Functional organization of motor cortex of adult macaque monkeys is altered by sensory loss in infancy

Hui-Xin Qi[a,1], Neeraj Jain[a,b,1], Christine E. Collins[a], David C. Lyon[c], and Jon H. Kaas[a,2]

[a]Department of Psychology, Vanderbilt University, Nashville, TN 37203; [b]National Brain Research Centre, Manesar, Haryana 122050, India; and [c]Department of Anatomy & Neurobiology, University of California, Irvine, CA 92697

Contributed by Jon H. Kaas, December 28, 2009 (sent for review December 18, 2009)

When somatosensory cortex (S1) is deprived of some of its inputs after section of ascending afferents in the dorsal columns of the spinal cord, it reorganizes to overrepresent the surviving inputs. As somatosensory cortex provides guiding sensory information to motor cortex, such sensory loss and representational reorganization could affect the development of the motor map in primary motor cortex (M1), especially if the sensory loss occurs early in development. To address this possibility, the dorsal columns of the spinal cord were sectioned between cervical levels (C3–5) 3–12 days after birth in five macaque monkeys. After 3–5 years of maturation (young adults), we determined how movements were represented in M1 contralateral to the lesion by using microelectrodes to electrically stimulate sites in M1 to evoke movements. Although the details of the motor maps in these five monkeys varied, the forelimb motor maps were abnormal. The representations of digit movements were reduced and abnormally arranged. Current levels for evoking movements from the forelimb region of M1 were in the normal range, but the lowest mean stimulation thresholds were for wrist or elbow instead of digit movements. Incomplete lesions and bilateral lesions produced fewer abnormalities. The results suggest that the development of normal motor cortex maps in M1 depends on sensory feedback from somatosensory maps.

intracortical microstimulation | motor map | primate | sensory deprivation | spinal cord injury

Sensory guidance plays an important role in movement control. When the somatosensory afferents from the forearm are removed or reduced in number by section of the dorsal roots or dorsal columns, monkeys become reluctant to use the affected forelimb, although they can be trained to do so (1–3). This reluctance to use the affected limb can largely be attributed to sensory loss. However, when the sensory loss is incomplete, the somatosensory system reorganizes over time so that cortical neurons deprived of their normal sources of activation become responsive to preserved somatosensory inputs (3–7). Most notably, a partial loss of inputs from the hand is followed by the reactivation of deprived parts of somatosensory cortex (area 3b) by preserved inputs from the hand, and even inputs from the face over longer periods of recovery. This reactivation produces a distorted sensory map in area 3b that no longer represents some parts of the hand and overrepresents others. This distorted map relays less than optimal sensory information to higher order sensory representations (8) and then to motor cortex, possibly altering the somatotopy of the motor representation in developing or even mature monkeys. Postlesion changes in the cortical motor map could reflect an altered use of the hand after the sensory loss, as motor cortex organization is shaped by experience (9).

Here we used electrical microstimulation techniques to study the organization of primary motor cortex of young adult macaque monkeys reared from infancy with a sensory loss produced by a lesion of somatosensory afferents in the dorsal columns of the spinal cord.

Results

The dorsal column lesions of the spinal cord were somewhat variable but extensive in all five monkeys. The lesions at cervical levels (C3–4 or C5) sectioned all or most ascending somatosensory afferents from the forelimb, and afferents from the lower body (3, 10–12). As expected, few neurons in contralateral somatosensory cortex (area 3b) were activated by tactile stimulation of the hand, and the somatotopy was grossly abnormal, as reported previously by Jain et al. (7, 13, 14). Microstimulation results from M1 were obtained by stimulating in long microelectrode penetrations down the cortex of the anterior bank of the central sulcus, or from M1 on the brain surface at depths of ~1.8 mm (Fig. S1). The locations of these stimulation sites, stimulation threshold, and types of movements are illustrated for the five lesioned monkeys in Figs. 1–3, S2, S3. The reconstructed spinal cord lesions and the reduced size of the lesioned dorsal columns are also shown. A total of 370 electrode penetrations were made in the five monkeys, and more than 92% of stimulation sites were responsive to intracortical microstimulation (1,847 of 2,000). Results from these monkeys can be compared with similarly illustrated and analyzed results from a normal monkey (15). Results from two of these monkeys (Fig. 1) reveal that large lesions of the contralateral dorsal columns did not disrupt the basic organization of motor cortex (other cases in *SI Text*). However, the organization of the hand representation was clearly abnormal in several ways. First, the cortical territory where digit movements could be evoked was small, and it was abnormally interrupted by sites producing wrist or proximal forelimb movements. There was no large core of digit movement sites, as commonly reported for normal macaque monkeys (16–18). In contrast, representations of wrist movements were enlarged. Second, multijoint movements or twitches of several different muscles were evoked at near threshold stimulation levels, and more muscle groups were easily recruited with slightly increased stimulus intensities. Also, there were several sites where foot and leg movements were adjacent to sites where wrist and elbow movements were evoked. In case MM-63 (Fig. 1*B*), there were sites where movements of the toes and wrist were evoked simultaneously with threshold currents of 19–24 μA. As in normal monkeys, there were sites that failed to evoke movements with our stimulating current levels, but these were largely where the electrode tip was too deep or shallow in cortex to involve layer 5 neurons. Most importantly, there were no large regions of cortex in the lesioned monkeys where stimulation failed to evoke movements.

