Local Circuit Properties Underlying Cortical Reorganization

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Hickmott, Peter W., and Michael M. Merzenich. Local circuit properties underlying cortical reorganization. J Neurophysiol 88: 1288–1301, 2002; 10.1152/jn.00994.2001. Peripheral denervation has been shown to cause reorganization of the deafferented somatotopic region in primary somatosensory cortex (S1). However, the basic mechanisms that underlie reorganization are not well understood. In the experiments described in this paper, a novel in vivo/in vitro preparation of adult rat S1 was used to determine changes in local circuit properties associated with the denervation-induced plasticity of the cortical representation in rat S1. In the present studies, deafferentation of rat S1 was induced by cutting the radial and median nerves in the forelimb of adult rats, resulting in a rapid shift of the location of the forepaw/lower jaw border; the amount of the shift increased over the times assayed, through 28 days after denervation. The locations of both borders (i.e., original and reorganized) were marked with vital dyes, and slices from the marked region were used for whole-cell recording. Responses were evoked using electrical stimulation of supragranular S1 and recorded in supragranular neurons close to either the original or reorganized border. For each neuron, postsynaptic potentials (PSPs) were evoked by stimulation of fibers that crossed the border site (CB stim) and by equivalent stimulation that did not cross (NCB stim). Monosynaptic inhibitory postsynaptic potentials (IPSPs) were also examined after blocking excitatory transmission with 15 μM CNQX plus 100 μM DL-APV. The amplitudes of PSPs and IPSPs were compared between CB and NCB stimulation to quantify effects of the border sites on excitation and inhibition. Previous results using this preparation in the normal (i.e., without induced plasticity) rat S1 demonstrated that at a normal border both PSPs and IPSPs were smaller when evoked with CB stimulation than with NCB stimulation. For most durations of denervation, a similar bias (i.e., smaller responses with CB stimulation) for PSPs and IPSPs was observed at the site of the novel reorganized border, while no such bias was observed at the suppressed original border site. Thus changes in local circuit properties (excitation and inhibition) can reflect larger-scale changes in cortical organization. However, specific dissociations between these local circuit properties and the presence of the novel border at certain durations of denervation were also observed, suggesting that there are several intracortical processes contributing to cortical reorganization over time and that excitation and inhibition may contribute differentially to them.

INTRODUCTION

Sensory maps of the adult cortex reorganize in response to large-scale changes in incoming inputs (Buonomano and Merzenich 1998; Kaas 1991). For example, peripheral denervation causes both rapid and sustained changes in cortical organization in the deafferented region of somatosensory cortex (Calford and Tweedale 1988; Kaas 1991; Kaas et al. 1983; McCandlish et al. 1996; Merzenich et al. 1983; Pons et al. 1991). Changes in cortical organization underlie a variety of important neurological phenomena, including referred “phantom” pain and sensation after amputation (Borsook et al. 1998; Knecht et al. 1996; Ramachandran and Hirstein 1998) and recovery of function after brain or peripheral nerve injury (Flor et al. 1995; Friel and Nudo 1998; Nudo 1997; Nudo and Millikan 1996). Furthermore, they are thought to underlie improvements in performance due to some forms of learning (Buonomano and Merzenich 1998; Jenkins et al. 1990; Merzenich et al. 1993; Nudo and Millikan 1996; Recanzone et al. 1992, 1993; Wang et al. 1995). An understanding of the mechanisms that underlie representational plasticity is a central issue in integrative neuroscience.

Two general classes of mechanism have been widely hypothesized to underlie these types of plasticity: 1) a rapid change in the efficacies of existing synapses and 2) a delayed phase involving the sprouting of new connections (Armstrong-James et al. 1994; Calford and Tweedale 1988; Donoghue et al. 1990; Florence et al. 1998; Merzenich et al. 1983; Pons et al. 1991; Sanes et al. 1990; Wall 1988). Such processes occur within the cortex for both extrinsic and intrinsic cortical connections (Antonini et al. 1999; Darian-Smith and Gilbert 1994, 1995; Rausell and Jones 1995; Trachtenberg and Stryker 2001) and also occur in subcortical structures (Jones and Pons 1998; Kaas et al. 1999). However, the specific and relative contributions of these changes to the plasticity recorded in the cortex are not well understood. Recent studies in the whisker barrel cortex of adult rats have suggested that changes in short-term synaptic dynamics and synaptic efficacy within superficial cortex are associated with changes in the cortical representation (Finnerty et al. 1999; Finnerty and Connors 2000).

To examine specific changes in intracortical circuitry related to changes in cortical representations, we studied neurons close to the border between the forepaw and lower jaw representations in rat primary somatosensory cortex (S1) after the radial forepaw representation had been deafferented. Many studies have documented changes in somatotopic representations resulting from peripheral denervation, with postdenervation durations extending to many years (e.g., Florence et al. 1998; Merzenich et al. 1983; Pons et al. 1991). In the rat, denervation-induced plasticity has been demonstrated for denervation...
of the whiskers, forelimb, hindlimb, and digits (e.g., Dykes and Lamour 1988; Lamour and Dykes 1988; McCandlish et al. 1996; Wall and Cusick 1984). In this last case, however, the focus of studies was on reorganization within the forepaw representation; these studies did not address the issue of reorganization of the adjacent lower jaw representation in detail. It was therefore important to examine the extent of reorganization at the forepaw/lower jaw border in the rat, as some experiments in primates have indicated that there may be little shift in the hand/face border after forepaw denervation (Manger et al. 1997, although see Merzenich et al. 1983).

Our previous work in rat S1 (Hickmott and Merzenich 1998a) has shown that intracortical excitation and inhibition are both significantly weaker when evoked from an adjacent representation than when evoked from within the representation. Thus properties of local cortical circuitry reflect the presence of a physiological discontinuity or “border” between adjacent, discontinuously represented skin surface zones in the normal adult rat. Similar results have been obtained in the whisker barrel cortex of rat S1 (Petersen and Sakmann 2000). In our animals, both the original and reorganized border sites were marked with different dyes. Intracellular recordings were made from neurons close to one of these sites, and the properties of intracortical excitation and inhibition were examined with respect to that border. Both the reorganized and the original forepaw/lower jaw border were examined. To assess possible differences between rapid and more sustained reorganization, the effects of peripheral denervation were examined for durations of denervation ranging from approximately 1 h up to 33 days.

