Expansion of the Cortical Representation of a Specific Skin Field in Primary Somatosensory Cortex by Intracortical Microstimulation

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Intracortical microstimulation (ICMS) was applied to a single site in the middle cortical layers (III–IV) in the koniocortical somatosensory fields of sodium pentobarbital–anesthetized rats (SmI) and new world monkeys (area 3b). Low-threshold cutaneous receptive fields were defined in the cortical region surrounding the stimulation site prior to and following 2–6 hr of 5 μA ICMS stimulation. ICMS stimulation did not usually affect the receptive field location, size, or responsiveness to tactile stimulation of neurons at the stimulation site. However, the number of cortical neurons surrounding the stimulation site with a receptive field that overlapped with the ICMS-site receptive field increased in all studied animals, resulting in an enlarged cortical representation of a restricted skin region spanning several hundred microns. The mean size of receptive fields changed in some but not all cases. These results provide evidence that the responses of cortical neurons are subject to change by the introduction of locally coincident inputs into a single location, and demonstrate a capacity for representational plasticity in the neocortex in the absence of peripheral stimulation. These experimental observations are consistent with hypotheses that the cerebral cortex comprises radially oriented populations of neurons that share a common input, and that these inputs are shaped by coincident activity (see Edelman, 1978, 1987; Merzenich, 1987; Merzenich et al., 1990; von der Malsburg and Singer, 1988).

Experimental and theoretical neuroscientists have argued that the basic functional unit of the cerebral cortex is a "minicolumn" or "group" of locally coupled neurons (Mountcastle, 1957, 1978; Hubel and Weisel, 1962; Edelman, 1978, 1987; Merzenich, 1987; von der Malsburg and Singer, 1988). In agreement with Mountcastle's definition of a "minicolumn" and on the basis of our own findings, we have hypothesized that this functional unit usually consists of a few hundred neurons with an average cortical diameter of a few tens of microns (see Merzenich et al., 1984, 1990; Merzenich, 1987). Key features of these hypothetical cell assemblies, or groups, are that (1) all neurons within a given functional column are strongly coupled to other group members, and are proportionally more weakly coupled to neurons in neighboring groups; and (2) excitatory neurons of each group are positively interconnected, and all excitatory neurons in the group share the results of the group's input-selecting processes.

By this hypothetical view, the specific inputs driving all neurons of a functional group are alterable through a process of selecting excitatory inputs by modifying local corticocortical excitatory and inhibitory connections and pericolumnar inhibition. The effectiveness of synaptic inputs from both extracortical and intracortical sources is thought to be regulated by the activity of the pre- and postsynaptic elements in a Hebb-like manner (Hebb, 1949). Predictions of this hypothesis of cortical organization include (1) inputs exciting neurons in a cortical minicolumn being altered and subject to competitive substitution, and (2) the horizontal extent of functional neuronal groups being modifiable as a result of individual neurons changing membership from one to a different functional group.

These predictions are tested in the present experiments. Intracortical microstimulation (ICMS) at low intensity will excite nearly all afferent input terminals and excitatory and inhibitory cortical neurons within a few tens of microns of the microstimulating electrode. This stimulation should result in nearly simultaneous activation of all local pre- and postsynaptic elements as well as the modulatory inputs projecting to that same cortical locus. This stimulus will therefore generate the type of temporally coincident responses believed necessary for altering neuronal group memberships.

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Previous studies in motor cortical areas of primates and rats have demonstrated that the representation of motor movements is altered by both surface electrical stimulation and ICMS (Graham Brown and Sherrington, 1912; Nudo et al., 1990). These studies could not determine if the changes in movement representations were due to changes in the recruitment of cortical neurons, and/or to changes in synaptic efficacies of the inputs to the red nucleus or the spinal cord. The present studies document changes in the representation of sensory stimuli in the cortex using stimulus parameters similar to those used by Nudo et al. (1990).

A related issue that has been raised by demonstrations of cortical plasticity is whether the reorganization observed at the cortical level is completely or only partially accounted for by representational changes at subcortical levels in the somatosensory neuraxis (see Killackey, 1990; Kaas, 1991). We (see Merzenich et al., 1984, 1990; Merzenich, 1987; Recanzone and Merzenich, 1992) have argued on the basis of the anatomical organization of the somatosensory system and on other grounds that the neocortex must itself be alterable after peripheral lesions or behavioral training in addition to subcortical contributions to cortically recorded reorganization. Recent evidence indicates that the divergence of afferent connections, when referenced to representational topographies, is much greater for the thalamocortical projection than at either the dorsal column nuclei or ventrobasal thalamus (Rainey and Jones, 1983; Hirai et al., 1988; Florence et al., 1989, 1991; Garraghty et al., 1989; Schwark and Jones, 1989; Garraghty and Sur, 1990). The divergence of the thalamocortical projection alone can account for the short-term peripheral lesion–induced changes recorded at the cortical level regardless of the subcortical contributions to reorganization. However, recent experiments have suggested that subcortical reorganizations play a larger role in the subsequent cortical representations over the long time course (Pons et al., 1991). By stimulating the cerebral cortex directly in the present studies, we bypass any role for peripheral inputs in driving representational change, thereby restricting the potential source of reorganization to activity in the cortex itself, to subcortical nuclei via descending projections from the cortex, or to the thalamus via anterograde stimulation of the thalamocortical afferents.

Several preliminary reports of some of these results have been previously published (Recanzone and Merzenich, 1988, 1992; Dinse and Merzenich, 1989; Dinse et al., 1990).

Materials and Methods

Results are from eight young adult male Sprague–Dawley rats weighing 300–600 gm, five adult owl monkeys, and one adult squirrel monkey. The basic methods were similar, and the following descriptions apply for all three species except where otherwise indicated. Treatment of all animals was within the National Institutes of Health Guide for Care and Use of Laboratory Animals (revised 1987).

Rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.). Monkeys were initially anesthetized with a mixture of halothane/nitrous oxide/oxygen (1.5%:50%:48.5%). After anesthetic induction, the femoral vein was cannulated in all species. Anesthetic state was monitored by eye blink and paw withdrawal reflexes, and supplemental doses of sodium pentobarbital were administered to maintain animals at an areflexive level of anesthesia. Lactated Ringer's solution with 5% dextrose was infused at a rate of 1 ml/hr and 3–5 ml/hr for rats and monkeys, respectively. The head was stabilized in a stereotaxic apparatus and the somatosensory cortex was exposed by a craniotomy. The dura was resected and the exposed cortex was maintained in a pool of silicon oil. A photograph or computer image of the cortical surface vasculature was recorded, and the relevant body surfaces were imaged in each experiment.

Microelectrodes were beveled micropipettes filled with 3.6 M NaCl, with 1.5–2.0 MΩ impedances at 1 kHz, and with 12–22 μm tip diameters. Pontamine sky blue was added to the electrode salt solution for visualization. Microelectrodes were introduced normal to the cortical surface to a depth of 700–900 μm from the surface. The position of electrode entry into the brain was recorded on a >40× enlarged photograph or computer image of the cortical surface. Extracellular potentials were recorded and displayed in the conventional manner. Receptive fields were defined as those areas of skin at which just-visible skin indentation or hair deflection evoked a reliable neural discharge as described previously (Merzenich et al., 1984; Stryker et al., 1987). These skin regions were reconstructed on a magnified photograph or image of the body surface. To assist in locating receptive fields on the trunk of rats, the fur was shaved and the skin was marked with a grid pattern using water-insoluble ink prior to imaging the body surface. The three dimensions of these body surface reconstructions were taken into account at the time of receptive field definition.

ICMS

Intracortical microstimulation (ICMS) was delivered through the same electrodes used to define cortical receptive fields. The stimulation depth was the depth that gave the qualitatively strongest neural responses to peripheral stimulation at that penetration location, which ranged from 700 to 850 μm in different experiments. No differences in results could be attributed to these differences in the depth of the ICMS stimulation site.

The ICMS stimulus consisted of capacitively coupled, charged-balanced pulses delivered once per second (see Nudo et al., 1990). Each stimulus pulse was 200 μsec in duration with an amplitude of 5 μA negative, with the actual current pulse converted to a biphasic current signal by the coupling capacitor. Pulses were delivered at 300/sec for 40 msec (13 pulses). This stimulus was generated using a Grass

model SD-9, BAK waveform generator and constant-current isolation unit (BAK BSI-2). Stimuli were monitored by measuring the current across a bleeder resistor. Stimulation was applied continuously for a variable time period and then terminated for 5–10 min to define receptive fields at, and at sites away from, the location of the stimulating electrode. Several cycles of this stimulation were applied in most experiments.

Blind-Investigator Experiments

In four rat experiments a "blind-investigator" paradigm was used. One investigator defined all receptive fields. This investigator was not present during a stimulation or sham-stimulation period. For sham-stimulation, the electrode was connected to the stimulus isolation unit, which remained switched off for a 4 hr period. In either case, the electrode was not moved and the cortical receptive field at the stimulation site was defined at 60 min intervals. The "blind" investigator then defined all receptive fields in the post-ICMS or post-sham condition.

