Exp Brain Res (2009) 199:377–390
DOI 10.1007/s00221-009-1859-5

REVIEW ARTICLE

Heterosynaptic plasticity in the neocortex

Marina Chistiakova · Maxim Volgushev

Received: 18 February 2009 / Accepted: 12 May 2009 / Published online: 5 June 2009

Abstract Ongoing learning continuously shapes the distribution of neurons' synaptic weights in a system with plastic synapses. Plasticity may change the weights of synapses that were active during the induction—homosynaptic changes, but also may change synapses not active during the induction—heterosynaptic changes. Here we will argue, that heterosynaptic and homosynaptic plasticity are complementary processes, and that heterosynaptic plasticity might accompany homosynaptic plasticity induced by typical pairing protocols. Synapses are not uniform in their susceptibility for plastic changes, but have predispositions to undergo potentiation or depression, or not to change. Predisposition is one of the factors determining the direction and magnitude of homo- and heterosynaptic changes. Heterosynaptic changes which take place according to predispositions for plasticity may provide a useful mechanism(s) for homeostasis of neurons' synaptic weights and extending the lifetime of memory traces during ongoing learning in neuronal networks.

Keywords Synaptic plasticity · Homosynaptic · Heterosynaptic · Induction · Synaptic weight normalization · Synaptic homeostasis

M. Chistiakova · M. Volgushev
Department of Neurophysiology,
Ruhr-University Bochum, Bochum, Germany

M. Chistiakova · M. Volgushev (✉)
Department of Psychology, University of Connecticut,
406 Babbidge Road Unit 1020, Storrs, CT 06269-1020, USA
e-mail: maxim.volgushev@uconn.edu;
maxim@neurop.ruhr-uni-bochum.de

Abbreviations

LTP	Long-term potentiation
LTD	Long-term depression
STDP	Spike timing dependent plasticity
PPF	Paired-pulse facilitation
NMDA	*N*-methyl-D-aspartate
AP	Action potential

Introduction

Every neuron in the neocortex receives thousands of synapses from thousands of other neurons. Activation of only a portion of them, dozens to hundreds, may evoke cell firing and under certain conditions induce plasticity. The input-specific associative plasticity, long-term potentiation (LTP) and long-term depression (LTD), occurring at that set of activated synapses is believed to be the synaptic mechanism of learning and memory. However, just as new learning always takes place on the background of existing memories, so synaptic plasticity is always induced on the background of the existing distribution of synaptic weights. When plasticity is induced by activation of a portion cells' inputs, what goes on at all the remaining synapses to that cell? Changes of transmission at synapses that were active during the induction are called homosynaptic, while changes at the synapses that were not active during the induction are called heterosynaptic. Since only a fraction of the neurons' inputs is active at a given time, or is involved in activity during a certain induction protocol, potential targets of heterosynaptic plasticity are much more numerous. Moreover, heterosynaptic plasticity mediates regulatory processes that are necessary for normal operation of learning neuronal networks, e.g., homeostasis of the neurons' total synaptic weights, prevention of their runaway

dynamics, or synaptic competition. Therefore, to understand, how memory traces are formed and stored in the distributions of synaptic weights, it is important to know, how the induction of plasticity at a specific group of synapses interacts with the existing pattern of synaptic weights.

This review is focused on heterosynaptic plasticity in the neocortex. However, to place neocortical heterosynaptic plasticity in the context of the plasticity field, we will also discuss some relevant properties of "canonical" homosynaptic plasticity, as well as data from other structures. We will consider three questions: What induces long-term plasticity? What determines its direction and magnitude? What are some possible functions of heterosynaptic plasticity?

We will argue, that (1) Homosynaptic and heterosynaptic plasticity are complementary processes, whereby heterosynaptic plasticity might accompany homosynaptic plasticity induced by typical pairing protocols, (2) Synapses are not uniform in their susceptibility for plastic changes, but have predispositions to undergo potentiation or depression, or not to change. The direction and magnitude of plastic changes depend on both, specific details of the induction protocol and predispositions of synapses for plasticity.

What induces homosynaptic and heterosynaptic long-term plasticity?

Long lasting changes of synaptic transmission can be induced in a number of ways. Below we will consider three groups of protocols leading to the LTP or LTD: afferent tetanization, pairing and intracellular tetanization (Fig. 1).

The afferent tetanization is achieved by stimulation of presynaptic fibers with electric pulses, repeated at a certain frequency or pattern. Low-frequency stimulation refers to 3 Hz and below, high-frequency tetanization refers to 20 Hz and above (usually 50–200 Hz). Since induction of most forms of plasticity requires generation of action potentials (spikes) in the postsynaptic neurons, the electric pulses used for afferent tetanization should be strong enough to activate a large number of presynaptic fibres, sufficient to evoke postsynaptic firing. The phenomenon of LTP in the dentate area of the hippocampal formation has been discovered using afferent tetanization (Bliss and Lomo 1973; Bliss and Gardner-Medwin 1973).

The high stability of extracellular recordings, e.g., field potentials, makes it possible to study plasticity induced with afferent tetanization over hours in vitro, and over days and even weeks in vivo (Abraham et al. 2002). Moreover, the sequence of events: stimulation of the presynaptic fibers and cells, synaptic transmission and activation and eventually firing of postsynaptic cells represents a natural sequence of events, which normally lead to activation of neurons. At least, this is a more natural way of cell activation than depolarization through the intracellular electrode. A drawback of strong extracellular stimulation, necessary for inducing plasticity with afferent tetanization, is that it activates essentially simultaneously large number of cells and fibers next to the stimulation electrode, which most probably never happens during operation of the brain in vivo. Synchronous activation of these axons, having different origin and heterogeneous targets of projection, leads to uncontrolled spread of activity in the brain. For this reason,

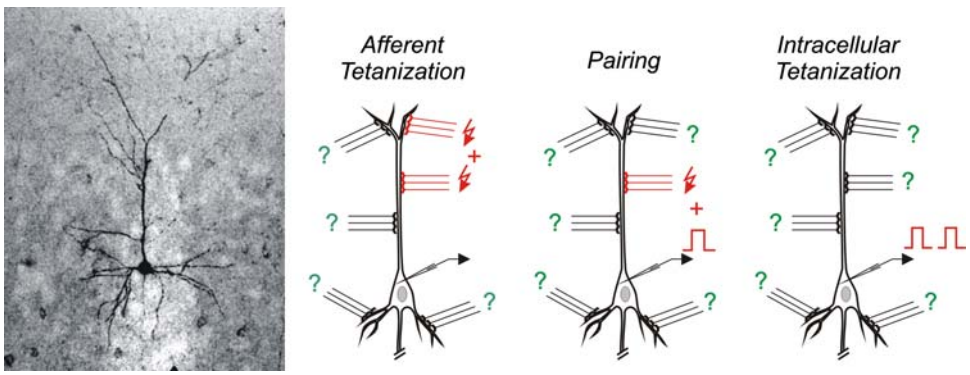

Fig. 1 Stimulation protocols, that may induce long-lasting synaptic plasticity. *Left* a microphotograph of a biocytin-filled layer 3 pyramidal neuron in rat visual cortex slice. *Right* (*Red*) stimulation during plasticity induction, afferent at synapses and/or depolarization pulses applied to the cell through the intracellular electrode. *Homosynaptic plasticity*: changes of transmission at synapses which were stimulated during the induction protocol (*red* synaptic inputs). *Heterosynaptic plasticity*: changes at synapses which were not stimulated during the induction protocol (*black* synaptic inputs, with *green* question marks). Afferent tetanization: stimulation of a number of presynaptic fibers, usually leading to action potentials, repeated at low (1–3 Hz) or high (20–200 Hz) frequency. Pairing: stimulation of several presynaptic fibers, usually not leading to action potentials in the cell, together with depolarization pulses applied to the cell through the intracellular electrode. Depolarization pulses are used to evoke action potentials. Intracellular tetanization: trains of depolarization pulses, applied to the cell through the intracellular electrode, usually leading to action potentials, see Fig. 2 for detail

afferent tetanization and field potential recording is best applicable in the structures with clear cut, systematic organization of synaptic pathways, e.g., hippocampal formation.

In the pairing protocol (Fig. 1), stimulation of presynaptic fibers is applied together with depolarization of the cell membrane via the intracellular electrode, first introduced by Gustafsson et al. (1987). Although originally pairing of weak and strong afferent stimuli, and extracellularly recorded field potential responses were used (Levy and Steward 1979, 1983; Kelso and Brown 1986), nowadays pairing protocol usually employs intracellular recording and depolarization-evoked spikes. The use of depolarization-induced firing as a substitute of strong afferent stimulation allows simplification of the synaptic circuit under study, reduce the number of variables and control the remaining parameters more precisely. The number of activated presynaptic fibers which evoke test responses can be reduced to few or just one in case of minimal stimulation or paired recording from monosynaptically connected cells (e.g., Markram et al. 1997; Sjöström et al. 2001; Kampa et al. 2007; Sjöström and Häusser 2006; Hardingham et al. 2007). The magnitude of postsynaptic depolarization and timing of the postsynaptic spikes can be controlled precisely. Further, activated synaptic input can be localized on the dendritic tree, allowing the study of location-typical dynamics of Ca^{2+} concentration (Gordon et al. 2006; Kampa and Stuart 2006; Nevian and Sakmann 2006; Sjöström and Häusser 2006). A drawback of the pairing protocol is that intracellular recording is technically more demanding, and the duration of intracellular recording is restricted to few hours at best. Further, depolarization through the recording electrode in the soma activates the cell in a different way than synaptic stimulation. It does not involve activation of large number of postsynaptic receptors, that normally precedes and accompanies the spiking, and might also evoke different profile of Ca^{2+} concentration changes over the dendritic tree.

