CHAPTER

4

Is Lesion-Induced Synaptic Rewiring Driven by Activity Homeostasis?

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OUTLINE

The Rewiring Brain
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1 INTRODUCTION

As shown by early neuroanatomical tracing studies[1–3] and recent high-resolution microscopy studies,[4–9] a lasting reduction in afferent activity to the brain, brought about by peripheral or central lesions (e.g., retinal lesions or stroke), triggers massive rewiring of synaptic connections. Synaptic rewiring is mediated by structural adaptations (structural plasticity), such as axon remodeling,[10] changes in spine numbers,[11] and synapse formation and deletion,[12] and contributes to the functional repair of brain networks. However, despite four decades of lesion studies, the principles governing lesion-induced structural plasticity remain poorly understood.

By modifying the input a neuron receives, lesions alter the level of neuronal electrical activity. An early in vivo rat study showed that reducing the level of electrical activity in cervical ganglion cells led to an increase in dendritic spine numbers,[13] enhancing the cells' potential to make synaptic connections with active neurons and, therefore, to restore activity. On the basis of this study, a role for activity homeostasis in synaptic rewiring was proposed,[14,15] but experimental limitations prevented further study into the guiding principles of synaptic rewiring.

Current experimental studies use in vivo time lapse imaging and advanced techniques for measuring electrical activity that enable detailed monitoring of dendritic spines,[4,16–18] axonal branches and boutons,[5,19] and electrical activity over extended periods of time.[20–23] Drawing on the results of such studies, here we hypothesize that the attempt of neurons to maintain their average electrical activity at a particular level (homeostatic regulation) may drive structural plasticity after loss of input caused by lesions. We define structural plasticity as encompassing all the structural changes, such as spine dynamics and axon remodeling, that lead to the formation or deletion of synapses. Structural plasticity can connect previously unconnected neurons, disconnect neurons, or change the number of synapses by which neurons are connected. By contrast, synaptic plasticity is defined as a change in the strength of existing synapses. Hebbian synaptic plasticity changes synapse strength depending on the correlation between pre- and postsynaptic activity,[24,25] whereas synaptic scaling (homeostatic synaptic plasticity) modifies the strengths of all the cell's incoming synapses so as to stabilize neuronal activity around some set-point value.[26]

In the next sections, we first present the current view on events following a lesion-induced loss of afferent activity. We then describe some limitations of the current view and present our hypothesis of homeostatic structural plasticity. We discuss in vitro and in vivo studies that may support our hypothesis and indicate how homeostatic structural plasticity could be tested experimentally. Lastly, we discuss the potential implications of homeostatic structural plasticity for brain function and neurological therapy.

2 CURRENT VIEW AND LIMITATIONS

Below, we present the prevailing view on cortical events following a loss of afferent activity, using retinal lesions and monocular deprivation as examples. We then describe some limitations of the current view.

2.1 Current View

Retinal lesions or monocular deprivation deprives a corresponding group of neurons (in the case of lesions, called lesion projection zone or LPZ) in the primary visual cortex of visual input, causing a drop in the neurons' level of electrical activity.[21,22,27–29] Activity levels then recover relatively quickly, over a couple of days,[21,22,29] by the strengthening and weakening of existing intracortical synapses through synaptic scaling[21] and Hebbian synaptic plasticity,[30] possibly in combination with a reduction in inhibition.[21,29] Not all neurons recover their activity, at least over the 2- to 3-day period during which the cortex is monitored.[29] In addition to changes in existing synapses, retinal lesions trigger massive structural changes such as axon sprouting and axonal bouton formation[5,31,32] and formation and deletion of dendritic spines.[4] By binding to boutons, newly formed spines may form transient synapses, which could become consolidated depending on the correlation between pre- and postsynaptic activity, i.e., according to Hebbian rules.[33–35] Although formation of new synapses may affect activity levels, the restoration of activity is believed to occur mainly through the relatively fast changes (hours to a few days) in the strength of existing synapses.

2.2 Limitations

The quick, partly recovery of activity in the visual cortex may not be stable and activity dynamics may continue beyond few days after deprivation. Some experimental studies indeed suggest that restoration of electrical activity is in fact a slow process taking place on a much longer timescale than homeostatic or Hebbian synaptic plasticity. One retinal lesion study showed that the level of electrical activity in the LPZ restored from the outside to the inside of the LPZ over a period of up to a year.[27] Such a slow restoration of activity was also evident from the neuronal activity markers c-fos and zif268.[28,36]

In addition, slow structural changes, including spine dynamics and ingrowth of axonal arbors from intact peri-LPZ to the LPZ,[5,31] may directly contribute to the restoration of activity. Although direct evidence is still lacking, the ingrowing axons[5,31] may form synapses with the newly formed spines in the LPZ[4] and so help restore activity in the LPZ. This view is supported by the observation that spreading of electrical activity from intact peri-LPZ to LPZ occurs only after more than 6 days postlesion,[20] a result that was interpreted to indicate that axon outgrowth and synapse formation with LPZ neurons are necessary for activity to propagate from intact to deprived areas.[20]

The current view on activity restoration following a loss of input relies on synaptic scaling and Hebbian rules. However, synaptic scaling can modify postsynaptic activity only when cells are connected to active presynaptic cells. Likewise, Hebbian rules can strengthen or consolidate synapses only after they are formed. When cells are unconnected, the formation of spines and boutons itself cannot be governed by Hebbian rules, as this would require information about both pre- and postsynaptic activity. Synapse formation and synaptic rewiring depend crucially on the availability of spines and boutons, but the factors regulating spine and bouton formation are little known.

