e-Neuroforum 2012 · 3:41–48
DOI 10.1007/s13295-012-0030-0

Franziska Greifzu[1] · Fred Wolf[2] · Siegrid Löwel[1]

[1] Systems Neuroscience, Johann-Friedrich-Blumenbach-Institut für Zoologie und Anthropologie, Bernstein Fokus Neurotechnologie, Georg-August-Universität Göttingen, Göttingen

[2] Theoretische Neurophysik, Max-Planck-Institut für Dynamik und Selbstorganisation, Göttingen

Network influences on cortical plasticity

The flexible brain

In the Systems Neuroscience Department of Göttingen University and the BMBF-funded consortium *Bernstein Focus Learning,* we investigate the mechanisms of neuronal plasticity in the mammalian cortex, particularly in the adult brain, i.e., after the periods of pronounced plasticity in early postnatal development, in the aging brain, and after diseases or lesions of the nervous system. We use the mouse visual system as a model since it offers the possibility to compare normal and genetically modified animals, thus allowing us to additionally gain entirely new insights into cellular and molecular mechanisms of neuronal plasticity.

The mouse visual system is in many ways similar to the human visual system: information about visual stimuli is encoded in the multilayered retina and then transmitted as action potential patterns in the optic nerve to the lateral geniculate nucleus in the thalamus, and from there to the primary visual cortex (V1) (**Fig. 1a**). In this pathway, projections from the nasal part of the retina cross to the other hemisphere in the optic chiasm, whereas fibers from the temporal part of the retina do not cross. As a result, information from the right visual field of both eyes arrives at the left hemisphere and vice versa. Neighborhood relations are preserved all along this pathway, i.e., adjacent stimuli in the visual field activate adjacent neurons in V1. This kind of ordered topographic representation of the peripheral receptor surface is called retinotopy.

Ocular dominance plasticity and its measurement

V1 is divided into a monocular (Greek *monos* for "one" and Latin *oculus* for "eye") and a binocular ("both eyes") part. Monocular nerve cells are only activated by stimulation of one eye, binocular cells by stimulation of both eyes. The classical experiments by Wiesel and Hubel have shown that early experience has a massive influence on the structure and function of nerve cell networks in the visual cortex [1]. Depriving animals of normal binocular visual experience by closing one eye [monocular deprivation (MD), an experimental model of a cataract] during an early phase of postnatal development caused irreversible modifications in the nerve cell networks of the visual

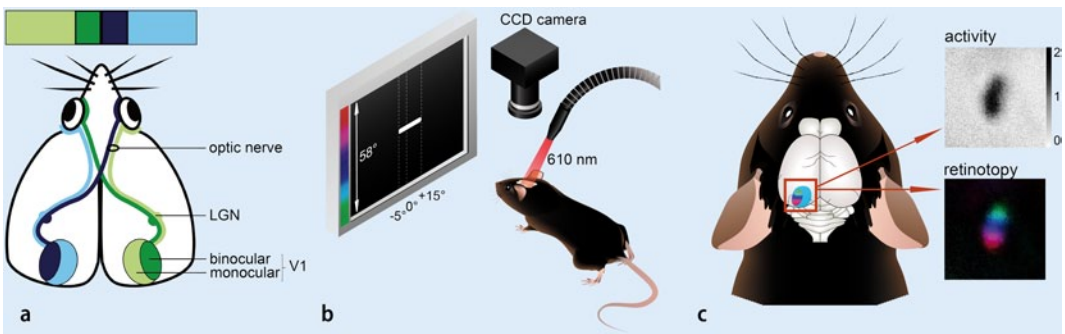

Fig. 1 ▲ Visualization of neuronal plasticity. **a** Visual pathways of a C57Bl/6J mouse. *LGN* lateral geniculate nucleus. **b** Minimally invasive optical imaging of neuronal activity. The brain of the mouse is illuminated with red light (610 nm). At this wavelength, the reflection difference between active and inactive brain tissue is particularly high. The visual stimulus consists of a white horizontal bar on a black background moving upwards or downwards on a monitor. The stimulus activates the binocular zone of the primary visual cortex (*V1*). The activity changes in V1 are recorded using a light-sensitive CCD camera and are extracted by Fourier analysis [8]. **c** Activity map (*top*) and retinotopic map (*bottom*) of the binocular zone of V1. The *color-coded* retinotopic map represents the neuronal response depending on the spatial position of the stimulus in the visual field

