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Sensory Nerve Crush and Regeneration and the Receptive Fields and Response Properties of Neurons in the Primary Somatosensory Cerebral Cortex of Cats

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Extracellular recordings were made of activity evoked in neurons of the forepaw focus of somatosensory cerebral cortex by electrical stimulation of each paw in control cats and cats that had undergone crush injury of all cutaneous sensory nerves to the contralateral forepaw 31 to 63 days previously. Neurons responding only to stimulation of the contralateral forepaw were classified as *sa*; neurons responding to stimulation of both forepaws were classified as *sb*; neurons responding to stimulation of both contralateral paws were classified as *sc*; and neurons responding to stimulation of at least three paws were classified as *m*. The ratio *sa*:*sb*:*sc*:*m* neurons was 46:3:0:0 in control cats and 104:15:3:26 in cats that had undergone nerve crush 1–2 months prior to study. *sa* neurons from experimental cats had depth distributions similar to those in controls and responded to contralateral forepaw stimulation with *more* spikes per discharge, *longer* latency, and *higher* threshold than *sa* neurons in control cats. *m* neurons from experimental cats were distributed deeper in the cortex than *sa* neurons, and, when compared to experimental *sa* neurons, they responded with longer latency and poorer frequency-following ability; however, the number of spikes per discharge and threshold were not significantly different. The appearance of wide-field neurons in this tissue may be explained in terms of strengthening of previously subthreshold inputs to neurons in the somatosensory system. If the neurons in sensory cortex play a requisite role in cutaneous sensations and if changes similar to those reported here occur and persist in human cortex after nerve crush, then "complete" recovery of sensation in such patients may occur against a background of changed cortical neuronal responsiveness.

INTRODUCTION

Injury to peripheral nerves is frequently followed by recovery of tactual sensation to an extent determined partly by the nature of the injury. Recovery is more likely to be complete following crush injuries than following transection of a nerve; normal tactual sensations are often regained after crush injuries, but inability to properly localize stimuli is frequently experienced following nerve transections, especially when nerves are allowed or forced to innervate foreign skin regions (12, 20). A popular theory states that complete recovery of sensory function occurs after peripheral nerve crush because the regenerating axons are guided back to their original connections by intact Schwann cell tubes. Following nerve transection, the Schwann cell tube is disrupted, and regenerating nerve axons reinnervate skin haphazardly and frequently incorrectly (15, 28). We may refer to this as the "peripheral theory" of sensory recovery.

Within a few minutes or hours of peripheral nerve transection or removal of a digit, many neurons in the primary cortical representation (SI) of that nerve or digit become silent; others respond to relatively intense stimulation in larger-than-normal receptive fields, precise boundaries of which are difficult to determine. After some time, neurons begin to respond to stimulation of skin around the denervated area or on digits adjacent to the amputated digit, with response thresholds gradually falling over time. These observations have been made repeatedly in both monkeys and raccoons (18, 24, 32, 33). Similar results occurred in rats (40) and cats (17), but a greater number of neurons in some of the representation of the denervated part remained unresponsive to peripheral stimulation over the period of study.

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If a peripheral nerve is cut and then allowed to repair, initially the representation of the cut nerve is occupied by inputs from surrounding skin areas, but later the regenerating nerve begins to regain its original representation (30, 42). There is apparently no somatotopic organization in the representation of the repaired nerve. Wall *et al.* (42) suggested that the lack of somatotopic organization indicated that many of the regenerated axons had grown back to inappropriate skin locations.

After nerve crush, the representation of the nerve came to be occupied by inputs from surrounding, innervated regions of skin, much as occurs after transection. After periods long enough for regeneration to occur, all deafferented skin regions were reinnervated, and the cortical representations appeared normal in size and location (41). The general picture—that in somatosensory cortex the representation of a nerve after crush and repair is indistinguishable from normal, whereas the representation after nerve transection and repair is considerably altered—appears to support the "peripheral theory." Cortical representations are disturbed by temporary denervation of the periphery, but peripheral fibers are able to reinnervate proper receptors and recover their territories in cortex after a nerve crush. Presumably, sensory discriminations are restored because *both* peripheral and central recovery is proper. After a transection, some peripheral fibers fail to reinnervate proper receptors. This failure may result in improper territories in cortex or there may be an additional, independent error in the cortex. Presumably, one or both of these changes result in faulty localization and other errors in skin sensation following transection injuries.

Most of the studies of changes in the somatosensory cortex following peripheral nerve damage have concentrated on somatotopic organization as indicated by multiunit samples of activity in the "middle layers" of cortex. We wondered what changes might be discernible in single unit samples from a single region—the forepaw representation in coronal cortex (SI) of cats. We, therefore, studied neurons at all depths of the cortex by making numerous penetrations into this area. In control animals, this area contains almost exclusively cells with small receptive fields confined to the contralateral forepaw. We were surprised to find a number of cells with large, bilateral receptive fields in this same tissue in animals that had undergone crush and repair of all of the cutaneous innervation of the contralateral forepaw. These results compromise the peripheral theory.

