Published in final edited form as:

Behav Brain Res. 2013 September 1; 252: 363–376. doi:10.1016/j.bbr.2013.05.058.

Impairment and recovery of hand use after unilateral section of the dorsal columns of the spinal cord in squirrel monkeys

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Abstract

Damage to the ascending forelimb afferents in the dorsal columns (DC) of the cervical spinal cord in monkeys impairs forelimb use, particularly hand dexterity. Although considerable recovery has been reported, interpretation of the results is complicated by the reproducibility of the lesion and behavioral assessment. Here we examine the effects of a unilateral DC lesion at the C4–C6 spinal cord level in 4 adult squirrel monkeys. Behavioral performance is assessed on a reach-to-grasp task over 5–13 weeks after lesion. Retrograde tracers were injected into the skin of the fingertips to determine the distribution of axon terminals in the cuneate nucleus and estimate the effectiveness of lesion at the conclusion of each case. The size and level of DC lesion was reflected in the proportion of spared afferents, which ranged from 1% to 25% across monkeys. The experiments produced two major findings. First, the extent of deafferentation in the dorsal column is directly related to the degree of reaching and grasping impairments, and to the reactivation profile and somatotopic reorganization in contralateral primary somatosensory cortex. Second, considerable behavioral recovery and cortical reorganization occurred even in the monkey with only 1% of axons spared in the dorsal column. Our findings suggest that cutaneous inputs from the hand and forelimb are critical to the integrity of functions such as grasping and reaching. In addition, axon branches from peripheral afferents that terminate on neurons in the dorsal horn of the spinal cord are likely central to the functional recovery.

Keywords

New World monkey; spinal cord injury; functional recovery; reach and grasp; forelimb trajectory

1. INTRODUCTION

In primates, identifying surfaces and objects by manual touch is dependent on a multisynaptic pathway that connects cutaneous receptors in the hand with somatosensory cortex (see [1] for review). The first segment of this pathway is comprised of afferents that originate from slowly and rapidly adapting receptors on the glabrous and hairy surfaces of the hand. These afferents bifurcate as they enter the spinal cord. One branch of afferents terminates on neurons in the dorsal horn of the spinal cord. The other branch of afferents

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CONFLICT OF INTERESTS

All authors have no conflict of interest.

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ascends in the dorsal columns of the spinal cord and terminates in the cuneate nucleus. Damage to this segment of the pathway, such as from spinal cord injury, produces a range of behavioral impairments that include hand use. Understanding the contributions of somatosensory deafferentation to the behavioral deficits is complicated because of the non-selective nature of spinal cord injuries, which can damage descending fibers from the motor system. This confound can be overcome in animal models, particularly non-human primates, as the ascending sensory afferents are spatially segregated in the spinal cord from the descending motor projections.

Nevertheless, the extent of behavioral impairments reported in monkeys from interrupting sensory afferents varies considerably. For example, dorsal column lesions in macaque monkeys have been reported to produce permanent deficits in precision grip and other digit movements [2–5]. In contrast, other work showed that damage to the dorsal column alone did not affect actions unless the dorsal lateral funiculus [6–10], or somatosensory cortex, is concurrently damaged [11]. Only one study examined the effects of dorsal column section on actions in New World monkeys. Although the dorsal column lesion did not affect reaching to grasp stationary targets, performance was impaired on an active bait catching task [12].

The size of the dorsal column lesion and its rostrocaudal location along the spinal cord are predictive of afferent sparing and ultimately behavioral outcome. This assertion is perhaps best exemplified with an alternative experimental approach in which the afferents are severed at the dorsal roots, before entering into the spinal cord. For example, Mott and Sherrington [13] comprehensively severed the dorsal roots of the forelimbs of macaque monkeys, which completely abolished grasping. Darian-Smith and Ciferri [14] confirmed those findings with comprehensive deafferentation that was confined to the thumb and/or index fingers. Recovery was minimal or absent for at least 8 months of testing [14]. Nevertheless, incomplete deafferentation of the same dorsal roots also produced severe impairments at the outset, but substantial recovery of precision grip occurred in the postoperative weeks. Similarly, Mott and Sherrington [13] showed that sparing of a single dorsal root, irrespective of its origins from within the hand, produced milder deficits.

Determining the relationship between amount of deafferentation, degree of behavioral impairment, and time course of recovery, could improve our understanding of the consequences of dorsal column lesions. We adapted the systematic approach developed for assessing reaching and grasping abilities in rats [15, 16] to measure the same abilities in squirrel monkeys. Addressing the following questions was our primary objective. (1) Does deafferentation from dorsal column lesion affect dexterity during grasping? (2) Does deafferentation from dorsal column lesion affect the forelimb trajectory during reaching? (3) What is the relationship between the extent of dorsal column lesion and the severity of reaching and/or grasping impairments? (4) What is the time course of behavioral recovery?

2. MATERIAL AND METHODS

Four adult male squirrel monkeys (1 *Saimiri sciureus* and 3 *Saimiri boliviensis*) were used for this study. Subjects were 3–5 years old and weighed 800–1200g. All experimental procedures were approved by the Vanderbilt University Animal Care and Use Committee, and followed the guideline of the National Institute of Health Guides for the Care and Use of Laboratory Animals.

2.1. Procedural timeline

Prior to surgery, the monkeys were trained and tested on a reach-to-grasp task to evaluate hand use. In addition, the somatotopy of the hand representation in cortical areas 3b and 1

was determined with functional magnetic resonance imaging (fMRI) before and several times after section of the contralateral dorsal columns of the spinal cord. Monkeys were tested on the reach-to-grasp task for up to 13 weeks post lesion. Seven to eighteen weeks after lesion, digits of both hands were injected with a retrograde tracer to label intact afferents in the dorsal column and axon terminals in the cuneate nuclei. Comparing the labeling patterns on the intact and lesion sides facilitate assessing the effectiveness of the lesion. Two to six days later, the responsiveness and somatotopy of the hand representations in cortical areas 3b and 1 were determined in a terminal procedure with optical imaging followed by multi-unit recordings using microelectrodes. Each study concluded with a lethal dose of anesthetic and perfusion with fixative. The brains and spinal cords were extracted and processed. The present study focuses on the effects of sensory deafferentation on reaching and grasping. Neurophysiological outcomes as determined with fMRI, intrinsic optical imaging, and microelectrode mapping, are reported elsewhere [17, 18].