Some of these results have been presented previously in abstract form (Hickmott and Merzenich 1997, 1998b).

**Methods**

**In vivo recording, forepaw denervation, and isolation of slices**

Methods for extracellular recording from anesthetized adult rat S1 were similar to those used previously (Hickmott and Merzenich 1998a). These methods are briefly summarized here. For all surgical procedures, adult Sprague–Dawley rats (280–350 g) were anesthetized to an areflexic level with pentobarbital (50 mg/kg ip) and mounted in a stereotoxic frame. Supplemental doses of anesthetic were administered as needed. For all recovery surgeries, aseptic procedures were used. All surgical procedures were approved by the University of California San Francisco Committee on Animal Research and the Chancellor’s Committee on Laboratory Animal Research at the University of California Riverside.

To determine the amount of shift in the forepaw/lower jaw border, the region of S1 around the border was mapped twice: 1) before the denervation, then 2) after specific durations of denervation (the phrase “duration of denervation” is used throughout the paper as shorthand for the more accurate “duration of survival after denervation”). For animals subject to chronic (>1 h) denervation, the first map was derived using transdural electrode penetrations. Since the rat dura is relatively transparent, it was possible to see the remaining cut ends of the nerves were tightly ligated with 6-0 suture thread to prevent nerve regeneration. These nerves innervate the volar and dorsal surfaces of the radial aspect of the forepaw (Fig. 1A, shading). Animals were then allowed to recover for the desired duration of denervation (<1 h or 7, 14, or 28 days) before the second mapping of the forepaw/lower jaw border in S1 was conducted in a similar manner to the first. The animal was anesthetized as described above, the craniotomy was reopened, the dura was removed, and the exposed cortex was covered by silicone oil. Response mapping of the forepaw/lower jaw region was performed using carbon-fiber electrodes (10-μm fiber diameter). The reorganized border sites were defined as at dual-response sites (Fig. 1C, diagonal hatched squares) or at a site midway between adjacent lower jaw responsive (Fig. 1C, vertical hatched circles) or nonresponsive (Fig. 1C, black squares) or between adjacent lower jaw responsive and forepaw responsive (Fig. 1C, horizontal hatched squares) penetrations. The reorganized border sites were marked with different dyes. Intracellular recordings were made from neurons close to one of these sites, and the properties of intracortical excitation and inhibition were examined with respect to that border. Both the reorganized and the original forepaw/lower jaw border were examined. To assess possible differences between rapid and more sustained reorganization, the effects of peripheral denervation were examined for durations of denervation ranging from approximately 1 h up to 33 days.

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exposed, but not cut or ligated. Sham animals were allowed to recover for either <1 h (acute sham group) or 28 days (28-day sham group) and the shift in the border was determined as for experimental animals. These controls were to ensure that the surgical, mapping, and marking procedures did not cause any significant shift in the border. The shortest and longest time points were chosen to span the entire duration of denervation. Since there was no evidence for nondenervation-induced shifts in the border were observed for these time points, the intervening durations of denervation were not tested using this sham procedure.

After the second border marking, the animal was decapitated, the brain was rapidly removed, and 400-μm thick coronal slices were cut on a vibratome (Leica VT1000s) from the marked region of cortex. Slices with DiI and Chicago blue marks locating the original and reorganized border were selected for use in vitro (Fig. 1D). Shifts in the border were defined as the horizontal distances between the two marked sites in any given 400-μm-thick section (Fig. 1D). Note only sections in which both dye marks were visible for each time point were used for subsequent analyses. The supragranular layers of the cortex were then isolated with a cut parallel to the cortical surface around layer 4 (500–700 μm from the cortical surface). Note that supragranular neurons were studied, as these layers appear to be more susceptible to representational plasticity, especially rapidly occurring plasticity (e.g., Armstrong-James et al. 1994). Slices were maintained in standard mammalian bicarbonate buffer (in mM: 119 NaCl, 2.5 KCl, 1.25 NaH2PO4, 1.3 MgSO4, 2.5 CaCl2, 26.2 NaHCO3, and 11 glucose, saturated with 95% O2–5% CO2) for intracellular recording. Slices were maintained at 30.5°C. These and all subsequent chemicals were obtained from Sigma Chemical unless otherwise stated. Slices were checked for viability and stability by recording maximal extracellular fields potentials in layer 3 in response to electrical stimulation at or above layer 4. Electrodes for field recording were glass pipettes with approximately 1.5- to 2.5-μm tip diameter, filled with 1 N NaCl (1–4 MΩ resistance). Only slices in which stable fields with a main negativity of >0.6 mV were used (see Fig. 2B in Hickmott and Merzenich 1998a).
Intracellular recording

Neurons for recording were obtained using blind whole cell recording (Blanton et al. 1989) from a region near the original or reorganized border (~100-300 μm distant) in cortical layer 2/3. Patch electrodes were pulled on a Flaming/Brown puller to a tip diameter of 1.5–2.5 μm and filled with 128 mM Cs-Gluconate (Aldrich), 7 mM CsCl, 1 mM EGTA, 10 mM HEPES, 10 mM QX-314, 2 mM Mg-ATP, 0.2 mM Na-GTP, and 0.3–0.5% biocytin, pH 7.0–7.4. Such electrodes had tip resistances of 3–8 MΩ. QX-314 (RB1) was included to block action potentials so that the amplitude of large postsynaptic potentials (PSPs) could be quantified. Only neurons with initial resting potentials of less than −60 mV and stable input resistances of more than 50 MΩ were used. For recording PSPs, positive or negative current was injected to maintain the membrane potential at −50 to −55 mV. Neurons were obtained for recording in one of two regions in any given slice: either close to the site of the original border (Fig. 3A) or close to the site of the reorganized border (Fig. 3B).