MATERIALS AND METHODS

This study employed 29 adult (2.5–5.0 kg) cats, parceled into an experimental and a control group. Both groups were treated similarly, except for the initial nerve crush. In experimental animals, the sensory cutaneous nerves to the right forepaw were crushed 31 to 63 days before electrophysiological recording. The cats were anesthetized with ketamine (33 mg/kg) and xylazine (0.5 mg/kg) and the lateral and medial branches of the superficial radial nerve, the dorsal and palmar branches of the ulnar nerve, and the median nerve were exposed at the wrist. The nerves were dissected free and crushed by applying pressure with hemostats (5.0-mm-wide jaw) for 2 min. This treatment was sufficient to prevent nerve conduction across the crush site (as determined by recording the compound action potential before and after the crush). Wounds were closed and the animals were returned to the animal facility and monitored for return of sensory function. Immediately after recovery from anesthesia, the animals were unresponsive to pinching the denervated paw distal to the wrist with toothed forceps. All cats experienced "footdrop" and failed to use the denervated paw, but function returned within 7 to 10 days. A withdrawal response to pinching with toothed forceps distal to the wrist was evoked in all experimental cats 14 to 18 days after crush, indicating some regeneration of the sensory nerves. No attempt was made to assess the recovery of low threshold tactile sensation. Assuming a regeneration rate of 2–4 mm/day for myelinated fibers following crush injuries (11, 16), the most rapidly regenerating fibers could have spanned the 4- to 5-cm distance from the crush site to the tip of the limb in 10–25 days. Slowly regenerating myelinated fibers perhaps were not regenerated, or at least remyelinated, at the time of these experiments. The regeneration of unmyelinated fibers would probably have occurred much earlier than that for myelinated fibers (14).

Recording techniques were identical for control and experimental cats. The cats were anesthetized with α-chloralose (60 mg/kg, ip), and maintenance doses of 30 mg/kg, ip, were given as needed. A cannula was placed in the femoral vein of the left hindleg for administration of paralyzing drugs, and a slow intravenous drip of lactated Ringer's solution was administered throughout the recording session. The trachea was cannulated and the cats were artificially ventilated to maintain end-expiratory CO_2 at 3.5 to 4.0%. Neuromuscular blockade was achieved with gallamine triethiodide (1.0 mg/h). Rectal temperature was monitored and maintained at 37°C with a servocontrolled dc heating pad. Bilateral pneumothorax, cisternal drainage, and suspension by one thoracic and one lumbar vertebral spinous process were performed to minimize cerebral pulsations.

Bipolar needle electrodes were placed into the central pad of each paw, and each paw was stimulated with square wave pulses of 0.10-ms duration and 25-mA intensity (supramaximal for the compound action potential in the superficial radial nerve). Hunting stimuli consisted of electrical shocks applied to the right (contralateral to the cortical recording site) forepaw at a rate of

one per second. The hunting stimuli were used to isolate extracellular action potentials from single neurons in the somatosensory cortex.

The cat was placed in a stereotaxic head holder, and single-unit extracellular recordings were obtained from neurons isolated in the forepaw focus of the left primary somatosensory cortex (SI) exposed by craniotomy. This focus is located just medial to the coronal sulcus and just anterior to the coronal plane containing the postcruciate dimple. Recording sites were located both by sulcal landmarks and by the characteristic shape of the primary evoked potential. (In two animals, histological examination showed the recording site to be in area 3b.) Exposed cortex was covered with a thin, polyethylene film except during recording to prevent desiccation. Glass capillary microelectrodes filled with 1.25 *M* sodium citrate and 5% pontamine blue (tip impedance of 2–5 MΩ) were used to record the extracellular responses from single cells. Signals from the electrodes were led to a Grass P15b AC preamplifier set at a gain of 100 and a half-amplitude bandwidth of 30 Hz to 10 kHz and displayed on a Tektronix 565 oscilloscope. The display was photographed using a Grass C4 kymograph camera. The film records were examined on a microfiche reader at 7× magnification. Response probabilities were computed for each paw input from 10 photographed trials. Latencies of all spikes in response to paw input were measured from the shock artifact. Depths of isolation for single units were read from the micrometer scale of the micromanipulator. (No attempt was made to mark recording sites because this gives no additional information in the absence of knowledge about what part of the cell is nearest the electrode tip.)

These data were compared for experimental and control animals using the Student *t* test for the comparison of two independent means or the X^2 test for contingency tables, employing the usual levels of significance.

In this study, we did not measure receptive field sizes directly; rather, we used responses to electrical stimulation of the central footpad of each limb as a quick, yet highly repeatable, estimate of receptive field size and location. Using this estimate, we placed neurons into sets as follows: *sa* neuron—responds to stimulation of the contralateral forepaw only; *sb* neuron—responds to stimulation of both forepaws but neither hindpaw; *sc* neuron—responds to stimulation of both contralateral paws but neither ipsilateral paw; *m* neuron—responds to stimulation of at least three paws, and usually all four. For this scheme, a neuron was said to respond if it discharged following at least 50% (i.e., to 5 of 10) of the test shocks to the footpad. Failure to respond was taken as a discharge following less than 50% of the test shocks (usually 0 of 10). *Sa* neurons in this scheme would be classified as small-field cells by others, whereas all other neurons would be classified as wide-field.

TABLE 1

Number (Percentage) of Neurons in Sets

	Set			
Condition	*sa*	*sb*	*sc*	*m*
Crushed	104 (70)	15 (10)	3 (2)	26 (18)
Control	46 (94)	3 (6)	0	0

Electrical stimulation was used because of its repeatability. "Natural stimulation," as usually employed, is not natural and varies from laboratory to laboratory, from investigator to investigator, and from time to time. Two previous studies of neurons in this tissue employed the same classification scheme, the same hunting stimuli and similar electrodes (26, 35). Data from these studies are included in this report for comparison because they are similar to our results from control cats. No attempt has been made to combine results from the three studies.

RESULTS

Extracellular recordings were obtained from 49 neurons in eight control cats and 148 neurons in 21 cats which had undergone sensory nerve crush 31–63 days previously.

