8. The functional organization of cortex was studied using standard multiunit microelectrode mapping procedures, as described (*11*). For reconstruction of the cortical maps for the distribution of label and for the microelectrode recordings, a series of drawings of the labeled cortical sections were digitally scanned into NIH Image, aligned, and rotated to generate a three-dimensional, "en face" view of the distribution of label in area 3b. The receptive field data were superimposed on these 3D reconstructions to produce summary maps of the forelimb representation, using methods described in (*1*).
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5 August 1998; accepted 8 October 1998

Thalamic and Brainstem Contributions to Large-Scale Plasticity of Primate Somatosensory Cortex

Edward G. Jones and Tim P. Pons

After long-term denervation of an upper limb in macaque monkeys, the representation of the face in somatosensory cortex expands over many millimeters into the silenced representation of the hand. Various brainstem and cortical mechanisms have been proposed to explain this phenomenon. Reorganization in the thalamus has been largely ignored. In monkeys with deafferented upper limbs for 12 to 20 years, it was found that the brainstem cuneate and the thalamic ventral posterior nuclei had undergone severe transneuronal atrophy, and physiological mapping in the thalamus revealed that the face and trunk representations were adjoined while the normally small representation of the lower face had expanded comparable to the expansion in cortex. Reorganization of brainstem and thalamic nuclei associated with slow transneuronal atrophy is likely to be a progressive process. When coupled with divergence of ascending connections, it is likely to make a substantial contribution to representational changes in cortex.

Maps of the body surface in the postcentral gyrus of adult monkeys are capable of reorganization under the influence of reduced or enhanced input from peripheral somatosensory receptors (*1*). These reorganizations are likely to be responsible for perturbed sensory experiences that occur after loss of peripheral input from a body part, such as phantom and painful sensations that follow amputation or deafferentation of a limb in humans (*2*). The neural mechanisms that underlie activity-dependent cortical reorganization may be the same as those normally responsible for improvements in perceptual skills that accompany extended sensory experience and, if harnessed, these mechanisms may provide a basis for promoting recovery of function after peripheral or central lesions of the nervous system (*3*). The most extensive reorganization of somatosensory cortex occurred in monkeys in which the dorsal roots of the spinal cord (*4*) or the spinal dorsal columns (*5*) had been cut or a hand had been amputated (*6*). In these cases, after months or years, the representation of the face in the contralateral postcentral gyrus had expanded for a distance of 15 to 20 mm into the adjacent part of the gyrus in which the contralateral upper limb is normally represented.

Mechanisms postulated to explain such extensive reorganization include (i) reorganization in the dorsal column nuclei, which is then projected upward to somatosensory cortex (*5*); (ii) divergence of ascending somatosensory projections whose more divergent synapses have been hitherto silent (*4*); and (iii) reorganization or sprouting of preexisting connections in cortex itself (*1*). Surprisingly, the thalamus, the second synaptic station in the ascending somatosensory pathways and the obligatory relay for all sensory inputs to the cerebral cortex, has been ignored in most explanations.

Earlier data, however, suggest that the somatosensory thalamus is not immune from activity-dependent map plasticity. Expansion of the forelimb representation into the silenced hindlimb representation in the ventral posterior (VP) thalamic nucleus was reported 1 week or more after destruction of the gracile nucleus in rats (*7*). Similar expansions of the VP upper limb representation into that of the lower limb were reported in monkeys after dorsal rhizotomies or section of the gracile fasciculus (*8*). A number of peripheral deafferentation-dependent expansions of receptive fields of individual cells or of the representations of whole body regions have recently been described in the somatosensory thalamus of rats, monkeys, and humans (*9*). We examined the somatosensory thalamus in *Macaca fascicularis* monkeys from the same group in which massive expansions of the cortical face representation after 12 or more years of upper limb deafferentation were first reported (*4*). The thalami and brainstems of the eight monkeys in the group were examined histologically, and in two (one deafferented for nearly 20 years), the thalamus was mapped electrophysiologically and showed extensive reorganization of the body map in a thalamus in which the upper limb representation was affected by severe transneuronal degeneration.

