Chondroitinase ABC promotes selective reactivation of somatosensory cortex in squirrel monkeys after a cervical dorsal column lesion

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After large but incomplete lesions of ascending dorsal column afferents in the cervical spinal cord, the hand representation in the contralateral primary somatosensory cortex (area 3b) of monkeys is largely or completely unresponsive to touch on the hand. However, after weeks of spontaneous recovery, considerable reactivation of the hand territory in area 3b can occur. Because the reactivation process likely depends on the sprouting of remaining axons from the hand in the cuneate nucleus of the lower brainstem, we sought to influence cortical reactivation by treating the cuneate nucleus with an enzyme, chondroitinase ABC, that digests perineuronal nets, promoting axon sprouting. Dorsal column lesions were placed at a spinal cord level (C5/C6) that allowed a portion of ascending afferents from digit 1 to survive in squirrel monkeys. After 11–12 wk of recovery, the contralateral forelimb cortex was reactivated by stimulating digit 1 more extensively in treated monkeys than in control monkeys. The results are consistent with the proposal that the treatment enhances the sprouting of digit 1 afferents in the cuneate nucleus and that this sprouting allowed these preserved inputs to activate cortex more effectively.

plasticity | primates

Immediately after a major loss of sensory inputs from an arm or other part of the body in primates and other mammals, most or all of the corresponding part of the somatotopic representation in the primary somatosensory cortex no longer responds to touch (1–3). However, preserved inputs may activate some of the deprived cortex, and over weeks of recovery more and more of the deprived cortex responds to remaining inputs. When somatosensory inputs from the hand have been largely removed in monkeys by cutting ascending branches of cutaneous afferents in the dorsal column pathways of the spinal cord (2, 4, 5) or by selectively cutting the dorsal roots of peripheral nerves subserving a part of the hand (3), most of the territory of the representation of the hand in the contralateral primary somatosensory cortex (area 3b) initially fails to respond to touch on the hand. In food-retrieval tasks, hand use is impaired, and the monkeys look for food pellets already in their hand as although unsure whether they have grasped the food object (5, 6). However, hand use rapidly recovers over days to weeks as the remaining inputs from the hand reactivate more and more of the cortical territory for the hand. Thus, the reactivation of cortex by preserved afferents from the hand appears to be important in the behavioral recovery.

The mechanisms of the reactivation are not understood completely, but at least some of the reactivation occurs at the first relay of information from the preserved dorsal column afferents in the cuneate nucleus of the lower brainstem and upper spinal cord (7, 8). It appears that preserved axon terminals of primary afferents, and possibly second-order neurons in the spinal cord (5), sprout in the cuneate nucleus to activate neurons more effectively (9, 10). Similar amplifications of the activating potential of the remaining afferents may occur in the ventroposterior nucleus of the contralateral somatosensory thalamus and in somatosensory cortex (11–13). Because the spontaneous reactivation seems to be important in functional recoveries, it may be possible to enhance and improve the process.

In the present study we sought to promote the sprouting and growth of preserved dorsal column afferents in the cuneate nucleus after extensive lesions of the dorsal column afferents in squirrel monkeys. By placing the lesions at an appropriate level of the cervical spinal cord (C5/C6), some of the afferents from digit 1 (the thumb, D1) were consistently spared, whereas those from the rest of the hand were largely or completely cut. We reasoned that any treatment that promoted sprouting of these preserved afferents in the cuneate nucleus would result in more of the hand representation in the contralateral somatosensory cortex being reactivated by afferents from D1. The promoting agent was the bacterial enzyme, chondroitinase ABC (chABC), which has been used to digest extracellular chondroitin sulfate proteoglycans (CSPGs), components of perineuronal nets (14–16). These perineuronal nets form around neuron cell bodies and dendrites to inhibit the formation of new connections as the central nervous system matures (17). After denervating spinal cord injuries in rats, perineuronal nets around denervated target neurons became enriched with newly expressed CSPGs (18). Treatment with chABC after spinal cord injury selectively increases the sprouting of afferent axons to the cuneate nucleus and the reactivation of cuneate neurons, leading to improved forelimb function (14, 19).