Recorded signals were amplified using an Axoclamp 2B amplifier (Axon Instruments), digitized at 10 kHz, and saved to the hard disk of a Gateway 486 or Macintosh G4 computer using Experimenters' Workbench (DataWave) or Igor Pro (WaveMetrics) data acquisition systems. PSPs were recorded in these neurons in current clamp mode by stimulating layer 2/3 at the same depth from the cortical surface as the sampled neuron. The stimulating electrode was a bipolar, parylene-coated tungsten electrode (resistance approximately 1 MΩ) with a tip separation of about 50 μm (FHC). For neurons close to the original or reorganized border, stimuli were delivered at two sites: one site that was across the border from the neuron and another site at an identical distance from the neuron in the opposite direction, i.e., without an intervening border (see Fig. 3). Brief electrical stimuli (100–μs duration, 0.1 Hz) were presented. Throughout this paper, the first case (crossborder stimulation) will be referred to as "CB" stimulation and the second case (non-crossborder stimulation) will be referred to as "N CB" stimulation. Both sites were at the same distance from the cortical surface as the implicated neuron. To minimize variability, the same stimulating electrode at the same polarity was used for both stimuli and was positioned with the aid of a microscope eyepiece graticule. PSPs were evoked at both these sites starting below the minimal intensity necessary to evoke a PSP and gradually increased to a supramaximal intensity, generating a complete input/output (I/O) curve for each neuron. The same stimulus intensities were used at both sites of stimulation except when lower and higher stimuli were necessary to define minimal and maximal responses. The progression of intensities was determined empirically based on our previous results (Hickmott and Merzenich 1998a). Since sodium-dependent spikes were blocked with intracellular QX-314, it was possible to record pure PSPs in most cells even at high stimulus intensities. However, in some cells large voltage-activated potentials were evoked by larger PSPs; these potentials were characterized by their sudden appearance near the peak of the PSP at some stimulus intensity (i.e., threshold), large amplitude that did not vary with further increases in stimulation intensity, and usually exhibited a "shoulder" on the rising and/or falling phase of the PSP. These cells were not used for PSP analysis, although they were sometimes used for analysis of pure inhibitory postsynaptic potentials (IPSPs; see following text), as the hyperpolarizing IPSPs did not elicit the potentials. PSPs were evoked around the reversal potential for IPSPs, typically at −50 to −55 mV. The average of 3–5 individual PSPs was used for quantification at each stimulus intensity (Fig. 4A).

Analysis of PSPs

To confirm that PSPs were stimulated from sites at equivalent distances, latencies from stimulus artifact to PSP initiation were also determined. Any neurons in which these latencies differed by >20% were not used for analyses. Because these latencies varied with PSP amplitude, it was always determined for a PSP of ~5 mV. In previous work using this model system, several parameters that reflected the presence of a normal representational border were defined based on the PSP I/O relations (Hickmott and Merzenich 1998a). In this study, a subset of those parameters that generally exhibited the most robust differences for CB versus NCB stimulation at the normal border were examined. Thus, to examine possible effects of either the original or reorganized border on the PSPs, the peak amplitude of the maximal PSP (P(kmax)) and the threshold current to evoke a minimal PSP (thresh) were determined for the PSPs evoked from across the border (CB stim) and for those evoked from within the representation (NCB stim). The ratio (NCB/CB) of these two values was then calculated as

\[
\frac{P(k_{\text{max}})}{\text{thresh}}
\]

FIG. 3. Schematics of the recording and stimulating sites for the in vitro slice preparation after peripheral denervation. A: preparation for probing the location of the original site of the forepaw/lower jaw border (which was determined and marked before the denervation), B: preparation for probing the reorganized border. Each schematic represents a coronal slice from a denervated animal through the region of S1 around the forepaw/lower jaw border delineated by in vivo response mapping. The hatched squares represent the sites of electrical stimulation, either at the cross-border (CB stim.) or noncross-border (NCB stim.) site, the filled circle and dotted line represent the site of the reorganized border, the open circle represents the site of the original border, the branched triangle represents the neuron, and the inverted angle marked rec represents the recording electrode. Cut indicates the location of the cut in layer 4 (L4) that isolated the supragranular layers of cortex. FP: forepaw responsive zone, LJ: lower jaw responsive zone.
an overall metric of the effect of the border (original or reorganized) on the parameter. Our previous data (Hickmott and Merzenich 1998a) indicate that the amplitude of the maximal PSP is a good measure of overall excitation: the reversal potential of the peak PSP was approximately 0 (mean −4 mV) and the peak amplitude was well correlated with the slope of the input/output function of the PSP amplitudes, therefore it also reflects the submaximal excitation. Of course, this measure includes contributions from intrinsic properties, excitatory synaptic strengths, distributions of stimulated fibers, etc., and is not a measure of synaptic strength per se. Maximal PSP amplitude does reflect the total ability to excite a given neuron from a given stimulation site. Furthermore, peak amplitude was also the parameter that most strongly exhibited the bias observed at the normal border. The later portion of the PSPs was dominated by inhibition (i.e., reversal potential approximately −50 mV) (Hickmott and Merzenich 1998a). However, since these potentials contain both excitatory and inhibitory components, we refer to them as PSPs rather than excitatory postsynaptic potentials (EPSPs) or IPSPs.

### Analysis of IPSPs

To isolate monosynaptic IPSPs, a combination of 10–15 μM 6,7-dinitroquinoxaline-2,3-dione (DNQX, RBI) or 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX, RBI) and 100 μM dl-2-amino-5-phosphonopentanoic acid (APV) was bath applied via the perfusion system for >10 min. IPSPs were recorded at −40 to −45 mV. IPSPs at several stimulus intensities from minimal to maximal were obtained for both CB and NCB sites, yielding complete I/O curves for the IPSPs. The amplitude and 50% fall time (t1/2) of the maximal IPSP and the threshold to evoke a minimal IPSP were determined for both CB and NCB stimulation. Again, the ratio of the values (NCB/CB) was used as a metric for the effects of the original or reorganized border on the given parameter.

### Statistical analyses

Throughout this paper, values are expressed as means ± SE, unless otherwise indicated. Generally, parametric tests were used, as the data involved were approximately normally distributed. However, the distances of neurons from the border site and the distances of stimulation from the recording sites were not normally distributed (e.g., Figure 2C in Hickmott and Merzenich 1998a). For these parameters, nonparametric tests (Kruskal–Wallis) were used. For other parameters, two statistical analyses were performed: 1) to examine differences between parameters at the original border site and the reorganized border site at each duration of denervation, corresponding parameters from neurons close to the original border (Table 2) and close to the reorganized border (Table 3) were compared using unpaired t-tests and 2) to look for patterns of change in the effects of the original and reorganized borders across the various durations of denervation, a factorial analysis of variance (ANOVA) was used to determine if there was a significant difference among the NCB/CB ratios (Figs. 5 and 6) or the raw values (Tables 2 and 3) for each parameter; parameters determined to differ significantly were further analyzed using a posthoc test [Fisher’s protected least-squares difference (PLSD)]. The level of significance for all tests was P < 0.05.