3 HOMEOSTATIC STRUCTURAL PLASTICITY

Below, we present a hypothesis for the regulation of spine and bouton formation, and describe what we expect on the basis of this hypothesis for the events following a lesion-induced decrease in activity.

3.1 Hypothesis

We postulate that a persistent decrease in a neuron's electrical activity below a desired value (set-point) triggers the formation of spines and boutons (Fig. 4.1). Likewise, we

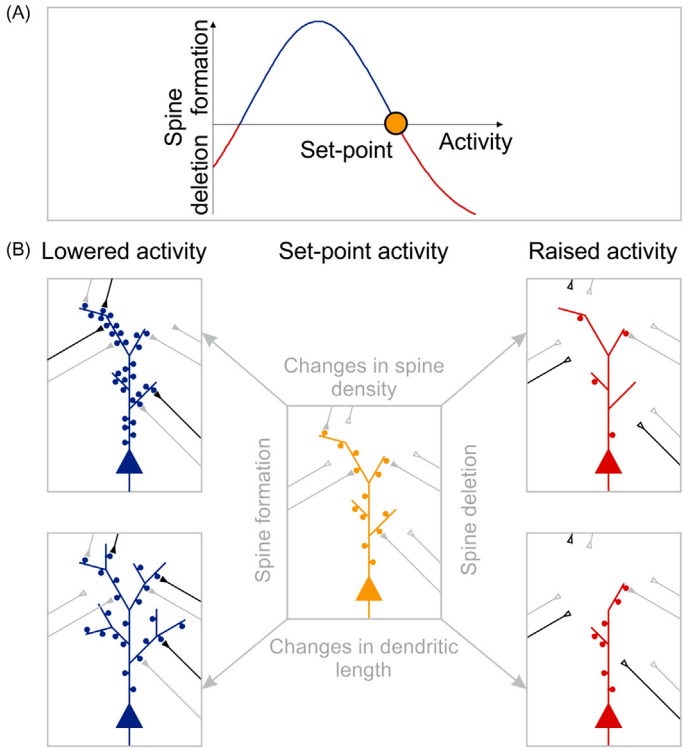

FIGURE 4.1 **Homeostatic structural plasticity.** Our hypothesis is that the attempt of neurons to maintain their average electrical activity at a desired level (homeostatic set-point) drives spine formation and deletion. (A) We postulate that neurons form new spines when their activity level is below the set-point and delete spines when their activity level is above the set-point or below a certain minimum level. (B) We further argue that a neuron can form or delete spines either through a change in spine density or through a change in dendritic length. The middle image shows a cell at set-point activity, showing spines (*filled circles*), axons (*straight lines with triangles*) from neighboring cells, and synaptic connections (*spines with filled axon triangles*). When the activity of the neuron is lowered below the set-point (*left*), new spines are formed through an increase in spine density (*top left*) or an increase in dendritic length (*bottom left*). The new spines enable axons from neighboring cells to make new synaptic connections (*bold filled triangles*), which may restore the neuron's activity level. When the activity of the neuron is raised above the set-point (*right*), spines are deleted through a decrease in spine density (*top right*) or a decrease in dendritic length (*bottom right*). Deletion of spines that are bound in synapses leads to the break-up of synaptic connections (*bold open triangles*), which may reduce the neuron's activity level.

hypothesize that a persistent increase in a neuron's electrical activity above the set-point results in deletion of spines and boutons. In addition, we assume that activity below a certain minimum level will also result in deletion of spines and boutons.

3.2 Expectations

We expect that after a lesion and the resulting drop in electrical activity, a neuron will increase its spine formation. A neuron may achieve this by directly upregulating de novo formation of spines,[37] attenuating the ongoing elimination of spines,[38] or retaining more of the spontaneously formed new spines.[16] The extra spines enable the neuron to make new synaptic input connections with active neurons, which may raise its level of electrical activity. Note that increased spine formation does not necessarily imply a higher total number of spines, because removal of spines (e.g., those that are not receiving input[39]) could counterbalance the increased formation. In addition to spine formation, we expect that a reduction in electrical activity triggers bouton formation.

By contrast, we expect that for persistently high levels of electrical activity, a neuron will delete spines and boutons. Deletion of spines that are bound in synapses breaks up existing connections, which may lower the neuron's level of electrical activity. Thus when a neuron deviates in either direction from a desired set-point activity, formation and deletion of spines have the potential to bring activity back to the set-point value (homeostasis). Such a cell-autonomous set-point value has been proposed before in the context of synaptic scaling[40] and has recently convincingly been demonstrated experimentally.[41]

A neuron may form or delete spines and boutons while keeping its dendritic and axonal length constant. Alternatively, a neuron could change spine or bouton number by changing its dendritic or axonal length, respectively (Fig. 4.1).

Spine and bouton formation triggered by low activity may be capable of restoring activity in the LPZ. The spines that would be formed in the LPZ as a result of the lesion-induced drop in activity could make new intracortical connections with boutons from active, peri-LPZ neurons and so raise the activity of LPZ neurons. However, restoration of activity could fail if activity drops below the minimum level for spine and bouton formation or if there are not enough boutons within reach with which the newly formed spines can make synapses. The latter could happen, e.g., if the LPZ is too big.

4 IN VITRO INDICATIONS FOR HOMEOSTATIC STRUCTURAL PLASTICITY

Because the impact of electrical activity on spine formation and neurite outgrowth may be seen clearer in vitro than in vivo owing to the fewer confounding network interactions in vitro, we first review in vitro studies. The prevalent view seems to be that in vitro spine formation and neurite outgrowth are triggered by increased electrical activity.[42–44] However, a large body of studies instead shows that low activity increases and high (but also very low) activity decreases spine number and neurite length.