2.2. Behavioral training and testing

2.1.1. Training—Monkeys were preoperatively trained on a reach-to-grasp task for 14 days. Monkeys that were pair-housed were separated for individual training in the home cage and were regrouped after training. The front of the home cage included two square apertures (44mm wide × 41mm high) that provided access to a feeding tray. To administer the reach-to-grasp task, the feeding tray was replaced with a modified Kluver Board (15.2cm × 9.9cm). The board included wells 1–4 of varying diameters (0.78cm (1.5cm for SM-R), 1.20cm, 1.14cm, 1.14cm,) and depths (0.14cm, 0.28cm, 0.38cm, 0.64cm, respectively) that represented incremental difficulties in the reach-to-grasp task.

Each daily training session consisted of 80 trials. For each trial, a 45 mg dustless precision banana-flavored pellet (product #F0021, Bioserve Inc., Frenchtown, NJ, USA), was placed in the well directly in front of the aperture. The monkey was allowed to reach for and retrieve the food pellet. Monkeys demonstrated a hand preference within the first day of testing. Accordingly, the board was mounted in front of the aperture contralateral to the preferred hand such that the monkey reached across its body and comfortably pronated its forelimb. After 20 trials per well, the board was repositioned such that a different well was centered in front of the aperture and another 20 trials were administered. For the first seven days, training proceeded from the easiest to the most difficult well (wells 1 to 4), but the order was randomized for the subsequent 7 days.

2.1.2. Video recording—Performance on the last day of training and each postoperative test day was video recorded using a Panasonic PV-GS320 (30 frames/sec, 1000th of a second shutter speed). A light source in addition to the overhead lights of the housing room provided the illumination necessary for filming. The camera was positioned orthogonally to the home cage such that the monkey's behavior was filmed from the front. A wide perspective captured the entire body of the monkey during each trial and a close-up perspective focused on the well and the hand during grasping. Video records were transferred onto a computer hard drive using iMovie software (Apple) and performance was analyzed frame-by-frame.

2.1.3. Reach-to-grasp quantitative score—Quantitative scoring was feasible during training/testing sessions, but was also confirmed from the video records. Two measures were used for quantitative scoring.

1. *Success*. A successful reach is one in which the food was grasped and transferred into the mouth using the designated hand. The rate of success was calculated for each well using the following formula:

Percent of total success=(number of pellets retrieved/20) × 100.

2. *Digit flexes per successful trial.* This measure reflects the average number of digit flexes for each successfully retrieved pellet. A single flexion of the digits for a successfully retrieved pellet was considered a perfect score. Digit flexes per success was calculated for each well using the following formula:

Digits flexes/success=total number of digits flexes in successful trials/number of successful trials

2.1.4. Reach-to-grasp kinematic analysis—For analysis of forelimb kinematics a trial was divided into three segments. (A) *Reach.* The forelimb was transported from inside the home cage, through the aperture, and the hand was pronated onto the board. (B) *Grasp.* The digits were flexed to contact the food pellet, and the pellet was typically secured between digits 1, 2, and 3. (C) *Retrieval.* The wrist was supinated as the forelimb was withdrawn from the board and into the cage. Additional wrist supination occurred near the mouth, and the digits were extended to release the food into the mouth.

The amount of time to execute each segment and its spatial trajectory were measured from the video records. Since digit 2 was visible in the video records throughout the three segments, we used the joint between the proximal and middle phalanges as the tracking point. Kinematic analysis was limited to the first five successful trials in well 1 (easiest well), which were analyzed frame-by-frame using Quick Time software.

1. *Time.* Calculated from the number of video frames (33 ms/frame) recorded for each segment.
2. *Spatial trajectory.* Determined from the travel distance of the tracking point. A transparency was mounted onto a computer screen and position of the tracking point was marked with a dot for each video frame. The dots that comprised each segment were serially connected with straight lines. The length of each connecting line was measured with a compass. The sum of measurements was calculated for each segment to determine the distances $D_{(film)}$ of reach, grasp, and retrieval.

This measurement required normalization because the distance between the camera lens and the aperture of the cage varied slightly across filming days. Thus, the dimensions of the aperture, which was visible in every filming session, was used as a constant for normalizing distance measurements. More specifically, the ratio between the width of the actual aperture (42 mm) and the width of the same aperture as it appeared in the video record (*FilmedWindowWidth*) was calculated for each filming session. Normalizations of the actual distances (D) measured for each segment were calculated according to the following formula:

$$D=D_{(film)} \times (42mm/FilmedWindowWidth)$$

Transparencies were scanned into a computer and sorted by segment and day. Traces for each segment in a given test day were superimposed onto each other using Adobe Illustrator software (Adobe CS2). Part of the results has appeared in abstract form.

2.3. Dorsal column section surgery

After pre-operative success scores reached a plateau, four squirrel monkeys received unilateral lesions in the dorsal column of the spinal cord at cervical segments C4-C6. The

lesion was ipsilateral to the hand trained on the reaching task. Detailed surgical procedures can be found in earlier studies [17, 19]. In brief, under aseptic conditions and general anesthesia, a portion of the cervical spinal cord was exposed at cervical level C4-C6. The dorsal columns were sectioned on one side with a pair of iris surgical scissors. The dura was replaced, the opening was closed, and the skin sutured. The monkeys were carefully monitored until they fully recovered from anesthesia before they were returned to their home cage. The monkeys received antibiotics and analgesics for 3 days after surgery.