Peristimulus Time Histogram Generation

Three monkey experiments included the construction of multiple-unit peristimulus time histograms by accepting all neural discharges with amplitudes more than two times the spike-free neural noise level, resulting in the acceptance of responses from one to five waveforms of neural origin. Skin stimuli of varying amplitudes were delivered by use of a force- and displacement-controlled mechanical stimulator (Chubbuck, 1966). Stimuli were trapezoidal step indentations of 300–700 msec duration, with a 50 msec on/off ramp. The interstimulus interval was approximately 1 sec. Stimulus durations and amplitudes were set at the start of each experiment and maintained constant for that animal throughout the experiment. The stimulus probe was a 1-mm-diameter monofilament rod with a hemispherical tip oriented normal to the skin surface. Histograms were constructed from 10 or 20 mechanical stimulation trials. In two monkeys, four skin locations were stimulated for each receptive field both before and after ICMS conditioning. In these experiments, the placement of the probe was kept constant by aligning the probe with small spots on the skin made with water-insoluble ink, and by maintaining constant probe displacements (1.0 mm) and initial contact forces (5.0 gm).

Analysis

Receptive fields and cortical areas were measured using computerized planimetry. Areas of cortical representation were taken as the inclusive area in which all cortical penetration sites shared the parameter in question. Statistical significance was tested using a one-tailed unpaired t test (STATVIEW 512+). P values <0.01 were considered significant.

The absolute areas of overlaps were measured as those sectors of the skin that were contained within both the receptive field defined at the stimulation site (ICMS-site RF) and each of the other sampled receptive fields in the pre- and post-ICMS condition (comparison RF). The ICMS site was used as the standard for these measures of percentage overlap. The percentage of the ICMS-site RF overlap was taken as (area of overlap/area of ICMS-site RF) × 100. A hypothetical receptive field three times larger than the ICMS-site RF but with the entire ICMS-site RF within it would have a value of 100%.

A second measure was the percentage that the comparison RF overlapped with the ICMS-site RF. This value was defined as (area of overlap/area of comparison RF) × 100. In this measurement, the hypothetical receptive field covering three times the area of the ICMS-site RF and in which the ICMS-site RF is completely contained would have a value of 33%.

Results

A period of 5 μA microstimulation in cortical area 3b (in monkeys) or SmI (in rats) resulted in a reorganization of the topographical representation of the skin in the cortical region surrounding the ICMS site. Changes in effective excitatory responses were recorded over distances extending several hundred microns away from the conditioning microstimulation site in every experiment. These ICMS-induced changes were observed in trunk and hindpaw representations in the rat, and in the hand representations of owl and squirrel monkeys.

Increase in the Cortical Representation of the ICMS-Site RF

The most striking consequence of ICMS conditioning was an increase in the cortical area of representation of the specific skin region represented at the ICMS location before stimulation was initiated. Examples of the cortical representations before and after ICMS from two monkeys and one rat are shown in Figure 1. Each pre- and post-ICMS penetration site is indicated as having a receptive field that overlapped the ICMS-site RF (see Materials and Methods) by 0–24%, 25–49%, 50–85%, and >85%. The zones of >50% and >85% overlap (solid symbols) increased significantly in each individual that received ICMS (right column).

The cortical area encompassed by the 50% and 85% overlap penetration sample sites was measured for each animal in which there was a sufficient number of penetration sites to make valid comparisons (seven rats and three monkeys). This area was not always completely bounded by penetrations with less overlap, making estimated areas in these cases underestimates of the dimensions of these ICMS-induced changes. These data are shown in Figure 2 as the area of representation for the ≥50% overlap region, and in Figure 3 for the ≥85% overlap region. In every experimental case, the cortical areas over which receptive fields closely overlapped with the ICMS-site RF were greater in the post-ICMS condition (solid bars) than in the maps derived before stimulation was initiated (shaded bars). This expansion ranged from about twofold to over twentyfold for the ≥50% over-

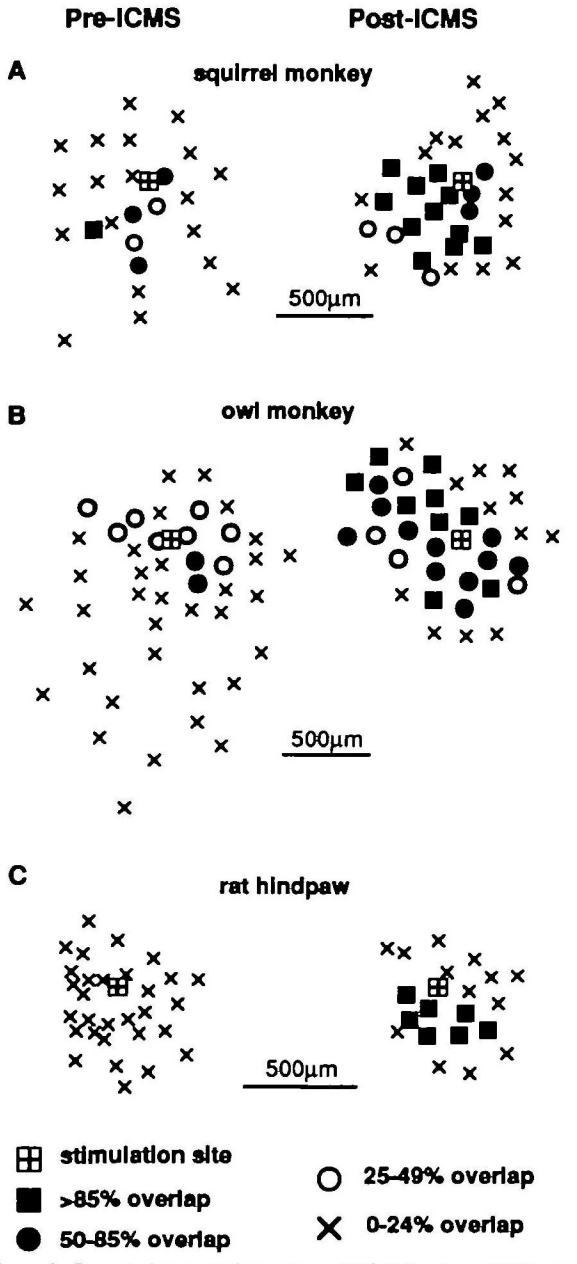

Figure 1. The cortical representations in the pre-ICMS (*left*) and post-ICMS (*right*) condition from three different experiments. In each representation, the percentage of the receptive field that overlaps the ICMS-site RF is indicated at the *bottom*. The *open square with the solid cross* denotes the stimulation site.

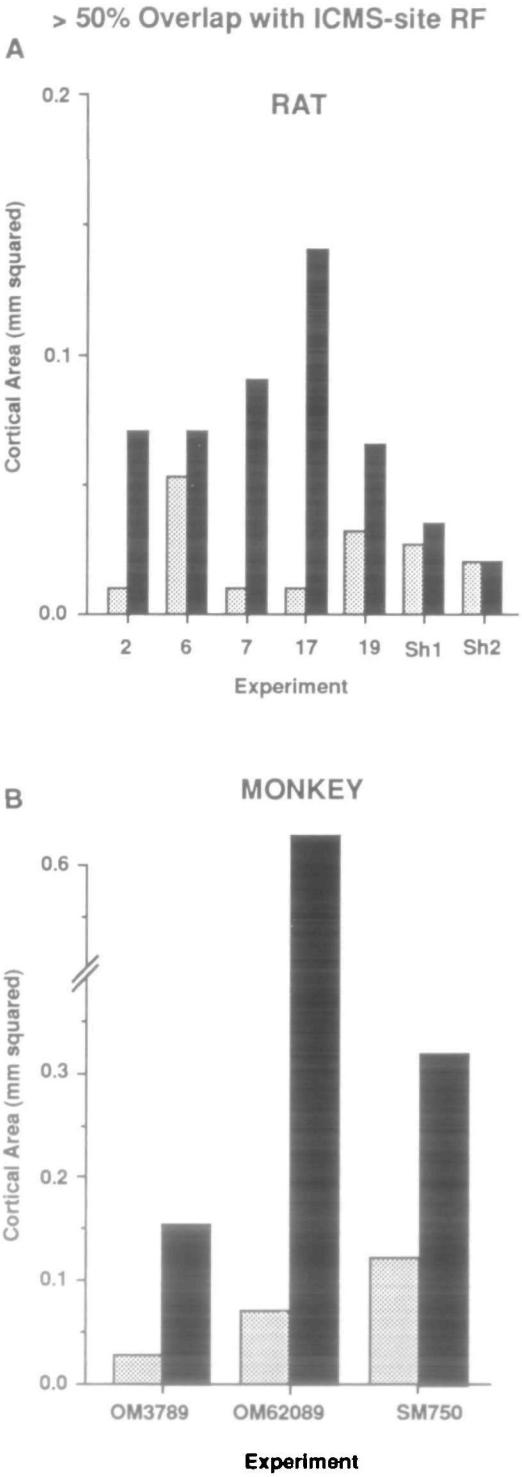

Figure 2. Area encircling the cortical locations with receptive fields that overlapped the ICMS-site RF by more than 50%. *Shaded bars* represent the pre-ICMS condition; *solid bars* represent the post-ICMS condition. This area was measured in square millimeters by including all cortical locations with ≥50% overlap as one continuous area. Rat experiments are shown at the *top*; monkey experiments, at the *bottom*. *Sh1* and *Sh2* are the no-ICMS control animals done in the blind-investigator experiments.

lap case. In most experiments the pre-ICMS ≥85% overlap condition was seen only for the ICMS site. In the post-ICMS condition, the area of this zone of ≥85% overlap was invariably many times larger. The two control rats did not show this effect (Sh1 and Sh2, Figs. 2*A*, 3*A*).