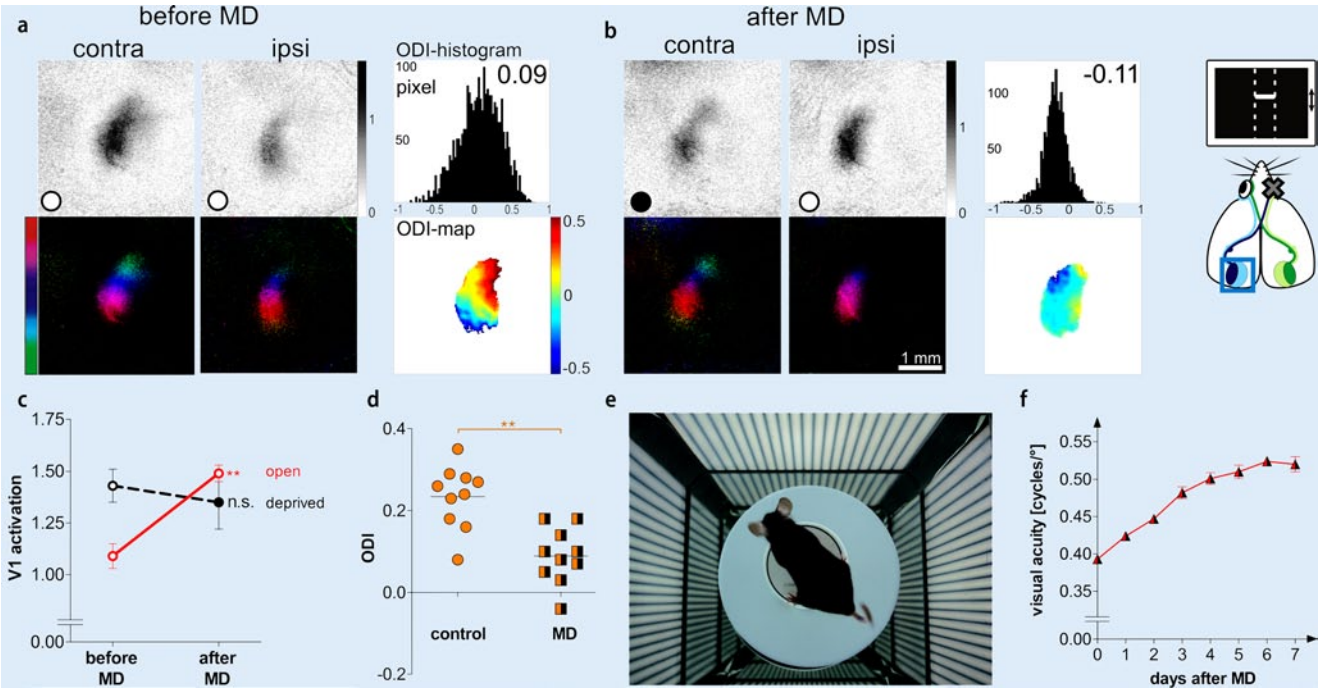

Fig. 2 ▲ Two models of experience-dependent plasticity in the mouse visual system: ocular dominance plasticity (**a–c**) and sensory learning (**e**, **f**) after monocular deprivation (*MD*). **a–c** Activation of the primary visual cortex (*V1*) after stimulation of the contra- or ipsilateral eye before (**a**) and after MD (**b**) and its quantification (**c**) in the same animal. Gray scale-coded activity (*top*) and color-coded retinotopic (*bottom*) maps from the binocular zone of the left visual cortex are shown (**a**, **b**). The magnitude of neuronal activation is displayed as fractional change in reflection $\times 10^4$. Before MD, the activity patch evoked by stimulation of the contralateral eye is darker than after stimulation of the ipsilateral eye, the ocular dominance index (*ODI*) is positive, and the ODI map mainly *yellow red* (*red* represents positive, *blue* negative ODI values), indicating that V1 activity is dominated by the contralateral eye (**a**). After 7 days of MD of the contralateral (*right*) eye, the ocular dominance shifts towards the open (ipsilateral) eye: the open eye now activates V1 much more strongly, the ODI is reduced, and cold colors prevail in the ODI map (**b**, **c**). **d** Changes of ODIs after MD: values decline from positive (contralateral dominance) to values around zero, indicating that both eyes activate V1 almost equally strongly. **e, f** Daily training in the optomotor system (**e**) causes a clear increase of the visual acuity of the open eye after MD (**f**) (**d** and **f** modified from [18])

cortex in these experiments: MD caused neurons that were normally activated by both eyes to react only to stimulation of the open eye; thus their so-called ocular dominance (OD) shifted towards the open eye. This is known as ocular dominance plasticity. Ocular dominance plasticity is the best studied model of neuronal plasticity in the cortex. In contrast to humans, mouse V1 is dominated by input from the contralateral eye and the binocular visual field is only about 30° wide (in humans, approximately 120°) [2]. Closing the "strong" contralateral eye of a mouse also shifts the ocular dominance of binocular neurons in V1 [3], and V1 gets activated almost equally strongly by stimulation of both eyes [4]. Thus mice also show ocular dominance plasticity, and it is precisely this kind of neuronal plasticity we are investigating in detail (we suggest [5] as an up-to-date review).

For a long time, the standard method to measure ocular dominance plasticity was to electrophysiologically record action potentials from single nerve cells in V1 [3, 4, 6]. Although high spatial resolution is achieved using this technique, it requires time-consuming and technically challenging experiments. In contrast, the activity of the visual cortex can be visualized much faster and with an excellent signal-to-noise ratio by using a minimally invasive optical imaging method (optical imaging of intrinsic signals; for examples see [7, 8]), which we have optimized for the analysis of ocular dominance plasticity [9]. To this end, the cortical surface is illuminated with red light: active brain regions absorb more of this red light than inactive ones and can be visualized as dark regions even through the intact skull using a highly light-sensitive CCD camera (**Fig. 1**). One major source of this signal is the higher light absorption of deoxyhemoglobin, which briefly accumulates in active brain tissue due to the increased oxygen consumption [10]. Using optical imaging of intrinsic signals, we can visualize experience-, learning-, and age-dependent changes in brain activity not only in a test series with a deprived and a non-deprived group, but it is also possible to follow activity changes in one and the same animal *in vivo* and over the course of time. A "chronic" experiment of this kind is illustrated in **Fig. 2a–c**: before MD, the activity patch in V1 induced by stimulation of the contralateral eye was darker than the activity patch of the ipsilateral eye, indicating that V1 was dominated by the contralateral eye. After MD, the ocular dominance shifted: in our example, the activity patch of the ipsilateral (non-deprived) eye was now even darker than that of the contralateral eye. To quantify

e-Neuroforum 2012 · 3:41–48
DOI 10.1007/s13295-012-0030-0

Franziska Greifzu · Fred Wolf · Siegrid Löwel

Network influences on cortical plasticity

Abstract
Neuronal plasticity forms the basis of our lifelong ability to learn and adapt to new challenges. Plasticity in adulthood, however, is often limited and learning becomes increasingly laborious. Using a combination of behavioral tests and imaging of brain activity, we investigate in the visual system of mice how learning and plasticity change in the course of aging and after lesions and modify the structure and function of nerve cell networks. We hope that answering these key questions not only helps to understand the rules underlying brain development, functioning, and learning, but will additionally open up new avenues to develop clinically relevant concepts to promote the regeneration and rehabilitation for diseased and injured brains. Our research has revealed clear evidence for a prominent influence of long-ranging neuronal interactions on cortical function and plasticity: they play a major role for the development of functional cortical architecture, and lesions in one cortical area affect function not only in the directly injured region but also in distant regions even on the opposite brain hemisphere.

