

Research report

Contralateral increase in thigmotactic scanning following unilateral barrel-cortex lesion in mice

Heiko J. Luhmann^a, Joseph P. Huston^b, Rüdiger U. Hasenöhr^{c,*}

^a *Institute of Physiology and Pathophysiology, University of Mainz, Duesbergweg 6, 55128 Mainz, Germany*

^b *Institute of Physiological Psychology and Center for Biological and Medical Research, University of Düsseldorf, 40225 Düsseldorf, Germany*

^c *Department of Psychology, University of Hertfordshire, College Lane, Hatfield, Herts AL10 9AB, UK*

Received 21 May 2004; received in revised form 8 June 2004; accepted 8 June 2004

Available online 6 August 2004

Abstract

Adult C57BL/6 mice received uni- or bilateral cryogenic or sham-lesions over the barrel field and their exploratory behaviour was assessed in an open field between 1 and 7 days post-lesion. Bilateral cortical lesions produced a short-lasting increase in thigmotactic scanning with both sides of the face on the first day of testing. Mice with a unilateral barrel-cortex lesion showed more contralateral wall scanning with a recovery to behavioural symmetry after 5–7 days. Furthermore, the increase in contralateral thigmotaxis was most pronounced in animals with damage to the left barrel field, indicative of a lateralization of the lesion-induced behavioural changes. The cortical lesions did not influence locomotor activity and the rate of habituation to the open field (habituation ‘learning’). Referring to recent electrophysiological findings, we hypothesize that the lesion established a lateralized source of increased neuronal excitability within the affected barrel-cortex, leading to more behaviour with its corresponding vibrissae. Alternatively, if the lesion results in contralateral ‘neglect’ in terms of input, the increased scanning with the affected vibrissae may reflect an attempt of the system to compensate for this with an increase in usage.

© 2004 Elsevier B.V. All rights reserved.

Keywords: Barrel-cortex; Freeze lesion; Open-field; Scanning; Mouse

1. Introduction

In rats and mice, the facial whiskers (mystacial vibrissae) are vital sensory organs that play a key role in exploration and discriminative behaviour. Acute removal of the vibrissae results in deficits in tactile discrimination, orientation, locomotion, and balance [20]. The whisker-to-barrel pathway represents a part of the trigeminal somatosensory system, which relays sensory information from the whiskers via trigeminal and thalamic nuclei to layer IV of primary somatosensory cortex [22]. The receptive fields for each individual vibrissa are somatotopically organized into ‘barrels’, which occupy about 20% of the somatosensory region [25]. The whisker-to-barrel pathway has frequently been used as a

model system to study the effects of sensory stimulation and deprivation on cortical activity parameters [19]. The barrel-cortex has been investigated most intensively with regard to its importance for neural plasticity associated with (patho-) physiological conditions, including learning of new stimulus configurations [3], experience-dependent receptive field re-organisation [18] and disease states like stroke [9] or epilepsy [11].

Previous work from our laboratory has shown a wide variety of time-dependent lateralized changes in behaviour and basal ganglia function after unilateral manipulation of the vibrissae-barrel-cortex system of rats [10]. Unilateral removal of the vibrissae (‘hemivibrissotomy’) produced transient asymmetries in turning and wall scanning from which the animals recovered within 1 week post-lesion. Time-related to these behavioural changes, we found neuronal alterations in striatal afferents arising from dif-

* Corresponding author. Tel.: +44 1707 28 4618; fax: +44 1707 28 5073.
E-mail address: r.u.hasenoehr@herts.ac.uk (R.U. Hasenöhr).

ferent brainstem nuclei, indicative of a functional link between the orofacial systems and the basal ganglia [21]. Furthermore, unilateral lesions in the cortical barrel fields led to a series of behavioural and biochemical changes that paralleled a number of those seen following hemivibrissotomy [1], suggesting that the barrel-cortex plays a decisive role in the proposed vibrissae-basal ganglia interaction.

