Monkey Models of Recovery of Voluntary Hand Movement After Spinal Cord and Dorsal Root Injury

Corinna Darian-Smith

Abstract

The hand is unique to the primate and manual dexterity is at its finest in the human (Napier 1980), so it is not surprising that cervical spinal injuries that even partially block sensorimotor innervation of the hand are frequently debilitating (Anderson 2004). Despite the clinical need to understand the neuronal bases of hand function recovery after spinal and/or nerve injuries, relatively few groups have systematically related subtle changes in voluntary hand use following injury to neuronal mechanisms in the monkey. Human and macaque hand anatomy and function are strikingly similar, which makes the macaque the favored nonhuman primate model for the study of postinjury dexterity. In this review of monkey models of cervical spinal injury that have successfully related voluntary hand use to neuronal responses during the early postinjury months, the focus is on the dorsal rhizotomy (or dorsal rootlet lesion) model developed and used in our laboratory over the last several years. The review also describes macaque monkey models of injuries to the more central cervical spine (e.g., hemisection, dorsal column) that illustrate methods to assess postlesion hand function and that relate it to neurophysiological and neuroanatomical changes. Such models are particularly important for understanding what the sensorimotor pathways are capable of, and for assessing the outcome of therapeutic interventions as they are developed.

Key Words: cervical spinal cord; dexterity; dorsal rhizotomy; dorsal root lesion; hand function; monkey; neuronal plasticity; nonhuman primate; precision grip; sensorimotor function

Introduction

Although behavioral testing has been widely used to assess dexterity, surprisingly few nonhuman primate studies have systematically measured the recovery of voluntary hand movements after either ascending somatosensory or descending corticospinal pathway injuries and then linked the results to neuronal reorganization. There is much to learn about the cellular mechanisms responsible for the recovery of hand function. Nonhuman primate lesion models that measure subtle changes in hand and digit use are thus increasingly important, as a tool not only for studying spontaneous changes after injury but also for evaluating new therapeutic interventions before clinical consideration.

This review begins with a brief overview of the major pathways responsible for voluntary, manipulative behaviors of the monkey, ape, and human hand. We then look at specific lesion models, and end with a brief overview of the major mechanisms responsible for the behavioral recovery and reorganization after such injuries.

Sensorimotor Pathways That Mediate Voluntary Hand Control

Precise volitional movements of the hand in the human and macaque monkey depend on the integrity of the major afferent and efferent pathways at the level of the cervical cord. The literature includes detailed descriptions of the somatosensory and motor circuitry of the spinal cord (for reviews see Willis and Coggeshall 2004a,b, and Snow and Wilson 1991). Very briefly, the major ascending somatosensory mechanoreceptor and proprioceptor input from the skin and deeper tissues of the hand enters the cervical spinal cord via dorsal roots C5-C8, and terminates in Rexed laminae II-V in the dorsal horn. The cuneate fasciculus of the dorsal column (either as a collateral branch of the first-order neuron or as a second-order neuron) transmits most input to the cuneate nucleus, and from there the input crosses the spinal cord via dorsal roots C5-C8, and terminates in Rexed laminae II-V in the dorsal horn. The cuneate fasciculus of the dorsal column (either as a collateral branch of the first-order neuron or as a second-order neuron) transmits most input to the cuneate nucleus, and from there the input crosses the midline as the medial lemniscus before terminating primarily in the thalamic ventroposterolateral nucleus (VPLc) on the contralateral side. A smaller mechanoreceptor input to the dorsal horn targets second-order neurons that cross the spinal cord (within one to two segments) at the level of entry, and then projects to the thalamus along the spinthalamic pathway. In the macaque monkey and in humans, these spinthalamic fibers terminate mainly in the VPLc, but also send a small projection to the anterior ventroposterolateral nucleus.

Abbreviations used in this article: CNS, central nervous system; CST, corticospinal tract; DREZ, dorsal root entry zone; DRL, dorsal root lesion; RFs, receptive fields; VLo, ventral lateral nucleus; VPLc, caudal ventroposterolateral nucleus; VPLo, anterior ventroposterolateral nucleus.
(VPLo), to the anterior pulvinar nucleus (Pulo), and to the suprageniculate nucleus of the thalamus. Thalamocortical projections from the VPcl terminate in the primary somatosensory cortex (areas 3a, 3b, 1, and 2), and those from the Pulo also terminate there as well as in the posterior parietal and even the caudal motor cortex (Baley diere and Maugiere 1987; Clark and Northfield 1937; Cusick and Gould 1990; C. Darian-Smith et al. 1990; Yeterian and Pandya 1991; for review see I. Darian-Smith et al. 1996). Sensory information is also transmitted to higher levels via spinoreticular, spinocerebellar, and spinocervical tracts, and there are feedback projections from all higher levels of the pathway to the spinal cord (e.g., the corticospinal tract sends collateral projections to the cuneate nucleus en route to the cervical cord). The primary motor cortex also receives input from more anteriorly located thalamic nuclei (including the anterior ventroposterolateral nucleus [VPLo] and the anterior ventral lateral nucleus [VLo]), which in turn receive input from the deep cerebellar nuclei and basal ganglia (Darian-Smith and Darian-Smith 1993; I. Darian-Smith et al. 1996).

Skilled voluntary manipulative tasks that involve sensory feedback from the monkey or human hand about a variety of tactile features (e.g., texture, shape, weight) continuously activate many of these ascending pathways and feedback projections.

In both humans and macaque monkeys, the major descending motor tract, the corticospinal tract (CST), also plays a critical role in fine directed movements of the hands and digits. The CST originates from multiple regions of the somatosensory and motor cortex (I. Darian-Smith et al. 1996; Dum and Strick 1991; Galea and Darian-Smith 1994; Nudo and Masterton 1990; Toyoshima and Sakai 1982) and is the most functionally important control pathway in voluntary manual dexterity. In the macaque monkey, 90% of the cervical projection is contralateral and descends in the dorsolateral CST. An additional 8% of fibers course in the ipsilateral dorsolateral tract and there is a further bilateral component in the ventral tract (~2%). Primates are the only mammals with corticospinal pathways that directly synapse with motor neurons that innervate the hand and forelimb (corticomotoneuronal projections) (Alstermark et al. 2004; Asanuma et al. 1979; Fetz et al. 1976; Kuypers 1981). Though it is clear that these monosynaptic corticomotoneuronal populations play an important role in shaping hand use (Bennet and Lemon 1994; Lemon 1993; Muir 1985; Phillips and Porter 1977), it remains unclear how different descending populations that terminate either directly or indirectly on motoneurons interact to produce the complex coordinated dexterity that humans typically take for granted and use effortlessly.