Both protocols have a clear-cut relation to classical conditioning and other associative learning paradigms. The analogy is especially clear for the pairing protocol (Levy and Steward 1979; Gustafsson et al. 1987). The weak synaptic input to a cell is analogous to a weak, "conditioned" stimulus for an organism, and strong stimulus or depolarization that evokes firing in a cell is analogous to an "unconditioned" stimulus in the classical conditioning paradigm. With afferent tetanization, sets of activated synapses can be considered as stimuli representations: a small set of synapses representing a "conditioned" stimulus, and remaining synapses representing strong "unconditioned" stimulus. With both protocols, repetitive presentation of weak and strong stimuli together leads to potentiation of synaptic transmission, and thus of the responses to the weak "conditioned" stimulus, analogous to learning in the conditioning paradigm. Moreover, the LTP induced by these protocols follows the Hebbian rule: synapses leading to the cell firing are strengthened. Synaptic plasticity induced in that way is called associative, or Hebbian-type.

The associative, Hebbian-type synaptic plasticity induced by the afferent tetanization or pairing is triggered by the rise of intracellular [Ca^{2+}] (Malenka et al. 1988; Bliss and Collingridge 1993). Whether LTP or LTD will be induced, depends on the amplitude and time course of the calcium signal: fast, large amplitude [Ca^{2+}] increases leading to potentiation, but slower and low amplitude [Ca^{2+}] rises leading to depression (Bienenstock et al. 1982; Lisman 1989; Hansel et al. 1997; Yang et al. 1999; Ismailov et al. 2004). High levels of calcium necessary for LTP induction can be achieved at activated synapses due to supralinear summation of local excitatory postsynaptic potentials with appropriately timed backpropagating APs (Magee and Johnston 1997; Stuart and Häusser 2001; Nevian and Sakmann 2006). Boosted depolarization enhances calcium influx, e.g., by the relief of NMDA-receptor gated channels from magnesium block (Nowak et al. 1984; Schiller et al. 1998), and/or activation of voltage-dependent calcium channels (Miyakawa et al. 1992; Magee and Johnston 1997; Stuart and Häusser 2001; Humeau et al. 2005). Enhanced calcium rise leads to plasticity at the synapses which were active during the induction protocol—*homosynaptic plasticity* (red synapses in Fig. 1). Homosynaptic changes are also referred to as input-specific plasticity.

During induction of homosynaptic plasticity, only a small portion of the total number of synapses, received by any cortical neuron is usually activated. It could be hundreds or dozens in the case of the afferent tetanization, and even less, just one in a limit with pairing. Obviously however, rises of intracellular [Ca^{2+}] during plasticity induction are not restricted to the activated synapses only, and can be evoked by bursts of backpropagating APs even without synaptic activation (Miyakawa et al. 1992; Petrozzino and Connor 1994; Yuste et al. 1994; Schiller et al. 1995, 1998). This poses a question: whether plasticity can be induced also at synapses that are not active during the plasticity induction, but which experience [Ca^{2+}] increase (Fig. 1, black synapses with question marks)? The answer is yes. These changes at non-active synapses are called *heterosynaptic plasticity*, often also referred to as non-associative plasticity.

Heterosynaptic LTD, which accompanied homosynaptic LTP was described soon after the phenomenon of LTP had been discovered (Lynch et al. 1977). In systems with regular spatial arrangements of inputs, as in the hippocampus or amygdala, high-frequency afferent tetanization induces a characteristic profile of response amplitude changes: LTP at stimulated inputs, surrounded by heterosynaptic LTD (White et al. 1990; Royer and Paré 2003). This profile is consistent with the above hypothesis on

Ca^{2+} dependence of LTP and LTD (Lisman 1989), and the expected profile of Ca^{2+} signal evoked by the afferent tetanization: strong at the focus of inputs and decaying with distance. With a pairing protocol, which allows more precise localization of the activated synapses, it was demonstrated that input specificity of LTP breaks down at short distances (few dozens of μm), and heterosynaptic LTP is induced at a local population of synapses (Bonhoeffer et al. 1989; Kossel et al. 1990; Engert and Bonhoeffer 1997). Moreover, the potentiation is even not restricted to the postsynaptic neuron that fired action potentials during the induction, but involves closely located synapses at neighboring neurons too (Schuman and Madison 1994). These results are consistent with the notion of the retrograde signaling, mediated by a diffusible short-living molecule such as NO, which is produced in the postsynaptic cell, diffuses through the cell membranes and mediates changes of transmitter release at a local population of synapses (Gally et al. 1990; Böhme et al. 1991; O'Dell et al. 1991; Schuman and Madison 1994; Hölscher 1997).

A symmetrical situation, with heterosynaptic LTP accompanying homosynaptic LTD, was reported recently in the amygdala (Royer and Paré 2003) and the hippocampus (Wöhrl et al. 2007). The profile of heterosynaptic changes observed after the LTD in the amygdala: depression close to the stimulated inputs, but potentiation at longer distances, is unexpected if the above logics of strong calcium signals leading to LTP and weak to the LTD is applied. This apparent inconsistency can be resolved by suggesting that induction of heterosynaptic plasticity depends on calcium release from internal stores (Royer and Paré 2003). Calcium release from internal stores was also suggested to be involved in induction of heterosynaptic LTD (Nishiyama et al. 2000) and heterosynaptic facilitation of LTP in the hippocampus (Dudman et al. 2007). Another interesting possibility suggested by Royer and Paré (2003) is that inactive synapses have an inversed sensitivity to local calcium signals: higher rises of intracellular Ca^{2+} leading to depression, while lower to potentiation of inactive synapses.

The dependence of heterosynaptic plasticity on distance from the synapses that were stimulated during the induction, results in a Mexican hat like profile of amplitude changes: same-sign plasticity occurring at shorter distances, and opposite-sign at longer distances (White et al. 1990; Royer and Paré 2003). This pattern of amplitude changes may provide a kind of lateral inhibition in plasticity space, serving to accentuate the impact of plastic change at a local population of synapses and contrast that local population against the other synapses (Schuman and Madison 1994). It may also help to preserve total synaptic weight to a cell by balancing the effect of homosynaptic potentiation or depression (Royer and Paré 2003).

Induction of heterosynaptic plasticity described above was dependent on the distance from the site of induction of homosynaptic plasticity. However, active backpropagation of action potentials into the dendrites leads to Ca^{2+} influx over the broad portions of the dendritic tree, including the locations at which any immediate biochemical interaction with the activated synapses is excluded because of the large distance. The following lines of evidence suggest that synapses can undergo plasticity even without any synaptic activation, and thus at locations remote from the active synapses. First, long-lasting plasticity, LTP or LTD can be induced by photolytic release of caged Ca^{2+} in neurons without synaptic activation (Neveu and Zucker 1996; Yang et al. 1999). Second, long-term plasticity in the hippocampus and the neocortex can be induced by intracellular tetanization—trains of bursts of action potentials, evoked by short depolarizing pulses applied through the intracellular electrode without presynaptic stimulation (Kuhnt and Voronin 1994; Volgushev et al. 1994-2000; Chistiakova et al. 1999; Fig. 2). Potentiation and depression induced by both these purely postsynaptic protocols occluded LTP and LTD induced by afferent tetanization or pairing, suggesting at least partial overlap of their mechanisms (Kuhnt and Voronin 1994; Neveu and Zucker 1996; Volgushev et al. 1999; Yang et al. 1999).

Since both protocols, the photolytic release of caged Ca^{2+} in a cell and the intracellular tetanization, did not involve synaptic stimulation during the induction, plasticity at any of the synapses on the cell can be considered as heterosynaptic (Fig. 1, rightmost panel, and Fig. 2a,b). In fact, intracellular tetanization imitates for all synapses of a cell the situation which is experienced during the afferent tetanization or pairing procedure by the synapses that are located far away from those activated, e.g., at other dendrites, or at locations that exclude immediate diffusional/biochemical interaction with the activated synapses. Moreover, the absence of synaptic stimulation eliminates distance to the stimulation site as a factor influencing plasticity induction, making intracellular tetanization a useful tool to study mechanisms responsible for fast cell-wide interactions, e.g., normalization of synaptic weights or coordination of their changes.