Receptive Fields

Control animals. Table 1 shows the numbers of neurons in each set found in the coronal cortex of control and experimental animals in this study. Most of the neurons (94%) in our control animals were *sa* neurons, whereas 6% had bilateral receptive fields and were classified as *sb* neurons. Examples of discharges of control *sa* neurons are shown in the upper panel of Fig. 1. The findings in the small sample of neurons from control animals in this study agreed with those reported by previous studies. In the study by Morse *et al.* (26), all neurons studied in the coronal cortex (n = 278) were found to be small-field neurons with receptive fields restricted to the contralateral forepaw and were classified as *sa* neurons. They reported no neurons with bilateral or wider receptive fields. In a later study by Satterthwaite *et al.* (35), the majority of neurons had receptive fields restricted to the contralateral forepaw (n = 71; 92%), but 8% (n = 6) of the neurons had receptive fields located on both forepaws and were classified as *sb* neurons. No published study of control forepaw SI cortex has reported any other types of receptive fields.

Experimental animals. In animals which had undergone sensory nerve crush and regeneration, 70% of neurons were of the *sa* set and 10% were *sb* neurons. However, in contrast to what has been seen in coronal cortex

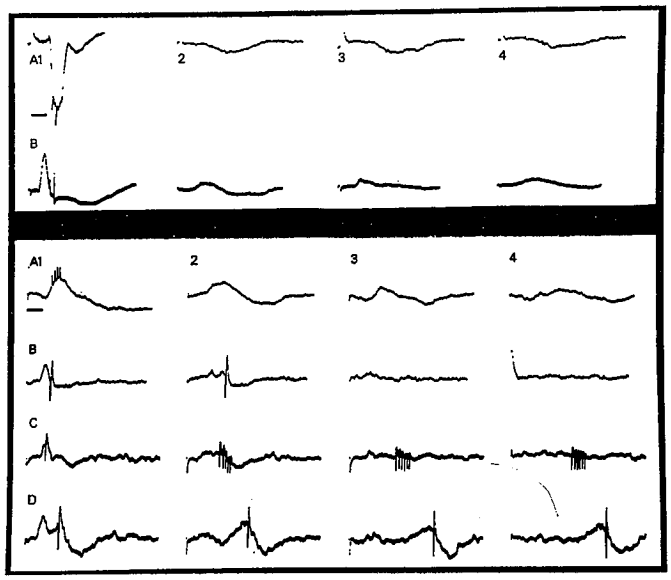

FIG. 1. Throughout the figure, columns show responses to stimulation of the contralateral forepaw (1), the ipsilateral forepaw (2), the contralateral hindpaw (3), and the ipsilateral hindpaw (4). The upper panel shows two different *sa* neurons in control animals (rows A and B). The lower panel shows responses of an *sa* neuron (A), an *sb* neuron (B), and two *m* neurons (C and D) from experimental cats. Time marks in both panels represent 10 ms.

in intact animals, 2% of the neurons in crush/regeneration animals had receptive fields restricted to the contralateral half of the body (*sc* neurons), and 18% had receptive fields on three or four paws (*m* neurons). Thus, one neuron in five had a receptive field not previously reported for neurons in this tissue. A 2% increase in *sc* neurons is not statistically significant, but the 18% increase in *m* neurons is ($P < 0.001$), and, when compared with a X^2 test, the distribution shown in Table 1 for control animals is significantly different from that for animals after nerve crush ($X^2 = 24.512$, $df = 2$, $P = 0.00004$).

Sample recordings from neurons in experimental animals are shown in Fig. 1, lower panel. Row A shows discharges of an *sa* neuron, row B those of an *sb* neuron, and rows C and D those of two *m* neurons. During recording in experimental animals, we encountered neurons that seemed to fire spontaneously and were not influenced at all by electrical stimuli applied to the contralateral forepaw. In addition, there were neurons that responded to stimulation with $P < 0.5$. Some of the neurons classified as *sa* actually discharged to off-focus input (for this tissue, on-focus is the contralateral forepaw, off-focus is any other paw) at $P = 0.3$–0.4. A less stringent criterion would classify these as *sb*, *sc*, or *m* neurons and increase the number of these aberrant neurons and decrease the number of *sa* neurons. These neurons with low probability discharges off-focus were not common in control animals.

Depth Distribution

Control animals. The left panel of Fig. 2 shows the distribution in depth of all neurons sampled in coronal cortex of intact animals from this study compared to that of Morse *et al.* (26). In both studies, neurons were isolated in all layers of the cortex, but most were concentrated in the middle and upper layers. The mode of their distribution occurred at 0.9 mm; ours occurred at 0.5 mm. The remainder of the distribution was similar in both studies, showing a decrease in numbers of neurons at deeper levels.

Experimental animals. The center panel of Fig. 2 presents the depth distribution for all neurons in the coronal cortex of cats that had undergone sensory nerve crush and regeneration and, for comparison, the distribution for all neurons from control animals. In experimental animals, there is a bimodal distribution of neurons in depth with nearly equal modes at 0.5 and 1.1 mm, in contrast to the control animals with a unimodal distribution, with mode at 0.5 mm. Also, relative to the control distribution, the experimental distribution is deficient in neurons below 1.7 mm, despite the fact that the experimental sample was larger.

The right panel of Fig. 2 shows the depth distribution of each set of neurons found in experimental animals. *Sa* neurons were found throughout the depth of the cortex, with a mode at 0.5 mm as in control animals; *sb* neurons were found between 0.5 and 2.1 mm, with a mode at 1.1 mm; and *m* neurons were found below 0.5 mm, with a mode at 1.1 mm. *Sc* neurons were found only superficially within the cortex—mean depth, 0.69 mm; maximum depth, 0.971 mm.

