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Social experience modulates ocular dominance plasticity differentially in adult male and female mice

Jenny Balog [a], Ulrike Matthies [a], Lisa Naumann [a], Mareike Voget [b], Christine Winter [b], Konrad Lehmann [a,*]

[a] Institut für Allgemeine Zoologie & Tierphysiologie, Friedrich Schiller-Universität Jena, Germany
[b] Department of Psychiatry, Technical University Dresden, 01062 Dresden, Germany

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ABSTRACT

Environmental factors have long been known to regulate brain plasticity. We investigated the potential influence of social experience on ocular dominance plasticity. Fully adult female or male mice were monocularly deprived for four days and kept a) either alone or in pairs of the same sex and b) either in a small cage or a large, featureless arena. While mice kept alone did not show ocular dominance plasticity, no matter whether in a cage or in an arena, paired female mice in both environmental conditions displayed a shift of ocular dominance towards the open eye. Paired male mice, in contrast, showed no plasticity in the cage, but a very strong ocular dominance shift in the arena. This effect was not due to increased locomotion, since the covered distance was similar in single and paired male mice in the arena, and furnishing cages with a running wheel did not enable ocular dominance plasticity in cage-housed mice. Confirming recent results in rats, the plasticity-enhancing effect of the social environment was shown to be mediated by serotonin. Our results demonstrate that social experience has a strong effect on cortical plasticity that is sex-dependent. This has potential consequences both for animal research and for human education and rehabilitation.

Introduction

All mammals are social animals. Social interaction is vital for their well-being and optimal neural functioning (Hendrichs, 1978; Liu et al., 2012), and social experience modulates cortex-dependent learning (Goeckner et al., 1973; Sterlemann et al., 2010). Social rearing of mice is sufficient to protect the prefrontal cortex to the same degree as an enriched environment from the detrimental effects of isolated rearing (Makinodan et al., 2012). Most recently, it was shown that colony housing of inbred mice in an enriched environment leads to increasing interindividual variability in hippocampal neurogenesis, which is correlated with exploratory behaviour (Freund et al., 2013). In the classical paradigm of cortical plasticity, i.e. the shift of ocular dominance after monocular deprivation (Gordon and Stryker, 1996; Wiesel and Hubel, 1963), however, an effect of social environment has as yet not been described, and even rather been discarded in rats (Baroncelli et al., 2012).

Ocular dominance plasticity in mice peaks during a critical period between postnatal days (PD) 22 and 35 (Gordon and Stryker, 1996), but can still be found during adolescence (Sawtell et al., 2003; Tagawa et al., 2005), until it ceases in adulthood, i.e. after PD 100 (Lehmann and Löwel, 2008). Beyond that age, we were unable to elicit a shift in ocular dominance even with prolonged periods, i.e. 14 days, of monocular deprivation. However, a variety of influences have been discovered in recent years that reinstate ocular dominance plasticity in adult animals: a period of dark exposure (Duffy and Mitchell, 2013; He et al., 2006, 2007), histone deacetylation (Putignano et al., 2007), fluoxetine treatment (Maya Vetencourt et al., 2008) and housing in an enriched environment (Greifzu et al., 2014; Sale et al., 2007). It has, moreover, been shown that environmental influences and fluoxetine treatment converge at an increased serotonergic transmission via the 5HT1A receptor, which in turn results in decreased GABAergic cortical inhibition enabling cortical plasticity (Harauzov et al., 2010; Maya Vetencourt et al., 2011; Sale et al., 2007).

Enriched environments comprise a multitude of different aspects with potentially different effects on neural function (Lehmann et al., 2009): They provide for visual stimulation, social interaction, learning opportunities and increased locomotion. A study in rats recently attempted to disentangle these factors and showed visual stimulation, increased locomotion and visual training to be effective in reinstating ocular dominance plasticity, whereas social experience was without effect (Baroncelli et al., 2012). In a recent study in fully adult mice, we showed that temporally highly coherent visual stimulation, presumably via spike-timing dependent plasticity, could induce critical period-like plasticity even after two days of monocular deprivation (Matthies et al., 2013). In the present study, we revisited the issue of social experience and reduced it to its fundamental function, i.e. the interaction

* Corresponding author at: Institut für Allgemeine Zoologie & Tierphysiologie, Erbertstr. 1, 07743 Jena, Germany. Fax: +49 3641 9 49102.
E-mail address: Konrad.Lehmann@uni-jena.de (K. Lehmann).

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of two individuals. We found a striking effect on ocular dominance plasticity, which was, however, synergistically dependent on spatial conditions.

Materials and methods

Animals and housing conditions

Male and female C57BL/6 mice older than postnatal day (PD) 110 at the start of monocular deprivation (MD) were reared in standard housing conditions, i.e. in sibling groups of the same sex kept in makrolon cages. In order to standardise the animals' previous experience, the animals were separated one week before MD and kept alone in type 2 cages (bottom inside dimension approx 190 mm × 100 mm, 125 mm high). After MD (see below), the animals were randomly assigned to the following two-by-two paradigm of experimental conditions for six hours per day: First, in the Single vs. Paired condition, mice were either kept alone throughout the deprivation period, or paired with a brother or sister, respectively. In this case, one mouse in each pair was shaved on a small spot on the back for distinguishing purposes; Second, in the Cage vs. Arena condition, they were either kept in a type 3 makrolon cage (210 mm × 160 mm × 125 mm) or an open field arena with a side length of 72 cm. After six hours, the animals were put back into their single cages. In the paired conditions, both animals were monocularly deprived. Control animals were treated identically.