The majority of studies focusing on behavioural consequences of vibrissae and barrel-cortex manipulations have been performed with rats, while only little is known about the effects of such manipulations in the mouse. The use of mice in neurobehavioural research is increasingly important because of the possibility of employing tools of molecular biology and genetics. The mouse has a well-developed barrel-cortex and mutations could serve as a model for investigating experience-dependent as well as lesion-induced barrel-cortex plasticity [6]. However, for a behavioural phenotyping of genetically modified mice, the existing animal models have to be re-evaluated, since differences in vibrissae-related behaviour between rats and mice are well-documented [23]. The present study was undertaken to gauge the behavioural consequences of uni- and bilateral lesions of the barrel-cortex in C57BL/6 mice. Focal cryogenic lesions were made in the cortical barrel field, and at different times after the lesion, a series of behaviours were measured that have been shown to be sensitive to lateralized manipulations of the vibrissae-barrel-cortex system in rats [1,2].

2. Materials and methods

2.1. Animals and surgery

The experiments were carried out in accordance with the German Law on the Protection of Animals and were approved by the state authority. Male C57BL/6 mice (starting weight 25–30 g; breeder: TVA University of Düsseldorf) were used and maintained under standard laboratory conditions with free access to food and water. A 12-h light/dark photo cycle was imposed (lights on at 07:00 a.m.) and behavioural testing was done between 09:00 a.m. and 07:00 p.m. Transcranial cryogenic lesions to the barrel-cortex were produced with a modification of the method described by Hermann et al. [7]. In brief, the mice were anesthetized with chloralhydrate (40 mg/100 g body-weight; i.p.) and the skin overlying the parietal cortex was cut along the midline over a distance of 3–4 mm with a small scalpel. A 1.0 mm in diameter copper cylinder cooled with liquid nitrogen was placed for 30 s on the exposed calvarium above the somatosensory cortex of one (50% left side; 50% right-side lesion) or of both hemispheres (bilateral lesion). Uni- and bilateral sham lesions were performed as above, except that the copper cylinder was not cooled. After surgery, the wound was closed with histoacryl tissue glue. The number of ani-

mals in the different treatment groups ranged from seven to nine.

2.2. Apparatus and behavioural procedure

Behavioural testing was conducted in a circular open field (83 cm in diameter) with white walls (45 cm high). The testing device was set up in a sound-protected experimental chamber dimly lit by a 25 W bulb. A noise generator provided masking noise (68 dB). The behaviour of the animals throughout the experiment was recorded by a video system. Open field tests were performed on the first, third, fifth and seventh day after surgery. On each postoperative day, the mice were placed in the open field for 10 min during which the following behavioural parameters were scored: frequency of *scanning* (wall-contacts with the left or the right vibrissae while traversing the edge of the open field), frequency of *rearing* (partial or total rising onto hind limbs) and duration of *locomotion* (forward and backward movements using all limbs).

2.3. Histology and data analysis

After termination of the behavioural tests, animals were deeply anaesthetized with diethylether for perfusion and subsequent histological survey regarding the lesion site. In agreement with previous studies using the same cortical le-

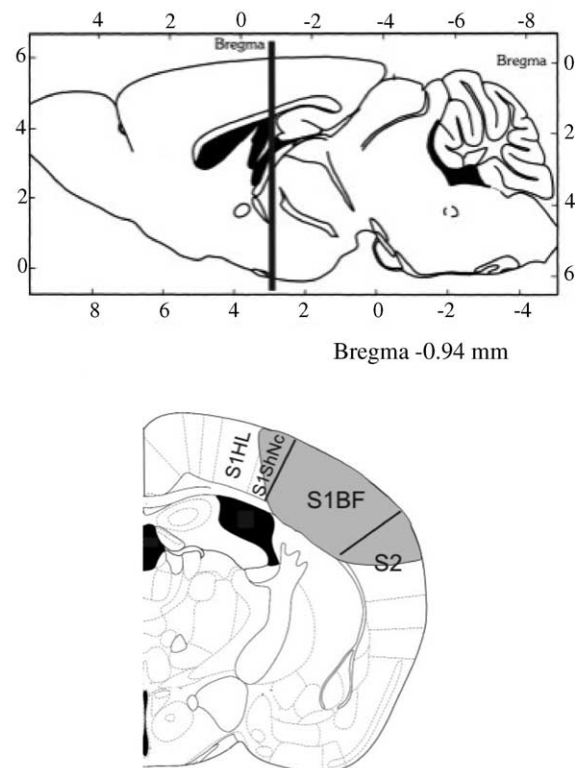


Fig. 1. Localization and extent of the freeze lesion in adult mouse somatosensory cortex (modified after [14]).