Neuronal Response Properties

Table 2 shows the mean response properties for sets of neurons in coronal cortex following contralateral forepaw stimulation. Properties of *sb* neurons in control cats and *sc* neurons in experimental cats are not included because of the small number of neurons in each set. Also, in a few cases the neurons were lost before all information could be collected.

Spikes per discharge: Control animals. In control cats, the *sa* neurons responded with 1.67 (median = 1.70; mode = 1.76) spikes on the average to a supramaximal stimulus applied to the contralateral forepaw. Figure 3 shows a frequency histogram of the number of spikes per discharge for *sa* neurons isolated in coronal cortex in control cats. Over 60% of *sa* neurons in the control animals responded with 1.0 to 1.5 spikes per discharge, and all *sa* neurons responded with less than five spikes per discharge.

Spikes per discharge: Experimental animals. Figure 3 also shows the distribution of the number of spikes per

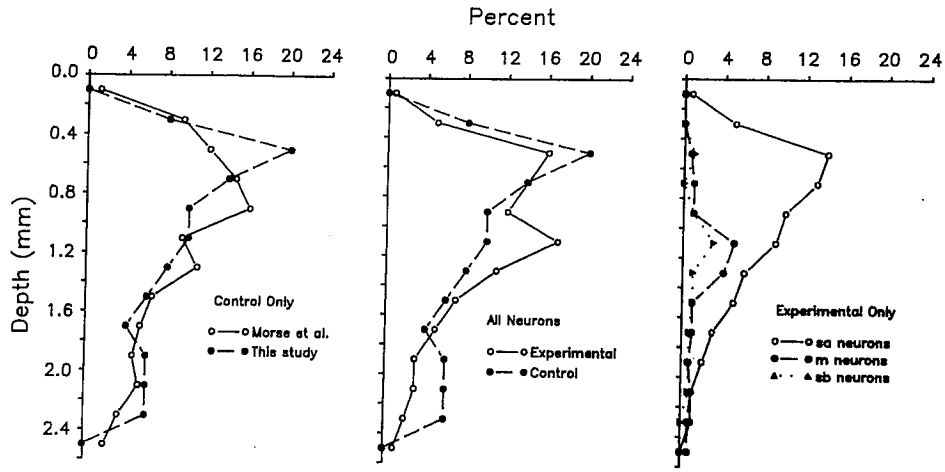

FIG. 2. Left: Depth-distribution of all neurons isolated in coronal cortex in intact cats as reported by Morse *et al.* ((26); solid line; $n = 268$) compared with control cats from this study (dashed line; $n = 48$). Center: Depth-distribution of all neurons isolated in coronal cortex in control cats (solid line; $n = 48$) compared with the distribution found in cats that had undergone nerve crush and regeneration (dashed line; $n = 148$). Right: Depth-distribution of each neuron type isolated in the coronal cortex of cats that had undergone sensory nerve crush and regeneration. Solid line, *sa* neurons. Dashed line, *sb* neurons. Dotted line, *m* neurons. Neuron depths are grouped into 0.2-mm bins and the number of cells in each bin is plotted as a percentage of the total sample.

discharge for *sa*, *sb*, and *m* neurons isolated in experimental cats. The numbers of spikes per discharge are not significantly different for *sa*, *sb*, and *m* neurons after nerve crush; however, *sa*, *sb*, and *m* neurons after crush responded with significantly more spikes per discharge than control *sa* neurons ($P < 0.01$). In experimental cats, neurons in the ranges 0 to 0.9 and 1.8 to 2.5 mm below the pial surface responded with more spikes per discharge when compared with those in control cats. Between 0.9 and 1.8 mm in cortical depth both control and experimental neurons responded with similar mean numbers of spikes per discharge.

Following contralateral forepaw stimulation, 60% of *sb* neurons responded with less than 2.5 spikes per discharge; only 13% responded with between 1.0 and 1.5 spikes per discharge. Following ipsilateral forepaw stimulation (not shown), 60% of *sb* neurons responded with 1.0 to 1.5 spikes per discharge. Two of the *sc* neurons discharged 3.10 and 3.60 spikes per discharge for contralateral forepaw stimulation and 3.44 and 3.70

TABLE 2

Mean Response Properties for Neurons in Coronal Cortex following Contralateral Forepaw Stimulation

	Control ($N = 49$)	Deafferented ($N = 148$)		
Property	*sa*	*sa*	*sb*	*m*
Number of neurons	46	104	15	26
Depth (μm)	1040 ± 608[a]	971 ± 509	1241 ± 479	1399 ± 477
Spikes per discharge				
CF	1.67 ± 0.91	2.33 ± 1.61	2.77 ± 1.61	2.75 ± 2.34
IF			2.21 ± 1.75	3.31 ± 1.86
CH				2.79 ± 1.99
IH				2.46 ± 1.64
First spike latency (ms)				
CF	12.11 ± 2.78	15.60 ± 5.07	15.53 ± 3.12	19.99 ± 6.07
IF			32.94 ± 7.18	32.17 ± 9.26
CH				42.42 ± 10.6
IH				46.66 ± 6.00
Threshold (mA)	6.79 ± 5.98	12.50 ± 6.35	11.20 ± 4.63	11.02 ± 4.66
Frequency-following (s^{-1})	5.39 ± 5.06	5.35 ± 6.53	4.71 ± 3.32	2.40 ± 1.76

[a] Mean ± standard deviation.