4.1 Dendritic Spines

Blocking electrical activity in mature hippocampal[45–47] or cerebellar cultures[48] by tetrodotoxin (TTX) resulted in increased spine density (Fig. 4.2A). By contrast, long-term elevations in activity, as in epileptic hippocampal tissue cultures, led to a reversible reduction in spine numbers[49–51] (Fig. 4.2B). Similarly, spines reduced in length[52] or even completely disappeared[53] after excessive stimulation of NMDA receptors. Furthermore, high activity not only decreases spine number but can also reduce spine motility,[54] hindering the spines' ability to search for axons and to form new synapses.

4.2 Dendrite and Axon Outgrowth

Application of the excitatory neurotransmitter glutamate caused dendrites to retract, an effect that was mediated by calcium influx through voltage-dependent calcium channels.[55] Likewise, increased neuronal electrical activity, as in epileptic seizures, resulted in dendritic retraction.[51,56] During development, low concentrations of glutamate allowed dendritic outgrowth, whereas elevated concentrations prevented outgrowth or caused retraction.[57]

Axons may respond to changes in electrical activity in the same way as dendrites. Reducing electrical activity through application of the NMDA receptor blocker MK-801 resulted in considerable axonal outgrowth and sprouting.[58] By contrast, raising activity by stimulation of kainate receptors caused axons to retract[59] (Fig. 4.2D) or resulted in the immobility of axonal filopodia,[60,61] hampering the axon's ability to find dendrites and to form synapses.[60]

4.3 Minimum Activity for Spine Formation and Neurite Outgrowth

As described earlier, lowering activity may induce spine formation and neurite outgrowth. However, when activity drops below a minimum level, spines may be deleted and neurites retracted.[62] A lasting reduction in activity promoted neurite outgrowth,[58] but a complete loss of activity by blocking both NMDA and AMPA receptors resulted in a loss of dendritic spines[63] and prevention of axonal outgrowth.[58] Thus the effect of electrical activity may be described by a bell-shaped curve, with an optimal activity level for growth, a homeostatic set-point above which, and a minimum level below which, neurites retract and spines are deleted (Fig. 4.1A). A bell-shaped response curve has indeed been observed for the formation of spine head protrusions[47] (Fig. 4.2C). Such a bell-shaped curve may account for the seemingly conflicting results on the effect of electrical activity.[42,43,46,48] When electrical activity is around the set-point, an increase in activity may elicit spine deletion and neurite retraction, whereas when activity is low, the same increase may trigger spine formation and neurite outgrowth. In addition, the duration of the activity change may be important. A short-lasting change in activity may have another effect on spine formation and neurite outgrowth than a long-lasting, lesion-induced change.