Author contributions: H.-X.Q., N.J., and J.H.K. designed research; H.-X.Q., N.J., C.E.C., and D.C.L. performed research; H.-X.Q. and N.J. analyzed data; and H.-X.Q., C.E.C., and J.H.K. wrote the paper.

The authors declare no conflict of interest.

[1]H.-X.Q. and N.J. contributed equally to this work.

[2]To whom correspondence should be addressed. E-mail: jon.h.kaas@vanderbilt.edu.

This article contains supporting information online at www.pnas.org/cgi/content/full/0914962107/DCSupplemental.

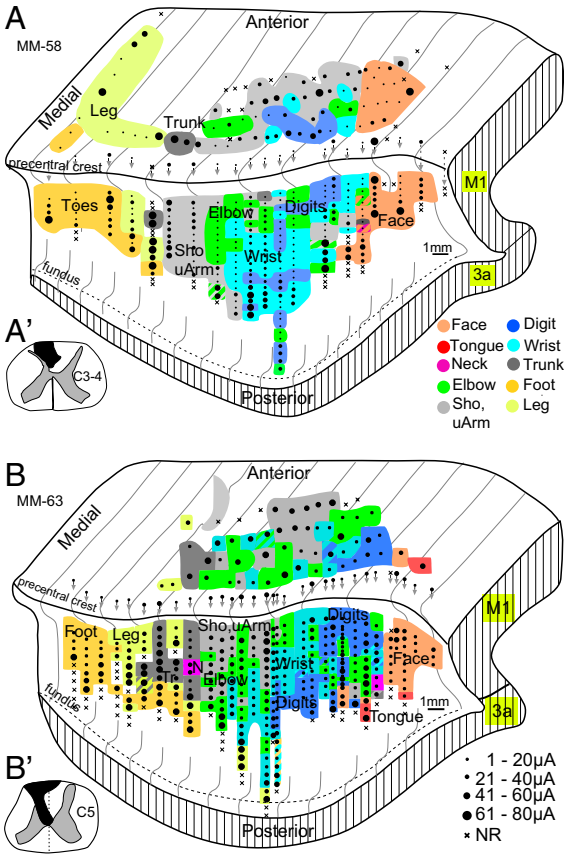

Fig. 1. Color-coded pseudo-3D view of a motor maps illustrating topographic organizations of primary motor cortex of two young adult macaque monkeys. (*A*) Macaque MM-58 received a unilateral dorsal column lesion of cervical spinal cord (C3–4) at 5 days of age. In the drawing, the central sulcus is opened to expose the face of the anterior bank of the central sulcus. The crest is to the top and the fundus is to the bottom. All of the initial mapping sites started at a depth of 1.8 mm in either the precentral gyrus or the anterior bank of the central sulcus. For the deep penetrations (indicated by arrows nearby), the initial mapping sites are projected to the dorsal surface, and continue at 500-μm intervals until no response was found. This motor output map includes the representation from face to toes in lateral to medial progression. Microstimulation sites are marked by dots. Size of dot indicates current threshold, with bigger dots indicating higher threshold intensity. Maximum current used was 80 μA. Letter "X" indicates that no evoked responses were found at currents up to 80 μA. 3a, Area 3a; M1, primary motor cortex; Sho, shoulder; uArm, upper arm. (*A′*) Reconstructed transverse view of spinal cord at cervical level (C3–4), indicating the extent of dorsal column lesion (black). (*B*) Macaque MM-63 received a dorsal column lesion at spinal cord cervical level (C5) at 3 days of age. 3a, Area 3a; M1, primary motor cortex; Sho, shoulder; uArm, upper arm. (*B′*) Reconstructed transverse view of spinal cord at cervical level (C34), indicating the lesion extent (black). Colored stripes indicate a combination of evoked movements.

The territories for the hand representation in M1 of the five lesioned monkeys and one normal monkey are shown in Fig. 2. Stimulation sites projected to the surface of the anterior bank of the central sulcus are marked with dots that vary in size to indicate stimulation thresholds. The organization portrayed in the normal monkey (Fig. 2*A*) is typical of that reported previously for macaque monkeys (16–18). In this normal monkey, digit movements were evoked from 54% of the distal forelimb territory (Fig. S4). Digit 1 movements were evoked from sites lateral to those for digit 5, and digit 2 sites were in between.