Action potentials generated during the intracellular tetanization backpropagate in the dendrites, leading to the Ca^{2+} influx and the increase of intracellular Ca^{2+} concentration (Fig. 2c). Details of action potential backpropagation and related Ca^{2+} influx may vary between neurons of different types, as well as between individual neurons, depending on the distribution of the sodium, potassium and calcium channels over the dendritic tree (Waters et al. 2004). Nevertheless, as Fig. 2c shows, in accordance with a wealth of other published data (e.g., Jaffe et al. 1992; Petrozzino and Connor 1994; Yuste et al. 1994; Schiller et al. 1995), the

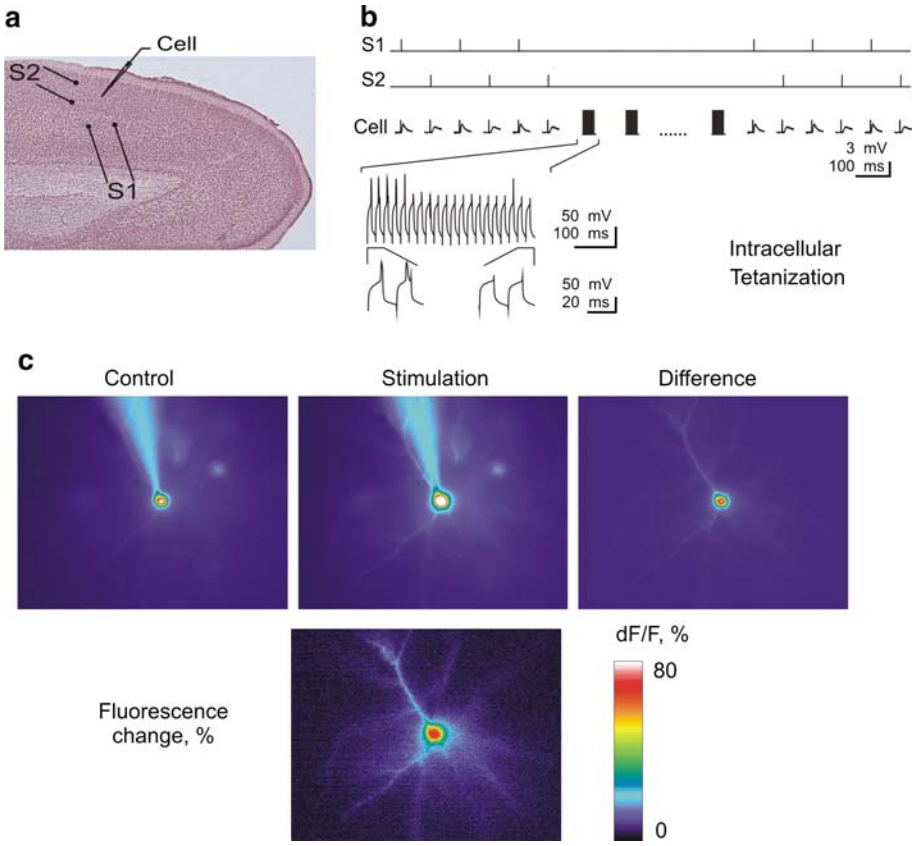

Fig. 2 Intracellular tetanization: Experimental protocol and calcium influx. **a** Positioning of the stimulation (*S1* and *S2*) and recording electrodes in a slice of the rat visual cortex. **b** Synaptic responses were evoked by test stimuli applied in alternation through the electrodes *S1* and *S2*. Synaptic stimulation was stopped during the intracellular tetanization. The intracellular tetanization consisted of 1 or 3 trains (1/min) of 10 bursts (1/s) of 20 short depolarizing pulses applied at 50 Hz. Each burst evoked 3–7 action potentials, a typical example is shown in the inset. After the intracellular tetanization, test stimulation was resumed (modified from Volgushev et al. 2000). **c** Calcium influx in a layer 2/3 pyramidal neuron in rat visual cortex evoked by a burst of depolarizing pulses (as used in the intracellular tetanization protocol, see **b**). Images of the neuron with fluorescent calcium-sensitive dye Oregon Green 488 BAPTA-1 before and during the stimulation; their difference and fluorescence change. Pseudocolor scale applies to fluorescence change image only (modified from Balaban et al. 2004)

intracellular Ca^{2+} concentration increases over broad areas of the dendritic tree, thus making numerous synapses located at these dendrites to potential targets for expressing heretosynaptic plasticity.

Firing of neurons during intracellular tetanization is comparable in strength and pattern to the activity of neurons in vivo, or during typical pairing protocols. Figure 3a shows in vivo intracellular recordings from two simple cells in cat visual cortex during presentation of optimally oriented moving gratings (Volgushev et al. 2003). A train of intracellular tetanization and a zoom-in of one burst of depolarizing pulses applied to the neuron is shown below these traces (Fig. 3b) at exact same temporal scales as responses in Fig. 3a. In the responses of visual cortex neurons in vivo the frequency of spike bursts can be higher than burst frequency in the intracellular tetanization protocol, and the number of action potentials in each burst can be about the same (Fig. 3a1) or higher (Fig. 3a2) than number of spikes in a burst during intracellular tetanization (3–7 spikes). Thus, activity evoked by the intracellular tetanization is well within the range of activity of visual cortical neurons in vivo.

Further, neuron firing evoked by the intracellular tetanization shares clear similarities to the pattern of postsynaptic activity evoked by pairing protocols. In Fig. 4, postsynaptic firing patterns evoked by several typical pairing protocols (all except d) and by intracellular tetanization (d) are compared. For the pairing protocols, the figure shows only the postsynaptic firing without the presynaptic stimuli that were applied at short intervals before or after the postsynaptic spikes. The protocols are sorted by the total number of postsynaptic cell discharges, in descending order from top to the bottom of the figure. Plasticity protocols express large variability in both, the gross pattern of postsynaptic activity they produce, as well as in detail, e.g., use of single APs or bursts consisting of 3–20 spikes, different number of bursts varying from 10 to 60, and a more than tenfold difference in the total number of postsynaptic spikes, from

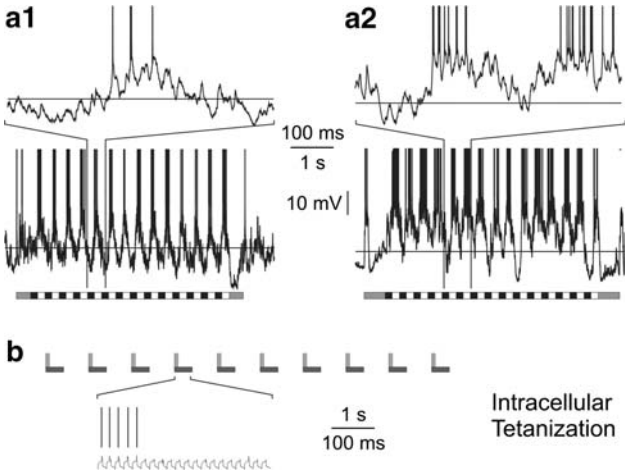

Fig. 3 Intracellular tetanization in slices and optimal stimulation of visual cortical neurons in vivo evoke comparable patterns of neuronal discharges. **a1**, **a2** Responses of two simple cells in cat visual cortex in vivo to moving grating of optimal orientation (modified from Volgushev et al. 2003, action potentials truncated). The intracellular tetanization, with action potentials as *vertical lines*, plotted at exact same time scales as in vivo recordings in **a**. The number of action potentials and their frequency in bursts during the intracellular tetanization is well within the range of firing patterns evoked by optimal visual stimulation in vivo

50 to 600. Thus, postsynaptic firing during the intracellular tetanization (Fig. 4d) is not extreme when compared to the pairing protocols.

Similarity of the neuron firing during intracellular tetanization to the firing during some pairing protocols and in vivo activity indicates that similar rises of intracellular Ca^{2+} concentration can be reached at nonactive synapses, leading to the induction of heterosynaptic plasticity by pairing protocols or in vivo activity. The following considerations show why these changes may remain unnoticed in the studies focused at associative, homosynaptic plasticity. With recordings from monosynaptically connected cells (e.g., Sjöström and Häusser 2006; Hardingham et al. 2007), possibilities for control procedures are limited for technical reasons. Even when control experiments replicating the postsynaptic firing pattern of the induction protocol but without presynaptic stimulation were made, their number was typically low ($n = 5$–10), well below the number of experiments with pairing. Taken into account that in the neocortex most protocols induce either potentiation or depression or no change even at the activated synapses (e.g., fig. 2b in Zhou et al. 2005; fig. 3 in Sjöström and Häusser 2006, fig. 2 in Hardingham et al. 2007), and that

