An Index of Topographic Normality in Rat Somatosensory Cortex: Application to a Sciatic Nerve Crush Model

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Received 10 January 2002; accepted in final form 24 April 2002

Barbay, Scott, Eric K. Peden, Gerald Falchook, and Randolph J. Nudo. An index of topographic normality in rat somatosensory cortex: application to a sciatic nerve crush model. J Neurophysiol 88: 1339–1351, 2002; 10.1152/jn.00019.2002. Previous studies have demonstrated that peripheral denervation of the skin is reflected in the CNS as a reorganization of somatotopic representations. In cases in which peripheral nerve regeneration occurs there is a gradual reactivation of cortex by novel receptive fields that is reassembled as regenerated nerves reestablish connections with the original skin surface. Functional recovery appears to depend on the pattern in which somatotopic organization in the cortex is reestablished. The relationship between functional recovery and cortical topography is not precise, however, since the descriptions of postinjury representations in the cortex have been largely descriptive and not quantitative. The purpose of this study was to derive an index to quantify deviations from normal somatotopic organization in the somatosensory cortex. Multitopic recordings of cutaneous representations in the somatosensory cortex (SI) of the rat were defined using Semmes-Weinstein monofilaments to stimulate the skin over the distal hindlimb of the rat 2 and 4 months after a sciatic nerve crush. To derive a sensitive index of topography, the sciatic nerve crush was selected as the injury model since nerve regeneration following crush injuries has been reported to re-establish preinjury cortical topography. Group comparisons were made with an intact control group. The results show that there were subtle, but significant differences in topography between rats with a regenerated sciatic nerve and normal rats. In addition, average thresholds for evoking cortical responses were higher than normal (but within normal range) 2 and 4 months after the crush. These results demonstrate that the index of topography derived for this study can reveal deviations that may not be distinguishable from normal topography when based on qualitative descriptions.

INTRODUCTION

Functional recovery from peripheral nerve injuries is largely related to appropriate regeneration of nerve fibers into their previous skin targets (Kaas et al. 1983). However, because of the divergence of central projections in the ascending somatosensory system, the cortical consequences of peripheral nerve injuries have long been of interest. Specifically, several studies have addressed the following questions: First, what is the relationship between the reestablishment of normal functional topography in the primary somatosensory cortex to peripheral nerve reinnervation? Second, what is the relationship between the reestablishment of normal functional topography and functional recovery?

Two early, nonhuman primate studies have shown that the degree of functional recovery associated with peripheral nerve regeneration depends on the accurate reinnervation of injured nerves into their original receptive fields, resulting in reestablishment of preinjury topography within the medial lemniscal pathway to somatosensory cortex (Wall et al. 1983, 1986). Both of these studies examined the central consequences of recovery from median nerve damage in the hand representation area of the primary somatosensory cortex. In the Wall et al. (1983) study it was demonstrated that, following a crush injury to the median nerve, normal topography of the hand area was progressively reestablished over time. In a subsequent study, Wall et al. (1986) transected and then immediately repaired the median nerve. This procedure resulted in a partially disorganized somatotopic representation of the hand in the primary somatosensory cortex. The differences in outcome between these two studies is thought to be due to reinnervation errors of the median nerve as indicated by abnormal receptive fields found only in the transection/repair study. These experimental observations are consistent with clinical observations that functional recovery from nerve cut repairs are usually not complete (e.g., Kostakoglu 1999) whereas functional recovery from crush injuries have a better outcome (e.g., Buchthal and Kuhl 1979). The consequence of these earlier experimental findings has been the assumption that behavioral or clinical recovery of function depends on the return of normal topography in the somatosensory cortex following nerve damage and that nerve regeneration following a crush injury will reestablish preinjury topographic organization in CNS structures.

However, now there is evidence showing that recovery from nerve crush injuries does not completely reestablish somatosensory cortex to its preinjury topography. Several studies have shown that minor regeneration errors do occur following nerve crush injuries (Munger and Renehan 1989; Povlsen et al. 1994; Sanders and Zimmerman 1986) and that these errors can distort cortical topography (Kawakami et al. 1989; Kis et al. 1999; and Korodi and Toldi 1998). The implication of these earlier studies is that cutaneous sensitivity in the reinnervated skin territories may be compromised by nerve crush injury. In turn, the

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probability of reestablishing a normal preinjury topography in somatosensory cortex may be reduced.

Former studies have provided qualitative descriptions of topographic changes after nerve injury (Barbay et al. 1999; Wall et al. 1983, 1986). The purpose of the present study was to derive a quantitative index of functional topography within the somatosensory cortex to describe the degree to which cortical organization returns to normal following a nerve crush injury. The rat sciatic nerve crush model was used since both functional recovery (Bridge et al. 1994; de Medinaceli et al. 1982) and topography of hindlimb representations in primary somatosensory cortex (S1) (Wall and Cusick 1984, 1986) have been well characterized. Topography was assessed in independent experimental groups 2 and 4 months following a sciatic nerve crush and compared with a normal control group. These groups were selected to assess reestablishment of cortical topography at an early time point when regeneration is estimated to be complete and at a later time point when the subsequent use and maturation of regenerated fibers is thought to result in normalization of cortical topography.

METHODS

Sixteen adult male Sprague-Dawley rats weighing between 400 and 500 g (approximately 5 to 6 mo of age) were used in this study. Cutaneous receptive fields were recorded within S1 during mechanical stimulation of the skin of the distal hindlimb (hindlimb skin surfaces distal to the ankle) and proximal hindlimb (hindlimb skin surfaces including and proximal to the ankle) as well as adjacent skin areas. In each rat, recordings were derived from the left somatosensory cortex using standard multiunit electrophysiological recording techniques (Barbay et al. 1999; Merzenich et al. 1978). Maps were derived 2 (n = 6) and 4 (n = 5) months after a sciatic nerve crush was applied to the right (contralateral) hindlimb. Five normal rats mapped in a previous experiment were included as a control group. These rats did not receive a sciatic nerve injury.

Determination of assessment times

Times for early and late assessment were chosen based on 1) the estimated rate of sciatic nerve regeneration and return of function to the entire distal hindlimb (Bridge et al. 1994; Devor and Govrin-Lippmann 1979) and 2) an estimated time for normalization of topography resulting from the subsequent use and maturation of regenerated fibers (see DISCUSSION).