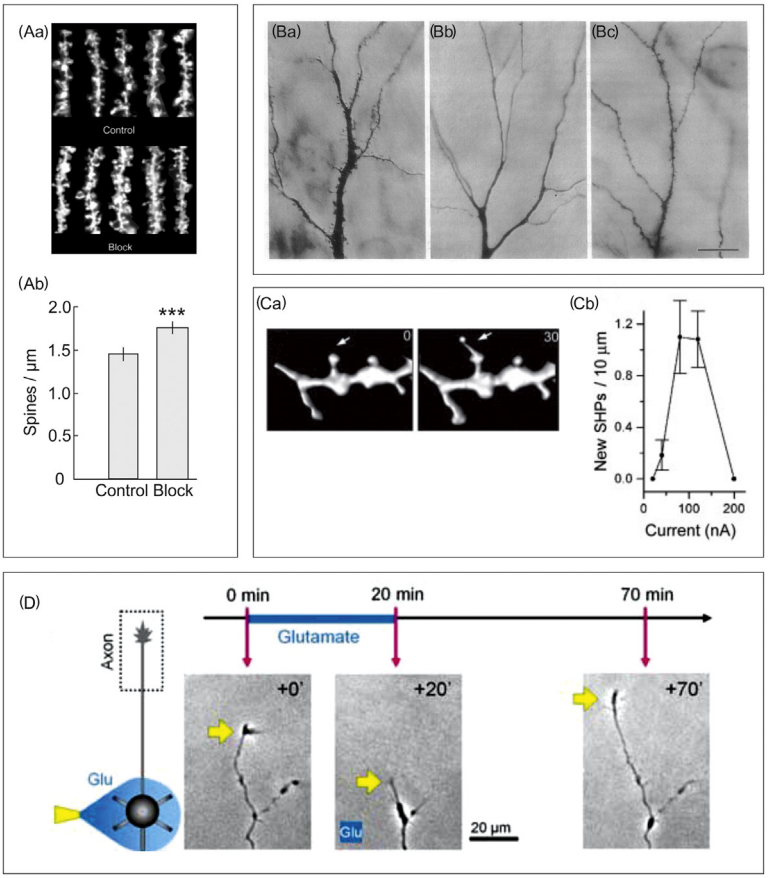

FIGURE 4.2 **In vitro indications for homeostatic structural plasticity.** Various findings indicate that low electrical activity increases and high activity decreases spine number and axon length. (A) Pyramidal neurons in hippocampal slice cultures became more spiny when electrical activity was blocked by TTX.[45,46] Cultures were taken from adult rats (62–80 days). (Aa) *Top row*: Five dendritic segments with spines from control situation. *Bottom row*: Dendritic segments and spines under TTX condition. (Ab) Dendritic spine densities were significantly higher under TTX condition. (B) High electrical activity due to epileptic seizures evoked by application of the $GABA_A$ receptor antagonist picrotoxin reversibly decreased spine densities[49] in hippocampal slice cultures. Cultures were taken from neonatal rat pups and incubated for 12–20 days before picrotoxin application. Picrotoxin caused cells to spontaneously exhibit paroxysmal depolarization shifts over several hours. (Ba) Pyramidal cell from control culture with normal spine density. (Bb) Reduced spine density after 3 days of picrotoxin treatment. (Bc) Spine density restored to normal levels when, after 3 days of picrotoxin treatment, cultures were put back in control medium for 1 week. (C) Spine head protrusions (SHPs) on pyramidal cells from hippocampal slice cultures formed in a window of reduced electrical activity.[47] Cultures were taken from 6-day-old mice and kept 3–6 weeks in vitro before TTX application. (Ca) New SHPs were seen within 30 minutes after TTX application. SHPs may have formed in response to a TTX-induced reduction in glutamate release from nearby presynaptic terminals. (Cb) SHP formation has a bell-shaped dependence on the amount of iontophoretically applied exogenous glutamate (amount of glutamate is proportional to the iontophoresis current). (D) Twenty minutes of perisomatic application of glutamate caused axons of isolated dentate granual cells to retract.[59] Cells were taken from 3-day-old rats. Axon retraction was mediated by intracellular calcium waves propagating from the soma to the axon terminals. Axons started to grow again when glutamate application was stopped. Source: *Reproduced with permission from (A) Kirov SA, Harris KM. Dendrites are more spiny on mature hippocampal neurons when synapses are inactivated. Nat Neurosci. 1999;2(10):878–883, Nature Publishing Group; (B) Müller M, Gähwiler BH, Rietschin L, Thompson SM. Reversible loss of dendritic spines and altered excitability after chronic epilepsy in hippocampal slice cultures. Proc Natl Acad Sci USA. 1993;90(1):257–261, copyright (1993) National Academy of Sciences, USA; (C) Richards DA, Mateos JM, Hugel S et al. Glutamate induces the rapid formation of spine head protrusions in hippocampal slice cultures. Proc Natl Acad Sci USA. 2005;102(17):6166–6171, copyright (2005) National Academy of Sciences, USA; (D) Yamada RX, Sasaki T, Ichikawa J, Koyama R, Matsuki N, Ikegaya Y. Long-range axonal calcium sweep induces axon retraction. J Neurosci. 2008;28(18):4613–4618, Society of Neuroscience.*

5 IN VIVO INDICATIONS FOR HOMEOSTATIC STRUCTURAL PLASTICITY

Below, we review in vivo studies in visual cortex, barrel cortex, and stroke that suggest that a long-term reduction in electrical activity triggers spine formation and promotes neurite outgrowth, leading to connectivity reorganization and activity restoration. In visual and barrel cortex studies, cortical cells have reduced peripheral input from the eyes or whiskers, respectively; whereas in stroke studies, cells have reduced central input from the stroke site.

5.1 Visual Cortex

Loss of visual input caused by monocular deprivation resulted in increased spine numbers in the primary visual cortex[37] (Fig. 4.3A). The newly formed spines likely established synapses with neurons in ocular dominance columns of the nondeprived eye,[37] thereby increasing the activity of the deprived columns.[21]

In focal retinal lesions experiments, a compact group of neurons in the primary visual cortex (the lesion projection zone or LPZ) is deprived of visual input.[4,64–66] In one such experiment, the loss of input triggered extensive formation and deletion of spines[4] (Fig. 4.4Aa), although the total number of spines did not increase. As indicated by the enhanced occurrence of persistent spines (Fig. 4.4Ab), many of the newly formed spines became stabilized,[4] probably by becoming bound into synapses. Consolidation of new synapses may have involved LTP,[34,67] and deletion of existing synapses may have entailed LTD.[35,39] We conjecture that LPZ neurons established new afferent synapses with active, peri-LPZ neurons while deleting afferent synapses with inactive, LPZ neurons, thereby keeping the total number of spines more or less constant. Other studies indeed showed that axon collaterals sprouted from the peri-LPZ into the LPZ[5,31] (Fig. 4.4B), enabling synapse formation of LPZ neurons with peri-LPZ neurons. The peri-LPZ lost some horizontal input from the LPZ and therefore may have had a mildly reduced level of electrical activity, which could have induced the axonal outgrowth.[68]

In another study, it was shown that the level of electrical activity in the LPZ, which drops after the lesion, slowly restored from the outside to the inside over a period of up to a year, with the border between normal and reduced activity slowly migrating toward the center of the LPZ.[27] This slow restoration of activity, also evident from the neuronal activity markers c-fos and zif268,[28,36] is more likely driven by structural plasticity than by homeostatic synaptic plasticity[21,22] or intrinsic neuronal plasticity,[40] as the latter two act on faster timescales of hours to a few days. Several studies suggest that the restoration of activity may be brought about by changes in intracortical connectivity.[20,32,69,70] The ingrowing axons from the peri-LPZ[5,31] may form synapses with the newly formed spines in the LPZ[4] and so slowly restore activity in the LPZ. Furthermore, the observation that electrical stimulation in the peri-LPZ can evoke suprathreshold activation in the LPZ only after more than 6 days postlesion[20] (Fig. 4.4C) also suggests that axon outgrowth and synapse formation are involved.