2.4. Tracer injection and histology

Six to thirteen weeks after dorsal column sections (13 weeks in SM-R, 6 weeks in SM-O, 8 weeks in SM-C after the effective lesion, and 7 weeks in SM-D), we injected transganglionic tracers subcutaneously into the digits of both hands to trace intact somatosensory afferents. In squirrel monkey SM-R, cholera toxin subunit B (CTB) conjugated with wheat germ agglutinin horseradish peroxidase (BHRP, 0.2%, List Biological) was injected into the tips of digits D1–D5 in the ipsilateral-to-lesion hand, and to the D1, D3, and D5 in the contralateral-to-lesion hand (5 μ l per injection site). In the other squirrel monkeys, CTB (Sigma; 1% in distilled water) was injected into the skin of digits D1, D3, and D5 of both hands (5 μ l per injection site).

Two days (SM-R with BHRP injection) or six days (SM-O, SM-C, and SM-D with CTB injections) were allowed for tracer transport before a terminal mapping procedure started. At the conclusion of each case, a lethal dose of anesthetic (sodium pentobarbital) was administered intravenously. When areflexive, each monkey was perfused transcardially with phosphate buffered 0.9% saline (PBS, pH 7.4) followed by 2–4 % paraformaldehyde in PB, followed by 2–4% paraformaldehyde with 10% sucrose in PB. The brain and spinal cord were removed. The brainstem and spinal cord were sectioned (40 μ m) in the coronal and horizontal planes, respectively. Every fourth section of the brainstem and every second section of the spinal cord was processed with immunohistochemistry to reveal CTB or 3,3', 5,5'-Tetramethylbenzidine (TMB) reaction to reveal BHRP. Another series of brainstem and spinal cord sections was processed for cytochrome oxidase to reveal brainstem and spinal cord architecture.

2.5. Evaluating the extent of dorsal column section

Methods for lesion reconstruction have been published in our recent paper [17]. In brief, we determined the extent of the lesion using two approaches. First, we reconstructed the lesion from horizontal sections of the spinal cord. Images of the spinal cord sections were acquired with a Nikon E800 microscope (Nikon Inc., Melville, NY) and Nikon DXM1200 camera (Nikon Inc., Melville, NY). With Adobe Illustrator software (v. CS2), digital images were aligned according to pinholes in spinal cord tissue that we strategically placed after perfusion, as well as tissue artifacts. The lesion was reconstructed in the coronal plane across horizontal spinal cord sections. Second, we compared the densities of afferents labeled from tracer injections into the digits of the impaired hand relative to the counterpart of the intact hand see [17] for more details). We focused on the sizes of the patches of terminals labeled in the cuneate nucleus and the density of axons traversing the dorsal columns. Differential labeling between the ipsilateral and contralateral sides of the lesion therefore reflected the extent of fiber sparing from the lesion. Conducting this comparison across multiple cervical levels of the spinal cord and sections of the cuneate nucleus allowed us to determine the relative deafferentation of individual digits.

3. RESULTS

The goal of this study was to investigate the effects of dorsal column section on reaching and grasping. Results are presented in three sections (1) extent of lesions; (2) effects of lesions on performance in a reach-to-grasp task; and (3) correlation between the amount of spared axon terminals in cuneate nucleus and performance in a reach-to-grasp task. As the extents and levels of the lesions varied, the results are presented on a case-by-case basis starting with the most impaired monkey.

3.1. Extent of lesions

Lesions from dorsal column were reconstructed for all four cases (Fig. 1). Lesions were restricted to the dorsal columns, but encroached into the central gray of the spinal cord in three cases. The corticospinal tract, one of the major motor pathways involved in controlling dexterity in non-human primates, was spared in all four monkeys.

SM-R—This was the most extensive dorsal column lesion (Fig. 1A). Tissue processing and reconstruction from horizontally cut spinal cord sections showed that the lesion was placed at the C4-C5 junction, where it was rostral to most of the dorsal root inputs from digit 1. Indeed, BHRP-injections into the distal phalanges of digits 1–5 did not label any axon terminals in the cuneate nucleus ipsilateral to the lesion, which confirms extensive or complete deafferentation of the digits (see Fig. 11 in [18]). The lesion also extended into the intermediate zone of the gray matter. Nevertheless, a portion of fibers in the gracile fasciculus from the lower body was spared.

SM-O—This dorsal column section was also extensive (Fig. 1B). The lesion was at the C4 level and interrupted nearly all inputs from digits of the right hand. Indeed, tracer injections into the distal phalanges of digits 1, 3, and 5 of both hands labeled <1% of axon terminals in the ipsilateral-to-lesion cuneate nucleus as compared to the opposite cuneate nucleus [17].

SM-C—An initial dorsal column section was delivered at the C4 level. This lesion produced only minor impairments in the ipsilateral-to-lesion hand. The transiency of the impairment prompted us to deliver another lesion after 68 days that was 1 mm caudal to the original site. Postmortem histology confirmed that the original lesion involved only lateral aspects of the target dorsal column, which would have inevitably spared some of the inputs from the hand. In contrast, the second lesion was extensive and likely severed most inputs from the hand (Fig. 1C). Tracer injections into the distal phalanges of digits 1, 3, and 5 of both hands labeled <2.2% of axons in the ipsilateral-to-lesion cuneate nucleus as compared to the opposite cuneate nucleus [17].

SM-D—This dorsal column section was extensive (Fig. 1D), but at a lower level within the spinal cord relative to lesions in the previous cases. The level of the lesion would have likely interrupted most inputs from digits 3–5 and to a lesser extent inputs from digit 2. Inputs from digit 1 would have been likely spared. Tracer injections into the distal phalanges of digits 1, 3, and 5 of both hands labeled 23.4% of axons in the ipsilateral-to-lesion cuneate nucleus as compared to the opposite cuneate nucleus [17]. The lesion encroached into dorsal horn, intermediate zone, and portions of the ventral horn.