The details of the hand representation in M1 of the lesioned monkeys varied with each spinal cord lesion. Case MM-58 and MM-63 had large, unilateral lesions that included nearly all of the cuneate fasciculus for the forelimb, as well as much of the more medial gracile fasciculus for the lower body. The digit representations in these two cases were reduced to 27% of the distal forelimb zone in MM-58 and 31% in case MM-63 (Fig. S4). In addition, the representations of the digits were more fragmented and disorganized in both cases (Fig. 2 *B* and *D*) than in the normal monkey (Fig. 2*A*). In other cases, M1 was less altered. Case MM-83 had a large representation of digits (42% of the distal forelimb region, Fig. S4), but there was still considerable fragmentation of the digit representations, and sites for shoulder and arm movements were abnormally located lateral to those for the digits. In this case, the lesion of the dorsal columns included the cuneate fasciculus and gracile fasciculus of both sides of the spinal cord, so that both hands were impaired, and the monkey had no normal hand to favor during development. Thus, MM-83 likely used the hand contralateral to the studied M1 more than the monkeys 58 and 63, and this could have resulted in more normal representations of digits. In case MM-18 with an incomplete lesion (Fig. 2*C*), a large proportion of the distal forelimb cortex produced digit movements. However, the sites for specific digits were scattered and mixed with those from the face, wrist, and elbow. Finally, the organization of the forelimb region of M1 in case MM-84 with an incomplete lesion (Fig. 2*F*) was the most normal. Digit sites occupied 45% of the distal forelimb region (Fig. S4). A large continuous region contained most of the sites where D1 movements were evoked. A multidigit region adjoined the D1 region. The more normal organization of M1 in this case may reflect the preservation of dorsal column afferents from the hand. In sections of the spinal cord just above the lesion, a large group of axons in the cuneate fasciculus were preserved.

Some of the abnormalities of the hand and forelimb representations in M1 of monkeys reared with dorsal column lesions are further illustrated by showing the movements evoked from successive stimulation sites along deep electrode penetrations down the anterior bank of the central sulcus (Fig. 3). In case MM-58, stimulation sites along a penetration just lateral to the digit region evoked face movements, but wrist and arm movements were combined with face movements at sites d and e, and other sites produced wrist, elbow, and even trunk movements (Fig. 3*A*). The results from a penetration through the hand representation in case MM-63 (Fig. 3*B*) reveals further abnormalities. Most notably, foot movements were evoked from a site (o) next to a wrist movement site (n), and both wrist and foot movements were evoked from a series of five sites (p–t). In contrast, a more normal sequence of movements was evoked by stimulating sites in the hand region in case MM-84 (Fig. 3*C*). Unusual digit movements were sometimes evoked, such as a combination of extending digit 2 while flexing digits 3–5 (i), or adducting digits 2 and 5 while producing a radial deviation of digit 3 (n).

The distributions of threshold current levels for evoked movements of different body parts were also abnormal in the lesioned monkeys. In normal monkeys, the levels of current needed to evoke movements vary by body part (15). In the present study, we calculated the mean threshold currents for the evoked movements of different body parts for each case (Fig. 4). The lowest mean thresholds were generally for wrist and elbow movements, rather than digit movements, which have the lowest thresholds in normal macaque monkeys (15–17, 19). Whereas digit movements normally are evoked at the lowest current levels, current thresholds for digits were not lower than those for other body parts in the five macaque monkeys with dorsal column sections in infancy.

Discussion

In the present study, the functional organization of primary motor cortex was revealed by microstimulation mapping procedures in adult macaque monkeys that had matured after a major