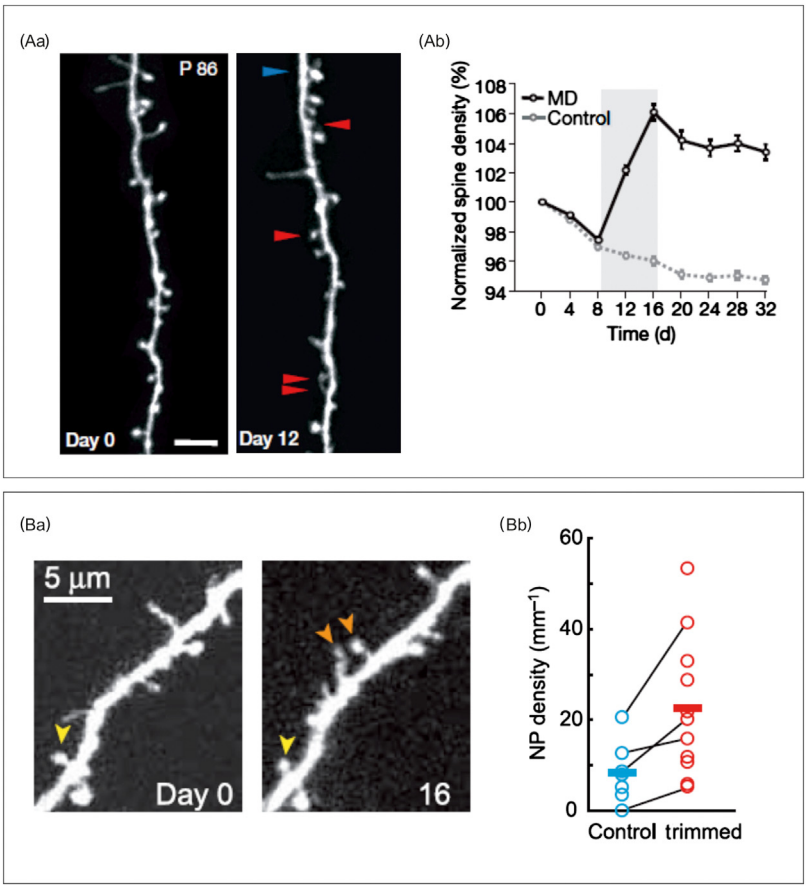

FIGURE 4.3 **Indications for homeostatic structural plasticity from sensory deprivation experiments.** Reduced electrical activity caused by sensory deprivation enhances spine formation in visual and barrel cortex. (A) Spine density in visual cortex increased after monocular deprivation in mature mice (postnatal day 86).[37] Deprivation began at day 8 of the experiment until day 16 (*gray area* in Ab). (Aa) Dendrite of a pyramidal cell in visual cortex. *Red arrows* point to newly formed spines 4 days after deprivation; the *blue arrow* points to a lost spine. (Ab) Normalized spine density after monocular deprivation (MD) and in controls. (B) Number of persistent spines in barrel cortex increased after whisker trimming in adult mice owing to an increased consolidation of newly formed spines.[16] Whiskers were trimmed at day 8 of the experiment. (Ba) Dendrite of a pyramidal cell in barrel cortex. *Yellow arrow* indicates a spine that was present before (day 0) until at least 8 days after whisker trimming (day 16); *orange arrows* indicate new persistent spines. (Bb) Density of new persistent spines (NP). Every circle (*blue*: control; *red*: whisker trimmed) represents a single pyramidal cell. Horizontal bars indicate group averages. *Black lines* connect paired experiments, in which a complete control period of 8 days was followed by 20 days of deprivation. Source: *Reproduced with permission from (A) Hofer SB, Mrsic-Flogel TD, Bonhoeffer T, Hübener M. Experience leaves a lasting structural trace in cortical circuits. Nature. 2009;457(7227):313–317, Nature Publishing Group; (B) Holtmaat A, Wilbrecht L, Knott GW, Welker E, Svoboda K. Experience-dependent and cell-type-specific spine growth in the neocortex. Nature. 2006;441(7096):979–983, Nature Publishing Group.*