sion model [7], freeze-lesioned animals revealed a sharply demarcated cortical lesion in the barrel field of the primary somatosensory cortex (S1BF; Fig. 1) and neighbouring cortical areas as the shoulder/neck representation in S1 (S1ShNc) and secondary somatosensory cortex (S2). There was no evidence for systematic between-group differences with regard to the site and the extent of the lesion. The behavioural data were analysed within and between groups using the Wilcoxon test or the Mann–Whitney *U*-test, where applicable.

3. Results

Animals, which had received a bi- or unilateral sham-lesion to the barrel-cortex, did not show substantial asymmetries in thigmotactic scanning in the course of postoperative behavioural testing (Fig. 2A, C and E). A bilateral cortical

lesion caused an increase in wall scanning with both sides of the face on the first day of testing (P -values <0.05), while the scores did not differ from the respective sham-lesioned controls on the subsequent days (Fig. 2B). Both groups of mice with a unilateral cortical lesion showed more contralateral thigmotaxis, that is, more scanning of the wall with the vibrissae represented in the damaged barrel-cortex. Animals with a lesion to the left barrel-cortex showed more scanning with the right than with the left vibrissae on days 1, 3 and 5 post-lesion (P -values <0.05), while thereafter scanning recovered to symmetry (Fig. 2D). A similar behavioural pattern was observed for the group of mice with a lesion to the right barrel-cortex (Fig. 2F). These animals showed more scanning with the left than with the right side of the face, especially during the initial period of postoperative testing (days 1 and 3; P -values <0.05). However, compared with left side lesioned animals, the contralateral asymmetry in thigmotactic scanning was less prominent and showed faster recovery reaching

