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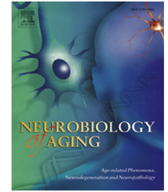

Environmental enrichment preserved lifelong ocular dominance plasticity, but did not improve visual abilities

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ABSTRACT

In standard cage (SC)-raised mice, ocular dominance (OD) plasticity of the primary visual cortex (V1) induced by monocular deprivation (MD) is maximal in juveniles, declines in adults, and is absent beyond postnatal day (PD) 110. Raising mice in an enriched environment (EE) preserved a juvenile-like OD plasticity after 7 days of MD until at least PD196, mediated by reductions of deprived eye responses in V1. Whether the sensitive phase for OD plasticity can be prolonged into older age and whether long-term EE modifies visual abilities was not yet known. Here, we demonstrate that EE raising enables lifelong OD plasticity. In contrast to PD200 EE-mice, the preserved OD shift in both >PD400 and >PD700 EE-mice was mediated by increases in open eye responses in V1 (adult OD plasticity). When SC-mice were transferred to EE after PD110, OD plasticity was restored until PD922. Moreover, visual abilities tested by both optomotry and the visual water task and interindividual variability were not different between PD700 SC- and EE-mice. Taken together, EE raising enabled a lifelong OD plasticity but did not affect basic visual performance.

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1. Introduction

Neuronal plasticity describes the ability of the brain to modify its circuitry in response to changing behaviors and environments. This ability to adapt is especially crucial for learning, memory, and recovery from brain injuries. Early in life, neuronal plasticity is high but declines during aging. A well-studied model to investigate cortical plasticity is ocular dominance (OD) plasticity in the visual cortex induced by depriving one eye of vision. Neurons in the binocular part of primary visual cortex (V1) receive inputs from both eyes but are dominated by the contralateral eye. Depriving V1 of input from one of the eyes by monocular deprivation (MD) causes a shift in the OD toward the open eye (Dräger, 1978; Wiesel and Hubel, 1963). This kind of plasticity is age dependent in mice raised in standard cages (SCs; Espinosa and Stryker, 2012): during the critical period of mice (PD19–32), 4 days of MD are sufficient to induce an OD shift toward the open eye (Gordon and Stryker, 1996). This juvenile OD shift is predominantly mediated by a decrease in the cortical responses to visual stimulation of the deprived eye. In contrast, in 2–3 month-old SC-raised mice, significant OD shifts need 7 days of MD and are primarily mediated by increased open eye responses in V1 (adult OD plasticity), while reductions of deprived eye responses are no longer observed (Heimel et al., 2007; Hofer et al., 2006; Sato and Stryker, 2008; Sawtell et al., 2003). Using optical imaging of intrinsic signals, OD plasticity after 7 days of MD is absent in SC-mice beyond PD110 (Lehmann and Löwel, 2008).

In contrast to SCs, an enriched environment (EE) provides increased physical (running wheels), social (bigger housing groups), and cognitive (regularly changed labyrinths or toys) stimulation (Rosenzweig et al., 1962). Housing rodents in EE cages has been shown to enhance plasticity of the visual cortex (Baroncelli et al., 2010, 2012; Sale et al., 2007b; Scali et al., 2012), to speed up visual system development (Cancedda et al., 2004; Landi et al., 2007b; Sale et al., 2007a) and elicit remarkable changes in the brain, ranging from molecular to anatomic and functional levels [for a review see Sale et al. (2014)]: increased levels of brain-derived neurotrophic factor (Cancedda et al., 2004; Falkenberg et al., 1992; Ickes et al., 2000; Sale et al., 2004), serotonin (Baroncelli et al., 2010) and insulin-like growth factor I (Sale et al., 2007a) reduced extracellular GABA (Baroncelli et al., 2010; Sale et al., 2007b) and local inhibition in V1 (Greifzu et al., 2014). EE raising

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is also able to restore already lost plasticity in rats (Baroncelli et al., 2010, 2012; Sale et al., 2007b) and mice (Greifzu et al., 2014).

When we raised C57BL/6J mice in an EE, OD plasticity after 7 days of MD was not only preserved up to PD196 (oldest animal tested) but also OD shifts in these EE-mice were mediated by reductions in deprived eye responses in V1. These reductions are a hallmark of juvenile OD plasticity, and in SC-mice not observed beyond the critical period. Thus, adult (PD200) enriched mice displayed juvenile-like OD plasticity (Greifzu et al., 2014).

Whether the sensitive phase for OD plasticity can be prolonged into even older age and whether long-term EE modifies visual abilities was not yet known. We, therefore, raised mice in EE cages until they were beyond 2 year old and then tested for OD plasticity with intrinsic signal optical imaging (Kalatsky and Stryker, 2003). We observed that OD plasticity was present lifelong in EE-mice, both in animals raised in EE from birth as well as in mice transferred from SCs to EE at PD110. The oldest mouse in our study was already 922 days old and still displayed an OD shift. Notably, the observed adult OD shifts in the old EE-mice (PD402-PD809) were mediated by increases in open eye responses in V1.