### Results

#### Reorganization of the forepaw/lower jaw border in vivo

The progression of reorganization at the forepaw/lower jaw border in rat S1 is shown schematically in Fig. 1E and is quantified in Fig. 2. Immediate consequences of denervation were 1) the appearance of a nonresponsive region of cortex that was originally activated by the denervated forepaw (Fig. 1E, stipple); 2) a medial-ward shift of the border, with the lower jaw region expanding into the deafferented forepaw region (see Fig. 2, horizontal hatched bar); and 3) a similar expansion of the nondeafferented region of the forepaw into the deafferented region. Note that acutely denervated animals never recovered from anesthesia so they never had a chance to use the denervated limb, as the other denervation groups did. This is one possible reason for the relatively small reorganization observed. After 7 days of denervation, the amount of nonresponsive cortex had substantially decreased (Fig. 1E, stipple), partly due to further expansion of the nondenervated region of the forepaw. There was a significant increase in the border shift between 1 h and 7 days (Fig. 2, diagonal hatched bar). By 14 days after the denervation, there was little or no nonresponsive
cortex (Fig. 1E, right) due to further shifting of both the forepaw/lower jaw border and expansion of the nondeafferented ulnar forepaw region (Fig. 2, vertical hatched bar). At the longest-tested durations of denervation (approximately 28 days), the shift in the border, accounted for by a still greater apparent expansion of the lower jaw representation, had apparently reached a plateau (Fig. 2, black bar). Since longer durations of denervation have not been examined, further shifts in the border may occur with longer denervations. Thus our denervation protocol resulted in a rapid and progressive reorganization of S1 around the denervated region of cortex, with a progressive medial-ward shift in the forepaw/lower jaw border location. This reorganization was qualitatively similar to that observed in the hand region of primates after median nerve section (Merzenich et al. 1983). No consistent shift in the forepaw/lower jaw border was observed in the acute sham (Fig. 2, open bar) or the 28-day sham (Fig. 2, gray bar) groups.

**FIG. 5.** Quantification of response ratios in neurons at the original border site (see Fig. 3A, left). Response ratios (values from NCB stimulation divided by those from CB stimulation) reflecting excitation (A and B) and inhibition (C-E, data taken in the presence of APV and CNQX) are shown. In all plots, the x-axis represents the duration of peripheral denervation in days; cont: data from control, nonborder sites in nondenervated animals, norm: data from neurons at the normal border in nondenervated animals (data in these two categories are from Hickmott and Merzenich 1998a), ac: acute (<1 h) denervation. Numbers in parentheses are the number of cells used to determine each average. Significance was determined using one-way ANOVA, followed by posthoc test (Fisher’s PLSD). *: significantly different from the mean at a normal border (norm), P < .001; **: significantly different from the mean at a normal border (norm), P < .05.
**In vitro recording**

Data from a total of 130 neurons from 71 animals are summarized in this paper. Note that data from neurons at control sites (sites in normal S1 that were far from the border, \( n = 12, 9 \) animals) and at the forepaw/lower jaw border in normal animals (\( n = 25, 16 \) animals) are included for comparison. These categories are referred to as “cont” and “norm,” respectively, in subsequent figures and tables. These data are described in detail in Hickmott and Merzenich (1998a). The remaining 93 neurons were from animals with varying durations of denervation: acute (\( n = 23, 13 \) animals), 7 days (\( n = 21, 10 \) animals), 14 days (\( n = 25, 12 \) animals), and 28 days (\( n = 24, 11 \) animals). The resting potentials of the neurons from different groups were not significantly different from one another (ANOVA, Table 1). However, the mean input resistances differed significantly (ANOVA, Table 1); the mean input resistances of neurons from all groups of denervated animals were lower than those of normal or control animals (Table 1). These data suggest that peripheral denervation causes a rapid and long-lasting change in some of the intrinsic properties of supragranular neurons in S1.

The responses of two populations of supragranular neurons in S1 were examined for each duration of denervation: one population was close to the original border site and the other...
was close to the reorganized border site (Fig. 3). Responses were evoked in neurons by electrical stimulation of supragranular cortex at the same distance from the cortical surface as the recorded neuron. The recording and stimulating configurations used are shown schematically in Fig. 3. Figure 3A shows the experimental configuration for examining responses near the original border (open circle), while Fig. 3B shows that used for examining responses near the reorganized border (filled circle, dotted line). For each neuron, responses were evoked with electrical stimulation at two sites (hatched squares): a site that was across the appropriate (original or reorganized) border (CB stim) and a site that was within the representation at the same distance from the neuron and distance from the cortical surface (NCB stim).

The mean distances (in μm) of neurons from the original border were 149 ± 10 for acute, 156 ± 11 for 7 day, 177 ± 13 for 14 day, and 181 ± 15 for 28 day; the mean distances of neurons (in μm) from the reorganized border were 145 ± 11 for acute, 155 ± 10 for 7 day, 148 ± 9 for 14 day, and 162 ± 6 for 28 day. These means were not significantly different across the different durations of denervation or among neurons at the reorganized and original borders (Kruskal–Wallis test). The mean distance of neurons from the border, pooled across denervation groups was 152 ± 4 μm. The mean distances (in μm) between recording and stimulating sites for the original border sites were 238 ± 16 for acute, 270 ± 19 for 7 day, 252 ± 18 for 14 day, and 268 ± 18 for 28 day; the mean distances (in μm) between recording and stimulating sites for the reorganized border sites were 214 ± 15 for acute, 260 ± 11 for 7 day, 253 ± 12 for 14 day, and 268 ± 11 for 28 day. The mean distances between recording and stimulating sites did not differ significantly across the durations of denervation (Kruskal–Wallis test). The mean distance between recording and stimulating sites, pooled across denervation groups was 239.9 ± 10.4 μm. Analysis of the latencies of the PSPs also showed no difference among the various denervation groups (see Tables 2 and 3), confirming the similarity of stimulating sites across groups.

