

# Interhemispheric Transfer of Plasticity in the Cerebral Cortex

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Each half of the body surface is represented topographically in the contralateral cerebral hemisphere. Physiological data are presented showing that homotopic regions of primary somatosensory cortex are linked such that plasticity induced in one hemisphere, in the form of receptive field expansion brought about by a small peripheral denervation, is immediately mirrored in the other hemisphere. Neurons which display the plasticity show no responsiveness to stimulation of the ipsilateral body surface. This suggests that the pathways and mechanisms mediating this transfer are specific to the role of maintaining balance, or integration, between corresponding cortical fields.

**D**ENERVATION OF A SMALL REGION of the body by amputation (1), nerve section, or local anesthesia (2) leads not to a lack of responsiveness in the affected areas of the representation in contralateral somatosensory cortex but, rather, to the immediate expression of new, or expanded, receptive fields. Because receptive fields are normally shaped by lateral inhibition (3), at least some of which is generated within cortex (4), the effect of a small denervation has been viewed as a disinhibition of viable, but normally suppressed, inputs from body areas adjacent to the affected region (1, 2).

We performed experiments on thirteen adult flying foxes (*Pteropus scapulatus*) (290 to 450 g) and three macaque monkeys (*Macaca fascicularis*) (2.5 to 3 years old, 1.4 to 1.8 kg), which were anesthetized and maintained with ketamine (50 mg per kilogram of body weight) and xylazine (5 mg/kg) (5). Somatosensory cortex on both sides of the brain was exposed, and crude somatotopic maps were derived with standard techniques (6). We used the topography of the forelimb representations and, in the monkey experiments, reconstruction of the electrode tracks on Nissl-stained sections to confirm that data were obtained from neurons in primary somatosensory cortex (Area 3b in monkeys). Two electrodes were positioned in mirror image locations with respect to the midline. In this way concurrent recordings could be made of single unit or multiunit receptive fields (7) representing nearly identical regions on either side of the body. In six of the flying foxes and all three of the monkeys, denervation of part of a digit was effected by local anesthesia. In addition to the direct effect (8) on the representation of the denervated digit, there was an effect on receptive fields of units representing the unaffected digit of the opposite limb (indirect effect).

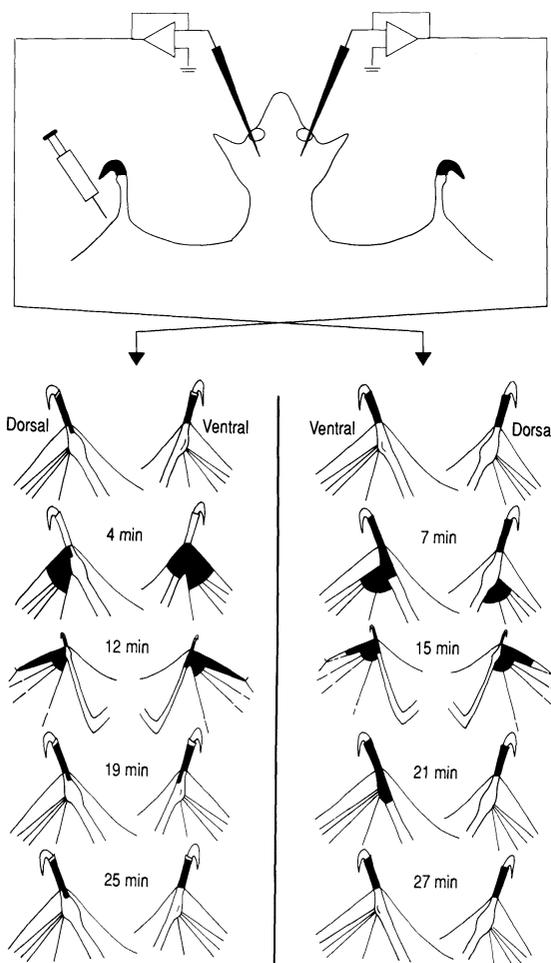
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The results of each of these experiments were very similar and are represented by the example in Fig. 1. In flying foxes the receptive fields of units that originally represented the thumb that was anesthetized (that is, in contralateral cortex) expanded within a few minutes of the injection. The receptive fields at electrodes in the opposite hemisphere located on or around the unaffected thumb also expanded, the onset of expansion being as rapid as for the direct effect. When stimulation of the anesthetized area began to

