Recovery of Normal Topography in the Somatosensory Cortex of Monkeys After Nerve Crush and Regeneration

Abstract. *After median nerve fibers to glabrous skin on the hands of monkeys were crushed and allowed to regenerate, normal topographical organization was recovered in the representation of the hand in primary somatosensory cortex. Similar recovery of normal cortical organization may underlie the sensory restoration that usually follows nerve crush injury in humans.*

In patients with nerve damage, recovery of normal sensory function is more likely after regeneration of crushed than of transected and reconnected nerves (*1*). This difference in recovery may depend on whether normal topographic organization is restored in central somatosensory representations after regeneration. After experimental nerve transection, repair, and regeneration in monkeys, the representation of the affected skin in the primary somatosensory cortex is topographically disorganized (*2*). If sensory recovery is related to cortical organization, cortical topography should be less abnormal when regeneration follows nerve crush injury. We tested this hypothesis by assessing topographical organization in somatosensory cortical area 3b (Fig. 1A) in monkeys with crushed and regenerated nerves. Three questions were addressed. (i) Is normal topography restored in the primary somatosensory cortex after regeneration? (ii) Since the organization in normal monkeys varies somewhat from individual to individual, is the organization specific to an individual monkey restored by regeneration? (iii) Are cortical representations for reinnervated skin regions reestablished in any sequence during regeneration?

We studied regeneration of the median nerve, a large nerve that innervates glabrous skin on the radial half of the hand (Fig. 1C) (*3*). Right median nerves in five owl monkeys (*Aotus trivirgatus*) were completely crushed in the distal forearm approximately 70 mm from the tip of digit 3. After recovery periods of 21 to 568 days, the hand representation in cortical area 3b was mapped (*4*). Three monkeys had also been mapped before nerve crush to allow detailed comparison of normal and regenerated organization in individual animals. All mapping data were collected in such a way that the investigator defining receptive fields did not know the location of the cortical recording site.

In normal monkeys the representation of mechanoreceptor inputs from the hand in area 3b is topographically organized (Fig. 1, B and C) (*5*). The topography for the monkey shown in Fig. 1 is similar to that of other normal monkeys in terms of the location and distribution of representations for individual digits and pads. For example, palmar pads are represented along the caudal margin of area 3b, whereas digits are represented in a strip along the anterior margin. Pads and digits on the ulnar side of the hand are represented medially, whereas skin areas on the radial hand are represented laterally in the cortex.

Figure 1D shows the hand representation for the same monkey 142 days after nerve crush. Receptive fields were found on all skin areas normally innervated by the median nerve (Fig. 1E), indicating a high degree of reinnervation (*6*). In addition, the representations of individual pads and digits were similar in location and extent in both normal and regeneration maps (Fig. 1, B and D). Although minor differences in the shapes of pad and digit representations were observed, representations of skin parts with regen-