3.2. Success scores

To assess performance on individual wells of the Kluver board, we compared mean success scores before and after lesion. To assess performance during individual testing weeks after lesion, we collapsed the results across wells of the Kluver board.

SM-R (no spared afferents in cuneate nucleus)—Success scores before lesion were similar for all 4 wells (Fig. 2A). However, the number of digit flexes suggested that pellets in wells 3 and 4 were more difficult to access than pellets in wells 1 and 2 (Fig. 3A). This monkey was too impaired during the initial 4 weeks after lesion to even attempt the task. Comprehensive testing started on week 6 after lesion and showed that performance was impaired in all wells. For example, the mean success score for well 4 before lesion was $98.52\% \pm 0.04$ (SD) and declined to $66.92\% \pm 1.92$ (SD) after lesion. Similarly, the number of digit flexes for well 4 before lesion was 1.86 ± 1.26 (SD) and changed to 2.14 ± 1.23 (SD) after lesion. This impairment is particularly apparent on individual testing days after lesion (Fig. 4).

Although mean success scores improved across test weeks after lesion, they did not recover to levels recorded before lesion (Fig. 5A). Similarly, the number of digit flexes improved across test weeks after lesion, but only approached levels recorded before lesion (Fig. 6A).

SM-O (<1% of afferents spared)—Success scores before lesion were similar for all 4 wells (Fig. 2B). Similarly, the numbers of digit flexes were comparable for wells 1–3 and were only marginally higher for well 4 (Fig. 3B). This monkey was not able to perform the task after lesion until day 13. Nevertheless, once performance recommenced, success scores for wells 1 and 2 were similar to success scores before lesion. However, the mean success scores recorded for wells 3 and 4 before lesion were $99.69\% \pm 0.01$ (SD) and $98.43\% \pm 0.02$ (SD) respectively, and declined to $91.82\% \pm 0.05$ and $89.88\% \pm 0.03$ after lesion. Similarly, the number of digit flexes recorded for well 3 and 4 before lesion were 1.04 ± 0.01 and 1.32 ± 0.02 respectively, and changed to 1.27 ± 0.63 and 1.41 ± 0.66 after lesion.

Mean success scores combined across all 4 wells declined to the lowest level $93.65\% \pm 0.07$ at week 3 after lesion. By week 4 after lesion, mean success scores returned to levels recorded before lesion (Fig. 5B). Similarly, the initial increase in the number of digit flexes in the two weeks after lesion was resolved by week 4 after lesion (Fig. 6B). The profile of this measurement is shown for individual testing days (well 4 only) in figure 7A.

SM-C (<2.2% of afferents spared)—Success scores before lesion were similar for all 4 wells (Fig. 2C). Similarly, digit flexes were comparable for wells 1–3 and were only marginally higher for well 4 (Fig. 3C). The first lesion produced only a mild reduction in mean success scores for wells 3 and 4, but had no effect on the number of digit flexes. The second lesion produced no additive effect that was detectable with either measure.

Mean success scores declined in the initial week after the first lesion (Fig. 5C). Nevertheless, by week 2 after lesion, success score returned to levels before lesion, which prompted delivery of an additional lesion. This manipulation produced only a marginal reduction in success scores that rapidly returned to levels recorded before either lesion. Similarly, the number of digit flexes increased only in the initial week after the first lesion (Fig. 6C). The profile of this measurement is shown for individual testing days (well 4 only) in figure 7B.

SM-D (<25% of afferents spared)—Success scores before lesion were similar for all 4 wells (Fig. 2D). However, the number of digit flexes for wells 3 and 4 suggested that they were less accessible than wells 1 and 2 (Fig. 3D). The lesion had no appreciable effect on success scores or the number of digit flexes for any of the wells. Figure 7C shows that after lesion the mean number of flexes was slightly increased in the most difficult well. The time course of performance showed no appreciable changes in success scores (Fig. 5D) or number of digit flexes (Fig. 6D).

In summary, success scores before lesion were comparable for all animals and were consistent across wells. The number of digit flexes was slightly higher for wells 3 and 4 as compared to wells 1 and 2, which may reflect the relative difficulty of the former. The location and extent of lesion was critically important to the behavioral outcome. The two monkeys (SM-R and SM-O) that showed decline in performance had the most complete lesions, which were located at C4-C5. In contrast, the extensive lesion in monkey SM-D had no appreciable effect on performance. This favorable outcome was likely due to the relatively lower location of the lesion within the spinal cord and the potential for sparing a large proportion of inputs from the hand/forelimb. The same explanation is tenable for monkey (SM-C) considering the follow up lesion was also at a relatively low level within the spinal cord.

3.3. Trajectory analysis

3.3.1. General observations on performance in reach-to-grasp task—Each trial was divided into three successive segments: (1) transport, (2) grasp, and (3) retrieval.

Before lesion: The three segments had defining features that were consistent across testing days. *(a) Transport.* The hand was typically closed in the early phase of forelimb transport. The digits extended and opened progressively as the hand emerged from the aperture of the home cage. Grip posture started to form as the hand approached the surface of the Kluver board and grip was completely shaped when the tips of the fingers contacted the board. *(b) Grasp.* For relatively shallow wells (1 and 2), digits 2–5 flexed to contact the food pellet and secure it against the palm. For deeper wells (3 and 4), digits 2 and 3 contacted the food pellet and secured it against the palm. The thumb was typically flexed throughout the grasp and was therefore not directly involved in handling the food pellet. Thus, grasping in the present task was achieved with a power grip. *(c) Retrieval.* The hand was supinated, lifted off the Kluver board, and withdrawn into the home cage. The hand was further supinated and the digits extended and opened to release the food into the mouth. Monkeys rarely looked at the pellet or their hand during retrieval, except monkey SM-R, which occasionally looked at its hand.