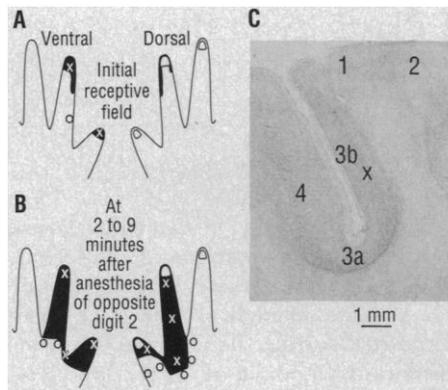
produce responses in contralateral cortex, the expanded receptive fields (both lateralities) began shrinking. Final fields were very similar to those seen before the peripheral manipulation. Comparable results were obtained for the monkeys in which the third phalangeal region of one digit was anesthetized. An example showing the indirect effect of changes in a single unit receptive field recorded ipsilateral to the denervation is shown in Fig. 2.

In the remaining seven experiments on flying foxes, denervation was effected by amputation. In these experiments there was also an indirect effect in which receptive fields of neurons within the representation of the intact thumb expanded (Fig. 3A) (9). These fields later contracted to match the original fields in five cases but remained partially expanded in the other two (examined for 3 hours). The time course for this contraction varied considerably (13, 26, 27, 32, and 35 min). All fields recorded in cortex contralateral to the amputation (direct effect) remained expanded for the period of the experiment (up to 4 hours), although we have previously shown that such fields contract over the following 7 to 10 days (1).

**Fig. 1.** Changes in cutaneous receptive fields of the flying fox determined through recording electrodes placed in nearly symmetrical positions in the somatosensory cortex of each cerebral hemisphere after local anesthesia of one thumb. Diagrams show dorsal and ventral views of the anesthetized thumb (left) and unanesthetized thumb (right); note the scale change necessary to show the large fields at 12 and 15 min. Temporary local anesthesia of one thumb was produced with two (6- $\mu$ l) subcutaneous injections of 2% lignocaine (Apex Laboratories) aimed at the passage of the digital nerves past the metacarpophalangeal joint. In response to this unilateral denervation, receptive fields recorded through both electrodes expanded into regions where stimulation originally produced no effect. Driven activity began to return in response to stimulation of the injected thumb at about 12 min; retraction of these fields to very close to the original occurred over the next 10 min.



**Fig. 2.** Changes in the receptive field of a single unit recorded through an electrode in the primary somatosensory cortex (Area 3b) of a monkey. The × in the photomicrograph (C) indicates the reconstructed position of the recording. The initial receptive field covered the tips of digits 1 and 2 (A). Stimuli to the hand ipsilateral to the electrode (not illustrated) did not evoke discharges of the unit (or inhibit discharges) but local anesthesia (four 4- $\mu$ l lignocaine injections subcutaneously) of the third phalangeal area of digit 2 of that hand increased the unit's receptive field (B). In addition to receptive field boundary determination, a controlled stimulus (10) at a fixed intensity (suprathreshold for the two regions of the original receptive field) was used to examine the area that evoked discharges from the single unit. ×, positions where discharges could be evoked; o, positions where there was no response.