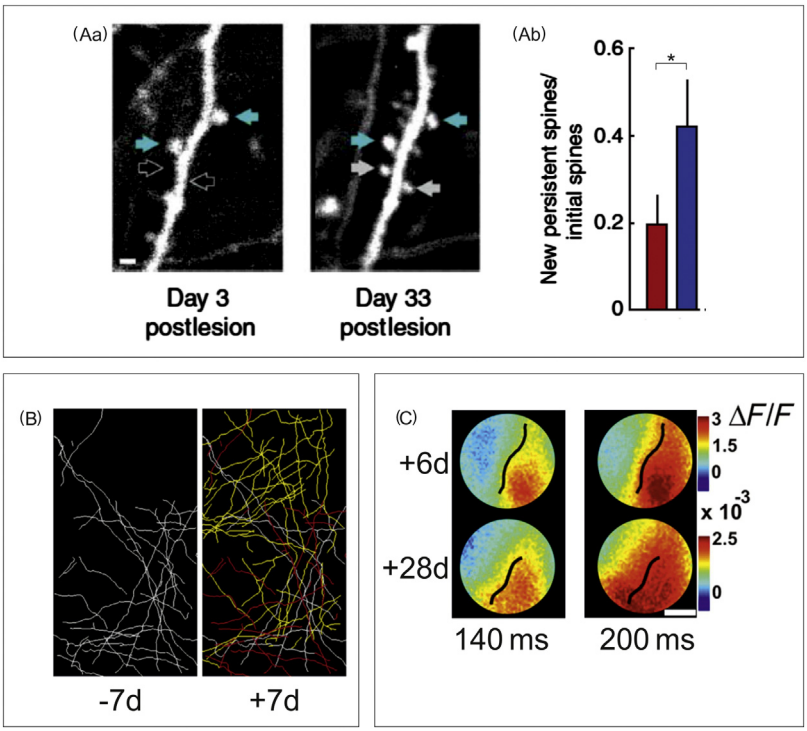

FIGURE 4.4 **Indications for homeostatic structural plasticity from retinal lesion experiments.** Focal retinal lesions, which deprive an area in visual cortex (the lesion project zone or LPZ) of visual input, trigger cortical spine formation and growth of new axonal branches. (A) Spine formation in the LPZ was enhanced after focal retinal lesions in adult mice.[4] (Aa) Dendrite of pyramidal cell in visual cortex. *Blue arrows* point to spines that were present before the lesion and at 3 and 33 days after the lesion. *Gray arrows* indicate spines that were formed after the lesion and were present at day 33 but not yet at day 3. All marked spines were persistent, being maintained over the entire 2-month duration of the experiment. (Ab) The ratio of numbers of new persistent spines to initial spines significantly increased after the lesion. (B) In adult monkeys, focal retinal lesions led to a substantial sprouting of axonal branches of cortical neurons in the peri-LPZ and ingrowth of the new fibers into the LPZ.[5] Persistent axonal branches 7 days before and 7 days after the lesion are shown in *gray*; newly formed axonal branches are shown in *yellow* and pruned branches in *red*. (C) Activity dynamics in visual cortex after a focal retinal lesion in adult rats.[20] At 28 days after the lesion (*bottom row*), but not at 6 days after the lesion (*top row*), electrical stimulation in the peri-LPZ (area at the right of the *black line*) caused a spread of activity into the LPZ (area at the left of the *black line*), indicating that connectivity from peri-LPZ to LPZ changed during the time period after the lesion. Activity was measured by voltage-sensitive dye imaging and is shown 140 ms and 200 ms after stimulation. Source: *Reproduced with permission from (A) Keck T, Mrsic-Flogel TD, Vaz Afonso M, Eysel UT, Bonhoeffer T, Hübener M. Massive restructuring of neuronal circuits during functional reorganization of adult visual cortex. Nat Neurosci. 2008;11(10):1162–1167, Nature Publishing Group; (B) Yamahachi H, Marik SA, McManus JN, Denk W, Gilbert CD. Rapid axonal sprouting and pruning accompany functional reorganization in primary visual cortex. Neuron. 2009;64 (5):719–729, Elsevier; (C) Palagina G, Eysel UT, Jancke D. Strengthening of lateral activation in adult rat visual cortex after retinal lesions captured with voltage-sensitive dye imaging in vivo. Proc Natl Acad Sci USA. 2009;106 (21):8743–8747, National Academy of Sciences, USA.*

5.2 Barrel Cortex

Reducing the activity of barrel cortex neurons by whisker clipping led to an increased number of new persistent spines[16,18] (Fig. 4.3B). The increase was due not to a higher rate of de novo spine formation but to a higher rate of consolidation of newly formed spines.[16] Similarly, in another study, whisker trimming prevented spine loss by reducing the rate of ongoing spine elimination, not by increasing the rate of de novo spine formation.[38] We postulate that by creating extra spines, either by keeping more of the newly formed spines[16] or by attenuating ongoing spine elimination,[38] neurons deprived of input can connect to neurons from intact barrels and thereby compensate for their loss of input. By contrast, raising the activity of barrel cortex neurons by whisker stimulation caused pruning of excitatory dendritic spines and an increase in inhibitory synaptic contacts.[71]

Dendritic morphology is generally stable in the mature brain.[11,72] In mouse barrel cortex, whisker ablation-induced loss of activity triggered formation of new dendritic spines but no changes in dendritic structure.[73] In rat barrel cortex, however, whisker ablation initiated dendritic outgrowth.[74] Since increasing the dendrite length may lead to formation of new spines and synapses, dendritic outgrowth could help restore neuronal electrical activity. Besides dendritic outgrowth, whisker clipping can trigger axonal outgrowth.[75]

5.3 Stroke

Neurons with afferent connections from the stroke site are deprived of input and can experience a significant reduction in electrical activity.[6,7,76–79] Input-deprived neurons create new spines,[6,80,81] enabling the formation of synapses with sprouting axons from intact surrounding tissue.[6,82–85] During stroke recovery, functional connectivity reorganizes and activity partly restores.[86] Restoration of activity may be brought about by synaptic scaling[86] and loss of inhibition,[87] but also by the formation of new excitatory synapses with intact tissue.[6]

By contrast, temporarily increased activity after stroke, so-called spreading depression, causes a reversible loss of dendritic spines in the peri-infarct area.[88] As seen in resected human brain tissue, the even higher electrical activity in temporal lobe epilepsy results in massive cell death as well as loss of dendritic structure[89] and synaptic connectivity[90] of surviving neurons.

Changes in dendritic morphology are sometimes observed after stroke. In adult mice, focal cortical stroke led to strongly enhanced rewiring of dendritic arbors.[91] Dendrites in the intact cortex withdrew their branches from the infarct and extended branches toward intact areas.[91] Interestingly, dendritic remodeling was inversely correlated with distance from the infarct,[80,81] suggesting that the loss of input from the infarct was compensated for by new synaptic contacts with the intact cortex. The farther a cell is from the infarct, the less it will be affected by a loss of input, and the less remodeling would be needed. In another study, however, no evidence was found for growth of dendrites in the peri-infarct area.[92]

Neurons distant from the stroke site may, via long-range connections, experience altered input (diaschisis),[93,94] which could trigger changes in dendritic morphology. After a stroke in one hemisphere, neurons in the contralesional hemisphere were found to have

increased dendritic length,[95,96] possibly induced by the loss of colossal input from the infarct site. However, such contralesional growth of dendrites is not always observed.[97]

6 EXPERIMENTAL TESTING OF HOMEOSTATIC STRUCTURAL PLASTICITY

Structural plasticity is a slow process,[27] so spine, bouton, and activity dynamics should be monitored beyond the first few days postlesion. Furthermore, the different processes affecting spine (and bouton) numbers should be well distinguished. The de novo formation of spines should be discriminated from the consolidation of spines and the ongoing deletion of spines. According to our hypothesis, an increase in spine formation events or a decrease in spine deletion events in response to reduced neuronal electrical activity will be an indication of homeostatic structural plasticity. Electrical activity should be lowered persistently and well away from its normal or set-point value. Around the normal value, the number of spines may predominantly be governed by Hebbian consolidation of spines[98] rather than by homeostatic structural plasticity.