Examples of the corresponding receptive fields from two experimental rats are shown in Figures 4 and 5. In Figure 4, some of the consequences of a 6 hr ICMS period in which the ICMS-site RF was located on the trunk are illustrated. In these experiments the microelectrode was inserted at many of the same locations as investigated in the prestimulation condition. In most of these instances, the electrode did not appear to encounter any resistance from the pia, suggesting that it had entered the previously made opening in the pia. Although we were unable to verify that the pre- and poststimulation recordings at these locations were from exactly the same neurons, we are confident that they were from neurons located no farther than 10–20 microns from those studied in the

prestimulation condition. In Figure 4*A*, the location of the ICMS-site RF is shown in the drawing at the left. To the right are all of the pre-ICMS RFs recorded at cortical locations that closely overlapped the ICMS-site RF (>85%) after ICMS, with their corresponding electrode penetration sites shown as solid stars in the center. These post-ICMS RFs are not drawn on this figure as they were all essentially the same as the ICMS-site RF. Two other penetration sites that were continuous with the ICMS-site RF but for which no pre-ICMS RF was determined are shown as solid squares. The stimulation site is shown as the square with the black cross. In Figure 4*B*, three other receptive fields that "moved" toward the ICMS-site RF (left) and three that "moved" away from the ICMS-site RF (right) are shown, with their corresponding cortical locations shown as open diamonds in the inset. Figure 5 shows a similar result from the hindpaw of a different rat. Again, Figure 5*A* shows all cortical locations with receptive fields that were essentially identical to the ICMS-site RF following stimulation. Receptive fields from other cortical locations are shown in Figure 5*B*. These two examples indicate that neurons in an enlarged cortical area near the stimulation site came to share its specific receptive field. At more distant locations, the receptive fields were almost randomly affected, and could appear to "move" either toward or away from the ICMS-site RF. The affected receptive fields did not appear simply to enlarge to include the ICMS-site RF, but to substitute the ICMS-site RF for the previous receptive field. They also demonstrate that this local stimulus exerts strong local influences across an asymmetric zone with a diameter of roughly 200–300 μm in rats to more than 600–700 μm in monkeys (see also Fig. 1).

Receptive fields defined before and after ICMS from two monkeys are shown in Figures 6 (squirrel monkey) and 7 (owl monkey). In these figures, examples of glabrous receptive fields derived in pre- and post-ICMS maps are shown for the same monkeys illustrated in Figure 1. In Figure 6*A*, the pre-ICMS survey defined receptive fields that covered a large area of the hand surface. The most striking consequence of ICMS in this squirrel monkey was that receptive fields over a wide cortical zone apparently both shifted and expanded to include the ICMS-site RF (Fig. 6*B*). Many receptive fields encompassed the pre-ICMS-site RF in its entirety, as well as some of the surrounding skin. This is the single case in which the ICMS-site RF itself slightly enlarged, to cover most of the surface of the second palmar pad. Most receptive fields in a surrounding cortical zone came to overlap this zone after a period of ICMS.

Figure 7 shows the receptive fields from one owl monkey in which the ICMS-site RF was on the middle segment of digit 5. In this monkey, there was primarily a substitution of receptive field location to that of the ICMS-site RF. Most receptive fields defined for neurons over a wide cortical zone came to closely or partially overlap the ICMS-site RF following a 5 hr ICMS period (see Fig. 1). This included receptive fields formerly exclusively representing skin surfaces on the hairy dorsum of the fingers (data not shown).

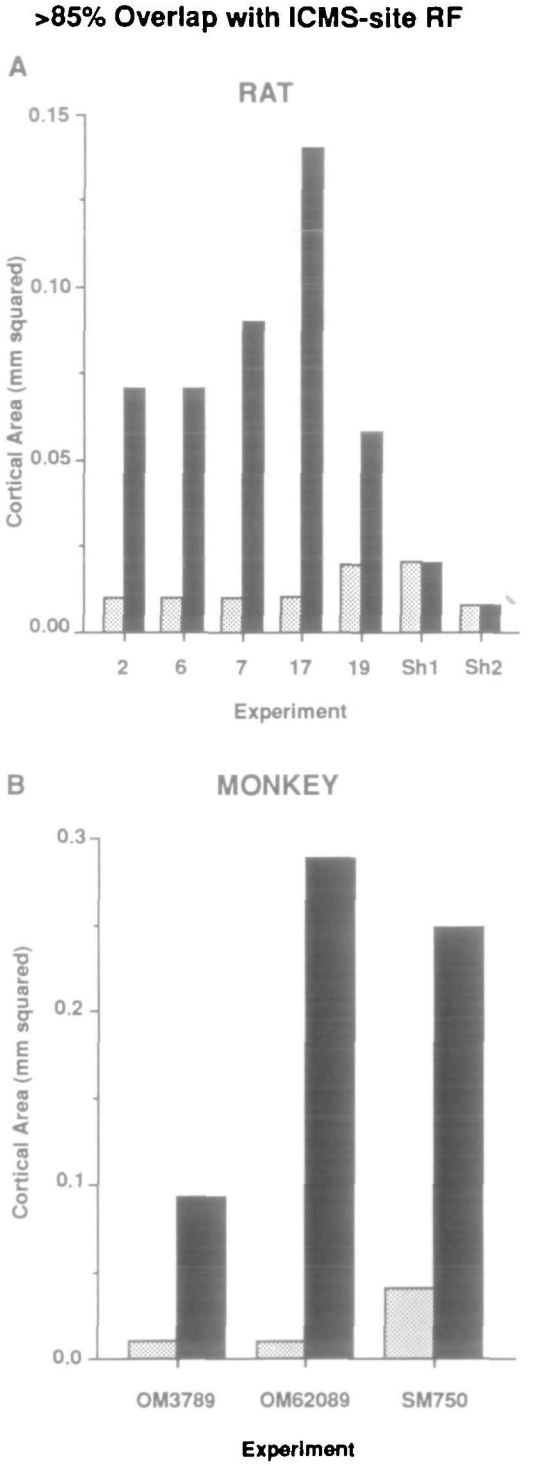

Figure 3. Areal extent of cortical locations with receptive fields ≥85% overlap with the ICMS-site RF. *Abbreviations* and *bars* are as in Figure 2. In most cases only the stimulation site had ≥85% overlap in the pre-ICMS condition. This area increased in all cases except the sham stimulation control.

"Blind-Investigator" Controls

No systematic changes were recorded in the cortical area surrounding a sham-stimulated electrode following a 6 hr no-stimulation period in two blind-investigator control rats. One example is shown in Figure