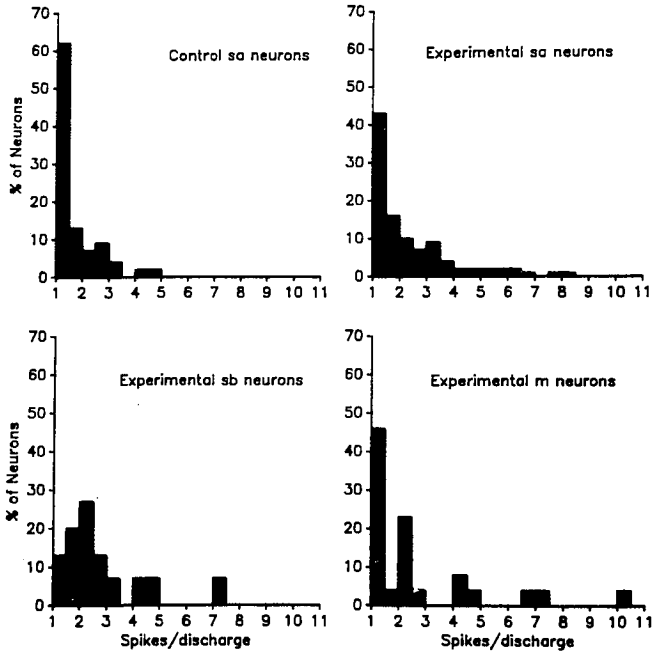

FIG. 3. Distribution of the mean number of spikes per discharge following supramaximal contralateral forepaw stimulation for *sa* neurons in control (upper left) and *sa* (upper right), *sb* (lower left), and *m* (lower right) neurons in deafferented/regenerated cats.

spikes per discharge for contralateral hindpaw stimulation.

Almost 50% of the *m* neurons responded with 1.0 to 1.5 spikes per discharge, and 87% responded with three or fewer spikes per discharge following contralateral forepaw stimulation. Following ipsilateral forepaw stimulation *m* neurons responded with a mean of 3.31 spikes per discharge. Twenty-nine percent of the neurons responded with between 2.5 and 3.0 spikes per discharge, and 59% of the *m* neurons responded with three or fewer spikes per discharge following ipsilateral forepaw stimulation. After contralateral hindpaw stimulation, *m* neurons responded with a mean of 2.79 spikes per discharge. Thirty percent of the neurons responded with between 1.0 and 1.5 spikes per discharge, and 69% of the neurons responded with three or fewer spikes per discharge. *M* neurons responded to ipsilateral hindpaw stimulation with a mean of 2.47 spikes per discharge. Thirty-three percent of the neurons responded with between 1.0 and 1.5 spikes per discharge, and 83% of the neurons responded with three or fewer spikes per discharge. When the numbers of spikes per discharge for *m* neurons were compared for all inputs using the Student *t* test, off-focus inputs were not significantly different from the contralateral forepaw input. Histograms for off-focus inputs are not presented in Fig. 3. In all sets of neurons after nerve crush, the majority of neurons responded with three or fewer spikes per discharge. The increase in the number of spikes per discharge and the presence of spontaneously active cells in experimental cats could be due to a change in excitability of neurons after the loss of cutaneous input.

First spike latency: Control animals. The mean first spike latency for *sa* neurons in control cats following supramaximal stimulation of the contralateral forepaw was 12.11 ms. Figure 4 shows a frequency histogram of first spike latencies of control *sa* neurons following contralateral forepaw stimulation. All *sa* neurons responded in less than 20 ms. Thirty-nine percent of control *sa* neurons responded between 10 and 12 ms after stimulation, and 58% responded with latencies less than 12 ms. The first spike latencies of the three *sb* neurons were 15.95, 15.89, and 10.38 ms following supramaximal contralateral forepaw stimulation.

First spike latency: Experimental animals. The mean first spike latency for *sa* neurons in experimental cats (15.60 ms) was significantly longer than that for control cats ($P < 0.001$). Figure 4 also shows the distribution of first spike latencies for *sa* neurons in experimental cats following contralateral forepaw stimulation. Perhaps these longer latencies can be attributed to a combination of increased nerve conduction time across the site of crush; the slower conduction of nerve impulses in immature, regenerating peripheral nerve fibers; the reduced numbers of myelinated fibers in the regenerating nerve, leading to greater synaptic summation time; or utiliza-

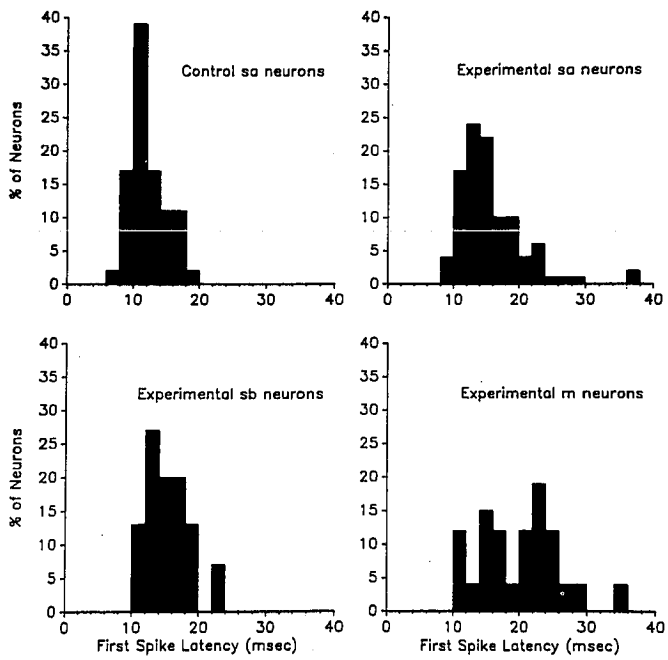

FIG. 4. Distribution of mean first spike latencies following supramaximal contralateral forepaw stimulation for *sa* neurons in control (upper left) and *sa* (upper right), *sb* (lower left), and *m* (lower right) neurons in deafferented/regenerated cats.