The rubrospinal tract is relatively insignificant in monkeys and almost nonexistent in humans, so it probably plays a minor role (if any) in recovery after cervical spinal injury. However, there is some evidence that the magnocellular red nucleus reorganizes and contributes to the recovery of forelimb motor function following pyramidal tract lesions (Belyantseva and Lewin 1999; Bradbury et al. 2000; Buonomano and Merzenich 1998; Ding et al. 2005; Jones 2000; Kaas 2002; Wall et al. 2002). The final phase involves the eventual atrophy of chronically deafferented neuronal populations and can continue for many years and even decades (Jones 2000). The most dramatic behavioral changes typically occur during the chronic second phase, and the models reviewed in this article focus on that period.

**Postinjury Phases of Reorganization**

The events that lead to reorganization and recovery generally fall into three postinjury phases. Changes begin with an acute phase of minutes or hours, and then progress to a chronic phase of days, weeks, and the early months, before ending with a longer-term or extended chronic period (i.e., years). For example, immediately after a median nerve cut a corresponding “silent” region is produced in the contralateral cortical hand map, and there is a rapid expansion of the representation of parts of the hand adjacent to the deafferented region that occurs within minutes or hours and can persist for many weeks (Merzenich et al. 1983a,b). During a chronic second phase (weeks to months), there is a consolidation of the cortical and subcortical body maps, as spared connections have the opportunity to establish stronger new and alternate pathways (for reviews see Belyantseva and Lewin 1999; Bradbury et al. 2000; Buonomano and Merzenich 1998; Ding et al. 2005; Jones 2000; Kaas 2002; Wall et al. 2002). The final phase involves the eventual atrophy of chronically deafferented neuronal populations and can continue for many years and even decades (Jones 2000). The most dramatic behavioral changes typically occur during the chronic second phase, and the models reviewed in this article focus on that period.

**Primate Models That Examine Dexterity and Neuronal Plasticity After Spinal Cord and Dorsal Root Injury**

While rodent studies are critical to the determination of cellular, molecular, and biochemical mechanisms underlying plastic changes in the central nervous system (CNS) after spinal cord and nerve injuries, they do not provide the clinical link for the study of hand function recovery after such injuries. Rats use their forelimbs and paws to reach for and grasp food objects quite effectively, but they do not have the fractionated digit use, hand anatomy, or spinal and brain circuitry that have evolved over 60 to 70 million years to support the sophisticated volitional sensorimotor movements of macaque and human hands.

Macaque monkeys can be taught to perform quite sophisticated sensorimotor tasks that test tactile sensation and fine motor control of the digits (e.g., I. Darian-Smith 1984). However, the more complex the task, the longer it takes to
train individuals, so there may be tradeoffs between task complexity and training time requirements. A simple task as opposed to a complex task that requires multiple training steps can mean the difference between 1 to 2 and 6 to 12 months of training. Given the ever increasing costs and difficulties associated with monkey research, and a desire to examine behavior, physiology, the cellular environment, and anatomy in a number of subjects, in my laboratory we use a simple precision grip task that is easily taught to monkeys, so that the total experimental pre- and postlesion time period does not exceed 6 to 8 months.

A Commonly Used Test of Postinjury Hand Function

The Kluver board, or a variation of it, is a popular way to assess manual performance in monkeys (Lawrence and Kuypers 1968; Nudo et al. 1992; Xerri et al. 1998). The board (or its likeness) comprises multiple wells or slots of differing widths and depths from which the monkey extracts a piece of food with the use of a precision grip. The board can be useful for testing coarse hand function in monkeys that are severely impaired by a particular lesion (e.g., complete spinal hemisection) and is especially useful for New World monkeys (e.g., cebus or squirrel monkeys) that do not have true digit opposition. Importantly, the task requires little learning, offers a range of difficulty through alterations in well depth, and enables the measurement and quantification of overall performance.

However, the Kluver board does not systematically or easily test individual digit function, and it can be difficult to record individual trials even with, for example, a high-speed camcorder. In addition, it does not prevent the primates from using visual cues during execution of the task and it does not directly test cutaneous feedback in conjunction with fine motor control. The latter is necessary in the dorsal root lesion (DRL\textsuperscript{1}) model (described below), which involves partial or complete deafferentation of the opposing digits of the hand. In the DRL model, the monkey uses visual cues to reach toward a clamp holding a small cylindrical candy. After the initial reach, however, view of the clamp (which holds the candy at one of a series of forces) is masked from sight behind the reaching hand, so that only cutaneous and not visual feedback is available during the contact, grasp, and retrieval components of the task. The monkey also has to use the opposing digits of the hand in a vertical plane that can be easily filmed and digitally analyzed using a single high-speed camcorder.

A Cervical Dorsal Root Lesion That Demonstrates Loss and Recovery of Hand Function

Overview and Background of the DRL Model

A large dorsal root section (i.e., cervical segments C4-T4 or C3-T3) can result in the complete deafferentation of the macaque’s hand and forearm, causing profound and lasting impairment of voluntary manipulative movements (Mott and Sherrington 1895; Vierck 1982) and considerable neuronal reorganization at different levels of the neuraxis (Pons et al. 1991; Woods et al. 2000). This result is also true in humans, where the loss of sensory feedback from the hand (e.g., following brachial plexus injury) also results in a severe loss of voluntary hand movements (Nagano 1998). Such reports, however, tell us little about the potential for the recovery of digit and hand movements after less devastating dorsal root injuries.

To investigate functional recovery along with associated neuronal changes following dorsal root injury, we developed a restricted DRL model that is readily reproducible across animals and that can be altered in its extent to test the limits of reorganization and recovery. This model has made it possible to investigate acute, chronic, and long-term changes (> 8 months) in the macaque monkey that accompany dorsal rhizotomies of a specific size. Only dorsal rootlets innervating the first two to three digits of one hand are cut in this model, so voluntary hand movements and changes related to neuronal reorganization can be assessed over a pre- and postlesion period of weeks and months. Importantly, this lesion model causes minimal distress to the monkey and requires only localized (often temporary) anesthesia of several digits of one hand. Motor innervation via ventral roots remains intact, so that climbing and moving about the cage is only very subtly impaired immediately after the lesion. The use of a restricted and well-defined model allows us to study mechanisms of recovery and reorganization that provide insight into far more serious clinical injuries, such as the dorsal root lesions in humans that are typically far more extensive and debilitating.

Making the Dorsal Root Lesion in the Macaque Monkey

We have been using young male Macaca fascicularis (2.5 to 3.5 kg) for our experiments, primarily because they do not yet have the back muscle bulk of older males. Surgery therefore causes less muscle damage than it would in a larger male, and the monkeys quickly recover from it, show surprisingly little if any demonstrable back discomfort, and do not manipulate or remove postoperative stitches.

