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Heterosynaptic Plasticity: Multiple Mechanisms and Multiple Roles

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Abstract

Plasticity is a universal property of synapses. It is expressed in a variety of forms mediated by a multitude of mechanisms. Here we consider two broad kinds of plasticity that differ in their requirement for presynaptic activity during the induction. Homosynaptic plasticity occurs at synapses that were active during the induction. It is also called input specific or associative, and it is governed by Hebbian-type learning rules. Heterosynaptic plasticity can be induced by episodes of strong postsynaptic activity also at synapses that were not active during the induction, thus making any synapse at a cell a target to heterosynaptic changes. Both forms can be induced by typical protocols used for plasticity induction and operate on the same time scales but have differential computational properties and play different roles in learning systems. Homosynaptic plasticity mediates associative modifications of synaptic weights. Heterosynaptic plasticity counteracts runaway dynamics introduced by Hebbian-type rules and balances synaptic changes. It provides learning systems with stability and enhances synaptic competition. We conclude that homosynaptic and heterosynaptic plasticity represent complementary properties of modifiable synapses, and both are necessary for normal operation of neural systems with plastic synapses.

Keywords

synaptic plasticity; runaway dynamics; weight normalization; heterosynaptic plasticity; neocortex; neuron model

Introduction

Plasticity is a universal property of synapses. It is expressed in a variety of forms mediated by a multitude of mechanisms. In this review, we will consider two broad kinds of plasticity that differ in their requirement for presynaptic activity during the induction. Homosynaptic plasticity occurs at synapses that were directly involved in activation of a cell during the induction. Induction of homosynaptic plasticity at a synapse requires its presynaptic

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activation. This form of plasticity is also called input specific or associative. Heterosynaptic plasticity can be induced at synapses that were not active during the induction. Thus, any synapse at a cell can be subject to heterosynaptic plasticity after episodes of strong postsynaptic activity. Both forms of plasticity can be induced by typical protocols used for plasticity induction. The two forms of plasticity have differential computational properties and play different roles in learning systems. Homosynaptic and heterosynaptic changes represent complementary forms of plasticity, both necessary for normal operation of neural systems with plastic synapses.

Synaptic Plasticity: Homosynaptic and Heterosynaptic

Plasticity is a universal property of synapses, vital for fundamental operations of the nervous system. Synaptic plasticity mediates formation and refinement of connectivity patterns in the nervous system during development and effective adaptive behavior in changing environment throughout life. Hebb's rule (Hebb 1949) formulates the basic principle according to which synaptic weights change: synaptic connections that repeatedly or persistently take part in firing of the postsynaptic neuron increase their strength. The original rule, suggested only for potentiation of synaptic connections, was later on extended to include depression: synapses that consistently do not take part in firing the postsynaptic neuron decrease their strength. After the discovery of the cellular basis of associative learning, the long-term potentiation (LTP) in the hippocampal formation (Bliss and Lomo 1973), the associativity rule has been complemented by the rules of cooperativity and input specificity (Bliss and Collingridge 1993). The rule of cooperativity states that activation should be strong, exceeding a certain threshold, to induce plastic changes. The rule of input specificity maintains that changes take place only at synapses that were activated during the induction but not at other synapses. Altogether, these Hebbian-type learning rules capture the associative nature of synaptic changes and explain a multitude of plastic phenomena in the nervous system, ranging from refinement of connectivity during development ("neurons that fire together wire together") to extraction of casual relations between events in the environment in Pavlovian conditioning and other types of associative learning, motor learning, and acquisition of sequences of behavioral actions.

Spike-timing dependent plasticity (STDP) explicitly implements relative timing between firing of the neuron and activity at its inputs (presynaptic spikes) as a determinant of the direction and the magnitude of synaptic weight changes. In the STDP learning rule, synaptic inputs that were active shortly before a postsynaptic action potential (pre before post) are potentiated, whereas synaptic inputs active shortly after the postsynaptic spike (post before pre) are depressed (Abbott and Nelson 2000; Caporale and Dan 2008; Magee and Johnston 1997; Markram and others 1997). Generalization of this rule includes models that take into account effects of multiple presynaptic and one postsynaptic spikes (Gjorgjieva and others 2011; Pfister and Gerstner 2006) but the main principle remains—presynaptic activation is required to induce changes.

