BRAIN RESEARCH REVIEWS 60 (2009) 287–305

available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainresrev

BRAIN RESEARCH REVIEWS

Review

# Activity-dependent structural plasticity

*Markus Butz*[a,*], *Florentin Wörgötter*[a], *Arjen van Ooyen*[b]

[a]*Bernstein Center for Computational Neuroscience (BCCN), Universität Göttingen, Bunsenstr. 10, 37073 Göttingen, Germany*
[b]*Arjen van Ooyen, Neuroinformatics Group, Department of Integrative Neurophysiology, Center for Neurogenomics and Cognitive Research (CNCR), VU University Amsterdam, De Boelelaan 1085, 1081 HV Amsterdam, The Netherlands*

ARTICLE INFO

*Article history:*
Accepted 22 December 2008
Available online 6 January 2009

*Keywords:*
Structural Plasticity
Lesion-induced plasticity
Experience-dependent plasticity
Synaptic rewiring
Homeostasis
Activity-dependent neurite outgrowth
Development

ABSTRACT

Plasticity in the brain reaches far beyond a mere changing of synaptic strengths. Recent time-lapse imaging in the living brain reveals ongoing structural plasticity by forming or breaking of synapses, motile spines, and re-routing of axonal branches in the developing and adult brain. Some forms of structural plasticity do not follow Hebbian- or anti-Hebbian paradigms of plasticity but rather appear to contribute to the homeostasis of network activity. Four decades of lesion studies have brought up a wealth of data on the mutual interdependence of neuronal activity, neurotransmitter release and neuronal morphogenesis and network formation. Here, we review these former studies on structural plasticity in the context of recent experimental studies. We compare spontaneous and experience-dependent structural plasticity with lesion-induced (reactive) structural plasticity that occurs during development and in the adult brain. Understanding the principles of neural network reorganization on a structural level is relevant for a deeper understanding of long-term memory formation as well as for the treatment of neurological diseases such as stroke.



## Contents



* *Corresponding author.*
E-mail address: mbutz@bccn-goettingen.de (M. Butz).

0165-0173/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainresrev.2008.12.023

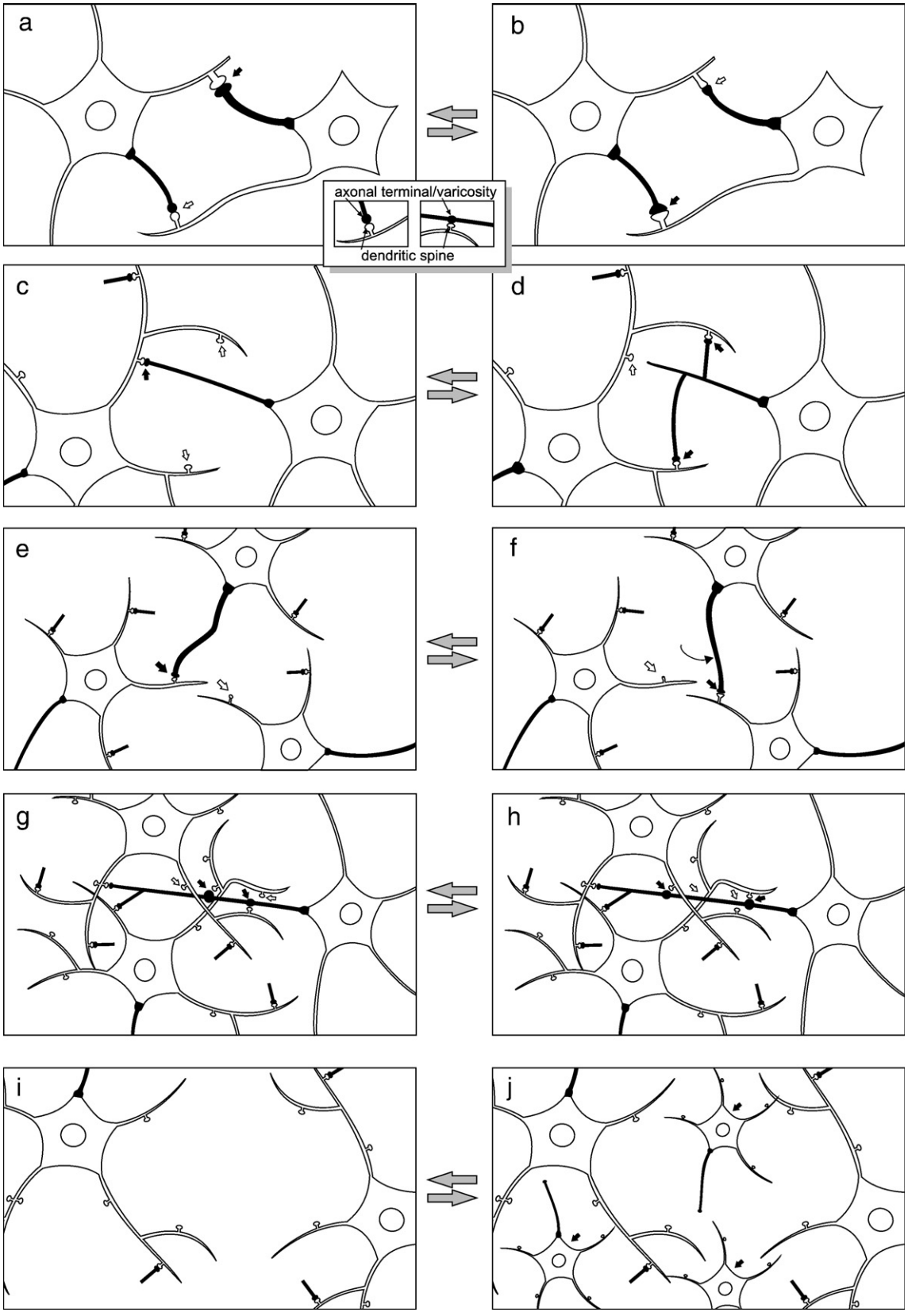
## 1. Introduction

Many studies about neural plasticity focus on Hebbian synaptic plasticity (Hebb, 1949) such as long-term potentiation (LTP) and depression (LTD) (extensively reviewed in Malenka and Bear, 2004; LTP is most recently reviewed in Raymond, 2007, and LTD in Massey and Bashir, 2007) or, with LTP and LTD combined, as spike-timing dependent plasticity (STDP; recently reviewed in Wörgötter and Porr, 2005 and Dan and Poo, 2006). Theoretically, this concept of plasticity considers synapses as variable amplification factors (synaptic strengths) within a hardwired network structure. In contrast to any forms of functional plasticity that change synaptic strengths without changing the anatomical connectivity between neurons, structural plasticity comprises changes in synapse numbers, axonal fibre densities, axonal and dendritic branching patterns, synaptic connectivity patterns, and even neuronal cell numbers (for a definition of terms see Fig. 1). Changes in the synaptic wiring scheme of a neural network arise from deleting (Wolff et al., 1989; Bastrikova et al., 2008) and/or forming new synapses (Kalisman et al., 2005; Knott et al., 2006). Moreover, synaptic rewiring can result from retraction and reformation of dendritic spines (Trachtenberg et al., 2002) and re-routing of axonal branches within cortical columns (De Paola et al., 2006). Even entirely new anatomic connections can be established under certain circumstances (Merzenich et al., 1983; Darian-Smith and Gilbert, 1994, 1995), as involved in the recovery from lesions of the nervous system, such as after stroke (Nudo, 2007). Not only for experimentalists, but also for theoreticians, structural plasticity raises a wealth of interesting issues, and also offers potential computational properties (Verzi et al., 2005) that can be tested experimentally (Poirazi and Mel, 2001; Stepanyants et al., 2002; Chklovskii et al., 2004).

That synaptic connectivity patterns may change as a result of structural plasticity was first observed by lesion experiments in adult brains in the late 1960s (Raisman, 1969). An important finding was that chemical neurotransmitters not only act as mediators of the bioelectrical activity but also act as neurotrophic factors. As Wolff et al. (1978) first described, the application of GABA evoked the formation of vacant postsynaptic spines that are not bound to a presynaptic element. Thus, neurotransmitters can initiate or suppress axonal and dendritic outgrowth (Wolff and Wagner, 1983; reviewed in Mattson, 1988; Wolff et al., 1993), spinogenesis (Shi et al., 1999; Maletic-Savatic et al., 1999; Richards et al., 2005) and synaptogenesis (Chang et al., 1991; Toni et al., 1999; Lamprecht and LeDoux, 2004). Neurotransmitters may influence neurite outgrowth by changing the postsynaptic membrane potential, which then, via voltage-depend calcium channels (or directly via ligand-dependent calcium channels) leads to modified

**Fig. 1 – Mechanisms of structural plasticity. There are different paradigms of plasticity that can be distinguished. We define that all kinds of mechanisms that change the strength of a single synapse are called functional plasticity throughout this paper. a) These mechanisms may include insertion or removal of postsynaptic receptors, changing the presynaptic release of transmitters or changing the thickness of the synapse (Axons are drawn in gray.). By contrast, every changing of the anatomical connectivity between neurons is defined as structural plasticity. b) Mechanisms causing structural plasticity are the increasing of multiple contact synapses between the same pairs of axons and dendrites leading to a structural doubling of enhanced synapses (Toni et al., 1999). Moreover, the expression of new axonal varicosities and terminals (here referred to as presynaptic offers or elements) or spinogenesis, the protrusion of new spines (postsynaptic offers/elements) gives rise to synaptogenesis — the formation of novel synapses. The formation of pre- and postsynaptic offers can, in turn, be associated with the outgrowth and branching of axons and dendrites, respectively. Accordingly, the retraction of axonal and dendritic branches may cause the loss of synaptic elements. The degeneration of pre- or postsynaptic elements may entail the loss of a synapse if the synaptic element was bound in a synapse before. c) Synaptic rewiring – meaning the retraction of a pre- or postsynaptic element from its target and the subsequent turnover to a different target in reach – constitutes a certain form of structural plasticity as, in this case, the formation of a new synapse depends on the deletion of an existing synapse. Synaptic rewiring is probably the most important feature of structural plasticity as adds further degrees of freedom for changing synaptic connectivity. Due to the condition that the synaptic element that forms a new synapse was bind in a different synapse before, synaptic rewiring can probably not be described in terms of any types of Hebbian synapse plasticity — making structural plasticity really phenomenologically different from functional plasticity. d) In a wider sense, neurogenesis either during ontogeny or within the adult hippocampal dentate gyrus belongs to structural plasticity as it constitutes the beginning of all anatomical changes in synaptic connectivity.**

intracellular calcium concentrations (Lipton and Kater, 1989). Calcium influx following postsynaptic activation influences growth cone behaviour at the tip of the axon or dendrite (Kater et al., 1988, 1989; Kater and Guthrie, 1989, 1990; Kater et al., 1990; Jourdain et al., 2003). Wolff and Wagner (1983) already recognized from lesioning studies at the cervical ganglion of cats that activity-dependent structural plasticity at the cellular and neural circuit level under certain conditions tends to



restore the homeostasis of the neural system (homeostatic plasticity) — a concept which is today re-addressed merely in the context of functional plasticity i.e. by synaptic scaling (Turrigiano and Nelson, 2000; Turrigiano, 2007).

The main idea that guides this review is that activity is crucial for governing structural plasticity in so far as neurons tend to maintain their homeostasis. We will show that structural plasticity, under pathological as well as physiological conditions, offers additional degrees of freedom as compared with functional plasticity for ensuring homeostasis. In this review, we distinguish between reactive structural plasticity, which occurs after pharmacological or surgical interventions at the peripheral or central nervous system, and spontaneous and experience-dependent structural plasticity, which occurs normally during development or in the adult brain. This distinction is not sharp because, for example, lesions (i.e. of the retina) can alter experience, while changes in experience (i.e. isolated rearing) may produce effects similar to those seen after a lesion in transmitter systems. We further regard (adult) neurogenesis as one form of structural plasticity, since it changes the number of cells in the network.

The structure of this review is as follows. First, we address structural plasticity as it occurs naturally in the developing nervous system and show how experience affects this plasticity. We then consider how lesion-induced (i.e., reactive) structural plasticity interferes with neural development, for example with the development of the circuitry of thalamocortical networks or even with the projection of far reaching meso-cortical and meso-limbic transmitter systems (e.g., dopamine). A second main topic is structural plasticity in the mature nervous system, again divided into structural changes occurring naturally (or in an experience-dependent manner) and those that are triggered by lesioning. We then review the crucial involvement of neuronal activity in governing structural plasticity, and the possible role of structural plasticity in learning. Finally, (adult) neurogenesis is discussed in its capability of inducing a whole range of other forms of structural plasticity, including neurite outgrowth, synapse formation, and synaptic rewiring. Throughout this review, results ranging from early lesioning studies up to recent *in vivo* time lapse imaging are integrated.

## 2. Occurrence of structural plasticity

Besides immunohistochemical techniques, electron microscopy was for very long the only technique for observing synaptic and subsynaptic structures. Nowadays, microscopic imaging techniques (Figs. 2a,b) even *in vivo* by confocal and two-photon laser imaging enable visualization of the dynamics of synapse formation and synaptic reorganization (Denk et al., 1990). Still, it is worth to consider previous anatomical studies. In particular, Gallyas-staining (Gallyas et al., 1980) enabled the quantitative assessment of the time course of structural plasticity in terms of synaptic rewiring (Figs. 2c,d) in a wide range of anatomical regions after lesions (Holzgraefe et al., 1981), during ontogeny (Teuchert-Noodt, 1989; Teuchert-Noodt et al., 1991; Teuchert-Noodt and Dawirs et al., 1996) and associated with adult hippocampal neurogenesis (Keller et al., 2000; Butz et al., 2008). (For an anatomical reference for the location of the occurrence of lysosomal processes in the hippocampal dentate gyrus, see TIMM fibre staining image in Fig. 2f.) Electron microscopy of Gallyas-stained ultra-thin sections (Fig. 2e) revealed selective staining of secondary (cyto-)lysosomes located in degrading axon terminals (Teuchert-Noodt, 1989; Teuchert-Noodt et al., 1991; Dawirs et al., 1992, 1996). This technique, in contrast to changes in synapse markers such as like synaptophysin or gap43, more directly indicates synaptic rewiring (Wolff et al., 1989; Wolff and Missler, 1992, 1993; Missler et al., 1993a, 1993b). It is beyond the scope of this review to give a complete methodological overview.

