located in either the cuneate (CN) or gracile nucleus. Axons from these neurons cross to the contralateral side of the medulla and ascend through the medial lemniscus where they synapse on cortically projecting neurons (areas 3b and 1) in the ventroposterior lateral nucleus (VPL) of the thalamus. Areas shown in red represent areas of potential reorganization following deafferentation by injury. The result of this neuroplasticity can result in either improved functional outcome or in the formation of maladaptive pathways that produce phantom sensations or other detrimental outcomes. The development of treatments that promote the formation of new synaptic contact from intact portions of the pathway while preventing the formation of pathological circuits is the focus of current investigation. **B) & C)** The dorsal columns of rats contain both the ascending fine touch and vibratory somatosensory fibers and the descending corticospinal (CST) motor pathway. In primates, the corticospinal pathway is contained in the lateral columns. Because of this anatomical difference, injuries to the dorsal columns produce different central nervous system deficits in rats and primates. Cuneate Fasciculus-Cuneate F.; Gracile Fasciculus-Gracile F.

Figure 2. Cortical somatosensory plasticity associated with dorsal column lesions in rodents and primates

After complete dorsal column lesions in rats (left), a portion of the map in primary somatosensory cortex becomes unresponsive and remains unresponsive. After complete dorsal column lesions in owl monkeys (right), a portion of the map in primary somatosensory cortex immediately becomes unresponsive, but is reactivated by adjacent intact regions that eventually expand into the unresponsive portion. Striped region at bottom right corresponds to a region responsive to both the forelimb and the face. Figure based on results in rats (Jain et al., 1995) and owl monkeys (Jain et al., 1997).

Figure 3. Confocal photomicrographs of the subdivisions of the primate cuneate nucleus

A) Microtubule associated protein-2 (Map2) immunoreactivity heavily labels the clusters of dendrites and cell bodies of cuneate neurons contained within the digit subdivisions of the cuneate nucleus of an adult squirrel monkey similar to that previously described in the rat (Massey et al., 2006;2007). Vesicular glutamate transporter 1 (vGlut1) immunoreactivity, known to label axon terminals of large myelinated dorsal column afferents (Todd et al., 2003;Massey et al., 2003), is also concentrated in a similar somatotopic distribution. **B)** In near adjacent sections from the same squirrel monkey, aggrecan is detected by Cat-301 immunoreactivity in the perineuronal nets of cuneate neurons contained within these subdivisions.