Once the monkey is anesthetized and secured in a primate stereotaxic frame with the head flexed to extend the neck and cervical spine, the C8 spine serves as a landmark for a dorsal cervical laminectomy to expose dorsal rootlets entering spinal segments C5-T1. With the rootlets exposed (Figure 1) and the dura cut and anchored with silk sutures, we record the sensory input to individual dorsal rootlets, taking digital photographs of the exposed cord and printing them before electrophysiological recording (this takes 5 to 10 minutes), so that we can use them to identify individual rootlets for further recordings. A low-impedance tungsten microelectrode (1.2 to 1.4 m at 1 kHz) is lowered into each.
rootlet (0.2 to 0.3 mm in diameter), and extracellular recordings are made of the discharge of one to a few axons at variable depths and locations in each fascicle (for further details see C. Darian-Smith 2004; C. Darian-Smith and Brown 2000; Darian-Smith and Darian-Smith 2004). Cutaneous receptive fields (RFs) are mapped while stimulating the hands with a camel hair brush, a small blunt-ended metal probe, and a series of calibrated von Frey hairs. Ten or more RFs are recorded from each rootlet to produce what we call a microdermatome map (Figure 1 illustrates a small portion of one of these maps). We use the microdermatome maps to reproduce the lesion accurately in multiple animals and to guide the selection of rootlets for cutting.

Removal of a 2- to 3-mm piece of rootlet from each fascicle enables the easy identification of cut rootlets. The lesion is permanent, and the cut central axon stumps do not regrow into the dorsal root entry zone (DREZ). For the period of our postlesion analysis (up to 8 months), the peripheral axons and cell bodies (in dorsal root ganglia) of cut neurons remain largely intact. On completion of the electrophysiological mapping of the microdermatomes and the transection of the rootlets, the overlying tissues are sutured in layers. Because suturing can lead to the formation of unwanted adhesions, the dura is repositioned but not sutured. We have found that the monkeys in this procedure recover remarkably quickly from anesthesia, and are up and alert and eating normally within a few hours. Surgery and recording sessions have lasted as long as 8 hours (but not longer). Because dorsal rhizotomy (i.e., dorsal root injury) is often correlated with neuropathic pain in humans, we note that, in our experience with this model in the macaque, we have observed very few transient behaviors suggesting mild localized discomfort. In such instances, the monkeys responded well to analgesics and the behaviors dissipated completely after 1 to 2 weeks.

Cortical and Subcortical Reorganization and Reactivation

We offer here a summary of the major findings from our dorsal root lesion model and resulting cortical and subcortical changes (also see C. Darian-Smith and Brown 2000; C. Darian-Smith 2004; C. Darian-Smith and Ciferri 2004, 2005). Immediately after a DRL, there is no electrophysiologically detectable input from the experimentally deafferented digits, and a silent region is present in the corresponding spinal dermatomal map (Figure 1; C. Darian-Smith and Brown 2000). Equally, corresponding regions in the somatotopic maps at the level of the brainstem (C. Darian-Smith and Ciferri 2006) and somatosensory cortex (Figure 2; C. Darian-Smith and Brown 2000) are functionally silent or unresponsive to stimulation of the deafferented digits. These silent zones persist for many weeks at all levels of the pathway and correspond to what can be an initially severe behavioral deficit in the affected hand (Figures 3-7; C. Darian-Smith and Ciferri 2005). Over the

![Figure 1](Image)

**Figure 1** Example of a partial microdermatome map, showing the exposed left dorsal cervical cord. After a laminectomy, recordings were made in dorsal rootlets through cervical segments C5-C8, to map cutaneous and proprioceptor receptive fields on the digits and hand. Dorsal rootlets have been outlined on the photo taken before the recording session. Cartoons of the palmar and dorsal hand surfaces indicate receptive fields. Receptive field distributions are shown only for rootlets at the borders of the lesion (indicated with white bar). Rootlets with any detectable RFs on digits one to three were cut (enclosed by box). Due to the divergence of inputs into the cord, many of these rootlets also carried input from the surrounding digits and parts of the hand. Scale bar = 3 mm. Reprinted with permission from Darian-Smith C, Ciferri M. 2005. Loss and recovery of voluntary hand movements in the macaque following a cervical dorsal rhizotomy. J Comp Neurol 491:27-45.
course of 8 to 12 weeks, and with regular hand use, there is some recovery of digit use (see below), and as this occurs there is a corresponding reorganization demonstrable at each level of the neuraxis. In the spared dorsal root fascicles immediately adjacent to the lesion, cutaneous responses can be elicited where this was not previously possible (C. Darian-Smith and Brown 2000). Significant somatotopic reorganization occurs in the cuneate nucleus of the brainstem and there is partial reemergence of input from the initially deafferented digits (C. Darian-Smith and Ciferri 2006). There is also partial or complete reactivation of the somatosensory cortical digit map, depending on both the initial size of the lesion and the length of the postlesion time period (C. Darian-Smith and Brown 2000; C. Darian-Smith and Ciferri 2006).

**Neuronal Changes Accompanying Performance Recovery**

A series of anatomical experiments in monkeys with the same DRL model (C. Darian-Smith 2004) have shown that a small population of spared afferent fibers continues to innervate the deafferented digits. These fibers, which enter the cord adjacent to the lesion site, are probably initially too weak in their signal response to drive the somatotopic map at any level of the pathway (e.g., cuneate nucleus, thalamus, cortex). But over several postlesion months, the axon terminals of these spared primary afferent fibers sprout locally in the spinal dorsal horn and cuneate nucleus. It seems plausible that these “sprouts” then form additional connections with input-deprived postsynaptic target neurons to play a role in driving reorganization at the spinal and higher levels of the neuraxis.

These studies show a limit to the amount of reorganization and recovery that is possible. Even so, extensive postlesion reorganization can occur in the spinal dorsal horn (and at higher levels) as long as a small population (< 5%) of uninjured primary afferents from the impaired digits remains intact. Optimizing the facilitation of these spared fibers is a major focus for future study.

**Precision Grip Task and Assessment**

The precision grip task developed for assessment of manual dexterity in our monkeys with DRLs has several favorable
features: (1) it is an essential component of the daily voluntary use of the hand, so the monkey learns to execute the task quickly; (2) the accurate execution of the task depends on tactile and proprioceptive feedback (both of which are removed by the lesion); and (3) the analysis of the task can be subdivided in order to assess the grasp and retrieval components separately from the initial reach (L. Darian-Smith et al. 1996; Jeannerod 1994a,b). This subdivision is important because there is some visual control during the initial reach but not during the subsequent grasp and retrieval.

We trained the monkeys in our experiment to sit in a plexiglass box and to extend one hand through a small window to retrieve a target object (a solid cylinder of glucose, $5 \times 5$ mm; Figures 3 and 7). A horizontally oriented clamp held the object 15 to 20 cm from the window, depending on the individual monkey’s arm length. The window was located either to the left or right of the box front, to encourage the use of either the normal or the impaired hand. Because reaching and retrieving form part of the daily repertoire of voluntary hand movements, monkeys acclimated and performed the task consistently within 2 to 3 weeks. A strict experimental schedule maintained motivation, and the monkeys fed after the afternoon training session.