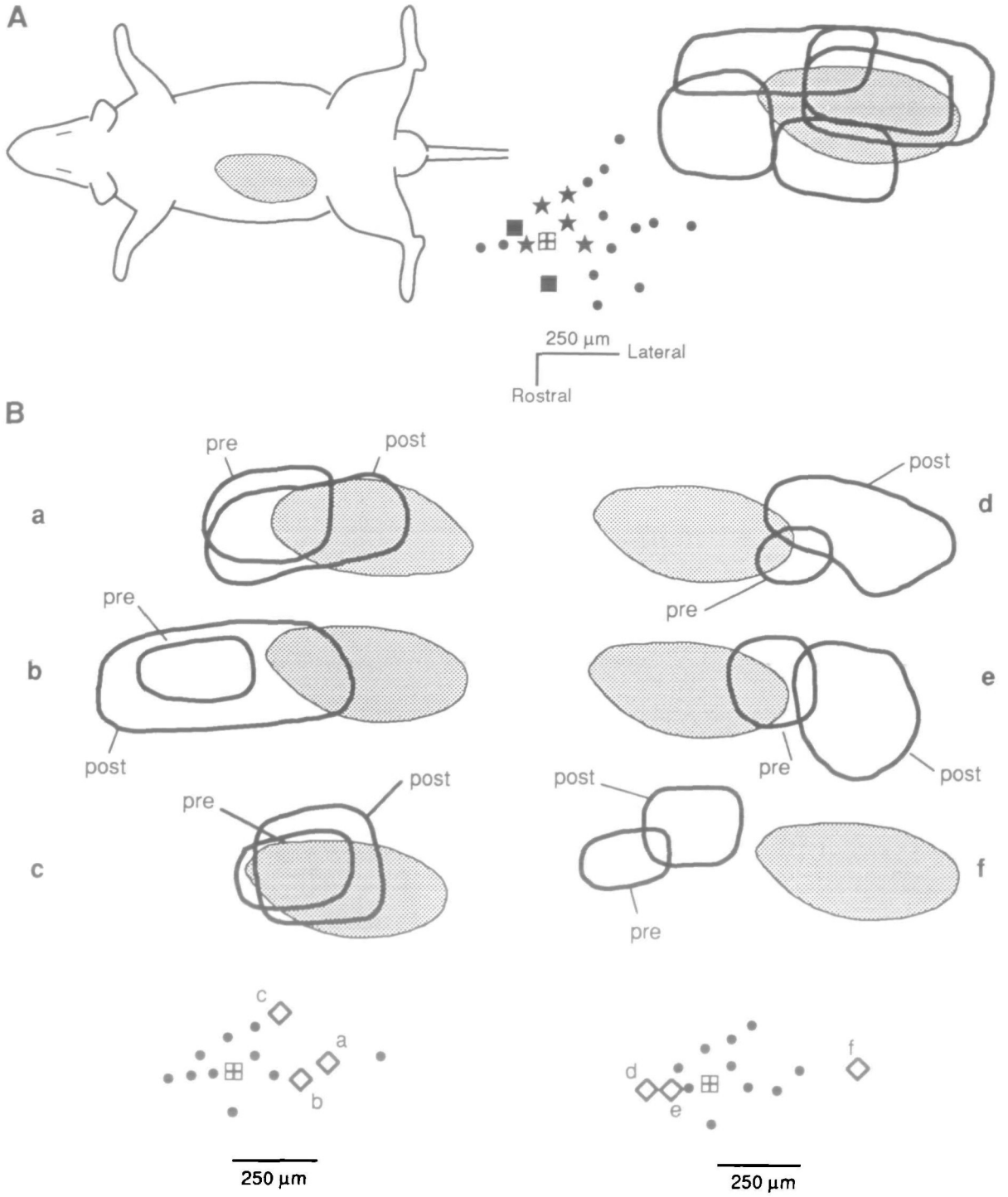

Figure 4. Receptive field size and locations of a representative rat trunk experiment. *A* shows the receptive field of the ICMS-site (*left*) and the pre-ICMS RFs that came to overlap the ICMS-site RF in the post-ICMS condition (*right*). The *inset* shows their corresponding cortical locations as *stars*, with all other pre-ICMS locations shown as *solid circles*. The *open square with the solid cross* denotes the stimulation site in all panels. The *solid squares* denote two cortical locations with ≥85% overlap with the ICMS-site RF that were not investigated in the pre-condition. *B* shows six cortical locations and their corresponding receptive fields (*a–f*) that did not overlap the ICMS-site RF ≥85% in the post-ICMS condition. Cortical locations shown as *open diamonds* correspond to the receptive fields shown in *B*.

8, in which the hindpaw representation was investigated before and after a 6 hr interval in which no microstimulation current was passed through an intracortical microelectrode. There was a reasonable correspondence between the receptive fields defined under the two conditions, as well as some changes in recorded receptive field sizes and locations. In striking contrast to experimental cases, there was a complete absence of cortical receptive fields that shared the size and location of the (sham) ICMS-site RF in these blind-investigator control rats.

Receptive Fields

The preceding analysis has demonstrated that the cortical representation of a restricted skin region is significantly increased following a period of ICMS. This

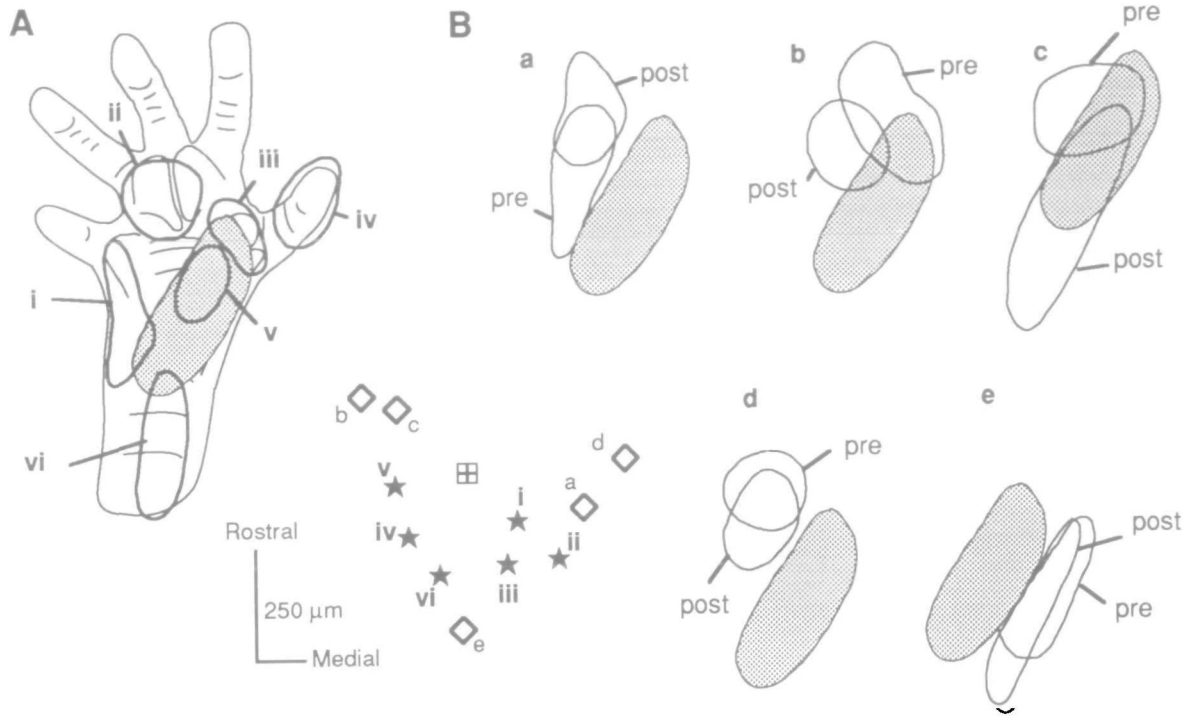

Figure 5. Examples from a representative experiment in the hindpaw of a rat, with the *inset* showing the cortical location for each of the illustrated receptive fields. *Abbreviations* and *symbols* are as in Figure 4. *A* shows the receptive fields (*i–vi*) that overlap the ICMS-site RF ≥85% in the post-ICMS condition (*stars* in the *inset*). *B* shows representative examples of five fields (*a–e*) that were relatively unaffected by the ICMS (*open diamonds* in the *inset*).

effect could arise in any one of three ways: (1) the pre-ICMS receptive fields could enlarge as a rule to include part or all of the ICMS-site RF; (2) receptive fields could translocate, to overlap progressively more strongly with the ICMS-site RF; or (3) part or all of the ICMS-site RF could be substituted for cortical fields formerly representing the surrounding skin.

Measurements of receptive field sizes and their distributions in the pre- and post-ICMS conditions were made in each experiment (Fig. 9). In each set of histograms, shaded bars represent the means and SDs of receptive field sizes in the pre-ICMS condition, while solid bars represent post-ICMS RFs. Single asterisks indicate P values <0.05; double asterisks indicate $P < 0.01$ (one-tailed unpaired t test). Data from the trunk representation of the rat revealed that receptive fields were larger (Fig. 9*A*) where $P < 0.05$ in three of four rats. Data from the rat hindpaw (Fig. 9*B*), in contrast, revealed smaller changes in receptive field sizes following ICMS (left two cases) or in sham-stimulation control animals (right two cases). In one experimental rat the p value was slightly below 0.05 ($P = 0.046$ for rat 17). Finally, Figure 9*C* shows results from the hand representations of the owl and squirrel monkeys. Receptive fields were significantly larger after stimulation in two of seven studied cases, but no significant differences in pre- and post-ICMS RF sizes were recorded in the remaining five cases.

The variability of receptive field size expansions between cases could be a result of the distribution of the receptive field sample with respect to the area of the cortex directly altered by the intracortical stimulation. To test this possibility, we considered receptive fields in the post-ICMS condition that had any overlap with the ICMS-site RF in the post-ICMS condition, and compared only these values to the population of pre-ICMS RFs. This analysis did not alter the results described above, with the caveat that the n was small in some of these cases.

A second test was to determine if the ICMS-site RF was itself larger or smaller than the mean receptive field size in the pre-ICMS condition. ICMS-site RFs were not altered by this chronic stimulation (with the exception of the squirrel monkey experiment), and were not systematically larger or smaller than were the mean receptive field sizes recorded in the pre-ICMS samples. Thus, receptive fields substituting for a larger-than-average receptive field cannot account for these differences.