### 2.1. *Structural plasticity in the juvenile brain*

#### 2.1.1. *Spontaneous and experience-dependent structural plasticity during ontogeny*

Structural plasticity during ontogeny is characterised by a considerable overshoot in axonal branches (Portera-Cailliau et al., 2005) and synapse numbers which is subsequently reduced to adult connectivity levels (Changeux and Danchin, 1976; Cowan et al., 1984; Cotman and Nieto-Sampedro, 1984; Missler et al., 1993a, 1993b; Rao and Jacobson et al., 2005). This phenomenon was recently re-assessed for the mammalian neuromuscular system in which the initial polyneuronal innervation of muscle fibres is transformed during development into a situation whereby each fibre is innervated by only one motor neuron (Lichtman and Sanes, 2003; Bishop et al., 2004). The dynamic of this process has also been studied by computational models (e.g., van Ooyen and Willshaw, 1999b). Cortical over-sprouting has recently been re-assessed by Le Be and Markram (2006), giving direct evidence for an activity-dependent pruning of predominantly weaker synapses during early development. Nelson and colleagues (Nelson et al., 1993) have previously reported that activity-dependent synapse elimination at the neuromuscular junction is inconsistent with the concept of Hebbian plasticity. Theoretical studies have shown that overshoot in synapse numbers can be the result of activity-dependent neurite outgrowth and synapse formation/deletion (van Ooyen and van Pelt, 1994; van Ooyen et al., 1995). A comprehensive overview of computational models of neural development is given in van Ooyen (2003).

Stages of a pronounced synaptic reorganization are hallmarks of critical phases during development (Teuchert-Noodt, 1989). A systematic study on synaptic rewiring during ontogeny (Teuchert-Noodt et al., 1991) using the Gallyas staining technique (Gallyas et al., 1980) on avian brains demonstrated a strong, synaptic rewiring sequence including olfactory, cortical sensory and motoric areas of the brain: At prehatching stages of the avian development, the olfactory pathway transiently projects into paralimbic areas and probably sets a predisposition for posthatching development of the premature neural networks. Posthatching sensory input promotes maturation of visual and auditory pathways. It was proposed in this study that sensory and finally motor afferents displace transient olfactory afferences in a competitive manner, accompanied by substantial synaptic rewiring (Teuchert-Noodt, 1989; Teuchert-Noodt et al., 1991). These findings may imply that multi-modal experiences are crucial for forming senso-motor associative networks in critical phases during development.

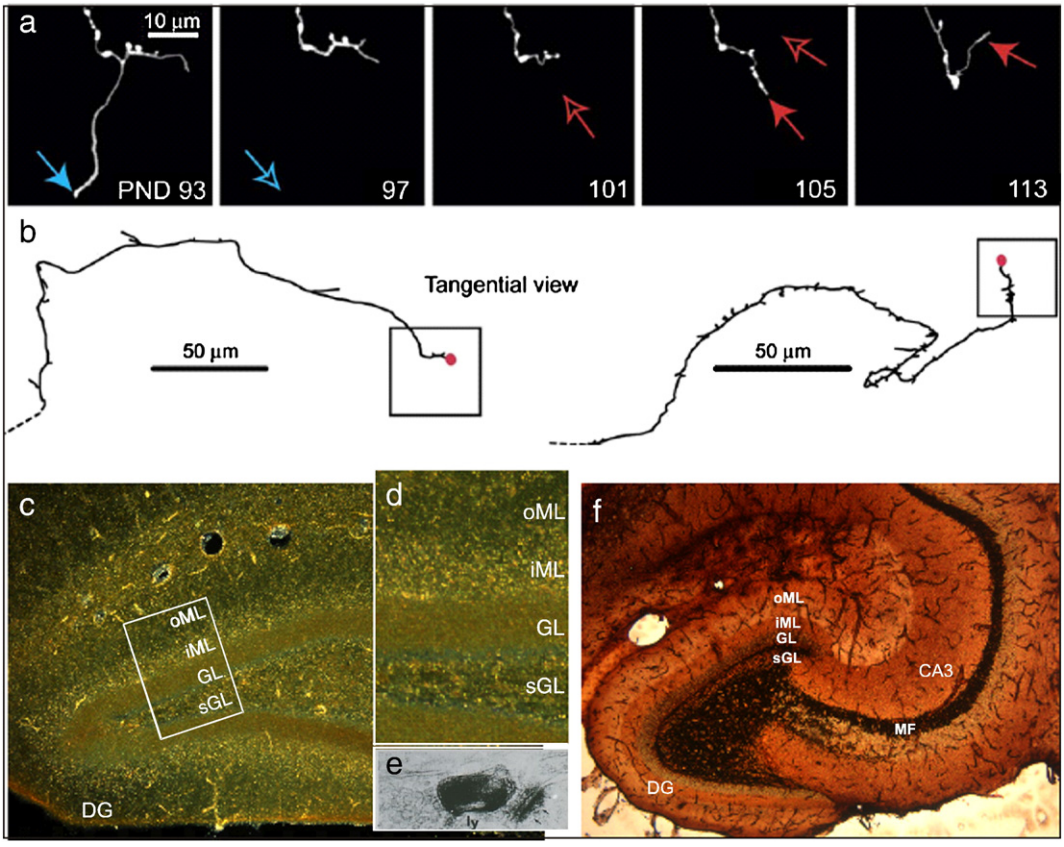



**Fig. 2 – Remodelling of axonal terminals. a) Time-laps imaging of axonal branches that retract (blue arrows) and grow out again (red arrows) over a time span of a couple of days (modified from De Paola et al., 2006). b) Three-dimensional reconstruction of the axon indicates large scale anatomical adaptations of the axon. c) Light microscopy dark field image of a silver staining of secondary lysosomes according to Gallyas et al. (1980) of the hippocampal dentate gyrus in gerbils (*Meriones unguiculatus*). DG: dentate gyrus; sGL: subgranular layer; GL: granular layer; iML: inner molecular layer; oML: outer molecular layer. d) Greater magnification of the laminated distribution of the silver-stained lysosomes in the different dentate layers. A dense pattern of silver-stained lysosomes was found in the iML indicating pronounced synaptic rewiring. e) Electron-microscopy image of a silver-stained lysosome located in a degrading axon terminal in close apposition to the synaptic cleft (modified from Teuchert-Noodt et al., 1991) Postsynaptic receptor densities are marked by arrows. f) In order to match the distribution of silver-stained lysosomes to anatomical conditions in the DG, we provide a TIMM staining picture staining mossy fibres (MF; black fibres) towards CA3 and to some extend recurrent fibres into the iML (dark brown shadow in the molecular layer). Bands of highest lysosome density in the Gallyas staining picture well corresponds to the iML in the TIMM staining picture.**

Recent developmental studies of the visual system show that structural plasticity of the ocular dominance column is characterised by a well-balanced formation of excitatory and inhibitory synapses (Hensch, 2005). Increasing or suppressing inhibition by agonists or antagonists of $GABA_A$ receptors, respectively, significantly alters not only the timing of critical phases but also the resulting width of the ocular dominance columns.

### 2.1.2. *Reactive structural plasticity of developing thalamo-cortical networks*

Sensory deprivation during development causes severe miss-wiring of the visual as well as the somato-sensory cortex (Fox and Wong, 2005). In rodents, visual deprivation during development causes suppression in axonal outgrowth and branching of thalamic neurons (Antonini and Stryker, 1993, 1996; Antonini et al., 1999). Moreover, visual deprivation affects dendritic orientation and branching of cortical neurons in the primary visual cortex. However, the extent of morphological alterations varies in different cell types (Tieman et al., 1995; Maravall et al., 2004). Results of *in vivo* studies by Sernagor and Grzywacz (1996) and Tian and Copenhagen (2003) seem to indicate that dendritic growth, particularly of cells receiving direct thalamic input (like lamina IV stellate neurons), tries to maximize sensory input to compensate for functional deprivation in the visual as well as in the somato-sensory cortex (barrel fields). Dark-reared turtles express retinal ganglion cells with extended receptive fields (Sernagor and Grzywacz, 1996). Mice develop more bistratified retinal ganglion cells under visual

deprivation that respond to both an onset and an offset of light (Tian and Copenhagen, 2003). In cats, dark rearing causes a dendritic outgrowth of lamina IV stellate neurons in the V1 area which is directed towards ocular dominance columns of the open eye (Kossel et al., 1995). In rats, mature stellate neurons in S1 located near barrel boundaries exhibit a highly biased orientation of their dendrites away from the boundaries and toward the centre of the barrel after juvenile whisker trimming (Datwani et al., 2002). Although the precise molecular signal cascade that mediates the directed outgrowth is not deciphered yet, it is known that NMDA receptor activation is a necessary condition to establish the reorientation of the dendritic arbors during development (Datwani et al., 2002).

#### 2.1.3. *Reactive structural plasticity of developing transmitter systems*

Following a single injection of methamphetamine (MA), we saw pronounced reactive structural plasticity occurring in the prefrontal cortex of gerbils (*Meriones unguiculatus*) (Dawirs et al., 1991; Dawirs et al., 1993). MA apparently acts as chemical scissors for the developing meso-prefrontal DA fibres (Dawirs et al., 1994, 1997) and entails measurable deficits in prefrontal cortex related behaviour (Dawirs et al., 1996). Within the prefrontal cortex, pyramidal cells overshoot in dendritic spine densities that secondarily fall slightly below control levels after about thirty days of postnatal life (Dawirs et al., 1991). Additionally, MA-treated gerbils show considerable alterations of their dendritic arborization in young adulthood (postnatal day 90) (Blaesing et al., 2001). Beyond morphological changes at cellular level, the loss of DA projections into the prefrontal cortex is compensated by a rewiring of local GABAergic circuits (Nossoll et al., 1997). We found the GABA innervation of pyramidal cell bodies to be reduced whereas the density GABAergic synapses is increased in distal dendrites (Brummelte et al., 2007). The loss of DA gives rise to systemic developmental mal-adaptations: i.e. the meso-prefrontal dopamine fibre density was significantly reduced, accompanied by an over-expression of the meso-limbic DA projection (reviewed in Teuchert-Noodt, 2000).

Moreover, gerbils are well-suited for observing the effects of isolated rearing on brain development (Winterfeld et al., 1998). Under enriched environmental rearing conditions, they develop native explorative and social behaviour but react highly sensitive to isolated and impoverished housing conditions after weaning. Under the latter condition, they develop pronounced stereotypic and temporarily epileptoid-like cramping behaviour (own observations). It has been shown that isolation may cause a form of experience-dependent structural plasticity which is comparable to reactive structural plasticity after MA intoxication lesioning the meso-prefrontal DA fibre tract (Winterfeld et al., 1998; Neddens et al., 2001).

A combination of both interventions induces large alterations in amount of neurotransmitters: glutamate (Bagorda et al., 2006; Witte et al., 2006), GABA (Brummelte et al., 2007) as well as monoaminergic projections to prefrontal and limbic areas (Busche et al., 2002; Neddens et al., 2002; Lehmann et al., 2003; Neddens et al., 2003; Lehmann et al., 2004; Neddens et al., 2004; Lesting et al., 2005; Brummelte and Teuchert-Noodt, 2006; Brummelte et al., 2006; Busche et al., 2006; Witte et al., 2006). A severe loss in meso-prefrontal DA projections is counterbalanced by an overexpression of meso-limbic DA projections (Busche et al., 2004). In addition, cortico-cortical deep lamina V glutamatergic projections show increased fibre densities whereas superficial glutamatergic fibres are excessively pruned (Bagorda et al., 2006). Computational modelling of prefronto-cortical networks (Butz and Teuchert-Noodt, 2006) and hippocampal networks (Butz et al., 2008) suggests that the experimentally observed changes in transmitter content might be explained as a structural but dysfunctional compensation to re-balance network activities. This mal-adaptive transmitter maturation following MA treatment might be considered as an animal model for a disconnection syndrome (Dawirs and Teuchert-Noodt, 2001) similar to that seen in human schizophrenic patients (Weinberger and Lipska, 1995).

### 2.2. *Structural plasticity in the adult brain*

#### 2.2.1. *Spontaneous structural plasticity in the mature brain*

*In vivo* imaging has revealed that under physiological conditions, the mature brain is not as hardwired as previously thought (Majewska et al., 2006). Although the spatial organization of cortical columns do not seem to change (Kalisman et al., 2005), there is still plenty of room for synaptic rewiring (Stepanyants et al., 2002; Chklovskii et al., 2004). Within cortical columns, dendritic spines and axonal varicosities are in close apposition forming so-called *potential synapses* (Stepanyants et al., 2002) of which only a small portion is actually realised. Spines are highly motile structures (Trachtenberg et al., 2002; Okamoto et al., 2004; Holtmaat et al., 2005) that bind to presynaptic elements, such as axonal terminals and varicosities, to form synapses (Ziv and Smith, 1996; Fiala et al., 1998; Jontes and Smith, 2000; Okabe et al., 2001; Petrak et al., 2005; Knott et al., 2006; Toni et al., 2007). However, only about one third of the spines in the barrel cortex is stable and persists for longer than a month (Trachtenberg et al., 2002). Semi-stable spines were tractable over a couple of days whereas instable spines appear and disappear within a day. Another study implies that the visual cortex is less plastic, since 90% of its spines were found to be stable (Grutzendler et al., 2002). Immature spines are elongated, and flexible filopodia can develop into stable mushroom-shaped mature spines if they are bound in a synapse (Knott et al., 2006). LTP can change spine shape through promoting spine maturation and stabilization (Engert and Bonhoeffer, 1999; Fischer et al., 2000; Geinisman, 2000; Yuste and Bonhoeffer, 2001; Matsuzaki et al., 2004; Nägerl et al., 2004). In contrast, LTD causes weakening of synapses and spines (Nägerl et al., 2004). Weak synapses can break apart again (Le Be and Markram, 2006; Bastrikova et al., 2008; Becker et al., 2008).

