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Induction of bilateral plasticity in sensory cortical maps by small unilateral cortical infarcts in rats

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Abstract

Behavioural impairments caused by brain lesions show a considerable, though often incomplete, recovery. It is hypothesized that cortical and subcortical plasticity of sensory representations contribute to this recovery. In the hindpaw representation of somatosensory cortex of adult rats we investigated the effects of focal unilateral cortical lesions on remote areas. Cortical lesions with a diameter of ≈2 mm were induced in the parietal cortex by photothrombosis with the photosensitive dye Rose Bengal. Subsequently, animals were kept in standard cages for 7 days. On day seven, animals were anaesthetized and cutaneous receptive fields in the cortical hindpaw representations ipsi- and contralateral to the lesion were constructed from extracellular recordings of neurons in layer IV using glass microelectrodes. Receptive fields in the lesioned animals were compared to receptive fields measured in nonlesioned animals serving as controls. Quantitative analysis of receptive fields revealed a significant increase in size in the lesioned animals. This doubling in receptive field size was observed equally in the hemispheres ipsi- and contralateral to the lesion. The results indicate that the functional consequences of restricted cortical lesions are not limited to the area surrounding the lesion, but affect the cortical maps on the contralateral, nonlesioned hemisphere.

Introduction

Plasticity of cortical and subcortical representations has been demonstrated in the cortex and in the thalamus of adult mammals (Buonomano & Merzenich, 1998; Kilgard & Merzenich, 1998). Reorganisations have been shown to develop after peripheral or central nervous system injury (Kaas *et al*., 1983; Jenkins & Merzenich, 1987; Jain *et al*., 1998). Substantial reorganisations can be induced by behavioural training that develop in parallel with an improvement in behavioural or perceptual performance (Kleim *et al*., 1998; Ziemann *et al*., 2001; Dinse & Merzenich, 2002). The functional relevance of plasticity is not yet clear. There is agreement that lesion-induced reorganization serves to regain function lost by the injury.

After focal cortical lesions, receptive field enlargement has been reported for somatosensory (Jenkins & Merzenich, 1987; Schiene *et al*., 1999) and visual (Eysel & Schweigart, 1999) cortex. Similar phenomena have also been observed after repetitive exercise (Classen *et al*., 1998) or tactile Hebbian learning (Pleger *et al*., 2001) in healthy human volunteers. Clinical studies have demonstrated that treatment-induced cortical reorganization can occur in stroke patients (Liepert *et al*., 2000a).

While all these findings describe perilesional phenomena, little is known about reorganisational effects occurring beyond the lesioned area or even contralaterally. In a morphological study, Jones & Schallert (1994) demonstrated structural alterations in the hemisphere contralateral to the lesion. They showed a use-dependent growth of pyramidal neurons subsequent to an electrolytic lesion in the forepaw sensorimotor area. A number of bilateral alterations have been described in studies using photothrombotically induced cortical lesions, providing evidence that cortical GABAergic inhibition decreases (Buchkremer-Ratzmann *et al*., 1996) in parallel with a down-regulation of $GABA_A$ receptor binding and $GABA_A$ receptor subunits (Schiene *et al*., 1996; Neumann-Haefelin *et al*., 1999). Evidence for intracortical disinhibition has also been demonstrated in human motor cortex (Liepert *et al*., 2000b). Changes in the calcium current following transient middle cerebral arterial occlusion have been demonstrated in the contralateral noninfarcted tissue (Bruehl *et al*., 2000). This may partially support the hyperexitability found contralateral to photothrombotic lesions (Buchkremer-Ratzmann *et al*., 1996).

In the present study we estimated electrophysiologically the size of tactile cutaneous receptive fields in the ipsi- and contralateral cortical hindpaw representation in adult rats. Our hypothesis was that small unilateral cortical infarcts cause functional impairment not only in the vicinity of the lesion but also remote from it.