The second possibility is that receptive fields moved in their entirety, or translocated, toward the ICMS-site RF. This would maintain the receptive field size, but progressively move the receptive field to overlap that of the ICMS-site RF. To investigate this possibility, we measured the influence of the ICMS-site RF on the receptive field recorded at each cortical location. This measure was defined as the percentage of the sampled receptive field that included some part of the ICMS-site RF (area of overlap/area of comparison RF; see Materials and Methods). Translocations of receptive fields to include the ICMS-site RF would result in a larger value of this measure. Statistical analysis of all experiments revealed a significant difference between the pre- and post-ICMS condition in only three cases: one example each in the representation of the rat hindpaw, rat trunk, and monkey hand (one-tailed unpaired t test, $P < 0.01$). This analysis was somewhat unreliable, as the number of receptive

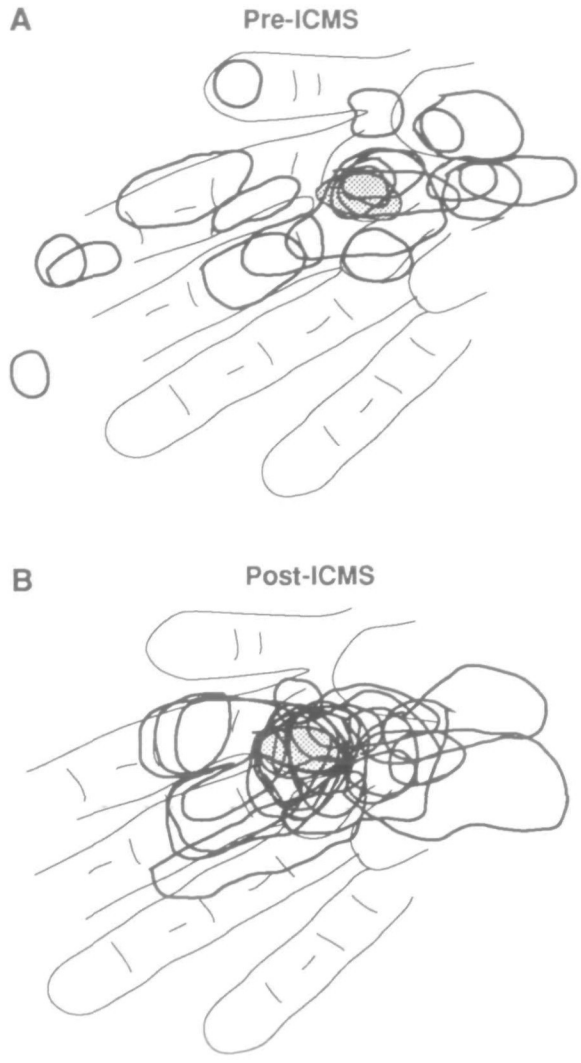

Figure 6. Receptive fields defined in the area 3b hand representation pre- and post-ICMS in the squirrel monkey. *A* shows pre-ICMS RFs on the glabrous skin. *B* shows post-ICMS RFs. The *shaded area* denotes the ICMS-site RF on the palmar pad.

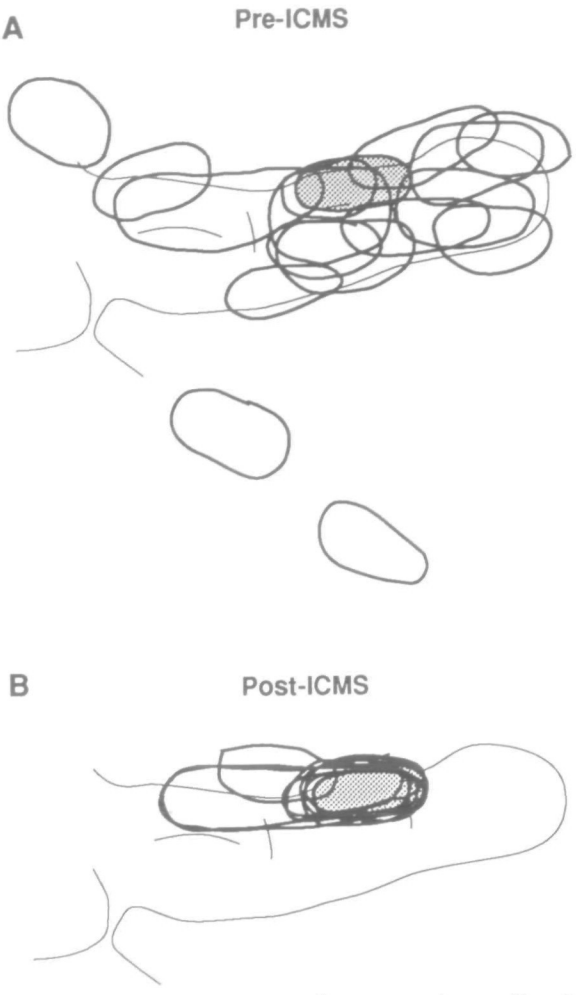

Figure 7. Receptive fields pre- and post-ICMS in one owl monkey, as in Figure 6. The ICMS-site RF was located on the middle phalange of digit 5.

fields with any overlap in the pre-ICMS condition was very small ($n < 5$) in most cases. Thus, although not conclusive, the available data suggest that translocation of receptive fields toward the ICMS-site RF alone cannot account for the increased representation of the ICMS-site RF, and receptive field expansion is not consistently seen across species or animals. The inconclusive evidence for the possibilities of receptive field size increases and translocation of receptive fields, coupled with the specific pre- and post-ICMS RF comparisons with respect to the same cortical position (Figs. 4–7), supports the hypothesis that there is a substitution of the ICMS-site RF for the former receptive field of neurons surrounding the ICMS-stimulated site.

Definition of Receptive Fields by a Tactile Stimulator

To verify objectively that these ICMS-induced changes in receptive fields apply to the low-threshold responses to skin stimulation, multiple-unit receptive fields were defined using a force- and displacement-controlled tactile stimulator. In these experiments, several skin sites were selected to be stimulated in the pre- and post-ICMS condition at each of a few cortical locations. These skin sites were chosen to be within and beyond the ICMS-site RF as defined using the hand-held probe. An example of this class of control experiment is shown in Figure 10. The neural responses to the tactile probe were recorded at each of four peripheral locations (sites A–D in inset) for each of three cortical locations (I–III). The peristimulus time histograms for the stimulation site are shown at the far left (I). The best response was at site B, with a smaller response at site C. The mismatch between receptive fields defined with the hand-held probe not including site C was probably due to an unreliable response at C. The qualitative criterion was that the neurons respond reliably at onset, whereas neurons sampled at this site only responded to 14 of 20 stimuli, as compared with strong responses to all stimuli at site B. Cortical location II was altered from having a minimal response at site B and a greater response at site D to clear responses at only sites B and C in the poststimulation case. These responses were comparable to those defined at the stimulation site. Finally, the third example (III) shows a location at which

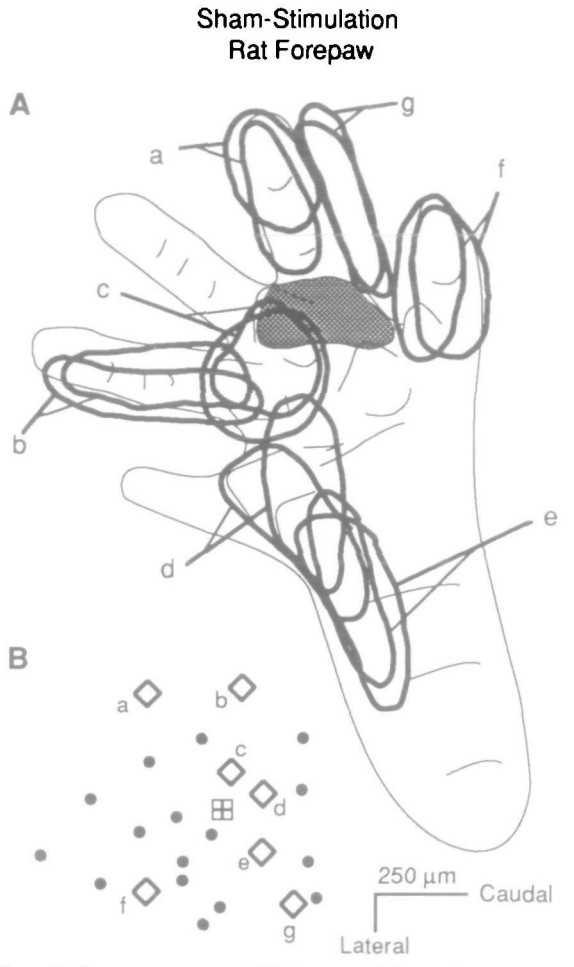

Figure 8. Representative receptive fields from a no-ICMS control rat, investigated using the blind-investigator protocol. *Abbreviations* and *symbols* are as in Figure 4*B*. The *thick lines* connect to the pre-ICMS RFs of the pair; the *thin lines* connect to the post-ICMS RFs.