Tactually elicited neuronal activity was recorded in the VP nucleus contralateral to an upper limb that had been denervated by surgical transection of the dorsal roots of the spinal cord from the second cervical (C2) to fourth thoracic (T4) segments (*10*). Microelectrodes spaced at 1-mm intervals entered the VP nucleus in the horizontal plane from behind and in a grid-like pattern. Neuronal responses to light stimulation of the body surface were systematically recorded in 100-μm steps as the electrode was advanced from posterior to anterior through the VP nucleus (*11*). In all eight monkeys, the thalamus, brain stem, and spinal cord were sectioned and stained by the Nissl method, histochemically for the metabolic marker cytochrome oxidase (CO), and immunocytochemically for the neuronal proteins calbindin or parvalbumin (*12*).

E. G. Jones, Center for Neuroscience, University of California–Davis, Davis, CA 95616, USA. T. P. Pons, Department of Neurosurgery, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA.

Normally, VP nucleus in monkeys consists of four sharply defined subnuclei (Figs. 1C and 2). The ventral posterior medial nucleus (VPM) contains the representation of the face and intraoral structures that are innervated by the trigeminal nerve. The ventral posterior lateral nucleus (VPL) contains the representation of the remainder of the contralateral body surface that is innervated by the spinal nerves. Two subsidiary nuclei, the basal ventral medial nucleus (VMb) and ventral posterior inferior nucleus (VPI), are not relevant to this investigation. VPM and VPL contain cells whose axons transmit sensory messages to the postcentral gyrus, VPM to the face representation and VPL to the representation of the upper limb and rest of the body. VPM and VPL are normally separated by a prominent lamella of white matter, the arcuate lamella (Fig. 1C). In VPM, the lips, cheek pouch, and tongue are represented laterally, adjacent to the arcuate lamella, separated by the lamella from the representation of the contralateral upper limb in VPL. The trunk, lower limb, and tail are represented progressively more laterally in VPL (Fig. 2) (*13*).

In all eight monkeys, the cuneate fasciculus of the spinal cord, which normally contains the axons of dorsal root ganglion cells innervating the upper limb, had almost completely disappeared as the result of degeneration of the central axons of the C2-T4 dorsal root ganglion cells (Fig. 1A). This was associated with a 30 to 45% (±10%) shrinkage of the cuneate nucleus (*14*) in which these axons normally synapse, resulting from primary transneuronal atrophy (*15*) of the deafferented cells (Fig. 1B). These cells normally send their axons to the part of the contralateral VPL abutting the arcuate lamella (*16*). Infiltration of the shrunken cuneate nucleus by neuroglial cells indicates the presence of active degeneration, even after 20 years (Fig. 1B). Many nerve cells remained in the deafferented cuneate nucleus, but the cells—especially those in the pars rotunda of the nucleus—were severely shrunken in comparison with those of the opposite side. Packing density of the cells was increased due to the loss of neuropil that had resulted from death of the afferent axons. The external cuneate nucleus, which also receives primary afferents from the upper limb but projects to the cerebellum, also showed gliosis and evidence of neuronal atrophy.

There were no visible alterations in the gracile or spinal trigeminal nuclei or in their relative dispositions with respect to the shrunken cuneate nucleus (Fig. 1B). By contrast, in the contralateral thalamus, the structure of the VP nucleus had become reorganized. Secondary transneuronal atrophy was clearly evident in VPL, with a 10 to 15% (±5%) shrinkage of the whole VP complex resulting from a 30 to 40% shrinkage of VPL. The VP nucleus was foreshortened anteroposteriorly. The posterodorsal half of the arcuate lamella had disappeared (Figs. 1, C and D, 2, and 3). The cells formerly belonging to the posterior half or more of VPM had collapsed into the former upper limb representation in VPL. Many neurons in this part of VP, presumably those originally belonging to VPM medially and to the lower trunk representation of VPL laterally, retained the normal characteristics of VP cells. That is, they were large and deeply staining. Others, presumably belonging to the deprived upper limb representation, were visibly shrunken, indicative of transneuronal atrophy. The region of the thalamus posteromedial to the shrunken VP nucleus was filled with the smaller, calbindin-rich and CO-weak cells expanding forward from the posterior thalamic nucleus, as previously reported (Fig. 1, C and D) (*12*).