Materials and methods

Introduction of photothrombotic lesion

Adult male Wistar rats (280–320 g) were anaesthetized with enflurane (2.0% vol. during preparation and 1.5% during lesioning). The lesions were induced photochemically, as described previously (Buchkremer-Ratzmann *et al*., 1996), using the rose-bengal technique introduced by Watson *et al*. (1985). For surgery, the animals were anaesthetised with enflorane in oxygen/nitrous oxide. The photosensitive dye Rose Bengal was injected over the tail vein. Illumination of the brain through the skull for 20 min after injection of the photosensitive dye caused a photothrombotic ischemia of the cortex underneath the light source with an average diameter of 2 min. A light source was placed stereotactically on the right hemisphere with a position 4 mm caudal to bregma and 4 mm lateral to the midline. The lesion usually

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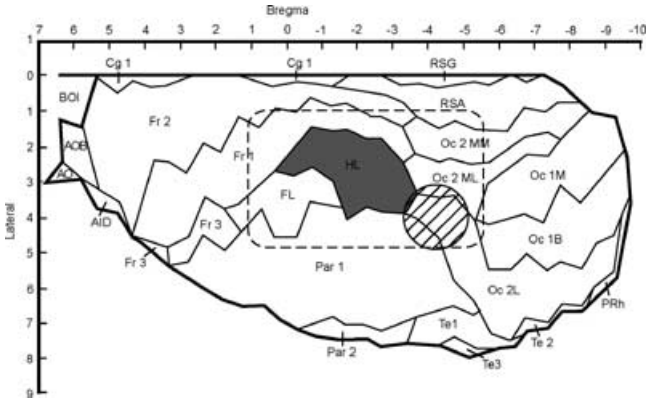

FIG. 1. Sketch of lesion location (hatched) and recording site (grey). Area of trepanation is marked with dashed line. Modified after Zilles (1985).

affected small parts of the hindlimb area of the left limb, the primary somatosensory area Par1 and the second occipital cortex (Zilles, 1985; Fig. 1). The resulting lesions had a diameter of ≈2.0–2.5 mm and were restricted to the cortical tissue with white matter intact. Eight untreated animals of the same weight were used as controls. Treatment of all animals was within the guidelines of the National Institution of Health Guide and Care for Use of Laboratory Animals (Revised 1987), all experiments were approved by the German Animal Care and Use Committee.

Electrophysiology

The *in vivo* experiments were performed 7 days after surgery under urethane anaesthesia. Action potentials were extracellularly recorded at depths of 700–750 μm using glass microelectrodes filled with concentrated NaCl (2 M, 1–2 MΩ). After bilateral opening of the skull over the left and right hindpaw representation, the dura was removed and the cortex was covered with silicon oil. Enlarged video images were taken from each hemisphere to use the blood vessels as landmarks for mapping.

Hindpaw stimulation and receptive field analysis

The location and the extent of receptive fields on the glabrous skin of the hindpaw was determined by hand-plotting (Merzenich *et al*., 1978; Merzenich *et al*., 1984) and marked in a schematic drawing of the paw. For these experiments, animals were anaesthetized with an initial dose