Housing conditions

All rats were group housed within solid-bottom, wire-mesh cages (three to four rats per cage) prior to and after the sciatic nerve crush procedures. Rats were given free access to food and water and were maintained on a 12/12-h light/dark cycle within a climate-controlled vivarium. All procedures were in accordance with the National Institutes of Health guidelines for the care and use of laboratory animals and were approved by the University of Texas Institutional Animal Care and Use Committee.

Surgical procedure

Each animal was anesthetized with an initial dose of 100 mg/kg ketamine ip and 5.0 mg/kg xylazine ip and positioned in a stereotaxic frame. The hair covering the dorsal handpad and the proximal hindlimb was trimmed close to the skin with an electric razor (Oster barber’s razor with surgical blade number 40). The cervical spinal column was exposed and a small incision was made in the dura between the atlas and the axis vertebrae. Cerebropinal fluid was allowed to drain from this incision for the duration of the mapping procedure by periodically absorbing the fluid using small cellulose surgical pads (Weck-Cel surgical sponges, Xomed Surgical Products, Jacksonville, FL). This procedure effectively controlled cortical swelling during the subsequent electrophysiological procedure. A craniectomy was then made above S1 using a small drill to thin the skull and then removing the thinned bone fragments with microforceps. During bone drilling, care was taken to prevent heating the skull and underlying cortex by liberally applying normal saline (kept at room temperature) to the area. The dura was carefully removed and the cortex was covered with warm silicone oil (dimethylpolysiloxane, Dow 200 fluid, Dow, Midland, MI). Core temperature was maintained within normal limits using a homeothermic blanket system. Throughout the electrophysiological procedures, 10 mg/kg sodium pentobarbitral im was given as needed to maintain a stable level of anesthesia as determined by periodically checking deep reflexes (toe pinch, tail pinch, and corneal reflexes) approximately every 15 min.

Mapping procedure

A high-magnification digital photograph of the exposed cortex was captured on a Macintosh computer using the public domain National Institutes of Health Image program (developed at the U.S. National Institutes of Health and available on the Internet at http://rsb.info.nih.gov/nih-image/) and frame grabber card (Scion Corp., Frederick, MD). A grid pattern was superimposed on the digitized cortical image to guide microelectrode penetrations with reference to surface vascular patterns and to provide an accurate measure of the distance between penetrations (interpenetration distances).

An insulated tungsten wire with an approximately 25-μm exposed tip was used for the microelectrode (impedance ~ 1.5 MΩ, Micro Probe, Potomac, MD). The microelectrode was attached to a micro-manipulator and at each site was lowered to a depth of approximately 500–800 μm beneath the pia, perpendicular to the cortical surface. Evoked responses were routinely observed at these depths, and minimal force thresholds required to evoke multiunit neuronal responses (see following text) rarely varied within these ranges. A high-resolution somatosensory map (200-μm interpenetration distances) was derived for each rat. Minimal cutaneous receptive fields were defined for the distal and proximal hindlimb by determining the skin field over which cortical neurons were activated by light tactile stimulation using a fine hand-held glass probe (e.g., Merzenich et al. 1978; Nelson et al. 1980). Evoked multiunit responses were amplified and monitored on an oscilloscope and audio loudspeaker. The experimenter responsible for defining receptive fields was unaware of the exact placement of the electrode within S1.

Minimal force thresholds required to evoke multiunit neuronal responses, hereafter called “cutaneous thresholds,” were measured with force-calibrated filaments (Semmes-Weinstein pressure aesthesiometer). Each filament is identified by a value that indicates the logarithmic value of the applied force [filament value = log 10 (force in milligrams), Stoelting, Wood Dale, IL]. These filaments were chosen to drive cutaneous thresholds because of their ease of use and the ability to define thresholds both rapidly and reliably. Stimulus intensity thresholds were defined periodically throughout the recording sessions by a second observer. Thresholds defined by the two observers rarely differed. The maximum force used to determine a cutaneous response was approximately 400 mg (filament 3.61) (Barbay et al. 1999). The minimum force was approximately 4.5 mg (filament 1.65). Thresholds for driving cortical responses were similar throughout the recording depths (500–800 μm). Cutaneous responses evoked by stimulation of skin innervated by the saphenous nerve are hereafter called “saphenous responses,” while those evoked by stimulation of skin innervated by the sciatic nerve are hereafter called “sciatic responses.” The borders of peripheral innervation for the sciatic and saphenous nerves used in this study were adapted from
Wall and Cusick (1984). Responses recorded from stimulation using an applied force of >400 mg were defined as “noncutaneous responses” and were not included in subsequent quantitative analyses of receptive fields since precise characterization of receptive fields is problematic at greater forces. This criterion was based on an estimated force for lightly stimulating the skin without stretching the surrounding skin or activating underlying receptors in deeper tissue (muscle and joint receptors) and is similar to that used in humans (see Schmidt 1986). Moreover, this stimulus intensity range corresponds to force used in this same laboratory to record evoked responses in somatosensory area 3b in primates (Nudo et al. 1997).

In addition to defining receptive fields throughout the entire distal and proximal hindlimb representation, adjacent representations of skin surfaces were also explored and receptive fields were defined. Borders were located by defining receptive fields in adjacent trunk/abdomen cutaneous representations rostral and lateral to the cutaneous hindlimb areas, cutaneous forelimb representations rostrolateral to cutaneous hindlimb representations, and nonresponsive areas rostral and medial to cutaneous hindlimb representations (Fig. 1).