6.1 Growth Curves

To test the postulated growth curves for bouton and spine formation (Fig. 4.1A), one could use two-photon glutamate uncaging[34] or optogenetics[99] to alter electrical activity in vivo. Gradually decreasing the cells' average electrical activity should promote spine formation, whereas increasing it should promote spine deletion.

Intracellular calcium mediates the effect of electrical activity on neuronal morphology.[100–103] To determine the growth curves more quantitatively, one could challenge in vitro neurons with rises in intracellular calcium of varying amplitudes by calcium uncaging[101] and measure the impact on neurite outgrowth and spine formation. This may also reveal differences between axons and dendrites or between different cell types. For example, neurons characterized by a high firing rate may have their homeostatic set-point at a higher activity level than neurons that fire less frequently.[41] In addition, excitatory and inhibitory neurons may have the same or different growth curves.

6.2 Activity Restoration

The direct involvement of homeostatic structural plasticity in activity restoration after lesions can be tested in several ways. We predict that in retinal lesion experiments, blocking spine formation,[104] axon outgrowth, or synapse formation[105] will prevent the long-term restoration of firing rates in the LPZ and the remapping of cortical representations.

To test whether a long-lasting drop in electrical activity from a desired set-point is indeed the trigger for morphological changes and activity restoration, one could artificially increase the average electrical activity in the LPZ by optogenetics,[99] two-photon glumamate uncaging,[34] or chronically implanted electrode arrays.[23] The increase in electrical

activity should prevent LPZ neurons from creating new dendritic spines and, therefore, thwart synapse formation and activity restoration in the LPZ.

Since we expect that synaptic scaling is not the only mechanism responsible for activity restoration, we predict that activity keeps changing well beyond the first few days postlesion as a result of compensatory structural adaptations. Moreover, we predict that restoration of activity will still take place in knockouts that block synaptic scaling.[106] Lastly, to show that activity does not merely increase owing to disinhibition, one could perform in vitro or in vivo lesion experiments under blockade of GABA receptors.

7 DISCUSSION

Below, we discuss the relation of homeostatic structural plasticity to other forms of plasticity, as well as the potential implications of homeostatic structural plasticity for cortical remapping, maladaptive compensatory responses, neurodegeneration, and the treatment of stroke.

7.1 Relation to Other Forms of Plasticity

We envisage that homeostatic structural plasticity operates in conjunction with synaptic plasticity and other forms of structural plasticity. In general, structural plasticity creates or deletes spines and synapses, whereas synaptic plasticity can modify the strength of newly formed synapses. These two forms of plasticity interact.[37] Once synapses become strengthened by Hebbian synaptic plasticity (LTP), spines grow in size and transform in shape.[33,34,107] Such potentiated synapses, and their spines, are less likely to be deleted than synapses weakened by LTD.[35,39]

In addition, Hebbian synaptic plasticity can influence synapse formation, as spine formation is enhanced in the vicinity of synapses potentiated by LTP.[108] Such spine formation can result in duplication of the potentiated synapse if its presynaptic neuron binds to the newly formed spine, effectively increasing the overall connection strength in a structural manner. This LTP-induced synapse formation might be referred to as Hebbian structural plasticity and may have an important role in motor learning.[109] Other studies, however, reported that synapse strengthening hampers spine formation.[110,111]

Homeostatic structural plasticity could help restore activity when homeostatic synaptic plasticity (synaptic scaling) alone may not be sufficient, as with large drops in activity caused by lesions. Synapse strength cannot increase indefinitely and when cells are not connected to active presynaptic neurons, synaptic scaling will not be able to restore postsynaptic activity. Homeostatic structural plasticity, which can lead to new connections, may help input-deprived neurons find new sources of activity. We propose a hierarchical organization of homeostatic mechanisms, with fast synaptic mechanisms constantly in place and slow structural mechanisms setting in when activity levels are persistently outside their desired range.

7.2 Cortical Remapping

The reshaping of cortical maps following deafferentation is a well-known phenomenon[3,65,112] that is generally interpreted as resulting from Hebbian synaptic plasticity.[113] By modifying anatomical connectivity, structural plasticity could complement this Hebbian synaptic plasticity.