Monkeys have a large representation of the forelimb in area 3b (S1) of somatosensory cortex, and the somatotopy can be evaluated in more detail with microelectrode recordings than the smaller and less accessible subcortical representations in the ventroposterior nucleus (20) or cuneate nucleus (21). The somatosensory forelimb cortical representation of squirrel monkeys is exposed on the cortical surface, just lateral to the short, shallow central sulcus, and the representation has the added advantage of being in 2D (22). We expected an expanded representation of the preserved afferents of D1 to emerge postoperatively in these squirrel monkeys, because a previous study in rats demonstrated that the application of chABC to the cuneate nucleus after dorsal column lesion promoted the reactivation of that nucleus (14). The significant results are from the forelimb region of the primary somatosensory cortex (area 3b), but limited recordings from the forelimb regions of rostrally adjoining cortex (area 3a) and caudally adjoining cortex (areas 1/2) demonstrate that reactivations occurred in these regions as well.

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Results

We found that 11–12 wk after the dorsal column lesions the preserved dorsal column afferents from D1 activated more of the primary somatosensory cortex in the chABC-treated group than in the penicillinase (P-ase)-treated control group. This large difference is apparent in the maps of cortical sites activated by touch on D1 from six representative monkeys, three treated and three untreated, in Fig. 1. In normal monkeys, digits 1–5 are represented in a lateral-to-medial sequence of oval territories along the rostral border of the primary somatosensory cortex (area 3b) (Fig. 1*B*, *Inset*). Parts of the palm are represented just caudal to the digits. The forearm representation is medial to those of the digits and palm, and the face is represented just lateral to that of the hand. Parallel representations of the hand and face exist in cortex caudal to area 3b (area 1/2) and rostral to area 3b (3a/M1). Whereas areas 3b and 1 respond most robustly to tactile stimulation, areas 3a and 2 usually are most responsive to proprioceptive inputs. Recordings from areas 3a and 1/2 were limited, and the results were not included in the analyses.