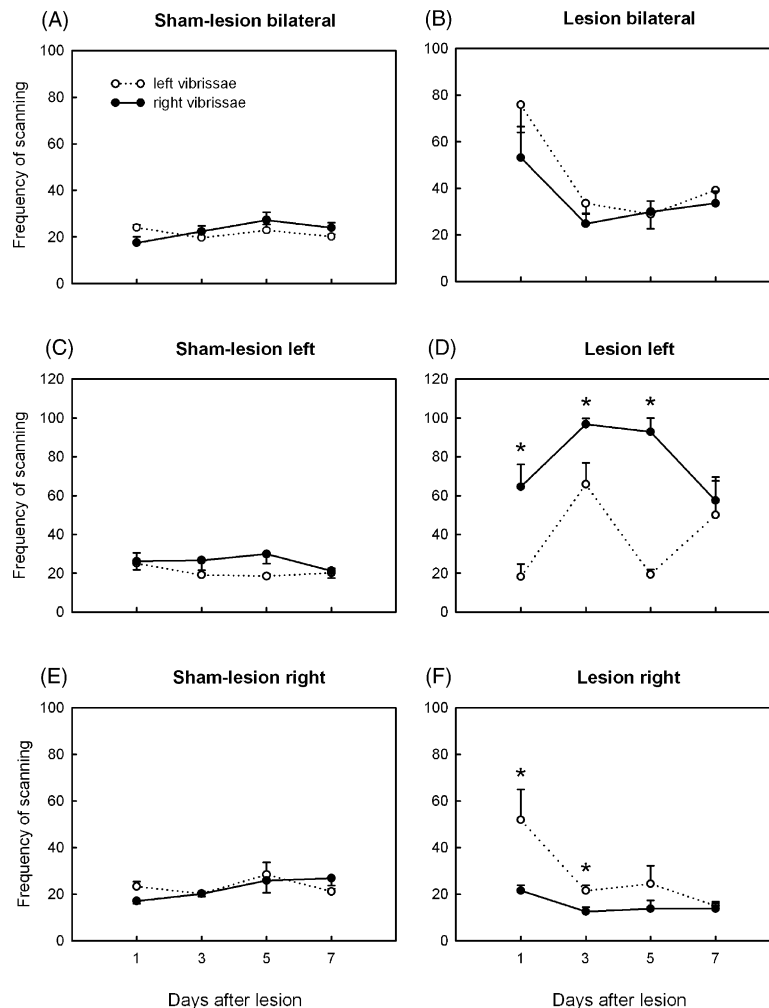


Fig. 2. Mean (\pm S.E.M.) frequency of thigmotactic scanning with the left and right vibrissae for mice, which had received a bi- (B) or unilateral cryogenic lesion (D, F) to the posteromedial barrel subfield of the primary somatosensory cortex. Control groups included animals with a bi- (A) or unilateral sham-lesion (C, E). Asterisks indicate significant within-group differences ($P < 0.05$) in the amount of wall scanning with the left and right side of the face during the 10 min test sessions in the open field, which were performed on days 1, 3, 5, and 7 after the (sham-) lesion.

symmetry within 5, rather than within 7 days, after the lesion. The levels of locomotion and rearing did not differ between the groups of mice across the testing days. Furthermore, no differences between groups were observed with regard to the rate of habituation to the novelty of the open field defined as a decrease in locomotion and rearing from day 1 to 3 of postoperative testing (P -values >0.10 ; data not shown).

4. Discussion

In the present study, a unilateral focal lesion to the barrel-cortex produced a time-dependent asymmetry in thigmotactic scanning in adult C57BL/6 mice. The time course of the behavioural asymmetry was similar to that previously observed in rats recovering from a unilateral damage to the cortical barrel fields [1]. In both species, the cortical lesion induced an acute asymmetry with a recovery to behavioural symmetry within 1 week after the intervention. However, during the acute phase, the mice showed more contralateral thigmotaxis, that is, more scanning of the wall with the vibrissae represented in the damaged barrel-cortex. This finding was unexpected and stands in contrast to our former observations in rats, where a unilateral barrel-cortex lesion resulted in less contra- than ipsilateral wall scanning behaviour [1]. The groups of mice did not differ in the amount of locomotion and rearing. Therefore, the observed differences in thigmotactic scanning cannot be attributed to differences in exploratory activity. Furthermore, no significant differences between groups were evident with regard to the rate of habituation to the novelty of the open field, indicating that the cortical lesions did not interfere with neural processes related to stimulus-orientated habituation ‘learning’.

The results of the present study seem to be at variance with recent studies focusing on the effects of unilateral manipulations of the barrel-cortex on exploration and discriminative behaviour. In these studies, unilateral lesions to the barrel-cortex consistently resulted in behavioural asymmetries with animals neglecting the ‘sensory-deprived’ side contralateral to cortical damage [1,4,8]. Besides factors such as species differences or different behavioural protocols, the following particulars of the present study may be of relevance for this discrepancy: for one, we used cryogenic lesions, whilst in the cited experiments the cortical damage was produced by cerebral contusion, ischemia, or radiofrequency hyperthermia. Secondly, we performed focal lesions centred over the barrel field, whereas most studies in the rat have used extensive lesions to somatosensory cortex to ensure the occurrence of behavioural deficits. The latter aspect might be of special importance because cortical lesions of different size can have seemingly paradoxical effects on behaviour and neurochemistry [13].

The relatively small size of the lesion implies that in the present study, the resulting damage to the somatosensory cortex was ‘subtotal’, leaving a reasonable amount of somatosensory cortical networks intact. Therefore, one might