Microelectrodes traversing VPM or VPL along posterior-to-anterior horizontal tracks, medial or lateral to the region in which the two nuclei had merged, encountered thalamocortical relay neurons with normal receptive fields on the face or trunk, respectively (and, more laterally, on the lower limb or tail) (Fig. 4). Neurons in the reorganized region were not silent; latencies and response thresholds to peripheral stimulation were not elevated; they showed the same range of specific responses to light tactile stimulation or manipulation of deep tissues as in normal animals. On many electrode tracks, at individual recording sites, adjacent neurons were found to have receptive fields on either the face or trunk—a phenomenon never encountered in normal monkeys. The majority of the neurons recorded through the reorganized region, however, had receptive fields on the skin of the lower part of the contralateral face, particularly that covering the outer and under surfaces of the lower jaw (Fig. 4). Normally, this representation, which receives its input from skin innervated by overlapping branches of the mandibular division of the trigeminal nerve (intact in this case) and of the second cervical nerve (severed in this case) (*17*), is small in both VPM and in the postcentral gyrus (*13, 18, 19*). In the postcentral gyrus, this lower-face representation separates the representation of the hand from that

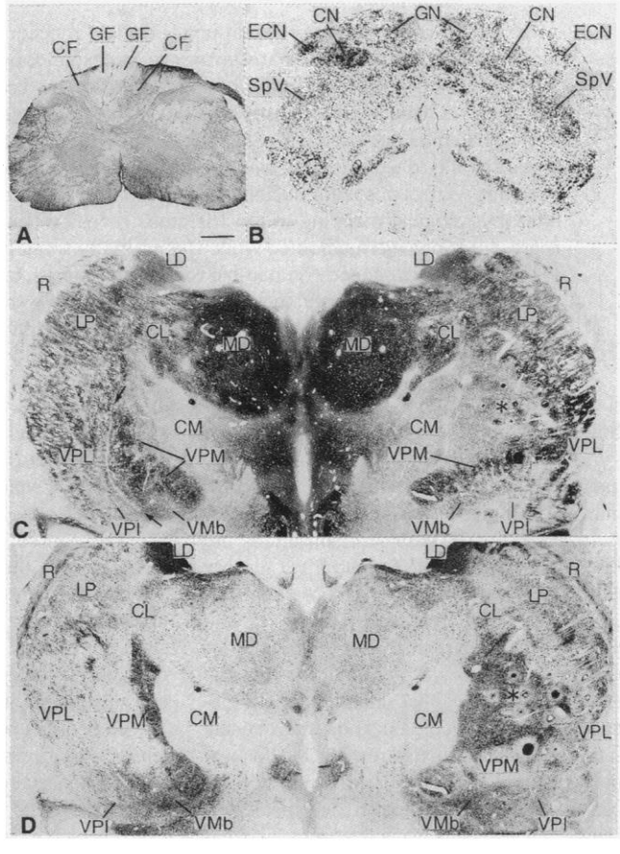

Fig. 1. Photomicrographs of the spinal cord, brain stem, and thalamus of a monkey subjected to deafferentation of the left upper limb for 20 years. (**A**) From a cross section of the first cervical segment of the spinal cord, stained immunocytochemically for parvalbumin, and showing the great reduction in size of the cuneate fasciculus (CF) on the left. The gracile fasciculus (GF) is intact. (**B**) From a cross section of the brainstem stained by the Nissl method, showing reduction in size with gliosis of the left cuneate (CN) and external cuneate (ECN) nuclei. The gracile nucleus (GN) and spinal nucleus of the trigeminal nerve (SpV) are normal. (C and D) From adjacent frontal sections of the diencephalon stained for CO (**C**) or immunocytochemically (**D**) for 28-kD calbindin. These show reduction in size of the right VP nucleus, loss of definition of its VPM and VPL subnuclei in comparison with the left, unaffected side, and expansion of the CO-weak, calbindin-enriched anterior pulvinar and posterior nuclear region (asterisk). On the normal left side at this level, the CO-weak, calbindin-enriched region is restricted to