As mentioned above, there are two basic components to any reach-retrieval task. In the first reaching component, the forearm and hand extend and the hand preshapes in anticipation of touching the object. This component of the task...
requires visual feedback and so was not used in our analysis because our goal was to look at sensory feedback. The second grasp and retrieval component begins when the digits make contact with the target and ends when they secure and remove the object. This component requires tactile and proprioceptive feedback from the digits and hand, and our analysis focused on the response parameters specific to movements of the thumb and index and middle fingers.

We used a high-shutter-speed digital video camera to record the reach-retrieval sequences from a lateral viewpoint, and arranged the apparatus so that finger and thumb opposition on the target was possible only in the vertical plane. We assessed performance for each hand on an alternating weekly basis, with two daily sessions and 10 to 20 trials per session. Standard software (Adobe Premiere 6.0) was effective for editing and analyzing video frame sequences. We trained each monkey to a stable level of performance with both hands (∼8 to 10 weeks) before the initial lesion. We typically reintroduced monkeys to the training box within 1 week after the operation (depending on the individual), and then assessed postlesion performance for 4 to 6 months.

The oppositional force that the monkey needed to overcome in order to retrieve the object could be changed randomly during each session, with four clamps calibrated to require a force of 0.5, 1.0, 1.5, and 2.0 Newtons for target removal. All clamps were mounted on a rotating turret (see Figure 3) to facilitate changes to the resistive force and the reloading of the clamp. The random presentation of the clamps required the monkey to reassess the force needed to remove the target in each trial. Before the lesion, the animals’ performance did not change significantly with the different resistive forces, but after the DRL these small differences often significantly altered performance (see Figure 4 for example).

Both before and after the dorsal rhizotomy, weekly data informed analysis of the following three performance parameters: (1) the percentage of successful retrievals of the object for each sequence of trials in a given week (Figure 4); (2) contact time (i.e., the time from first contact with the target to its successful displacement from the clamp) (Figure 5); and (3) the stratagem (i.e., the pattern of finger movements used to manipulate and retrieve the object, characterized according to the use of the opposing pads of the digits and palmar surface) (Figure 6).

In our behavioral analyses (C. Darian-Smith and Ciferri 2005), we found it helpful to divide monkeys into two groups according to removal of input either from the thumb and index finger (Group 1) or from these digits plus the middle finger and thenar palm (Group 2). During the first postoperative week, hand function was severely impaired in all monkeys. Over the following weeks, Group 1 monkeys recovered the ability to retrieve the object by opposing the index finger and thumb in more than 80% of trials. Group 2 monkeys also regained function in the impaired hand, but while recovery in these monkeys was sometimes dramatic (see Figure 7) it was never complete.

Our behavioral studies, which focused on hand sensormotor function, consistently demonstrated that the sparing of even very small numbers of somatosensory fibers (<5%) can lead to quite dramatic behavioral recovery during the early postinjury months.

**Dorsal Column Transection Models in the Macaque That Characterize Hand and Digit Movements**

Investigations into the effects of dorsal column lesions on hand and digit function over the last several decades have been inconsistent in their findings. Deficits described for ostensibly similar lesions have ranged from subtle to
chronic and debilitating (Brinkman et al. 1978; Cooper et al. 1993; Glendinning et al. 1992, 1993; Leonard et al. 1992). The inconsistency in results appears to be due to differently sized lesions and a lack of systematic lesion reconstruction across studies.

Studies by Vierck and colleagues, who have examined the effects of a dorsal column transection on hand function over many years (and who have correlated function with lesion size), have shown that the cuneate fasciculus regulates finger positioning and that the loss of this regulation after a complete transection of the tract disrupts fine motor control of the digits. Transection of the dorsal spinal column also initially impairs a monkey’s ability to distinguish the frequency or duration of tactile stimulation (Vierck and Cooper 1998). Some monkeys recovered this ability over several months of testing, but others did not. The monkeys that did recover may have learned to use alternate cues and pathways to assess and distinguish textures.

In addition to making purely descriptive observations about digit use in the cage environment (Leonard et al. 1992), Vierck and colleagues have also tested very specific parameters of hand function after dorsal column section. For example, the authors observed that monkeys with dorsal root lesions (DRLs) that removed input from the thumb and index and middle fingers showed a flat performance throughout the period of assessment. The left hand was initially quite impaired, as indicated by a significant increase in contact times, which decreased as the monkey recovered some function and compensated for it. In contrast, monkeys with larger lesions, where an alternative strategy was necessarily employed following some recovery in the impaired digits, did not show the same recovery.

Figure 5 Contact time graphs from two monkeys with dorsal root lesions (DRLs) that removed input from the thumb and index and middle fingers. (A, B) Contact times for both hands in monkey M-6 before and after a DRL (arrow) on the left side. The control right hand shows a flat performance throughout the period of assessment. The left hand was initially quite impaired, as indicated by a significant increase in contact times, which decreased as the monkey recovered some function and compensated by adopting an alternative strategy. (C) Contact times for M-3 with a slightly larger DRL (lesion side only). This monkey was unable to perform the retrieval task at all for the initial 2-month period. At 11 weeks, retrieval was possible but contact times were significantly longer than before the lesion. These times steadily decreased over the ensuing weeks to near prelesion times, although the monkey did not return to the stratagem used before the lesion. Only trials in which the retrieval was successful were used to measure contact times. Bars = SEM. Data for different resistive forces are shown with different symbols as indicated. Reprinted with permission from Darian-Smith C, Ciferri M. 2005. Loss and recovery of voluntary hand movements in the macaque following a cervical dorsal rhizotomy. J Comp Neurol 491:27-45.

Figure 6 Graphs showing the initial postlesion loss and gradual recovery of the index finger and thumb precision grip in monkey M-2 that had all detectable input removed from the index finger and thumb. The opposition of the distal pads of the thumb and index finger was the preferred stratagem before the DRL, and in the control hand (open circle) for all resistive forces (two shown here). This stratagem was lost immediately after the lesion, but gradually recovered over the 20-week postlesion period. This did not occur for monkeys with larger lesions, where an alternative stratagem was necessarily employed following some recovery in the impaired digits. Reprinted with permission from Darian-Smith C, Ciferri M. 2005. Loss and recovery of voluntary hand movements in the macaque following a cervical dorsal rhizotomy. J Comp Neurol 491:27-45.
example, when it was important to test the monkey’s ability to position digits after transection, the monkey was trained to place its hand in a mechanical arm with a digit splint device (see Figure 1 in Glendinning et al. 1993). The monkey then watched a computer screen and moved the index finger (identified by a cursor) into a target region on the screen, as a specified load was applied to the finger splint in order to perturb digit movement. Monkeys were unable to reposition or adjust finger position when the cuneate fasciculus lesion was complete. However, when the lesion was less than complete, a tiny population of spared fibers could reorganize and take over the job. In another study by the same group that looked at fractionated movements of digits after a dorsal column lesion, macaques were trained to perform a key press task with individual digits to obtain a food reward (Cooper et al. 1993). The study, which examined...
hand use over 2 years, showed that monkeys lost their ability to fractionate to key press and instead used a subtle compensatory strategy to perform the task. Such observations would not have been apparent with a less specific task.