As we already know from earlier electron microscopy studies, not only spines but also axon terminals contribute to structural plasticity in the mature brain under physiological conditions (Wolff et al., 1989). Presynaptic terminals can be autophagocytised or their organelles can be removed by cytolysosomes. This focal synaptic degradation is reversible as long as the outer membrane of the axon terminal is

maintained. Recent *in vivo* imaging studies (De Paola et al., 2006; Stettler et al., 2006; Nishiyama et al., 2008) showed persistent synaptic rewiring in the mature cortex whereby whole axonal branches were re-routed to different postsynaptic targets. Thereby, axonal branches can elongate up to 300 μm, which is about the diameter of one cortical column. Thus, spontaneous synaptic rewiring by axonal turnover takes place within a single column or between one column and its direct neighbours. Our own recent studies on axonal turnover using the Gallyas-technique (Gallyas et al., 1980) indicate that synaptic rewiring is permanently going on in limbic areas, but less so in the sensory cortex and in motor areas (Butz et al., unpublished data).

How much impact spontaneous synaptic rewiring has on the function of neuronal networks depends on the filling fraction of the network (Stepanyants et al., 2002), which is a measure for the amount of potential synapses. If all pre- and postsynaptic elements are connected, synaptic rewiring will not be possible; but if many potential synapses are within reach of a neuron, synaptic rewiring can considerably change network structure, with potential consequences for the network's computational properties (Poirazi and Mel, 2001). Modelling studies analysing synaptic rewiring usually distinguish between wiring changes among pre- and postsynaptic elements in direct proximity (<2 μm) and those that require remodelling of axonal or dendritic branches (Chklovskii et al., 2004). Both contribute to structural plasticity.

#### 2.2.2. *Reactive structural plasticity in the mature brain*

In mature primary sensory cortices, the gross morphology of neurons and their circuitry does not change dramatically under normal conditions (Trachtenberg et al., 2002; Grutzendler et al., 2002; Mizrahi and Katz, 2003). However, following lesions also the mature central nervous system, even areas that are regarded as stable such as primary sensory-motor areas, can express profound reactive plasticity (Cotman and Lynch, 1978; Merzenich et al., 1983, 1984; Wolff et al., 1989; Anthes et al., 1993; Darian-Smith and Gilbert 1994, 1995; Florence et al., 1998; Kossut and Juliano, 1999; Florence and Kaas, 2000). Raisman (1969) lesioned two afferent fibre systems of the septal nuclei complex. First he lesioned the hippocampal input to the septal nuclei by cutting the fimbrial fibres and second he cut the medial forebrain bundle providing hypothalamic input to the septal nuclei. He was the first to show that reactive sprouting of intact fibre tracts can reoccupy vacant postsynaptic targets. With this study, he paved the way for reactive plasticity research.

Reactive plasticity may even modify laminar distribution patterns of afferent fibres. In the hippocampus, for example, commissural and associative fibres (C/A) (Lynch et al., 1973; Nadler and Cotman, 1978; Frotscher et al., 1995) terminate in the inner molecular layer of the dentate gyrus. After cutting the perforant path terminating in the outer molecular layer, C/A fibres sprouted and made contact with targets in the outer molecular layer, too (Lynch, 1974; Nadler and Cotman, 1978). In the central nervous system, mechanisms inducing sprouting 'par distance' are still enigmatic. In the peripheral nervous system, however, target cell-derived trophic factors play an important role. Denervated motor endplates release neurotrophic factors which attract axonal terminals (Purves and Lichtman, 1985; Tessier-Lavigne and Goodman, 1996) and thereby possibly induce synaptic reinnervation.

Even peripheral lesions are able to induce reactive plasticity in the primary senso-motor cortex. Cutting the medianus nerve in monkeys innervating the medial half of the hand and the first two and a half fingers is compensated by the nervus ulnaris taking over the lost innervation (Merzenich et al., 1983). Thus, sensory deafferentation of cortical tissue can lead to substantial remapping of somato-sensory representations (Pons et al., 1991). In the adult primary visual cortex, structural plasticity was found after partial retinal lesions (Darian-Smith and Gilbert, 1994, 1995). Recovery from a lesion may involve unmasking of pre-existing, but latent, horizontal connections (reviewed in Sanes and Donoghue, 2000) and modulation of synaptic efficacy by long-term potentiation (LTP) (Hess and Donoghue, 1994; Hess et al., 1996; but see also Smirnakis et al., 2005) or long-term depression (LTD) (Hess and Donoghue, 1996). In addition, deafferented neurons within the lesion projection zone (LPZ) seem to change their receptive field properties (Giannikopoulos and Eysel, 2006) by synaptic rewiring, since they significantly increase their number of instable spines and additionally form novel stable spines (Keck et al., 2008). In addition, neurons bordering the LPZ begin with axonal sprouting after the lesion possibly due to disinhibition (Darian-Smith and Gilbert, 1994; Antonini and Stryker, 1996; Antonini et al., 1999). Remarkably, prior experience matters for the outcome of reorganization (Hofer et al., 2006). As in the visual cortex, partial deafferentation of the barrel fields by selective whisper clipping weakened postsynaptic spines (Trachtenberg et al., 2002). However, whisker clipping may not cause a complete removal of sensory input from the clipped area, as is the case with focal retinal lesions. Nevertheless, it is remarkable that a change in sensory input is sufficient to induce synaptic rewiring to such an extent.

The time course of reactive structural plasticity was extensively studied by Holzgraefe et al. (1981). By undercutting the visual cortex in adult rats, the entire thalamic input to the visual cortex was completely removed; associative and commissural connections, however, were left intact by this procedure. Acutely, an enormous amount of lysosomal degradation predominantly appeared in intermediate layers. Up to post-lesion day 5, lysosomal degradation processes were prominent in layers III and VI indicating structural plasticity. The pattern became more diffuse and density decreased during the following two weeks. Remarkably, lysosomal degradation re-appeared spontaneously after 30, 60 and 90 days post-lesioning now including superficial layers. Fibre tracing by the retrograde transport of horse reddish peroxidise revealed that a rewiring of cortical circuits had taken place in so far as limbic archicortical projections had sprouted and re-occupied the deafferented visual cortical area. Increased measures for lysosomal processes did not return to normal values until 150 days post lesion.

Interestingly, this prolonged reorganization period in rats corresponds to time courses of neurologic patients. That is, increased responsiveness to therapy was found for the rehabilitation of stroke patients (Liepert et al., 2001) and, as we found in a recent unpublished clinical study, in rehabilitation of infant and adolescent patients with cerebral palsy after complex orthopaedic multi-level surgical treatment (Butz et

al., unpublished data). Studying the time course of rehabilitation in human patients suffering from facial palsy offers insight into the changing cortical representation of the sensorimotor innervation of affected face and neck muscles (Yildiz et al., 2007). Peripheral lesions of rat facial nerve may serve as an animal model of human facial palsy (Farkas et al., 2000).

Such experiments revealed that reactive structural plasticity was not restricted to the primary motor cortex of the contra-lateral hemisphere but included the corresponding cortex area ipsi-lateral to the lesion (Laskawi et al., 1996). The authors argued that bilateral rewiring is caused by interhemispheric disinhibition. Unmasking of pre-existing callosal connections was confirmed by electrophysiological methods, which revealed that the underlying mechanism depends on $GABA_A$ receptors (Farkas et al., 2000). Wolff and colleagues already discussed the impact of afferent activity for structural plasticity (Wolff and Wagner 1983; Wolff et al., 1989). Recently, Tailby et al. (2005) demonstrated that the loss of input due to vibrissal-deafferentation in adult rats causes reorientation of the dendritic arbors away from their centres towards intact neighbouring columns assumingly in order to increase their synaptic input. Further studies on cortical reorganization in an animal model of focal stroke (Carmichael et al., 2001) in human stroke patients (Seitz et al., 2004), and even in healthy subjects (that were subjected to temporary deafferentation by cooling limbs in ice water till complete desensitising) (Ziemann et al., 1998), focus on functional plasticity in terms of LTP-like processes. However, it needs to be explained how lasting changes in input activity after deafferentation may cause network reorganizations by structural plasticity.

### 2.3. *Role of activity in structural plasticity*

Structural plasticity is in many cases influenced by electrical activity. Depolarization and synaptic transmission may increase the postsynaptic intra-cellular calcium concentration by activating ligand-gated calcium channels or voltage-dependent calcium channels (Lipton and Kater, 1989). Calcium as a second messenger regulates growth cone motility and therewith affects neurite outgrowth (Mattson and Kater, 1987; Mattson et al., 1988; Kater et al., 1988, 1989; Korkotian and Segal, 2007; Hutchins and Kalil, 2008) and dendritic spinogenesis (Jourdain et al., 2003). Recently, a new technique has been introduced to monitor simultaneously calcium dynamics within the dentritic tree and structural plasticity (Lang et al., 2006).

It is well known that functional plasticity such as LTD and synaptic scaling may contribute to the homeostasis of neuronal activities at the synaptic level (Turrigiano et al., 1998; Wierenga et al., 2005; review in Turrigiano and Nelson, 2004). Here, we review experimental data (Wolff and Wagner, 1983; Pratt et al., 2003) that supports that structural plasticity is involved in counterbalancing changes in the overall level of neuronal activity. (Fig. 3) what might be called a "*neuron-centric view of plasticity*". For this, we have to assume that 1) neurons develop their synaptic elements in accordance to their level of activity and 2) they do so independently from possible synaptic contact partners.

1) At the dendrite, the postsynaptic side of the synapse, a global reduction of neuronal activity increases spine density

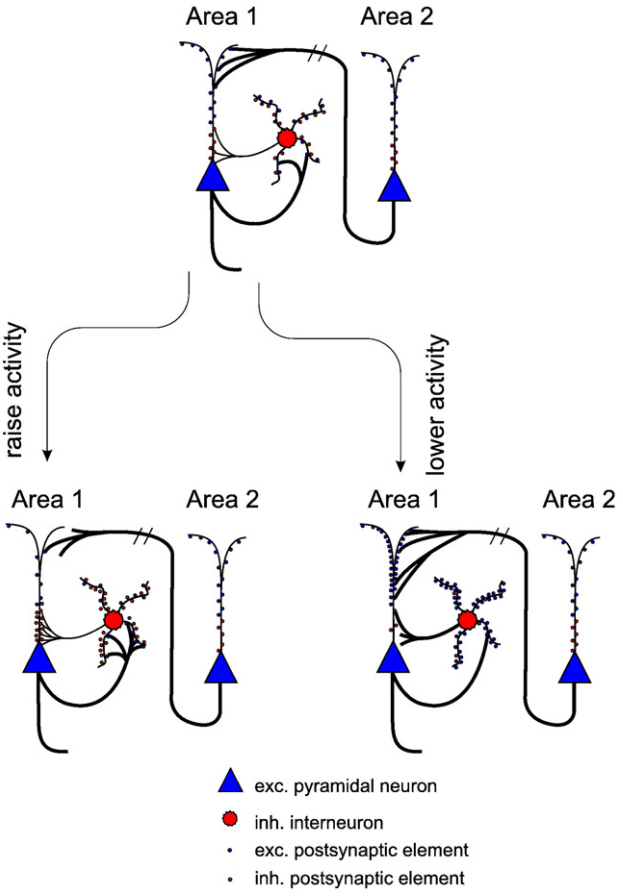



**Fig. 3 – Activity-dependent rewiring of neuronal networks. We postulate a basic principle for network rewiring. If network activity is raised, postsynaptic neurons reduce excitatory postsynaptic elements to lower excitation and offer more inhibitory postsynaptic elements to increase the chance to receive more inhibition. At the same time, they respond with axonal sprouting (Axons are drawn in bold.). Sprouting axons of inhibitory interneurons serve the demand of highly activated neurons so that an increasing feedback inhibition brings the network in balance again. The opposite happens if activities are too low. Then, inhibition is reduced and the amount of excitatory postsynaptic elements increases. As activity is needed for axonal sprouting, compensation of low network activity needs the supply of additional axonal offers from different areas that are highly activated. The style of this figure was inspired by a figure illustrating homeostatic plasticity in a former article by Turrigiano and Nelson (2004).**

(Kirov and Harris, 1999; Kirov et al., 2004 but see also Portera-Cailliau et al., 2003). In rodents, whisker stimulations raise neuronal activities that cause a transient increase in spine numbers. Subsequently, synapses and spines are pruned and only inhibitory synapses are maintained (Knott et al., 2002). Together, these findings imply a structural realisation of homeostatic plasticity. On dendritic arbor development, the impact of activity is twofold; it promotes dendritic outgrowth in early development but stabilizes dendritic branches at later stages (Rajan and Cline, 1998).

At the axon, the presynaptic side of the synapse, neuronal activity mediated by glutamatergic synaptic transmission promotes outgrowth (Merzenich et al., 1984; Mattson, 1988; Lipton and Kater 1989; Wolff and Missler, 1992; Rekart et al., 2007; Hutchins and Kalil, 2008), which can be prevented by application of GABA (Mattson, 1988). Stabilization of immature axonal branches is further regulated by competition among ingrowing axons for postsynaptic targets as well as competition between growing branches of the same axon (Hua et al., 2005; Hutchins and Kalil, 2008; see also related theoretical studies by Van Ooyen and Willshaw, 1999a, van Ooyen and Willshaw, 2000 and Van Ooyen et al., 2001). Whereas changes at the postsynaptic side affect local connectivity only, presynaptic changes may also cause synaptic rewiring in distant brain regions. Activity-dependent structural plasticity was already predicted from lesion studies at cervical ganglion by Wolff and Wagner (1983) and again discussed in the context of homeostatic plasticity (Turrigiano and Nelson, 2000; Turrigiano, 2007).

2) We find good evidence in the experimental literature for vacant synaptic elements as potential precursors for synaptogenesis. In fact, synapse-free axon terminals/varicosities or vacant postsynaptic-like densities were found during normal development and after lesions (reviewed in Wolff et al., 1989; Arellano et al., 2007). Vacant synaptic elements, which are either newly formed or arise from the break down of existing synapses, can induce synaptic rewiring.