**Sciatic nerve crush**

The sciatic nerve was exposed and isolated from the surrounding gluteal muscle above the right knee, just below the iliac crest by a transverse incision. The exposed sciatic nerve was then crushed with a smooth-jawed clamp for 1 s. Complete crush of the nerve was achieved by stretching the gluteal muscle above the right knee, just below the iliac crest by a straight line from the medial to lateral edge of the distal hindlimb and sciatic glabrous skin; and medially (see Fig. 2, A). The sciatic innervated dorsal surface of the distal hindlimb (on the fibular side) is represented from the central area of S1 to the medial border (d3 to d5, respectively, and extends back to the ankle; Fig. 2B). The dorsal surface of the distal hindlimb that is innervated by the saphenous nerve (d1 to d3 back to the ankle on the tibial side) is represented in the lateral caudal area of S1 but may extend rostrally and medially (see Fig. 2B). To assign a value to each responsive site in S1 with respect to its spatial position within the S1 map, the distal hindlimb area was divided into rostrocaudal and mediolateral quadrants (see Fig. 2, A and B). The rostrocaudal bisector was determined by drawing a straight line from the medial to lateral edge of the distal hindlimb area in S1 dividing the rostrocaudal recording sites into a rostral half and a caudal half of the distal hindlimb representation; this resulted in half of the column of sites being in the rostral area and half in the caudal area. The mediolateral bisector in S1 was determined by finding the center of each column of response sites from the rostral to caudal limits of the hindlimb representation in S1. Only columns of sites not interrupted by large blood vessels were used in determining the mediolateral bisector. In maps derived for the 2-mo crush group, the rostromedial quadrant was determined by referring to the high-threshold response sites (>400 mg of force), considered here to be noncutaneous response sites as explained above in METHODS. This was necessary since sciatic responses are reinstated progressively from caudal S1 (present at 2 mo postcrush) to rostral S1 (incomplete at 2 mo postcrush) following a sciatic nerve crush. The rostral limit of the

**Analysis**

Receptive fields were distinguished as either “typical” or “atypical.” Statistical analyses were used to compare group differences based on receptive fields within the typical and atypical categories. Typical receptive fields were the most common receptive fields observed in the control group and were similar to those reported by Wall and Cusick (1984). These receptive fields were confined to either the dorsal hairy skin or glabrous skin and were driven by stimulation of either sciatic or saphenous innervated skin exclusively. There were several types of atypical receptive fields: 1) those that covered both sciatic dorsal hairy skin on the fibular (lateral) side of the hindpaw and glabrous skin; 2) those that covered saphenous dorsal hairy skin on the tibial (medial) side of the distal hindlimb and sciatic glabrous skin; and 3) those that covered both sciatic and saphenous dorsal hairy skin.

Both the cutaneous representational area of the distal hindlimb in S1 (cortical area from which stimulation of specific skin surfaces resulted in suprathreshold evoked responses) and the cutaneous thresholds of evoked responses within this area were quantified for group comparisons. Changes in representational area were determined by comparing the area (mm²) of sciatic and saphenous distal hindlimb representations in S1 [including areas yielding mixed sciatic and saphenous responses (sci/saph)] of control rats to those in rats with a sciatic nerve crush. For this analysis a two-dimensional representation of the hindlimb and adjacent skin surfaces was constructed by delineating cortical regions with similar receptive fields (distal hindlimb, proximal hindlimb, trunk/abdomen, tail, and forelimb). Borders were established between adjacent cutaneous representations midway between microelectrode penetration sites by using customized software. The extent of representational area in each map was measured using image analysis software (National Institutes of Health Image). Statistical comparisons of the sciatic and saphenous components of the distal hindlimb area as well as those areas with mixed sciatic and saphenous components were made for the control and crush groups using the Scheffe method for multiple mean comparisons.

Cutaneous thresholds were also analyzed separately for sciatic and saphenous components of the distal hindlimb area and for those areas that contained mixed sciatic and saphenous components. For these analyses each threshold was quantified as the force required to drive a reliable audible response from the loudspeaker monitor. Average thresholds for evoking responses were calculated by pooling cutaneous threshold data. Because of the wide range of forces available using the Semmes–Weinstein monofilaments, the filament values are expressed as a logarithmic transformation of force (see above). Therefore the monofilament values could be used directly in statistical analyses without further transformation (Zar 1984). For clarity, only the filament values are provided in the results: filament value = log 10 (force in milligrams). Comparisons were made by the Scheffe method for multiple comparisons of the mean.

**Topography**

Normal topography for the distal hindlimb representation in S1 of the rat was derived from normal control rats. These representational maps were consistent with those determined previously (e.g., Barbas et al. 1999; Wall and Cusick 1984). Deviations from this idealized normal topography were quantified by deriving an index of somatotopic organization 2 and 4 months after a sciatic nerve crush. For this analysis, each cutaneous response site in S1 was assigned a value according to the appropriateness of its receptive field relative to its spatial position within S1 (see following text). Mean index values for each group were compared using the Scheffe method for multiple mean comparisons. To determine whether deviations in topography were due to reinstated sciatic input, novel saphenous input, or an overlap of sciatic and saphenous input, the percentage of sites in each category was compared using the Scheffe method for multiple mean comparisons. Because the index values and the percentage data form binomial distributions, an arcsine transformation was used to normalize these values as required for the parametric analysis (Zar 1984).
Normal Maps

2 Mos Post-Crush Maps

4 Mos Post-Crush Maps
hidlimb representation is easily determined as it is bordered rostrocaudally by the forelimb area of S1. This is particularly important when determining the extent of hindlimb representation 2 months after the nerve crush since rostral sciatric responses have not been fully reinstated at this time (see RESULTS).

In rats recovering from the sciatric nerve crush, two receptive fields may be recorded from the same recording site in S1 (a sciatric and a saphenous receptive field), with only one appropriate for its location in S1. In this case only the inappropriate site is assigned a value. Another situation that needs noting is that receptive fields containing digit 3 are defined according to adjacent areas within the receptive field. For example, the appropriate quadrant for digits 1 to 3 would be in the rostrocaudal quadrant of S1 whereas the appropriate quadrant for digits 3 to 5 would be in the rostrolateral quadrant.