After lesion: The lesion affected the three segments. *(a) Transport.* Inaccurate forelimb trajectories resulted in the hand undershooting, overshooting, or laterally missing the food pellet. In addition, hand posture was noticeably abnormal during transport. For example, in some instances, digits were prematurely extended during the early phase of transport and grip formation was delayed until the digits contacted the surface of the board. In other instances, the hand was closed during transport and only opened at the start of the grasp segment. *(b) Grasp.* Dexterity was impaired as evidenced by clumsy attempts to scoop the food pellet. *(c) Retrieval.* The hand was withdrawn towards the mouth over a long and inconsistent path. Eye contact was maintained with the hand throughout this segment. Nevertheless, the hand approached the mouth regardless of whether a food pellet was grasped. This behavior suggests that the monkey was “unaware” if indeed the food pellet was secured in its hand, which was not the case before lesion.

3.3.2. Distance and speed of hand movement in reach-to-grasp task—Video records were analyzed frame-by-frame to plot the trajectories of the hand during transport, grasp, and retrieval. The time and distance for completing each segment were measured, and the speed was calculated accordingly. We limited this analysis to the first five successful trials in well 1 for one time point before lesion and multiple time points after lesion.

SM-R (no spared afferents in cuneate nucleus): Distances for completing all three segments were longer after lesion, but returned to measurements recorded before lesion 10

weeks after lesion (Fig. 8A). *Transport*. Long trajectories after lesion showed that the hand followed a long and often inconsistent path from inside the cage to the pellet. Although transport trajectories improved across weeks, they did not return to baseline even 89 days after lesion (Fig. 9). *Grasp*. Long trajectories after lesion were a reflection of impaired dexterity and increased hand movements to secure a food pellet. *Retrieval*. Long trajectories after lesion were a reflection of the long and often inconsistent path that the hand followed from the Kluver board to present the pellet to the mouth. Speed for completing all three segments was slightly reduced after lesion (Fig. 10A). Please note that the testing well was not centered for those trials before the lesion, we realized and corrected this problem when we started to analyze the film, which was after the lesion. The maximal distance of center shift was 21 mm, however the abnormality of the trajectories was much larger than this (Fig. 9). Besides, the well position was actually easier after lesion.

SM-O (<1% of afferents spared): Distance for completing all three segments were longer after lesion and the effect was particularly pronounced for the retrieval segment (Fig. 8B). *Reach*. Long trajectories after the lesion showed that the hand followed a long and often inconsistent path from inside the cage to the pellet (Fig. 11). *Grasp*. Long trajectories after lesion were a reflection of the impaired dexterity and increased hand movements to secure a food pellet. Nevertheless, 3 weeks after lesion, trajectories returned to measurements recorded before lesion. *Retrieval*. Long trajectories lasted up to 26 days after lesion and reflected a propensity for supinating the wrist and visually inspecting whether it secured the pellet in the hand. Figure 12 demonstrates one such example. We considered that the exaggerated supination of the wrist for visual inspection was the main reason of increasing the length of retrieval trajectories. Speeds for grasping and retrieval segments were slower in weeks 2 and 3 after lesion, and slightly improved by week 4. Nevertheless, those measurements never returned to levels recorded before lesion. In contrast, the speed for transport segment was only slightly reduced in week 3 after lesion, and it returned to normal range in week 4 after lesion (Fig. 10B).

SM-C (<2.2% of afferents spared): The first dorsal column section did not affect the trajectories of any of the three segments. After the second lesion, the distance for completing all three segments were longer and the effect was particularly pronounced for the retrieval segment (Fig. 8C). *Reach*. Long trajectories after second lesion showed that the hand followed a long and often inconsistent path from the inside the cage to the pellets. *Grasp*. Long trajectories after lesions reflected impaired dexterity and increased movements to secure a food pellet. Three weeks after lesions, trajectories returned to measurements recorded before lesions. *Retrieval*. Trajectories were much longer within 2 weeks of recording after the effective lesion. The long trajectories reflected extended supination for visual inspection if the pellet was secured in hand. Three weeks after the effective lesion trajectories returned to measurements recorded before lesion (Fig. 13). Speed for completing all three segments was slightly reduced after the first lesion; and the second lesion produced further decreases in the speed for grasping and retrieval segments, but not for the transport segment (Fig. 10C).

SM-D (<25% of afferents spared): Distance for completing all three segments was largely unchanged after lesion, except the grasp segment was slightly longer (Fig. 8D). Long trajectories for the grasp segment after lesion reflected that dexterity was slightly impaired and hand movements increased to secure a food pellet (Fig. 14). Nevertheless, 3 weeks after lesion, the trajectory for grasping returned to levels recorded before lesion. For the results of speed, only the retrieval segment was slightly decreased. Transportation and grasp segments were initially faster. At 4 weeks after lesion, the speed for all three segments returned to levels recorded before lesion (Fig. 10D).

3.4. Increased reliance on vision to guide behavior after lesion

Before lesion: Monkeys appeared to maintain gaze on the food pellet as soon as it was placed on the Kluver board. Gaze was maintained throughout the transport segment until the tips of the digits contacted the surface of the board. At this point eye contact was redirected towards the front of the home cage (possibly towards the experimenter) until the pellet was grasped and released into the mouth. Thus, monkeys visually engaged the target only during the transport segment, which is consistent with observations in human subjects [20].

After lesion: Gaze was maintained with the food pellet once it was placed on the Kluver board and until it was grasped (Fig. 12). Even when the pellet was successfully grasped, the monkey did not break eye contact with the general direction of the hand and the Kluver board. Our interpretation of this extended eye contact was that monkeys were visually confirming that the pellet was removed from the board. This compensatory strategy was likely adopted to overcome the somatosensory deficit that ensued from the lesion.