a narrow strip along the medial edge of VPM. Arrows in (C) (left) indicate the arcuate lamella, normally separating VPM and VPL, but which is disrupted on the right. Round profiles in (C) and (D) are microelectrode tracks. Bar, 1 mm. Other thalamic nuclei indicated are basal ventral medial (VMb), central lateral (CL), centre médian (CM), lateral dorsal (LD), lateral posterior (LP), mediodorsal (MD), reticular (R), and ventral posterior inferior (VPI).

of the rest of the face. It is highly significant, therefore, that the cortical representation of the face that had expanded into the silenced upper limb representation in these monkeys also consisted mainly of neurons with receptive fields on the lower part of the face (*4*), consistent with the expansion of the lower face representation in the thalamus. The large extent of the expansion of this normally small representation in the thalamus suggests that considerable reorganization had occurred in the transneuronally affected thalamus and that these changes were relayed to the cortex. In both cortex (*4*) and thalamus, the representation of the trunk had not obviously expanded, although the techniques may not have had sufficient resolving power to detect an expansion of the lower trunk representation (with intact innervation) into that of the (deafferented) upper trunk.

This study provides a basis for the expansion of the lower face representation in the somatosensory cortex by demonstrating a functional expansion of this representation in the thalamic nucleus providing input to the reorganized region of cortex. It introduces a hitherto unsuspected contributing mechanism by demonstrating, for the first time in the somatosensory system, the presence of a major degree of transneuronal degeneration in the upper limb representation of VP, undoubtedly secondary to loss of inputs resulting from primary transneuronal degeneration of deafferented cuneate nucleus cells. Transneuronal degenerations of this type in other systems are normally progressive and occur slowly over many years (*15*). We envision in the present case that there is a progressive, slow atrophy of cells in the cuneate nucleus, whose efferent axons slowly die or are withdrawn from the upper limb part of the VPL. The loss of this innervation leads to an even slower atrophy of many cells in the upper limb representation of VPL, and the accompanying breakdown of the arcuate lamella (undoubtedly due to loss of incoming axons) progressively brings VPM and VPL cells, normally innervated by inputs from the face or trunk, into close proximity. Degeneration