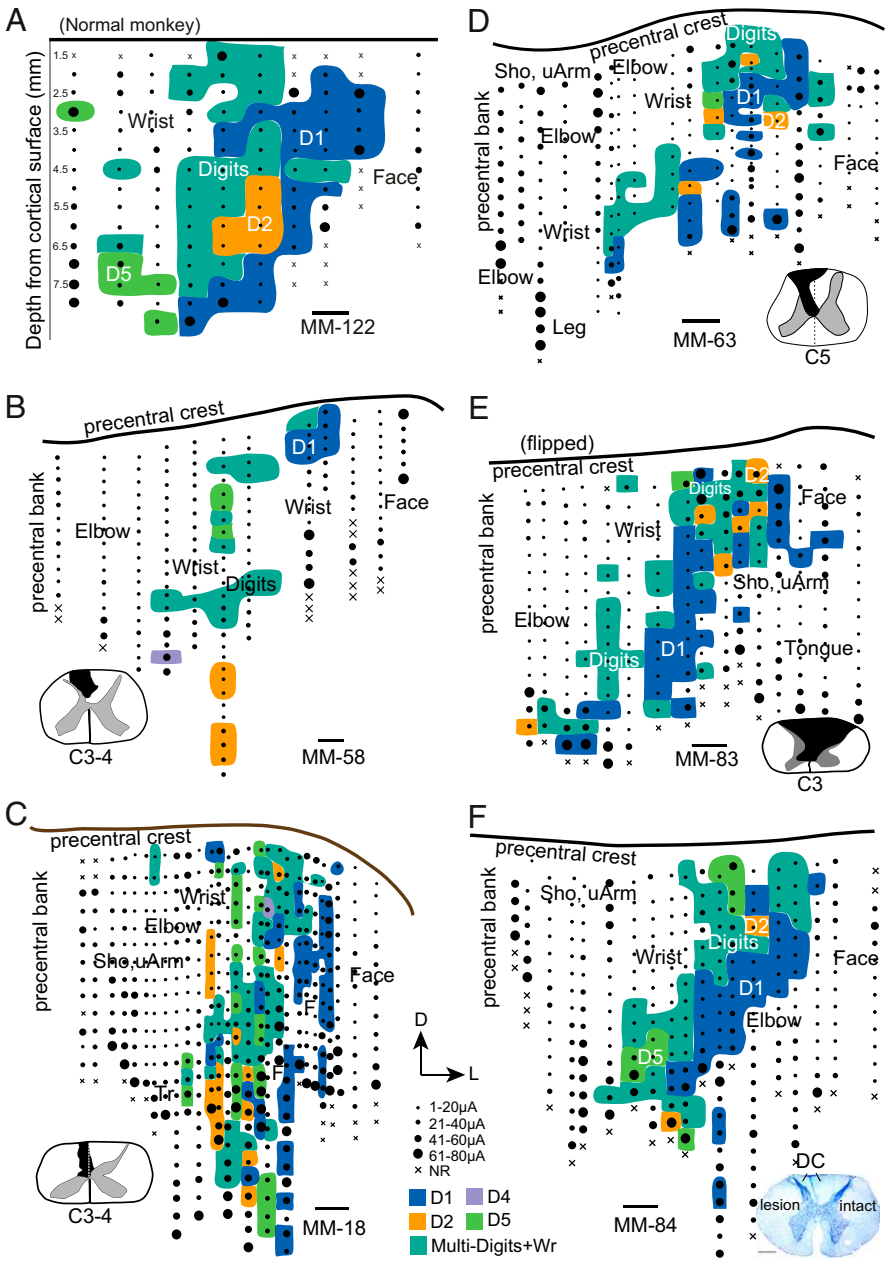

Fig. 2. Color-coded motor maps of digit representations in motor cortex. Only the evoked digit movements in the anterior bank of the central sulcus are shown. Individual digit movements are color coded. Thumb, 1 (blue); index finger, 2 (orange); ring finger, 4 (purple); little finger, 5 (lime green). Teal indicates multiple digit movements. (*A*) Evoked digit movement from normal adult macaque monkey (MM-122). Illustration is based on a subset of published data (15). D1–5, digits 1–5. (*B–F*) Evoked digit movements from dorsal column lesion cases. D1–5, digits 1–5; F, face; Sho, shoulder; Tr, trunk; uArm, upper arm; Wr, wrist. *Insets* in lower-left (*B* and *C*) or lower-right (*D* and *E*) corner are reconstructed transverse views of spinal cord indicating extents of lesions (black). In *F,* the reconstruction of spinal cord lesion was not available because of histological complications. However, a photomicrograph from a Nissl-stained transverse section through a spinal cord cervical segment C2 rostral to the lesion depicts an asymmetry in the dorsal columns (DC) with a large reduction on the lesion side. (Scale, 1 mm.) Arrows in *C* indicate dorsal (D) and lateral (L). Other conventions as in Fig. 1.

loss of somatosensory inputs a few days after birth. The sensory loss of low-threshold mechanoreceptor inputs from the forearm and lower body was produced by a unilateral or bilateral transection of the dorsal column pathway that consists of ascending branches of axons of cutaneous afferents that enter the spinal cord. The immediate consequence of such a lesion, if complete, is to totally deactivate the somatotopically matched parts of the somatosensory representation in primary somatosensory cortex (area 3b) of the contralateral cerebral hemisphere. As other somatosensory areas, such as areas 1, 2, S2, and PV depend on the cortical outputs of area 3b for activation by cutaneous receptors (20–22), the total cortical impact of such a lesion is extensive. Nevertheless, the behavioral consequences are relatively mild. The locomotive behavior of monkeys with lesions is nearly normal; but on closer examination, such monkeys are reluctant to reach for food or other objects with the affected hand, and they are no longer dexterous in tasks that require fine motor control of the digits (e.g., 23). The motor impairments observed after dorsal column lesions misled Wall (24) to conclude that these impairments are all related to movement.