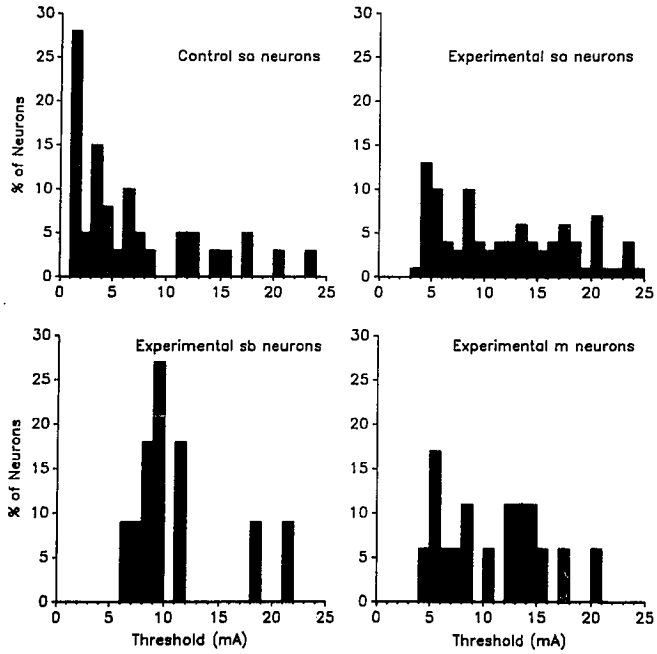

FIG. 5. Distribution of response thresholds for contralateral forepaw stimulation for *sa* neurons in control (upper left) and *sa* (upper right), *sb* (lower left), and *m* (lower right) neurons in deafferented/regenerated cats.

tion of polysynaptic pathways. Horch (15) reported that normal nerve conduction does not return until 180 days after crush injury, i.e., after the time of our studies.

The mean first spike latency for *sb* neurons (15.53 ms) following contralateral forepaw stimulation was not significantly longer than that for *sa* neurons after nerve crush. The mean latency for *sb* neurons following ipsilateral forepaw stimulation was 32.94 ms compared with 49.75 ms for *sb* neurons in control animals. The distribution of latencies for *sb* neurons following contralateral forepaw stimulation is shown in the lower left panel of Fig. 4. Two of the *sc* neurons responded with latencies of 13.74 and 13.69 ms for contralateral forepaw stimulation and 23.36 and 20.87 ms for contralateral hindpaw stimulation.

The mean first spike latency for *m* neurons following contralateral forepaw stimulation (19.99 ms; distribution shown in Fig. 4) was significantly longer than that for *sa* neurons ($P < 0.001$). The mean first spike latencies for *m* neurons following ipsilateral forepaw, contralateral hindpaw, and ipsilateral hindpaw stimulation were 32.17, 42.42, and 46.66 ms, respectively (Table 2).

Threshold: Control animals. Figure 5 shows the distribution of response thresholds for contralateral forepaw stimulation in control *sa* neurons. The mean threshold for *sa* neurons in control cats was 6.79 mA. Although thresholds for *sa* neurons were distributed over the range from 0 to 25 mA, most were in the lower range. Twenty-eight percent of the thresholds were between 1.0 and 2.0 mA, and more than half (56%) were below 5.0 mA.

Threshold: Experimental animals. The mean response threshold for *sa* neurons in experimental cats (12.50 mA) was significantly higher than that for control cats ($P < 0.001$). Figure 5 also shows the distribution of response thresholds for contralateral forepaw stimulation in *sa* neurons in experimental cats. The thresholds ranged from 3.0 to 25.0 mA, but, for *sa* neurons after nerve crush, only 14% of the thresholds were below 5.0 mA.

The mean response threshold for *sb* neurons (11.20 mA) was significantly higher than that for *sa* neurons in control cats ($P < 0.05$), but not significantly different from *sa* or *m* neurons in experimental cats. The distributions of response thresholds for both *sb* and *m* neurons are also shown in Fig. 5.

The mean response threshold for *m* neurons (11.02 mA) was significantly higher than that for *sa* neurons in control cats ($P < 0.01$), but not significantly different from that for *sa* or *sb* neurons in experimental cats. Most of the thresholds were distributed in the middle range from 4.0 to 21.0 mA and only 6% of the *m* neuron thresholds were below 5.0 mA. The mean response thresholds for the three neuron sets in experimental cats were not significantly different from each other. No threshold data were obtained for *sc* neurons.

Frequency-following: Control animals. Figure 6 shows the distribution of stimulus frequencies that were followed by *sa* neurons. The mean stimulus frequency that *sa* neurons in control cats faithfully followed was 5.39/s. Only 11% of *sa* neurons faithfully followed stimuli applied at a rate greater than 10/s.

Frequency-following: Experimental animals. The distributions of stimulus frequencies followed by *sa*, *sb*, and *m* neurons in experimental cats are shown in Fig. 6. The mean frequency-following ability of *sa* neurons before nerve crush, *sa* neurons after nerve crush, and *sb* neurons after nerve crush were not significantly different. However, the mean frequency-following ability of *m* neurons after crush was significantly lower than that of *sa* and *sb* neurons after nerve crush and *sa* neurons before crush ($P < 0.05$ for all comparisons). No frequency-following data were obtained for *sc* neurons.