3.5. Relationship between the amount of spared afferents and behavioral impairment

In the present group of monkeys, we previously reported that the extent of the dorsal column section is directly correlated with the amount of cortical reactivation. Nevertheless, the deprived somatosensory cortical area 3b underwent extensive reactivation even when <1% of axon terminals in cuneate nucleus were spared ([17]. Here we identify a parallel correlation between the extent of the dorsal column section and impairment in reaching and grasping. The severity of impairment after lesion was ranked according to success scores, number of digit flexes, and kinematic characteristics (e.g., distance and speed). The collective measurements suggest that SM-R was the most impaired, SM-D was the least impaired, and SM-O and SM-C were ranked in between (Table 1). Tracer injections suggested that 0%, 1%, 2.2% and 23.4% of the fiber terminals were spared in SM-R, SM-O, SM-C and SM-D, respectively (Fig. 15). Thus, the behavioral deficit was directly correlated with the amount fiber terminals spared in the cuneate nucleus.

4. DISCUSSION

The main finding of the present study is that damage to the dorsal column of the mid-cervical spinal cord affects reaching and grasping in squirrel monkeys. The degree of impairment and the potential for recovery is directly related to the amount of axon terminals spared in the cuneate nucleus. Nevertheless, the capacity for recovery should be interpreted cautiously because qualitative examination of the behavior after presumptive recovery shows that monkeys adopt alternate strategies to achieve the same end point.

4.1. The integrity of the dorsal column pathway is important for cortical function

Dorsal column sections in the present squirrel monkeys were at spinal cord C4-C6 level. This type of lesion interrupts the low threshold mechanoreceptor inputs from the forelimb and lower body to the cuneate nucleus. Consequently, the ventral posterior nucleus of thalamus and the somatosensory cortex, which are the main relay targets of the cuneate nucleus, are indirectly deprived of inputs. We previously reported the effects of this lesion on the hand representation in somatosensory cortex. Using multi-unit recordings and optical imaging, we showed that extensive reactivations occurred in the deafferented hand representations in cortical areas 3b and 1, even when less than 1% of labeled dorsal column terminations in the cuneate nucleus remained [17, 18]. Our results support previous findings that complete dorsal column lesions immediately deactivate area 3b [19, 21]. Deactivation can also be expected in higher order somatosensory areas, such as areas 1, 2, secondary somatosensory area (S2) and somatosensory parietal ventral (PV) area, since their activity is

dependent on area 3b [22–24]. It follows that primary motor cortex, which receives somatosensory information from areas 3a, 1, 2, S2 and PV [25–30], is deprived of sensory feedback pertinent to the deafferented body parts. Consequences on motor behaviors, such as reaching and grasping in the present study, are therefore an indirect, but expected consequence of dorsal column section.

4.2. The integrity of the dorsal column pathway is important for skilled hand use

Motor impairments from dorsal column section have been reported in other laboratory species. For example, dorsal column section in cats impairs reach-to-grasp, serial order acts, coordinated walking, turning on a narrow beam, and jumping to a moving target [31–33]. This work suggests that information relayed by the dorsal columns is needed for selecting appropriate motor programs. Dorsal column sections at the C2 level in rats result in a transient impairment in success scores on a reaching-to-grasp task [15]. However, rotatory limb movements (aiming, pronation, supination) are chronically impaired. The study concluded that “sensory input conveyed by the dorsal columns is important for both proximal and distal limb movements used for skilled reach; in the absence of the dorsal columns, other sensorimotor pathways support endpoint success in reaching”. For reviews of other related studies, see [34–37].

The outcome of dorsal column sections in primates appears to be more varied. For example, fine motor skills in humans are also compromised after dorsal column section [38, 39]. In macaque monkeys, dorsal column section severely impairs manual dexterity, contact placing, and hopping reflexes [2, 3, 6, 40, 41]. The results of our study are consistent with those observations. In contrast, other studies reported that dorsal column section alone did not affect motor behavior unless the dorsal lateral funiculus was also severed [6, 7, 9, 10], or somatosensory cortex was concurrently damaged [11].

Several factors could have contributed to the seemingly inconsistent outcomes. (1) Extent and location of the lesion within the spinal cord. (2) Amount of spared fibers that terminate in the cuneate nucleus. (3) Sensitivity of behavioral measures. The design of our study accounted for these potential confounds. Thus, we attempted to section the dorsal columns at the same cervical level across monkeys. We reconstructed the extent and location of the lesion in postmortem tissue. We also traced sensory afferents from their origins in the digit tips in order to quantify the amount of terminals spared in the cuneate nucleus [17]. Last, we systematically tested the ability to reach and grasp after lesion. In addition to end point measures such as success scores, we traced movement trajectories to index movement kinematics.

4.3. Behavioral recovery is correlated with the amount of spared axon terminals in the cuneate nucleus

Our results show that the degree of impairment and capacity to recover reaching and grasping abilities after dorsal column section is directly correlated with the amount of fibers that the lesion spares in the cuneate nucleus. The ratio of fibers spared on the lesion side compared to the intact side was 0% in SM-R, 0.9% in SM-O, 2.2% in SM-C, and 23.4% in SM-D. The responsiveness of the deprived portion of the hand representation in area 3b, indexed as the percentage of responsive sites was 90% in SM-R, 45.5% in SM-O, 56.9% in SM-C, and 75.8% in SM-D. The responsiveness in SM-R is somewhat surprising, nevertheless, the majority of responses were weak and topography was highly abnormal. As expected, SM-R was the most impaired case in the reach-to-grasp task, SM-O was moderately impaired, SM-C was less impaired, and SM-D was least impaired. The present findings suggest that differences in the lesion sizes and levels are correlated with the amount

of spared axons in the cuneate nuclei and behavioral recovery, and with the extent of cortical reorganization.

Our present results show a non-linear relationship between axon sparing and behavioral outcome. It seems that the mild behavioral impairment and favorable recovery is similar in the cases with 2.2% and 23.4% of axons spared. Although this may suggest that 2.2% of sensory afferents or more are sufficient to retain the skills for reaching and grasping, several factors preclude us from defining such a firm threshold. First, the two-stage DC lesion in monkey SM-C could have facilitated the favorable behavioral outcome. Although the first lesion did not produce detectable impairments on the reach-to-grasp task, we cannot rule out the possibility that the monkey still acquired compensatory strategies, which were implemented immediately after the second lesion. In this case, more severe impairments could be expected had both lesions been induced in a single procedure. Second, a more challenging reach-to-grasp task could have better differentiated the abilities of each case in the present study. Third, the use of BHRP to trace spared axons in monkey SM-R complicates direct comparison with the other three cases in which spared axons were traced with CTB. Nevertheless, bilateral tracer injections in each case in the present study make it possible to compare the density of axon terminals in the deafferented and intact sides the cuneate nucleus within each subject.