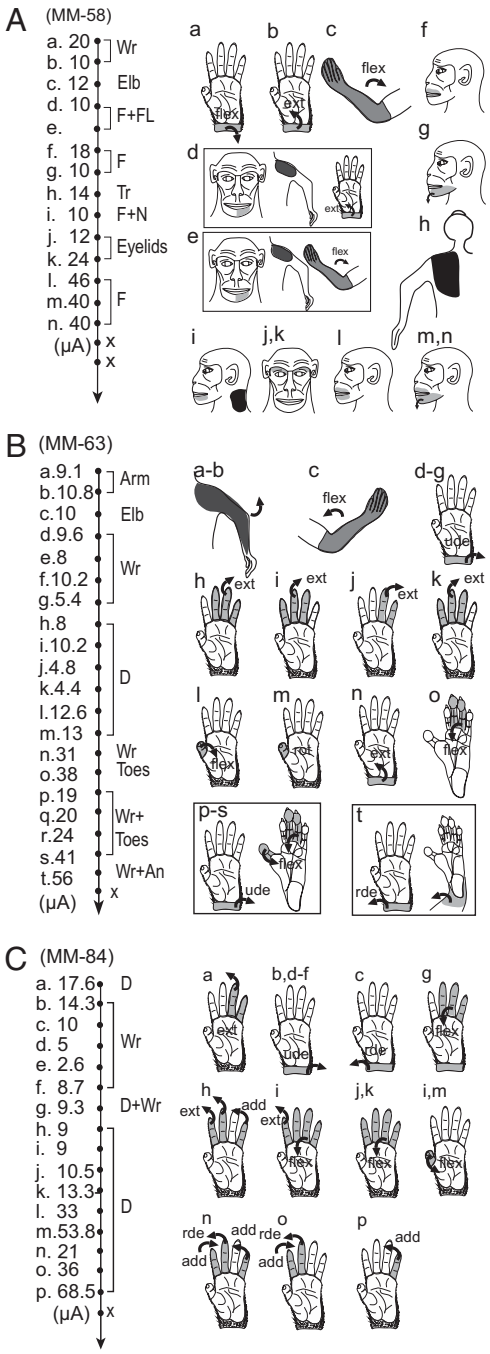

Fig. 3. Typical examples of threshold currents (left side of tract) and evoked movements (right side of tract) along microelectrode tracts (vertical bars). Distance between mapping sites is 500 μm. Although the threshold at the stimulation site "e" was not recorded, the value was most likely similar to that in "d." add, adduction; An, ankle; D, digits; Elb, elbow; ext, extension; F, face; FL, forelimb; flex, flexion; N, neck; rde, radial deviation; Tr, trunk; ude, ulnar deviation; Wr, wrist.

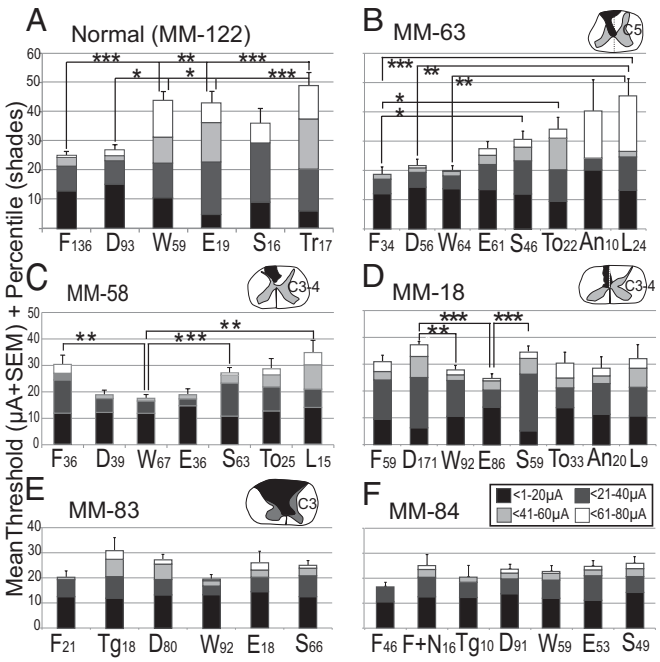

Fig. 4. Mean threshold currents for movements of major body parts for each studied case. Mean threshold and SEM are indicated on *y* axis and evoked body movement on *x* axis. Symbols on top of columns show statistically significant differences in mean thresholds (Kruskal–Wallis, nonparametric multivariate analysis). Numbers in the *x* axis labels indicate the number of mapping sites for movement of that body part. An, ankle; D, digits; F, face; E, elbow; L, leg; N, neck; S, shoulder; Tg, tongue; Tr, trunk; To, toes; W, wrist. (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$).