Keywords
Visual cortex · Aging · Ocular dominance · Stroke · Visual acuity

ocular dominance plasticity we compare how strongly V1 gets activated by stimulation of each eye before and after MD, and calculate an ocular dominance index (ODI, [9]): in healthy C57Bl/6J mice, the ODI decreases from positive values before MD to values close to 0 after MD, corresponding to an equally strong activation of V1 by both eyes. Thus the ocular dominance clearly shifts towards the open eye (**Fig. 2d**).

Sensory learning—the optomotor system

Although the visual system is not the most important sensory system for the survival of mice, they can use their sense of vision to orient themselves in space [11]. It was recently shown that MD in mice followed by daily "training" in a behavioral apparatus, used to measure vision by means of the optomotor response, improved visual abilities in this test [12]: the visual acuity of the open (non-deprived) eye increased by approximately 25%–30% after daily training (**Fig. 2e**, **f**). The increase occurred faster with repeated training epochs and persisted longer if the animals were tested twice daily [12]. This form of "sensory learning" thus showed essential characteristics of classic learning paradigms. In contrast to behavioral tests that are based on positive reinforcement and need extensive training, such as the visual water task [11, 13, 14], the optomotor test does not need any training because it is based on a reflex—the optomotor reflex—in response to a moving stimulus. As long as the mice can see the moving vertical gratings, they will follow them with reflexive head and body movements, which can be observed by an experimenter via a camera in the lid of the apparatus. While mechanically operated, striped cylinders (rotating drums) have been in use for a long time; the specific characteristic of the apparatus developed by Prusky et al. [15] is the virtual cylinder, which is created by four flat screen monitors surrounding the mouse and which can be centered on the eye position of the mouse. Therefore, the spatial frequency of the presented gratings can always be adjusted precisely, even if the mouse is moving. We would like to mention here that the "visual acuity" measured optomotorically does not correspond to the animals' maximal visual acuity. However, the measured values are in a relatively constant relationship with maximal visual acuity, which can be measured for example with visual evoked potentials, optical imaging, or with the visual water task [13, 16, 17], so that they can be taken as a valid measure of the visual ability of mice. While the optomotor reaction is based on a reflex mediated by networks outside the cortex (subcortical), the increase in visual acuity after MD depended on the visual cortex [12].

1x Mouse—2x plasticity

By combining these two analysis techniques—optical imaging of intrinsic signals and the virtual-reality optomotor system to measure visual abilities—one can examine two models of experience- and learning-dependent plasticity in one and the same animal: ocular dominance plasticity as an established model of cortical plasticity and additionally the enhancement of visual acuity of the open eye after MD as a model of sensory learning in a behavioral test.

Do ocular dominance plasticity and sensory learning change with age and after lesions?

Ocular dominance plasticity is age-dependent (**Fig. 3**). In critical period mice, i.e., 19- to 32-day-old animals, ocular dominance plasticity can readily be induced with only 4 days of MD [4, 18]. With increasing age, however, plasticity declines and a longer MD duration (7 days) is necessary to induce ocular dominance plasticity [18, 19, 20]. In addition, the ODI decreased less strongly, indicating a less strong ocular dominance shift compared to younger animals. In mice older than 110 days, ocular dominance plasticity eventually ceased and no shift could be observed [18], not even after 14 days of MD. Which molecular and cellular changes underlie this process and how plasticity in the aging brain can be enhanced are intensely studied questions and also crucial for regeneration after lesions [21, 22, 23].

Sensory learning is age-dependent (**Fig. 4**). Interestingly, sensory learning after MD in mice also exhibited a pronounced age dependency [18, 24]. In 1- to 3-month-old animals, sensory learning was significantly higher than in 4- to 7-month-old mice and declined further until the age of almost 2 years: the increase in visual acuity of the open eye measured optomotorically was reduced by more than half compared to 4- or 7-month-old animals (**Fig. 4a**, **b**). Moreover, the increase in visual acuity became more variable with age in individual animals (**Fig. 4c–f**): at the age of 23 months, i.e., almost 2 years, some mice displayed an increase in visual acuity after MD as high as in younger animals, whereas others only showed little or no increase at all. Thus the interindividual variability of the sensory

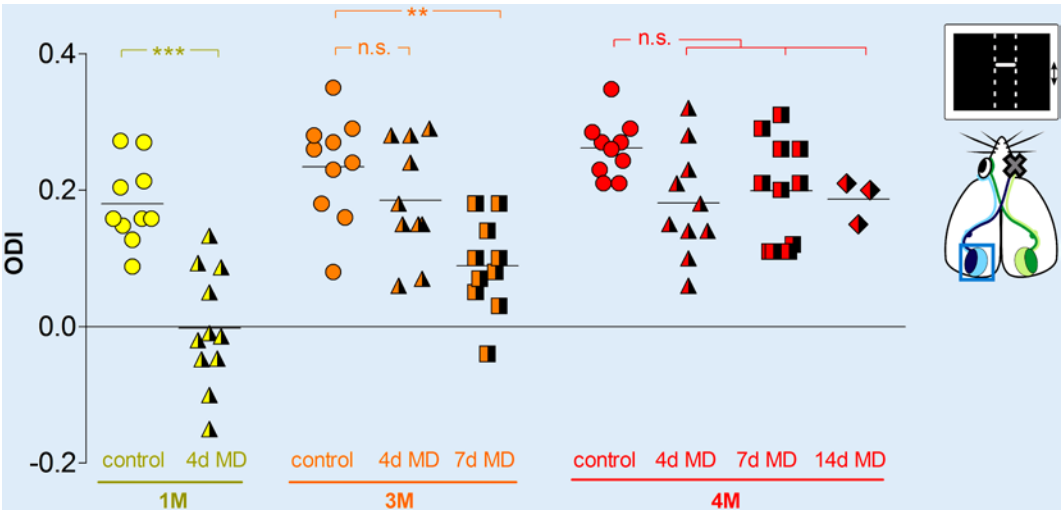

Fig. 3 ▲ Ocular dominance plasticity declines with age. Ocular dominance indices (*ODIs*) of mice of different age groups before (*control*) and after MD are shown. *Symbols* represent ODI values of individual animals, *horizontal bars* mean values. In 1-month-old mice (*1 M*), 4 days of MD (*4d MD*) are sufficient to induce a significant ocular dominance shift, while 7 days of MD are necessary in 3-month-old animals (*3 M*). In animals older than 110 days (*4 M*), ocular dominance plasticity can no longer be induced, not even after 14 days of MD. (Modified from [18])

learning dramatically increased with age. Why this is the case and how one can promote learning during aging is a particularly exciting scientific question.