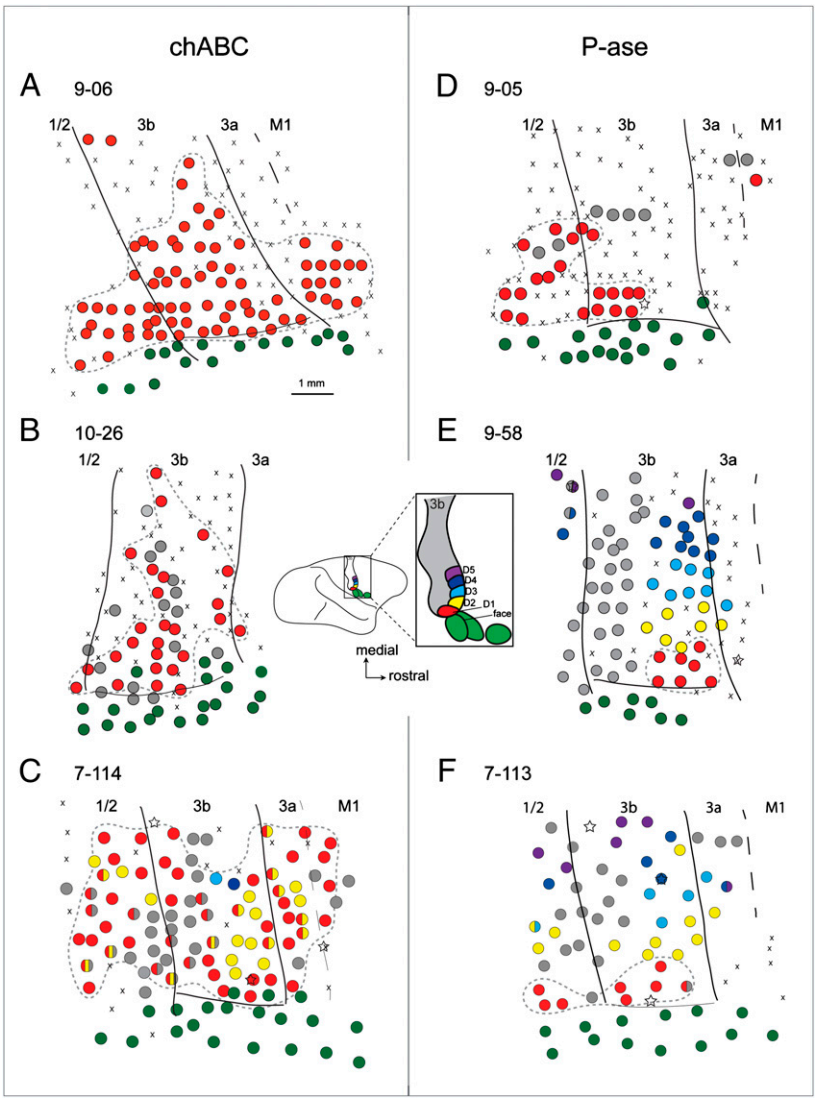

Fig. 1. The organization of the forelimb region of the primary somatosensory cortex (area 3b) of treated (chABC) and control (P-ase) monkeys 11–12 wk after a unilateral lesion of the contralateral dorsal columns of the cervical spinal cord. The lesion was placed at the C5-C6 level to preserve some of the ascending afferents from D1 while removing most or all ascending afferents from digits 2–5 to the cuneate nucleus of the lower brainstem. At the time of the lesion, the squirrel monkey received either a brainstem injection of chABC or a control injection of P-ase. The injection was made just lateral to the cuneate nucleus to avoid damage but to digest the perineuronal net and promote axon sprouting. In each illustrated case, a surface view of somatosensory cortex indicates the locations of microelectrode penetrations where neurons responded to touch on the face (green dots), D1 (red dots), digits 2–5 (colors shown in *Inset*), or other parts of the palm and forearm (gray dots). Penetration sites where neurons failed to respond to touch are marked with Xs. The gray dotted line indicates cortical territory where D1 receptive fields (in red) were heavily represented. Note that the treated cases (*A–C*) had more sites with neurons responsive to touch on D1 than did the cases with a control injection (*D–F*). *Inset* shows the location of primary somatosensory cortex on a lateral view of a squirrel monkey brain. The view of somatosensory cortex is enlarged on the right, with the normal locations of the territories activated by touch on digits 1–5 and the face indicated by colors. Cortex caudal to the digit territories is activated from the palm; cortex medial to the digits is activated from the forearm. In *A–F*, cortex caudal to area 3b (S1) is area 1 followed by area 2 (1/2); cortex rostral to area 3b is area 3a and primary motor cortex (M1). Stars indicate locations where an electrolytic microlesion was placed for reference. The thin line across area 3b marks the location of a myelin-light septum that marks the face/hand boundary in normal monkeys and was identified in these monkeys histologically.

In each of the lesioned monkeys, neurons in the face representations in area 3b and rostrally and caudally adjoining somatosensory cortex were responsive to touch on the face. In Fig. 1, green dots mark the locations of microelectrode penetrations where neurons were recorded that were highly responsive to touch on the face. This result was as expected, because afferents from the face enter the brainstem well above the dorsal column lesions and thus were unaffected. In the control P-ase–treated monkeys, cortex just medial to the face representation responded to light touch on D1 (red dots). This result was expected, because the dorsal column lesions were at a level that would spare some D1 afferents as they entered the spinal cord above the lesions. The cortical territories activated by D1 in the control P-ase–treated monkeys were restricted to about the size of a normal D1 representation, although many D1 afferents were cut. In contrast to the control monkeys, touch on D1 activated larger portions of the forelimb representation region in the chABC-treated monkeys (Fig. 1 *A*–*C*). Not only were lateral regions of the hand territory activated by D1, as in normal monkeys, but neurons in more medial recording sites extending across most of the forearm territory were activated by D1. This activation was most apparent in the primary somatosensory cortex (3b), which was most fully explored, but also was observed in somatosensory areas rostral (3a) and caudal (1/2) to the primary somatosensory cortex (Fig. 1 *A* and *C*). Results from two other treated and two other control monkeys were highly similar to those in Fig. 1. These treated monkeys had more sites responsive to D1 than did untreated animals, and their D1 territories were more scattered medially across forelimb representation territory.