**Cervical Hemisection Lesion Models in Macaques That Study Dexterity**

The corticospinal pathway comprises the single most important descending motor tract involved in distal forelimb muscle innervation and the execution of fine voluntary hand and digit movements. We have used macaque monkeys to study the behavioral effects of a spinal hemisection, which involves the corticospinal tract and dorsal column in addition to other ascending and descending pathways on the lesion side of the cord (Galea and Darian-Smith 1997b). In this model, the monkeys received a near complete hemisection at spinal segments C3-C4 and initially presented with a severe hemiparesis on the side of the lesion. However, by the end of the first postlesion month, the monkeys, independent of their age, regained the ability to pick up objects with the impaired hand and were able to perform a reach-grasp-retrieval task quite efficiently. The recovery was quite dramatic, but it was never fully complete (up to 3 years after the injury).

The reach-retrieval task used in these spinal hemisection experiments was simpler than that of our DRL model. The monkeys also had to reach to a clamp and remove a target object held at a set force, but the resistive force holding the target could not be altered quickly for random presentation (although this difference was not particularly important, as the goal was to test the impairment and recovery of the efferent innervation of the hand). Despite some visual input, the initial reach phase of the task proved to be a significant parameter to measure, indicating that a persistent behavioral deficit involved a less direct trajectory and preshaping of the hand during the reach.

Corticospinal pathway transection also led to a persistent weakness of the opposing digits, which was indirectly assessed with the reach-retrieval task, as digit strength was required in the removal of the target at higher resistive forces and there was a persistent increase in contact times at higher resistive forces. The greater contact times, however, may also have resulted from the loss of primary afferent input in addition to a residual weakness of the digits. It was also clear that the somatosensory component of the task was impaired, if only partially. Hand representation maps in the SI cortex showed reorganization of the deprived region of cortex and a reduced hand map with abnormally large cutaneous receptive fields. However, input from all digits was clearly apparent in the somatotopic maps.

Studies from this group (Galea and Darian-Smith 1997a,b) suggested that previously existing "crossover" corticospinal projections were responsible, at least in part, for mediating behavioral recovery. The studies also proposed that the localized sprouting of these or other preexisting pathways may play a role (see Figure 8 and the discussion below on mechanisms). A recent examination of the behavioral effects of cervical hemisection in fully grown rhesus macaques supports these findings (personal communication, Tuszynski and colleagues, University of California, San Diego, 2006).

![Figure 8](https://academic.oup.com/ilarjournal/article-abstract/48/4/396/644621) Data from a macaque monkey that received a near complete cervical hemisection at C6 (insert). (A) Shows changes in the time taken for the monkey to execute a reach-retrieval task. Solid circles = mean retrieval time for the left hand, triangles = right hand. This monkey was not able to perform the task with the impaired hand for the first postlesion month, but then gradually recovered some ability to retrieve the object over the ensuing months. (B) Shows the trajectories of the pads of the index finger (squares) and thumb (circles) of the left hand of the same monkey during the reach, grasp, and retrieval of the target object. Note that the prelesion trajectory is smooth and mean retrieval time <1 second. At 45 days after lesion, the trajectory is clumsy and retrieval slow, but by 94 days performance has greatly improved. Reprinted with permission from Galea MP, Darian-Smith I. 1997b. Manual dexterity and corticospinal connectivity following unilateral section of the cervical spinal cord in the macaque monkey. J Comp Neurol 381:307-319.
Neuronal Mechanisms That Mediate Reorganization and the Recovery of Hand Function After Injury

A major reason to assess hand function is to enable the matching of behavioral changes with underlying neuronal and cellular mechanisms, in the hope that development of therapeutic manipulations of these mechanisms can improve and optimize postinjury performance. The following sections provide a brief overview of some of these mechanisms in the spinal sensorimotor pathways of the monkey, though it should be emphasized that many mechanisms have not been directly correlated with voluntary hand movements and behavioral recovery.

Neuronal Microstructural Changes

While more limited than in peripheral or developing neuronal populations, adult neuronal structural plasticity can occur in the CNS throughout life, and can be most dramatically induced after injury. Postinjury axonal sprouting, for example, has been demonstrated in a range of species and across all levels of the sensorimotor pathway (for reviews see Feldman and Brecht 2005; Kossut and Juliano 1999; Maier and Schwab 2006). Due to the cellular processes involved, axon terminal growth that leads to functional recovery must include such steps as axonal extension, synapse formation, and activity-driven strengthening and stabilization, and therefore typically takes weeks to months.

Primary afferent sprouting may occur in the CNS after damage to the peripheral axon of the primary afferent (Florence and Kaas 1995; Goldberger and Murray 1974; Jain et al. 2000; LaMotte and Kapadia 1993; Liu and Chambers 1958; Molander et al. 1988; Woolf et al. 1995), or it can be induced in central and uninjured neurons in adult mammals. Studies have shown axonal growth in nonhuman primates in response to various forms of deafferentation in the spinal cord (C. Darian-Smith 2004; Florence and Kaas 1995; Florence et al. 1993, 1998; Wu and Kaas 2002), in brainstem nuclei (Darian-Smith 2004; Jain et al. 2000; Wu and Kaas 2002), and in the sensory cortex (C. Darian-Smith and Gilbert 1994; Florence et al. 1998).

Primate studies have also demonstrated that, after injury in the sensorimotor pathways, spared central neurons (adjacent to the site of injury or of reorganization) can sprout locally. Jain and colleagues (2000) found that over many months after dorsal column lesions or arm amputation, “face” afferents from the trigeminal nucleus grew into the ILAR Journal on 27 July 2018 by guest Downloaded from https://academic.oup.com/ilarjournal/article-abstract/48/4/396/644621
nucleus (C. Darian-Smith 2004). This process took several months and likely contributed to cuneate nucleus map reorganization (C. Darian-Smith and Ciferri 2006) and the circuitry changes that mediated recovery of dexterity in the deprived digits (C. Darian-Smith and Ciferri 2005). We have proposed that axon terminal sprouting enables local synapse formation on deprived postsynaptic neurons, which then amplifies an initially weak signal from the periphery to supra-threshold levels (presumably using a process similar to long-term potentiation). There are few other examples of injury-induced axonal growth in the somatosensory and motor pathways of the adult monkey. Corticospinal axonal sprouting after hemisection or other spinal injuries may mediate circuit reorganization and functional compensation, but the normal collateral branching of descending fibers in the macaque monkey has so far made this difficult to assess (Galea and Darian-Smith 1997a).