The increased variability in old mice suggests that the diminishing sensory plasticity is not only due to age-dependent processes, which are similar in all animals, but additionally due to individual conditions and environmental influences. It was recently shown that inflammatory processes are more common in the aging brain [25] and that the learning-induced histone acetylation is impaired [26]. Both processes might be individually different and additionally depend on individual environmental conditions, nutrition, stress, and overall health status.

Stroke impairs both cortical plasticity and sensory learning in distant brain regions

A practical example of the successful combination of the two described plasticity models in the same animal is our recently published study about the influence of stroke on neuronal plasticity [27]. In this study, we managed to show that local stroke can impair even distant brain regions that were not affected in the first place. If the blood supply to the brain is disrupted by a blocked or ruptured blood vessel, oxygen and nutrients are also lacking. Nerve cells in the affected brain area will die and body parts which are controlled by these areas are no longer able to function correctly. Stroke is the third leading cause of death in Germany. However, the majority of individuals who survive stroke suffer persistent damage. Some of this damage can be remedied or at least reduced by appropriate rehabilitation measures. Often, even basic abilities such as walking or speaking need to be relearned.

In our study, we induced stroke in 3-month-old mice in a local area outside V1. We used the photothrombosis technique of Watson et al. as our experimental stroke model [28]. In our case, the lesion was positioned in the primary somatosensory cortex (S1; **Fig. 5**). We then examined plasticity in the visual system of mice *in vivo*. Closing one eye for 7 days in control animals without stroke led to both an increase in visual acuity of the open eye and a shift of ocular dominance towards the open eye (**Fig. 2**). After stroke, this plasticity was totally eliminated (**Fig. 6**): V1 was still dominated by the contralateral (deprived) eye, as prior to MD, and the ODIs did not change. Similarly, visual acuity of the open eye did not increase despite the animals' daily training in the optomotor system. Hence there was neither a significant ocular dominance shift nor sensory learning after stroke.

The lack of improvement in visual acuity was all the more surprising since experiments by Glen Prusky and his colleagues [12] have shown that the hemisphere contralateral to the open eye is needed in order for visual acuity to improve after MD. In our experiments, this hemisphere was opposite the lesion and therefore not damaged initially. What do we learn out of this? Obviously there is nothing like an "intact" hemisphere, since even a small and local brain lesion may impact nerve cell networks in both hemispheres [29].

Likewise, the lost ocular dominance plasticity indicates that long-ranging networks have a prominent influence on neuronal plasticity: apparently, changes in the activity of the major projections from the eyes via the thalamus to the visual cortex are *not* sufficient to induce ocular dominance plasticity, and that the sensitivity of the cortex to changes in afferent input can be modulated. As a result, ocular dominance plasticity cannot be conceptualized solely as a local process, but is rather co-determined by network influences from outside V1 and independent of the major thalamocortical projections. This brings to mind older observations about the influence of the modulatory systems (e.g., cholinergic and noradrenergic) on plasticity in kitten visual cortex [30]. After eliminating modulatory afferents to the cortex,