The marked difference in activation patterns was quantified and compared for all five control and all five treated monkeys in Fig. 2. A significantly greater proportion of the forelimb cortical territory was responsive to cutaneous stimulation of D1 in the chABC-treated group than in the P-ase control group (one-way ANOVA, $P < 0.05$).

As previously noted, the C5/C6 lesions could have variably spared some of the afferents from digit 2 (D2). In the control P-ase–treated monkeys, D2 activation sites, when they occurred (Fig. 1 *E* and *F*), were mostly next to D1 activation sites, as in normal monkeys. However, the sites activated by D2 in a chABC-treated monkey (Fig. 1*C*) were widespread and mixed with D1 sites, and some sites responded to both D1 and D2. Thus, the treatment likely also affected D2 afferents when they were partially preserved.

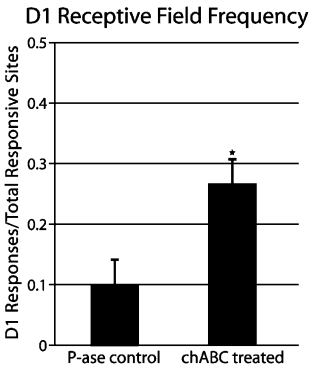

Fig. 2. The proportion of recording sites responsive to touch on D1 to the total number of responsive sites in the forelimb area of 3b for the five control (P-ase) and five treated (chABC) cases. A significantly greater proportion of cortical territory was responsive to cutaneous stimulation of D1 in the chABC-treated group. $n = 10$. $P < 0.05$.

In addition to recording sites where neurons were activated by touch on D1 and D2, there were sites within the territory of the hand representation that failed to respond to tactile stimulation or responded to touch on the palm or digits 3–5 in both treated (chABC) and untreated (P-ase) cases (Fig. 1). The existence of both unresponsive sites and sites responsive to various locations on the hand have been reported in previous studies of the effects of spontaneous reactivation of hand cortex after dorsal column lesions in monkeys (2, 4, 5). Even with nearly complete lesions of the dorsal columns at a high cervical level, considerable spontaneous reactivation of hand cortex by hand inputs, as well as a variable number of unresponsive sites, may occur. Some of the reactivation may result from inadvertent preservation of some of the ascending branches of peripheral nerve afferents in the dorsal columns, but inputs to the cuneate nucleus of second-order neurons in the dorsal horn of the spinal cord could be another source of this activation (5). Such second-order inputs to the cuneate nucleus also could be potentiated by the chABC treatment, but these inputs would not have been labeled by our cholera toxin B (CTB) injections. When the proportions of sites activated in area 3b by digits 2, 3, 4, 5, or the palm were compared separately in chABC-treated and control (P-ase–treated) groups, there were no significant differences in activation. Because the chABC treatment mainly affected the preserved D1 afferents with some possible effect on preserved D2 afferents, it seems likely that the chABC treatment preferentially promoted sprouting of the preserved branches of the peripheral nerve afferents into deprived portions of the cuneate nucleus over any growth of inputs from spinal cord neurons. Overall, the recordings revealed that an average of 62 ± 6.4% of forelimb sites recorded from area 3b were responsive in the treated monkeys, whereas 53 ± 9.9% of sites were responsive in the control monkeys. Because this difference was not significant in our sample size, it is not clear that an overall increase in cortical activation followed treatment.