It is now generally accepted that the reduced capacity for axon growth in the adult CNS (as opposed to the embryonic or peripheral nervous system) is determined more by the permissiveness of the cellular environment than by any specific differences in the CNS neurons. This has long been established in primary afferent neurons (David and Aguayo 1981; Richardson et al. 1980), with their peripheral and central axonal branches having different capacities for regeneration. In the cellular environment, both physical (e.g., glial scarring, hemorrhagic cysts) and chemical barriers can inhibit growth in the CNS, and a number of proteins and neurotrophic factors have been identified that inhibit or augment axon growth (e.g., brain-derived neurotrophic factor, chondroitin sulphate proteoglycans, semaphorin-3A, Nogo-A).

Among the better known of the myelin-associated inhibitors is Nogo-A, which is synthesized mainly in oligodendrocytes and localized in myelin (for reviews see Maier and Schwab 2006; Schwab 2004). By using one of the neutralizing antibodies now available against Nogo-A (mAb IN-1), Schwab and others have begun investigating the role of this growth inhibitor in the CNS of adult rats and monkeys. After a complete transection of the corticospinal tract and mAB IN-1 treatment in rats, they observed sprouting from the rubrospinal tract into the cervical spinal ventral horn. In the ventral horn terminal sprouts then synapsed with forelimb motor neurons that do not normally receive rubrospinal input (Raineteau et al. 2001, 2002). In other studies, adult rats treated with mAb IN-1 after a focal cortical ischemic lesion recovered the ability to perform a forelimb reaching task (Papadopoulos et al. 2002; Wiessner et al. 2003) and motor cortical neurons increased in their dendritic arbor complexity (Papadopoulos et al. 2006), suggesting cortical circuitry remodeling.

There is also recent anatomical evidence of corticospinal axonal terminal sprouting in marmosets that received mAB IN-1 after a unilateral corticospinal lesion (Fouad et al. 2004). But the evidence for this or any corresponding functional recovery remains inconclusive in the macaque monkey (Freund et al. 2006; Ho and Tessier-Lavigne 2006). Future work will be needed to establish whether or not...
sprouts find functionally relevant targets and whether the results are clinically meaningful. The difficulties associated with such investigations underscore the need for simple, effective, and well-defined nonhuman primate models, in which results are not so open to ambiguity.

Dendritic spines are the postsynaptic target for most cortical synapses, and they are frequently quantified as an indirect measure of synapse density along dendrites. With the recent introduction of 2-photon imaging (in rodent models), it is now possible to study the dynamics of dendrites in living neurons in vivo that express fluorescent proteins (e.g., green fluorescent protein, or GFP; for review see Hickmott and Ethell 2006; Lendvai et al. 2000). Most studies of dendritic structural plasticity have been in rodents. Some have looked at dendritic spine density changes and dynamics in the S1 cortex with respect to changes in activity and experience (Kleim et al. 2002; Knott et al. 2002; Trachtenberg et al. 2002; Zuo et al. 2005; for reviews see Feldman and Brecht 2005; Fox and Wong 2005). Others report an increase in dendritic arborization in the adult rat cortex following sensorimotor cortical lesions (forelimb region), and this increase was directly related to forelimb use in the rat (Jones and Schallert 1994). Dendritic arbor bias can also change after denervation (Hickmott and Merzenich 1999; Hickmott and Steen 2005; Taliby et al. 2005). All of these studies indicate that activity-driven changes in synaptic circuitry and dendritic structure adapt throughout life, in response to changes in activity brought on by injury.

There has been little equivalent work in the primate. However, one study (Churchill et al. 2004) has demonstrated similar changes in dendritic structure in S1 in the monkey after a peripheral nerve cut that partially denervated the hand. In this study it was found that distal branches of pyramidal neuron dendrites have a greater complexity in deprived cortex, as compared with unaffected cortex. Future investigations will be needed to determine whether such changes correlate directly with functional improvements and whether they can be manipulated to improve behavioral outcome (see Hickmott and Ethell 2006 for a review of hormonal, neurotrophic, and neurotransmitter cues linked with neuronal structural alterations).

Degeneration and Scar Formation

Atrophy and degeneration (e.g., wallerian) occur in any chronic peripheral nerve, spinal root, or central injury that involves the death of axons that enter or course through the spinal cord. In the shorter term and to some extent chronically, degeneration invariably results in the recruitment and activation of a number of nonneuronal cell types (e.g., macrophages, oligodendrocytes, microglia, and astrocytes). These cells perform many roles in addition to cleaning up and managing the structural integrity of the injury site. In traumatic injuries of the spinal cord and CNS, astrocytes play a major role in gliosis and the formation of the glial scar. Activated astrocytes in the scar tissue secrete molecules (e.g., chondroitin sulphate proteoglycans, ephrins) that either permit or inhibit axon terminal growth and synapse formation (Fawcett and Asher 1999; Miller and Silver 2006; Ullian et al. 2004). Their secretion of inhibitory factors can present a major barrier to axon growth and may prevent a certain amount of recovery after traumatic spinal injury. Not surprisingly, then, the effects of these cells and their inhibitory factors on neural reorganization are an important focus of investigation.

In chronic injuries of many years, transneuronal atrophy can be considerable, as has been demonstrated in monkeys that received large-scale dorsal root injuries (C4-T2) 12 to 20 years earlier. In these monkeys, the brainstem cuneate and thalamic VPLc nuclei lost as much as 50% in overall volume, although the loss involved neuropil more than the total neuron numbers (see Jones 2000 for review). The loss at first has little bearing on the recovery of forelimb and hand function, but it does indicate a reduction in the size of composite neurons (presumably their dendrites and somata) rather than their death over many years. This distinction raises the possibility that these neurons could be recruited back to a functioning pathway with appropriate activation many years after the original injury.

Additional Mechanisms

The role of other neural mechanisms in functional reorganization and behavioral plasticity is less clear. The divergence of afferent pathways from the spinal cord to brainstem to thalamus to cortex is clearly responsible for some forms of short-term plasticity. After a peripheral nerve cut, for example, receptive fields from adjacent body parts enlarge to “fill in” the edges of the deafferented (silent) cortex, a process that can occur within minutes to hours and is mediated by the normal divergence of thalamocortical afferent terminals in the cortex (up to 2 mm in the monkey) as well as the “unmasking” of connections that normally keep receptive fields in check. Unmasking occurs when excitatory inputs to inhibitory neurons in the cortex are removed by the lesion. The removal of these inputs inhibits the local GABAergic connections in adjacent cortex and unmasks preexisting circuitry. Disinhibition may involve the modulation of GABAergic pathways at different levels of the neuraxis and may occur after spinal and nerve injuries that affect hand function (for reviews see Chen et al. 2002; Ding et al. 2005; Ojakangas and Donoghue 2006). However, its role in longer-term changes and functional and behavioral recovery of hand function remains unclear.