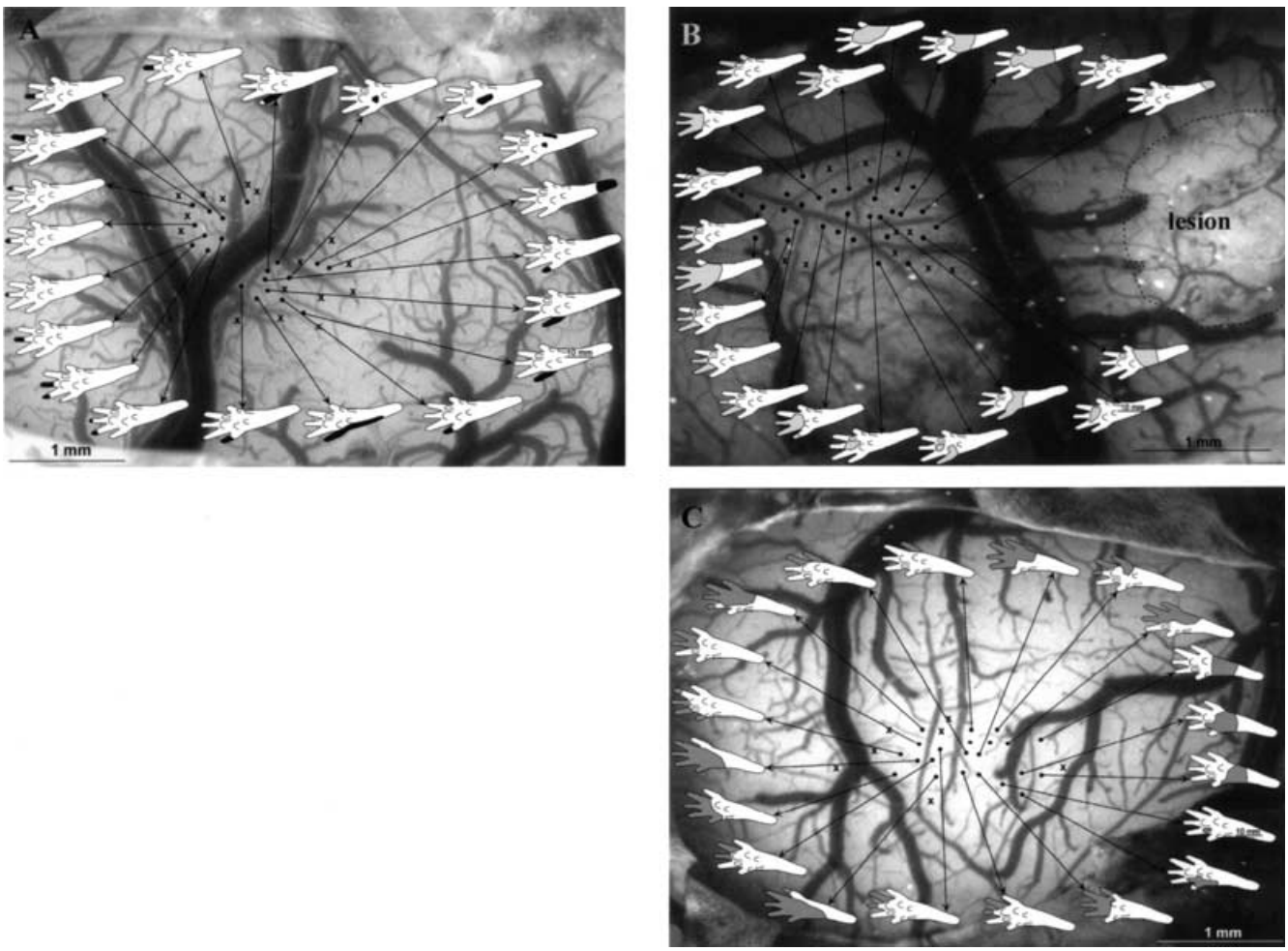

FIG. 2. Examples of receptive fields on the hindpaw skin of somatosensory cortical neurons recorded in (A) the right hemisphere of a normal, control animal and in (B) the right and (C) left hemisphere of a rat with a photothrombotic lesion in the right hemisphere 1.5 mm caudal to the hindpaw representation. The border of the lesion is marked by a dotted line. Recordings were made 7 days after induction of the lesion. Shown are the dorsal surface of the cortex with blood vessels. Dots indicate penetration sites in the representation of the hindpaw. The arrows connect each penetration site with its corresponding receptive field drawn in a figurine of the left (A,B) or right (C) hindpaw. Crosses mark positions with no cutaneous responses. A and B, frontal is on the left and the sutura sagitalis is near the bottom; C, frontal is on the left and sutura sagitalis is near to the top. Scale bar, 1 mm.

of 1.5 mg/g body weight urethane (Sigma, 20% in water, i.p.). Additional anaesthetic (1/8 of the initial quantum) was administered when eye-blink or paw-withdrawal reflexes could be elicited. The cisterna magna was drained to prevent swelling of the cortex. After an unilateral craniotomy and resection of the dura, the cortex was covered with warm silicone oil (DC 200 50cst, Serva). Rectal temperature was kept at 37 °C using a feedback-controlled heating pad. The ECG and respiration rate were stable throughout every individual experiment. Receptive fields were defined as those areas of skin at which just visible skin indentation evoked a reliable neural discharge. Other studies have shown that just-visible indentation is in the range of 250–500 μm, which is in the middle of the dynamic range of cutaneous mechanoreceptors (Johnson, 1974; Gardner & Palmer, 1989a; Gardner & Palmer, 1989b). Cells responding either to high threshold stimuli, joint movements or deep inputs were classified as noncutaneous and were excluded from further evaluation. Receptive field size (area of skin in mm^2) was quantitatively analysed by planimetry (CANVAS 3.51 and higher; Deneba Systems, Inc.)

Results are presented as mean values ±SD.

All experimental procedures were conducted according to protocols approved by the Governmental Animal Care Committee.