ASSIGNING VALUES TO CUTANEOUS SITES IN THE DISTAL HINDLIMB AREA OF S1. A score of 1 was assigned to a site with a receptive field in a normal location with respect to its rostrocaudal and mediolateral dimensions; a score of 0 was assigned to a site with a receptive field in an abnormal location with respect to both its rostrocaudal or mediolateral dimensions; and a score of 0.5 was assigned to a site with a receptive field in a normal location with respect to one dimension but not both its rostrocaudal and mediolateral dimensions. For example, Fig. 3, B and C, shows how a typical receptive field would be scored in each quadrant. The appropriate spatial position for the site used in this example is in the rostrolateral quadrant (digit 4 and digit 5 plus the lateral (tibula) aspect of the hindpaw). Accordingly, if the site is actually located in the rostrolateral area of S1, it will receive a score of 1; if the site is located rostrally but in the lateral area of S1 or caudally in the medial area of S1 it will receive a score of 0.5; and if the site is located in the caudolateral area of S1 it will receive a score of 0. These scores were summed for each animal and then divided by the total number of cutaneous response sites recorded for that animal. This resulted in an index score between 0 (not congruent with ideal organization) and 1 (ideal organization). For example, the rat 9620’s index was 15 × (1) + 4 × (0.5) + 3 × (0)/22 = 0.77. To summarize, this index is designed to distinguish various maps based on their deviation from an expected organization. That is, as the somatotopie organization deviates from the ideal, the index values decrease. All of the values between 0 and 1 indicate the degree to which somatotopic organization deviates from an expected, standardized organization.

RECEPTIVE FIELDS ATYPICALLY LOCATED REPRESENTATIONS IN S1. The relative contribution of reinervated sciatic inputs, novel saphenous inputs, and mixed sci/saph inputs to the overall topography of somatosensory maps were determined. For this analysis the percentage of sciatic, saphenous, and sci/saph receptive fields was determined. For this analysis the percentage of sciatic, saphenous, and sci/saph receptive fields to the overall topography was calculated by dividing the total number of cutaneous response sites recorded for that animal by the total number of cutaneous response sites recorded for that animal. This resulted in an index score between 0 and 1. An arcsine transformation was used to normalize the percentages for parametric comparisons (Zar 1984). Group comparisons of the means were made using the Scheffe method for multiple mean comparisons. Group statistics are presented as the mean ± SE for comparisons.

FIG. 2. A: somatotopic organization of glabrous skin within the distal hindlimb area of S1. B: somatotopic organization of the dorsal skin within the distal hindlimb area of S1. The ovals in A and B represent distal hindlimb S1, which is divided into rostrocaudal and mediolateral quadrants. The entire glabrous hindlimb in A is innervated by the sciatic nerve. The dorsolateral hindlimb in B is in the medial half of the oval is also innervated by the sciatic nerve. The saphenous nerve innervates the dorso medial hindlimb depicted in the lateral half of the oval. Digit 3 is represented in both the medial and lateral half of the oval because of the difficulty in defining receptive fields confined to digit 3 (see METHODS).

RESULTS

Receptive field classification

NORMAL CONTROL GROUP. Neurophysiological maps in the control group were derived from an average of 32 ± 2.4 (mean ± SD) distal hindlimb cutaneous recording sites in each rat. The normal topography of the S1 hindlimb representation was similar to that of earlier reports by other investigators (e.g., see Barbay et al. 1999; Wall and Cusick 1986). Briefly, as stated in METHODS, within S1, the hindlimb is represented from digits to heel in a rostrocaudal orientation, respectively, with...
locations of individual receptive fields on the distal aspect of digit 3 dorsum (hairy skin) (also see Wall 1988). The distal aspect of digit 3 is innervated by the sciatic nerve and the proximal aspect of digit 3 is innervated by the saphenous nerve. The digit 3 overlap did not result in any significant ambiguity, since the largest part of the receptive field could still be associated with either the saphenous or sciatic nerve. We found no receptive fields exclusively on the distal aspect of digit 3 dorsum. Receptive fields confined to either the glabrous or dorsal skin that unambiguously could be associated with either the saphenous or sciatic nerve were called “typical” receptive fields and accounted for the vast majority of all receptive fields (84%; see Table 1). In addition, there were 15 receptive fields (9%) associated with the sciatic nerve that extended across both glabrous and dorsal hairy skin and there were 10 receptive fields (6%) associated with both the sciatic and saphenous nerves, extending across the dorsal surface of the distal hindlimb. One receptive field on the second digit was associated with both the sciatic and saphenous nerves on the glabrous and dorsal skin, respectively (see Fig. 5). Receptive fields extending across both the glabrous and dorsal sciatic innervated skin or both the glabrous sciatic and dorsal saphenous innervated skin are referred to here as “atypical.” These atypical receptive fields represented a small minority of all receptive fields in normal animals (Table 1).

SCATIC CRUSH GROUPS. Maps for the 2-mo crush group (n = 6) were derived from 23 ± 4 (mean ± SD) distal hindlimb cutaneous recording sites, and maps for the 4-mo crush group (n = 5) were derived from an average of 28 ± 4,1 distal hindlimb cutaneous recording sites. The number of atypical receptive fields recorded in each group is given in Table 1.

Noncutaneous (high-threshold) responsive sites in S1

Noncutaneous responses to distal hindlimb stimulation were also documented in the S1 hindlimb representation following taps to the distal hindlimb using an applied force of >400 mg (i.e., using a filament larger than 3.61). It is possible that these high-threshold response sites are actually cutaneous responses but are not detectable over background noise (spontaneous neural activity) associated with the multiunit recording techniques described in this study. Alternatively, these sites are truly noncutaneous response sites resulting from stimulation of deep (muscle or joint) receptors within the hindlimb (see Chapin and Lin 1984). Noncutaneous responses were rare in the control group (total = 3 of 171 sites). Noncutaneous responses were primarily observed in the 2-mo crush group, surrounding a central core of cutaneous responsive area in S1. The caudal aspect of S1 had fewer noncutaneous sites than the lateral, medial, or rostral aspects of S1 (see Fig. 1). The average number of noncutaneous response sites in the 2-mo crush group was 15.8 ± 4.1 (mean ± SD). The average number of noncutaneous response sites in the 4-mo crush group was 2.6 ± 2.1.

Areal extent of sciatic and saphenous representations in S1

Areal measurements were restricted to the distinguishable typical and atypical types of receptive field representations in S1: typical sciatic response area (sciatic area) and typical saphenous response area (saphenous area) and the atypical...
areas with both sciatic and saphenous responses (sci/saph overlap area). Group comparisons of the means were made using the Scheffé method for multiple group comparisons (see Fig. 6). Group statistics are presented as the mean ± SE.