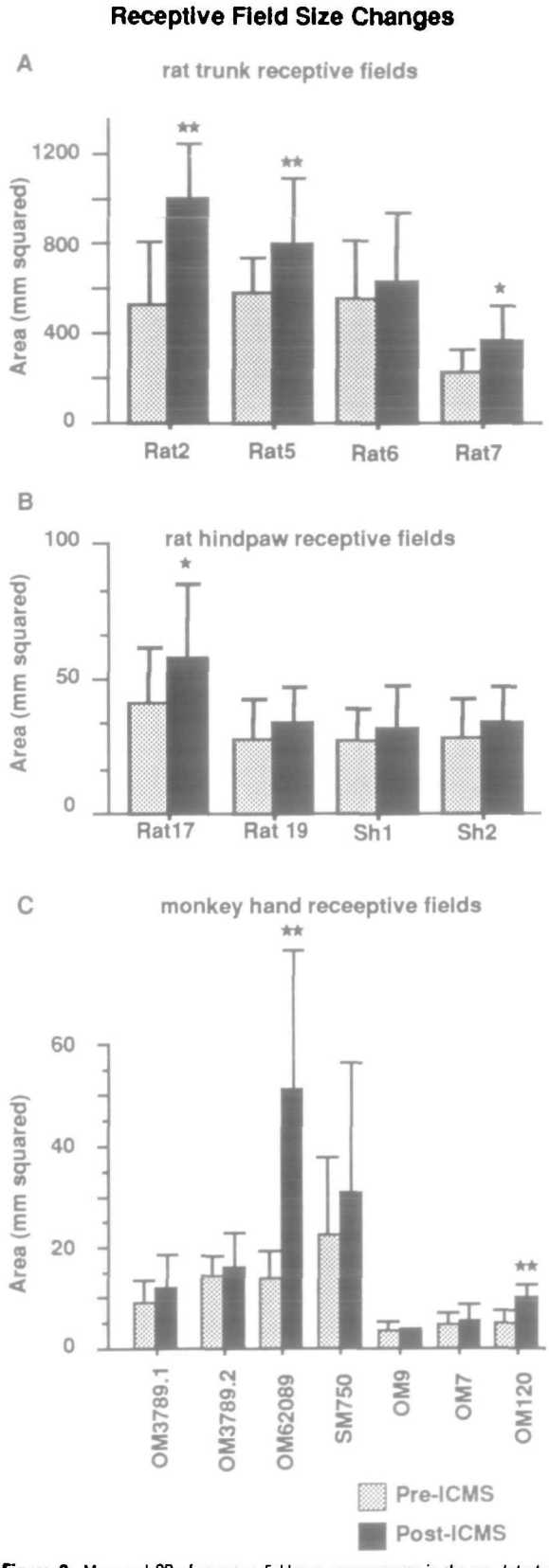

Figure 9. Mean and SD of receptive field size measurements in the pre- (*shaded bars*) and post- (*solid bars*) ICMS periods. *Single asterisks* denote experiments with $P < 0.05$; *double asterisks*, $P < 0.01$ (one-tailed unpaired t test). Results from experiments in the trunk representation of the rat are shown in *A*, those from the hindpaw representation of the rat are shown in *B*, and all monkey experiments are shown in *C*.

tactile stimulation did not evoke a response in the pre-ICMS condition, while following stimulation a clear response was evoked at site B, again as in the ICMS-site RF. Such experiments are all consistent with the interpretation that a response from the ICMS-site skin emerges as an effective and selective site for evoking responses for neurons in a zone surrounding the ICMS locus.

Time Course of ICMS-Induced Changes

To determine the time course of these effects, we sampled selected cortical sites that were previously examined in the pre-ICMS condition at different intervals during the course of stimulation. Figure 11 shows results from three rats in which ICMS was applied in the trunk representation. In each case, cortical locations with receptive fields that approximately corresponded with the receptive field of the stimulation site (≥85% overlap) are shown as solid squares; those that included some part of the ICMS-site RF are shown as large, shaded circles. The small solid circles are penetration sites that were not tested at that particular time period. In each case, receptive fields resembled and overlapped with the ICMS-site RF at

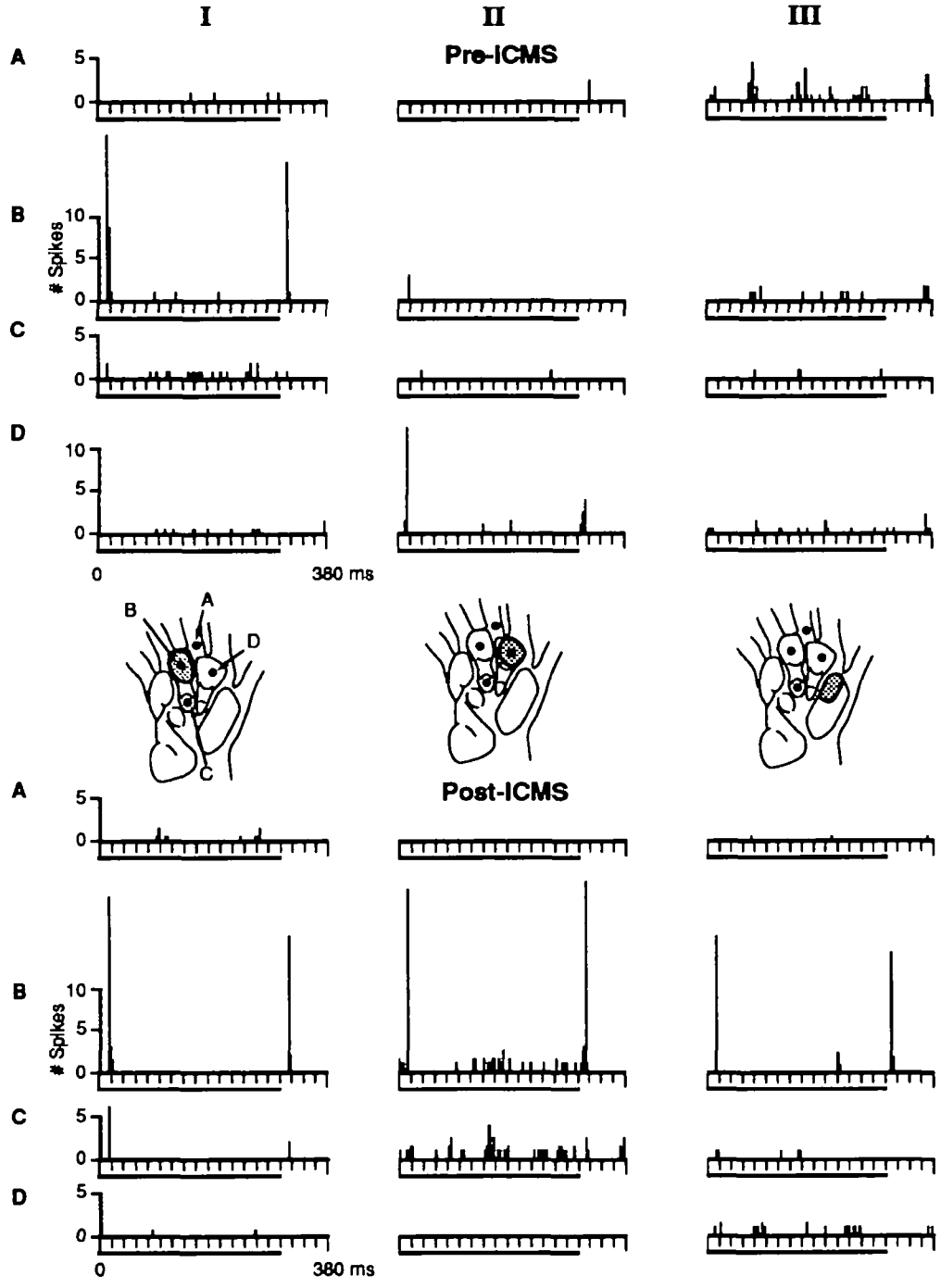

Figure 10. Peristimulus time histograms of the response of neurons at three cortical locations (*I–III, left to right*) to punctate stimulation at four different locations on the hand (*A–D*; see *insets*). The pre-ICMS RF is shown as the *shaded region* in the inset for each cortical location. The corresponding peristimulus time histograms for each of these cortical locations are shown at the *bottom*. The ICMS-site RF is the cortical location in column *I*. Cortical sites *II* and *III* both had receptive fields virtually indistinguishable from that of site *I* following ICMS. The *horizontal bar* under each histogram indicates the period of tactile stimulation.

increasingly greater distances from the stimulation site with progressively longer stimulus conditioning times. In the final condition illustrated in the bottom row, receptive fields were defined at least 1 hr after the final ICMS stimulation period. Even in the absence of continued stimulation, effects persisted, and in fact further poststimulation expansion appeared to occur in several cases. Similar results were observed in two monkeys using a similar experimental paradigm.