Results

Typical examples of receptive fields found within the hindpaw representation in a control animal are shown in Fig. 2A. Shown is the dorsal surface of the somatosensory cortex with blood vessels. The penetration sites are marked by dots and receptive fields are marked in a figurine of the hindpaw for each recording site. In control animals, maps of the rat SI hindpaw representation were characterized by small low-threshold cutaneous receptive fields, located on single toes, pads or parts of the heel (Fig. 2A), defining a fine-grained topographic representation (Spengler & Dinse, 1994; Godde *et al.*, 1996). On average, receptive field size in control animals was $37.0 \pm 38.3\,mm^2$ (mean ± SD, $n = 208$). A typical example of a lesioned animal is illustrated in Fig. 2B. The diameter of photothrombotic lesions was in the range 2–3 mm. The rostral border of the lesion was between 1 and 1.5 mm from the caudal border of the hindpaw representation. As a rule, receptive fields ipsilateral to the lesion were enlarged, confirming previous reports on the effects of cortical lesions. However, examination of receptive fields in the hemisphere contralateral to the lesion revealed a similar degree of receptive field size change (Fig. 2B and C). In the ipsilateral hemisphere, receptive fields extended over two or more toes or covered several pads and/or large portions of the heel. On average, the receptive fields ipsilateral to the lesion were $75.0 \pm 58.5\,mm^2$, $n = 123$. In the hemisphere contralateral to the lesion, the mean size of receptive fields was $75.1 \pm 49.5\,mm^2$, $n = 128$. A quantitative evaluation of the receptive field magnitudes is shown in Fig. 3. Control animals (Fig. 3A) had mostly small receptive fields in the range 2–30 mm^2 with only a few of medium size (31–120 mm^2) and almost no large receptive fields (>120 mm^2). In the lesioned animals, in both hemispheres (Fig. 3B and C) we observed a clear shift from small to medium and large receptive fields. The lesioned animals were characterized by only a few small receptive fields (2–30 mm^2), but had more medium-sized receptive fields (31–120 mm^2). Only in the lesioned animals, a portion of the total sample had large receptive fields (>120 mm^2). The increase in the size of receptive fields in the lesioned animals were statistically highly significant (Mann–Whitney test, one-sided, $P < 0.001$) compared with control animals. There were no differences between the size of receptive fields in the two hemispheres in lesioned animals (Mann–Whitney test, two-sided, $P = 0.377$).

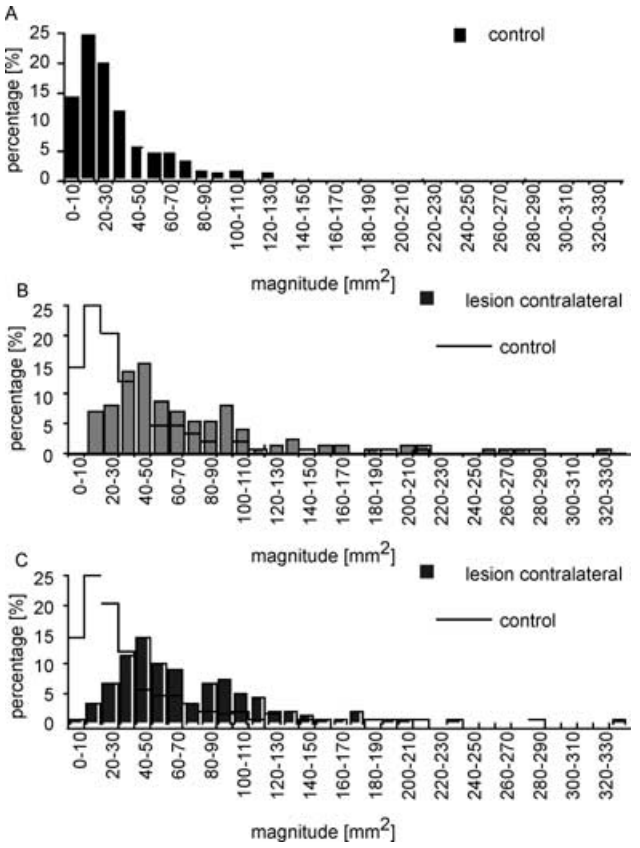

FIG. 3. Distribution pattern of receptive field size of neurons recorded in the somatosensory cortex of (A) control animals (right hemisphere), and in (B) the right and (C) left hemisphere of photothrombotically lesioned animals. Percentage of different receptive field sizes as observed in the concerned hemisphere (bin size, 10 mm^2). Controls (A) show a narrow distribution of receptive field size with mostly small receptive fields. The distribution found in controls is overlaid as a line plot over the distributions in the lesioned animals (B and C). In the lesioned animals, neurons recorded in both hemispheres (B and C) show a clear shift towards larger receptive fields.