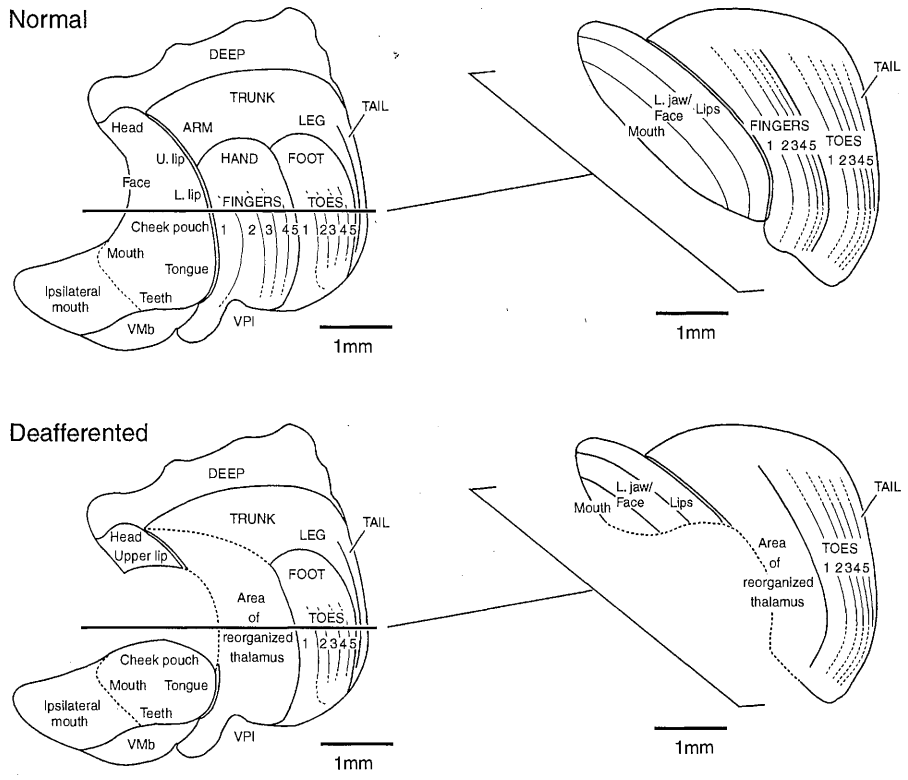

Fig. 2. Frontal (left member of each pair) and horizontal (right member of each pair) sections through the middle of the thalamus of a normal macaque monkey (Normal) and of a monkey subjected to deafferentation of the upper limb for 12 or more years (Deafferented), showing the normal representation of the body (*13, 16*) and the reorganized representation revealed in our investigation. Horizontal sections are taken from the level indicated by the thick line.

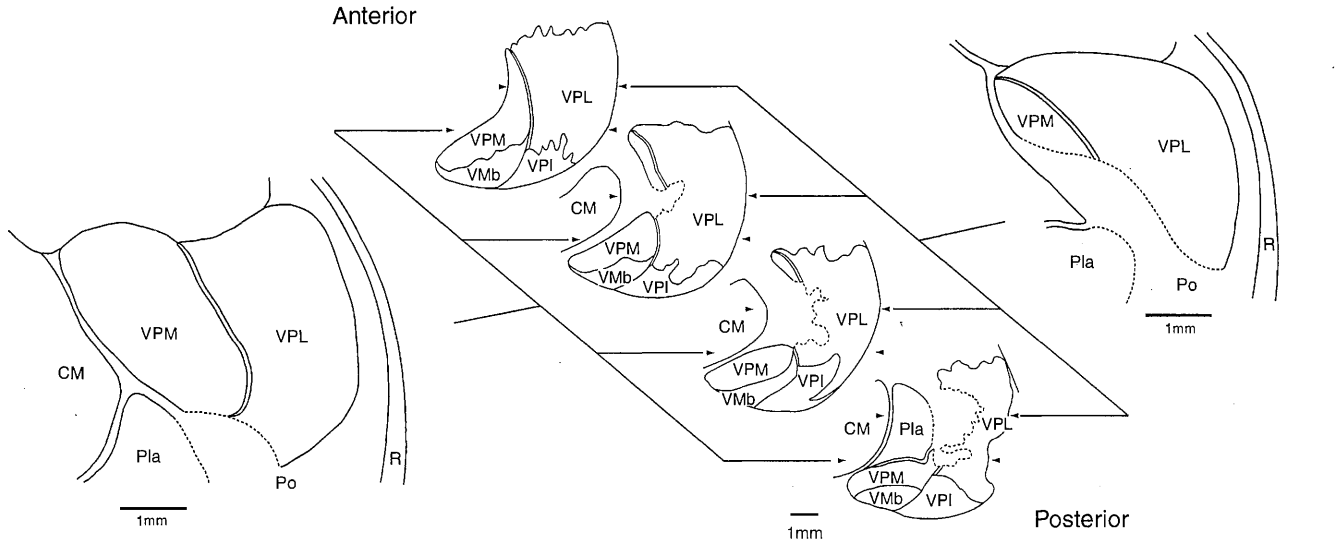

Fig. 3. Middle portion of figure shows outlines of sections of the VP complex of nuclei at approximately 1-mm intervals through the thalamus contralateral to the deafferented upper limb in the monkey illustrated in Figs. 1 and 4. These show the shrinkage of VPL, breakdown of the arcuate lamella separating VPL and VPM, and the loss of definition of VPM posteriorly. Left and right portions are reconstructions of horizontal views through the affected thalamus at ventral (left) and dorsal (right) levels, as indicated by the lines and arrowheads, and showing the reduction in volume and loss of definition between VPM and VPL. Pla, anterior pulvinar nucleus; Po, posterior nucleus.