4.4. Possible mechanisms of motor deficits after loss of sensory inputs

Sensory inputs play an important role in guiding movement accuracy. Monkeys are reluctant to use an affected forelimb after its sensory inputs are damaged [13, 14, 40], See [42] for review). Reluctance to use the affected limb materializes irrespective of whether sensory inputs are interrupted at the dorsal roots or in the dorsal columns. Reluctance to use a hand after focal damage to area 3b in squirrel monkeys further supports the possibility that sensory loss inhibits the use of a forelimb even when its motor outputs are seemingly intact [43]. When the monkeys with focal lesions of area 3b started to reuse their affected hand, their impairments on a reach-to-grasp task shared the characteristics reported here after dorsal column sections. Similar results have been reported in macaque monkeys after lesions in the forelimb representations of somatosensory cortex [44–48].

Several factors could contribute to motor deficits and recovery that ensue after dorsal column section:

1. *Loss of sensory input to motor areas.* M1 and premotor areas receive most of their sensory inputs from areas 3a, 1, 2, S2 and PV [22, 26, 29, 49–51]. Dense interconnections of those sensory areas with area 3b [25–27, 29, 30, 52, 53] suggest that the sensory inputs of M1 are indirectly compromised from dorsal column section. Indeed, neuronal responses in M1 to sensory stimulation are compromised after dorsal column section. Partial recovery of response properties in M1 to sensory stimulation parallels recovery of hand dexterity [11]. Dorsal column section also compromises the topographic organization of movements in M1 as determined with microstimulation [54, 55]. Given that the motor outputs are preserved, distortions in the motor map may be related to somatotopic reorganization in area 3b and other somatosensory areas.
2. *Sensory inputs to M1 via the motor thalamus.* M1 and premotor cortex are sparsely connected with ventral posterior nucleus of thalamus (VPL). Despite their relative weakness, those connections reflect the accessibility of cortical motor area to dorsal column and spinothalamic pathways. Moreover, neurons in the motor thalamus (VLp), the main source of thalamic inputs to M1, are responsive to short-latency stimulation of forelimb nerve [56, 57]. Other studies have also confirmed the short-latency relay of somatosensory inputs from thalamus to motor cortex [56–58]. This

short-latency input to M1 is abolished by dorsal column section [59, 60]. Stepniewska et al [61] further confirmed that some VLp neurons that project to M1 also receive spinothalamic input (for retrospect review, see [62]).

3. *The involvement of the intersegmental propriospinal network.* Wall's [34] review of dorsal column function stressed that the dorsal columns contain not only branches of primary afferents but also some ascending and descending fibers of intrinsic cord origin. Dorsal column section, especially if the lesion includes lamina IV–VI of the dorsal horn, may interrupt some of the intersegmental propriospinal network. Spinal interneurons contribute to the control of hand grasping in primates by combining and coordinating multiple finger muscles [63]. To evaluate the functions of spinal interneurons, double-infection with a viral vector was used to reversibly interrupt signaling between M1 and spinal cord motor neurons via the propriospinal neurons [64]. The treatment impaired reaching and grasping for 2–3 days before the behavior gradually recovered. This work confirms the importance of the propriospinal network, which could have been damaged in our study, for reaching and grasping.

5. CONCLUSIONS

Our study shows that dorsal column section impairs reaching and grasping in squirrel monkeys. The severity of the impairment and the capacity for recovery are correlated with the amount of axon terminals spared in the cuneate nucleus. The latter is closely with the capacity of restoring neuronal responses in somatosensory cortex. Most notable is that the sparing of a small fraction of sensory inputs from the hand may have been sufficient to facilitate the development of compensatory strategies to achieve the same end point on the reach-to-grasp task.

Acknowledgments

We thank Laura Trice for excellent technical support; Thao Bui for behavioral data analysis; Dr. Mary Baldwin for illustration 12; Dr. Jamie L. Reed for comments on the manuscript; and Dr. Limin Chen for providing three monkeys. This research was supported by NIH grants NS057399 and NS067017 to HXQ; NIH grant NS16446, Christopher and Dana Reeve Foundation to JHK; NIH grant K99 NS079471-01 and a postdoctoral fellowship from the Canadian Institutes of Health Research to OAG.

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HIGHLIGHT

- Hand use in a grasp task was evaluated pre- and post- dorsal column lesion in monkeys.
- Damage to the sensory afferents at the cervical spinal cord produced impairment.
- Spontaneous recovery was observed over weeks of testing.
- The degree of behavioral recovery depended on the spared axons in the brainstem.

Fig. 1.