Like visual cortical remapping after retinal lesions,[4] somatotopic remapping following digit or limb amputations may partly be governed by homeostatic structural plasticity. Amputations dramatically disturb electrical activity in the somatosensory cortex and give rise to cortical rewiring resulting in enlarged representations of neighboring body parts into the silenced representation of the amputated digit or limb.[3,112,114] Such cortical remapping may also have an important role in functional reorganization after stroke.[115] If stroke-induced cortical lesions leave somatosensory representations partially intact, remapping may extend neighboring representations into impaired representations, and may so contribute to functional recovery. Interestingly, spine turnover, dendritic rerouting, and axonal sprouting co-occur with cortical remapping after stroke.[6,80,81,91]

7.3 Maladaptive Responses

In our view, homeostatic structural plasticity is not a goal-directed process that necessarily results in recovery of activity or regaining of impaired function. A neuron changes spine and bouton formation depending solely on its own activity level, and establishes connections depending only on the availability of spines and boutons on other cells, which could lead to changes in network connectivity that are in fact maladaptive. Homeostatic structural plasticity might therefore also have a role in the etiology of such neurological symptoms as phantom pain[116–119] writers' or musicians' cramp,[120,121] tinnitus after hearing loss,[122] and spasticity following spinal cord injury.[123] In spinal cord injury, alpha motor neurons that suffer from a loss of input from the (partially) damaged pyramidal tract increase their spine numbers[123] and may restore activity by whatever axonal branches are available for synapse formation. Synapse formation with peripheral proprio- or nociceptive afferents may then give rise to the typical spasticity syndrome. Late-onset epilepsy after stroke could likewise result from homeostatically driven network rewiring.[124–126]

7.4 Neurodegeneration

In neurodegenerative disorders, such as Alzheimer's disease and multiple sclerosis (MS), the damage to cells, axons, and dendrites may move neurons away from their homeostatic set-point of electrical activity, triggering compensatory structural changes. In Alzheimer's disease, cell death[127] decreases the input to surviving neurons, possibly initiating dendritic remodeling,[128] including dendritic prouting.[129,130]

In MS, axons (white matter) are lost as a result of demyelination. MS typically shows a biphasic progression, with a primary phase in which the brain is still able to recover from relapses, and a secondary, irreversible phase characterized by accelerated decline.[131,132] Interestingly, not only white matter but also gray matter (dendrites and neurons) is affected in MS,[133,134] and the course of gray matter degeneration, but not that of white

matter degeneration, reflects the secondary phase of accelerated decline.[132] However, the cause of this sudden increase in gray matter degeneration is unknown. We hypothesize that a steady loss of axons disturbs the homeostasis of neuronal activity, triggering compensatory changes that can restore the network initially but when axon loss becomes too severe initiate a sudden degeneration of gray matter. Neuronal activity may indeed be involved in the entire course of MS. In the early stages of MS, cortical networks show increased synchronization of network activity,[135] while glutamate release is permanently enhanced.[136] Furthermore, neurons loose synaptic input,[137] and reorganization of brain networks takes place predominantly in the earliest phases of MS, when the brain may try to counterbalance neuronal and axonal damage.[138]

7.5 Neurological Therapy

Current therapies of stroke rehabilitation principally aim at promoting Hebbian synaptic plasticity by stimulating neural and motor activity. Homeostatic structural plasticity, however, implies that pauses in treatment may have a cardinal role, too. During pauses, when activity is low, homeostatic structural plasticity can trigger the formation of new synaptic circuits that may later be reinforced by LTP during subsequent stimulation periods. A modeling study[139] showed that after lesions, pauses in stimulation led to more stable network repair than continuous stimulation. Interestingly, clinical studies found that the effect of continued neurological treatment ceases[140] and that intensive physical therapy shortly after stroke can be detrimental.[141,142] The notion of homeostatic structural plasticity may also help guide recent methods for promoting stroke recovery, such as pharmacological interventions[143] and noninvasive brain stimulation (tDC and TMS).[144,145] Indeed, therapeutic approaches based on homeostatic plasticity have recently been proposed by clinicians.[146]

7.6 Computational Modeling

To explore the potential consequences of homeostatic structural plasticity, we recently built a computational model of structural plasticity,[125] partly based on earlier models,[14,147–151] that describes each neuron as having separate axonal elements (boutons) and dendritic elements (spines) (see also Chapters 7, 8, and 18 of this book). In the model, synapses are formed by random combination of axonal and dendritic elements. Neurons generate new elements when neuronal electrical activity is below a desired set-point value, and delete elements, including those bound in synapses, when activity is above the set-point or below a certain minimum level. Axonal or dendritic elements that remain after their synaptic counterparts have been deleted become again available for synapse formation. The model was used to explore the response of a network to a focal loss of external input.[125] The simulations revealed that as a result of the lesion, activity dropped in the network but that the ensuing changes in the number of axonal and dendritic elements led to a rewiring of the network and a restoration of activity, with spine dynamics and connectivity changes resembling those observed experimentally.[125,126]

8 CONCLUSION

The majority of plasticity studies over the past two decades have focused on synaptic plasticity[25,152] rather than on structural plasticity. Theoretical work has underlined the potential of Hebbian synaptic plasticity for learning[153] and cortical remapping.[113] With the progress in synaptic plasticity research,[154] the field moved largely away from structural plasticity. Only recently have new imaging techniques made it possible to monitor spine and synapse dynamics in the living brain and has interest in structural plasticity resurged, but the principles governing structural plasticity remain unclear. We hypothesized here that spine and bouton formation may be driven by activity homeostasis, and that this homeostatic structural plasticity may account, at least partly, for the connectivity and activity changes that occur in response to lesions.[1,4,5,31]

In homeostatic structural plasticity, neurons, by adapting their number of synaptic contact sites (spines, boutons), endeavor to change their connectivity so as to reach and maintain a desired level of neuronal activity. Homeostatic structural plasticity does not require information about pre- and postsynaptic activity, as does Hebbian synaptic plasticity (synapse-centric plasticity), but only needs the local activity state of the neuron (neuron-centric plasticity). In general, homeostatic structural plasticity may act as organizing principle driving both the formation of networks[149,150,155–157] and the compensatory structural changes following loss of input or neurons.[125,126] Further investigating this form of plasticity, both experimentally and computationally, may deepen our understanding of the brain's response to injury and might ultimately lead to novel treatments for stimulating brain repair after stroke or neurodegeneration.

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