or retraction of the axons of atrophic thalamic upper limb cells in the somatosensory cortex should permit the divergent axon branches of thalamic face cells to be expressed functionally in the cortex. Previously silent inputs from the lower face region to thalamic cells whose dominant inputs from the upper limb have been silenced could also be uncovered. Potentially, there may also be sprouting of intact mandibular nerve inputs to deafferented upper limb cells in the VP, although this needs to be demonstrated. The slow atrophy of afferent axons to VP is unlikely to be a passive process and is probably accompanied by release of numerous trophic signals that might promote reorganization of connections in the zone of mixed normal and atrophic cells (*20*).

In recent accounts of map expansions in the somatosensory thalamus, it has been assumed that the deprived part of the representation is static (*21*) and merely occupied by expansions of adjacent representations, possibly by uncovering of latent projections. Our findings indicate the presence of an active process likely to be continuing over many years, thus serving to make the reorganization of cortex also a progressive phenomenon dependent on slow degenerative changes in both the cuneate and VP nuclei. The evidence that the cortical upper limb representation is initially silent but later becomes active (*5*) is likely to reflect the slow, progressive nature of secondary and tertiary transneuronal degenerations.

Even without sprouting and the formation of new connections, the normal divergence in the intact thalamocortical projections may be sufficient to underlie map expansion in the cortex of these monkeys. The normal extent of a finger representation in area 3b of the macaque somatosensory cortex is ~10 to 12 mm^2 (*22*). The divergence and overlap in the projections from regions of VP nucleus representing adjacent body parts is much greater than this (*23*). So great is this divergence that upward of 35% of the VPL, including a substantial part of the representation of a single digit, can be destroyed before the representation of that digit in area 3b starts to shrink and that of adjacent digits begins to expand (*24*). The effects of thalamocortical divergence must be magnified by any similar divergence earlier in the system, such as in the projections of the dorsal column nuclei to the thalamus and from the primary afferents to the dorsal column nuclei themselves. The extent of divergence in the projections of individual dorsal column afferents to the cuneate and gracile nuclei, or of the cells of these nuclei to the thalamus, has not been documented. However, in an experiment comparable to that on the reduction of thalamocortical projections, survival of only a few primary afferent fibers after section of the dorsal columns was sufficient to cause retention of at least part of the upper limb map in the somatosensory cortex, a map which was completely silenced if all the fibers were cut (*5*).

The thalamic changes that were demonstrated, although secondary to atrophy of the cuneate nucleus, may tend to predominate in effects upon the cortex, because we observed no morphological evidence of reorganization in the cuneate nucleus, and electrophysiological evidence for reorganization of the dorsal column nuclei that would support new innervation by trigeminal afferents bearing sensory information from the face is lacking (*25*).

Although thalamic reorganization of the kind we report, when coupled with the exposure of the normal ascending divergence in the somatosensory pathway, may be sufficiently great to account for the large-scale expansion of the cortical face representation following upper limb deafferentation, we cannot rule out the possibility of contributing intracortical mechanisms as well. Intracortical microstimulation has the same effect as heightened activity at the periphery in promoting short-term expansions of body part representations in the somatosensory cortex (*26*). Long-range intracortical connections of sufficient extent (3 to 4 mm) exist that could be recruited in order to promote expansion of one representation at the expense of an adjoining one (*27*). To date, there is no evidence for sprouting of these connections in the deprived somatosensory cortex, so our discussion will focus on preexisting intracortical connections (*28*).