However, the sensory impairments that follow dorsal column lesions, and the loss of sensory feedback that results, undoubtedly affect the guidance of voluntary motor behaviors (23, 25). As a further complicating factor after dorsal column lesions, somatosensory cortex does not remain unresponsive to tactile stimulation; instead, deprived zones of somatosensory cortex become responsive to preserved cutaneous inputs, such as those from the face or from the hand and lower body that survived the lesions. Thus, a few preserved cutaneous inputs from the hand may activate most of the territory of the hand representation in area 3b of monkeys in a matter of weeks, and inputs from the lower face may activate this cortex within 6–8 months (7, 13). Humans with forearm amputation may feel touch on the missing hand when touched on the face or arm stump (26). Thus, motor behaviors in monkeys with dorsal column lesions would be guided by not only incomplete sensory information but by sensory misinformation.

Here we provide evidence for additional factors contributing to the abnormal motor behavior of monkeys with dorsal column lesions. Normal motor maps of body movements apparently fail to develop in monkeys deprived of dorsal column afferents soon after birth. In adult macaque monkeys with unilateral dorsal column lesions in infancy, the representation of body movements in M1, from foot to tongue, was in a normal mediolateral sequence across cortex. However, the hand representation was abnormal in several ways. Most notably, the sites where digit movements were evoked were reduced in number and more scattered within the hand territory. Moreover, stimulation of these sites sometimes evoked an unusual combination of digit movements with each other and with other parts of the forelimb. In addition, stimulation thresholds were often lower for movements of wrist and other body parts than for the digits, which normally have the lowest stimulation thresholds (15–17, 19). Although we found that the territory of the hand and digit representation in M1 is abnormal in macaques reared after section of the contralateral dorsal columns, the degree of the abnormality was variable across the five cases. Notably, the organization of motor cortex in the case with a bilateral lesion of the dorsal columns seemed to be less disrupted. This suggests that a cause for M1 abnormality could be the favored use of the normal arm over the arm with the sensory loss in day-to-day behaviors, as monkeys and humans with a sensory loss tend not to use the

impaired limb in behaviors that require skill (ref. 3 and references therein). The resulting disuse could affect the development of a normal map in motor cortex or possibly lead to a degeneration of the normal map in adult primates. Motor behavior is likely to be abnormal after dorsal column lesions, not only because sensory feedback is partially missing and partially abnormal, but because normal motor maps in primary motor cortex fail to develop.

Although little is known about the role of sensory deprivation on the development of motor cortex in primates, the motor map is altered in adults and infants by the loss of a limb. In adult macaque monkeys, squirrel monkeys, and prosimian galagos studied years after a therapeutic amputation of a limb after injuries as infants, juveniles, or adults, microstimulation of the territories in M1 of the missing limb evoked movements of the limb stump and adjoining shoulder or trunk at threshold current levels comparable to those for evoked movements in normal primates (15, 27, 28). Similar results have been obtained in rats (29). Thus, regardless of the age at which the amputation occurs, the deprived portion of motor cortex does not remain nonfunctional but instead mediates new muscle movements. Other studies indicate that many motor neurons in the spinal cord that had innervated the missing limb survived and formed new connections with remaining muscles in the stump, thereby possibly contributing to the reorganization of the M1 motor map (30, 31). Evidence for the reorganization of motor cortex has also been obtained from patients years after amputations (32). There is also evidence for somatotopic changes in motor cortex of monkeys (9) and humans (33) after motor skill learning. Thus, motor maps in primates appear to be modifiable as a result of motor and sensory loss as well as unusual experience.

There are several possible mechanisms of alterations in motor output after dorsal column lesions in infancy. As monkeys with sensory loss likely altered forearm use (24, 25, 34), changes in motor cortex could have been partly or completely use dependent (35). In addition, the impact of sensory loss on the motor system of newborn monkeys could have been particularly severe, as the monosynaptic connections of M1 corticospinal neurons are not yet present at birth, and the adult pattern of connections does not emerge until 6–8 months after birth (36). Once developed, these connections provide monkeys with the ability to perform relatively independent hand and finger movements. Abnormal sensory feedback as a result of sensory loss and the reorganization in the ascending somatosensory pathway could have altered the development of monosynaptic connections of M1 neurons in the cervical spinal cord, thereby accounting for the cortical sites where abnormal patterns of digit responses were evoked.

Material and Methods

Experimental Animals. Four bonnet macaques (*Macaca radiata*) and one rhesus macaque (*Macaca mulatta*) were used for these experiments (Table S1). All procedures used were included in protocols that were reviewed and approved by the Vanderbilt Institutional Animal Care and Use Committee. All procedures followed National Institutes of Health guidelines.

Dorsal Column Lesions. Unilateral dorsal column sections at the cervical segments C3–5 of the spinal cord were made in five 3-to 12-day-old macaque monkeys under aseptic conditions while animals were deeply anesthetized with a mixture of ketamine (15 mg/kg) and xylazine (0.4 mg/kg). The dorsal columns were sectioned with fine forceps. The side for the lesion was selected to minimize damage to surface blood vessels (7, 13). After the infants were fully awake, they were returned to their mothers for normal rearing.