Differences in the sizes of the spinal cord lesions do not account for the more pronounced reactivation of cortex by inputs from D1 in the treatment group. All the lesions of the dorsal column axon tracts were extensive and included all or almost all of the ascending branches of cutaneous afferents from the hand in the cuneate fasciculus (Fig. 3). The lesions were reconstructed from a series of aligned spinal cord sections cut in the horizontal plane (Fig. 1 *A*–*D*). The extent of each lesion then was overlaid onto a representative cross-section of the cervical spinal cord. For both the chABC-treated cases and the control (P-ase–treated) cases, the lesions included most or all of the cuneate fasciculus and variably preserved some of the gracile fasciculus for afferents from the lower body. The gray matter of the spinal cord also was variably involved, as were the dorsal columns bilaterally in one case (case 10–25). The locations of afferent terminations labeled by CTB in the cuneate nucleus indicated that some afferents from D1 and possibly a few from D2 were preserved as they entered the spinal cord above the levels of the spinal cord lesions, but there was not clear evidence for sprouting. Overall, the extents of the lesions of the cuneate fasciculus in the chABC-treated and control monkeys were very comparable. In addition, the experimenters collecting the recording data were blind to the treatment or nontreatment of the individual monkeys. Thus, an experimenter bias in data collection did not account for differences in results from the two groups.

Discussion

The results indicate that the application of the digestive bacterial enzyme chABC to the cuneate nucleus in primates can promote the effectiveness of surviving D1 afferents after section of most or all of the dorsal column cutaneous afferents for other digits. The enzyme is known to digest components of the perineuronal