** Characteristics of PSPs and IPSPs from denervated animals **

Figure 4A shows examples of PSPs evoked by CB and NCB stimulation in a neuron close to the reorganized border in an animal that had a 14-day denervation. The quantitation of various parameters derived from PSPs similar to these for the entire population studied is shown in Tables 2 and 3. Minimal stimulation evoked a small, relatively long PSP; increasing stimulus intensity yielded PSPs with larger amplitude and shorter duration. Both amplitude and duration eventually reached a maximal or minimal value. At the membrane potential used in these studies (−55 to −50 mV), there was also a late hyperpolarization in response to stronger stimulus intensities. These PSPs were similar in amplitude, kinetics, and threshold to PSPs evoked in S1 close to a normal forepaw/lower jaw border (Hickmott and Merzenich 1998a). However, the PSPs from denervated animals, whether at the original or reorganized border, tended to have larger peak amplitudes than those evoked in normal animals (Tables 2 and 3).

Inhibition was accurately quantified by examining isolated monosynaptic IPSPs. Figure 4B shows examples of IPSPs evoked in the same neuron as in Fig. 4A after bath application of 15 μM CNQX plus 100 μM APV. As observed previously (Hickmott and Merzenich 1998a), monosynaptic IPSPs increased in both amplitude and duration with increasing stimulus intensity, until reaching a maximal value. To quantify inhibition, the amplitude and 50% fall time (τ1/2) of the maximal IPSP and the threshold to evoke a minimal IPSP were measured. These IPSPs were also similar to those observed in normal animals. However, as observed for PSPs (i.e., for excitation), there was generally an increase in the magnitude (as measured by both amplitude and fall time) of inhibition. There were significant increases for both these parameters at both the original and reorganized border sites, although the increases were more pronounced at the reorganized border (Tables 2 and 3). One interesting observation was that the increase in IPSP peak amplitude observed at denervations ≤14 days was not observed at 28 days; however, the increase in IPSP τ1/2 was still present at 28 days of denervation.

In general, the means of these parameters from neurons close to the original border were not significantly different from those from neurons close to the reorganized border (unpaired t-tests). However, a few parameters, almost exclusively from animals denervated for 14 days, were different: 1) thresholds for evoking PSPs and IPSPs were larger at original border sites and 2) amplitudes of IPSPs were larger at original border sites. Note that, to quantify bias, a within-animal comparison was used (ratio of NCB/CB responses), which detected significant differences (Figs. 5 and 6) that were not apparent in comparing the mean response data in Tables 1 and 2.

** PSPs and IPSPs at the original border site **

In Fig. 5, the responses of single neurons close to the original border site in denervated rats (Fig. 3A) are quantified for excitation (Fig. 5, A and B) and inhibition (Fig. 5, C–E). These data reflect properties of the intracortical circuitry at a site where a preexisting representational border was suppressed by the denervation. To quantify differences between the intracortical circuitry activated by stimuli within the representation (i.e., NCB stimulation) versus stimuli activated in the adjacent representation (i.e., CB stimulation), the ratios of the responses to CB and NCB stimulation are plotted for each duration of

### TABLE 1. Intrinsic properties of neurons after various durations of denervation

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Normal</th>
<th>Acute</th>
<th>7 Day</th>
<th>14 Day</th>
<th>28 Day</th>
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<tr>
<td>Resting potential, mV</td>
<td>−68.0 ± 1.1 (12)</td>
<td>−70.6 ± 1.1 (25)</td>
<td>−70.1 ± 1.1 (27)</td>
<td>−72.4 ± 1.2 (29)</td>
<td>−73.4 ± 1.2 (32)</td>
<td>−72.3 ± 1.1 (31)</td>
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<tr>
<td>Input resistance, MΩ</td>
<td>122.0 ± 6.4 (11)</td>
<td>117.5 ± 4.1 (25)</td>
<td>97.8 ± 5.8* (27)</td>
<td>91.4 ± 6.0* (29)</td>
<td>97.7 ± 6.3* (32)</td>
<td>99.6 ± 3.7* (31)</td>
</tr>
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</table>

Values are means ± SE with number of neurons in parentheses. Control, data from neurons close to the normal border in nondenervated animals (from Hickmott and Merzenich 1998); normal, data from neurons close to a nonborder site in nondenervated animals (from Hickmott and Merzenich 1998); and acute, 7 day, 14 day, and 28 day; data from neurons close to the normal or reorganized border sites after the indicated duration of denervation. * Significantly different from control value, P < 0.05. † Significantly different from normal value, P < 0.05.
TABLE 2. Quantification of response parameters in neurons at original border sites

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Normal</th>
<th>Acute</th>
<th>7 Day</th>
<th>14 Day</th>
<th>28 Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSP peak amplitude CB, mV</td>
<td>24.1 ± 2.7 (11)</td>
<td>21.5 ± 2.7 (18)</td>
<td>31.2 ± 4.8b (10)</td>
<td>29.2 ± 4.0h (9)</td>
<td>30.9 ± 4.0h (15)</td>
<td>30.9 ± 2.1h (14)</td>
</tr>
<tr>
<td>PSP peak amplitude NCB, mV</td>
<td>24.6 ± 1.8</td>
<td>26.6 ± 2.5</td>
<td>36.2 ± 2.9b,b,b,b</td>
<td>32.8 ± 2.2a,b</td>
<td>31.3 ± 2.4a,b</td>
<td>30.9 ± 2.9a,b</td>
</tr>
<tr>
<td>PSP threshold CB, μA</td>
<td>25.7 ± 4.0</td>
<td>20.3 ± 3.5</td>
<td>29.3 ± 5.6</td>
<td>21.3 ± 2.8</td>
<td>26.5 ± 1.7</td>
<td>29.1 ± 8.7</td>
</tr>
<tr>
<td>PSP threshold NCB, μA</td>
<td>25.9 ± 3.7</td>
<td>14.5 ± 3.0</td>
<td>17.8 ± 3.1</td>
<td>15.2 ± 2.9</td>
<td>15.3 ± 2.8</td>
<td>14.6 ± 2.5</td>
</tr>
<tr>
<td>PSP latency CB, ms</td>
<td>2.4 ± 0.11</td>
<td>2.6 ± 0.13</td>
<td>2.8 ± 0.31</td>
<td>2.7 ± 0.18</td>
<td>2.5 ± 0.13</td>
<td>2.5 ± 0.11</td>
</tr>
<tr>
<td>PSP latency NCB, ms</td>
<td>2.4 ± 0.14</td>
<td>2.6 ± 0.13</td>
<td>2.7 ± 0.27</td>
<td>2.7 ± 0.27</td>
<td>2.6 ± 0.13</td>
<td>2.5 ± 0.09</td>
</tr>
<tr>
<td>IPSP peak amplitude CB, mV</td>
<td>4.6 ± 0.33 (11)</td>
<td>6.4 ± 0.53 (9)</td>
<td>7.3 ± 1.0h (9)</td>
<td>7.7 ± 0.87h (10)</td>
<td>5.8 ± 0.53 (10)</td>
<td></td>
</tr>
<tr>
<td>IPSP peak amplitude NCB, mV</td>
<td>5.3 ± 0.44</td>
<td>8.2 ± 0.43b</td>
<td>8.9 ± 0.73c,a,b</td>
<td>6.6 ± 0.80</td>
<td>6.1 ± 0.52</td>
<td></td>
</tr>
<tr>
<td>IPSP latency CB, ms</td>
<td>121.3 ± 15.9</td>
<td>112.0 ± 13.2</td>
<td>190.4 ± 23.1,b,c,b,a,b</td>
<td>173.9 ± 14.2</td>
<td>192.4 ± 17.6,b,c,b,a,b</td>
<td></td>
</tr>
<tr>
<td>IPSP latency NCB, ms</td>
<td>159.8 ± 17.3</td>
<td>145.4 ± 8.6</td>
<td>195.4 ± 17.8</td>
<td>179.9 ± 15.9</td>
<td>192.6 ± 18.2</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE with number of neurons in parentheses. Data categories are as in Table 1 and Figs. 5 and 6. a Significantly different from control, P < 0.05. b Significantly different from normal, P < 0.05. c Significantly different from acute, P < 0.05. d Significantly different from 7 day, P < 0.05. e Significantly different from 14 day, P < 0.05. f Significantly different from 28 day, P < 0.05.