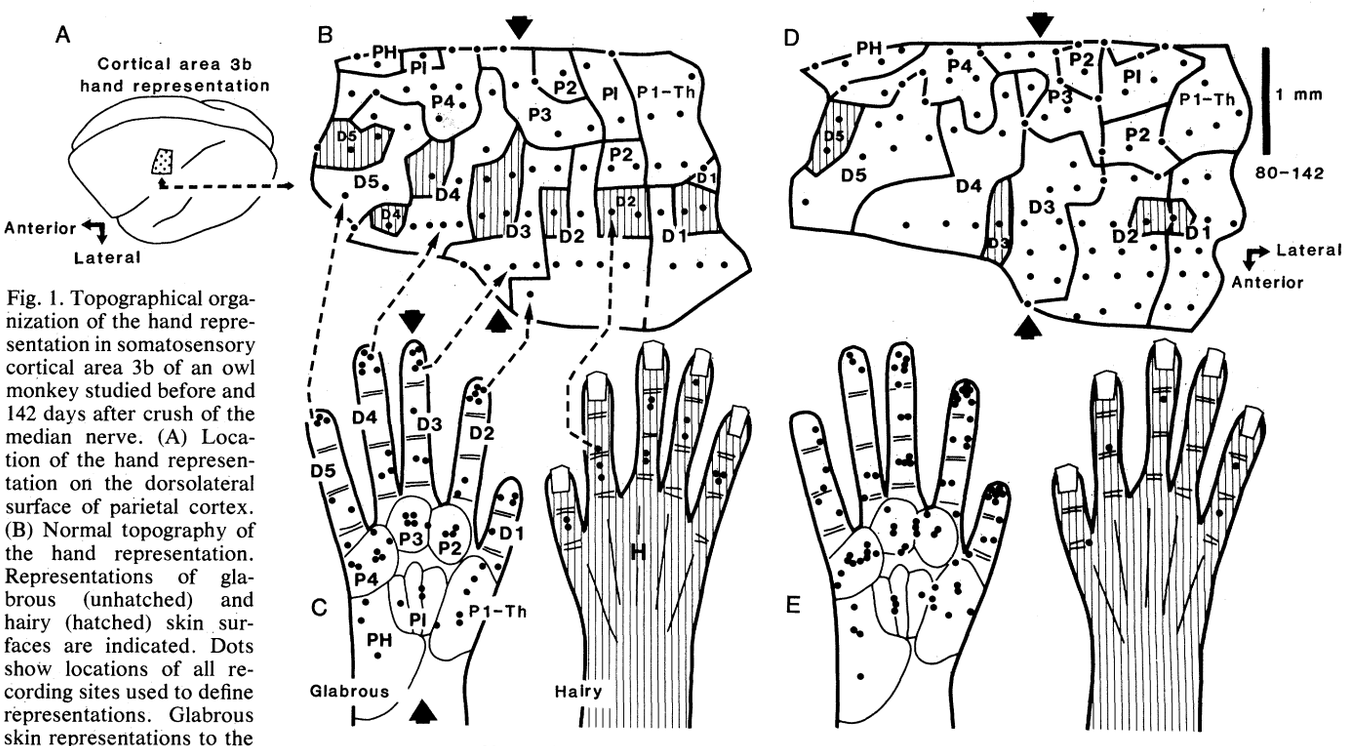

Fig. 1. Topographical organization of the hand representation in somatosensory cortical area 3b of an owl monkey studied before and 142 days after crush of the median nerve. (A) Location of the hand representation on the dorsolateral surface of parietal cortex. (B) Normal topography of the hand representation. Representations of glabrous (unhatched) and hairy (hatched) skin surfaces are indicated. Dots show locations of all recording sites used to define representations. Glabrous skin representations to the right of the large arrowheads receive inputs from the median nerve. Abbreviations: *PH*, hypothenar pad; *PI*, insular pads; *P1–Th*, pad 1 and thenar pad; *P2–P4*, pads 2 to 4; D1–D5, digits 1 to 5; and *H*, hairy hand proximal to knuckles. Spatial calibration and orientation are indicated in D. (C) Glabrous (left) and hairy (right) hand surfaces showing locations of receptive field centers for the recording sites shown in (B). The median nerve innervates glabrous areas to the right of the large arrowheads. (D) The representation of the hand for the monkey shown in (B) as it appeared 142 days after crush of the median nerve. (E) Locations of receptive field centers for all recording sites shown in (D).

erated (for example, P1–Th, P2, and glabrous D1–3) and normal (for example, P4, PH, and glabrous D4–5) inputs underwent comparable degrees of change. These and similar findings from the other monkeys indicate that normally appearing topography can be reestablished after nerve crush and regeneration.

The second question, whether regeneration replicates connections existing prior to injury, was studied in three monkeys mapped before and after nerve crush. As suggested in Fig. 1, B and D, some of the variability between maps can be attributed to sampling factors since the distribution of cortical recording sites was not identical for different mapping sessions in an individual monkey. To minimize this variability, cortical recording sites sampled before crush were matched with closely located recording sites sampled after regeneration, with blood vessel patterns on the brain photographs used as a reference. By comparing the receptive fields observed at these matched sites it was possible to assess the extent to which receptive fields were replicated after regeneration. Figure 2A shows 52 locations where it was possible to match recording sites within 50 to 300 μm of each other and indicates representative receptive fields for ten of these locations. Prior to crush, locations 1 to 5 had receptive fields (bottom left) on skin not innervated by the median nerve, whereas locations 6 to 10 had fields (bottom right) within the median nerve innervation zone. The range of overlap for receptive fields at normally innervated skin varied and resembles the range for fields at reinnervated skin; moreover, some receptive fields at reinnervated skin were similar before and after nerve crush. These findings indicate that preinjury skin-to-cortex correspondences can be replicated accurately.