Throughout the experiments, food and water were provided *ad libitum*. All experimental procedures have been performed according to the German Law on the Protection of Animals and the corresponding European Communities Council Directive of November 24, 1986 (86/609/EEC), and were approved by the Thüringer Landesamt für Lebensmittelsicherheit und Verbraucherschutz (Thuringia State Office for Food Safety and Consumer Protection) under the registration number 02-027/11.

Monocular deprivation

For probing visual cortical plasticity, we monocularly deprived mice according to published protocols (Gordon and Stryker, 1996; Lehmann et al., 2012). In all cases, the right eyes were sutured shut. Animals were checked daily to make sure that the eyes remained closed; animals in which the eye was not completely closed were excluded from the experiments.

Optical imaging

Using the imaging method of temporally encoded maps (Kalatsky and Stryker, 2003), visual cortical responses in the left hemisphere were recorded as described previously (Lehmann and Löwel, 2008; Lehmann et al., 2012; Yeritsyan et al., 2012) under halothane (1% in 1:1 O_2/N_2O) anaesthesia, supplemented by chlorprothixene (0.2 mg/mouse, i.m.), atropine (0.3 mg/mouse, s.c.) and dexamethasone (0.2 mg/mouse, s.c.). With a 135 mm × 50 mm tandem lens configuration (Nikon, Inc., Melville, NY), we recorded optical images of intrinsic signals in a cortical area of 4.6 × 4.6 mm^2 at a wavelength of 610 ± 3 nm.

Horizontal drifting bars (2° wide), spaced 80° apart, were presented at a temporal frequency of 0.125Hz in the binocular visual field of the recorded left hemisphere (- 5° to + 15° azimuth) in front of the animal. Visual stimuli were presented alternately to the left and right eye. Ocular dominance indices (ODIs) were calculated as described previously (Cang et al., 2005; Lehmann and Löwel, 2008). Briefly, activity maps were thresholded at 30% of peak amplitude, and OD was calculated for each pixel in the binocularly responsive region as (contra-ipsi)/(contra + ipsi), and averaged across all selected pixels. At least three ODIs per animal were obtained and averaged; experiments with less than three ODIs were discarded.

Locomotor tracking

To assess locomotor activity in male mice, a video camera was set up to record the first hour in the arena. The movie was binned at 4 frames/second, and out of each quarter of an hour of recorded time, the first five minutes were clipped and used for quantification. Thus, twenty minutes were evaluated for each single and paired mouse in the arena. Freeware software for automated tracking (Tracker, Open Source Physics) was used to determine the position of the mice in each frame, and covered distance was thus calculated.

Behavioural analysis

Using the same recording setup, we quantified the behaviour of paired male animals during four five-minute-intervals in one hour after half-time in the condition. To this end, we defined an ethogramme based on a published template (Olsson and Sherwin, 2006). The following behaviours were defined and their frequency and duration quantified:

Non-social behaviours
- Locomotion – movements that result in a change of position
- Exploration – frequent rearing or active sniffing during locomotion
- Food intake – nibbling on food pellets or drinking

Social behaviours
- Huddling – peaceful body contact while lying
- Attack – jumping at or chasing the other mouse, biting, kicking, wrestling
- Flight – avoidance of contact, direct withdrawal from the other mouse
- Head sniff – sniffing directed to the head (mostly nose) of the other mouse
- Anal sniff – sniffing directed to the anus of the other mouse
- Social grooming – licking and nibbling the other mouse at different areas of the body

Post-mortem HPLC

Additional sets of male Single and Paired Arena animals were used for this experiment. The mice were monocularly deprived and exposed to the social conditions as described above. After optical imaging, the scalp was sutured and the animals were allowed to re-awake. The following day, they were again transferred to their respective condition. After six hours, the animals were killed by cervical dislocation, the brains were quickly dissected and frozen immediately at −40 °C.

Neurotransmitter contents were measured using high performance liquid chromatography (HPLC). Micropunches were taken from 1 mm V1 slices at −3.28 from Bregma and homogenized by ultrasonication in 20 vol of 0.1 N perchloric acid at 4 °C immediately after collection. A total of 100 ml of the homogenate was added to equal volumes of 1 N sodium hydroxide for measurement of protein content. The remaining homogenate was centrifuged at 17 000 g and 4 °C for 10 min. Supernatants were used for immediate measurement of 5HT and its metabolite 5HIAA via HPLC with electrochemical detection as previously described (Enard et al., 2009; Giovanoli et al., 2013; Winter et al., 2009). Briefly, the perchloric acid extracts were seperated on a column (Prontosil 120-3-C18-SH; length 150 mm, inner diameter 3 mm; Bischoff Analysentechnik und -geräte GmbH, Leonberg, Germany) at a flow rate of 0.55 ml/min. The mobile phase consisted of 80 mM sodium dihydrogene phosphate, 0.85 mM octane-1-sulfonic acid sodium salt, 0.5 mM ethylenediaminetetraacetic acid disodium salt, 0.92 mM phosphoric acid and 4% 2-propanol (all chemicals Merck KGaA, Darmstadt, Germany). Monoamines were detected using an electrochemical detector (41 000, Chromsystems Instruments & Chemicals GmbH, Munich, Germany) at an electrode potential of 0.8 V. For calibration, 0.1 M perchloric acid containing 0.1 mM 5HIAA and 5HT was

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