SCIENTIFIC AREA. The mean area for the normal control group (1.2 ± 0.02 mm²) was significantly larger than the mean area for the 2-mo crush group (0.6 ± 0.08 mm²; P < 0.001) but was not significantly different from the 4-mo crush group (1.1 ± 0.08 mm²; P > 0.53). In addition, the mean area for the 2-mo crush group was significantly smaller than the mean area for the 4-mo crush group (P < 0.001).

SAPHENOUS AREA. There were no statistically significant differences between the normal control group mean (0.05 ± 0.02 mm²) and the two crush group means (2-mo crush = 0.07 ± 0.04 mm² and 4-mo crush = 0.05 ± 0.02 mm²; P > 0.94) nor were there any significant differences between the 2-mo crush group and the 4-mo crush group (P > 0.94).

SCUSAPH OVERLAP AREA. The mean atypical sci/saph overlap area for the 2-mo crush group (0.35 ± 0.05 mm²; P < 0.01) was significantly larger than that found for the normal control group (0.10 ± 0.03 mm²). There was no statistically significant difference between the normal control group and the 4-mo crush group means (0.09 ± 0.004 mm²; P > 0.99). The mean sci/saph area for the 2-mo crush group was significantly larger than the mean sci/saph area for the 4-mo crush group (P < 0.004). These results are consistent with the observations made above in that there were only a few atypical receptive fields found in control rats and in rats 4 mo after a sciatic nerve crush. However, many atypical sites were found 2 mo after the nerve crush (see Fig. 6).

Thresholds of sciatic and saphenous responses

The sensitivity of responses to cutaneous stimulation (≤400 mg or filament value = 3.61) after a sciatic nerve crush was determined at each cortical site by recording the minimum force necessary to evoke a response. For this analysis, mean cutaneous thresholds of evoked responses (i.e., mean filament values) in the sciatic, saphenous, and sci/saph overlap areas in S1 of control rats (distal hindlimb) were compared with cutaneous thresholds observed within similar areas of S1 in the 2-mo crush group and the 4-mo crush group. Group comparisons of the mean filament values were made using the Scheffé method of multiple mean comparisons (see Fig. 7). Group statistics are presented as the mean ± SE.

SCUSAH THRESHOLDS. The mean sciatic threshold for the normal control group (2.29 ± 0.05) was significantly lower than the mean sciatic threshold for the 2-mo crush group (2.54 ± 0.07; P < 0.001) and the 4-mo crush group (2.47 ± 0.05; P < 0.01; Fig. 7A). There were no statistically significant differences between the mean sciatic thresholds for the 2- and 4-mo crush groups (P > 0.38).

SAPHENOUS THRESHOLDS. Saphenous thresholds were similar for all groups. That is, there were no significant statistical differences between the mean filament values for the normal control group (2.45 ± 0.14) and the 2-mo crush group (2.23 ± 0.25; P > 0.35) or the 4-mo crush group (1.98 ± 0.21; P > 0.74). Also, there were no significant statistical differences between the mean filament values for the 2- and 4-mo crush groups (P > 0.74; Fig. 7B). Differences in thresholds between groups were not significant, there appeared to be a trend for saphenous thresholds to become lower in months following the sciatic nerve crush.

SCUSAHTHRESHOLDS. The mean filament value for the 2-mo crush group (2.20 ± 0.09; P < 0.05) was significantly greater than the mean filament value for the normal control group (1.78 ± 0.08; Fig. 7C). There was no significant difference between mean filament values for the normal control group and the 4-mo crush group (1.20 ± 0.17; P > 0.64) nor was there a significant difference between mean filament values for the 2- and 4-mo crush groups (P > 0.58).

**TABLE 1.** Cutaneous receptive fields: distal hindlimb

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Typical Receptive Fields</th>
<th>Atypical Sciatic (Glabrous/Dorsal)</th>
<th>Atypical Sciatic/Saphenous (Dorsal)</th>
<th>Atypical Sciatic/Saphenous (Glabrous/Dorsal)</th>
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<tbody>
<tr>
<td>Normal</td>
<td>5</td>
<td>133 (84)</td>
<td>15 (9)</td>
<td>10 (6)</td>
<td>1 (1)</td>
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<tr>
<td>2-Mo crush</td>
<td>6</td>
<td>79 (59)</td>
<td>10 (7)</td>
<td>27 (20)</td>
<td>19 (14)</td>
</tr>
<tr>
<td>4-Mo crush</td>
<td>5</td>
<td>130 (92)</td>
<td>2 (1)</td>
<td>9 (6)</td>
<td>1 (1)</td>
</tr>
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</table>

Values in parentheses are percentages.

**FIG. 4.** Typical cutaneous receptive fields recorded in S1 of normal control rats.

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**The sensitivity of responses to cutaneous stimulation (≤400 mg or filament value = 3.61) after a sciatic nerve crush was determined at each cortical site by recording the minimum force necessary to evoke a response. For this analysis, mean cutaneous thresholds of evoked responses (i.e., mean filament values) in the sciatic, saphenous, and sci/saph overlap areas in S1 of control rats (distal hindlimb) were compared with cutaneous thresholds observed within similar areas of S1 in the 2-mo crush group and the 4-mo crush group. Group comparisons of the mean filament values were made using the Scheffé method of multiple mean comparisons (see Fig. 7). Group statistics are presented as the mean ± SE.

**SCUSAH THRESHOLDS.** The mean sciatic threshold for the normal control group (2.29 ± 0.05) was significantly lower than the mean sciatic threshold for the 2-mo crush group (2.54 ± 0.07; P < 0.001) and the 4-mo crush group (2.47 ± 0.05; P < 0.01; Fig. 7A). There were no statistically significant differences between the mean sciatic thresholds for the 2- and 4-mo crush groups (P > 0.38).