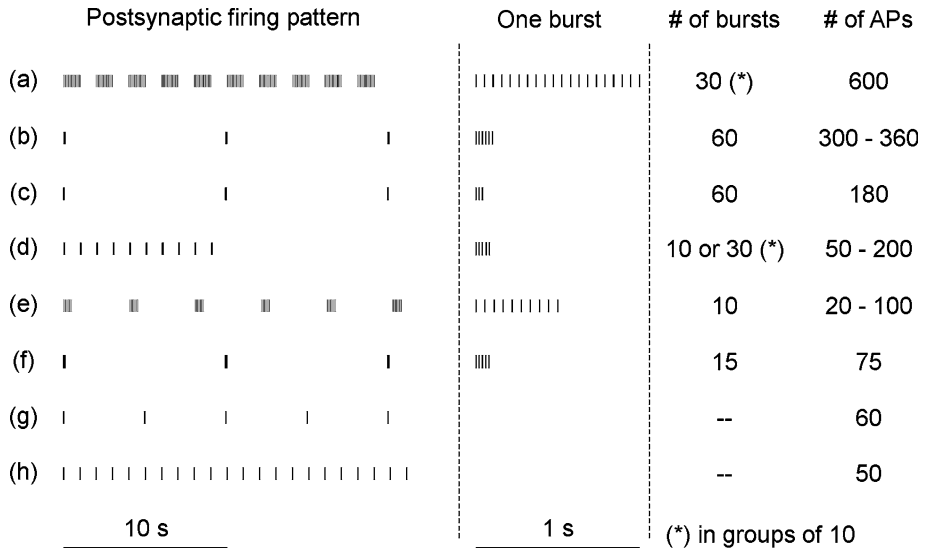

Fig. 4 Postsynaptic firing during plasticity induction: comparison of protocols from *left* to the *right*, for each protocol: initial 20 s of postsynaptic firing; zoom in of one burst, each *vertical line* representing one action potential; total number of bursts and postsynaptic action potentials in the protocol. Protocols are sorted by total number of postsynaptic action potentials (APs, rightmost column), which decreases from *top* (*a*) to the *bottom* (*h*). Protocols used in (*a*) 20 APs at 20 Hz, ×10 times at 0.5 Hz, ×3 times every 2 min (Hardingham et al. 2007). (*b*) ~6 APs evoked by 100-ms depolarization pulses, ×60 times at 0.1 Hz (Ismailov et al. 2004). (*c*) 3 APs at 50 Hz, ×60 times at 0.1 Hz (Nevian and Sakmann 2006). (*d*) Intracellular tetanization. 3–7 APs evoked by 10 depolarization pulses at 50 Hz, ×10 times at 1 Hz, ×1–3 times every min (Volgushev et al. 2000). (*e*) 2–10 APs at 20 Hz, ×10 times at 0.25 Hz (Markram et al. 1997). (*f*) 5 APs at 50 Hz, ×15 times at 0.1 Hz (Sjöström et al. 2008; Sjöström and Häusser 2006). (*g*) 1 AP, ×60 times at 0.2 Hz (Froemke et al. 2005). (*h*) 1 AP, ×50 times at 0.1–1 Hz (Zhou et al. 2005). In (*g*) and (*h*) postsynaptic action potentials were evoked as single spikes, not in bursts. The protocols were used to induce plasticity in pyramidal cell from layer 2/3 (*a*, *b*, *c*, *d*, *g*, *h*), or layer 5 (*e*, *f*) in the neocortex. In all protocols except (*d*), presynaptic stimulation (not shown) was applied in conjunction with the postsynaptic spikes. In the studies of spike-timing-dependent plasticity (*STDP*) presynaptic stimuli were applied at several different intervals before or after the postsynaptic spikes

data from control experiments are typically presented as averages, failure to notice heterosynaptic changes is not surprising. In fact, large variability in control series reported in some studies show that amplitude changes did take place (e.g., ±20% SEM with $n = 6$, which is ±43% SD; Nevian and Sakmann 2006). Notably, in papers aimed at investigating mechanisms of heterosynaptic plasticity, it was readily induced by regular pairing (Nishiyama et al. 2000) or afferent tetanization (Royer and Paré 2003; Bauer and LeDoux 2004; Wöhrl et al. 2007) protocols.

From the results discussed above we conclude, that heterosynaptic plasticity and input specific homosynaptic plasticity are complementary processes. Further, long-term heterosynaptic changes might accompany homosynaptic plasticity which is induced by typical pairing or afferent tetanization protocols.

What determines the direction and magnitude of plasticity?

Long-term synaptic plasticity may occur in both directions, potentiation and depression, and have different magnitude. What determines whether LTP or LTD will be induced, and how much response amplitude will change? A simple answer for the homosynaptic plasticity is that its direction and the magnitude is determined by the plasticity inducing protocol.

In the case of afferent tetanization, the direction of the change depends as a rule on the frequency (Dunwiddie and Lynch 1978). Tetanization at high frequency (20 Hz and above) leads to potentiation, while stimulation at low frequency (3 Hz and below) leads to depression (Dudek and Bear 1992; Mulkey and Malenka 1992).

In pairing protocols, induction of LTP or LTD critically depends on timing of the presynaptic activity relative to the postsynaptic firing or ongoing network activity. A pioneering study exploited in vivo field potential responses in the dentate gyrus, evoked by contra- and ipsilateral stimulation in the entorhinal cortex (Levy and Steward 1983). Contralateral inputs evoked weak responses, which did not express plasticity when stimulated alone. However, they could be potentiated or depressed if stimulated together with the strong ipsilateral inputs. The weak inputs expressed LTP, if they were stimulated shortly before (20 ms or less) or simultaneously with the strong inputs. Stimulation in a reversed order, with weak inputs activated after the strong, induced LTD of the weak inputs. The temporal window for inducing associative depression was longer, about 200 ms. Dependence of the direction of plasticity of synaptic inputs on the precise timing of their activation relative to natural-like rhythmic activity was demonstrated in hippocampal slices. During carbachol-induced theta oscillations, a burst of stimuli applied at the peak of the theta-oscillation lead to LTP, while stimuli applied in the trough of the oscillation were depressed (Huerta and Lisman 1995, 1996). LTP was accompanied by heterosynaptic LTD of non-stimulated inputs.

The rules for the associative synaptic plasticity, which correspond to temporal contiguity requirement in conditioning paradigm, also hold true at the level of individual cells and synaptic connections between pairs of neurons. Both in the hippocampus and in the neocortex, LTP is induced at synapses activated shortly, 10–20 ms, before the postsynaptic cell fires action potentials, but LTD is induced if the inputs are activated 10–20 ms after the postsynaptic firing (Magee and Johnston 1997; Markram et al. 1997). These results and further studies of time relations between the presynaptic and postsynaptic activity lead to formulation of spike-timing dependent plasticity (STDP) rule (see reviews by Abbott and Nelson 2000; Kampa et al. 2007; Caporale and Dan 2008; Sjöström et al. 2008). The STDP rule expresses the ability of a neuron to capture causal relations between the input activation and generation of action potentials: inputs preceding the spikes and thus capable of influencing their generation are potentiated, while inputs activated after the spikes are depressed. The magnitude of the LTP or LTD induced by pairing depends on the frequency and number of postsynaptic potentials in each pairing burst and the number of pairings (e.g., Markram et al. 1997; Sjöström et al. 2008; Birtoli and Ulrich 2004; Nevian and Sakmann 2006), the increase in these parameters leading to the higher magnitude of plastic changes.

Although the rules relating the direction and magnitude of plasticity to specific properties of the induction protocol hold in principle, details make the picture more complicated. To start with, rules for inducing homosynaptic potentiation or depression are not uniform across the synapses. Synaptic connections express substantial variability of STDP plasticity windows width, as well as the magnitude of the potentiation and depression induced with optimal timing. For example, synapses made by axons of pyramidal cells onto low threshold spiking inhibitory neurons express STDP, but at synapses formed by the same axons on the fast spiking interneurons only LTD is induced at either positive or negative intervals between the pre and postsynaptic activation (Lu et al. 2007). Synapses of the same neuron also express different requirements for plasticity induction with STDP protocol, depending on the distance from the soma and on whether they are located on the apical or basal dendrites (Froemke et al. 2005; Gordon et al. 2006; Letzkus et al. 2006; Sjöström and Häusser 2006). The dependence of STDP rules on the dendritic location may be at least partially explained by the dynamics of action potential back-propagation and related local dynamics of the Ca^{2+} signal (e.g., Letzkus et al. 2006). However, these are not sole factors. In the amygdala, inputs from the cortex converge onto

the same dendrites as the inputs from the thalamus, but express less plasticity (Humeau et al. 2005). Thus, synapses on the same cell, as well as the synapses formed by the same axon onto different target neurons may express different requirements for induction of homosynaptic plasticity.

Rules for induction of heterosynaptic potentiation or depression are also not uniform. As discussed above, one of the factors is distance from the site of activation during the plasticity induction (White et al. 1990; Royer and Paré 2003). Another factor is the sign of homosynaptic plasticity: heterosynaptic plasticity of the same sign is induced at short distances (Schuman and Madison 1994; Engert and Bonhoeffer 1997; Royer and Paré 2003), and of the opposite sign further away from the focus of activation (Royer and Paré 2003).

Heterosynaptic plasticity can be also induced by distance-independent mechanism(s), without any presynaptic stimulation, by rise of intracellular Ca^{2+} concentration evoked by photolytical release of caged Ca^{2+} (Neveu and Zucker 1996; Yang et al. 1999), or intracellular tetanization (Kuhnt and Voronin 1994; Volgushev et al. 1994–2000). In experiments with photolytical release of caged Ca^{2+}, the direction of synaptic changes was related to the amplitude and the time course of the Ca^{2+} rise. Fast, large amplitude Ca^{2+} rises (10 µm, 10 s) induce LTP, while slow, low amplitude Ca^{2+} signals (0.75 µM, 1 min), induce LTD (Yang et al. 1999). However, brief submicromolar elevations of intracellular Ca^{2+} may induce changes in either direction, potentiation or depression (Neveu and Zucker 1996). Notably, each of the three patterns of intracellular Ca^{2+} rise failed to elicit plasticity in some experiments.