Spatial Distribution of the Affected Cortical Area

Inspection of the cortical maps shown in Figures 1, 4, 5, and 11 shows three features of the spatial extents of ICMS-induced effects. First, the representationally altered cortical area can extend for several hundred microns away from the ICMS site in any given direction. Second, the affected region is often distributed asymmetrically around the stimulation site. Third, there can be sharp discontinuities at some lo-

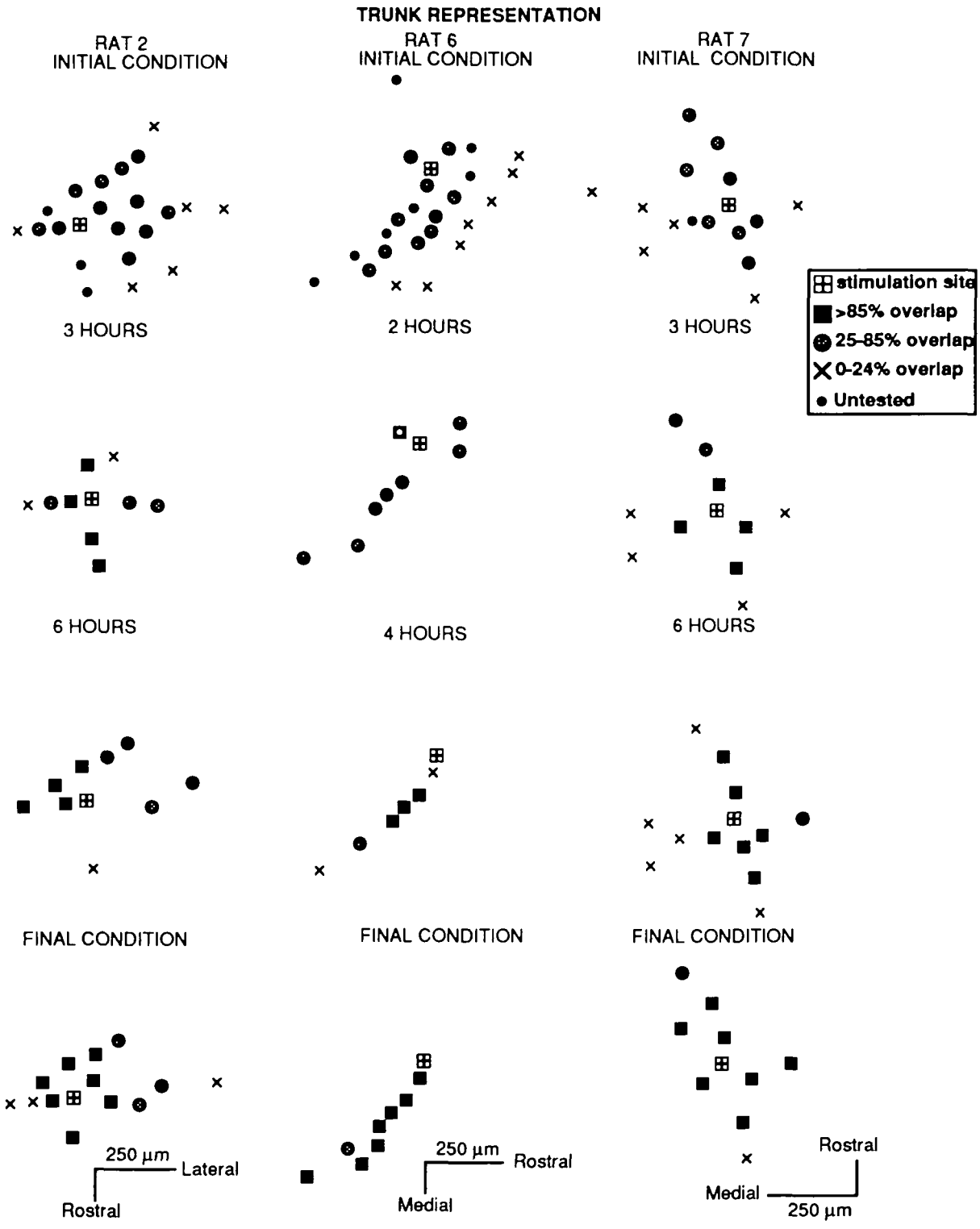

Figure 11. Time course of representation in three rat experiments in the trunk representation. The *top row* corresponds to the pre-ICMS mapping condition and shows all locations tested in that animal. The *open square with the solid cross* denotes the stimulation site. The *solid squares* represent ≥85% overlap with the ICMS-site RF, *large shaded circles* represent 25–85% overlap, and ×s represent 0–24% overlap. *Small solid circles* show locations that were not tested in the initial condition. The *next two rows* show the representation at the time periods indicated at the *top*. The *bottom row* shows the final condition, which was at least 1 hr after ICMS was terminated.

cations between the ICMS-site RF overlap zone and an adjacent, nonoverlapping representational area. Examples of these features could be seen in every experiment. In some experiments, boundaries between zones in which neurons had complete overlap with their neighbors and zones with no overlap with their neighbors were separated by no more than 50 μm. A clear example is shown in Figure 4*B*, where location e has no overlap with the ICMS-site RF while two of the immediately adjacent locations had com-

plete overlap. A second example is evident in Figure 5, where penetration sites a and c are adjacent to ICMS-site RFs.

Discussion

The effect of microstimulation in all experimental animals was to increase the horizontal extent of cortical neurons responding to all or part of the skin region defined at the stimulation site (ICMS-site RF). This result is consistent with hypotheses that describe the response properties of cortical neurons and local topographies as emerging from the temporal coincidence of pre- and postsynaptic activity (Edelman, 1978, 1987; Merzenich, 1987; von der Malsburg and Singer, 1988). They also support predictions that horizontal interactions between neurons within a limited cortical area result in the formation and experience-dependent shaping of functional "minicolumns" or "groups," and contribute to the selection of response properties of group members. These results also demonstrate that ascending input to the cortex originating at the peripheral receptor is not necessary for inducing functional cortical reorganization. However, they do not rule out the possibility that reorganization at subcortical levels has also occurred, effected either by descending inputs from the cortex or by antidromic stimulation of thalamic afferents.

One possibility to account for this effect is that the simple expansion of all receptive fields accounted for the increase in the cortical representation of a given skin area. Electrical stimulation of a peripheral cutaneous nerve leads to SI receptive field size increases in the cat (Recanzone et al., 1990). Like ICMS, whole-nerve stimulation provides a temporally synchronized, repetitive input, yet the cortical effects extended beyond the zone of innervation of the stimulated nerve, and the receptive field expansion did not favor the representation of any given skin region. In the present experiments, the receptive field size increases were not consistent between individual animals. These differences could not be accounted for by the sample size of the affected region, or by the relative size of the ICMS-site RF. Receptive field size expansion alone cannot explain the observed topographic reorganization in most of these cases.

A second possibility is that the receptive fields translocated toward the ICMS-site RF during the course of stimulation. Inspection of receptive field data in the rat experiments again indicated that this is not a likely explanation, as examples of receptive fields migrating away from the ICMS-site RF in the region surrounding the stimulation location were about as common as receptive fields that translocated toward the ICMS-site RF. In the rat experiments, most receptive fields that came to overlap with the ICMS-site RF did so in their entirety. For the primate experiments, the distinction was not as clear. Many receptive fields exclusively represented the ICMS-site RF, yet many represented only a fraction of it. It could be that the receptive fields with partial overlap represent a translocation from one receptive field location to the ICMS-site RF. The time course in which these experiments were performed does not eliminate the possibility that the translocation was completed by the time that the receptive fields were defined in the post-ICMS condition for most receptive fields.

The final possibility is that of substitution. This explanation is the most obvious on inspection of the raw data, as several cortical locations with receptive fields that were nearly identical to the ICMS-site RF emerged in all cases. The cortical locations with receptive fields that completely overlapped the ICMS-site RF increased following stimulation, particularly for the rat experiments. Again, the effect was not as consistent for primate experiments as for the rats, but striking examples of receptive field substitution were still recorded (i.e., Fig. 7). The observation that any two or more receptive fields share such a high degree of common skin is essentially never seen in the same cytoarchitectural area in the normal animal, and is only seen in the ICMS-stimulated animals.

One possible explanation of the differences seen in the rat and monkey experiments could be the reliability of receptive field definition on the body parts investigated. Neuronal responses of the rat trunk and hindpaw representations, at least under the experimental conditions described above, were not as robust or reliable as in the monkey hand representation. This variability was clear in the control experiments. Although the sham-stimulation control experiment was not done in the monkey, a similar study testing the reliability of receptive field definitions at different times and between different investigators in the hand representations of anesthetized owl monkey has shown less variability (Stryker et al., 1987). An alternative possibility is in the differences of the body surface representations. Receptive fields in the trunk representations showed increases in receptive field size more reliably than in the hindpaw and hand representations. Trunk receptive fields were much larger than hindpaw and hand receptive fields, showed more variability within animals, and were somewhat less topographically organized. It may be that the less refined representations of the trunk are more susceptible to the effects of ICMS.

One concern of the relatively subjective nature of receptive field definition is that the investigator may have been biased toward including all or most of the neural response as emanating from the ICMS-site RF, when in fact some smaller, more ambiguous part of the receptive field was actually outside of those boundaries. The use of the blind-investigator protocol attempted to reduce this bias; however, it became clear to the blind investigator that ICMS had been applied after defining a few receptive fields that were nearly identical, a condition that occurs infrequently with this sampling density in normal animals. This control procedure could not eliminate experimenter bias completely, but does confirm that the overall representation of a restricted skin field was increased following the stimulation period, and that relatively minor changes occurred in the absence of stimulation. These controls also confirm that the electrical stimulation was necessary to induce the effect, and

local trauma, leakage of the electrolyte solution, or long-term anesthetic effects could not account for the observed phenomenon.

The sharp discontinuity of receptive field locations implies that after ICMS, there are areas of the periphery that may no longer be represented cortically. The small region of cortical territory sampled in these experiments cannot directly address this issue unequivocally, as it is possible that the zones representing skin that were formerly located in the ICMS-affected zone came to be represented at a distance.