Synaptic rewiring can occur within neuronal networks without necessarily changing total synapse numbers (see our recent theoretical study for the role of synaptic rewiring for the homeostasis of neuronal networks: Butz et al., 2008). An indication for synaptic rewiring could be an increased number of instable spines as the breaking of prior stable synapses give rise to an increased number of vacant axonal terminals or varicosities that might undergo synaptic rewiring. In fact, Trachtenberg showed that the amount of instable spines significantly increased with unbalancing neuronal activities in the barrel cortex after whisker cutting (Trachtenberg et al., 2002) which might be an indicator for a compensatory synaptic rewiring. In general, both the formation and the break down of synapses might be described in terms of 'market-like mechanisms' of supply and demand of, respectively, pre- and postsynaptic elements. The activity-dependence of synaptogenesis and neurite outgrowth causes a reciprocal interaction between neuronal transmission/activity, neuronal morphogenesis and the connectivity structure of the neuronal network (Wolff and Wagner, 1983; van Ooyen and van Pelt, 1994; van Ooyen et al., 1995; van Ooyen, 2003).

### 2.4. *Structural plasticity and learning*

As discussed before, structural plasticity in the mature brain is guided by neuronal activity. A wealth of studies address the problem of how experience may change cortical connectivity (Zuo et al., 2005; Holtmaat et al., 2006; Keck et al., 2008; Hofer et al., 2008). These are recent examples for experience-dependent plasticity still implying the use of lesions or the removal of whiskers to elicit structural changes in connectivity. However, due to methodical limitations, experimental data directly indicating that structural plasticity is involved in learning are rare. For instance, a link between functional remapping and structural plasticity was observed by Chang and Greenough (1982), Bailey and Kandel (1993), Buonomano and Merzenich (1998), Rekart et al. (2007) and Kleim et al. (2007). Kleim et al. (2002, 2004) reported a specific enlargement of the cortical paw representation (at the expense of foreleg representation, which shrinks) associated with synapse formation after seven days of motor skill learning. Some studies suggest that synaptogenesis takes place in the close vicinity of synapses that are strongly enhanced by LTP (Chang et al., 1991; Toni et al., 1999; rev. in Lamprecht and LeDoux, 2004). That is, Toni and colleagues reported a significant increase of multiple-spine synapses as a result of a focal induction of LTP. These multiple-spine synapses may have come about by the duplication of existing synapses. In line with this, an increase of synaptophysin staining was found after motor skill learning (Derksen et al., 2007). Thus, experience-dependent cortical remapping is not only the result of a mere functional change in connectivity (i.e. by synaptic plasticity such as LTP) but is also associated with structural plasticity in terms of synapse formation and deletion.

### 2.5. *Adult neurogenesis*

Adult neurogenesis occurring in the hippocampal dentate gyrus and the olfactory bulb of the mammalian brain (Altman and Das, 1965; Gould and Gross, 2002) is a considerable source for structural plasticity and because of its occurrence in hippocampal circuits may be involved in learning and memory consolidation (Kempermann et al., 2006). One may assume that for the synaptic integration of newly formed granule cells into pre-existing hippocampal circuits formation of new synapses is necessary. This assumption is backed-up by experimental data on neurogenesis in general (as reviewed in Linden, 1994) and for adult hippocampal neurogenesis in particular (as reviewed in Lehmann et al., 2005). Specifically, it was shown that depolarization of young neurons in the central nervous system increases their chance to survive (Scott, 1977; Bennett and White, 1981; Gallo et al., 1987; Larmet et al., 1992). Rewiring of synapses impinging onto young granule cells may arise from the fact that initially synapses are somatic, which are then later replaced by axo-dendritic synapses (Stanfield and Trice, 1988; Markakis and Gage, 1999). Young granule cells migrate from the subgranular layer into the granule cell layer (Schlessinger et al., 1975; Rickmann et al., 1987). Thereby, they extend their dendritic branches through the inner and outer molecular layers (Kaplan and Bell, 1983; Cameron et al., 1993; Seki and Arai 1995) The larger dendrites provide new positions for axonal terminals to target on (Toni et al., 2007). The GABAergic synapses initially have an excitatory effect on young granule cells (Ge et al., 2006; Ge et al., 2007), which is later converted into an inhibitory effect during their maturation. This change in the nature of GABAergic transmission onto young granule cells in the adult dentate gyrus is comparable to the development of GABAergic innervation during ontogeny of the central nervous system (Esposito et al., 2005).

Maturing granule cells compete for synaptic input from commissural and associative fibres and from perforant path fibres in the inner and outer molecular layer, respectively, by emitting neurotrophic factors that attract innervating axons (Cameron et al., 1993; Seki and Arai, 1993). Possibly due to adult neurogenesis, the outer molecular layer continuously gains new synapses and expands over time whereas the inner molecular layer has a remarkably fixed size (Duffy and Rakic, 1983; Anthes et al., 1993). Gallyas staining (Gallyas et al., 1980) of hippocampal slices (Figs. 2c,d) revealed a dense staining of lysosomal degradation processes exclusively within the inner molecular layer, indicating considerable synaptic rewiring of commissural and associative fibres (Dawirs et al., 1992; Dawirs et al., 2000; Butz et al., 2008). According to Teuchert-Noodt (2000), growing synapse numbers within the outer molecular layer may be called "*progressive synaptogenesis*", and the synaptic rewiring within the inner molecular layer "*regressive synaptogenesis*".

The explanation for this increased synaptic rewiring within the inner molecular layer might be that the still developing granule cells meet with the high capacity for axonal sprouting of the C/A fibres. Recently, *in vivo* imaging of dentate granule cells visualized immature dendritic filopodia that extend towards existing synapses (Toni et al., 2007). Although the signaling cascade by which young cells induce synaptic rewiring still remains to be unravelled, one may assume from available data that initial filopodia, which form multiple synapses with pre-existing axon terminals, are subsequently pruned in a competitive manner to form a single synaptic junction. Remodelling of the young cells' connectivity continues for at least two weeks after mitosis (Zhao et al., 2006; Piatti et al., 2006; Laplagne et al., 2006; Ge et al., 2007; Tashiro et al., 2007; Toni et al., 2007).

Recent data suggest a causal relationship between adult neurogenesis and synaptic rewiring (Keller et al., 2000; Butz et al., 2008). Apparently, adult neurogenesis is a considerable drive for structural plasticity and network rewiring in the hippocampus. Theoretical work suggests that synaptic rewiring in networks with permanent neurogenesis is subject to the homeostatic requirements that young neurons and pre-existing networks have to fulfil (Butz et al., 2006, 2008).

## 3. Discussion

### 3.1. *Summary*

As we reviewed here, structural plasticity is not only an integral part of neural development; it is also ubiquitously present in the mature brain. As known from early lesion studies, structural plasticity goes along with the recovery from central and peripheral lesions. Particularly during ontogeny, this reactive structural plasticity can cause the reorganization of entire transmitter systems. The main driving force for structural plasticity in these cases is a change in overall level of neural activity that can last for up to several days. We propose a 'neuron-centric view' of plasticity in which remodelling of afferent and efferent synapses occurs so as to maintain desired levels of activity (homeostasis). Long-term changes in neuronal activity are not only induced by lesions but also occur as a result of experience-dependent functional changes in connectivity. Changes in activity induced by functional plasticity may be counterbalanced by compensatory changes at the structural level. In addition, structural plasticity may also directly contribute to learning and memory. Remarkably, pronounced structural plasticity associated with adult neurogenesis persists in hippocampal networks, which may signify the need of structural network reorganization for memory formation and consolidation.

### 3.2. *Structural plasticity and homeostasis*

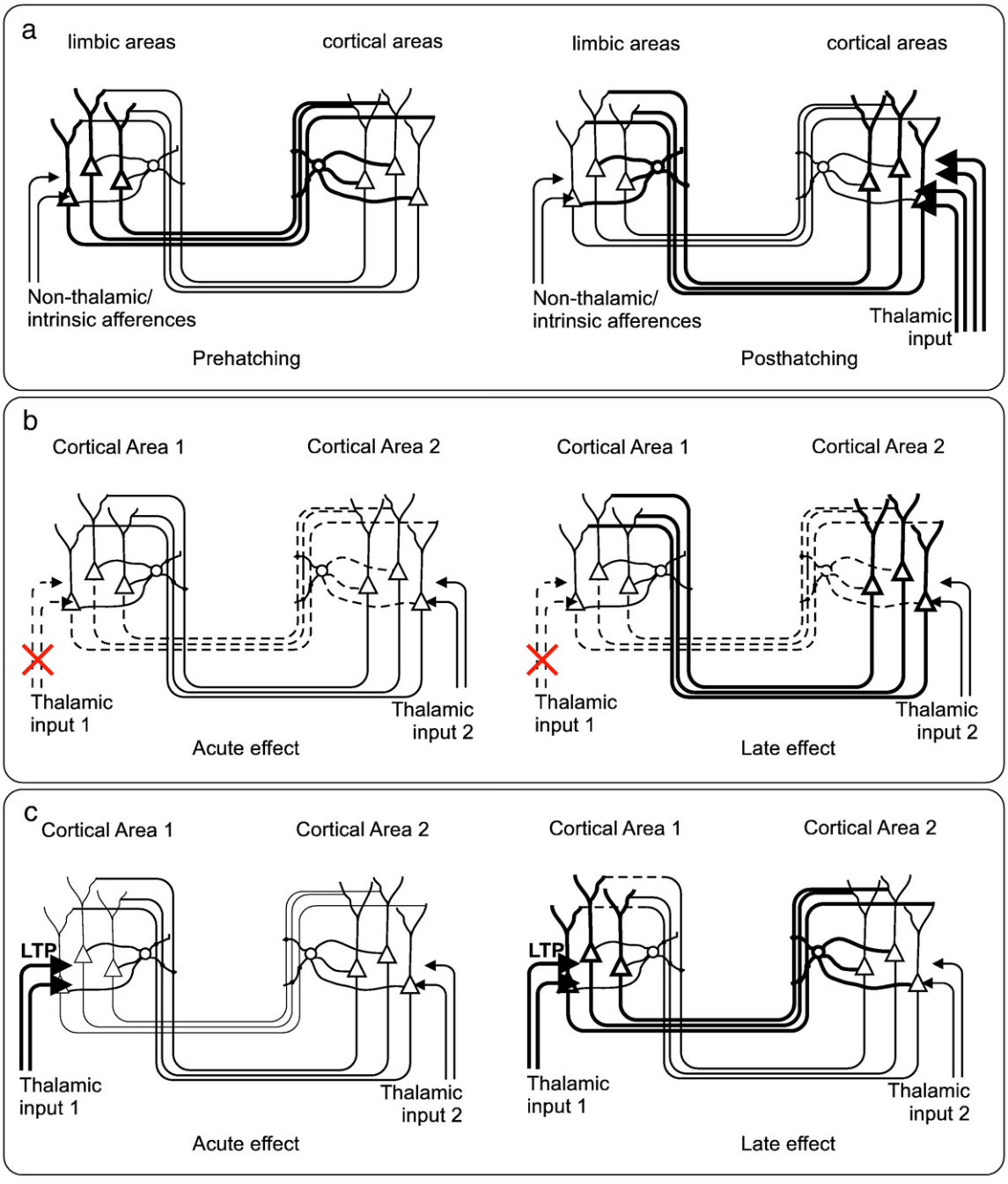
The need for homeostasis may elicit phases of pronounced structural plasticity as seen in critical periods in the developing brain. During development (Fig. 4a), overshooting synapse numbers lead to rising network activities, followed by a compensatory pruning of synapses (Changeux and Danchin, 1976; Cowan et al., 1984; Le Be and Markram, 2006; see also van Ooyen et al., 1995). During adulthood (Fig. 4b), lesions and/or long-lasting functional modifications may disturb the balance of excitation and inhibition. (Farkas et al., 2000; Shimizu et al., 2002). After deafferentation, disinhibition may cause reactive axonal sprouting (Wolff and Wagner, 1983; Darian-Smith and

**Fig. 4 – Different examples of rewiring cortical circuits. a) Synaptic rewiring during avian development. According to Teuchert-Noodt (1989), intrinsic afferents to cortical sensory and motor areas predominantly from para-limbic areas activate immature networks at prehatching stages (left panel) in development (bold lines). At posthatching stages (right panel), a period of pronounced synaptic rewiring in the respective cortical areas arises which correlates with the timing of the critical period for imprinting on behavioural level. The early interpretation by the author was – which is in line with recent findings on activity-dependent structural plasticity – that posthatching thalamic inputs (bold arrows) increase activity in cortical networks. In a compensatory manner, limbic inputs to cortical areas (thin lines) become inhibited in support of the development of sensory and motor circuits (bold lines). b) Pronounced synaptic rewiring occurs in adult cortical networks for instance after deafferentation. The acute effect (left panel) comprises a first synaptic degeneration and degradation (dashed lines). A late synaptic degradation of synapses was found 30 and 60 days after the primary lesion. This late effect (right panel) was interpreted in terms of a compensatory synaptic rewiring driven by disinhibition of principal cells bordering the lesion projection zone. These cells respond with an activity-dependent sprouting (bold lines) and re-occupy vacant postsynaptic targets within the lesion projection zone. c) We hypothesize that the same rules for synaptic rewiring also apply for long-term memory formation and cortical remapping. We would expect that an acute enhancement in excitability of cortical columns by LTP (bold arrows) is followed by axonal outgrowth after a couple of days (bold lines in right panel) leading to an enlargement of the cortical representation. At later stages in this development, we would further expect increasing inhibitory synapses (bold interneurons) and pruning of non-potentiated synapses (dashed lines), which might entail the shrinkage of an adjacent representation.**

Gilbert, 1994, 1995). Disinhibition of the ipsi- and contralateral hemisphere is known to occur as a consequence of an acute stroke (Liepert et al., 2000; Manganotti et al., 2002; Shimizu et al., 2002; Takeuchi et al., 2007). Post-lesion disinhibition goes along with alterations at cellular and molecular levels (Carmichael, 2006) as well as with reactive sprouting and synaptogenesis (Stroemer et al., 1995).