PSPs and IPSPs at the reorganized border site

In Fig. 6, the responses of single neurons close to the reorganized border site in denervated rats (Fig. 3B) are quantified for excitation (Fig. 6, A and B) and inhibition (Fig. 6, C–E). These data reflect properties of the intracortical circuitry at a site where a novel representational border was expressed during the denervation. Intracortical excitation and inhibition were quantified in the same manner as detailed above for the original border, i.e., the mean NCB/CB ratio was determined for each parameter (PSP and IPSP peak amplitudes, thresholds, and IPSP 50% fall time) and compared across durations of denervation (ac, 7, 14, and 28) and to the ratio at a normal border (norm); for excitation, these values were also compared with the ratio at a control site (cont). In contrast to the results observed at the original border, at the reorganized border the NCB/ CB ratios generally were not significantly different from the value observed at a normal border (norm), indicating an effect of the reorganized border on that parameter (i.e., a NCB/CB ratio > 1). Thus the ratios for the various durations of denervation tended to be similar to the ratios obtained at a normal forepaw/lower jaw border (norm). However, there are

TABLE 3. Quantification of response parameters in neurons at reorganized border sites

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Normal</th>
<th>Acute</th>
<th>7 Day</th>
<th>14 Day</th>
<th>28 Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSP peak amplitude CB, mV</td>
<td>24.1 ± 1.9 (11)</td>
<td>21.5 ± 2.6 (18)</td>
<td>31.3 ± 4.8h (10)</td>
<td>29.2 ± 4.0h (9)</td>
<td>30.9 ± 4.0h (15)</td>
<td>30.9 ± 2.1h (14)</td>
</tr>
<tr>
<td>PSP peak amplitude NCB, mV</td>
<td>24.6 ± 1.8</td>
<td>26.6 ± 2.5</td>
<td>36.2 ± 2.9b,b,b,b</td>
<td>32.8 ± 2.2a,b</td>
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</tr>
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some interesting exceptions to this general finding. For excitation, at 14 days of denervation there was no apparent effect of the border on either parameter (maximal PSP amplitude, Fig. 6A; PSP threshold, Fig. 6B), and, at 28 days of denervation, there was no apparent effect on PSP threshold (Fig. 6B). For IPSP fall time ($t_{1/2}$), there was a similar lack of effect of the border, but for this parameter the lack was first apparent after 7 days of denervation and was sustained through 28 days (Fig. 6D).

**DISCUSSION**

**Reorganization of the forepaw/lower jaw border**

The reorganizations documented in this report were similar in direction and magnitude to changes observed in S1 in rats and in other animals after denervation or amputations (e.g., McCandlish et al. 1996; Merzenich et al. 1983; see Kaas 1991 for review). We observed a rapid expansion of the adjacent lower jaw responsive region into the denervated forepaw region that progressed over the duration of denervation (Figs. 1 and 2). Due to the high density of electrode penetrations used to define the border (<50 μm separation), we are confident that our mapping protocol accurately reconstructed changes in border location (>150 μm, Fig. 2). Our previous results indicated that normally the forepaw/lower jaw border lies near the middle of the perigranular region between the forepaw and lower jaw granular regions (Hickmott and Merzenich 1998a). Thus, for durations of denervation of 7 days or greater, the observed shifts (150–250 μm; Fig. 2) place the reorganized border close to or in the forepaw granular zone, as the perigranular zone is about 200- to 300-μm wide (e.g., Chapin and Lin 1984). Interestingly, inputs to the perigranular zone come from the posterior nucleus of the thalamus (POm) while those to the granular zones come from the ventral posterior nucleus (VP) (Koralek et al. 1988). Thus the border has the capability to shift from regions dominated by POM to those dominated by VP. It is possible that some of the observed reorganization results from changes in POM relayed to the cortex. However, given the significant changes in supergranular cortex observed, some of the reorganization may occur in cortex. Furthermore, the distances involved in the shift would be short range in the cortex (150–250 μm), but, in the thalamus, they might need to invade a separate nucleus (POm to VP).

**Changes in intrinsic neuronal properties after denervation**

Regardless of whether neurons were located close to the original or reorganized border site, there were significant changes in their intrinsic and synaptic properties. Neurons from reorganized cortex had slightly but significantly smaller input resistances than did those from normal S1 (Table 1), suggesting regulation of intrinsic properties of neurons. Changes in intrinsic properties have been observed after reorganization (Davis et al. 1998; Dykes et al. 1995; Webster et al. 1997), although sensory deprivation by whisker trimming yields no change in intrinsic properties of S1 neurons (Finnerty and Connors 2000; Finnerty et al. 1999). Due to the presence of cesium and QX-314 in our electrodes, no attempt was made to characterize the spiking characteristics of recorded neurons. Considering that neural activity can regulate ion channels important for various intrinsic properties (e.g., Perrier and Hounggaard 2000) and that peripheral denervation had pronounced effects on incoming activity, such a finding is not surprising. Studies directly examining intrinsic properties in S1 neurons are necessary to differentiate between such changes in intrinsic properties and possible changes in synapses.