In area 3b of normal macaque monkeys, dense, horizontal corticocortical connections join the lower face representation to the upper limb representation but not the latter to the remainder of the face representation (*18, 29*). Therefore, in the absence of inputs to the lower face representation from cervical spinal nerves in the deafferented monkeys, the remaining inputs from the mandibular nerve could potentially gain access to the silenced upper limb representation via the horizontal intracortical connections. This may be another potential route for spread of the lower face

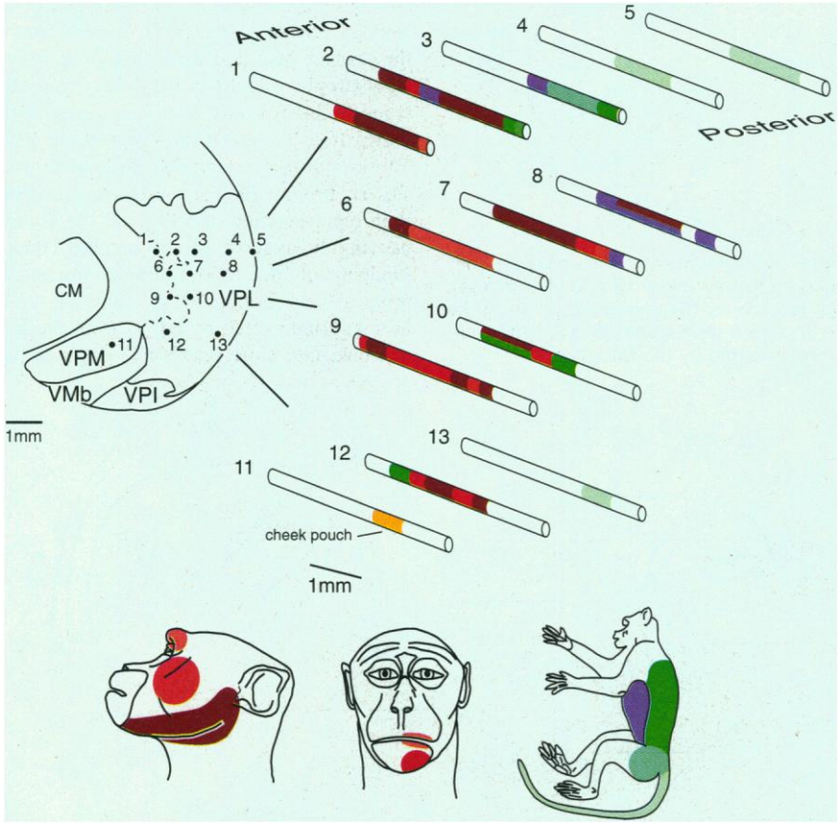

Fig. 4. Summary of the results of physiological mapping in the VP nucleus of the monkey illustrated in Figs. 1 and 2 and deafferented for 20 years. The frontal section of the thalamus at left shows the tracks of 13 microelectrodes driven horizontally from posterior to anterior through the VP nucleus. Each penetration is indicated by a rodlike profile at right. Colored sections of each penetration indicate regions over which VP neurons had receptive fields on particular parts of the body, as matched to figurines at bottom. Note the unusually large representation of the lower face region and the presence, especially on tracks 8 and 10, of adjacent neurons with receptive fields on the lower face and trunk. For clarity, the exact positions of the neurons or clusters of neurons recorded from and the exact outlines of each of their receptive fields are not shown. These data can be obtained on application to either of the authors.

representation into that of the hand (*30*), and it would reinforce a thalamic-based expansion, especially if the effects were accompanied by activity-dependent alterations in the balance of excitation and inhibition (*31*) and if they were fed back to the thalamus by corticothalamic connections (*32*). As the cortical representation expands, corticothalamic and corticobulbar efferents feeding the expansion back to the thalamus and brainstem could serve to reinforce a thalamocortical divergence-based expansion (*33*).