### 3.3. *Neuron-centric view of plasticity*

In all these cases presented, functional plasticity in terms of changes in synaptic efficacies (Heynen et al., 2003), including synaptic scaling (Turrigiano et al., 1998), of existing synapses may not be sufficient to rebalance neuronal activities. Structural plasticity may be required to form novel or to delete existing synapses. The neuron-centric view of plasticity poses that synapses are formed in two steps: Neurons present their 'offers', i.e. vacant pre- and postsynaptic elements, to the other neurons in the 'neuropil'. Then, in a combinatorial process, new synapses are formed when transmitter-/receptor properties of vacant pre- and postsynaptic elements fit together. Moreover, vacant postsynaptic elements seem to be able to induce the breaking of adjacent synapses by attracting axonal elements bound in synapses (Toni et al., 2007; Butz et al., 2008). Thus, synapse formation may also depend on synapse deletion when vacant synaptic elements arise from remodelling axons (De Paola et al., 2006; Stettler et al., 2006; Nishiyama et al., 2008) or possibly from spine



turnover (Trachtenberg et al., 2002; Grutzendler et al., 2002; Brown et al., 2007). This gives the possibility of rearranging structural connectivity without changing gross numbers of synapses. Particularly, in neuronal networks with a moderate filling fraction (Stepanyants et al., 2002) this synaptic rewiring offers further degrees of freedom for plasticity in general.

### 3.4. *Links between structural and functional plasticity*

Functional plasticity is coupled to structural plasticity in the context of learning and memory. There is ample evidence that during memory formation strengthening of existing synapses occurs in a Hebbian sense. This may temporarily maintain the sensory activation pattern to be learned or may allow fine tuning of already learned tasks (Martin et al., 2000; Lisman et al., 2003; Melamed et al., 2004). Structural plasticity may hard-wire those functional changes, as, for example, when new synapses are formed in close apposition to existing synapses enhanced by LTP (Toni et al., 1999) or when synapses are deleted in association with LTD (Becker et al., 2008). We further hypothesize that the experience-dependent increase in excitability as seen in cortical networks in TMS studies on motor learning, occurring as a result of functional plasticity, subsequently drives an activity-dependent axonal outgrowth and an enlargement of the cortical representation area (Fig. 4c). It further remains to be tested whether local induction of

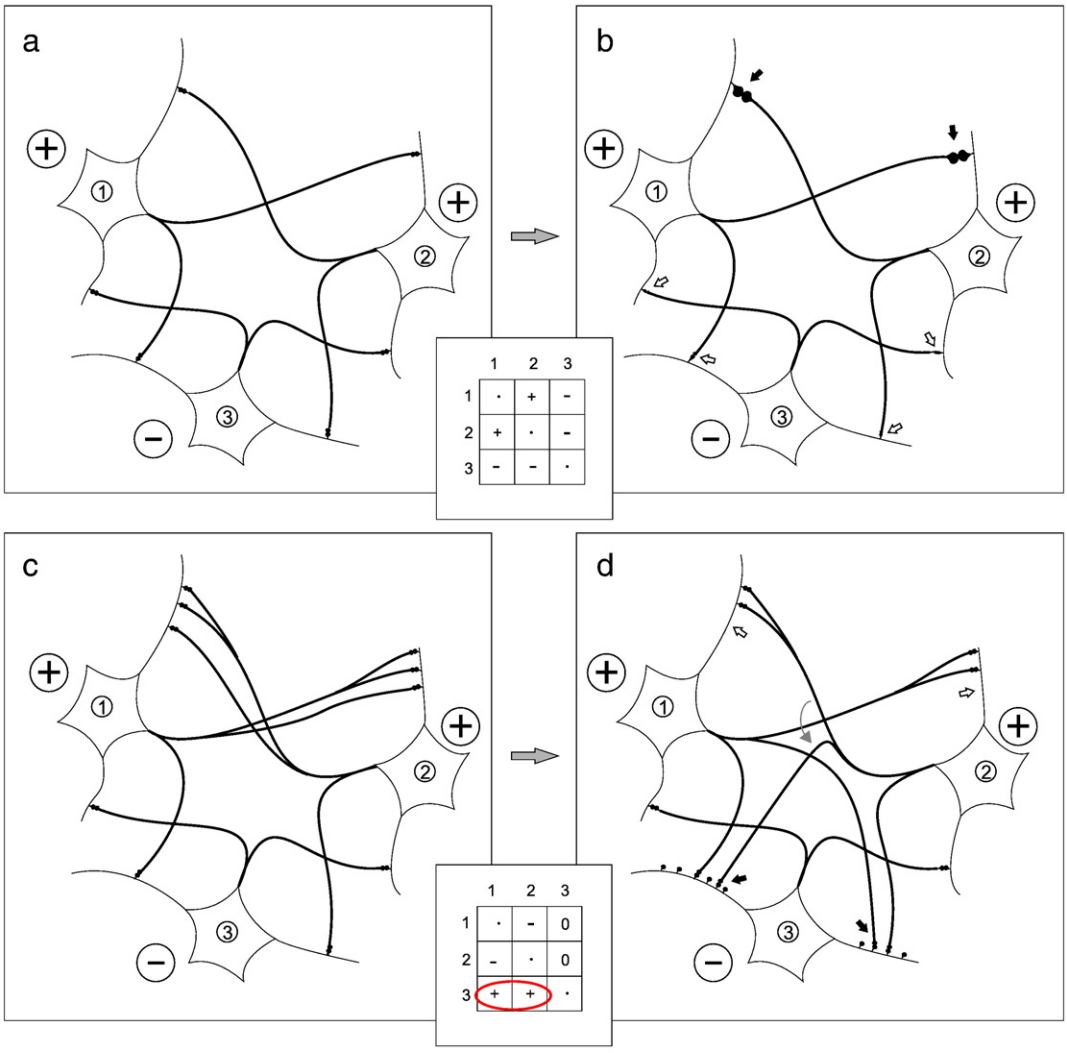



**Fig. 5 – Differences between functional plasticity (e.g., LTP and LTD) and structural plasticity (in particular synaptic rewiring). In a and b, a network with only functional plasticity, and in c and d with only structural plasticity. In this example, neuron one and two have high and correlated levels of activity, whereas neuron three has a low level of activity not correlated with neuron one and two. Due to functional plasticity, neurons one and two increase their synapse strengths, whereas the incoming and outgoing synaptic connections of neuron three are weakened (Axons are drawn in bold.). The two insets indicate these changes with + (strengthening) and – (weakening), whereas zero means no change. The dots indicate that there are no recurrent connections. Filled arrows in b) indicate strengthened synapses, and open arrows weakened synapses. Figures c) and d) show the same neurons but now interconnected by multiple synapses. The same pattern of neuronal activity in the network now causes the removal of postsynaptic elements of neurons one and two (open arrows in d) and the expression of vacant postsynaptic elements at the dendrites of neuron three (filled arrows in d). The loss of postsynaptic elements of neurons one and two causes the breaking up of synapses, and the remaining axonal branches redirect to neuron three.**

LTP is accompanied by a compensatory pruning of possibly noisy or interfering input synapses from non-associated cortical columns or areas, as is for instance known from ontogeny (Le Be and Markram, 2006).

### 3.5. *Need for computational models*

*In vivo* assessment of structural plasticity associated with experience and learning still requires highly sophisticated experimental approaches. Moreover, observations are usually limited to single synapses or parts of single neurons such as dendritic or axonal branches. Thus, there remains a gap between *in vivo* observations at the single cell level and anatomical studies revealing structural plasticity at the network level. This gap might be bridged by novel computational modelling approaches for structural plasticity that implement rules for structural modifications at the cell level and then compute the network dynamics over time (Butz and Teuchert-Noodt, 2006). A learning rule based on synaptic rewiring implies a hard combinatorial problem if all possible contact partners have to be tested (Chklovskii et al., 2004). It can be shown theoretically that structural plasticity, in terms of only synapse elimination, is able to maintain homeostasis in artificial networks with Hebbian synaptic plasticity (Helias et al., 2008). This result is in line with previous theoretical studies on activity-dependent structural plasticity by Dammasch (1989), van Ooyen and van Pelt (1994), van Ooyen et al. (1995), and Van Oss and Van Ooyen (1997). More recent studies have shown that synaptic rewiring contributes to homeostasis of neuronal and network activity Butz and Teuchert-Noodt (2006), Butz et al. (2006) and Butz et al. (2008).

### 3.6. *Additional dynamics by structural plasticity*

An important issue is whether novel network dynamics can be obtained from structural plasticity that cannot also be achieved from functional plasticity alone. For (adult) neurogenesis and the imbedding of new neurons into existing neuronal networks, it is of course necessary that new synapses are being formed before they can be strengthened or weakened by means of structural plasticity. However, even in a network with all-to-all connectivity between neurons, structural plasticity offers ways of rearranging connectivity that would not possible by functional plasticity alone. The aspect that adds a fundamental new dimension to plasticity is synaptic rewiring. As illustrated in Fig. 5, when a synapse is broken due to the loss of its pre- or postsynaptic element, synaptic rewiring can take place by merging the remaining synaptic counterpart with a vacant synaptic element from another neuron. Thus, the formation of a synapse between two neurons by synaptic rewiring depends on the breaking of a synapse between another pair of neurons. Therefore, synaptic rewiring involves at least three neurons. By contrast, functional plasticity typically involves just two neurons, since it depends only on the levels of activity in the pre- and postsynaptic cells of the synaptic connection. From a theoretical point of view, structural plasticity therefore allows more complex rules for changing connectivity than functional plasticity.

### 3.7. *Neurogenesis-induced structural plasticity*

Synaptic rewiring is particularly relevant in the context of adult neurogenesis (Butz et al., 2006), since young neurons have to become imbedded into pre-existing networks by the formation of new synapses. It is likely that the imbedding of young neurons depends on the synaptic offer of pre-existing neurons in a supply-and-demand fashion (Toni et al., 2008; reviewed in Lehmann et al., 2005). In the dentate gyrus of gerbils, we observed (Butz et al., 2008) a pronounced synaptic rewiring accompanying the ingrowth of new cells. Synaptic rewiring may therefore substantially contribute to the correct synaptic integration of new cells. Although the computational properties and advantages of synaptic rewiring and cell proliferation are not fully understood, they might hold the key for understanding the role of neurogenesis in hippocampal networks.

## Acknowledgments

The author thanks Prof. Wolff, Developmental Neurobiology, University of Göttingen for helpful comments on the manuscript and Dipl. Ing. Patrick Marsch for proof-reading.

## REFERENCES

Altman, J., Das, G.D., 1965. Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. J. Comp. Neurol. 124, 319–335.

Anthes, D.L., LeBoutillier, J.C., Petit, T.L., 1993. Structure and plasticity of newly formed adult synapses: a morphometric study in the rat hippocampus. Brain Res. 626, 50–62.

Antonini, A., Stryker, M.P., 1993. Rapid remodeling of axonal arbors in the visual cortex. Science 260, 1819–1821.

Antonini, A., Stryker, M.P., 1996. Plasticity of geniculocortical afferents following brief or prolonged monocular occlusion in the cat. J. Comp. Neurol. 369, 64–82.

Antonini, A., Fagiolini, M., Stryker, M.P., 1999. Anatomical correlates of functional plasticity in mouse visual cortex. J. Neurosci. 19, 4388–4406.

Arellano, J.I., Espinosa, A., Fairen, A., Yuste, R., DeFelipe, J., 2007. Non-synaptic dendritic spines in neocortex. Neuroscience 145, 464–469.

Bagorda, F., Teuchert-Noodt, G., Lehmann, K., 2006. Isolation rearing or methamphetamine traumatisation induce a "dysconnection" of prefrontal efferents in gerbils: implications for schizophrenia. J. Neural. Transm. 113, 365–379.

Bailey, C.H., Kandel, E.R., 1993. Structural changes accompanying memory storage. Annu. Rev. Physiol. 55, 397–426.

Bastrikova, N., Gardner, G.A., Reece, J.M., Jeromin, A., Dudek, S.M., 2008. Synapse elimination accompanies functional plasticity in hippocampal neurons. PNAS 105 (8), 3123–3127.

Becker, N., Wierenga, C.J., Fonseca, R., Bonhoeffer, T., Nägerl, U.V., 2008. LTD induction causes morphological changes of presynaptic boutons and reduces their contacts with spines. Neuron 60 (4), 590–597 2008 Nov 26.

Bennett, M.R., White, W., 1981. The survival and development of cholinergic neurons in potassium-enriched media. Brain Res. 173, 549–553.

Bishop, D.L., Misgeld, T., Walsh, M.K., Gan, W.B., Lichtman, J.W., 2004. Axon branch removal at developing synapses by axosome shedding. Neuron 44, 651–661.

Blaesing, B., Nossoll, M., Teuchert-Noodt, G., Dawirs, R.R., 2001. Postnatal maturation of prefrontal pyramidal neurones is sensitive to a single early dose of methamphetamine in gerbils (*Meriones unguiculatus*). J. Neural. Transm. 108, 101–113.

Brown, C.E., Li, P., Boyd, J.D., Delaney, K.R., Murphy, T.H., 2007. Extensive turnover of dendritic spines and vascular remodeling in cortical tissues recovering from stroke. J. Neurosci. 27 (15), 4101–4109.

Brummelte, S., Grund, T., Czok, A., Teuchert-Noodt, G., Neddens, J., 2006. Long-term effects of a single adult methamphetamine challenge: minor impact on dopamine fibre density in limbic brain areas of gerbils. Behav. Brain Funct. 2, 12.

Brummelte, S., Teuchert-Noodt, G., 2006. Postnatal development of dopamine innervation in the amygdala and the entorhinal cortex of the gerbil (*Meriones unguiculatus*). Brain Res. 1125, 9–16.

Brummelte, S., Neddens, J., Teuchert-Noodt, G., 2007. Alteration in the GABAergic network of the prefrontal cortex in a potential animal model of psychosis. J. Neural. Transm. 114, 539–547.

Buonomano, D.V., Merzenich, M.M., 1998. Cortical plasticity: from synapses to maps. Annu. Rev. Neurosci. 21, 149–186.

Busche, A., Neddens, J., Dinter, C., Dawirs, R.R., Teuchert-Noodt, G., 2002. Differential influence of rearing conditions and methamphetamine on serotonin fibre maturation in the dentate gyrus of gerbils (*Meriones unguiculatus*). Dev. Neurosci. 24, 512–521.