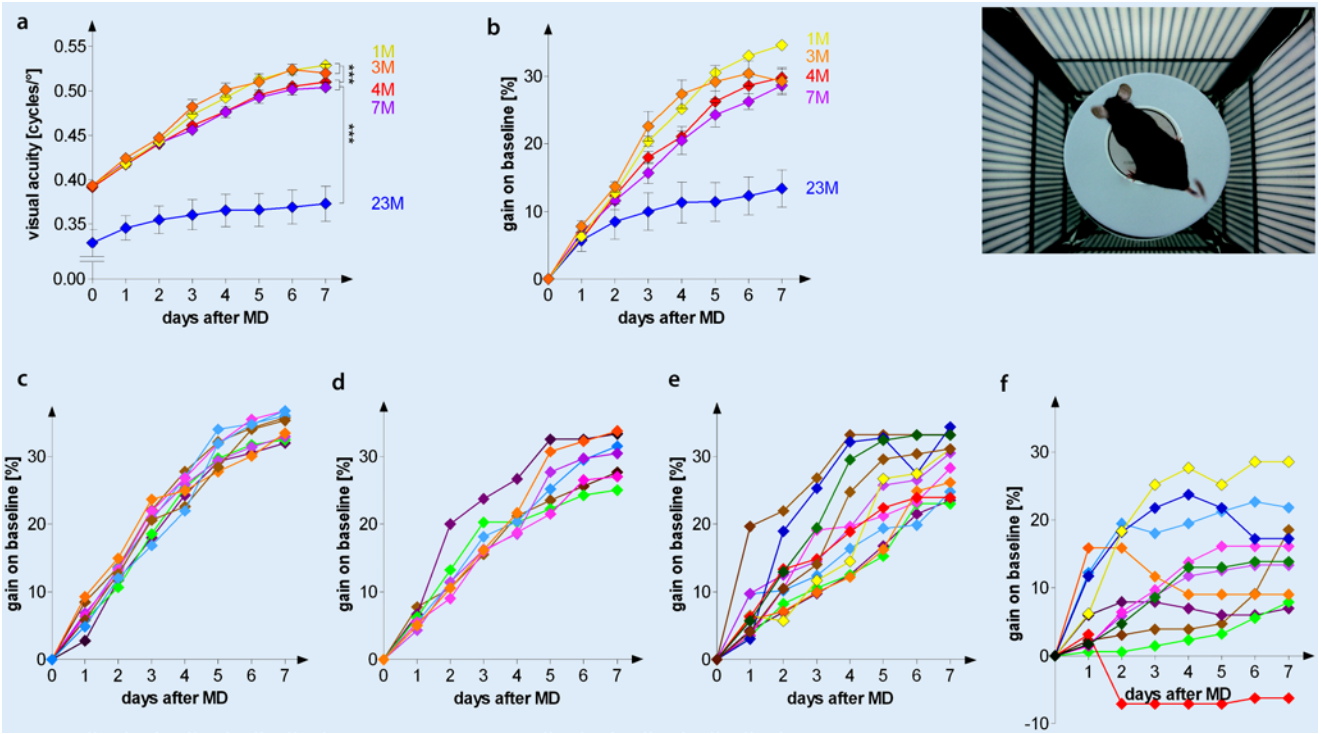

Fig. 4 ▲ Sensory learning declines with age. Mice of different age groups [1, 3, 4, 7, and 23 months (*M*)] were monocularly deprived (*MD*) and tested daily in the virtual-reality optomotor system. Visual acuity (cycles per degree, **a**), or the gain on baseline (in percent) after MD are illustrated (**b–f**).There was a significant increase in visual acuity of the open eye in all age groups analyzed; however, this increase was reduced by more than half in 23-month-old-mice compared to 4- or 7-month-old animals. Most strikingly, the increase of visual acuity varies more with increasing age: some of the *23M* mice show sensory learning comparable to 4-month-old animals, while others show little or no increase at all. (Modified from [18, 24])

MD had almost no effect on the binocular connections in V1: thus ocular dominance plasticity is co-determined by extraretinal factors.

Long-ranging interactions control plasticity processes also in the healthy brain

A number of additional results support our interpretation of an influence of long-ranging networks on neuronal plasticity. For instance, recent experiments in rats show that ocular dominance plasticity was highly dependent on projections between the two hemispheres through the *corpus callosum* (Latin *corpus* for "body") [31]. In this study, predominantly inputs from the ipsilateral eye were routed through the corpus callosum, and these afferents played an important role in the reduction of inputs from the deprived eye during MD. In our stroke experiments, however, callosal inputs from the non-lesioned hemisphere should have remained intact, but nevertheless ocular dominance plasticity was absent. Whether these results imply that callosal connections are less important in mice (compared to rats) is not yet known.

There is also evidence that plasticity processes can be controlled by long-ranging interactions in the brains of larger mammals. In cats and primates, neurons with similar functional properties are not randomly positioned in the cortex, but form rather regular patterns, so-called "maps"; the layout of neurons with the same ocular dominance (OD map) or the same orientation preference (orientation preference map) can be visualized by metabolic or hemodynamic imaging techniques in large regions of V1. By analyzing the geometrical characteristics of these maps in cats of different age groups, we could demonstrate that both kinds of maps reorganized during the critical period. For example, the number of OD domains in cat visual cortex increased between the fourth and tenth postnatal week by more than 20% [32]. Likewise, the orientation preference map reorganized as the late phase of the critical period unfolded [33]. By comparing map layouts in both brain hemispheres and between different visual cortical areas, we observed that the process of reorganization in the two hemispheres was happening in a coordinated manner: orientation domains in mutually connected brain areas progressively became better matched in size [33].

Theoretical studies had already predicted that long-ranging connections within the visual cortex are also crucial for the formation and stabilization of the orientation map layout [34, 35]. The mathematically predicted signatures of long-ranging interactions in the patterns of orientation domains could be demonstrated in the visual cortex of cats, ferrets, tree shrews, and bush babies with surprising precision [36, 37]. It is known that the visual cortex in all these species contains an extensive network of long-ranging fibers. This neuronal architecture seems to be sufficient to imprint a species-independent geometry on these maps, which can only be successfully simulated in com-

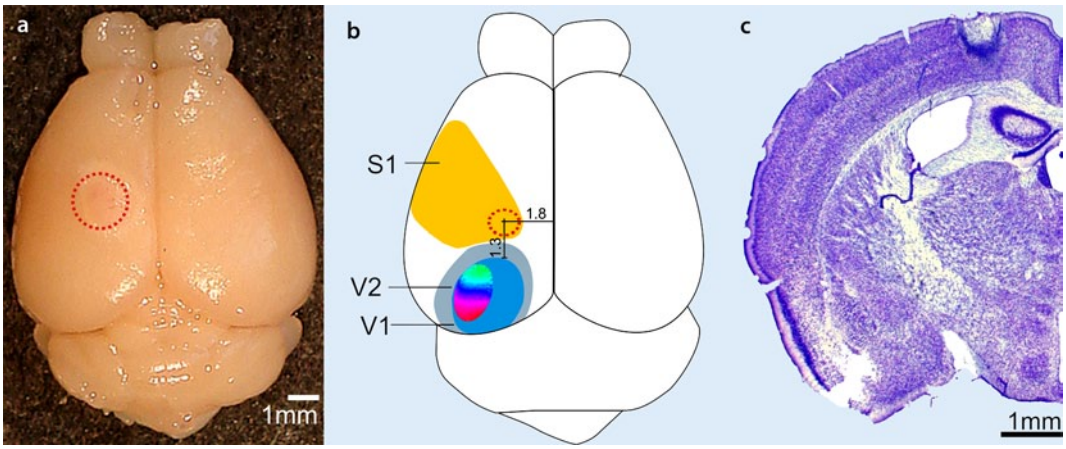

Fig. 5 ▲ Location and size of the photothrombotic lesion (PT) in the mouse cortex. **a** Top view of a mouse brain with a PT lesion in the left hemisphere (*red dotted circle*). **b** Average lesion location and size: the center of the lesion was located in the left primary somatosensory cortex (*S1*), on average 1.3 mm anterior to the anterior border of V1 and 1.8 mm lateral to the midline. An optically recorded retinotopic map from the binocular zone of V1 was superimposed on the diagram to illustrate the spatial relationship of the PT lesion and V1. **c** The lesion is clearly visible in the left S1 in a Nissl-stained frontal section of mouse brain. (Modified from [27])

puter models of cortical plasticity if long-ranging interactions are implemented. Results like these give us some confidence that explaining the nature of long-ranging modulations of neuronal plasticity after stroke might also provide insights into general mechanisms of plasticity and stabilization of neuronal networks in the cortex.