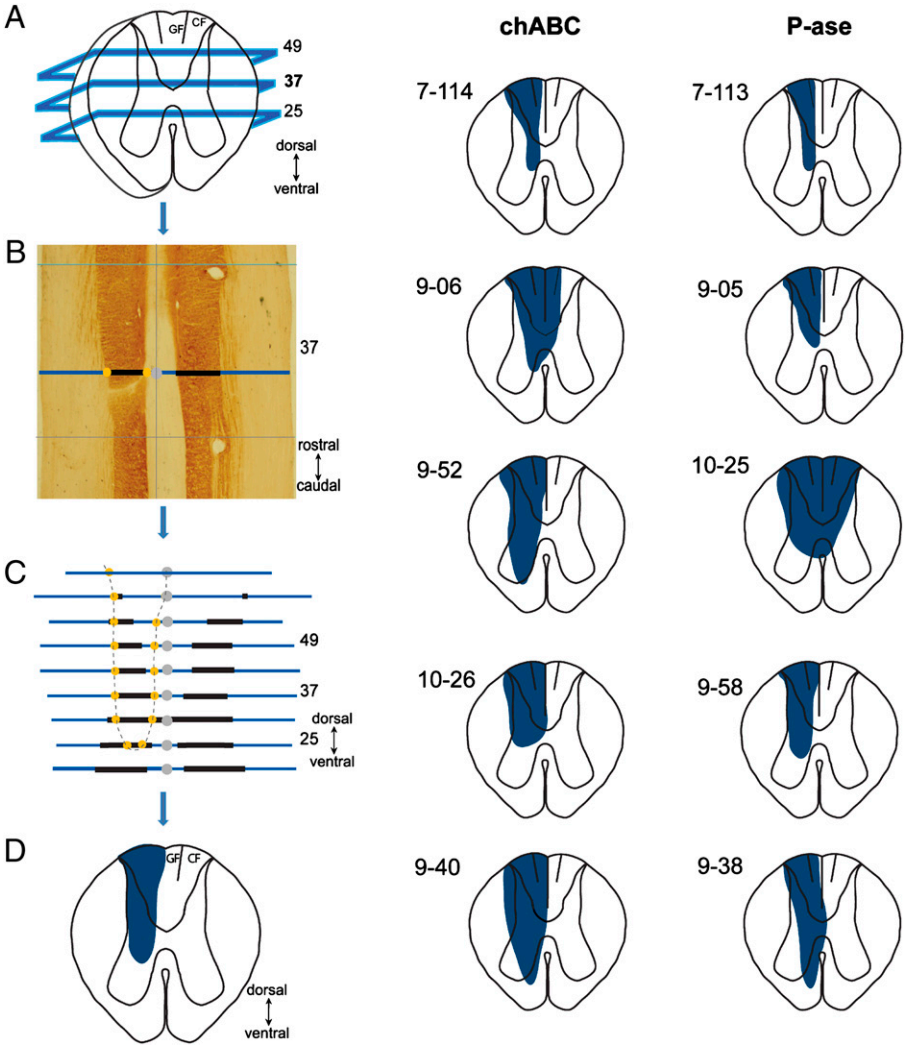

Fig. 3. The extent of the spinal cord lesions in the five treated monkeys (chABC) and the five control monkeys (P-ase). (*A*) The lesions were reconstructed from a series of horizontal sections through the lesion site in the cervical spinal cord. Section numbers and the locations of the cuneate fasciculus (CF) and the gracile fasciculus (GF) are indicated. (*B*) A photomicrograph of section 37 stained for cytochrome oxidase. The white matter, gray matter (black), midline (gray), and lesion borders (yellow) were outlined for each section, and these lines were stacked as in *C* to produce *D*. The pinholes on the right in *B* were made in the intact spinal cord and later were used for realignment of each section. In both groups, the lesions of the cuneate fasciculus were complete or nearly complete.

nets that inhibit axon growth and the formation of new connections (14–19, 23–25) and has been used previously to enhance the reactivation of the cuneate nucleus in rats after dorsal column transections (14). Because of the small size of the cuneate nucleus, we did not assess reactivation of the cuneate nucleus directly but instead evaluated the large and accessible primary somatosensory cortex to which dorsal column afferents are relayed. By intentionally sparing dorsal column afferents from D1, we were able to demonstrate that, months after the dorsal column lesion and cuneate nucleus treatment, forelimb cortical territory in area 3b of somatosensory cortex was activated by touch on D1 more extensively in chABC-treated than in control monkeys. In our present cases, we injected a tracer into D1 and other digits before the cortical mapping procedure (*Materials and Methods*), but our results were not consistent enough to demonstrate whether the sprouting of D1 afferents in the cuneate nucleus occurred. However, the treatment did promote cortical reactivations via the spared D1 afferents, and the treated location was the cuneate nucleus. We therefore propose that enough sprouting of D1 axon terminals did occur in the cuneate nucleus to promote a greater relay of D1 activation. Additional sprouting of axons responsive to D1 may have occurred at thalamic and cortical levels. Thus, our maps of reactivated somatosensory cortex possibly reflect the summation of plastic changes at three levels of processing.

We do not suggest that the selective reactivation of large amounts of forelimb cortex by D1 was particularly useful in guiding behavior. Instead, we selectively preserved D1 afferents to determine if treatment with chABC would promote cortical reactivation by a small population of preserved peripheral nerve afferents. By placing spinal cord lesions at an appropriate level, we consistently preserved a portion of the D1 cutaneous afferents projecting to the cuneate nucleus. The results clearly demonstrate that chABC treatment can selectively enhance the reactivation of cortex by spared peripheral nerve inputs after spinal cord injury in primates. The potential for such chABC treatment to improve functional recoveries in humans after accidental spinal cord injuries has not been explored. However, the effectiveness of chABC in promoting axonal sprouting has been shown for various parts of the nervous system (17). Thus, it

remains possible that chABC treatments in the somatosensory thalamus and cortex also will be useful in promoting the selective reactivation of cortex. Additionally, our monkeys received a single chABC injection at the time of the dorsal column lesion. It is reasonable to suppose that a series of treatments or a slow-release treatment (24, 25) could enhance axon sprouting and cortical reactivation more effectively.