Busche, A., Polascheck, D., Lesting, J., Neddens, J., Teuchert-Noodt, G., 2004. Developmentally induced imbalance of dopaminergic fibre densities in limbic brain regions of gerbils (*Meriones unguiculatus*). J. Neural. Transm. 111, 451–463.

Busche, A., Bagorda, A., Lehmann, K., Neddens, J., Teuchert-Noodt, G., 2006. The maturation of the acetylcholine system in the dentate gyrus of gerbils (*Meriones unguiculatus*) is affected by epigenetic factors. J. Neural. Transm. 113, 113–124.

Butz, M., Teuchert-Noodt, G., 2006. A simulation model for compensatory plasticity in the prefrontal cortex inducing a cortico-cortical dysconnection in early brain development. J. Neural. Transm. 113, 695–710.

Butz, M., Lehmann, K., Dammasch, I.E., Teuchert-Noodt, G., 2006. A theoretical network model to analyse neurogenesis and synaptogenesis in the dentate gyrus. Neural. Netw. 19, 1490–1505.

Butz, M., Teuchert-Noodt, G., Grafen, K., van Ooyen, A., 2008. Inverse relationship between adult hippocampal cell proliferation and synaptic rewiring in the dentate gyrus. Hippocampus 18 (9), 879–898.

Cameron, H.A., Woolley, C.S., McEwen, B.S., Gould, E., 1993. Differentiation of newly born neurons and glia in the dentate gyrus of the adult rat. Neuroscience 56, 337–344.

Carmichael, S.T., Wei, L., Rovainen, C.M., Woolsey, T.A., 2001. New patterns of intracortical projections after focal cortical stroke. Neurobiol. Dis. 8, 910–922.

Carmichael, S.T., 2006. Cellular and molecular mechanisms of neural repair after stroke: making waves. Ann. Neurol. 59, 735–742.

Chang, F.L., Greenough, W.T., 1982. Lateralized effects of monocular training on dendritic branching in adult split-brain rats. Brain Res. 232, 283–292.

Chang, P.L., Isaacs, K.R., Greenough, W.T., 1991. Synapse formation occurs in association with the induction of long-term potentiation in two-year-old rat hippocampus in vitro. Neurobiol. Aging 12, 517–522.

Changeux, J.P., Danchin, A., 1976. Selective stabilization of developing synapses as a mechanism for specification of neuronal networks. Nature 264, 705–712.

Chklovskii, D.B., Mel, B.W., Svoboda, K., 2004. Cortical rewiring and information storage. Nature 431, 782–788.

Cotman, C.W., Lynch, G., 1978. Reactive synaptogenesis in the hippocampus. In: Cotman, C.W. (ed.), Neuronal Plasticity. Raven Press, New York, pp. 227–271.

Cotman, C.W., Nieto-Sampedro, M., 1984. Cell biology of synaptic plasticity. Science 225, 1287–1294.

Cowan, W.M., Fawcett, J.W., Oleary, D.D.M., Stanfield, B.B., 1984. Regressive events in neurogenesis. Science 225, 1258–1265.

Dammasch, I.E., 1989. Structural realization of a Hebb-type learning rule. In: Cotterill, R.M.J. (ed.), Models of Brain Functions. University Press, Cambridge.

Dan, Y., Poo, M.M., 2006. Spike timing-dependent plasticity: from synapse to perception. Physiol. Rev. 86 (3), 1033–1048.

Darian-Smith, C., Gilbert, C.D., 1994. Axonal sprouting accompanies functional reorganization in adult cat striate cortex. Nature 368, 737–740.

Darian-Smith, C., Gilbert, C.D., 1995. Topographic reorganization in the striate cortex of the adult cat and monkey is cortically mediated. J. Neurosci. 15, 1631–1647.

Datwani, A., Iwasato, T., Itohara, S., Erzurumlu, R.S., 2002. NMDA receptor-dependent pattern transfer from afferents to postsynaptic cells and dendritic differentiation in the barrel cortex. Mol. Cell. Neurosci. 21, 477–492.

Dawirs, R.R., Teuchert-Noodt, G., Busse, M., 1991. Single doses of methamphetamine cause changes in the density of dendritic spines in the prefrontal cortex of gerbils (*Meriones unguiculatus*). Neuropharmacology 30, 275–282.

Dawirs, R.R., Teuchert-Noodt, G., Kacza, J., 1992. Naturally occurring degrading events in axon terminals of the dentate gyrus and stratum lucidum in the spiny mouse (*Acomys cahirinus*) during maturation, adulthood and aging. Dev. Neurosci. 14, 210–220.

Dawirs, R.R., Teuchert-Noodt, G., Molthagen, M., 1993. Indication of methamphetamine-induced reactive synaptogenesis in the prefrontal cortex of gerbils (*Meriones unguiculatus*). Eur. J. Pharmacol. 241, 89–97.

Dawirs, R.R., Teuchert-Noodt, G., Czaniera, R., 1994. The postnatal maturation of dopamine innervation in the prefrontal cortex of gerbils (*Meriones unguiculatus*) is sensitive to an early single dose of methamphetamine. A quantitative immunocytochemical study. J. Hirnforsch. 35, 195–204.

Dawirs, R.R., Teuchert-Noodt, G., Czaniera, R., 1996. Ontogeny of PFC-related behaviours is sensitive to a single non-invasive dose of methamphetamine in neonatal gerbils (*Meriones unguiculatus*). J. Neural. Transm. 103, 1235–1245.

Dawirs, R.R., Teuchert-Noodt, G., Nossoll, M., 1997. Pharmacologically induced neural plasticity in the prefrontal cortex of adult gerbils (*Meriones unguiculatus*). Eur. J. Pharmacol. 327, 117–123.

Dawirs, R.R., Teuchert-Noodt, G., Hildebrandt, K., Fei, F., 2000. Granule cell proliferation and axon terminal degradation in the dentate gyrus of gerbils (*Meriones unguiculatus*) during maturation, adulthood and aging. Journal of Neural. Transmission 107, 639–647.

Dawirs, R.R., Teuchert-Noodt, G., (2001) A novel pharmacological concept in an animal model of psychosis. Acta Psychiatr. Scand. (Suppl.) 10–17.

De Paola, V., Holtmaat, A., Knott, G., Song, S., Wilbrecht, L., Caroni, P., Svoboda, K., 2006. Cell type-specific structural plasticity of axonal branches and boutons in the adult neocortex. Neuron 49, 861–875.

Denk, W., Strickler, J.H., Webb, W.W., 1990. Two-photon laser scanning fluorescence microscopy. Science 248 (4951), 73–76.

Derksen, M.J., Ward, N.L., Hartle, K.D., Ivanco, T.L., 2007. MAP2 and synaptophysin protein expression following motor learning suggests dynamic regulation and distinct alterations coinciding with synaptogenesis. Neurobiol. Learn. Mem. 87, 404–415.

Duffy, C.J., Rakic, P., 1983. Differentiation of granule cell dendrites in the dentate gyrus of the rhesus monkey: a quantitative Golgi study. J. Comp. Neurol. 214, 224–237.

Engert, F., Bonhoeffer, T., 1999. Dendritic spine changes associated with hippocampal long-term synaptic plasticity. Nature 399, 66–70.
Esposito, M.S., Piatti, V.C., Laplagne, D.A., Morgenstern, N.A., Ferrari, C.C., Pitossi, F.J., Schinder, A.F., 2005. Neuronal differentiation in the adult hippocampus recapitulates embryonic development. J. Neurosci. 25, 10074–10086.
Farkas, T., Perge, J., Kis, Z., Wolff, J.R., Toldi, J., 2000. Facial nerve injury-induced disinhibition in the primary motor cortices of both hemispheres. Eur. J. Neurosci. 12, 2190–2194.
Fiala, J.C., Feinberg, M., Popov, V., Harris, K.M., 1998. Synaptogenesis via dendritic filopodia in developing hippocampal area CA1. J. Neurosci. 18, 8900–8911.
Fischer, M., Kaech, S., Wagner, U., Brinkhaus, H., Matus, A., 2000. Glutamate receptors regulate actin-based plasticity in dendritic spines. Nat. Neurosci. 3, 887–894.
Florence, S.L., Taub, H.B., Kaas, J.H., 1998. Large-scale sprouting of cortical connections after peripheral injury in adult macaque monkeys. Science 282, 1117–1121.
Florence, S.L., Kaas, J.H., 2000. Cortical plasticity: growth of new connections can contribute to reorganization. In: Rowe, M.J., Iwamura, Y. (eds.), Somatosensory Processing: From Single Neuron to Brain Imaging. Harwood, St. Leonards, NSW, Australia, pp. 167–186.
Fox, K., Wong, R.O., 2005. A comparison of experience-dependent plasticity in the visual and somatosensory systems. Neuron 48, 465–477.
Frotscher, M., Heimrich, B., Deller, T., Nitsch, R., 1995. Understanding the cortex through the hippocampus: lamina-specific connections of the rat hippocampal neurons. J. Anat. 187 (Pt 3), 539–545.
Gallo, V., Kingsbury, A., Balázs, R., Jørgensen, O.S., 1987. The role of depolarization in the survival and differentiation of cerebellar granule cells in culture. J. Neurosci. 7 (7), 2203–2213.
Gallyas, F., Wolff, J.R., Bottcher, H., Zaborszky, L., 1980. A reliable and sensitive method to localize terminal degeneration and lysosomes in the central nervous system. Stain Technol. 55, 299–306.
Ge, S., Goh, E.L., Sailor, K.A., Kitabatake, Y., Ming, G.L., Song, H., 2006. GABA regulates synaptic integration of newly generated neurons in the adult brain. Nature 439, 589–593.
Ge, S., Yang, C.H., Hsu, K.S., Ming, G.L., Song, H., 2007. A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. Neuron 54, 559–566.
Geinisman, Y., 2000. Structural synaptic modifications associated with hippocampal LTP and behavioral learning. Cereb. Cortex. 10, 952–962.
Giannikopoulos, D.V., Eysel, U.T., 2006. Dynamics and specificity of cortical map reorganization after retinal lesions. Proc. Natl. Acad. Sci. U. S. A. 103, 10805–10810.
Gould, E., Gross, C.G., 2002. Neurogenesis in adult mammals: some progress and problems. J. Neurosci. 22, 619–623.
Grutzendler, J., Kasthuri, N., Gan, W.B., 2002. Long-term dendritic spine stability in the adult cortex. Nature 420, 812–816.
Hebb, D.O., 1949. The Organization of Behaviour. Wiley, New York.
Helias, M., Rotter, S., Gewaltig, M., Diesmann, M., 2008. Structural plasticity controlled by calcium based correlation detection. Front Comput. Neurosci. 2, 7 doi:10.3389/neuro.10.007.2008.
Hensch, T.K., 2005. Critical period plasticity in local cortical circuits. Nat. Rev. Neurosci. 6, 877–888.
Hess, G., Donoghue, J.P., 1994. Long-term potentiation of horizontal connections provides a mechanism to reorganize cortical motor maps. J. Neurophysiol. 71, 2543–2547.
Hess, G., Donoghue, J.P., 1996. Long-term depression of horizontal connections in rat motor cortex. Eur. J. Neurosci. 8 (4), 658–665.
Hess, G., Aizenman, C.D., Donoghue, J.P., 1996. Conditions for the induction of long-term potentiation in layer II/III horizontal connections of the rat motor cortex. J. Neurophysiol. 75, 1765–1778.
Heynen, A.J., Yoon, B.J., Liu, C.H., Chung, H.J., Huganir, R.L., Bear, M.F., 2003. Molecular mechanism for loss of visual cortical responsiveness following brief monocular deprivation. Nat. Neurosci. 6, 854–862.
Hofer, S.B., Mrsic-Flogel, T.D., Bonhoeffer, T., Hübener, M., 2006. Prior experience enhances plasticity in adult visual cortex. Nat. Neurosci. 9 (1), 127–132.
Holtmaat, A.J., Trachtenberg, J.T., Wilbrecht, L., Shepherd, G.M., Zhang, X., Knott, G.W., Svoboda, K., 2005. Transient and persistent dendritic spines in the neocortex in vivo. Neuron 45, 279–291.
Holtmaat, A., Wilbrecht, L., Knott, G.W., Welker, E., Svoboda, K., 2006. Experience-dependent and cell-type-specific spine growth in the neocortex. Nature 441 (7096), 979–983.
Holzgraefe, M., Teuchert, G., Wolff, J.R., 1981. Chronic isolation of visual cortex induces reorganization of cortico-cortical connections. In: Flohr, H., Precht, W. (eds.), Lesion-induced Neuronal Plasticity in Sensorimotor Systems. Springer-Verlag, Berlin, Heidelberg, New York, pp. 351–359.
Hua, J.Y., Smear, M.C., Baier, H., Smith, S.J., 2005. Regulation of axon growth in vivo by activity-based competition. Nature 434, 1022–1026.
Hutchins, B.I., Kalil, K., 2008. Differential outgrowth of axons and their branches is regulated by localized calcium transients. J. Neurosci. 28, 143–153.
Jontes, J.D., Smith, S.J., 2000. Filopodia, spines, and the generation of synaptic diversity. Neuron 27, 11–14.
Jourdain, P., Fukunaga, K., Muller, D., 2003. Calcium/calmodulin-dependent protein kinase II contributes to activity-dependent filopodia growth and spine formation. J. Neurosci. 23, 10645–10649.
Kalisman, N., Silberberg, G., Markram, H., 2005. The neocortical microcircuit as a tabula rasa. Proc. Natl. Acad. Sci. U. S. A. 102, 880–885.
Kaplan, M.S., Bell, D.H., 1983. Neuronal proliferation in the 9-month-old rodent-radioautographic study of granule cells in the hippocampus. Exp. Brain Res. 52, 1–5.
Kater, S.B., Mattson, M.P., Cohan, C., Connor, J., 1988. Calcium regulation of the neuronal growth cone. Trends Neurosci. 11, 315–321.
Kater, S.B., Mattson, M.P., Guthrie, P.B., 1989. Calcium-induced neuronal degeneration: a normal growth cone regulating signal gone awry (?). Ann. N. Y. Acad. Sci. 568, 252–261.
Kater, S.B., Guthrie, P.B., 1989. The neuronal growth cone: calcium regulation of a presecretory structure. Soc. Gen. Physiol. Ser. 44, 111–122.
Kater, S.B., Guthrie, P.B., 1990. Neuronal growth cone as an integrator of complex environmental information. Cold Spring Harb. Symp. Quant. Biol. 55, 359–370.
Kater, S.B., Guthrie, P.B., Mills, L.R., 1990. Integration by the neuronal growth cone: a continuum from neuroplasticity to neuropathology. Prog. Brain Res. 86, 117–128.
Keck, T., Mrsic-Flogel, T.D., Vaz Afonso, M., Eysel, U.T., Bonhoeffer, T., Hübener, M., 2008. Massive restructuring of neuronal circuits during functional reorganization of adult visual cortex. Nat. Neurosci. 11 (10), 1162–1167.
Keller, A., Bagorda, F., Hildebrandt, K., Teuchert-Noodt, G., 2000. Effects of enriched and of restricted rearing on both neurogenesis and synaptogenesis in the hippocampal dentate gyrus of adult gerbils (*Meriones unguiculatus*). Neurol. Psychiatry Brain Res. 8, 101–107.
Kirov, S.A., Harris, K.M., 1999. Dendrites are more spiny on mature hippocampal neurons when synapses are inactivated. Nat. Neurosci. 2, 878–883.
Kirov, S.A., Goddard, C.A., Harris, K.M., 2004. Age-dependence in the homeostatic upregulation of hippocampal dendritic spine number during blocked synaptic transmission. Neuropharmacology 47, 640–648.
Kleim, J.A., Barbay, S., Cooper, N.R., Hogg, T.M., Reidel, C.N., Remple, M.S., Nudo, R.J., 2002. Motor learning-dependent