Therapeutic approaches

Since stroke is known to be associated with inflammatory processes [38], we also investigated whether these may be responsible for the observed lesion-induced impairments. To this end, we treated the animals once daily with the anti-inflammatory drug ibuprofen directly after stroke. In fact, we could completely restore impaired sensory learning—both visual acuity and contrast sensitivity of the open eye increased as early as on the first day after treatment onset and reached values comparable to control animals (**Fig. 6d**). Giving the brain 2 weeks to recover after stroke, sensory learning after MD was also restored [27]. This result supports our hypothesis that inflammatory processes can influence this kind of sensory learning, since inflammatory processes usually cease within 1 week after stroke [39, 40]. Our investigations therefore suggest that inflammation can have a direct influence on neuronal activity patterns, which are essential for sensory learning processes in the brain. Moreover, this repressive influence is non-local, since proinflammatory mediators can be distributed all over the brain (and body) via the blood stream. Therefore, we have reason to assume that anti-inflammatory drugs may be a useful adjuvant therapy to promote rehabilitation after stroke.

In contrast to sensory learning, ocular dominance plasticity could neither be rescued by anti-inflammatory treatment nor by a delay between stroke and MD (**Fig. 6c**). This demonstrates that these two models of visual plasticity are mediated by different mechanisms and neuronal networks. According to experiments by Prusky et al. [12], the enhancement of vision of the open eye after MD is restricted to the monocular segment of V1, while ocular dominance shifts are the result of competition between the afferents of the two eyes for cortical territory and take place in the binocular segment of V1 [4, 5, 41].

Conclusion

To watch the brain while it is learning—this longstanding dream of neuroscientists is now within reach. The experimental methods described here are perfectly suited to combine behavioral tests with the visualization of neuronal activity in the same animal: it is possible to observe experience-, learning-, and aging-dependent changes in brain activity directly in the living animal and even over long periods of time. Thanks to the possibility of additionally analyzing genetically modified mice, we can gain completely new insights into cellular and molecular mechanisms underlying neuronal plasticity. Finally, we can directly compare changes in brain activity patterns with changes in the behavior or sensory capabilities of the same animal [17, 27, 42].

Corresponding address

Franziska Greifzu
Systems Neuroscience, Johann-Friedrich-Blumenbach-Institut für Zoologie und Anthropologie, Bernstein Fokus Neurotechnologie, Georg-August-Universität Göttingen
Von-Siebold-Str. 4, 37075 Göttingen
Germany
Franziska.Greifzu@biologie.uni-goettingen.de

Franziska Greifzu. studied biology, psychology, and geography at the Friedrich-Schiller-Universität Jena and at the Universidad Complutense in Madrid. She started her PhD in 2009 in the research group of Prof. Dr. Siegrid Löwel at the University in Jena. Since 2011, she works at the Georg-August-Universität in Göttingen, where she was accepted to the Göttingen Graduate School for Neurosciences, Biophysics, and Molecular Bioscience.