Adult neurogenesis is also being investigated as a potential mechanism that may play a role in circuit reorganization after spinal injury. Adult neurogenesis is critical to hippocampal function, and several groups have reported its occurrence following neuropathic conditions such as ischemia, and even in conjunction with various learning paradigms (Arvidsson et al. 2002; Danilov et al. 2006; Magavi et al. 2000; Ming and Song 2005; Mirescu and Gould 2006;
Nakatomi et al. 2002). Although neurogenesis has not been observed in spinal injuries that involve direct trauma to the cord, recent work in our laboratory suggests it may play a role in pathway reorganization in dorsal root lesions that do not directly involve trauma to the spinal cord and that do not produce the massive gliosis (or glial scarring) associated with central trauma (C. Darian-Smith and Vessal 2006).

Concluding Remarks

Future studies are needed to build a systemwide understanding of the neuronal and cellular changes that underlie the recovery of hand function after spinal cord or nerve injury in the primate. It will be necessary to look at reorganization at all levels of the affected sensorimotor pathways. Some of these pathways are phylogenetically new in the primate and uniquely prominent in humans (e.g., the rubro-olivary-cerebellar loop), and their potential clinical relevance has yet to be determined. Such studies can be effective only in a primate model of spinal cord or nerve injury that correlates neuronal changes with hand function.

In addition, researchers are starting to define the basic mechanisms that mediate postinjury recovery of hand function. Rodent models are necessary for the study of cellular, molecular, and biochemical responses to injury in the CNS. However, only well-defined models of spinal cord and nerve injury in the primate, correlating behavior with cellular changes, can provide the clinical link for developing therapeutic interventions that will optimize the recovery of hand function after injury.

References

Alstermark B, Ogawa J, Isa T. 2004. Lack of monosynaptic corticomotor-neuronal EPSPs in rats: Disynaptic EPSPs mediated via reticulospinal neurons and polysynaptic EPSPs via segmental interneurons. J Neurophysiol 91:1832-1839.

Anderson KD. 2004. Targeting recovery: Priorities of the spinal cord-injured population. J Neurotrauma 21:1371-1383.

Arvidsson A, Collin T, Kirik D, Kokaia Z, Lindvall O. 2002. Neuronal replacement from endogenous precursors in the adult brain after stroke. Nat Med 8:963-970.

Asanuma H, Zarzecki P, Jankowska E, Hongo T, Marcus S. 1979. Projection of individual pyramidal tract neurons to lumbar motor nuclei of the monkey. Exp Brain Res 34:73-89.

Baleydier C, Mauguire F. 1987. Network organization of the connectivity between parietal area 7, posterior cingulate cortex and medial pulvinar nucleus: A double fluorescent tracCereb study in monkey. Exp Brain Res 1987:385-393.

Belhaj-Saif A, Cheney PD. 2000. Plasticity in the distribution of the red nucleus output to forearm muscles after unilateral lesions of the pyramidal tract. J Neurophysiol 83:3147-3153.

Belyantseva IA, Lewin GR. 1999. Stability and plasticity of primary afferent projections following nerve regeneration and central degeneration. Eur J Neurosci 11:457-468.

Bennett KMB, Lemon RN. 1994. The influence of single monkey corticomotorneuronal cells at different levels of activity in target muscles. J Physiol (Lond) 477:291-307.

Bradbury EF, McMahon SB, Ramer MS. 2000. Keeping in touch: Sensory neurone regeneration in the CNS. Trends Pharmacol Sci 21:389-394.

Brinkman J, Bush BM, Porter R. 1978. Deficient influences of peripheral stimuli on precentral neurones in monkeys with dorsal column lesions. J Physiol 276:27-48.

Buonomano DV, Merzenich MM. 1998. Cortical plasticity: From synapses to maps. Ann Rev Neurosci 21:149-186.

Burman K, Darian-Smith C, Darian-Smith I. 2000a. Geometry of rubrospinal, rubroolivary, and local circuit neurons in the macaque red nucleus. J Comp Neurol 423:197-219.

Burman K, Darian-Smith C, Darian-Smith I. 2000b. Macaque red nucleus: Origins of spinal and olivary projections and terminations of cortical inputs. J Comp Neurol 423:179-196.

Chen R, Cohen L, Hallett M. 2002. Nervous system reorganization following injury. Neuroscience 111:761-773.

Churchill J, Tharp J, Wellman C, Sengelaub D, Garraghty P. 2004. Morphological correlates of injury-induced reorganization in primate somatosensory cortex. BMC Neurosci 5:43.

Clark WEL. Northfield DWC. 1937. The cortical projection of the pulvinar in the macaque monkey brain. Brain 60:126-142.

Cooper BY, Glendingin DS, Vierck C. 1993. Finger movement deficits in the stumptail macaque following lesions of the fasciculus cuneatus. Somatosens Mot Res 10:17-29.

Cusick CG, Gould H. 1990. Connections between area 3b of the somatosensory cortex and subdivisions of the ventroposterior nuclear complex and the anterior pulvinar nucleus in squirrel monkeys. J Comp Neurol 292:83-102.

Danilov AI, Covacu R, Moe MC, Langmoen IA, Johansson CB, Olsson T, Brundin L. 2006. Neurogenesis in the adult spinal cord in an experimental model of multiple sclerosis. Eur J Neurosci 23:394-400.

Darian-Smith C. 2004. Primary afferent terminal sprouting after a cervical dorsal rootlet section in the macaque monkey. J Comp Neurol 470:134-150.

Darian-Smith C, Brown S. 2000. Functional changes at periphery and cortex following dorsal root lesions in adult monkeys. Nat Neurosci 3:476-481.

Darian-Smith C, Ciferri M. 2005. Loss and recovery of voluntary hand movements in the macaque following a cervical dorsal rhizotomy. J Comp Neurol 491:27-45.

Darian-Smith C, Ciferri M. 2006. Cuneate nucleus reorganization following cervical dorsal rhizotomy in the macaque monkey: Its role in the recovery of manual dexterity. J Comp Neurol 498:552-565.

Darian-Smith C, Darian-Smith I. 1993. Thalamic projections to areas 3a, 3b, and 4 in the sensorimotor cortex of the mature and infant macaque monkey. J Comp Neurol 355:173-199.

Darian-Smith C, Darian-Smith I, Cheema SS. 1990. Thalamic projections to sensorimotor cortex in the macaque monkey: Use of multiple retrograde fluorescent tracers. J Comp Neurol 299:17-46.

Darian-Smith C, Gilbert CD. 1994. Axonal sprouting accompanies functional reorganization in adult cat striate cortex. Nature 368:737-740.

Darian-Smith C, Vessal M. 2006. Neurogenesis occurs in the spinal cord of adult macaque monkeys following a cervical dorsal rhizotomy. Soc Neurosci Abstr 31:555:1.

Darian-Smith I. 1984. The sense of touch: Performance and peripheral neural processes. In: Darian-Smith I, Brookhart JM, Mountcastle VB, eds. Handbook of Physiology. Section 1. The Nervous System. Bethesda MD: American Physiological Society. p 739-788.

Darian-Smith I, Darian-Smith C. 2004. Touch, tangible surfaces and their neuronal representation. In: Adelman G, Smith B, eds. Encyclopedia of Neuroscience. 3rd ed. Amsterdam: Elsevier.