**SAPHENOUS THRESHOLDS.** Saphenous thresholds were similar for all groups. That is, there were no significant statistical differences between the mean filament values for the normal control group (2.45 ± 0.14) and the 2-mo crush group (2.23 ± 0.25; P > 0.35) or the 4-mo crush group (1.98 ± 0.21; P > 0.74). Also, there were no significant statistical differences between the mean filament values for the 2- and 4-mo crush groups (P > 0.74; Fig. 7B). Differences in thresholds between groups were not significant, there appeared to be a trend for saphenous thresholds to become lower in months following the sciatic nerve crush.

**SCUSAH THRESHOLDS.** The mean filament value for the 2-mo crush group (2.20 ± 0.09; P < 0.05) was significantly greater than the mean filament value for the normal control group (1.78 ± 0.08; Fig. 7C). There was no significant difference between mean filament values for the normal control group and the 4-mo crush group (1.20 ± 0.17; P > 0.64) nor was there a significant difference between mean filament values for the 2- and 4-mo crush groups (P > 0.58).
The topographic map of the body surface in S1 is highly ordered, with the lateral skin surface and medial skin surface represented from medial to lateral aspects, and digits and heel represented from rostral to caudal aspects respectively (Wall and Cusick 1984) (see also METHODS). However, not all receptive fields conformed to this topography, especially in each of the two sciatic nerve crush groups. For example, a receptive field on the heel, which is typically recorded in caudal S1, was occasionally located in rostral S1, where digits are typically represented. While these displaced receptive fields were infrequent it seemed that an index of topographic order was needed to quantify any systematic change in topography as a result of sciatic nerve crush.

**Topography index**

Details regarding the derivation of the topography index are contained in METHODS. Inter-rater reliability was calculated by comparing values (436 receptive fields) assigned by one of the authors with a naive rater who was guided only by the protocol contained in METHODS ($r = 0.81, P < 0.001$). Figure 8 shows the distribution of each rat’s index score on a scale from 0, which indicates random organization, to 1, which indicates an idealized topography based on previous studies (see METHODS). Arcsine transformations of index scores were used for group comparisons. Comparisons of the means were made using the Scheffé method. Group statistics are presented as the mean ± SE. Rats in the normal control group varied from the idealized topography index of 1; the range was 0.83 to 0.95. The range of index scores for the 4-mo crush group was 0.70 to 0.84 and the range of index scores for the

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Values are percentages.

**S1 topography**

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2-mo crush group was 0.64 to 0.83. The mean index value for the normal control group (0.88 ± 0.02) was significantly greater than the mean for the 2-mo crush group (0.76 ± 0.03; P < 0.03) and the 4-mo crush group (0.78 ± 0.02; P < 0.03). This indicates that the sensory maps for the 2- and 4-mo crush groups were less somatotopically organized than the sensory maps for the control group. There was no significant difference between somatotopic organization of sensory maps for the 2- and 4-mo crush groups (P > 0.995).

Atypically located receptive fields in S1

The total number of atypically located receptive fields for each rat was divided into three categories: those that were associated with the sciatic nerve, the saphenous nerve, or a mix of both sciatic and saphenous nerves. This analysis of atypically located receptive fields differs from the analysis of atypical fields presented above in that this analysis identifies the types of receptive fields that were mislocated and thus contributed to the index number obtained above. This analysis was done to determine the relative influence of the sciatic, saphenous, or sci/saph receptive fields in determining the topographic index. Percentages of atypically located receptive fields within each category, relative to total number of atypically located fields in each rat, were averaged and analyzed as an arcsine transformation by the Scheffé method for multiple mean comparisons. Group statistics are presented as (mean percentages ± SE).

ATYPICALLY LOCATED SCIATIC RECEPTIVE FIELDS. All rats in each group had atypically located sciatic receptive fields. Most of the atypically located receptive fields for the normal control group (89.2 ± 6.6%) and the 4-mo crush group (85.4 ± 9.4%) were sciatic receptive fields; there was no statistically significant difference between normal control and the 4-mo crush groups (P > 0.97). Approximately half of the atypically located receptive fields for the 2-mo crush group were sciatic receptive fields (49.5 ± 7.2%); this is significantly fewer sciatic receptive fields than both the normal control group (P < 0.02) and the 4-mo crush group (P < 0.03).

ATYPICALLY LOCATED SAPHENOUS RECEPTIVE FIELD REPRESENTATIONS. There were no atypically located saphenous receptive fields in the control group. Only one of six rats in the 2-mo crush group and one of five rats in the 4-mo crush group had an atypically located saphenous receptive field.

ATYPICALLY LOCATED SCI/SAPH RECEPTIVE FIELD REPRESENTATIONS. Two of five rats in both the control group (10.8 ± 6.4%) and the 4-mo crush group (13.0 ± 8.1%) had atypically located sci/saph receptive fields, whereas all six rats in the 2-mo crush group had atypically located sci/saph receptive fields (48.8 ± 7.8%). There was no statistically significant difference between the normal control group and the 4-mo crush group (P > 0.79). The 2-mo crush group had significantly more atypically located sci/saph receptive fields than the normal control group (P < 0.01) and the 4-mo crush group (P < 0.01).

DISCUSSION

The principal aim of this study was to characterize cortical plasticity in S1 of the rat induced by peripheral nerve damage and subsequent regeneration. This was accomplished by quantifying cutaneous receptive field topography in S1 at 2 and 4 mo after a sciatic nerve crush with a derived index of topo-
graphic normality and by quantifying cutaneous response thresholds with force-calibrated monofilaments. Additionally, a qualitative depiction of the general adaptive capacity of S1 is also provided. The general observations are consistent with the results from previous studies in primates (Wall et al. 1983, 1986) that have demonstrated that long-term reorganizational plasticity in the somatosensory cortex is reversible. First, injury-induced plasticity in the somatosensory cortex is observed when the cortex is deprived of its typical cutaneous input: somatosensory evoked responses in the deafferented cortex reveal altered receptive field properties typical of adjacent cortical areas. Second, recovery-induced plasticity is observed in association with regeneration of damaged nerve fibers: the deprived cortex eventually becomes responsive to input from formerly denervated skin as the injured peripheral nerve fibers reinnervate their former skin targets. The accuracy in which denervated skin is reinnervated can affect both behavioral and physiological recovery of function. In general, it has been shown that nerve crush injuries result in fewer reinnervation errors than repaired nerve cut injuries and are associated with good recovery (Wall et al. 1983). The index of topography and the cutaneous threshold measures used in this study were employed to establish a more precise, quantitative measure of physiological recovery from nerve crush injuries (Kawakami et al. 1989; Kis et al. 1999; Korodi and Toldi 1998). These quantitative measures allow for statistical comparisons between various nerve repair techniques (e.g., end-to-end repair versus tubulization) (see Lundborg et al. 1997; Meyer et al. 1997) and possible rehabilitative therapies (e.g., Florence et al. 2001; Xerri et al. 1998).