STDP, and Hebbian-type learning rules in general, extract casual relations between events by using temporal order of their occurrence. This dictates the necessity of activity of both presynaptic and postsynaptic neurons for plasticity induction. Furthermore, the rule of input

specificity explicitly restricts plasticity induction to synaptic inputs that were active during the induction. Thus, plasticity governed by Hebbian-type learning is input-specific, or homosynaptic (Fig. 1).

Functional Roles for Homosynaptic Plasticity

Synaptic plasticity governed by Hebbian-type learning rules mediates formation and refinement of neuronal connectivity during development and thus plays a pivotal role in establishing the hardware for future neuronal computations. Similar mechanisms may be involved in trauma-induced compensatory and repair processes. During the whole life, Hebbian-type plasticity mediates a multitude of processes underlying the abilities of organisms to adapt their behavior to the changing environment. Such processes include learning of specific and repeatedly occurring in the environment relations between sensory stimuli and behaviorally relevant events, associations between sensory stimuli, learning of motor programs, and sequences of behavioral actions. Ultimately, homosynaptic plasticity is believed to provide a cellular mechanism underlying processes of new memory formation and learning.

Why Heterosynaptic Plasticity Is Required in Addition to Hebbian-Type Learning Rules

However, learning systems in which all plastic changes are governed by Hebbian-type learning rules have two major drawbacks. First, Hebbian-type learning rules have intrinsic positive feedback. Potentiation, by making synapses stronger, increases their chances to take part in firing a neuron, and thus increases probability of these synapses to be potentiated further. Similarly, synapses weakened by depression have a lower chance to lead to spikes, and thus increased probability for being further depressed. Because of this positive feedback loop the synaptic weights tend to be either potentiated to the maximal value or depressed to zero. The runaway of synaptic weights leads to overexcitability or silencing of neurons, which compromises computational abilities of neuronal networks by disturbing input–output relations of neurons and inducing runaway activity. Second, Hebbian-type learning rules introduce only a weak degree of competition between synapses. Although synaptic weights can change in both directions, these changes require repetition of specific patterns of the input activity. For two groups of inputs to change in opposite directions, both groups should be repeatedly activated either with different patterns, low frequency for induction of long-term depression (LTD) but high frequency for induction of LTP, or be systematically active at different timing relative to postsynaptic activity to change by STDP mechanism. Although possible in theory, such a scenario imposes strict requirements on the relations between specifics of plasticity rules and patterns of input activity.

The need for additional mechanisms that maintain stability of synaptic weights and neuronal activity, and support strong synaptic competition in learning systems with Hebbian-type rules, has been appreciated since early theoretical studies (Miller 1996; Miller and MacKay 1993; Von der Malsburg 1973). The requirements for both stabilization and competition can be solved by introducing heterosynaptic plasticity—changes at synapses that were not active during plasticity induction (Fig. 1). This can be achieved by normalization: after a weight change at any synapse, all synaptic weights are normalized so that their total remains constant (Von der Malsburg 1973). This mechanism, although not eliminating the possibility

of saturating potentiation or depression of an individual synapse, effectively prevents runaway of activity, and introduces synaptic competition that does not require repetition of a specialized LTD-inducing activity pattern at a synapse to decrease its weight. Later studies elaborated the use of normalization as mechanism of stability and synaptic competition (e.g., Elliott and Shadbolt 2002; Finelli and others 2008; Kempter and others 2001; Wu and Yamaguchi 2006) and further corroborated the requirement for stabilizing and balancing mechanisms in STDP-based models of learning and decision making in the framework of the complex tasks (Skorheim and others 2014). A recent theoretical study by Zenke and others (2013) established one further requirement for heterosynaptic plasticity: to be able to prevent runaway dynamics in neuronal networks and achieve robust stability of their operation, it should operate on the time scale of seconds to minutes, similar to the time scale on which homosynaptic plasticity is induced.

Thus, whereas the necessity of heterosynaptic plasticity to solve the issues associated with homosynaptic plasticity has been recognized since early theoretical studies, those normalization rules remained a theoretical concept until discovery of the heterosynaptic LTD —a form of plasticity involving synapses that were not activated presynaptically—in the hippocampus (Lynch and others 1977).