Darian-Smith I, Galea MP, Darian-Smith C, Sugitani M, Tan A, Burman K. 1996. The Anatomy of Manual Dexterity. Berlin: Springer.

David S, Aguayo A. 1981. Axonal elongation into peripheral nervous system “bridges” after central nervous system injury in adult rats. Science 214:931-933.

Ding Y, Kastin A, Pan W. 2005. Neural plasticity after spinal cord injury. Curr Pharmaceut Design 11:1441-1450.
prerogative? In: Goodwin AW, Darian-Smith I, eds. Hand Function and the Neocortex. New York: Springer. p 155-174.
Nagano A. 1998. Treatment of brachial plexus injury. J Orthop Sci 3:71-80.
Nakatomi H, Kurui T, Okabe S, Yamamoto S, Hatano O, Kawahara N, Tamura A, Kirino T, Nakafuku M. 2002. Regeneration of hippocampal pyramidal neurons after ischemic brain injury by recruitment of endogenous neural progenitors. Cell 110:429-441.
Napier J. 1980. Hands. London: Allen and Unwin.
Nudo RJ, Masterton RB. 1990. Descending pathways to the spinal cord. III: Sites of origin of the corticospinal tract. J Comp Neurol 296:559-583.
Nudo RJ, Jenkins WM, Merzenich MM, Prejean T, Grenda R. 1992. Neurophysiological correlates of hand preference in primary motor cortex of adult squirrel monkeys. J Neurosci 12:2918-2947.
Ojakangas CL, Donoghue JP. 2006. Plasticity of cerebral motor functions: Implications for repair and rehabilitation. In: Selzer M, Clarke S, Cohen L, Duncan P, Gage F, eds. Textbook of Neural Repair and Rehabilitation: Neural Repair and Plasticity. Cambridge: Cambridge University Press. p 126-146.
Papadopoulos C, Tsai S, Alsbiei T, O’Brien T, Schwab M, Kartje G. 2002. Functional recovery and neuroanatomical plasticity following middle cerebral artery occlusion and IN-1 antibody treatment in the adult rat. Ann Neurol 51:433-441.
Papadopoulos C, Tsai S, Cheatwood J, Bollnow M, Kolb B, Schwab M, Kartje G. 2006. Dendritic plasticity in the adult rat following middle cerebral artery occlusion and Nogo-a neutralization. Cereb Cortex 16:529-536.
Phillips CG, Porter R. 1977. Corticospinal neurons: Their role in movement. Monogr Physiol Soc 34:1-450.
Pons TP, Garraghty PE, Ommaya AK, Kaas JH, Taub E, Mishkin M. 1991. Massive cortical reorganization after sensory deafferentation in adult macaques. Science 252:1857-1860.
Raineau O, Fouad K, Bareyre F, Schwab M. 2002. Reorganization of descending motor tracts in the rat spinal cord. Eur J Neurosci 16:1761-1771.
Raineau O, Fouad K, Noth P, Thallmair M, Schwab M. 2001. Functional switch between motor tracts in the presence of the mAb IN-1 in the adult rat. Proc Natl Acad Sci U S A 98:6929-6934.
Richardson P, McGuinness U, Aguayo A. 1980. Axons from CNS neurons regenerate into PNS grafts. Nature 284:264-265.
Schwab ME. 2004. Nogo and axon regeneration. Curr Opin Neurobiol 14:118-124.
Snow PJ, Wilson P. 1991. Plasticity in the somatosensory system of developing and mature mammals: The effects of injury to the central and peripheral nervous system. In: Ottoson D, ed. Progress in Sensory Physiology. Berlin: Springer. p 1-482.
Taliby C, Wright L, Metha A, Calford M. 2005. Activity-dependent maintenance and growth of dendrites in adult cortex. Proc Natl Acad Sci U S A 102:4631-4636.
Toyoshima K, Sakai H. 1982. Exact cortical extent of the origin of the corticospinal tract (CST) and the quantitative contribution to the CST in different cytoarchitectonic areas: A study with horseradish peroxidase in the monkey. J Hirnforsch 23:257-269.
Trachtenberg J, Chen B, Knott G, Feng G, Sanes J, Welker E, Svoboda K. 2002. Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex. Nature 420:788-794.
Ullian EM, Christopherson KS, Barres BA. 2004. Role for glia in synaptogenesis. Glia 47:209-221.
Vierck C. 1982. Comparison of the effects of dorsal rhizotomy or dorsal column transection on motor performance of monkeys. Exp Neurol 75:566-575.
Vierck CJ, Cooper BY. 1998 Cutaneous texture discrimination following transection of the dorsal spinal column in monkeys. Somatosens Mot Res 15:309-315.
Wall JT, Xu J, Wang X. 2002. 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 39:181-215.
Wissner C, Bareyre F, Allegrini P, Mir A, Frenzel S, Zurini M, Schnell L, Oertle T, Schwab M. 2003 Anti-Nogo-A antibody infusion 24 hours after experimental stroke improved behavioral outcome and corticospinal plasticity in normotensive and spontaneously hypertensive rats. J Cereb Blood Flow Metab 23:154-165.
Willis WD,Coggeshall RE. 2004a. Sensory Mechanisms of the Spinal Cord: Ascending Sensory Tracts and Their Descending Control. Vol 2. New York: Kluwer Academic/Plenum Publishers.
Willis WD, Coggeshall RE. 2004b. Sensory Mechanisms of the Spinal Cord: Primary Afferent Neurons and the Spinal Dorsal Horn. Vol 1. New York: Kluwer Academic/Plenum Publishers.
Woods TM, Cusick CG, Pons TP, Taub E, Jones EG. 2000. Progressive transneuronal changes in the brainstem and thalamus after long-term dorsal rhizotomies in adult macaque monkeys. J Neurosci 20:3884-3899.
Woolf CJ, Shortland P, Reynolds M, Ridings J, Doubell T, Coggeshall RE. 1995. Reorganization of central terminals of myelinated primary afferents in the rat dorsal horn following peripheral axotomy. J Comp Neurol 360:121-134.
Wu CW, Kaas JH. 2002. The effects of long-standing limb loss on anatomical reorganization of the somatosensory afferents in the brainstem and spinal cord. Somatosens Mot Res 19:153-163.
Xerri C, Merzenich MM, Peterson BE, Jenkins W. 1998. Plasticity of primary somatosensory cortex paralleling sensorimotor skill recovery from stroke in adult monkeys. J Neurophysiol 79:2119-2148.
Yeterian EH, Pandya DN. 1991. Corticthalamic connections of the superior temporal sulcus in rhesus monkeys. Exp Brain Res 83:268-284.
Zuo Y, Yang G, Kwon E, Gan W-B. 2005. Long-term sensory deprivation prevents dendritic spine loss in primary somatosensory cortex. Nature 436:261-265.