Furthermore, in general, the amplitudes of both PSPs and isolated IPSPs tended to be larger in animals subject to denervation (Tables 2 and 3), indicating a general increase in response magnitude, even after very short durations of denervation. This change is probably not directly caused by the decrease in input resistance observed with denervation, as that change was relatively small and would actually tend to reduce response amplitude. It is possible that changes in some other intrinsic properties could be playing a role in this increase or that the changes in activity caused by the denervation might influence the release of some neurotrophic factor that causes a local increase in synaptic efficacies (Stoop and Poo 1996). It is interesting that the increase in amplitude was not observed in all cases: in particular, the peak amplitudes of IPSPs after 28 days of denervation (at both original and reorganized borders) were not greater than those in normal animals, even though the peak IPSP amplitude was increased for the other durations of denervation. This and other exceptions suggest that there may be separate mechanisms underlying reorganizations induced by denervation, such as 1) changes in synaptic efficacy, 2) sprouting of new connections, and 3) changes in neuronal intrinsic properties (although these changes would need to differentially affect different parts of a single neuron) and that the mechanisms may contribute collectively to the observed changes but with different time courses.

**Comparison of responses observed at original and reorganized borders**

We previously observed significant physiological biases associated with the forepaw/lower jaw border in normal rat S1 (Hickmott and Merzenich 1998a). The present studies show that in general these physiological biases parallel the suppression of the original and emergence of a novel border during reorganization induced by peripheral denervation. At the original border site, little bias was observed for horizontal excitation (Fig. 5, A and B) or inhibition (Fig. 5C–E) after any duration of peripheral denervation. Thus the original border site resembled a nonborder site (cont) and not a normal border site (norm). However, at the site of the novel reorganized border, bias for excitation (Fig. 6, A and B) and inhibition (Fig. 6C–E) was observed for most durations of denervation, with a few interesting exceptions (see following text for discussion). Therefore the novel border, which was a nonborder site prior to denervation, in most ways resembled a normal representational border (norm) after denervation. These data suggest that changes in the properties of horizontal excitation and inhibition play a role in changes in large-scale cortical organization. Similar results have been obtained in rat whisker barrel cortex of S1 after reorganization induced by “whisker trimming” (Finnerty and Connors 2000; Finnerty et al. 1999). These experiments implicated changes in short-term synaptic dynamics and synaptic efficacy of EPSPs in the physiological reorganization associated with whisker pairing. Our results are consistent with changes in synaptic efficacy being associated with shifts in the location of the forepaw/lower jaw border.
caused by peripheral denervation. However, we cannot rule out changes in the relative numbers of synapses (rather than efficacy, per se) as underlying the changes in bias that were observed. Changes in intrinsic properties of neurons in the reorganized region could also play a role in these changes. However, given that the changes observed were nonuniform both for excitation versus inhibition (e.g., IPSP amplitude is not increased with 28 days of denervation, while PSP amplitude is; Tables 2 and 3) and at the original versus novel border (the relative changes in CB and NCB responses must differ to produce the observed changes in bias), we believe that changes in intrinsic properties are not the sole mechanism underlying the observed changes.

The rapidity of changes in both the representation (Figs. 1 and 2, ac) and in the local circuit properties (Figs. 5 and 6, ac) suggest that at least initial changes in both are due to modulation of the efficacy of previously existing synapses, directly or indirectly driven by changes in incoming activity. Indeed, activity-dependent increases (long-term potentiation, LTP) and decreases (long-term depression, LTD) have been observed at excitatory synapses of horizontal connections in the cortex (e.g., Hess and Donoghue 1996; Hess et al. 1996; Hirsch and Gilbert 1993; Lee et al. 1991). With longer durations of denervation, however, sprouting of new connections has been documented in other regions of cortex (Darian-Smith and Gilbert 1994; Florence et al. 1998). Changes in axonal structure have been observed after short periods (2 days) of strabismus in the visual cortex (Trachtenberg and Stryker 2001), so such changes may be occurring during early phases of S1 reorganization. Furthermore, the relative ability to induce changes in synaptic efficacy (“metaplasiticy”, see Abraham and Bear 1996; Abraham and Tate 1997) has been shown to depend on levels of incoming activity. For example, the Bienenstock, Cooper, and Munro theory (BCM) (Bienenstock et al. 1982) postulates that there is a moving synaptic modification threshold (\(\theta_M\)) that determines both the amount of change in synaptic efficacy for a given stimulus and also whether the change is an increase or a decrease. The value of \(\theta_M\) at any moment changes in relation to the activity into the system in the recent past (Bear et al. 1987). The original BCM theory postulated that changes in \(\theta_M\) were global, acting at all synapses on a neuron; however, recent evidence suggests that there may by effects at specific subsets of synapses rather than global effects on all synapses (Abraham and Tate 1997). We hypothesize that interplay among these sorts of mechanisms can explain the observed progression of change in the observed bias in excitatory responses to NCB and CB stimulation with increasing duration of denervation (Figs. 5A and 6A).

Our data do not allow us to determine the possible contributions of these processes to the changes observed. However, we hypothesize that the initial changes observed in neurons at the original border reflect the loss of peripheral input from the forepaw following denervation and the subsequent strengthening of the jaw input to this region. Figure 7B, left shows the experimental configuration at the original border following acute denervation. Before denervation, CB inputs are weaker than NCB (Fig. 7A). After denervation (Fig. 7B, left), CB stimulation occurs in an area that has lost its dominant peripheral input from the forepaw. This loss of paw input would leave previously present but subthreshold inputs from the lower jaw representation as the dominant activators of neurons in this region. Activity coming to these neurons from both CB sites (cross the original border) and NCB sites (not cross the original border) would then be very well correlated, as both are driven by lower jaw stimulation. Such highly correlated activity could be a trigger for Hebbian mechanisms, such as LTP, causing potentiation of both CB and NCB connections. However, the formerly weaker synapses driven by CB stimulation should be highly susceptible to modification by LTP (i.e., \(\theta_M\) shifted to the right, according to the BCM model) and should reach a final level of potentiation equal to those synapses coming from within the original representation. Thus, when the paw input is removed, existing jaw inputs activate neurons in the deafferented cortex, making the connections from these neurons more competitive at driving neurons across the original border. Similar mechanisms based on changes in competition among inputs are associated with reorganization in rat whisker barrel cortex caused by whisker trimming (Finnerty and Connors 2000). Since changes in input competition are maintained throughout the course of denervation, this potentiation to a similar level would be maintained for longer durations of denervation (Fig. 7, C and D, left). Although this hypothesis relies on LTP at existing synapses, the data do not exclude sprouting of new connections within or between forepaw and lower jaw representations. Indeed, our data at the reorganized border suggests that at least two mechanisms underlie cortical reorganization and that they occur at different rates.