Discussion

The present study describes the consequences of small photothrombotic cortical infarcts in morphologically undamaged cortex (Bidmon *et al.*, 1998a) on receptive fields located several millimetres away from the lesion or located in the hemisphere contralateral to the lesion. We demonstrated an increased size of cutaneous receptive fields in response to tactile stimulation. These alterations could be found in both hemispheres and were observed well outside the lesioned area.

The receptive field size is determined by an integration of excitatory and inhibitory processes (Alloway *et al.*, 1989). While excitatory and inhibitory networks are part of the columnar cortical architecture, they also form long-ranging horizontal connections, which even may cross the midline (see Discussion in Hagemann *et al.*, 1998). Inhibitory networks are more localized and are assumed to sharpen the functional parcelling of the neocortex (Tremere *et al.*, 2001). Taking this into account, the increase of the receptive field size might be explained by the GABAergic disinhibition which is induced by the cortical infarct (Buchkremer-Ratzmann *et al.*, 1996; Reinecke *et al.*, 1999), accompanied by a down-regulation of $GABA_A$ receptor binding and subunits (Neumann-Haefelin *et al.*, 1999).

A possible mechanism underlying the extensive alterations might be deafferentation. It has been shown that the lesion destroys connections between the infarcted areas and bilateral associative areas (Bidmon

et al., 1998b). This could help to explain the alterations in the contralateral hemisphere. The link between deafferentation and metabolism was first discussed by von Monakow who coined the term diaschisis (von Monakow, 1895; von Monakow, 1914). He presumed the loss of excitatory input from infarcted areas to cause a lower sensibility in remote but connected areas. Electrophysiological diaschisis was described, in variance to von Monakow, as hyperexcitability following photothrombotic lesions (Buchkremer-Ratzmann *et al*., 1996) and middle cerebral arterial occlusion (Reinecke *et al*., 1999). Also, the connections between cortical and subcortical structures can be destroyed by deafferentation. The corticothalamic pathway can be affected by cortical lesions. Krupa *et al*. (1999) showed a change in the receptive fields of vibrissae in the thalamus after inactivation of the cortex. Parker & Dostrovsky, 1999) described an increased somatosensory representation of extremities in the thalamus induced by a nucleus gracilis lesion which could be prevented by a simultaneously induced cortical lesion. This evidence does not allow determination of the level in the somatosensory pathway at which the alterations occur, highlighting the need for complementary investigations.

Increased receptive field sizes after application of bicuculline, as demonstrated for the cortex, have not been found after application of bicuculline in the thalamus (Hicks *et al*., 1986). These findings suggest that the changes seen in the present study are presumably caused not subcortically but by cortical alterations.

It has been shown in animal experiments as well as in human subjects that changes in cortical maps can be induced within minutes to hours by functional adaptations (Dinse *et al*., 1997; Pleger *et al*., 2001). Functionally inactive connections may become activated by reduction of intracortical inhibition (Feldman *et al*., 1999). The increase in receptive field size observed in this study therefore does not necessarily imply the development of structural plastic changes (Alloway *et al*., 1989).

Functionally, the observed alterations in sensory representations may cause perceptual and motor impairments. This applies for spatial resolution as intracortical inhibition sharpens perception (Costanzo & Gardner, 1980). On the other hand, the stronger extension of the sensory impact might facilitate associative plasticity in the sensory connections. Post-stroke epilepsy (Kotila & Waltimo, 1992) and impaired sensory discrimination (Kim & Choi-Kwon, 1996) are frequently observed in human patients suffering from stroke. With time-consuming therapies the affected hand can be trained and discrimination ability can improve (Carey *et al*., 1993).

It is interesting to note that in old animals functional impairment of hindpaw movements was associated with increased receptive field sizes (Spengler *et al*., 1995). However, exposure of aged animals to an enriched environment resulted in a restoration, i.e. decrease, of receptive field sizes as found in adult animals in parallel with an improvement in sensorimotor functions (Churs *et al*., 1996; Reinke & Dinse, 1996).

In conclusion, the present study demonstrates that local brain ischemia causes bilateral changes in receptive fields. These alterations may be crucial for our understanding of ensuing functional deficits after stroke. Conceivably, large-scale bilateral reorganisations will also affect the degree of functional recovery and must therefore be considered a contributing factor in studies on sensory plasticity following focal brain lesion.

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Abbreviations

GABA, gamma-aminobutyric acid; $GABA_A$, gamma-aminobutyric acid, type-A.

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