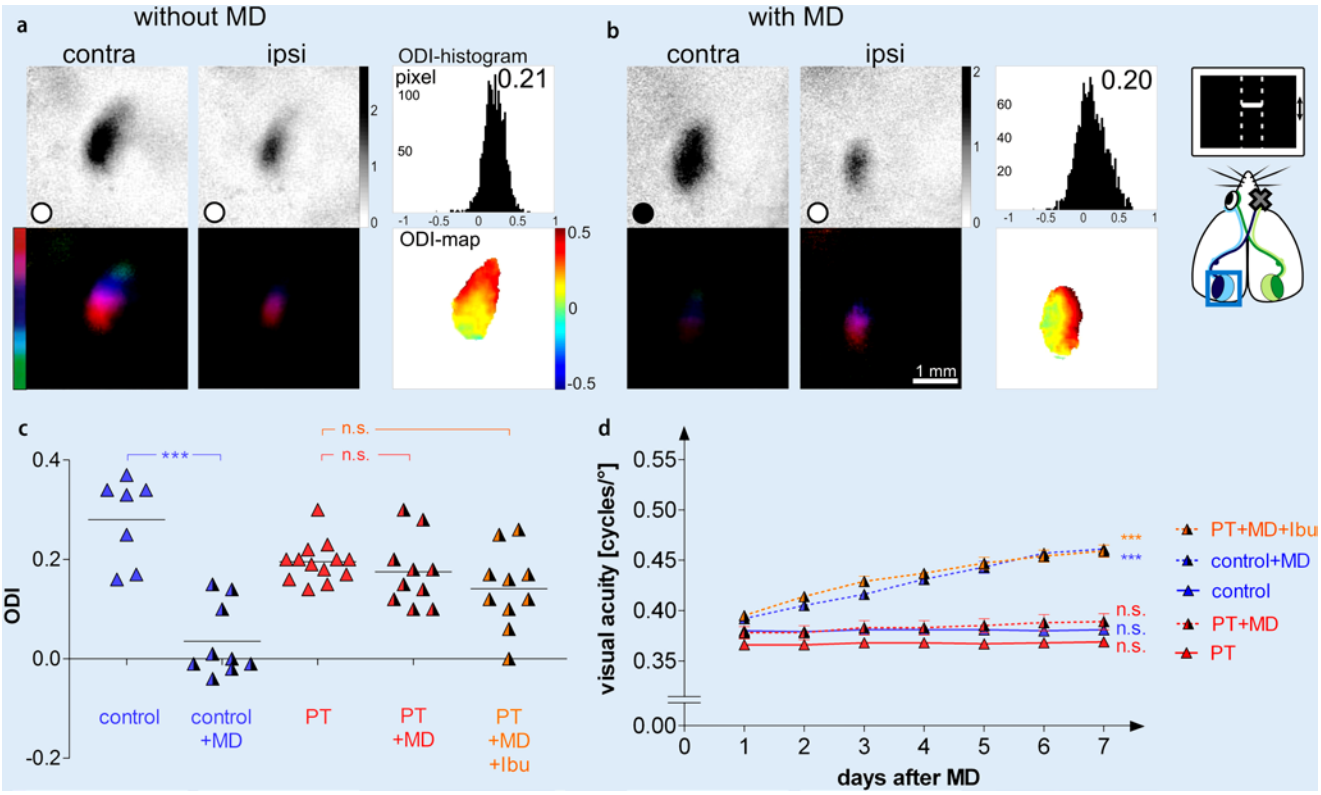

Fig. 6 ▲ Local stroke disturbs plasticity and learning even in remote brain areas. Anti-inflammatory treatment is partially effective. **a–c** Optically recorded V1 activity after stimulation of the contra- or ipsilateral eye without (**a**) and with (**b**) monocular deprivation (*MD*) in mice with a photothrombotic lesion (*PT*) in S1. Design as in Fig. 2 and Fig. 3. In contrast to control animals (Fig. 2), MD in animals with stroke did not induce a significant ocular dominance shift: V1 was still more strongly activated by the contralateral (closed!) eye, ODI values were unchanged, and warm colors prevailed in the ODI maps. **d** A PT lesion also prevented a visual acuity increase after MD. The visual acuity of the various groups over 7 days is shown. In control animals, visual acuity of the open eye increased significantly during MD (control+MD). In contrast, in PT animals with a lesion, this effect was absent (PT+MD). Treatment of the animals with the anti-inflammatory drug ibuprofen (PT+MD+Ibu) was able to completely restore sensory learning. Ocular dominance plasticity, however, could not be rescued (**c**). (Modified from [27])

Corresponding address

Prof. Dr. Fred Wolf
Theoretische Neurophysik, Max-Planck-Institut für Dynamik und Selbstorganisation
Am Faßberg 17, 37077 Göttingen
Germany
fred@nld.ds.mpg.de

Prof. Dr. Fred Wolf. studied physics and neurosciences in Frankfurt am Main, receiving his doctorate in Theoretical Physics (Dr. phil. nat.) in 1999. After his PhD, Fred Wolf worked as an Amos de Shalit fellow of the Minerva Foundation at the Hebrew University of Jerusalem (Israel) and participated in a research program at the University of California in Santa Barbara (USA). Since 2004, he has been head of the Research Group "Theoretical Neurophysics" at the Max Planck Institute for Dynamics and Self-Organization in Göttingen. He is a board member of the Bernstein Center for Computational Neuroscience and has been honorary professor of Physics at the Georg-August-Universität in Göttingen since 2008. In 2011, he served as a program director of the program Emerging Techniques in Neuroscience at the Kavli Institute for Theoretical Physics at the University of California, Santa Barbara (USA). Wolf was the first recipient of the Altdorfer Leibniz Prize in 1999 and was a visiting professor for mathematical neuroscience at the University of Marseilles (France) in 2011.

Corresponding address

Prof. Dr. Siegrid Löwel
Systems Neuroscience, Johann-Friedrich-Blumenbach-Institut für Zoologie und Anthropologie, Bernstein Fokus Neurotechnologie, Georg-August-Universität Göttingen
Von-Siebold-Str. 4, 37075 Göttingen
Germany
sloewel@gwdg.de

Prof. Dr. Siegrid Löwel. studied biology in Würzburg and Frankfurt am Main. 1988: doctorate (Dr. phil. nat.) and 1995: habilitation in zoology at the Johann-Wolfgang-Goethe-Universität in Frankfurt am Main. Until 1996: research fellow at the Max-Planck-Institut für Hirnforschung in Frankfurt in the Department of Neurophysiology of Prof. Dr. Wolf Singer. 1997–2005: Head of the research group "Visual development and plasticity" at the Leibniz-Institut für Neurobiologie in Magdeburg. 2002–2003: Research associate professor at the Keck Center at the University of California in San Francisco (USA), in the laboratory of Prof. Dr. Michael Stryker. 2003–2004: Dorothea-Erxleben visiting professor at the Otto-von-Guericke-Universität Magdeburg. 2004–2005: Scholarship in the Hertie Excellency Program "Neurosciences". 2005–2010: University professor (W2) for neurobiology at the Friedrich-Schiller-Universität Jena. Since August 2011: University professor for Systems Neuroscience at the Bernstein Fokus Neurotechnologie and the Biological Faculty of the Georg-August-Universität Göttingen.

Acknowledgements. The authors wish to thank all colleagues with whom they have cooperated during the projects presented here. Special thanks go to Prof. Dr. Hans-Joachim Bischof for his helpful comments on the manuscript and to Christian Spalthoff for his assistance in the preparation of Fig. 1. The presented work was funded by the *Bundesministerium für Bildung und Forschung* (BMBF) 01GQ0430, 01GQ0922, 01GQ1005, 01GQ0811, 01GQ0810 and 01GQ0921, the Human Frontier Science Program Organization (HFSP), the Volkswagen Foundation and the Max-Planck-Society.

Conflict of interest. On behalf of all authors, the corresponding author states that there are no conflicts of interest.