DISCUSSION

The forepaw focus of SI cortex in chloralose-anesthetized cats was chosen for this study because most neurons in this tissue have small receptive fields on the contralateral forepaw, and none has a receptive field on all

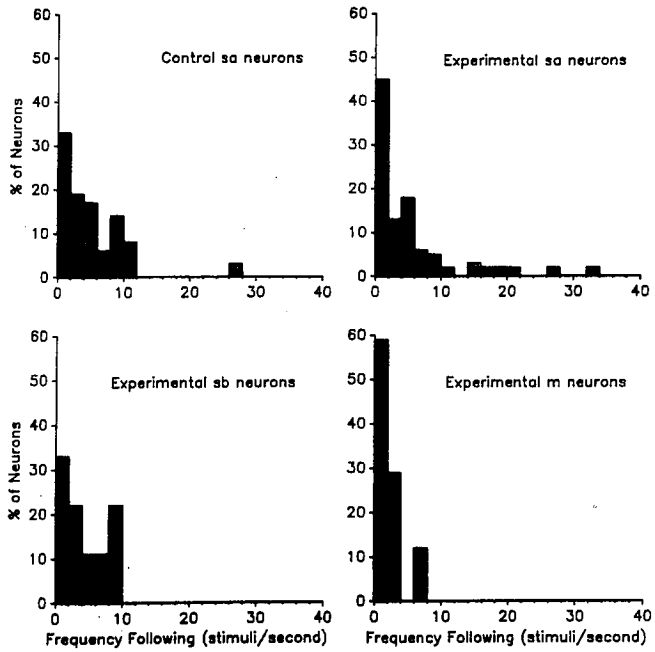

FIG. 6. Distribution of mean frequency-following for supramaximal contralateral forepaw stimulation by *sa* neurons in control (upper left) and *sa* (upper right), *sb* (lower left), and *m* (lower right) neurons in deafferented/regenerated cats.

four limbs.[3] Against this baseline, a change in receptive field size after loss of sensory input would easily be seen. Our results indicate that 31 to 63 days after crushing the cutaneous sensory nerves of the forepaw, unusual types of neurons—wide-field or *sc* and *m* neurons—appear in samples from this tissue. The response properties of these *sc* or *m* neurons, though significantly different from those of *sa* neurons in control cats, are not totally comparable to those of *sc* or *m* neurons found normally in other cortical fields (21). The *m* neurons that appeared after nerve crush did not respond with significantly more spikes per discharge or lower thresholds than *sa* neurons as they do in pericruciate tissue; however, they did have a significantly longer mean first spike latencies and lower mean frequency-following abilities. In normal pericruciate cortex, the *m* neurons are thought to be facilitated by the *sa* neurons, which accounts for the increased number of spikes per discharge and lower thresholds of *m* neurons for contralateral forepaw stimulation relative to off-focus stimulation. The *m* neurons in this study did not respond with significantly more spikes per discharge or lower thresholds; perhaps *m* neurons in this tissue do not receive a facilitatory input from *sa* neurons.

Neurons with enlarged receptive fields have been noted in the dorsal column nuclei, thalamus, and cortex after deafferentation, but these findings are confounded by the fact that wide-field neurons are normally present in these tissues (5, 21, 22, 31). For example, Franck (8, 9) studied the effect of dorsal rhizotomy on the organization of the hindlimb sensorimotor cortex in the cat. Over 33% of the neurons in the deafferented cortex responded to several submodalities of stimulation and had bilateral or multiple receptive fields, compared to only 7% of neurons that had such properties in control animals. On the other hand, 36% of the neurons in normal hindlimb SI of chloralose-anesthetized cats are wide-field or *m* neurons (21). Thus, it is not clear that Franck's bilateral neurons were unusual for this tissue. In addition, no recovery from the rhizotomy was allowed in Franck's study.

Why Haven't Others Obtained These Results?

Previous deafferentation studies have not revealed the presence of wide-field neurons in the forepaw focus of SI cortex after nerve transection (17, 18) or crush (41). We think the most likely explanations for this failure to see *m* neurons are as follows: (1) The existence of ipsilateral responsiveness may not have been examined because of the prevailing ideas about cortical organization. Some investigators do not expect to find *m* neurons so they don't look for them. (2) The use of barbiturates blocked the responsiveness of *m* neurons. Kalaska and Pomeranz (17) specifically reported the absence of ipsilateral forelimb and hindlimb input to the coronal cortex after deafferentation. Their failure to observe wide-field neurons is most likely explained by the use of barbiturate anesthesia, which is known to block the activity of wide-field or *m* neurons (13). *m* neurons have been seen in a wide variety of experimental conditions, including unanesthetized, paralyzed cats (2); unanesthetized, nonparalyzed cats (1); and chloralose-anesthetized cats (29, 38), but because of the wide-spread use of barbiturates and the sensitivity of *m* neurons to these agents, wide-field or *m* neuron activity is not frequently reported. It is doubtful that the use of electrical stimulation accounts for our observation of wide fields because at least some of these neurons have wide fields when tested with natural stimulation, but we did not explore this property systematically.

Possible Mechanisms of Reorganization in Somatosensory Systems

There are several possible classes of explanation for the appearance of wide-field or *m* neurons in samples taken after deafferentation and regeneration. Explanation in terms of migration of intact cells into the

[3] Actually, there is one published account of *m* neurons in coronal cortex, in a paper by Mann (21), citing a personal communication from A. L. Towe. Even in these data, the number of *m* neurons, 20 in a sample of 675, makes up only 3%. This is significantly fewer than in the present study, $P < 0.0001$. The details of this study are not published.

deafferented region or collateral sprouting in peripheral or central nerve fibers (10, 19, 39), although possible, seems unlikely given the distance to the nearest wide-field cells in normal cats, the bilaterality of "regenerated" fields, and the short latency of changes observed by others (25).