Similar arguments underlie our hypothesis for the changes in the bias for excitation at the reorganized border. Prior to denervation, the future CB and NCB (reorganized border) sites in our experiments are within the forepaw representation (Fig. 7, A and B, left). However, those neurons in this region nearer to the original border (i.e., those stimulated by CB stimulation) would also have significant subthreshold input from the lower jaw representation. Thus, upon loss of activity from the forepaw, the neurons closer to the original border will continue to have input from the jaw in the absence of forepaw input. There will also be a large area in the middle of the previously forepaw-responsive zone that now does not respond to any peripheral stimulation (Fig. 7, shaded region). Immediately on denervation, the reorganized border would be that point at which the previously subthreshold jaw input ends, which abuts this nonresponsive zone. Thus, at acute and 7-day timepoints, the border is between jaw-responsive cortex and nonresponsive cortex. At these timepoints, there is a great difference in activity on one side of the reorganized border compared with the other, i.e., the CB projections would be activated by jaw stimulation, but their activity would be communicated onto neurons that were relatively inactive [in the nonresponsive zone]. Active presynaptic elements (CB) synapsing onto these relatively inactive neurons could activate LTD-like phenomena in these CB connections (Fig. 7B, right), leading to a relative decrease in the efficacy of these CB connections. The NCB projection would be entirely within the nonresponsive zone and would experience relatively little activation; thus the NCB projection would not change its efficacy. Overall, at acute and 7-day timepoints, there would be a net bias in excitation between CB and NCB connections at the reorganized border, as was observed (Fig. 6A).

The situation becomes drastically different at 14 days (Fig. 7D), when the nonresponsive zone has been completely over-taken by the movements of surrounding borders: the jaw rep-
representation and the remaining ulnar paw representations (only the radial paw is denervated) have shifted through the nonresponsive zone and now abut each other. At this point there is no longer a great disparity in the amount of activity on either side of the border. This would tend to drive our hypothetical LTD-like mechanism less effectively, leading to a relative increase in the efficacy of the CB projection and reducing the bias, which was observed (Fig. 6A). Why, then, is the bias observed again after 28 days of denervation, given the apparent similarity of the border regions at 14 and 28 days (Fig. 1E)? We suggest that, in part, the continued lack of correlation between the two representations (now both active, rather than one active and one not) contributes to the bias. It is possible that other delayed and/or long-term mechanisms, such as sprouting of novel connections, may also be occurring.

The above arguments best explain the changes observed in the bias in excitation. However, activity-dependent changes in the efficacy of inhibitory synapses have been observed in the brain (Kano et al. 1992; Komatsu 1994; Morishita and Sastry 1993; Perez et al. 1999). It is possible that similar synaptic mechanisms mediated the observed effects on the parameters of IPSPs. Some of the changes observed in inhibition may reflect changes in excitation, as excitation is responsible for driving inhibition in the cortex. However, the data in Figs. 5 and 6 (especially Fig. 6D) demonstrate that the progression of change for excitation and inhibition can differ over the course of reorganization, indicating that the change in excitation is not the sole basis of changes in inhibition. Overall, there will be a complex interaction between synaptic modification of excitatory and inhibitory synapses, given that 1) stimuli that cause potentiation of excitatory synapses can cause either potentiation or depression of inhibitory synapses (Kano et al. 1992; Komatsu 1994; Morishita and Sastry 1993; Perez et al. 1999), 2) local potentiation of excitation can result in either depression of excitatory drive onto inhibitory neurons or potentiation of IPSPs (McMahon and Kauer 1997; Perez et al. 1999), and 3)
inhibition strongly affects the induction of potentiation and depression of excitation (Steele and Mauk 1999). Furthermore, it may be that excitatory and inhibitory connections are more or less able to sprout novel connections in response to prolonged denervation. Thus it is difficult to predict how the these complex phenomena will interact to produce the changes in the representation, which are reflected in the observed dissociation between the properties of local excitation and inhibition.

The dissociation between the IPSP amplitude and fall time over the duration of denervation (Fig. 6D) could reflect changes in the expression of GABA<sub>A</sub> receptors or changes in GABA release and/or uptake. Other studies have demonstrated changes in the amount of GABA or the GABA<sub>A</sub> receptor in S1 associated with representational plasticity (Fuchs and Salazar 1998; Garraghty et al. 1991; Land et al. 1995; Micheva and Beaulieu 1995). Thus both the release of GABA and the properties of the postsynaptic response to GABA could be altered during reorganization in S1. In other systems, changes in the composition of receptors associated with development or plasticity affect the kinetics of the postsynaptic response (e.g., Carmignoto and Vicini 1992; Hestrin 1992; Hickmott and Constantine-Paton 1997). Another possibility is that a change in the intrinsic properties of neurons after denervation could underlie the change in the fall time of the IPSPs. Voltage-clamp analysis of the kinetics of the IPSCs would begin to unravel these issues.

We have used this novel <i>in vivo in vitro</i> preparation to begin to elucidate local circuit mechanisms in the cortex that underlie some aspects of rapid and sustained changes in cortical organization. We propose that the basic cellular and synaptic mechanisms examined in this report are conserved across brain areas, and thus better understanding of their characteristics is important for understanding plasticity and the behavioral changes associated with plasticity throughout the CNS. However, the dissociation between these local circuit properties and the expression of a novel representational border suggests that the changes in local circuitry documented in this report are insufficient to explain all the changes in the cortical organization. For example, similar types of changes in the circuitry in other layers of the cortex or at subcortical sites probably contribute to the changes in the cortical representation. Nevertheless, we believe that the general correspondence and specific dissociations between local circuit properties and the novel border provides clues to the mechanisms underlying the plasticity of cortical representations.

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