speculate that the increase in contralateral scanning reflects a behavioural adaptation that serves to compensate for the lesion-induced imbalance between the intact and the partially damaged somatosensory cortex in their capacity to process vibrissal-tactile information. In line with this suggestion, it has recently been shown that the rate of functional recovery following unilateral cortical damage can be enhanced by stroking or by the forced use of the affected whisker pad [8]. However, this interpretation is somewhat questioned by the present data, which also provided evidence for a lateralization of the behavioural effects produced by left versus right barrel-cortex lesions. Damage to both the left and the right barrel field resulted in more contra- than ipsilateral wall scanning. However, in mice with a lesion to the left cortex the observed asymmetry in thigmotaxis was much stronger and persisted for a longer time after the intervention before returning to symmetry. This observation is in keeping with previous studies in rats, which showed innate ‘handedness’ in thigmotactic scanning [17] and demonstrated asymmetrical effects of cortical damage on the performance in different whisker-related tasks [4]. However, the lateralized effects also suggest that the over-expression of contralateral wall scanning was ‘maladaptive’ and actually interfered with the speed of functional recovery from the cortical lesion. Alternatively, because the cryogenic lesion was followed by more contra- than ipsilateral scanning, it is feasible that the intervention established a lateralized source of stimulation or irritation of the underlying cortex, leading to more behaviour with its corresponding vibrissae. Empirical support for this assumption comes from electrophysiological studies demonstrating that focal lesions to somatosensory cortex produced an increase of neuronal excitability in perifocal brain regions [12,15]. Such an increased excitability can promote recovery from the lesion by facilitating receptive field reorganization and cortical remapping [24] but may also cause functional disorganization or even epilepsy [12]. A lesion-induced cortical hyperexcitability could explain, for one, why bilateral damage led to a temporary increase in scanning with both sides of the face and, secondly, why mice with a unilateral lesion showed more scanning with the affected vibrissae compared with respective sham-lesioned controls. Interestingly, unilateral mechanical stimulation of the barrel-cortex by skull trephination also led to asymmetries in thigmotactic scanning [2], which were quite similar to those seen in the present study following unilateral cryogenic lesions.

Finally, another aspect should be pointed out. There is evidence that behavioural asymmetries in vibrissae-related tasks are closely related to brain monoamine systems. The effect of cortical lesions on both the dopaminergic [1] and noradrenergic [16] systems varies with laterality. In addition, the importance of noradrenergic neurotransmission in the extent of behavioural deficits seen after cortical damage is well-documented [5], whilst the dopaminergic nigro-striatal pathway is known to be closely related to vibrissal use and function [10]. With regard to these findings, it is

imperative to further characterize the present mouse model neurochemically, focusing on monoaminergic mechanisms. Furthermore, the above mentioned perilesional neuronal hyperexcitability observed after focal cortical damage may also be associated with a downregulation of GABA receptor subunits [15]. Thus, future studies with drugs influencing GABA as well as glutamate transmission or experiments with genetic mouse models of cortical hyperexcitability could be instrumental in elucidating the cascade of events triggered by the cortical lesion leading to the observed behavioural asymmetries and recovery.

In summary, the present data demonstrate that focal freeze lesions in the barrel-cortex can induce profound behavioural changes in the mouse. Most striking was the over-expression of thigmotactic scanning contralateral to the side of the cortical damage, which might be related to (a) a lesion-induced increase in neuronal excitability within the affected barrel field, leading to more behaviour with its corresponding vibrissae or (b) increased scanning with the affected vibrissae to compensate for diminished input as a result of sensory neglect. Furthermore, the freeze-lesion model of cortical dysfunction used in the present experiment might be useful for the assessment of behavioural, functional, and structural consequences of barrel-cortex manipulations in genetically modified mice.

Acknowledgements

This work was supported by DFG grant GRK 320/2.