Mapping. The motor cortex of five adult macaque monkeys was systematically explored with intracortical microstimulation techniques (15). The stimuli consisted of 60-ms trains of 0.2-ms monophasic cathodal pulses at 300 Hz up to 80-μA intensity. Trains were repeated at each cortical site to detect the minimum current level (threshold) required to evoke movements. Stimulations were made at sites from 1.8 mm below the surface and in 0.5-mm steps vertically down the anterior wall of the central sulcus until movements were no longer evoked. Electrode penetrations were usually placed in a grid with 0.5–1.5 mm separating stimulating sites. Limb movements and muscle contractions that were evoked by cortical stimulation were visually detected and confirmed by two observers. Limb posture was adjusted to keep limbs relaxed before stimulation, and anesthesia level was closely monitored to keep it as stable as possible.

Histology. At the end of the stimulation session, reference locations in M1, such as representational boundaries, were marked with electrolytic microlesions by passing a DC current at 10 μA for 10 s. These lesions allowed later relation of the stimulation results to cortical histology. The macaque monkeys were deeply anesthetized with pentobarbital and perfused transcardially with 0.1 M PBS, pH 7.4, followed by 2–3% paraformaldehyde in PB, and finally with buffered paraformaldehyde with 10% sucrose in PB. The brain was removed, and cortex was separated from subcortical structures and cryoprotected in 30% sucrose. The cortices were cut in 50-μm thick sections in a plane perpendicular to the central sulcus that was slightly tilted toward the horizontal from the parasagittal plane. Sets of sections from the cortex were stained for Nissl substance, myelin, and cytochrome oxidase as detailed by Jain et al. (7). A three-dimensional view of the anterior bank of central sulcus and the surrounding cortex was reconstructed. The spinal cords in the region of the lesion were cut in a horizontal plane at a thickness of 50 or 60 μm. A block from the spinal cord rostral to the lesion was cut in the coronal plane at a thickness of 50 μm. Sets of sections were processed for Nissl substance or cytochrome oxidase. The extent of the dorsal column lesion was reconstructed from the horizontally cut spinal cord sections and projected onto a transverse view (Fig. 1 *A* and *B*). Reconstruction procedures were detailed by Jain et al. (7).

Statistical Analysis. Averages of the threshold currents for evoked movements were calculated for each body part and compared with means for different body movements, and are reported as mean ± standard error of the mean (SEM). A nonparametric ANOVA (Kruskal-Wallis; InStat software, v. 3.0; GraphPad) was used, followed by a posthoc test for statistical comparisons of mean thresholds across body representations. A probability value of less than 0.05 was considered statistically significant (15).

ACKNOWLEDGMENTS. This work was supported by National Institutes of Health Grant RO1 NS16446 (to J.H.K).

1. Vierck CJ, Jr. (1982) Comparison of the effects of dorsal rhizotomy or dorsal column transection on motor performance of monkeys. *Exp Neurol* 75:566–575.
2. Taub E, Uswatte G, Elbert T (2002) New treatments in neurorehabilitation founded on basic research. *Nat Rev Neurosci* 3:228–236.
3. Darian-Smith C, Ciferri MM (2005) Loss and recovery of voluntary hand movements in the macaque following a cervical dorsal rhizotomy. *J Comp Neurol* 491:27–45.
4. Merzenich MM, et al. (1983) Topographic reorganization of somatosensory cortical areas 3b and 1 in adult monkeys following restricted deafferentation. *Neuroscience* 8: 33–55.
5. Florence SL, Kaas JH (1995) Large-scale reorganization at multiple levels of the somatosensory pathway follows therapeutic amputation of the hand in monkeys. *J Neurosci* 15:8083–8095.
6. Florence SL, Taub HB, Kaas JH (1998) Large-scale sprouting of cortical connections after peripheral injury in adult macaque monkeys. *Science* 282:1117–1121.
7. Jain N, Qi HX, Collins CE, Kaas JH (2008) Large-scale reorganization in the somatosensory cortex and thalamus after sensory loss in macaque monkeys. *J Neurosci* 28:11042–11060.
8. Tandon S, Kambi N, Lazar L, Mohammed H, Jain N (2009) Large-scale expansion of the face representation in somatosensory areas of the lateral sulcus after spinal cord injuries in monkeys. *J Neurosci* 29:12009–12019.
9. Nudo RJ, Milliken GW, Jenkins WM, Merzenich MM (1996) Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *J Neurosci* 16:785–807.
10. Dykes RW, Terzis JK (1981) Spinal nerve distributions in the upper limb: The organization of the dermatome and afferent myotome. *Philos Trans R Soc Lond B Biol Sci* 293:509–554.
11. Florence SL, Wall JT, Kaas JH (1988) The somatotopic pattern of afferent projections from the digits to the spinal cord and cuneate nucleus in macaque monkeys. *Brain Res* 452:388–392.
12. Dykes RW, Avendaño C, Leclerc SS (1995) Evolution of cortical responsiveness subsequent to multiple forelimb nerve transections: An electrophysiological study in adult cat somatosensory cortex. *J Comp Neurol* 354:333–344.
13. Jain N, Catania KC, Kaas JH (1997) Deactivation and reactivation of somatosensory cortex after dorsal spinal cord injury. *Nature* 386:495–498.