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11. For details of the stereotaxic approach and recording procedures, see (*16*). Animals were anesthetized with intramuscular ketamine hydrochloride (25 to 50 mg/kg body weight) and intubated, after which they were maintained on a mixture of 1.5% isofluorane gas and oxygen. After placement in a stereotaxic frame, the skull and dura mater were opened over the occipital lobe contralateral to the side of the deafferentation, and tungsten microelectrodes (5 megohm at 1 kHz) were introduced and advanced with a microdrive in the horizontal Horsley-Clarke plane. Single and multiunit neuronal activity was recorded, using conventional methods of amplification and display, in response to stimulation of body parts with fine probes. All procedures were approved by the relevant institutional animal care and use committees.
12. At the conclusion of the experiment, the animals were given an overdose of Nembutal, and the brain and spinal cord were fixed by perfusion through the heart with normal saline followed by 4% paraformaldehyde and 0.5% glutaraldehyde in 0.1 M phosphate buffer. Serial frozen sections of the brains and spinal cords were cut at 25 μm and stained alternately with thionin, for cytochrome oxidase, or immunocytochemically for the calcium binding proteins 28-kD calbindin or parvalbumin, or for various other antigens. For details, see E. Rausell, C. G. Cusick, E. Taub, and E. G. Jones [*Proc. Natl. Acad. Sci. U.S.A.* **89**, 2571 (1992)].
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25. After partial deafferentation or temporary blocking of inputs to the gracile or cuneate nuclei, deafferented cells can immediately acquire larger receptive fields [J. Millar, A. I. Basbaum, P. D. Wall, *Exp. Neurol.* **50**, 658 (1976); M. J. Pettit and H. D. Schwark, *Science* **262**, 2054 (1993)], and over time, silenced cells can become activated by inputs from regions of the body adjoining those denervated [J. O. Dostrovsky, J. Millar, P. D. Wall, *Exp. Neurol.* **52**, 480 (1976); J. Kalaska and B. Pomeranz, *Brain Res.* **236**, 35 (1982)], but these experiments involved expansions of representations already contained within the nuclei, not invasion of the upper limb representation by the trigeminal system.
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28. C. Darian-Smith and C. D. Gilbert [*Nature* **368**, 737 (1994)] describe corticocortical sprouting in the visual cortex.
29. H. Burton and M. Fabri, *J. Comp. Neurol.* **355**, 508 (1995).
30. J. P. Lund, G.-D. Sun, and Y. Lamarre [*Science* **265**, 546 (1994)] suggested that divergence of thalamic inputs from VPM to the lower face representation and to a second partial representation of the occipital region of the head (innervated peripherally by the ophthalmic division of the trigeminal nerve and the posterior division of the second cervical nerve), normally located medial to the upper limb representation, should be sufficient to account for expansions of the face representation into an upper limb representation silenced by total deafferentation. The medial head representation, however, does not appear to expand in the deafferented monkeys.
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33. We do not yet know if the hand representation in area 3b of the somatosensory cortex (the area that receives the densest thalamic input from VPL and in which the face representation expands in these monkeys) is affected by tertiary transneuronal atrophy, which might lead to its shrinkage. Loss of cells, shrinkage of layers, and patchy disorganization in the cortex of the anterior wall of the postcentral gyrus (area 3b) was described by A. W. Campbell [*Histological Studies on the Localisation of Cerebral Function* (Cambridge Univ. Press, Cambridge, 1905), pp. 86–94] in long-standing cases of tabes dorsalis. In this manifestation of tertiary syphilis, death of dorsal root ganglion cells results in loss of axons in the dorsal columns of the spinal cord akin to that produced in the cuneate fasciculus by the more limited dorsal rhizotomies in the monkeys studied.

34. We thank R. Blanchard, P. J. Gerone, M. Mishkin, M. Ratteree, W. Raub, and E. Taub for helping to make this research possible; M. Ratteree and C. G. Cusick for assistance during and subsequent to the experiments; G. J. Popken, E. Rausell, and T. M. Woods for help in analyzing the material; and P. Ngyuen for expert histological assistance. Supported by NIH USPHS grants NS21377 (E.G.J.) and NS35246 and MH53369 (T.P.P.).

4 August 1998; accepted 8 October 1998