Possible Mechanisms

The mechanisms hypothesized below depend in part on the dimensions of the cortical zone directly excited by the ICMS stimulation. In the motor cortex, the stimulus parameters we used have been estimated to cause excitation at a distance of several tens of microns (Stoney et al., 1968; Snow et al., 1988; Nudo et al., 1990). Studies defining representational borders in motor cortex have shown that currents <60 μA do not cause movements represented less than 100 μm away, while 5 μA of current were used in the present study. At this low current level, the ICMS stimulus may plausibly engage the neural elements within the dimensions of a single, or only a few, hypothetical minicolumns or groups. These studies do not address the extent of subthreshold depolarization of neighboring neurons either through direct activation by the electrical current, or by synaptic activation.

A second issue relevant to a discussion of mechanism is the aphysiological nature of the stimulus parameters used. High-frequency, short-duration bursts of electrical pulses are commonly used in studies of motor movements and are considered to engage the neurons simultaneously in the immediate vicinity of a stimulating microelectrode (see references cited above). Although perhaps unnatural, this stimulus has allowed us to isolate a small region of cortex from its varied input sources and to excite all of the neural elements synchronously. During tactual stimulation in normal behaviors and in the acquisitions of new skills and perceptual abilities, temporally synchronous activity in small regions of the cortex like that induced by ICMS stimulation is undoubtedly occurring (see Delacour et al., 1987; Jenkins et al., 1990; Recanzone et al., 1992a–c).

The two broadest classes of mechanism that can account for the present results are those entailing either sprouting of axons and/or dendrites and the creation and elimination of synapses, or a mechanism of strengthening and weakening of existing synapses. Changes in dendritic arborization have been demonstrated following prolonged exposure to complex environments or to specific sensory-motor tasks (Connor and Diamond, 1982; Greenough et al., 1985; Withers and Greenough, 1989). The data from this report cannot exclude this possibility, but the time course of the effect is shorter than one would predict by an anatomical model involving large morphological changes. Large morphological changes seem less likely than do more local changes in the effectiveness of preexisting synapses.

An alternative possibility is that the synaptic efficacies are altered in the thalamocortical relay cells. Electrical stimulation of the thalamic afferent arbors should anti- and orthodromically activate other branches of thalamocortical afferents, thereby increasing the influence of those particular afferents in the surrounding cortical zone. In that case, direct activation of the afferent terminals would stimulate the surrounding cortical neurons coincidentally, thereby strengthening their specific synapses. This mechanism is unappealing because individual thalamocortical axons arborize beyond the physiological borders of the cortical neuron's receptive field and broadly overlap with each other (Landry and Deschenes, 1981; Snow et al., 1988; Garraghty et al., 1989; Garraghty and Sur, 1990; see Recanzone and Merzenich, 1992), indicating that many afferent inputs are not effective in driving the cortical neuron. ICMS would activate all afferents (effective and ineffective) within the activation distance of the stimulating electrode. This would result in an increase in effectiveness for all thalamic afferents that project to the ICMS site and cause a consistent increase in receptive field size and response magnitude.

A third possibility is that the stimulus evokes changes at the thalamic level via anterograde stimulation of thalamic afferents and/or descending inputs from the cortex. Changes in thalamic representational topographies have been documented (Fadiga et al., 1978), but whether this is the result of ascending or descending projections, or both, is unclear. Similarly, a long-term study of cortical representations conducted several years after peripheral deafferentation suggests that subcortical reorganization can occur (Pons et al., 1991). Changes in representations at the subcortical level may indeed be occurring, but this does not eliminate the possibility that the cerebral cortex can generate local mechanisms of altering synaptic strengths. There is evidence that cortical representational changes occur in second-order cortical areas that receive their predominant input from primary cortical areas (Pons et al., 1988), and that representational plasticity does not occur in animals with NMDA antagonists infused into the cortex following peripheral denervation (Kano et al., 1991).

Another possibility is predicted from models of cortical organization in which neighboring neurons form cooperative cell assemblies, or "groups," that generate and share common response properties (Edelman, 1978, 1987; Merzenich, 1987; von der Malsburg and Singer, 1988). These functional "minicolumns" or "groups" are thought to be oriented radially, with a horizontal dimension of approximately 50 μm. Local corticocortical as well as thalamocortical synapses could be modified in a Hebb-like manner, which would define the specific group in which an individual was a member (see Edelman, 1987; Merzenich, 1987). Any synchronizing stimulus would be expected to strengthen interconnections within the group, as well as provide a cortical source of correlated out-

put to neighboring cortical neurons and groups. These intrinsic network connections selectively representing a restricted skin region could then competitively influence the surrounding neurons, with the possibility of "recruiting" them to then create a larger functional column of coupled neurons.

This mechanism would result in a progressively larger area of cortex being synaptically stimulated by both these intrinsic cortical projections (e.g., the collaterals of pyramidal cells) and by inputs from the same thalamic afferents. The neighboring minicolumns would now be excited by essentially the same inputs as those for neurons of the original ICMS site minicolumn, and thus be indistinguishable from it. This process of effective input substitution would be continuously repeated for new neighboring neurons, resulting in the emergence of the very large representations of the ICMS-site RF.

One obvious problem with this hypothesis is that the ICMS activates not only the excitatory neurons, but the inhibitory and neuromodulatory neurons as well. If all synaptic efficacies were equally strengthened, it is difficult to account for the present results. If, however, only a subset of synapses are differentially affected, changes in synaptic strengths can occur. For example, if only the excitatory synapses were strengthened/weakened (i.e., via an NMDA-type channel), the resulting inhibition would also be altered due to increased/decreased activity of the inhibitory neurons' input from the excitatory neurons. These excitatory/inhibitory interactions could conceivably result in an overall alteration of synaptic efficacies over a large cortical area.

This model makes the prediction that changes in the positive coupling of neurons should emerge in ICMS-enlarged groups. Such positive changes in coupling strengths have been recorded over topographically remodeled ICMS zones in a parallel study (Dinse et al., 1990).

This class of model is attractive because it can account for several features of the present results. The model intuitively requires the effect to proceed sequentially across the horizontal cortical dimension, but not necessarily in a symmetrical manner. Asymmetries could be the result of either differences in the spreads of anatomical arborizations of the thalamic afferents and/or the cortical axons and dendrites, or the competitive influences of specific neighboring groups relative to others. The sharp discontinuities seen in every case could be borders between the expanded region and the adjacent, unrecruited group. These unrecruited neighbors could remain unresponsive to stimulation of the ICMS-site RF, but there would presumably be an ongoing subthreshold influence of the ICMS-site RF on these neurons that could ultimately result in input substitution.

Evidence from other studies supports this type of mechanism. Changes in the response properties of cortical neurons have been shown to occur over a short time course following a variety of stimulation and conditioning paradigms that synchronize stimulation of pre- and postsynaptic elements (Woody et al., 1976; Diamond and Weinberger, 1986; Sakamoto et al., 1987; Frégnac et al., 1988; Iriki et al., 1989). The anatomical spreads of thalamocortical afferents and of the intrinsic afferents of cortical neurons are adequate for the range of effects described in this report (see Recanzone and Merzenich, 1992). ICMS is also expected to stimulate the inputs from neuromodulatory elements in the region, which have been shown to facilitate changes in the response properties of cortical neurons (see Metherate et al., 1987; Weinberger et al., 1990). The molecular mechanisms of altering synaptic efficacy could be the same as those seen in other systems, for example, by an NMDA receptor (see Cotman et al., 1988; Kano et al., 1991), changes in inhibition and/or differential expression of specific proteins (Jones, 1990).

The observation that repetitive stimulation of the cerebral cortex results in representational changes was first observed by Sherrington and colleagues (Graham Brown and Sherrington, 1912), who suggested that the stimulation of the motor cortex used to generate the motor maps of monkeys and great apes was actually affecting those representations. This observation has been confirmed in rat motor cortex, again by using low-level ICMS stimulation (Nudo et al., 1990). The study by Nudo et al. was done by stimulation of deep cortical layers and showed a progressive increase in the representation of a specific motor movement; thus, the effect is not dependent on activation of cortical layers III–IV. Other laboratories have recently reported a similar effect of ICMS in the barrel field of rat somatosensory cortex (Sirois and Hand, 1991) as well as in rat auditory cortex (Maldonado et al., 1991).

Finally, these results may be related to the results described following synchronized stimulation of a much larger cortical area in models of epilepsy, known as kindling (Goddard et al., 1969; McNamara et al., 1980). Simultaneous activation of several groups over a relatively large cortical area could lead to the incorporation of all of these neurons into a single amalgamated group. This large cortical area could then exert very strong influences on the neurons within the same cortical area as well as in other cortical areas receiving input from this region. This activity could then spread throughout these cortical areas, resulting in the synchronized seizures described in kindling studies. If this is the case, one might expect a large area of cortical neurons with receptive fields that closely overlapped throughout the area of the seizures.

In conclusion, intracortical microstimulation resulted in a large horizontal area of the cortex that was responsive to tactile stimulation of a small skin region. Results were most consistent with the hypothesis that effective inputs in the ICMS zone were substituted for other, formerly effective inputs in a progressively expanding cortical zone. These data demonstrate that cortical representational remodeling can be induced by changing activity patterns in the cortex itself. They are also consistent with proposed models of cortical representational organiza-

tion and plasticity based on (1) an activity-dependent Hebb-like rule of altering synaptic efficacies and (2) hypothetical functional "minicolumns" or "groups" as the fundamental processing unit of the cerebral cortex.

Notes

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