synaptogenesis is localized to functionally reorganized motor cortex. Neurobiol. Learn Mem. 77, 63–77.
Kleim, J.A., Hogg, T.M., VandenBerg, P.M., Cooper, N.R., Bruneau, R., Remple, M., 2004. Cortical synaptogenesis and motor map reorganization occur during late, but not early, phase of motor skill learning. J. Neurosci. 24, 628–633.
Kleim, J.A., Kleim, E.D., Cramer, S.C., 2007. Systematic assessment of training-induced changes in corticospinal output to hand using frameless stereotaxic transcranial magnetic stimulation. Nat. Protoc. 2, 1675–1684.
Knott, G.W., Quairiaux, C., Genoud, C., Welker, E., 2002. Formation of dendritic spines with GABAergic synapses induced by whisker stimulation in adult mice. Neuron 34, 265–273.
Knott, G.W., Holtmaat, A., Wilbrecht, L., Welker, E., Svoboda, K., 2006. Spine growth precedes synapse formation in the adult neocortex in vivo. Nat. Neurosci. 9, 1117–1124.
Korkotian, E., Segal, M., 2007. Morphological constraints on calcium dependent glutamate receptor trafficking into individual dendritic spine. Cell. Calcium. 42, 41–57.
Kossel, A., Lowel, S., Bolz, J., 1995. Relationships between dendritic fields and functional architecture in striate cortex of normal and visually deprived cats. J. Neurosci. 15, 3913–3926.
Kossut, M., Juliano, S.L., 1999. Anatomical correlates of representational map reorganization induced by partial vibrissectomy in the barrel cortex of adult mice. Neuroscience 92, 807–817.
Lamprecht, R., LeDoux, J., 2004. Structural plasticity and memory. Nat. Rev. Neurosci. 5, 45–54.
Lang, S.B., Bonhoeffer, T., Lohmann, C., 2006. Simultaneous imaging of morphological plasticity and calcium dynamics in dendrites. Nat. Protoc. 1, 1859–1864.
Laplagne, D.A., Esposito, M.S., Piatti, V.C., Morgenstern, N.A., Zhao, C., van, P.H., Gage, F.H., Schinder, A.F., 2006. Functional convergence of neurons generated in the developing and adult hippocampus. PLoS. Biol. 4, e409.
Larmet, Y., Dolphin, A.C., Davies, A.M., 1992. Intracellular calcium regulates the survival of early sensory neurons before they become dependent on neurotrophic factors. Neuron. 9 (3), 563–574.
Laskawi, R., Landgrebe, M., Wolff, J.R., 1996. Electron microscopical evidence of synaptic reorganization in the contralateral motor cortex of adult rats following facial nerve lesion. ORL J. Otorhinolaryngol. Relat. Spec. 58, 266–270.
Le Be, J.V., Markram, H., 2006. Spontaneous and evoked synaptic rewiring in the neonatal neocortex. Proc. Natl. Acad. Sci. U. S. A. 103, 13214–13219.
Lehmann, K., Lesting, J., Polascheck, D., Teuchert-Noodt, G., 2003. Serotonin fibre densities in subcortical areas: differential effects of isolated rearing and methamphetamine. Brain Res. Dev. Brain Res. 147, 143–152.
Lehmann, K., Hundsdorfer, B., Hartmann, T., Teuchert-Noodt, G., 2004. The acetylcholine fiber density of the neocortex is altered by isolated rearing and early methamphetamine intoxication in rodents. Exp. Neurol. 189, 131–140.
Lehmann, K., Butz, M., Teuchert-Noodt, G., 2005. Offer and demand: proliferation and survival of neurons in the dentate gyrus. Eur. J. Neurosci. 21, 3205–3216.
Lesting, J., Neddens, J., Busche, A., Teuchert-Noodt, G., 2005. Hemisphere-specific effects on serotonin but not dopamine innervation in the nucleus accumbens of gerbils caused by isolated rearing and a single early methamphetamine challenge. Brain. Res. 1035, 168–176.
Lichtman, J.W., Sanes, J.R., 2003. Watching the neuromuscular junction. J. Neurocytol. 32, 767–775.
Liepert, J., Storch, P., Fritsch, A., Weiller, C., 2000. Motor cortex disinhibition in acute stroke. Clin. Neurophysiol. 111, 671–676.
Liepert, J., Uhde, I., Graf, S., Leidner, O., Weiller, C., 2001. Motor cortex plasticity during forced-use therapy in stroke patients: a preliminary study. J. Neurol. 248, 315–321.
Linden, R., 1994. The survival of developing neurons: a review of afferent control. Neuroscience 58, 671–682.
Lipton, S.A., Kater, S.B., 1989. Neurotransmitter regulation of neuronal outgrowth, plasticity and survival. Trends Neurosci. 12, 265–270.
Lisman, J., Lichtman, J.W., Sanes, J.R., 2003. LTP: perils and progress. Nat. Rev. Neurosci. 4, 926–929.
Lynch, G., 1974. Functional recovery after lesions of the nervous system. 3. Developmental processes in neural plasticity. The formation of new synaptic connections after brain damage and their possible role in recovery of function. Neurosci. Res. Program Bull. 12, 228–233.
Lynch, G.S., Mosko, S., Parks, T., Cotman, C.W., 1973. Relocation and hyperdevelopment of the dentate gyrus commissural system after entorhinal lesions in immature rats. Brain Res. 50, 174–178.
Majewska, A.K., Newton, J.R., Sur, M., 2006. Remodeling of synaptic structure in sensory cortical areas in vivo. J. Neurosci. 26, 3021–3029.
Maletic-Savatic, M., Malinow, R., Svoboda, K., 1999. Rapid dendritic morphogenesis in CA1 hippocampal dendrites induced by synaptic activity. Science 283, 1923–1927.
Malenka, R.C., Bear, M.F., 2004. LTP and LTD: an embarrassment of Riches. Neuron 44, 5–21.
Manganotti, P., Patuzzo, S., Cortese, F., Palermo, A., Smania, N., Fiaschi, A., 2002. Motor disinhibition in affected and unaffected hemisphere in the early period of recovery after stroke. Clin. Neurophysiol. 113, 936–943.
Maravall, M., Koh, I.Y., Lindquist, W.B., Svoboda, K., 2004. Experience-dependent changes in basal dendritic branching of layer 2/3 pyramidal neurons during a critical period for developmental plasticity in rat barrel cortex. Cereb. Cortex 14 (6), 655–664.
Markakis, E.A., Gage, F.H., 1999. Adult-generated neurons in the dentate gyrus send axonal projections to field CA3 and are surrounded by synaptic vesicles. J. Comp. Neurol. 406, 449–460.
Martin, S.J., Grimwood, P.D., Morris, R.G., 2000. Synaptic plasticity and memory: an evaluation of the hypothesis. Annu. Rev. Neurosci. 23, 649–711.
Massey, P.V., Bashir, Z.I., 2007. Long-term depression: multiple forms and implications for brain functions. Trends Neurosci. 30 (4), 176–184.
Matsuzaki, M., Honkura, N., Ellis-Davies, G.C., Kasai, H., 2004. Structural basis of long-term potentiation in single dendritic spines. Nature 429, 761–766.
Mattson, M.P., Kater, S.B., 1987. Calcium regulation of neurite elongation and growth cone motility. J. Neurosci. 7, 4034–4043.
Mattson, M.P., 1988. Neurotransmitters in the regulation of neuronal cytoarchitecture. Brain. Res. 472, 179–212.
Mattson, M.P., Taylor-Hunter, A., Kater, S.B., 1988. Neurite outgrowth in individual neurons of a neuronal population is differentially regulated by calcium and cyclic AMP. J. Neurosci. 8, 1704–1711.
Melamed, O., Gerstner, W., Maass, W., Tsodyks, M., Markram, H., 2004. Coding and learning of behavioral sequences. Trends Neurosci. 27, 11–14.
Merzenich, M.M., Kaas, J.H., Wall, J.T., Sur, M., Nelson, R.J., Felleman, D.J., 1983. Progression of change following median nerve section in the cortical representation of the hand in areas 3b and 1 in adult owl and squirrel monkeys. Neuroscience 10, 639–665.
Merzenich, M.M., Nelson, R.J., Stryker, M.P., Cynader, M.S., Schoppmann, A., Zook, J.M., 1984. Somatosensory cortical map changes following digit amputation in adult monkeys. J. Comp. Neurol. 224, 591–605.