There is also a debate in the field whether enriched raising conditions affect sensory performance and interindividual variability (Bayne and Würbel, 2014). We, therefore, used 2 different vision tests in both SC- and EE-mice of about PD700. First, the visual water task, a cortex-dependent visual discrimination paradigm, to measure visual acuity and orientation discrimination (Prusky et al., 2000b). Second, the virtual-reality optomotry setup (Prusky et al., 2004) to measure the spatial frequency threshold ("visual acuity") and the contrast threshold ("contrast sensitivity") of the optomotor reflex and its experience-induced changes after MD (Prusky et al., 2006). We did neither find evidence for increased visual abilities of enriched mice nor for an increased interindividual variability. Taken together, EE preserved lifelong OD plasticity in mouse V1 but did not affect basic visual abilities.

2. Materials and methods

2.1. Animals

C57BL/6J mice were obtained from the mouse colony of the central animal facility of the University Medical Center, Göttingen, Germany, and housed in an animal room with a 12-h light/dark cycle, with food and water available ad libitum. All experimental procedures were approved by the local government: Niedersächsisches Landesamt für Verbraucherschutz und Lebensmittelsicherheit.

We used both male and female mice for our study. In the EE >PD400 group, male mice with an age range of PD400–487 were used. The EE >PD700 mice were females and PD730-816. The "late EE-mice" (mice transferred from SC to EE cages at PD110, details in the following) were females and PD847–922. All mice that were analyzed with optical imaging were measured in the optomotor setup before. For the visual water task measurements, we used male SC-mice (PD690) and female EE-mice (PD687). We had to use female mice for the oldest EE groups because male mice in the EE cages tend to fight a lot, especially when they grow older. Moreover, for the late EE group, we had to transfer mice from different SCs to EE to obtain a sufficiently large number of animals for the social enrichment. Because adult male mice from different cages would seriously fight if put together, we had to use female mice for that group. We had already addressed the issue of different sexes in a previous study and observed that the prolonged sensitive phase for OD plasticity in the EE-mice was due to the EE rearing and not caused by a sex difference of the experimental animals (Greifzu et al., 2014).

2.2. Housing conditions

2.2.1. Standard cages

Our SCs were 26 × 20 × 14 cm large, and we housed 3–5 animals of the same litter and sex together. The cages were translucent with an open grid cover and wood chip bedding.

2.2.2. Enriched environment

To raise EE-mice, pregnant dams were put into commercially available EE cages (Marlau; Fares et al., 2012; Greifzu et al., 2014) about 1 week (3–7 days) before delivery. Females and males were separated at PD30. Mice were housed in groups of 9–15 animals. For the late EE paradigm, mice were raised in an SC and transferred to EE at PD110. The EE cages (56 × 37 × 32 cm) are about 9 times larger than our SCs, with 2 floors linked by a ladder for going up and a tube for sliding down. They are equipped with 3 running wheels and a red tunnel to protect the animals from light. The mice had to pass through the maze in the upper compartment to get both food and water positioned in the lower compartment. The maze was changed 3 times a week, and there were in total 12 different configurations.

2.3. Monocular deprivation

The right eye was deprived for 7 days according to published protocols (Cang et al., 2005; Gordon and Stryker, 1996; Lehmann and Löwel, 2008). Animals were checked daily to make sure that the eyes remained closed.

2.4. Visual water task

To measure perceptual thresholds, we used the visual water task, a visual discrimination task based on reinforcement learning (Prusky and Douglas, 2004; Prusky et al., 2000b).

For measuring visual acuity, animals are initially trained to distinguish a low spatial frequency grating (0.086 cyc/deg) from equiluminant gray and then their ability to recognize higher spatial frequencies is tested. The apparatus consists of a trapezoidal-shaped pool with 2 monitors placed side by side at one end. A midline divider is extended from the wide end into the pool, creating a maze with a stem and 2 arms. An escape platform that is invisible to the animals is placed below the monitor, where the grating is projected. The position of the grating and the platform is alternated in a pseudorandom sequence over the training and test trials. When 90% accuracy is achieved 3 times (training phase), the testing phase starts: an individual's visual acuity threshold is determined by increasing the spatial frequency of the grating until performance falls below 70% accuracy. The highest spatial frequency at which 70% accuracy is achieved is taken as the maximum visual acuity. To measure visual acuity, both SC- (PD690) and EE-raised mice (PD689, at last day of measurements) were trained and tested in the visual water task.

As a second parameter, we determined the animals' orientation discrimination, using the visual water task. To this end, mice were trained to distinguish between horizontal and vertical square wave gratings of a low spatial frequency (0.086 cyc/deg, training phase). Once 90% accuracy was achieved, the test phase was started. To test the orientation discrimination ability of each mouse, the orientation difference of the 2 gratings was reduced stepwise by 5° until performance fell below 70% accuracy. The smallest orientation difference at which 70% accuracy was achieved was taken as the minimum orientation discrimination.

2.5. Virtual-reality optomotor setup

Both the spatial frequency and the contrast thresholds of the optomotor reflex of all mice (animals with and without MD) were

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