Conduction through alternate pathways. The dorsal column–medial lemniscal pathway is the most direct somatosensory pathway, with fewest synaptic connections. Damage to fibers in this pathway would leave less direct polysynaptic pathways to transmit somatosensory information to the cortex (9). It has been suggested that, in the cat, input from the spinocervicothalamic tract is "unmasked" when transmission through the dorsal columns is blocked (7), but we know of no evidence for input from this pathway to SI in the cat.

Ineffective synapses that become effective after partial deafferentation (sensitization). Wall (23, 43) has suggested that preexisting modulatory circuitry may become much more effective after partial deafferentation and recovery. Careful studies of the interactions of on-focus and off-focus inputs to coronal neurons in control animals should reveal any modulatory influences that are present.

The time course of changes in previous deafferentation studies (25) suggests that an immediate change in effectiveness of preexisting modulatory circuitry or the use of an alternate pathway is the only likely explanation. However, the possibility of a slower, more prolonged contribution from altered neural connections cannot be ruled out. Whatever the explanation for the appearance of *m* neurons, it is clear from these results that factors other than temporal correlation of inputs (3) are also responsible for the size and location of receptive fields of neurons at particular sites in the cortex.

Possible Sources of m Fields after Deafferentation

Perhaps *m* neurons like those observed in SI cortex after peripheral nerve crush and regeneration are present in control cats, but they normally do not respond to contralateral forepaw stimulation. Such neurons would be absent in samples of neurons isolated with a contralateral forepaw hunting stimulus. Satterthwaite and Towe (36) found such neurons in pericruciate cortex using a hunting stimulus applied to the ventral medulla; such a stimulus activates fibers in the medial lemniscus, including those carrying activity from fore-, hind-, contralateral and ipsilateral paws. Only two-thirds of the neurons in their sample would have been identified by a contralateral forepaw hunting stimulus. The set of normally silent neurons may be even larger in the forepaw focus of SI cortex (6), but chloralose-anesthesia has not been used in studying this set of neurons. Given the "facilitating" quality of chloralose, it seems likely that there will be fewer silent neurons than in animals under barbiturates or in unanesthetized animals. Dykes and Lamour (6) reported that the silent neurons were either superficial or deep within the tissue, the deep location being similar to the predominant location of wide-field neurons in this study.

Perhaps deafferentation could change the excitability of these neurons such that they would respond to cutaneous input and be classified as wide-field neurons. However, under this condition the relative proportions in Table 1 should be different (there should be more *m* than *sa* neurons), and there should have been more neurons per track and per animal after crush compared to controls. Our records show no difference in either neurons per track or per animal.

Explanation in terms of normally silent neurons is tenable, but we prefer an explanation in terms of sensitization of preexisting modulatory circuits. Satterthwaite *et al.* (35) found a few cells in coronal tissue which were classified as *sa* neurons, but which received subthreshold excitation from the ipsilateral forepaw and no influence from the hindpaws or received inhibition from off-focus. If deafferentation enhanced the known facilitatory inputs, then an increase in *sb* neurons would be expected. On the other hand, conversion of inhibitory inputs from the three off-focus paws to excitation, would make *sa* neurons with off-focus inhibition appear to be *m* neurons. Such conversion of inhibition to excitation was reported by Nakahama *et al.* (27) for the ventroposterolateral nucleus of the thalamus after cutaneous nerve block.

Wide-field effects could also be involved at other levels of the dorsal column–medial lemniscus system, or even outside it. Dostrovsky *et al.* (5) reported finding cells in the main part of the gracile nucleus which responded to "stimulation of the ipsilateral forepaw, the contralateral hind paw, or sometimes both, as well as to electrical stimulation of the ipsilateral hind limb." Many of the cells had axons in the medial lemniscus. Neurons responsive to stimulation anywhere on the body have been found in the nucleus ventralis posterolateralis of chloralose-anesthetized cats (22) and in the posterior part of ventralis posterior in unanesthetized monkeys (31). Such neurons have been found in the cerebral cortex of cats under a variety of conditions, but not in the SI forepaw focus. It is possible that the effectiveness of off-focus inputs to wide-field cells at some subcortical level is strengthened following removal of on-focus (contralateral forepaw in our experiments) inputs. These strengthened inputs could remain stronger than normal even after regeneration of the on-focus input, perhaps permanently. Under these circumstances, what was apparently an *sa* neuron at the cortex (subthreshold off-focus inputs to subcortical cells would not necessarily be detectable at the cortical level) would take on *m*-neuron responsiveness.

Implications in Recovery from Peripheral Nerve Damage

We did not attempt to determine the sensory capacities of the cats in our study, but it is apparent that peripheral nerve damage was present following the crush operation and that at least some sensory recovery had occurred before our recording sessions. At a rate of 2–4 mm/day, there was ample time in this study for regeneration of myelinated axons, but there was probably not complete regeneration of the crushed nerves. No attempt has yet been made to determine how long *m* neurons may persist in the cortex under these conditions. If the neurons in sensory cortex play a requisite role in cutaneous sensations, and if changes similar to those reported here occur and persist in human cortex after nerve crush, then a "complete" recovery of sensation in such patients may occur against a background of changed cortical neuronal responsiveness, *not* against a background of neuronal responsiveness restored to original conditions.

It is appropriate to point out that this tissue may not play such a requisite role in cutaneous sensation. Neither SI nor SII is required for cats or monkeys to localize stimuli applied to the skin (4, 37), and roughness discrimination is only "slightly impaired" by bilateral removal of SI (34, 37, 44). If this tissue is not required for cutaneous sensation itself, then perhaps we should not be surprised to find it changed following deafferentation and regeneration at a time when sensation may be normal.

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