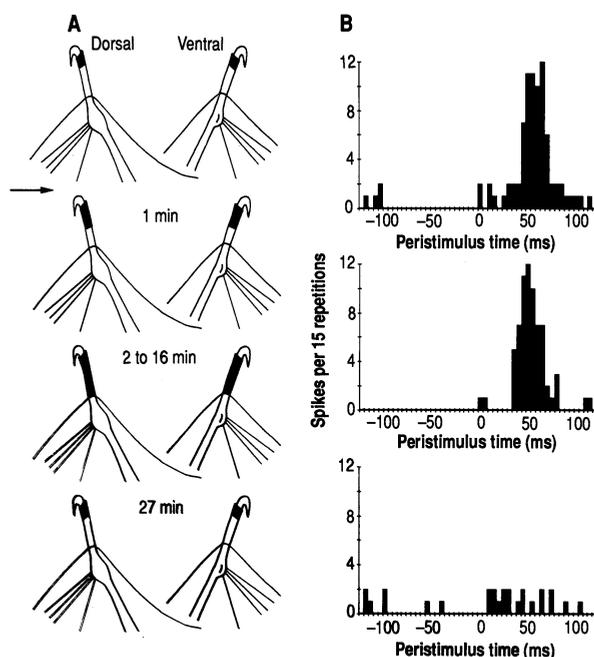


No effect of ipsilateral stimulation (10) on the activity at primary somatosensory cortical loci was demonstrable either normally or during the period of expansion (Fig. 3B) (11). Nevertheless, removal of ipsilateral input results in a dramatic change of receptive fields representing the contralateral body surface. That this change is an expansion indicates that the effect of the ipsilateral influence is normally inhibitory. Because we could not find any evidence of ipsilateral inhibition that was time-locked to the stimulus, the indirect effect may result from the disruption of an inhibition with a long time course such as a neuromodulatory input (12).

The anatomical basis for the expansion of cortical receptive fields, both in the direct effect of our experiments and in cases where chemical disinhibition has been used (4), is

probably the wide arborization of thalamocortical afferents (13). However, it is not clear which pathway subserves the indirect effect. Ipsilateral receptive fields have been reported in regions other than primary somatosensory cortex of many species (14) but, with a few exceptions (15), have not been reported in primary somatosensory cortex. Callosal connections have been demonstrated between homotopic regions of primary somatosensory cortex but are thought to be sparse between representations of distal regions of the forelimb (16). In contrast, callosal connections between sensory representations are responsible for the immediate interhemispheric transfer of learned tasks (17). In our study, irrespective of whether denervation was produced by amputation or by local anesthesia, the ex-

**Fig. 3.** (A) Example of changes in the receptive field of a single unit after the amputation of the thumb ipsilateral to the recording electrode. The unit's receptive field, which was originally confined to the tip of the intact thumb, rapidly expanded to cover the entire phalangeal region. This field was stable from 2 to 16 min after amputation (arrow) and then contracted back to the original boundaries. (B) Responses of the same single unit to 15 repetitions of a controlled-brush stimulus (10), recorded before the amputation. The stimulus within the receptive field (contralateral thumb) was at an intensity 15 dB above threshold, and the ipsilateral stimulus (corresponding position to the contralateral thumb) was 6 dB greater than this. For this example, and other single units studied, comparisons of the response to contralateral stimulation alone (upper histogram) to that obtained with bilateral (middle histogram) or ipsilateral (lower histogram) stimulation revealed no evidence of direct ipsilateral responsiveness, or of facilitation or inhibition of the contralateral response.



pansion of receptive fields in the representation of the unaffected digit matched that of the direct effect, raising the possibility that the indirect effect results from a mechanism which primarily allows for a balance in the processing at corresponding positions in the cerebral cortices. A mechanism providing balanced transfer of changes in corresponding regions of the two hemispheres has implications for all cortical representations. The rapidity of the interhemispheric transfer we have described suggests that these mechanisms would be involved in the initial reaction of the brain to any form of denervation.

#### REFERENCES AND NOTES

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3. S. E. Laskin and W. A. Spencer, *J. Neurophysiol.* **42**, 1061 (1979); A. L. Towe and V. E. Amassian, *ibid.* **21**, 292 (1958).
4. T. P. Hicks and R. W. Dykes, *Brain Res.* **274**, 160 (1983); R. W. Dykes, P. Landry, R. Metherate, T. P. Hicks, *J. Neurophysiol.* **52**, 1066 (1984).
5. Flying foxes appear to have a higher than normal incidence of ketamine-induced convulsions. Three animals that showed early signs of convulsion (for example, rapid twitching of the jaw) were given barbiturate (sodium pentobarbitone). The results from animals so treated were indistinguishable from those of the other animals in this study.
6. M. B. Calford, M. L. Graydon, M. F. Huerta, J. H. Kaas, J. D. Pettigrew, *Nature* **313**, 477 (1985). In three of the experiments with flying foxes where the primary aim was to examine the quantitative response of a single unit, and in one experiment in which multiple electrodes were placed ipsilaterally, cortex contralateral to the denervation was not exposed.
7. Receptive fields were defined as the maximal area over which a clear response could be evoked to stimulation with a hand-held brush. Such receptive fields are larger than the "best area" fields often used in somatotopic mapping studies. The impedance of our electrodes (approximately 1 megohm at 1 kHz) was such that multiunit clusters consisted of discharges of clearly identifiable units. However, because monitoring rapid changes in receptive fields is generally incompatible with accurate determination of the boundaries of fields of discriminated single units, most of the data come from considering the behavior of the multiunit cluster as a whole. Recruitment of units with receptive fields in the expanded areas of multiunit receptive fields is not an explanation for our data because, in most experiments, when expanded fields were stable, single units were responsive to stimuli in both the original region and the expanded region. In six experiments (four flying foxes, two monkeys) the changes to the receptive fields of isolated single units were monitored throughout the experiment and did not differ from those for multiunits.
8. The crossed nature of the sensory representation can cause problems with terminology. Each half of the body surface is represented in the contralateral cerebral cortex. In this report, with respect to a peripheral denervation, plasticity induced in contralateral cortex is termed the direct effect and plasticity induced in ipsilateral cortex is termed the indirect effect.
9. The experimental strategy was to follow closely any changes in receptive fields. This approach, and our interpretation that it would be invalid to repeat the experiment within an animal, limited the number of