A third goal was to characterize the sequence of recovery. Two monkeys were mapped shortly after crush to study cortical organization prior to complete regeneration. Figure 2B illustrates the hand representation of a monkey mapped 32 days after crush. Reinnervation was incomplete since most receptive fields for median nerve skin were located on the palmar pads (Fig. 2B, bottom left). Representations of reinnervated pads (P1–Th, P2) appear near their normal locations (Fig. 1B) even though reinnervation is incomplete. Cortical regions normally representing median nerve inputs from glabrous digits 1 to 3 instead represent skin on the hairy hand or hairy digits 1 to 3 innervated by the radial or ulnar nerves. Similar substitution of glabrous with hairy skin inputs were seen in experiments in which the median nerve was transected and ligated to prevent regeneration (*6*). Thus, the replacement of median nerve inputs with other inputs is a direct result of nerve injury and is unrelated to nerve regeneration. Due to this substitution, the proportion of the hand area representing median nerve inputs is smaller than normal at this time. Some cortical regions responded only weakly to tactile stimulation of the median nerve skin. Overall, these observations suggest that cortical reactivation occurs in a specific sequence which primarily reflects the proximal to distal reinnervation of the skin; that is, representations of proximally located pads appear before the more distally located digit skin becomes reinnervated (*7*). Thus, reestablishment of organized representations for reinnervated skin does not depend on complete reinnervation or on complete reactivation of the median cortex by regenerated inputs. These findings also indicate that, prior to complete reinnervation, cortical organization reflects the combined effects of the crush injury and early regeneration.

These experiments demonstrate that cortical topography undergoes a series of changes after nerve crush and regeneration. Among the earliest consequences are changes resulting from the crush injury and entailing substitution of injured inputs with normal inputs from skin regions surrounding the deafferented area. Similar changes have been seen after median nerve transection injury (*6*), which suggests a general pattern of corti-