References

- [1] Adams FS, Schön H, Schwarting RK, Huston JP. Behavioral and neurochemical indices of barrel cortex-basal ganglia interaction. *Brain Res* 1992;597:114–23.
- [2] Adams FS, Schwarting RK, Huston JP. Behavioral and neurochemical asymmetries following unilateral trephination of the rat skull: is this control operation always appropriate? *Physiol Behav* 1994;55:947–52.
- [3] Diamond ME, Armstrong-James M, Ebner FF. Experience-dependent plasticity in adult rat barrel cortex. *Proc Natl Acad Sci USA* 1993;90:2082–6.
- [4] Dunn-Meynell AA, Levin BE. Lateralized effect of unilateral somatosensory cortex contusion on behavior and cortical reorganization. *Brain Res* 1995;675:143–56.
- [5] Feeney DM, Westerberg VS. Norepinephrine and brain damage: alpha noradrenergic pharmacology alters functional recovery after cortical trauma. *Can J Psychol* 1990;44:233–52.
- [6] Fox K. Anatomical pathways and molecular mechanisms for plasticity in the barrel cortex. *Neuroscience* 2002;111:799–814.
- [7] Hermann DM, Mies G, Hossmann KA. Effects of a traumatic neocortical lesion on cerebral metabolism and gene expression of rats. *Neuroreport* 1998;9:1917–21.
- [8] Hoffman JR, Greenberg JH, Furuya D, Craik RL, Fanelli P, Breslow S, et al. Rats recovering from unilateral barrel-cortex ischemia are capable of completing a whisker-dependent task using only their affected whiskers. *Brain Res* 2003;965:91–9.
- [9] Hurwitz BE, Dietrich WD, McCabe PM, Watson BD, Ginsberg MD, Schneiderman N. Sensory-motor deficit and recovery from thrombotic infarction of the vibrissal barrel-field cortex. *Brain Res* 1990;512:210–20.
- [10] Huston JP, Steiner H, Weiler HT, Morgan S, Schwarting RK. The basal ganglia-orofacial system: studies on neurobehavioral plasticity and sensory-motor tuning. *Neurosci Biobehav Rev* 1990;14:433–46.
- [11] Luhmann HJ, Raabe K, Qü M, Zilles K. Characterization of neuronal migration disorders in neocortical structures: extracellular in vitro recordings. *Eur J Neurosci* 1998;10:3085–94.
- [12] Mittmann T, Luhmann HJ, Schmidt-Kastner R, Eysel UT, Weigel H, Heinemann U. Lesion-induced transient suppression of inhibitory function in rat neocortex in vitro. *Neuroscience* 1994;60:891–906.
- [13] Moran TH, Kubos KL, Sanberg PR, Robinson RG. Marked behavioural and biochemical sensitivity to lesion size in the posterior cortex of the rat. *Life Sci* 1984;35:1337–42.
- [14] Paxinos G, Franklin KB. *The mouse brain in stereotaxic coordinates*. San Diego: Academic Press; 2001.
- [15] Qü M, Mittmann T, Luhmann HJ, Schleicher A, Zilles K. Long-term changes of ionotropic glutamate and GABA receptors after unilateral permanent focal cerebral ischemia in the mouse brain. *Neuroscience* 1998;85:29–43.
- [16] Robinson RG. Differential behavioral and biochemical effects of right and left hemispheric cerebral infarction in the rat. *Science* 1979;205:707–10.
- [17] Schwarting RK, Steiner H, Huston JP. Asymmetries in thigmotactic scanning: evidence for a role of dopaminergic mechanisms. *Psychopharmacology* 1991;103:19–27.
- [18] Simons DJ, Land PW. Early experience of tactile stimulation influences organization of somatic sensory cortex. *Nature* 1987;326:694–7.
- [19] Steiner H, Gerfen CR. Tactile sensory input regulates basal and apomorphine-induced immediate-early gene expression in rat barrel cortex. *J Comp Neurol* 1994;344:297–304.
- [20] Vincent SB. The function of vibrissae in the behavior of the white rat. *Behav Monogr* 1912;1:1–82.
- [21] Weiler HT, Steiner H, Huston JP. Plasticity in crossed and uncrossed tuberomammillary-striatal projections in relation to recovery from behavioral asymmetries induced by hemivibrissotomy. *Neuroscience* 1990;37:463–9.
- [22] Welker E, Hoogland PV, Van der Loos H. Organization of feedback and feedforward projections of the barrel cortex: a PHA-L study in the mouse. *Exp Brain Res* 1988;73:411–35.
- [23] Wilson RC, Vacek T, Lanier DL, Dewsbury DA. Open-field behavior in muroid rodents. *Behav Biol* 1976;17:495–506.
- [24] Witte OW. Lesion-induced plasticity as a potential mechanism for recovery and rehabilitative training. *Curr Opin Neurol* 1998;11:655–62.
- [25] Woolsey TA, Van der Loos H. The structural organization of layer IV in the somatosensory region (SI) of mouse cerebral cortex. The description of a cortical field composed of discrete cytoarchitectonic units. *Brain Res* 1970;17:205–42.