Finally, there is the considerable reactivation of hand cortex by touch on digits 2–5 in both the treated and untreated monkeys, even when the lesions of afferents from these digits apparently were complete or nearly complete. Similar results have been reported in other studies of monkeys after dorsal column lesions (2, 4, 5). The source of this activation is not known: It could result from a few undetected surviving dorsal column axons from those digits, but it also could be from axons of spinal cord neurons that also terminate in the cuneate nucleus (reviewed in ref. 5). Cutaneous afferents from the digits and other parts of the hand bifurcate after they enter the spinal cord, with one branch ascending in the dorsal columns and the other terminating on neurons in the dorsal horn of the spinal cord. Thus, information from the hand is not necessarily lost after dorsal column lesions, and it may be recovered and relayed to somatosensory cortex by spontaneous mechanisms of sprouting and the formation of new connections. If so, treatments such as chABC, even at chronic time points after the sensory loss (16), may be useful in promoting recoveries based on higher-order pathways as well as preserved peripheral nerve pathways.

Materials and Methods

All procedures were approved by the Vanderbilt Animal Care and Use Committee and followed the National Institutes of Health guidelines. Ten adult male squirrel monkeys (*Saimiri sciuresis*) received a unilateral dorsal column lesion at C5/C6 level and survived postoperatively for 11–12 wk. Animals were divided into two groups: Five animals received P-ase (monkey IDs: 7–113, 9–05, 9–38, 9–58, and 10–25), and five received chABC (monkey IDs: 7–114, 9–06, 9–40, 9–52, and 10–26). Surgeries and other procedures followed those described elsewhere (5, 26).

Dorsal Column Lesion and Enzyme Delivery. Each monkey was anesthetized with a mixture of ketamine (8–10 mg/kg) and xylazine (0.4 mg/kg) and was treated to prevent brain swelling, secretions, and infection. Monkeys were intubated and held in a stereotaxic instrument. Anesthesia was maintained with 0.5–3.0% isoflurane for the duration of the surgery, and the heart rate, respiratory rate, and body temperature were monitored. A portion of the spinal cord was exposed, and the dorsal columns were cut unilaterally at the C5/C6 level. The lower brainstem was exposed, and monkeys received either chABC (treatment) or the P-ase (control). The experimenters were blind to the treatment, which was revealed only after the data were analyzed. A nanoinjector was used to inject 1.4 μL (46 nL every 10 s for 5 min) of either 50 U/mL P-ase (Sigma) or 50 U/mL protease-free chABC (Seikagaku America) just lateral to the cuneate nucleus at the junction of the cervical spinal cord and the lower brainstem, where most of the inputs from the hand terminate. Injections were made at depths of 0.7 mm and 0.3 mm. The openings were closed, and the squirrel monkeys were monitored carefully while recovering from anesthesia. Buprenorphine (0.005–0.01 mg/kg) (Reckitt & Colman Pharmaceuticals) was administered i.m/s.c. twice daily for 3 d postoperatively.

CTB Injections. Eleven to twelve weeks following the dorsal column lesions and 4–7 d before microelectrode mapping, each monkey was anesthetized with ketamine, as before, and small injections (5–10 μL) of the anterograde tracer CTB 1% (wt/vol) (Sigma) were placed s.c. into the distal digit pads of some digits of the left and right hands. CTB immunoreactivity within the cuneate nucleus was used later to demonstrate that the dorsal column lesions greatly or completely sectioned axon terminals from digits 2–5 while leaving intact many from D1. However, the labeling was not consistent enough to demonstrate more sprouting of preserved terminals in the chABC-treated than in the P-ase–treated cases.

Electrophysiological Recording. To assess the proportion of cortical area 3b activated by each part of the forelimb, microelectrode recordings were made to reveal whether a recording site was responsive to tactile stimulation of D1 or another forelimb region. The microelectrode recordings were made with the experimenters blind as to whether the monkey had been treated with chABC or was a control. Each monkey was anesthetized and prepared for recording as for spinal cord surgery. Anesthesia was maintained with ketamine (i.v.) via an infusion pump at 0.25–1.53 mL/h for the duration of the experiment, with supplemental doses of xylazine every 2–4 h. Heart rate, respiratory rate, and temperature were monitored throughout.