In the present study, cutaneous stimulation of distal hindlimb revealed a distinction between different clusters of cutaneous response sites in S1. This observation determined how cutaneous thresholds would be categorized for further analysis.
Most S1 receptive fields were associated with skin areas innervated exclusively either by the sciatic nerve or by the saphenous nerve, but there were receptive fields in each group that were associated with skin areas covering both sciatic and saphenous innervated skin. The normal innervation pattern of the sciatic and saphenous nerves within the distal hindlimb skin of the rat was determined by Wall and Cusick (1984) and has been used in subsequent experiments to determine somatotopic representations in S1 of the rat (e.g., Barbay et al. 1999; Cusick et al. 1990). According to these studies, there is a tightly defined border between the sciatic and saphenous innervated skin that is represented somatotopically in S1. Immediately following sciatic nerve damage, cortical areas formerly responsive to stimulation of skin exclusively associated with the sciatic nerve becomes responsive to stimulation of skin exclusively associated with the saphenous nerve (Barbay et al. 1999; Cusick et al. 1990). In the present study, the return of sciatic input to S1 resulted in overlapping or mixed sciatic/saphenous receptive fields in S1. Therefore stimulation of typical saphenous and sciatic innervated skin occasionally evoked responses within the same cortical area of S1. Eventually, by 4 mo after the sciatic nerve crush, sciatic input is reestablished and postcrush, novel saphenous responses are silenced (see Wall et al. 1983 for similar findings in primates following a median nerve crush). An alternative explanation is that the overlapping sciatic/saphenous responses in S1 can be accounted for by collateral sprouting of saphenous fibers into denervated skin. In this case stimulation of sciatic skin would also inadvertently stimulate saphenous fibers. However, earlier electrophysiological (Devor et al. 1979) and anatomical evidence (Kinman and Aldskogius 1986) suggest that, following sciatic nerve damage in the rat, the collateral sprouting of saphenous fibers into the denervated sciatic skin area is limited to high-threshold, nociceptive fibers. This is consistent with mapping studies that have shown that cutaneous stimulation over the typical sciatic skin area also fails to evoke a cortical response in S1 when tested several months after the sciatic nerve has been cut and ligated to prevent regeneration (Cusick et al. 1990; Wall and Cusick 1984). In these studies cutaneous responses in S1 can only be evoked by stimulation of the typical saphenous skin area. The few overlapping receptive fields found for normal rats in this study may be due to variations in sciatic and saphenous innervation along borders or to errors in defining cutaneous receptive fields.

To determine differences in thresholds between presumptive regenerated fibers and normal fibers, cutaneous thresholds were averaged separately into their respective categories: exclusive sciatic, saphenous, and mixed sciatic/saphenous responses for each group (normal, 2-mo postcrush, and 4-mo postcrush). This analysis revealed that the sciatic nerve crush and subsequent regeneration did not alter the sensitivity of typical saphenous input to S1, but reestablished sciatic input to S1 was slightly diminished. Although the sciatic response thresholds were diminished, they remained within the normal range (~4.5 to 400 mg of applied force; see Methods). Sciatic input to S1 may have been compromised by incomplete nerve reinnervation into the distal hindlimb, deficiency of myelination, or immaturity of some of the regenerated neurites (Munger and Renehan 1989; Sunderland 1978). Response thresholds in areas with mixed sciatic and saphenous receptive fields were higher in rats 2 mo after the nerve crush than in normal rats or in rats 4 mo after the nerve crush. However, as stated above, there were very few mixed sciatic/saphenous receptive fields in the normal and 4-mo crush groups. The thresholds observed at 2- and 4-mo postcrush reflect subtle deviations from normal and do not appear to have a meaningful consequence on function, since the thresholds were well within the normal range for cutaneous responses. Also, such small threshold differences did not result in obvious behavioral deficits as observed in their home cages and as they walked along a narrow runway prior to mapping.

Subtle but significant differences were also seen between groups regarding somatotopic organization of cutaneous receptive fields in S1. For this analysis an index was derived to quantify organization of cutaneous representations in distal hindlimb area of S1, based on an idealized cortical topography. First, it was observed that cutaneous representations were reinstated from caudal to rostral S1, representing skin surfaces from heel to toe, respectively. Much of the rostral area (i.e., corresponding to digit representations) in S1 was nonresponsive or responsive to high-threshold stimulation 2 mo after the nerve crush injury. Both crush groups had lower topography scores than the normal group, indicating less somatotopic organization within S1 maps. The index scores for the crush groups were based solely on reinstated cutaneous sites (i.e., scores for the 2-mo crush group were not affected by the large number of nonresponsive or noncutaneous sites observed). Therefore, though there were fewer sites at 2-mo postcrush than observed a 4 mo, the organization of these sites could be compared. The results from this comparison indicate that between 2 and 4 mo after the nerve crush injury the CNS did not appreciably compensate for innervation errors. The precise time course for topographic alterations is not yet clear. For example, it is possible that normalization of somatotopy begins prior to 2 mo. It is also possible that somatotopic organization eventually returns to normal, but after 4 mo.