- observations. However, there are no negative results to report; in the 16 animals studied we observed the indirect effect of receptive field expansion for all single units and multiunits studied that had initial receptive fields overlapping with the region corresponding to that denervated on the opposite side of the body. The areal extent of the indirect effect in ipsilateral cortex has not been fully determined. However, recordings from neurons in flying fox somatosensory cortex with receptive fields on the contralateral foot, upper arm, and chin (vibrissae) showed no changes to the fields when the ipsilateral thumb was amputated.
10. Controlled stimuli were delivered by a pair of speaker coil-operated brushes. The complex stimulus provided by such a system was appropriate to quantify cutaneous responsiveness because it is similar to the stimulus used in receptive field determinations. Movements of the brushes were triggered by computer-generated square pulses of 10-ms duration, which were fed through a resistance attenuator (calibrated in decibels) to a power amplifier. The electrode signals were digitized on-line by the computer (Televideo 386, 40 kHz per channel), and clear single units were discriminated (BrainWave Systems, Discovery software) and records stored so that peristimulus-time response histograms could be formed off-line.
  11. Where single units could not be discriminated, the stimulus pulse was used to trigger an oscilloscope, which displayed the multiunit signal. In no case was there evidence of direct ipsilateral drive or bilateral facilitation or competitive suppression of discharges in cortex when the ipsilateral stimulus was placed in a mirror image position to the contralateral receptive field. In early experiments an air-jet stimulus controlled by the same system was used in place of the controlled-brush stimulus.
  12. Such modulation has been postulated to operate in a number of systems, for example, the noradrenergic projection from locus ceruleus [L. Descarries, K. C. Watkins, Y. Lapierre, *Brain Res.* **133**, 197 (1977); T. Itakura, T. Kasamatsu, J. D. Pettigrew, *Neuroscience* **6**, 159 (1981)].
  13. The extensive arborization of incoming afferents to cortex [P. Landry and M. Deschênes, *J. Comp. Neurol.* **199**, 345 (1981)] is not reflected in the normal receptive field size seen electrophysiologically because of the extensive inhibitory interneuron network that provides the basis for lateral inhibition [see p. 96 of R. W. Dykes, *Brain Res. Rev.* **6**, 47 (1983)].
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  17. A global lack of transfer is found in split-brain patients [R. W. Sperry and M. S. Gazzaniga, in *Brain Mechanisms Underlying Speech and Language*, F. L. Darley, Ed. (Grune and Stratton, New York, 1967), p. 108]. Selective lesion of the region of the callosum linking the somatosensory representations is sufficient to block the normally immediate transfer of a roughness discrimination from one paw to the other [F. F. Ebner and R. E. Myers, *J. Neurophysiol.* **25**, 380 (1962)], and lesion of one sensorimotor cortex affects tactile discrimination ipsilaterally as well as contralaterally [J. Semmes and M. Mishkin, *ibid.* **28**, 473 (1965)].
  18. Supported by grants from the National Health and Medical Research Council of Australia, The University of Queensland's Brain Research Fund, and a Commonwealth Special Research Centres Grant. We thank L. Martin and L. Little for providing facilities for the care and housing of the flying foxes and J. Dann, E. Buhl, and C. Macquoen for help during experiments. We express special thanks to R. Porter and K. Collins for providing the monkeys.

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"It turns out that the drug which we thought was patient friendly is really virus friendly."