References

1. Wiesel TN, Hubel DH (1963) Single-cell responses in striate cortex of kittens deprived of vision in one eye. J Neurophysiol 26:1003–1017
2. Dräger UC (1975) Receptive fields of single cells and topography in mouse visual cortex. J Comp Neurol 160:269–290
3. Dräger UC (1978) Observations on monocular deprivation in mice. J Neurophysiol 41:28–42
4. Gordon JA, Stryker MP (1996) Experience-dependent plasticity of binocular responses in the primary visual cortex of the mouse. J Neurosci 16:3274–3286
5. Levelt CN, Hübener M (2012) Critical-period plasticity in the visual cortex. Annu Rev Neurosci 35:309–330
6. Fagiolini M, Fritschy JM, Low K et al (2004) Specific GABAA circuits for visual cortical plasticity. Science 303:1681–1683
7. Grinvald A, Lieke E, Frostig RD et al (1986) Functional architecture of cortex revealed by optical imaging of intrinsic signals. Nature 324:361–364
8. Kalatsky VA, Stryker MP (2003) New paradigm for optical imaging: temporally encoded maps of intrinsic signal. Neuron 38:529–545
9. Cang J, Kalatsky VA, Löwel S, Stryker MP (2005) Optical imaging of the intrinsic signal as a measure of cortical plasticity in the mouse. Vis Neurosci 22:685–691
10. Pouratian N, Toga AW (2002) Optical imaging based on intrinsic signals. In: Toga A, Mazziotta JC (Hrsg) Brain mapping: the methods, 2nd edn. Elsevier Science, San Diego, pp 97–138
11. Prusky GT, West PW, Douglas RM (2000) Behavioral assessment of visual acuity in mice and rats. Vision Res 40:2201–2209
12. Prusky GT, Alam NM, Douglas RM (2006) Enhancement of vision by monocular deprivation in adult mice. J Neurosci 26:11554–11561
13. Prusky GT, Douglas RM (2003) Developmental plasticity of mouse visual acuity. Eur J Neurosci 17:167–173
14. Gianfranceschi L, Fiorentini A, Maffei L (1999) Behavioural visual acuity of wild type and bcl2 transgenic mouse. Vision Res 39:569–574
15. Prusky GT, Alam NM, Beekman S, Douglas RM (2004) Rapid quantification of adult and developing mouse spatial vision using a virtual optomotor system. Invest Ophthalmol Vis Sci 45:4611–4616
16. Porciatti V, Pizzorusso T, Maffei L (1999) The visual physiology of the wild type mouse determined with pattern VEPs. Vision Res 39:3071–3081
17. Goetze B, Schmidt KF, Lehmann K et al (2010) Vision and visual cortical maps in mice with a photoreceptor synaptopathy: reduced but robust visual capabilities in the absence of synaptic ribbons. Neuroimage 49:1622–1631
18. Lehmann K, Löwel S (2008) Age-dependent ocular dominance plasticity in adult mice PLoS ONE 3(9):e3120
19. Sawtell NB, Frenkel MY, Philpot BD et al (2003) NMDA receptor-dependent ocular dominance plasticity in adult visual cortex. Neuron 38:977–985
20. Sato M, Stryker MP (2008) Distinctive features of adult ocular dominance plasticity. J Neurosci 28:10278–10286
21. Bavelier D, Levi DM, Li RW et al (2010) Removing brakes on adult brain plasticity: from molecular to behavioral interventions. J Neurosci 30:14964–14971
22. Smith GB, Bear MF (2010) Bidirectional ocular dominance plasticity of inhibitory networks: recent advances and unresolved questions. Front Cell Neurosci 4:1–7
23. Baroncelli L, Braschi C, Spolidoro M et al (2011) Brain plasticity and disease: a matter of inhibition. Neural Plast 286073
24. Lehmann K, Schmidt KF, Löwel S (2012) Vision and visual plasticity in ageing mice. Restor Neurol Neurosci 30:161–178
25. Sparkman NL, Johnson RW (2008) Neuroinflammation associated with aging sensitizes the brain to the effects of infection or stress. Neuroimmunomodulation 15:323–330
26. Stilling RM, Fischer A (2011) The role of histone acetylation in age-associated memory impairment and Alzheimer's disease. Neurobiol Learn Mem 96:19–26
27. Greifzu F, Schmidt S, Schmidt K-F et al (2011) Global impairment and therapeutic restoration of visual plasticity mechanisms after a localized cortical stroke. Proc Natl Acad Sci U S A 108:15450–15455
28. Watson BD, Dietrich WD, Busto R et al (1985) Induction of reproducible brain infarction by photochemically initiated thrombosis. Ann Neurol 17:497–504
29. Andrews RJ (1991) Transhemispheric diaschisis—a review and comment. Stroke 22:943–949
30. Bear MF, Singer W (1986) Modulation of visual cortical plasticity by acetylcholine and noradrenaline. Nature 320:172–176
31. Restani L, Cerri C, Pietrasanta M et al (2009) Functional masking of deprived eye responses by callosal input during ocular dominance plasticity. Neuron 64:707–718
32. Keil W, Schmidt K-F, Löwel S, Kaschube M (2010) Reorganization of columnar architecture in the growing visual cortex. Proc Natl Acad Sci U S A 107:12293–12298
33. Kaschube M, Schnabel M, Wolf F, Löwel S (2009) Interareal coordination of columnar architectures during visual cortical development. Proc Natl Acad Sci U S A 106:17205–17210
34. Wolf F (2005) Symmetry, multistability, and long-range interactions in brain development. Phys Rev Lett 95:208701–208704
35. Kaschube M, Schnabel M, Wolf F (2008) Self-organization and the selection of pinwheel density in visual cortical development. New J Phys 10:015009
36. Kaschube M, Schnabel M, Löwel S et al (2010) Universality in the evolution of orientation columns in the visual cortex. Science 330:1113–1116
37. Keil W, Kaschube M, Schnabel M et al (2012) Response to comment on "Universality in the evolution of orientation columns in the visual cortex". Science 336:413
38. Garcia JH (1975) The neuropathology of stroke. Hum Pathol 6:583–598
39. Liu T, McDonnell PC, Young PR et al (1993) Interleukin-1 beta mRNA expression in ischemic rat cortex. Stroke 24:1746–1750
40. Wang X, Siren AL, Liu Y et al (1994) Upregulation of intercellular adhesion molecule 1 (ICAM-1) on brain microvascular endothelial cells in rat ischemic cortex. Brain Res Mol Brain Res 26:61–68
41. Hubel DH, Wiesel TN, Levay S (1977) Plasticity of ocular dominance columns in monkey striate cortex. Philos Trans R Soc Lond B Biol Sci 278:377–409
42. Krempler K, Schmeer CW, Isenmann S et al (2011) Simvastatin improves retinal ganglion cell survival and spatial vision after acute retinal ischemia/reperfusion in mice. Invest Ophthalmol Vis Sci 52:2606–2618