Intracellular tetanization can induce bi-directional changes of synaptic transmission, occasionally inducing potentiation and depression simultaneously at different synapses to the same cell (Fig. 5). On the population level, after the intracellular tetanization synaptic transmission was potentiated in about 45% of cases, depressed in 30%, and at did not change in the remaining 25% of cases (Volgushev et al. 2000). One possible interpretation of these results is that in different experiments and at different synaptic inputs, the amplitude of Ca^{2+} rise fell within the range of potentiation, depression, or in the no mans' land between the LTD and LTP regions, or even did not reach the lower threshold required for LTD induction (Lisman 2001). Another possibility is that synapses have individual requirements for plasticity induction, much like different susceptibility for homosynaptic plasticity, discussed above. In that case, the outcome of plasticity induction will depend on the relation between these individual requirements and the local rise of intracellular Ca^{2+} concentration. This suggestion is supported by the fact that after the intracellular tetanization, the direction and the magnitude of plastic change was related to the properties of presynaptic release mechanisms (Fig. 6). Release properties were assessed with

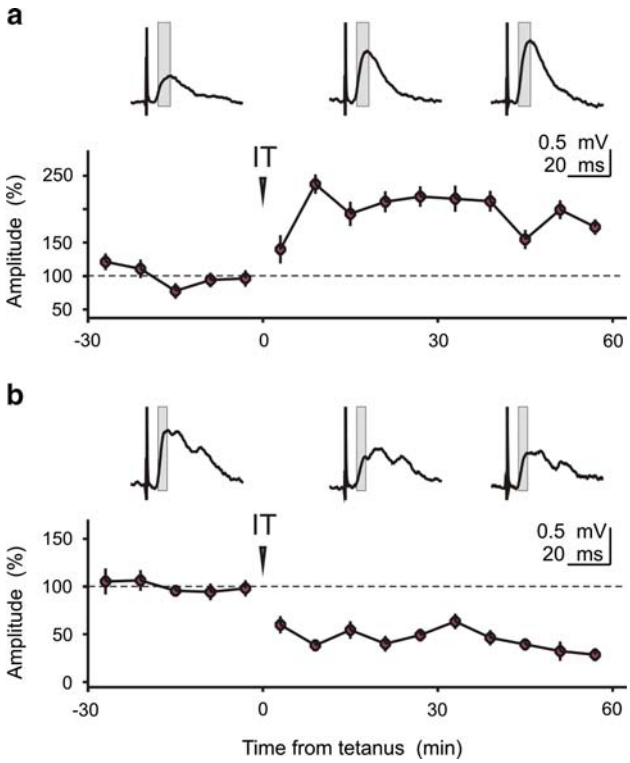

Fig. 5 LTP and LTD, induced by intracellular tetanization. **a** and **b** show responses of the same cell to alternating stimulation applied through the S1 and S2 electrodes (see Fig. 2). Intracellular tetanization simultaneously induced LTP and LTD at these inputs. Insets show averaged responses ($n = 50$) before, 10–25 min after and 30–45 min after the intracellular tetanization (modified, from Volgushev et al. 2000)

paired-pulse facilitation (PPF) ratio. The PPF depends on the release probability, high PPF ratios indicative of low release probability, and low PPF ratios (or paired-pulse depression) indicative of the higher release probability (Zucker 1989). After the intracellular tetanization, synapses with initially high PPF ratio, indicative of low release probability, were most often potentiated. The synaptic inputs with low PPF ratio, indicative of high release probability, were most often depressed or did not change (Fig. 6a). Segregation of the inputs in two groups according to the initial PPF further supports this conclusion. The net effect of intracellular tetanization in the group with initially low PPF was depression, while in the group of inputs with initially high PPF the net effect was a potentiation (Fig. 6b). Based on these results it was suggested, that synapses have different predispositions to undergo plastic changes (Volgushev et al. 1997, 2000). Some synapses have predisposition to undergo potentiation, some to undergo depression, while at some synapses, predispositions for changes in either direction are low or absent, making these synapses stable under most of experimental conditions.

Do predispositions, correlated with presynaptic release properties of the input, also influence the outcome of

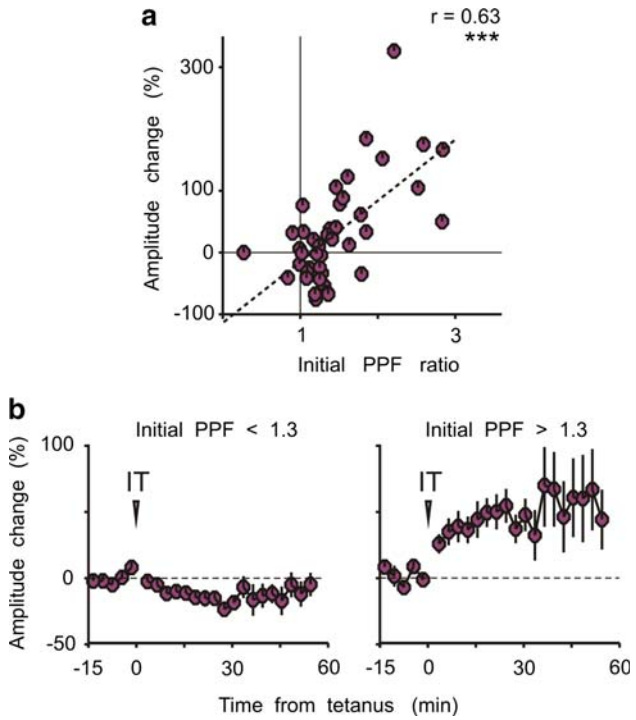

Fig. 6 Long-term changes in synaptic transmission induced by the intracellular tetanization depend on the initial state of presynaptic release mechanisms. **a** Correlation between the initial paired-pulse facilitation (*PPF*) ratio measured before the tetanization and the amplitude change after the tetanization. PPF was calculated as the ratio between the amplitude of responses to the second and to the first stimulus, which were applied with a short (in our case 50 ms) interval. **b** Time course of the amplitude changes in the inputs with initially low (<1.3) and initially high (>1.3) PPF. The whole sample was divided to nearly equally populated parts, with $n = 21$ and $n = 22$ (modified, from Volgushev et al. 2000)

homosynaptic plasticity? Several lines of evidence support this conjecture. In the neocortex, excitatory synapses between pyramidal cells and low-threshold spiking interneurons express PPF, and repetitive presynaptic activation followed by postsynaptic spikes leads to LTP at these synapses (Lu et al. 2007). Synapses from pyramidal cells to fast-spiking interneurons express paired-pulse depression, and the same induction protocol leads to LTD at these synapses. Interestingly, the predispositions of these two types of synapses for potentiation or depression were preserved even when plasticity was induced by pairing protocols that excluded short-term interaction during the induction. These results indicate that dependence of the direction of synaptic changes on PPF indeed reflects intrinsic predispositions of synapses for plasticity, rather than it is due to difference in postsynaptic responses during the induction. Dependence of the direction and the magnitude of plastic changes induced by a pairing protocol on the initial PPF and initial release probability was directly demonstrated in a recent study on monosynaptically connected pyramidal neurons in the neocortex (Hardingham et al. 2007). After a pairing protocol, potentiation was induced at synaptic connections characterized by the low release probability and high initial PPF ratio, while depression was induced in the synapses with high initial probability and low PPF ratio. Results of this study correspond most closely to the effects of the intracellular tetanization described above, probably because they were obtained in the same cells, layer 2/3 pyramids from rat visual cortex, and the pairing protocol used by Hardingham et al. (2007) was very similar to the intracellular tetanization.

Thus, the direction of plasticity and magnitude of response changes depend on both specific details of the induction protocol and predisposition of the synapse under study to undergo plastic changes. At different synapses, the same protocol may induce changes of response amplitude of an opposite sign and different magnitude, or no changes at all. Moreover, exact same plasticity protocol applied to synapses of the same type may still induce a broad range of response changes of different magnitude and often even opposite polarity. This can be seen in almost any published figure which presents synaptic changes as distribution of individual data points but not just averages (e.g., Sjöström et al. 2008; Ismailov et al. 2004; Zhou et al. 2005; Sjöström and Häusser 2006; Letzkus et al. 2006; Hardingham et al. 2007). Predispositions of synapses for plasticity, with some synapses more susceptible for potentiation, some for depression, while some others tend not to change but remain stable, may be one of the reasons for this heterogeneity of the effects of pairing and STDP protocols. What makes synapses different, and how their predispositions for plasticity may be regulated?