A craniotomy contralateral to the spinal cord lesion exposed the region of the hand representation in area 3b of the somatosensory cortex, and the brain surface was coated with silicone to prevent drying of the cortex. The placements of the electrode penetrations were marked on a high-resolution picture of the brain. A low-impedance tungsten microelectrode (1 mΩ at 1 kHz) (Microprobe) was advanced perpendicular to the brain surface using a step microdrive, and multiple recordings made within a 0.5 mm × 0.5 mm grid across area 3b. Adjacent rows/columns points then were interspersed methodically to maximize sampling across the cortex so that the sampling density was 0.25 mm × 0.25 mm, with small deviations to avoid blood vessels. Recordings were made at several depths in each electrode penetration with the strongest response occurring in the middle cortical layers. Low-threshold tactile responses were elicited with cotton-tipped brushes and fine-tipped pliable probes. Several electrolytic lesions (10 μA) were made later at strategic sites within the cortex to enable reconciliation of the cortical tissue with the electrode penetrations recorded. These methods have been described previously in detail (5).

Immunohistochemistry and Anatomical Reconstruction. ***Cortex.*** At the completion of the recording session, the animal was perfused transcardially with buffered 4% paraformaldehyde (PFA) (23) and then with 4% (wt/vol) PFA with 10% (wt/vol) sucrose. After perfusion, the mapped hemisphere was separated and in some instances was blocked, flattened, and cut parallel to the surface at 40-μm intervals. One series of alternating sections was processed for metabolic-indicative cytochrome oxidase to delineate architectonic boundaries, and the other series of sections was processed for myelin to visualize the myelin-dense somatosensory area 3b (26). These sections then were used to relate the recording sites and electrophysiological data to the cortical architecture. Architectonic borders of area 3b were outlined from brain sections stained for myelin using a Bausch & Lomb microprojector. Sections were aligned with each other via landmarks, including the lateral sulcus, blood vessels, and the electrolytic lesions made during mapping.

Spinal cord and brainstem. The spinal cord and brainstem were processed after perfusion, and two pins were inserted into known levels of the spinal cord above and below the lesion to serve as alignment landmarks during reconstruction of the lesion. The perilesioned spinal cord was sectioned horizontally, and the tissue rostral to this region was sectioned coronally. Alternating horizontal sections were reacted for cytochrome oxidase, enabling clear demarcation of the gray and white matter. The other sections were incubated with primary goat anti-CTB (1:4,000) (#703; List Biological Laboratories) diluted in Tris-buffered saline containing 0.25% (vol/vol) Triton X-100 (Sigma) and 2.5% (vol/vol) normal rabbit serum (Millipore) to visualize the forelimb primary afferents and terminal fields. The brainstem was separated, blocked, and left in 30% (wt/vol) sucrose overnight. Sections then were cut coronally at 40-μm intervals. One series of alternating sections was processed for cytochrome oxidase to visualize the cuneate nucleus, and another was processed for CTB-IR.

Data Analysis. After reconstruction, comparisons between the chABC and P-ase groups were made by counting the number of cortical electrode penetrations in each animal where neurons were responsive to touch on a digit or other parts of the forelimb. The electrode penetrations responsive to D1 and to each other part of the forelimb were represented successively as a fraction of the total number of forelimb responses and were analyzed with a one-way ANOVA. This approach also was used to compare the overall responsiveness of cortex between the two groups: The number of responsive points and the number of electrode penetrations were counted and the ratios analyzed. Because of the dense and systematic placement of electrode penetrations, ratios of recording sites responsive to various parts of the forelimb correspond closely to the ratios of amounts of cortex responsive to these parts.

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