Missler, M., Eins, S., Merker, H.J., Rothe, H., Wolff, J.R., 1993a. Pre- and postnatal development of the primary visual cortex of the common marmoset. I A changing space for synaptogenesis. J. Comp. Neurol. 333 (1), 41–52.
Missler, M., Wolff, A., Merker, H.J., Wolff, J.R., 1993b. Pre- and postnatal development of the primary visual cortex of the common marmoset. II.Formation, remodelling and elimination of synapses as overlapping processes. J. Comp. Neurol. 333 (1), 53–67.
Mizrahi, A., Katz, L.C., 2003. Dendritic stability in the adult olfactory bulb. Nat. Neurosci. 6, 1201–1207.
Nadler, J.V., Cotman, C.W., 1978. Interactions between afferents to the dentate gyrus after entorhinal lesion during development: long-term regulation of choline acetyl-transferase activity. Brain Res. 142, 174–181.
Nägerl, U.V., Eberhorn, N., Cambridge, S.B., Bonhoeffer, T., 2004. Bidirectional activity-dependent morphological plasticity in hippocampal neurons. Neuron 44, 759–767.
Neddens, J., Brandenburg, K., Teuchert-Noodt, G., Dawirs, R.R., 2001. Differential environment alters ontogeny of dopamine innervation of the orbital prefrontal cortex in gerbils. J. Neurosci. Res. 63, 209–213.
Neddens, J., Lesting, J., Dawirs, R.R., Teuchert-Noodt, G., 2002. An early methamphetamine challenge suppresses the maturation of dopamine fibres in the nucleus accumbens of gerbils: on the significance of rearing conditions. J. Neural. Transm. 109, 141–155.
Neddens, J., Bagorda, F., Busche, A., Horstmann, S., Moll, G.H., Dawirs, R.R., Teuchert-Noodt, G., 2003. Epigenetic factors differentially influence postnatal maturation of serotonin (5-HT) innervation in cerebral cortex of gerbils: interaction of rearing conditions and early methamphetamine challenge. Brain Res. Dev. Brain Res. 146, 119–130.
Neddens, J., Dawirs, R.R., Bagorda, F., Busche, A., Horstmann, S., Teuchert-Noodt, G., 2004. Postnatal maturation of cortical serotonin lateral asymmetry in gerbils is vulnerable to both environmental and pharmacological epigenetic challenges. Brain Res. 1021, 200–208.
Nelson, P.G., Fields, R.D., Yu, C., Liu, Y., 1993. Synapse elimination from the mouse neuromuscular junction in vitro: a non-Hebbian activity-dependent process. J. Neuobiol. 24 (11), 1517–1530.
Nishiyama, H., Fukaya, M., Watanabe, M., Linden, D.J., 2008. Axonal motility and its modulation by activity are branch-type specific in the intact adult cerebellum. Neuron 56 (3), 472–487.
Nossoll, M., Teuchert-Noodt, G., Dawirs, R.R., 1997. A single dose of methamphetamine in neonatal gerbils affects adult prefrontal gamma-aminobutyric acid innervation. Eur. J. Pharmacol. 340, R3–R5.
Nudo, R.J., 2007. Postinfarct cortical plasticity and behavioral recovery. Stroke 38, 840–845.
Okabe, S., Miwa, A., Okado, H., 2001. Spine formation and correlated assembly of presynaptic and postsynaptic molecules. J. Neurosci. 21, 6105–6114.
Okamoto, K., Nagai, T., Miyawaki, A., Hayashi, Y., 2004. Rapid and persistent modulation of actin dynamics regulates postsynaptic reorganization underlying bidirectional plasticity. Nat. Neurosci. 7, 1104–1112.
Petrak, L.J., Harris, K.M., Kirov, S.A., 2005. Synaptogenesis on mature hippocampal dendrites occurs via filopodia and immature spines during blocked synaptic transmission. J. Comp. Neurol. 484, 183–190.
Piatti, V.C., Esposito, M.S., Schinder, A.F., 2006. The timing of neuronal development in adult hippocampal neurogenesis. Neuroscientist 12, 463–468.
Poirazi, P., Mel, B.W., 2001. Impact of active dendrites and structural plasticity on the memory capacity of neural tissue. Neuron 29, 779–796.
Pons, T.P., Garraghty, P.E., Ommaya, A.K., Kaas, J.H., Taub, E., Mishkin, M., 1991. Massive cortical reorganization after sensory deafferentation in adult macaques. Science 252, 1857–1860.
Portera-Cailliau, C., Pan, D.T., Yuste, R., 2003. Activity-regulated dynamic behavior of early dendritic protrusions: evidence for different types of dendritic filopodia. J. Neurosci. 23, 7129–7142.
Portera-Cailliau, C., Weimer, R.M., De Paola, V., Caroni, P., Svoboda, K., 2005. Diverse modes of axon elaboration in the developing neocortex. PLoS Biol. 3 (8), e272.
Purves, D., Lichtman, J.W., 1985. Principles of Neural Development. Sinauer Ass, Sunderland USA.
Pratt, K.G., Watt, A.J., Griffith, L.C., Nelson, S.B., Turrigiano, G.G., 2003. Activity-dependent remodeling of presynaptic inputs by postsynaptic expression of activated CaMKII. Neuron 39 (2), 269–281.
Raisman, G., 1969. Neuronal plasticity in the septal nuclei of the adult rat. Brain Res. 14, 25–48.
Rao, M.S., Jacobson, M., 2005. Developmental Neurobiology. Kluwer Academic Publishers, New York.
Rajan, I., Cline, H.T., 1998. Glutamate receptor activity is required for normal development of tectal cell dendrites in vivo. J. Neurosci. 18, 7836–7846.
Raymond, C.R., 2007. LTP forms 1, 2 and 3: different mechanisms for the 'long' in long-term potentiation. Trends Neurosci. 30 (4), 167–175.
Rekart, J.L., Sandoval, C.J., Routtenberg, A., 2007. Learning-induced axonal remodeling: evolutionary divergence and conservation of two components of the mossy fiber system within Rodentia. Neurobiol. Learn Mem. 87, 225–235.
Richards, D.A., Mateos, J.M., Hugel, S., de Paola, V., Caroni, P., Gähwiler, B.H., McKinney, R.A., 2005. Glutamate induces the rapid formation of spine head protrusions in hippocampal slice cultures. Proc. Natl. Acad. Sci. U. S. A. 102 (17), 6166–6171.
Rickmann, M., Amaral, D.G., Cowan, W.M., 1987. Organization of radial glial cells during the development of the rat dentate gyrus. J. Comp. Neurol. 264, 449–479.
Sanes, J.N., Donoghue, J.P., 2000. Plasticity and primary motor cortex. Annu. Rev. Neurosci. 23, 393–415.
Schlessinger, A.R., Cowan, W.M., Gottlieb, D.I., 1975. An autoradiographic study of the time of origin and the pattern of granule cell migration in the dentate gyrus of the rat. J. Comp. Neurol. 159, 149–175.
Scott, B.S., 1977. The effect of elevated potassium on the time course of neuron survival in cultures of dissociated dorsal root ganglia. J. Cell. Physiol. 91, 305–316.
Seitz, R.J., Butefisch, C.M., Kleiser, R., Homberg, V., 2004. Reorganisation of cerebral circuits in human ischemic brain disease. Restor. Neurol. Neurosci. 22, 207–229.
Seki, T., Arai, Y., 1993. Highly polysialylated neural cell adhesion molecule (NCAM-H) is expressed by newly generated granule cells in the dentate gyrus of the adult rat. J. Neurosci. 13, 2351–2358.
Seki, T., Arai, Y., 1995. Age-related production of new granule cells in the adult dentate gyrus. Neuroreport 6, 2479–2482.
Sernagor, E., Grzywacz, N.M., 1996. Influence of spontaneous activity and visual experience on developing retinal receptive fields. Curr. Biol. 6, 1503–1508.
Shi, S.H., Hayashi, Y., Petralia, R.S., Zaman, S.H., Wenthold, R.J., Svoboda, K., Malinow, R., 1999. Rapid spine delivery and redistribution of AMPA receptors after synaptic NMDA receptor activation. Science 284, 1811–1816.
Shimizu, T., Hosaki, A., Hino, T., Sato, M., Komori, T., Hirai, S., Rossini, P.M., 2002. Motor cortical disinhibition in the unaffected hemisphere after unilateral cortical stroke. Brain 125, 1896–1907.
Smirnakis, S.M., Brewer, A.A., Schmid, M.C., Tolias, A.S., Schuz, A., Augath, M., Inhoffen, W., Wandell, B.A., Logothetis, N.K., 2005. Lack of long-term cortical reorganization after macaque retinal lesions. Nature 435, 300–307.

Stanfield, B.B., Trice, J.E., 1988. Evidence that granule cells generated in the dentate gyrus of adult rats extend axonal projections. Exp. Brain. Res. 72, 399–406.
Stepanyants, A., Hof, P.R., Chklovskii, D.B., 2002. Geometry and structural plasticity of synaptic connectivity. Neuron 34, 275–288.
Stettler, D.D., Yamahachi, H., Li, W., Denk, W., Gilbert, C.D., 2006. Axons and synaptic boutons are highly dynamic in adult visual cortex. Neuron 49 (6), 877–887.
Stroemer, R.P., Kent, T.A., Hulsebosch, C.E., 1995. Neocortical neural sprouting, synaptogenesis, and behavioral recovery after neocortical infarction in rats. Stroke 26, 2135–2144.
Tailby, C., Wright, L.L., Metha, A.B., Calford, M.B., 2005. Activity-dependent maintenance and growth of dendrites in adult cortex. Proc. Natl. Acad. Sci. U. S. A. 102, 4631–4636.
Takeuchi, N., Tada, T., Chuma, T., Matsuo, Y., Ikoma, K., 2007. Disinhibition of the premotor cortex contributes to a maladaptive change in the affected hand after stroke. Stroke 38, 1551–1556.
Tashiro, A., Makino, H., Gage, F.H., 2007. Experience-specific functional modification of the dentate gyrus through adult neurogenesis: a critical period during an immature stage. J. Neurosci. 27, 3252–3259.
Tessier-Lavigne, M., Goodman, C.S., 1996. The molecular biology of axon guidance. Science 274, 1123–1133.
Teuchert-Noodt, G., 1989. Central nervous system ontogeny. An evaluation of the recapitulation hypothesis. In: Splechtna, H., Hilgers, H. (eds.), Trends in Vertebrate Morphology. Gustav Fischer Verlag, Stuttgart, New York.
Teuchert-Noodt, G., Breuker, K.H., Dawirs, R.R., 1991. Neuronal lysosome accumulation in degrading synapses of sensory-motor and limbic subsystems in the duck *Anas platyrhynchos*: indication of rearrangements during avian brain development? Dev. Neurosci. 13, 151–163.
Teuchert-Noodt, G., Dawirs, R.R., 1996. Naturally occurring synapse degradation in the developing cerebellum of the mallard (*Anas platyrhynchos*) and the Peking duck (*Forma domestica*). J. Hirnforsch. 37, 547–560.
Teuchert-Noodt, G., 2000. Neuronal degeneration and reorganization: a mutual principle in pathological and in healthy interactions of limbic and prefrontal circuits. J. Neural. Transm. Suppl. 315–333.
Tian, N., Copenhagen, D.R., 2003. Visual stimulation is required for refinement of ON and OFF pathways in postnatal retina. Neuron 39, 85–96.
Tieman, S.B., Zec, N., Tieman, D.G., 1995. Dark-rearing fails to affect the basal dendritic fields of layer 3 pyramidal cells in the kitten's visual cortex. Brain Res. Dev. Brain Res. 84 (1), 39–45.
Toni, N., Buchs, P.A., Nikonenko, I., Bron, C.R., Muller, D., 1999. LTP promotes formation of multiple spine synapses between a single axon terminal and a dendrite. Nature 402, 421–425.
Toni, N., Teng, E.M., Bushong, E.A., Aimone, J.B., Zhao, C., Consiglio, A., van, P.H., Martone, M.E., Ellisman, M.H., Gage, F. H., 2007. Synapse formation on neurons born in the adult hippocampus. Nat. Neurosci. 10, 727–734.
Trachtenberg, J.T., Chen, B.E., Knott, G.W., Feng, G., Sanes, J.R., Welker, E., Svoboda, K., 2002. Long-term in vivo imaging of experience-dependent synaptic plasticity in adult cortex. Nature 420, 788–794.
Turrigiano, G., 2007. Homeostatic signaling: the positive side of negative feedback. Curr. Opin. Neurobiol. 17, 318–324.
Turrigiano, G.G., Nelson, S.B., 2004. Homeostatic plasticity in the developing nervous system. Nat. Rev. Neurosci. 5 (2), 97–107.
Turrigiano, G.G., Nelson, S.B., 2000. Hebb and homeostasis in neuronal plasticity. Curr. Opin. Neurobiol. 10, 358–364.
Turrigiano, G.G., Leslie, K.R., Desai, N.S., Rutherford, L.C., Nelson, S.B., 1998. Activity-dependent scaling of quantal amplitude in neocortical neurons. Nature 391, 892–896.
van Ooyen, A., van Pelt, J., 1994. Activity-dependent outgrowth of neurons and overshoot phenomena in developing neural networks. J. Theor. Biol. 167, 27–43.
van Ooyen, A., van Pelt, J., Corner, M.A., 1995. Implications of activity dependent neurite outgrowth for neuronal morphology and network development. J. Theor. Biol. 172, 63–82.
Van Ooyen, A., Willshaw, D.J., 1999a. Competition for neurotrophic factor in the development of nerve connections. Proc. R. Soc. Lond. B. 266, 883–892.
van Ooyen, A., Willshaw, D.J., 1999b. Poly- and mononeuronal innervation in a model for the development of neuromuscular connections. J. Theor. Biol. 196, 495–511.
van Ooyen, A., Willshaw, D.J., 2000. Development of nerve connections under the control of neurotrophic factors: parallels with consumer-resource systems in population biology. J. Theor. Biol. 206, 195–210.
Van Ooyen, A., Graham, B.P., Ramakers, G.J.A., 2001. Competition for tubulin between growing neurites during development. Neurocomputing 38–40, 73–78.
van Ooyen, A., 2003. Modeling Neural Development. MIT Press, Cambridge MA, London GB.
Van Oss, Van Ooyen, 1997. Effects of inhibition on neural network development through activity-dependent neurite outgrowth. J. Theor. Biol. 185, 263–280.
Verzi, D.W., Rheuben, M.B., Baer, S.M., 2005. Impact of time-dependent changes in spine density and spine shape on the input–output properties of a dendritic branch: a computational study. J. Neurophysiol. 93, 2073–2089.
Weinberger, D.R., Lipska, B.K., 1995. Cortical maldevelopment, anti-psychotic drugs, and schizophrenia: a search for common ground. Schizophr. Res. 16, 87–110.
Wierenga, C.J., Ibata, K., Turrigiano, G.G., 2005. Postsynaptic expression of homeostatic plasticity at neocortical synapses. J. Neurosci. 25, 2895–2905.
Winterfeld, K.T., Teuchert-Noodt, G., Dawirs, R.R., 1998. Social environment alters both ontogeny of dopamine innervation of the medial prefrontal cortex and maturation of working memory in gerbils (*Meriones unguiculatus*). J. Neurosci. Res. 52, 201–209.
Witte, A.V., Bagorda, F., Teuchert-Noodt, G., Lehmann, K., 2006. Contralateral prefrontal projections in gerbils mature abnormally after early methamphetamine trauma and isolated rearing. J. Neural. Transm.
Wörgötter, F., Porr, B., (2005) Temporal sequence learning, prediction and control: a review of different models and their relation to biological mechanisms. Neural Comput 17(2):245:319.
Wolff, J.R., Joó, F., Dames, W., 1978. Plasticity in dendrites shown by continuous GABA administration in superior cervical ganglion of adult rat. Nature 274 (5666), 72–74.
Wolff, J.R., Wagner, G.P., 1983. Selforganization in synaptogenesis: interaction between the formation of excitatory and inhibitory synapses. In: Basar, E., Flohr, H., Haken, H., Mandell, A.J. (eds.), Synergetics of the Brain. Springer, Berlin; Heidelberg; New York; Tokyo, pp. 50–59.
Wolff, J.R., Leutgeb, U., Holzgraefe, M., Teuchert, G., 1989. Synaptic remodelling during primary and reactive synaptogenesis. In: Rahmann, H. (ed.), Fundamentals of Memory Formation: Neuronal Plasticity and Brain Function. Gustav Fischer Verlag, Stuttgart; New York, pp. 68–82.
Wolff, J.R., Missler, M., 1992. Synaptic reorganization in developing and adult nervous systems. Ann. Anat. 174, 393–403.
Wolff, J.R., Joo, F., Kasa, P., 1993. Modulation by GABA of neuroplasticity in the central and peripheral nervous system. Neurochem. Res. 18, 453–461.
Wolff, J.R., Missler, M., 1993. Synaptic remodelling and elimination as integral processes of synaptogenesis. APMIS Suppl. 40, 9–23.
Yildiz, S., Bademkiran, F., Yildiz, N., Aydogdu, I., Uludag, B., Ertekin, C., 2007. Facial motor cortex plasticity in patients with

unilateral peripheral facial paralysis. NeuroRehabilitation 22, 133–140.
Yuste, R., Bonhoeffer, T., 2001. Morphological changes in dendritic spines associated with long-term synaptic plasticity. Annu. Rev. Neurosci. 24, 1071–1089.
Zhao, C., Teng, E.M., Summers Jr., R.G., Ming, G.L., Gage, F.H., 2006. Distinct morphological stages of dentate granule neuron maturation in the adult mouse hippocampus. J. Neurosci. 26, 3–11.
Zuo, Y., Yang, G., Kwon, E., Gan, W.B., 2005. Long-term sensory deprivation prevents dendritic spine loss in primary somatosensory cortex. Nature 436 (7048), 261–265.
Ziemann, U., Hallett, M., Cohen, L.G., 1998. Mechanisms of deafferentation-induced plasticity in human motor cortex. J. Neurosci. 18, 7000–7007.
Ziv, N.E., Smith, S.J., 1996. Evidence for a role of dendritic filopodia in synaptogenesis and spine formation. Neuron 17, 91–102.