One of the factors influencing susceptibility of synapses for plastic changes is pre-history of the cell and synapses. For example, prior potentiation leads to a higher susceptibility for depression, or de-potentiation (Staubli and Lynch 1990), and prior synaptic activity may increase the threshold for LTP induction (Huang et al. 1992). Changes of the ability of synapses to undergo plasticity are accounted for in the concept of metaplasticity—"plasticity of synaptic plasticity" (Abraham and Bear 1996). Although originally proposed to explain input-specific, homosynaptic effects, metaplasticity can also influence heterosynaptic changes (Abraham et al. 2001). Prior induction of potentiation shifted susceptibility to heterosynaptic changes toward depression in experiments with photolytic release of caged Ca^{2+} (Neveu and Zucker 1996). In control conditions, brief submicromolar elevations of intracellular calcium led to potentiation, depression or no change, but after prior potentiation same calcium elevations led to depression or no change, but never to a potentiation. Heterosynaptic metaplasticity can also influence selectively late phases of the LTP. In the hippocampus, low-frequency stimulation decreased the stability of late LTP which was induced at the

same or at the other synapses to the same cells (Young and Nguyen 2005). Early LTP which lasted <2 h was not affected, suggesting that prior low-frequency stimulation disrupted consolidation of the early LTP to the late LTP. Another example of the heterosynaptic influence on the late LTP phase is de-potentiation of the LTP, normally lasting for days and weeks in vivo, by a strong high-frequency stimulation of another pathway (Abraham et al. 2006). This heterosynaptic NMDA-receptor dependent de-potentiation also occurred without tetanization, but in the enriched environment, suggesting that similar processes take place in the hippocampal neurons during natural learning.

Susceptibility of synapses for plasticity may depend on the presence of AMPA receptors and their mobility, as hypothesis of discrete synaptic states suggests (Montgomery and Madison 2002, 2004). Another possibility is a switch between different mechanisms, mediating multiple forms of plasticity. In the course of massive reorganization in somatosensory cortex, induced by single-whisker experience, the NMDA-receptor dependent LTP in the remaining barrel gets saturated, and pairing protocols induce LTD instead. However, under blockade of NMDA-receptors, further LTP can be induced via mGluRs dependent mechanisms (Clem et al. 2008). Given the multitude of plasticity mechanisms at cortical synapses described so far (Bliss and Collingridge 1993; Malenka and Nicoll 1993; Malinow et al. 2000; Malenka and Bear 2004), transition between plasticity mechanisms, or change of the availability or sensitivity of different mechanisms may provide a rich repertoire for regulation of susceptibility of cells and synapses to plastic changes. One further possibility to control and modify predispositions for synaptic changes could be neuromodulation, a long-known factor regulating cortical plasticity (e.g., Bear and Singer 1986; Kilgard and Merzenich 1998). Recent study shows that neuromodulators regulate the STDP rules in visual cortex neurons. An STDP protocol which does not induce plasticity under control conditions, can reliably induce LTP if applied on the background of activation of adenylyl cyclase, e.g., via beta-adrenergic receptors (Seol et al. 2007). If the same pairing protocol is applied on the background of phospholipase C activation, e.g., via muscarinic M1 receptors, it induces LTD. Thus, depending on the activation of neuromodulatory systems and the relative level of their activity, one and the same pairing protocol may induce potentiation or depression of synaptic transmission, or no changes at all.

Results discussed above allow us to conclude that synapses are not uniform in their susceptibility for plastic changes, but have predispositions to undergo potentiation, depression, or not to change. Predispositions may influence both, homosynaptic and heterosynaptic plasticity. Moreover, predispositions of synapses for plasticity are not fixed, but can change. The direction and magnitude of plastic changes depend on both specific details of the induction protocol and predispositions of synapses for plasticity.

How neurons manage their plastic synapses, or what heterosynaptic plasticity is good for?

Experimental studies considered above analyzed plasticity at one, sometimes two, but only occasionally more (e.g., White et al. 1990; Royer and Paré 2003) sets of synapses on a neuron simultaneously. This restriction is due to obvious technical reasons. However, each neuron in a neuronal network receives thousands of synaptic inputs. Theoretical analysis identified several problems faced by neurons and learning networks equipped with plastic synapses.

One set of problems is due to a positive feedback that is intrinsic to unrestrained Hebbian learning: when synaptic inputs leading to spikes are potentiated, this increases their chances to evoke spikes and thus to be further potentiated. Such positive feedback would result in a runaway dynamics of synaptic weights, with synapses either potentiated or depressed to extremes. To prevent the runaway dynamics, normalization mechanisms are implemented in the models since early theoretical analysis of the development of orientation maps in the visual cortex (von der Malsburg 1973). In this model, the total weight of all synapses received by a cell was used as normalization factor to rescale all synaptic weights as plasticity took place, thus conserving the total synaptic weight. Although stability of synaptic weights distribution can be achieved by carefully balanced local learning rules, e.g., STDP with a broader time window for depression (Song et al. 2000; Song and Abbott 2001) or by different dependence of potentiation and depression on the absolute values of synaptic weights (Sjöström et al. 2008), a cell-wide process ensuring homeostasis of synaptic weight distribution at the level of a single neuron would make a learning network much more robust.

Another problem of a system equipped exclusively with homosynaptic plasticity is the lack of mechanisms of competition between synapses (Miller 1996). The necessity for competition between synapses and cells stands out especially clear in development, when some sets of synapses should be strengthened and preserved, but others weakened and discarded to achieve and refine specificity of receptive fields and representations, e.g., in the visual system (Hubel and Wiesel 1970; Miller et al. 1989; Katz and Shatz 1996). Although homosynaptic LTD may play a role in this process, high requirements for temporally precise activity patterns that are inducing activity dependent forms of LTD (Dudek and Bear 1992; Mulkey and Malenka 1992; Malenka and Bear 2004; Caporale and Dan 2008) are unlikely to be met at all of those-to-be-eliminated inputs, indicating the necessity of heterosynaptic, cell-wide mechanisms of synaptic competition

(Miller 1996). In fact, cell-wide mechanisms preserving total synaptic weights, e.g., normalization (von der Malsburg 1973), implement competition between synapses. With synaptic weights normalization, any change at one synapse will be accompanied by compensatory, opposite-direction changes of weights of the other synapses.

For both of the above processes, conservation of total synaptic weights and synaptic competition, mechanisms for cell-wide regulation of synaptic changes, including heterosynaptic, would be advantageous. Some of the experimental results discussed above indicate possible mechanisms that may support a cell-wide homeostasis of synaptic weights (Volgushev et al. 1997, 2000; Royer and Paré 2003; Hardingham et al. 2007). Operation of these or other mechanisms supporting homeostasis of synaptic weights at single cell level looks plausible also in a view of the existence of network-wide homeostatic mechanisms capable of scaling synaptic efficacy depending on the large-scale level of network activity (Turrigiano et al. 1998; Abbott and Nelson 2000).

A problem of a different sort, faced by learning networks with plastic synapses is the dilemma between plasticity and stability (review: Abraham and Robins 2005). Highly plastic synapses allow fast learning, but these memory traces are rapidly erased by the ongoing new learning. With less plastic synapses memories can be retained longer, but ability to learn new is reduced. No simple solution, such as normalization for the runaway or competition problems discussed above, appears to resolve this dilemma. However, recent theoretical analysis indicates that endowing neuronal networks with a mechanism of regulation of plastic abilities of the modified synapses allows substantial increase in the duration of memory storage without compromising ongoing learning (Fusi et al. 2005). In these models, a synapse can switch between a potentiated and a depressed weight, each weight having a cascade of plasticity states with progressively decreasing ability for switching to the other weight. Plasticity-inducing activity patterns may either switch the weight of a synapse, or decrease its plastic ability, e.g., potentiating challenge may turn the depressed synapses into potentiated, or shift plastic ability of already potentiated synapses down the cascade, making them more stable. One of the predictions of such a scheme is that synapses have different susceptibilities for plastic changes (Fusi et al. 2005). This prediction is in agreement with the experimental data on predispositions of synapses for potentiation or depression, discussed above.

Gradual regulation of a synapses' ability to change, as suggested in cascade models, helps a learning system to prolong retention of memory traces, but for permanent life-long memory additional mechanisms are required. Candidate mechanism for this task is rehearsal and active re-storing of the old information (Wilson and McNaughton 1994; Nádasdy et al. 1999; Ji and Wilson 2007). Suggested ways to exploit rehearsal mechanism range from dynamic representations of memories in a system without synapse stabilization, but permanently occurring rehearsal during spontaneous activity (Routtenberg and Rekart 2005; Routtenberg 2008), to iterative processing and resolving new configuration of synaptic weights that encodes new information while preserving the old (Abraham and Robins 2005). That latter process might involve cell-wide coordination of synaptic weight modifications, and thus heterosynaptic plasticity.

The discussed results of theoretical analysis of neuronal learning networks show the necessity of cell-wide regulation and coordination of synaptic weight modifications, and thus of heterosynaptic plasticity for preventing runaway dynamics of synaptic weights and network activity, and achieving competition between cells' synapses. Moreover, regulation of plastic abilities of a synapse (or "predispositions") may help to extend duration of memory traces, preserving them from rapid overwriting by ongoing learning.