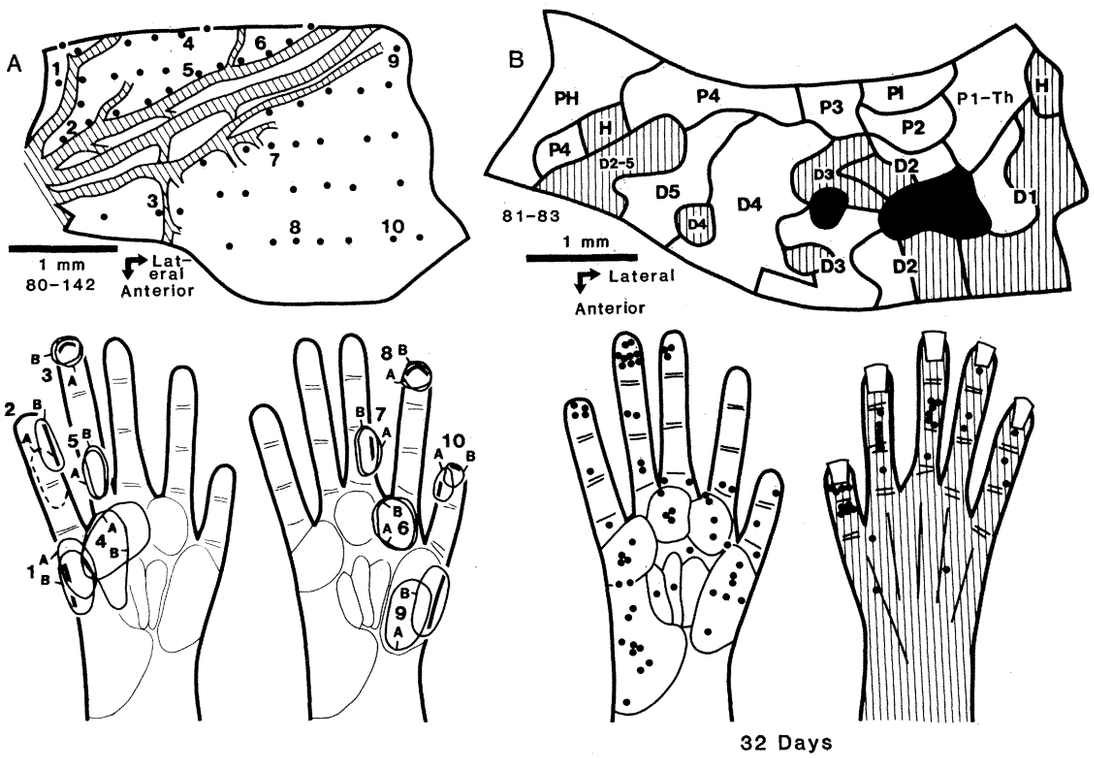

Fig. 2. (A) Comparison of receptive fields at identified cortical locations before and after regeneration. (Top) Dots indicate recording sites sampled before nerve crush which were within 300 μm of a recording site sampled 142 days after nerve crush (the monkey is the one shown in Fig. 1). Recording sites were identified relative to large blood vessels, some of which are also illustrated. (Bottom) Receptive fields observed before nerve crush (*A*'s) are compared to receptive fields seen after regeneration (*B*'s) for cortical sites 1 to 10. Field 2A is shown with dashes to indicate its location on the hairy side of D5. (B) Topography in the hand representation before complete reinnervation. (Top) The hand representation of a monkey 32 days after nerve crush. Blackened areas were poorly reponsive to light tactile stimuli. All other conventions as in Fig. 1B. (Bottom) All receptive field centers for recording sites sampled 32 days after crush.

cal reorganization following any nerve injury that results in degeneration. With subsequent regeneration, inputs progressively reestablish cortical representations and replace inputs that appear after nerve injury. When regeneration follows nerve crush, representations of reinnervated skin areas become sequentially reestablished, and normal features of cortical topography, including preinjury skin-to-cortex correspondences, can be recovered. In contrast, cortical topography is aberrant after nerve transection, repair, and regeneration primarily because many cortical neurons have multiple receptive fields or fields out of topographic sequence (2). Peripheral regeneration thus reestablishes cortical activation from deafferented skin regions after both crush and transection injuries, but the likelihood of replicating preinjury topography is quite different for these injuries. Presumably this difference largely reflects the extent to which normal peripheral innervation patterns are reestablished after regeneration. In view of the good sensory restoration which usually follows nerve crush injuries (*1*), it seems reasonable to conclude that sensory recovery is more readily ensured when preinjury skin to cortex correspondences are reestablished. Recovery of preinjury state may not, however, be the only means of restoring sensory function since sensory impairments after regeneration can be significantly rectified by sensory therapy (*8*). Recovery may be promoted by sensory experience even when regeneration creates abnormal skin to cortex correspondences.

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3. Skin areas innervated by the median nerve have been defined from peripheral nerve recording studies and from cortical mapping studies following median nerve transection and ligation.
4. Mapping methods have been previously described (*5, 6*). Briefly, electrodes angled perpendicular to the cortical surface were lowered to the middle layers and receptive fields were defined from multiple unit responses to light tactile stimuli in monkeys anesthetized with ketamine hydrochloride (25 to 50 mg/kg, injected intramuscularly). Penetrations were closely spaced across the entire hand representation and adjacent cortex. Since there is no central sulcus in owl monkeys, the hand representation is located over a flat, accessible region of cortex (Fig. 1A). Recording sites were marked on an enlarged photograph of the brain surface, and receptive fields were drawn on hand illustrations. Map borders were established midway between adjacent penetrations with receptive fields on different hand parts. If the receptive field straddled more than one hand part, the border distinguishing the involved representations was placed at the penetration location.
5. M. M. Merzenich, J. H. Kaas, M. Sur, C. S. Lin, *J. Comp. Neurol.* **181**, 41 (1978).
6. When the median nerve is transected and regeneration is prevented by ligation, low-threshold inputs from the ulnar or radial nerves do not sprout into the denervated skin [M. M. Merzenich *et al.*, *Neuroscience* **9**, 33 (1983)]. Thus, recovery of inputs from the skin of the median nerve depends on regeneration of the median nerve.
7. After mapping in another experiment with a short regeneration period, the innervation field of the partially regenerated median nerve was defined with nerve recordings. The extent of reinnervation estimated by nerve recording closely corresponded to the extent of reinnervation estimated from the cortical map. This suggests that cortical reactivation closely follows peripheral reinnervation after crush injuries.
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9. We thank C. Cusick, M. Powers, and R. Wiley for their helpful criticisms.