It is reasonable to assume that, after peripheral nerve injury, the reestablishment of normal functional topography within somatosensory cortex parallels sciatic nerve regeneration. The rate of sciatic nerve regeneration has been estimated to be as fast as 3.3 mm per day using a method of mechanically stimulating regenerated nerve fibers with a small hemostat (i.e., the pinch test) to elicit a muscle contraction (e.g., Kanje et al. 1988; Sjöberg et al. 1988). Devor and Govrin-Lippmann (1979) have employed electrophysiological stimulation along a segment of sciatic nerve fibers between a crush injury and the heel to estimate the rate of sciatic nerve regeneration to be 2.2 mm per day. In the present study the distance from the sciatic crush to the heel is ~50 mm and from the heel to the toe is approximately 40 mm. This means that nerve reinnervation should be completed by approximately 41 days. However, following a sciatic nerve crush, a rat’s response to mechanical stimulation across the entire distal hindlimb has been estimated to take no less than 60 days (Bridge et al. 1994; Devor et al. 1979; Devor and Govrin-Lippmann 1979). Furthermore, conduction velocities of parent sciatic nerve fibers were shown to return to normal by ~60 days (Bridge et al. 1994) to 80 days after the crush injury (Devor and Govrin-Lippmann 1979). In the present study the decision to map the somatosensory cortex beginning 2 mo after the sciatic nerve crush is based on the time needed for sensory function to return to the entire distal...
The topography index is particularly useful in rat models of peripheral nerve injury and repair, since the normal topographic organization of rat somatosensory cortex is not as orderly as in other species, such as primates. The topography scores in the group of normal rats ranged from 0.83 to 0.95. Thus subtle differences with maps in rats with nerve injury could be detected, even though the maps did not appear drastically different qualitatively. As this index can be applied to various recovery paradigms in which normalization of somatosensory topography is desired, minor modifications in the index will be required to reflect the degree of organization typical of the sensory maps being assessed. For example, the scale used to assign index values may require refinement to reflect the inherent orderliness of the hand representation in primate somatosensory cortex.

In addition, the scale may require modification for use in within-subject designs. In these designs, the same animal is tracked before and after nerve injury. It has been shown that within a given species there are individual differences in normal somatotopic organization within primary somatosensory cortex (Merzenich 1985). Thus a within-subject design may be necessary when correlating subtle behavioral changes with cortical reorganization to control for individual behavioral strategies and motivational states (Florence et al. 2001). The main disadvantage of this approach is the additional risk of performing multiple surgeries in the same animals.

The present study employs a between-group design in which an “ideal” topography is used as a standard by which to measure all variations in somatotopic organization that includes normal variations as well as those introduced by reinnervation errors. Parametric statistical analysis allows inferences about whether the crush group deviated more from the standard map than the control group. The group design in this study was sufficient to determine subtle differences in topography between the control and experimental groups while avoiding the difficulties inherent in doing multiple surgeries on the same animals. An analysis of variance showed that deviations from the standard, expected topography observed within the two crush groups exceeded those observed for the control group. The extension of this model to a within-subjects design would further enhance the sensitivity by controlling for individual variation.

It is not clear whether subtle changes in topography disrupt normal adaptive sensory processing, as seems to be the case following major disruptions in sensory organization following nerve transection (Wall et al. 1986), limb amputation (Doetsch 1998), or dystonia (Byl et al. 1997; Byl and Melnick 1997). However, a sensitive quantitative measure of topography following injury, especially when correlated with sensitive behavioral measures of recovery, will contribute to our understanding of the functional significance of somatotopic organization in sensory cortex and the extent that deviations in topography can place constraints on rehabilitation and recovery after peripheral nerve injury.

The authors thank Dr. Shawn Frost, Dr. Erik Plautz, K. Friel, N. Dancause, and A. Stowe for helpful comments on this manuscript. We also thank C. K. De Bois and M. Marruchi for technical assistance.

This study was supported by National Institutes of Health Grants NS-30853, training grant NS-07373, and grant HD-02528.

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Hindlimb as demonstrated by Devor and Govrin-Lippmann (1979) and Bridge et al. (1994).

Diverse opinions concerning the functional significance of map topography in sensory cortices still exist (Kaas 1997; Weinberg 1997). However, there seems to be mounting evidence in favor of a functional, adaptive value for topographical organization of sensory input. Recent studies by Diamond and colleagues addressed this issue in the somatosensory cortex of rodents and humans. Harris et al. (1999) demonstrated that tactile learning in the rat involving an isolated vibrissae did not generalize beyond the extent of overlap between the receptive field barrel associated with the test vibrissae and neighboring barrels. An additional study by Harris et al. (2001) with normal human volunteers suggests that vibratory stimulation, punctate cutaneous stimulation, and texture of different stimuli are processed in a topographically organized manner. Discrimination training between these stimuli did not generalize from a specific digit used during training to other digits assessed during the test phase.

Further evidence for the functional significance of somatotopic organization in the cortex was presented in a recent study by Florence et al. (2001). The authors show that, following a median nerve cut and repair in young macaque monkeys, rehabilitative training on a sensory enrichment task enhanced behavioral recovery of fine motor skills. The recovery of skilled use of the affected hand was associated with normalization of many cutaneous receptive fields and, to a lesser extent, a partial reinstatement of normal cutaneous topography in area 3b of the sensory cortex compared with control monkeys with a median nerve repair and no rehabilitative training. Interestingly, no significant changes in the cutaneous topography in the thalamus were observed, indicating that the influence of sensory training was cortically mediated.

Considering the evidence cited above supporting the relationship between somatotopic organization in primary sensory cortex and behavior, the application of the quantitative index of topography being presented in this study could be useful for distinguishing between various nerve repair techniques and rehabilitative strategies. One of our intentions for deriving a sensitive index of topography was to establish a measure for distinguishing differences between various peripheral nerve cut repair techniques. For example, reinnervation errors are thought to be exacerbated by the orientation of the joined nerve fibers to find their appropriate peripheral targets more accurately (e.g., tubularization or “gap repair”) (Lundborg et al. 1997). Reinnervation errors manifested in somatotopic organization should reveal the efficacy of alternative or novel repair techniques for improving the accuracy of nerve regeneration into appropriate target areas. Additionally, index values can be correlated with functional indices of recovery to determine the extent that reinnervation errors and consequential distortions of cortical topography contribute to behavioral deficits associated with peripheral nerve damage. Even if novel repair techniques only partially restore topography, it may be enough to enhance sensorimotor behavior. The Florence et al. (2001) study suggests that partial normalization of topography in area 3b was sufficient to support recovery of fine motor skills following sensory rehabilitation.
AN INDEX OF TOPOGRAPHIC NORMALITY IN RAT CORTEX

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