Conclusions

Taken together, the experimental and theoretical results discussed above allow to draw the following conclusions. (1) Heterosynaptic and homosynaptic plasticity are complementary. Heterosynaptic plasticity might accompany homosynaptic changes induced by typical pairing protocols, and may help to achieve normalization of synaptic weights and homeostasis of their distribution at a single neuron during repeated learning. (2) Synapses are not equally susceptible to plastic changes, but have predispositions to undergo potentiation or depression, or not to change. Predispositions may influence both, homosynaptic and heterosynaptic plastic changes. (3) Moreover, predispositions of synapses for plasticity are not fixed, but can change. Downregulation of plastic abilities of a synapse may help to prolong memory traces, preserving them from being rapidly overwritten by ongoing learning.

Acknowledgments We are grateful to Harvey Swadlow for comments and improving English. Research in authors' lab is supported by the grants from the Bundesministerium für Bildung und Forschung, and startup funds from the University of Connecticut to MV. Some of the results were obtained with the support from the Deutsche Forschungsgemeinschaft, SFB 509 TP-A5.

References

Abbott LF, Nelson SB (2000) Synaptic plasticity: taming the beast. Nat Neurosci 3:1178–1183

Abraham WC, Bear MF (1996) Metaplasticity: the plasticity of synaptic plasticity. TINs 19(4):126–130

Abraham WC, Robins A (2005) Memory retention—the synaptic stability versus plasticity dilemma. TINs 28:73–78

Abraham WC, MasonParker SE, Bear MF, Webb S, Tate WP (2001) Heterosynaptic metaplasticity in the hippocampus in vivo: a BCM-like modifiable threshold for LTP. Proc Nat Acad Sci USA 98:10924–10929

Abraham WC, Logan B, Greenwood JM, Dragunow M (2002) Induction and experience-dependent consolidation of stable long-term potentiation lasting months in the hippocampus. J Neurosci 22:9626–9634

Abraham WC, Mason-Parker SE, Irvine GI, Logan B, Gill AI (2006) Induction and activity-dependent reversal of persistent LTP and LTD in lateral perforant path synapses in vivo. Neurobiol Learn Mem 86:82–90

Balaban P, Chistiakova M, Malyshev A, Volgushev M (2004) Dependence of calcium influx in neocortical cells on the temporal structure of depolarization, number of spikes and blockade of NMDA-receptors. J Neurosci Res 76:481–487

Bauer EP, LeDoux JE (2004) Heterosynaptic long-term potentiation of inhibitory interneurons in the lateral amygdala. J Neurosci 24:9507–9512

Bear M, Singer W (1986) Modulation of visual cortical plastisity by acetilcholine and noradrenaline. Nature 320:172–176

Bienenstock EL, Cooper LN, Munro PW (1982) Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex. J Neurosci 2(1):32–48

Birtoli B, Ulrich D (2004) Firing mode-dependent synaptic plasticity in rat neocortical pyramidal neurons. J Neurosci 24:4935–4940

Bliss TV, Collingridge GL (1993) A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361:31–39

Bliss TV, Gardner-Medwin AR (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the unanaestetized rabbit following stimulation of the perforant path. J Physiol 232(2):357–374

Bliss TV, Lomo T (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol 232(2):331–356

Böhme GA, Bon C, Stutzmann JM, Doble A, Blanchard JC (1991) Possible involvement of nitric oxide in long-term potentiation. Eur J Pharmacol 199(3):379–381

Bonhoeffer T, Staiger V, Aersten A (1989) Synaptic plasticity in rat hippocampal slice cultures: local "Hebbian" conjunction of pre- and postsynaptic stimulation leads to distributed synaptic enhancement. PNAS 86(20):8113–8117

Caporale N, Dan Y (2008) Spike timing-dependent plasticity: a Hebbian learning rule. Annu Rev Neurosci 31:25–46

Chistiakova M, Balaban P, Eysel UT, Volgushev M (1999) NMDA-receptor blockade prevents LTD, but not LTP induction by intracellular tetanization. NeuroReport 10:3869–3874

Clem RL, Celikel T, Barth AL (2008) Ongoing in vivo experience triggers synaptic metaplasticity in the neocortex. Science 319:101–104

Dudek SM, Bear MF (1992) Homosynaptic long-term depression in area CA1 of hippocampus and effects of N-methyl-D-aspartate receptor blockade. Proc Natl Acad Sci USA 89:4363–4367

Dudman JT, Tsay D, Siegelbaum SA (2007) A role for synaptic inputs at distal dendrites: instructive signals for hippocampal long-term plasticity. Neuron 56:866–879

Dunwiddie T, Lynch G (1978) Long-term potentiation and depression of synaptic responses in the rat hippocampus: localization and frequency dependency. J Physiol 276:353–367

Engert F, Bonhoeffer T (1997) Synapse specificity of long-term potentiation breaks down at short distances. Nature 388:279–284

Froemke RC, Poo Mu-ming, Dan Y (2005) Spike-timing-dependent synaptic plasticity depends on dendritic location. Nature 434:221–225

Fusi S, Drew PJ, Abbott LF (2005) Cascade models of synaptically stored memories. Neuron 45:599–611

Gally IA, Montague PR, Reeke GN, Edelman GM (1990) The NO hypothesis: possible effects of a short-lived, rapidly diffusible signal in the development and function of the nervous system. PNAS 87:3547–3551

Gordon U, Polsky A, Schiller J (2006) Plasticity compartments in basal dendrites of neocortical pyramidal neurons. J Neurosci 26:12717–12726

Gustafsson B, Wigström H, Abraham WC, Huang YY (1987) Long-term potentiation in the hippocampus using depolarizing current pulses as the conditioning stimulus to single volley synaptic potentials. J Neurosci 7:774–780

Hansel C, Artola A, Singer W (1997) Relation between dendritic Ca2 + levels and the polarity of synaptic long-term modifications in rat visual cortex neurons. Eur J NeuroSci 9:2309–2322

Hardingham NR, Hardingham GF, Fox KD, Jack JB (2007) Presynaptic efficacy directs normalization of synaptic strength in layer 2/3 rat neocortex after paired activity. J Neurophysiol 97:2965–2975

Hölscher C (1997) Nitric oxide, the enigmatic neuronal messenger: its role in synaptic plasticity. Trends Neurosci 20:298–303

Huang YY, Colino A, Selig DK, Malenka RC (1992) The influence of prior synaptic activity on the induction of long-term potentiation. Science 255:730–733

Hubel DH, Wiesel TN (1970) The period of susceptibility to the physiological effects of unilateral eye closure in kittens. J Physiol 206:419–436

Huerta PT, Lisman JE (1995) Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1 in vitro. Neuron 15(5):1053–1063

Huerta PT, Lisman JE (1996) Low-frequency stimulation at the troughs of theta-oscillation induces long-term depression of previously potentiated CA1 synapses. J Neurophysiol 75(2):877–884

Humeau Y, Herry C, Kemp N, Shaban H, Fourcaudot E, Bissiere S, Lüthi A (2005) Dendritic spine heterogeneity determines afferent-specific Hebbian plasticity in the amygdala. Neuron 45:119–131

Ismailov I, Kalikulov D, Inoue T, Friedlander MJ (2004) The kinetic profile of intracellular calcium predicts long-term potentiation and long-term depression. J Neurosci 24:9847–9861

Jaffe DB, Johnston D, Lasser-Ross N, Lisman J, Miyakawa H, Ross WH (1992) The spread of Na + spikes determines the pattern of dendritic Ca2 + entry into hippocampal neurons. Nature 357:244–246

Ji D, Wilson MA (2007) Coordinated memory replay in the visual cortex and hippocampus during sleep. Nat Neurosci 10:100–107

Kampa BM, Stuart GJ (2006) Calcium spikes in basal dendrites of layer 5 pyramidal neurons during action potential bursts. J Neurosci 26:7424–7432

Kampa BM, Letzkus JJ, Stuart GJ (2007) Dendritic mechanisms controlling spike-timing-dependent synaptic plasticity. Trends Neurosci 30:456–463

Katz LC, Shatz CJ (1996) Synaptic activity and the construction of cortical circuits. Science 274:1133–1138

Kelso SR, Brown TH (1986) Differential conditioning of associative synaptic enhancement in hippocampal brain slices. Science 232:85–87

Kilgard MP, Merzenich MM (1998) Cortical map reorganization enabled by nucleus basalis activity. Science 279:1714–1718

Kossel A, Bonhoeffer T, Bolz J (1990) Non-Hebbian synapses in rat visual cortex. NeuroReport 1(2):115–118

Kuhnt U, Voronin L (1994) Interaction between paired-pulse facilitation and long-term potentiation in area CA1 of guinea-pig hippocampal slices: application of quantal analysis. Neuroscience 62:391–397

Letzkus JJ, Kampa BM, Stuart GJ (2006) Learning rules for spike timing-dependent plasticity depend on dendritic synapse location. J Neurosci 26:10420–10429

Levy WB, Steward O (1979) Synapses as associative memory elements in the hippocampal formation. Brain Res 175:233–245

Levy WB, Steward O (1983) Temporal contiguity requirements for long-term associative potentiation/depression in the hippocampus. Neuroscience 8(4):791–797