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Cortical Dopaminergic Involvement in Cocaine Reinforcement

Abstract. *Neuronal systems involved in the initiation of cocaine reinforcement were investigated by identifying brain sites where direct application of the drug was reinforcing. This was accomplished by allowing rats to self-administer picomolar concentrations of cocaine into discrete brain regions. The medial prefrontal cortex supported self-administration, while the nucleus accumbens and ventral tegmental area did not. Self-administration could be attenuated by including equimolar concentrations of the dopaminergic D_2-receptor antagonist sulpiride in the microinjection system. These results imply that cocaine reinforcement is mediated in part through a direct action on mesocortical dopaminergic receptors.*

Cocaine is a local anesthetic agent that is used by millions of people (*1*). Parallels between the use of cocaine by humans and self-administration of the drug by animals have recently been established (*2*). Behavioral studies have shown that cocaine is a potent reinforcing stimulus that will maintain responding on operant schedules of reinforcement (*3*). Self-administration occurs in the absence of demonstrable physiological dependence (*4*), suggesting that cocaine-seeking in humans results principally from the reinforcing properties of this drug and not from a desire to postpone the discomforts of withdrawal.

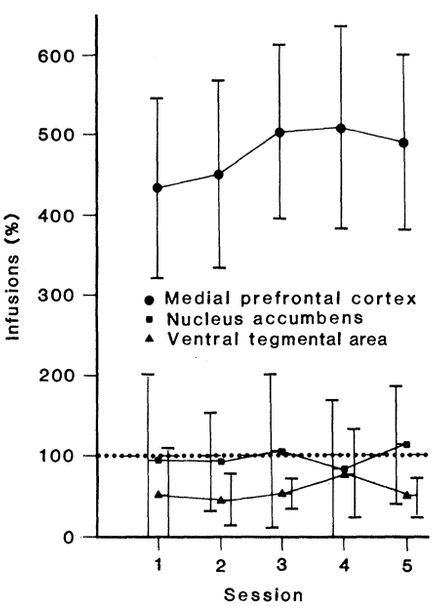

Fig. 1. Intracranial self-infusions of cocaine hydrochloride (100 pmole per microinfusion), presented as the percentage of infusions of vehicle (artificial cerebrospinal fluid), by rats with cannulas implanted into the nucleus accumbens, ventral tegmental area, or medial prefrontal cortex. Values are means ± standard deviations for five animals per group.

Even though little is known about the neuronal mechanisms mediating cocaine reinforcement, neuropharmacological investigations suggest an involvement of the biogenic amines. Cocaine inhibits reuptake of norepinephrine (*5*), dopamine (*6*), and serotonin (*7*) in vitro and increases the turnover of dopamine in rat brain (*8*). Pimozide, a dopaminergic receptor antagonist, attenuates the intravenous self-administration of cocaine by rats while the noradrenergic receptor blocker phentolamine does not (*9*), suggesting a role for dopaminergic neurons in this behavior. More recently, 6-hydroxydopamine lesions of the nucleus accumbens were shown to decrease the rate of intravenous self-administration of cocaine (*10*), further implicating mesolimbic dopaminergic neurons. We attempted to directly explore the neuronal circuitry involved in cocaine reinforcement by using an intracranial self-administration (ICSA) methodology. We report that the application of cocaine into the medial prefrontal cortex results in the initiation of reinforcing neuronal activity.

Experimentally naïve male Fischer 344 rats 90 to 150 days old were stereotaxically implanted unilaterally with 22-gauge guide cannulas into the nucleus accumbens, ventral tegmental area, or