Photomicrographs showing the terminations of peripheral afferents in the dorsal horn of the spinal cord and cuneate nucleus of the brainstem. (A) Dark field photomicrograph from a horizontally cut spinal cord section reacted with 3,3',5,5'-Tetramethylbenzidine (TMB) to reveal cholera toxin subunit B (CTB) conjugate with horseradish peroxidase (BHRP) label, and the location of the dorsal column lesion in monkey SM-R. BHRP (5 μ l each) was subcutaneously injected into distal phalanges of digits 1 to 5 on the left hand (same side to the lesion). The same tracer was also injected into identical sites of digits 1, 3 and 5 on the right hand (non-lesion side, 5 μ l each) that served as control. (B–D) Photomicrographs of horizontally cut spinal cord sections showing the dorsal column lesions and the labeled foci of axon terminals in the cuneate nuclei after CTB subcutaneously injected into digits 1, 3, and 5 of both hands in monkeys SM-O (B), SM-C (C) and SM-D (D). Cervical segments C4–C7 are indicated, and foci of label from injections are marked with arrows. Dashed lines indicate the midline of the spinal cord. Rostral is to the top, caudal is to the bottom. (E) Dark field photomicrographs of coronally cut TMB reacted sections through dorsal column nuclei of brainstem showing labeled axons and terminals in monkey SM-R. (F–H) Photomicrographs of coronally cut CTB immunoreacted sections in monkeys SM-O, SM-C, SM-D, respectively. The cuneate nuclei are outlined with dashed lines, and foci of label are marked with arrows. The numbers on the right indicate the section numbers in a series. (I–L) Bar graphs showing the areal sizes of BHRP (I) or CTB (J–L) labeled axon arbor foci in the cuneate nuclei of the brainstem of four monkeys. The numbers in the x-axis are the distance (in mm) measured from the beginning of the obex. The negative values indicate the measured distances were caudal to the obex. The value in y-axis is the areal size of the combined foci of label for each coronal section through the cuneate nucleus of the

brainstem. The total volumes for SM-R are less than for other cases as the tracer BHRP and the transport time (2 days) were different than the other cases (CTB + 6 days). While less amount of label was observed on the intact side, none was found on the lesion side suggesting that the dorsal column lesion was complete for digit afferents. Abbreviations: D1 to D5, digits 1 to digit 5. Asterisks in the spinal cord mark a needle hole placed to aid reconstruction; asterisks in the brainstems mark a needle hole placed to identify the intact side of the brainstem. Scale bars, A–D, and F–H = 1 mm; E = 0.25 mm.

Fig. 2.

Pre- and post-operational success score (mean, $\pm$ SD) obtained from 4 testing wells of increasing depth/difficulties, in which the well 1 is the easiest, and well 4 is the most difficult. (A–D) Success scores of 4 monkeys.

Fig. 3.

Pre- and post-operative mean number of flexes per success (mean, $\pm$ SD) from 4 testing wells of increasing depth/difficulties. (A–D) Data from 4 monkeys. Squirrel monkey SM-R was most impaired.

Fig. 4.

Post-lesion changes in the average number of flexes per success (mean, $\pm$ SD) in reaching and grasping task in squirrel monkey SM-R. Each data point is an average number of flexes per successful trial on each testing day. The figure shows that after the dorsal column lesion, the monkey made more flexes even in the easiest well (well 1) to retrieve pellets. The arrow indicates the time of the dorsal column section.

Fig. 5. Post-operational changes in the percentage of successful retrievals (mean, $\pm$ SD) in the reach and grasping task. (A–D) Success scores in percent retrieval success for summed trials of all 4 testing wells per post-op week. Pre-op final week trials were summed. The figure shows that after dorsal column section monkey SM-R had the lowest success score.

Fig. 6.

Post-operational changes in mean number of flexes (mean, $\pm$ SD) for the 4 tested monkeys (A to D). Each data point within each panel is the averaged number of flexes from the sum of all 4 wells over each testing week. Note that SM-C received 2 dorsal column sections.

Fig. 7. Post-operational changes in the average number of flexes per success (mean, $\pm$ SD) from well 4 testing. (A–C) Results from 3 monkeys.

Fig. 8.
The distance the monkey's hand moved through space during the reach, grasp, and retrieval sequences. (A–D) Results from 4 monkeys.

Fig. 9. Spatial distributions of the trajectories of hand movements between starting and ending points during the task for monkey SM-R. Each panel represents 5 traces superimposed on a window aperture (box). The hand movements span larger territories post-lesion than those of pre-lesion.

Fig. 10. The speed of the monkey's hand movement through space during the reach, grasp, and retrieval sequence. (A–D) Results from 4 monkeys.

Fig. 11.

Spatial distributions of the trajectories of hand movements between starting and ending points during the task in monkey SM-O. Each panel represents 5 traces superimposed on a window aperture (box). Note that the post-lesion retrieval pattern is clearly different than the pre-lesion pattern, reflected by spanning larger territories and making extra loops (pointed by arrows) during pellet retrieval.

Fig. 12.

Drawings from the captured photo-frames taken from monkey SM-O during the reach and grasp task on pre- and post-op Day 15. As shown in left and right panels, the pre-lesion monkey looks at the trainer after visually locating the food pellet, while the post-lesion monkey continues to fixate on the pellet during the entire sequence of the reach, grasp, and retrieval. The figure illustrates that after the spinal cord lesion, the monkey compensates for reduced tactile information by relying more on vision.

Fig. 13.

Spatial distributions of the trajectories of hand movements between starting and ending points during the task in monkey SM-C. Each panel represents 5 traces superimposed on a window aperture (box). Although the trajectories between pre- and post-lesion were similar after the first dorsal column lesion, the second lesion did produce extra loops (pointed by arrows) during the first 2 weeks, occasionally reappearing in a later stage of recovery (i.e., post-lesion day 37). Numbers represent days after lesion.

Fig. 14. Spatial distributions of the trajectories of hand movements between starting and ending points during the task in monkey SM-D. The lesion did not produce major changes in the trajectory of hand movement during the task.

Fig. 15.

Relationship between the severity of impairments and the amounts of spared axon terminals in cuneate nuclei of brainstem of 4 testing monkeys. Note that the deficit ranking were based on success scores, number of digit flexes, and kinematic characteristics (e.g., distance and speed).

Table 1

Ranking performance on the reach-to-grasp task.

Ranking category	SM-R	SM-O	SM-C	SM-D
Days unable to perform after lesion	4	3	1	1
Mean Success change	4	3	2	1
Mean Flexes change	4	3	1	2
Mean Distance change	4	3	2	1
Mean Speed change	2	3	4	1
Total	18	15	10	6

The four animals were ranked for their relative performance on each category. "1" was best performance and "4" was most impaired. The "Mean change" in each category is a subtraction of the mean measurements before and after DC lesion.