Lisman JE (1989) A mechanism for the Hebb and the anti-Hebb processes underlying learning and memory. PNAS 86:9574–9578

Lisman JE (2001) Three Ca2 + levels affect plasticity differently: the LTP zone, the LTD zone and no man's land. J Physiol 532.2:285

Lu J, Li C, Zhao J, Poo M, Zhang X (2007) Spike-timing-dependent plasticity of neocortical excitatory synapses on inhibitory interneurons depends on target cell type. J Neurosci 27:9711–9720

Lynch GS, Dunwiddie T, Gribkoff V (1977) Heterosynaptic depression: a postsynaptic correlate of long-term potentiation. Nature 266:737–739

Magee JC, Johnston D (1997) A synaptically controlled, associative signal for Hebbian plasticity in hippocampal neurons. Science 275:209–213

Malenka RC, Bear MF (2004) LTP and LTD: an embarrassment of riches. Neuron 44:5–21

Malenka RC, Nicoll RA (1993) NMDA-receptor-dependent synaptic plasticity: multiple forms and mechanisms. TINs 16:521–527

Malenka RC, Kauer JA, Zucker RS, Nicoll RA (1988) Postzsynaptic calcium is sufficient for potentiation of hippocampal synaptic transmission. Science 242:81–83

Malinow R, Mainen ZF, Hayashi Y (2000) LTP mechanisms: from silence to four-lane traffic. Curr Opin Neurobiol 10:352–357

Markram H, Luebke J, Frotscher M, Sakmann B (1997) Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. Science 275:213–215

Miller KD (1996) Synaptic economics: competition and cooperation in synaptic plasticity. Neuron 17:371–374

Miller KD, Keller JB, Stryker MP (1989) Ocular dominance column development: analysis and simulation. Science 245:605–615

Miyakawa H, Ross WH, Jaffe D, Callaway JC, Lasser-Ross N, Lisman JE, Johnston D (1992) Synaptically activated increases in Ca2 + concentration in hippocampal CA1 pyramidal cells are primarily due to voltage-gated Ca2 + channels. Neuron 9:1163–1173

Montgomery JM, Madison DV (2002) State-dependent heterogeneity in synaptic depression between pyramidal cell pairs. Neuron 33:765–777

Montgomery JM, Madison DV (2004) Discrete synaptic states define a major mechanism of synapse plasticity. TINs 27:744–750

Mulkey RM, Malenka RC (1992) Mechanisms underlying induction of homosynaptic long-term depression in area CA1 of the hippocampus. Neuron 9(5):967–975

Nádasdy Z, Hirase H, Czurkó A, Csicsvari J, Buzsáki G (1999) Replay and time compression of recurring spike sequences in the hippocampus. J Neurosci 19:9497–9507

Neveu D, Zucker RS (1996) Long-lasting potentiation and depression without presynaptic activity. J Neurophysiol 75:2157–2160

Nevian T, Sakmann B (2006) Single spine Ca2 + signals evoked by coincident EPSPs and backpropagating action potentials in spiny stellate cells of layer 4 in the juvenile rat somatosensory barrel cortex. J Neurosci 26:11001–11013

Nishiyama M, Hong K, Mikoshiba K, Poo M, Kato K (2000) Calcium stores regulate the polarity and input specificity of synaptic modification. Nature 408:584–588

Nowak L, Bregestovski P, Ascher P, Herbet A, Prochiantz A (1984) Magnesium gates glutamate-activated channels in mouse central neurones. Nature 307:462–465

O'Dell TJ, Hawkins RD, Kandel ER, Arancio O (1991) Tests of the roles of two diffusible substances in long-term potentiation: evidence for nitric oxide as possible early retrograde messenger. PNAS 88:11285–11289

Petrozzino JJ, Connor JA (1994) Dendritic Ca^{2+} accumulations and metabotropic glutamate receptor activation associated with an NMDA receptor-independent long-term potentiation in hippocampal CA1 neurons. Hippocampus 4:546–558

Routtenberg A (2008) The substrate for long-lasting memory: if not protein synthesis, then what? Neurobiol Learn Memory 89:225–233

Routtenberg A, Rekart JL (2005) Post-translational protein modification as the substrate for long-lasting memory. Trends Neurosci 28:12–19

Royer S, Paré D (2003) Conservation of total synaptic weight through balanced synaptic depression and potentiation. Nature 422:518–522

Schiller J, Helmchen F, Sakmann B (1995) Spatial profile of dendritic calcium transients evoked by action potentials in rat neocortical pyramidal neurones. J Physiol 487.3:583–600

Schiller J, Schiller Y, Clapham DE (1998) NMDA receptors amplify calcium influx into dendritic spines during associative pre- and postsynaptic activation. Nat Neurosci 1:114–118

Schuman EM, Madison DV (1994) Locally distributed synaptic potentiation in the hippocampus. Science 263:532–536

Seol GH, Ziburkus J, Huang SY, Song L, Kim IT, Takamiya K, Huganir RL, Lee HK, Kirkwood A (2007) Neuromodulators control the polarity of spike-timing-dependent synaptic plasticity. Neuron 55:919–929

Sjöström PJ, Häusser M (2006) A cooperative switch determines the sign of synaptic plasticity in distal dendrites of neocortical pyramidal neurons. Neuron 51:227–238

Sjöström PJ, Turrigiano GG, Nelson SB (2001) Rate, timing and cooperativity jointly determine cortical synaptic plasticity. Neuron 32:1149–1164

Sjöström PJ, Rancz EA, Roth A, Häusser M (2008) Dendritic excitability and synaptic plasticity. Physiol Rev 88:769–840

Song S, Abbott LF (2001) Cortical development and remapping through spike timing-dependent plasticity. Neuron 32:339–350

Song S, Miller KD, Abbott LF (2000) Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. Nat Neurosci 3:919–926

Staubli U, Lynch G (1990) Stable depression of potentiated synaptic responses in the hippocampus with 1–5 Hz stimulation. Brain Res 513:113–118

Stuart GJ, Häusser M (2001) Dendritic coincidence detection of EPSPs and action potentials. Nat Neurosci 4:63–71

Turrigiano GG, Leslie KR, Desai NS, Rutherford LC, Nelson SB (1998) Activity-dependent scaling of quantal amplitude in neocortical neurons. Nature 391:892–896

Volgushev M, Voronin LL, Chistiakova M, Singer W (1994) Induction of LTP and LTD in visual cortex neurons by intracellular tetanization. NeuroReport 5:2069–2072

Volgushev M, Voronin LL, Chistiakova M, Singer W (1997) Relations between long-term synaptic modifications and paired-pulse interactions in the rat neocortex. Eur J NeuroSci 9:1656–1665

Volgushev M, Mittmann T, Chistiakova M, Balaban P, Eysel UT (1999) Interaction between intracellular tetanization and pairing-induced long-term synaptic plasticity in the rat visual cortex. Neuroscience 93:1227–1232

Volgushev M, Chistiakova M, Balaban P, Eysel UT (2000) Retrograde signalling with nitric oxide at neocortical synapses. Eur J NeuroSci 12:4255–4267

Volgushev M, Pernberg J, Eysel UT (2003) Gamma-frequency fluctuations of the membrane potential and response selectivity in visual cortical neurons. Eur J NeuroSci 17:1768–1776

Von der Malsburg C (1973) Self-organization of orientation sensitive cells in the striate cortex. Kybernetik 14:85–100

Waters J, Schaefer A, Sakmann B (2004) Backpropagating action potentials in neurons: measurement, mechanisms and potential functions. Progr Biophys Mol Biol 87:145–170

White G, Levy WB, Steward O (1990) Spatial overlap between populations of synapses determines the extent of their associative interaction during the induction of long-term potentiation and depression. J Neurophysiol 64(4):1186–1198

Wilson MA, McNaughton BL (1994) Reactivation of hippocampal ensemble memories during sleep. Science 265:676–679

Wöhrl R, von Haebler D, Heinemann U (2007) Low-frequency stimulation of the direct cortical input to area CA1 induces homosynaptic LTD and heterosynaptic LTP in the rat hippocampal-entorhinal cortex slice preparation. Eur J NeuroSci 25(1):251–258

Yang SN, Tang YG, Zucker RS (1999) Selective induction of LTP and LTD by postsynaptic [Ca2 +]i elevation. J Neurophysiol 81:781–787

Young JZ, Nguyen PV (2005) Homosynaptic and heterosynaptic inhibition of synaptic tagging and capture of long-term potentiation by previous synaptic activity. J Neurosci 25(31):7221–7231

Yuste R, Gutnick MJ, Saar D, Delaney KR, Tank DW (1994) Ca2 + accumulations in dendrites of neocortical pyramidal neurons: an apical band and evidence for two functional compartments. Neuron 13:23–43

Zhou YD, Acker CD, Netoff TI, Sen K, White JA (2005) Increasing Ca2 + transients by broadening postsynaptic action potentials enhances timing-dependent synaptic depression. PNAS 102:19121–19125

Zucker RS (1989) Short-term synaptic plasticity. Ann Rev Neurosci 12:13–31