14. Jain N, Florence SL, Qi HX, Kaas JH (2000) Growth of new brainstem connections in adult monkeys with massive sensory loss. *Proc Natl Acad Sci USA* 97:5546–5550.
15. Qi HX, Stepniewska I, Kaas JH (2000) Reorganization of primary motor cortex in adult macaque monkeys with long-standing amputations. *J Neurophysiol* 84:2133–2147.
16. Kwan HC, MacKay WA, Murphy JT, Wong YC (1978) Spatial organization of precentral cortex in awake primates. II. Motor outputs. *J Neurophysiol* 41:1120–1131.
17. Sessle BJ, Wiesendanger M (1982) Structural and functional definition of the motor cortex in the monkey (Macaca fascicularis). *J Physiol* 323:245–265.
18. Park MC, Belhaj-Saïf A, Gordon M, Cheney PD (2001) Consistent features in the forelimb representation of primary motor cortex in rhesus macaques. *J Neurosci* 21: 2784–2792.
19. Asanuma H, Rosén I (1972) Functional role of afferent inputs to the monkey motor cortex. *Brain Res* 40:3–5.
20. Burton H, Sathian K, Shao DH (1990) Altered responses to cutaneous stimuli in the second somatosensory cortex following lesions of the postcentral gyrus in infant and juvenile macaques. *J Comp Neurol* 291:395–414.
21. Garraghty PE, Florence SL, Kaas JH (1990) Ablations of areas 3a and 3b of monkey somatosensory cortex abolish cutaneous responsivity in area 1. *Brain Res* 528:165–169.
22. Pons TP, Garraghty PE, Mishkin M (1992) Serial and parallel processing of tactual information in somatosensory cortex of rhesus monkeys. *J Neurophysiol* 68:518–527.
23. Cooper BY, Glendinning DS, Vierck CJ, Jr. (1993) Finger movement deficits in the stumptail macaque following lesions of the fasciculus cuneatus. *Somatosens Mot Res* 10:17–29.
24. Wall PD (1970) The sensory and motor role of impulses travelling in the dorsal columns towards cerebral cortex. *Brain* 93:505–524.
25. Eidelberg E, Woolf B, Kreinick CJ, Davis F (1976) Role of the dorsal funiculi in movement control. *Brain Res* 114:427–438.
26. Ramachandran VS, Rogers-Ramachandran D, Cobb S (1995) Touching the phantom limb. *Nature* 377:489–490.
27. Schieber MH, Deuel RK (1997) Primary motor cortex reorganization in a long-term monkey amputee. *Somatosens Mot Res* 14:157–167.
28. Wu CW, Kaas JH (1999) Reorganization in primary motor cortex of primates with long-standing therapeutic amputations. *J Neurosci* 19:7679–7697.
29. Donoghue JP, Suner S, Sanes JN (1990) Dynamic organization of primary motor cortex output to target muscles in adult rats. II. Rapid reorganization following motor nerve lesions. *Exp Brain Res* 79:492–503.
30. Wu CW, Kaas JH (2000) Spinal cord atrophy and reorganization of motoneuron connections following long-standing limb loss in primates. *Neuron* 28:967–978.
31. Qi HX, Stewart Phillips W, Kaas JH (2004) Connections of neurons in the lumbar ventral horn of spinal cord are altered after long-standing limb loss in a macaque monkey. *Somatosens Mot Res* 21:229–239.
32. Chen R, Corwell B, Yaseen Z, Hallett M, Cohen LG (1998) Mechanisms of cortical reorganization in lower-limb amputees. *J Neurosci* 18:3443–3450.
33. Rosenkranz K, Kacar A, Rothwell JC (2007) Differential modulation of motor cortical plasticity and excitability in early and late phases of human motor learning. *J Neurosci* 27:12058–12066.
34. Asanuma H, Arissian K (1984) Experiments on functional role of peripheral input to motor cortex during voluntary movements in the monkey. *J Neurophysiol* 52: 212–227.
35. Chakrabarty S, Shulman B, Martin JH (2009) Activity-dependent codevelopment of the corticospinal system and target interneurons in the cervical spinal cord. *J Neurosci* 29:8816–8827.
36. Armand J, Olivier E, Edgley SA, Lemon RN (1997) Postnatal development of corticospinal projections from motor cortex to the cervical enlargement in the macaque monkey. *J Neurosci* 17:251–266.