Experimental Evidence for Heterosynaptic Plasticity

Heterosynaptic LTD accompanying induction of LTP has been first described in the hippocampus shortly after the phenomenon of LTP was discovered (Fig. 2A; Lynch and others 1977). Induction of LTP at inputs to apical dendrites of CA1 pyramidal neurons, formed by Schaffer collateral-commissural fibers, was accompanied by an LTD at inputs to basal dendrites made by commissural fibers that were not stimulated during the induction. And vice versa, induction of LTP at the inputs to the basal dendrites was accompanied by LTD of inputs to the apical dendrites. Because of the clear separation of the presynaptic fibers and synapses mediating the two groups of inputs, this work presented a strong case for heterosynaptic plasticity. Heterosynaptic LTD accompanying the induction of homosynaptic LTP clearly has potential for both balancing plastic changes and supporting synaptic competition.

Heterosynaptic LTP was first discovered at synapses adjacent to potentiated inputs (Fig. 2B). After pairing of one input to a CA1 neuron, synapses formed by nearby fibers on that cell and even on nearby neurons were potentiated too (Bonhoeffer and others 1989; Engert and Bonhoeffer 1997; Kossel and others 1990; Schuman and Madison 1994). These results demonstrated that input specificity breaks down at short distances: LTP protocols induce plasticity not only at the activated synapses but also at those not active during the induction.

Further studies of the spatial distribution of plastic changes induced in structures with regular organization of the inputs, such as the hippocampus or amygdala, revealed a Mexican hat type profile of plasticity (Fig. 2C; Royer and Paré 2003; White and others 1990). Induction of LTP at a set of synapses was accompanied by a biphasic profile of heterosynaptic changes: a weaker LTP at nearby inputs, LTD at more distant inputs, and finally no changes at yet more distantly located synapses. A symmetrical profile was observed around the site of LTD induction: weaker LTD at close distances and LTP at more

distant inputs (Royer and Paré 2003). Importantly, the spatial profiles of plastic changes were balanced, so that neither LTP nor LTD induction at activated synapses resulted in net changes of the total synaptic input. Induction of balanced profiles of plastic changes can provide a powerful local mechanism of both normalization of synaptic weights and synaptic competition.

Heterosynaptic plasticity can be induced by purely postsynaptic protocols that do not involve any presynaptic stimulation during the induction. Long-term plasticity can be induced by rises of intracellular calcium concentration produced by photolysis of caged calcium (Fig. 2D; Neveu and Zucker 1996; Yang and others 1999). The direction of plastic changes in these experiments depended on the dynamics of intracellular calcium signal: large increases of $[Ca^{2+}]_{in}$ could induce LTP, and smaller amplitude prolonged $[Ca^{2+}]_{in}$ increases could lead to LTD.

Long-term plastic changes can be also induced by intracellular tetanization—bursts of spikes evoked by short depolarizing pulses applied through the recording electrode (Fig. 3A; Chistiakova and Volgushev 2009; Kuhnt and others 1994; Lee and others 2012; Volgushev and others 1994; Volgushev and others 1997; Volgushev and others 1999; Volgushev and others 2000; see also references to work from other labs in the section on mechanisms of heterosynaptic plasticity). The rationale behind the intracellular tetanization protocol is the following. Each neuron in the neocortex receives thousands of synaptic inputs. Repetitive activation of a fraction of these inputs, few dozens to hundreds, can lead to repetitive firing of a cell and under certain conditions induce synaptic plasticity. During the induction, all synapses but for those of the activated fraction will experience postsynaptic activity without activation of their presynaptic fibers. This situation, postsynaptic activity without presynaptic activation, is mimicked by the intracellular tetanization. Because no synaptic inputs were stimulated during the intracellular tetanization, any synaptic changes induced can be considered heterosynaptic.

Figure 3B shows examples of long-term plastic changes induced by intracellular tetanization in pyramidal neurons from slices of rat visual cortex. Amplitudes of synaptic responses could increase, decrease, or do not change after tetanization. In the illustrated example, intracellular tetanization simultaneously induced LTP in one input and LTD in the other (top and middle plots in Fig. 3B). The direction of plastic changes was correlated with initial paired-pulse ratio, which is inversely related to the release probability (Fig. 3C; Chen and others 2013b; Lee and others 2012; Volgushev and others 1997; Volgushev and others 2000). Inputs that expressed high initial paired-pulse ratio, and thus had low release probability, were typically potentiated. Inputs that expressed low initial paired-pulse ratio, and thus had high release probability, were typically depressed or did not change. We have suggested that the weight-dependence of plasticity reflected history-dependent predispositions of synaptic inputs to undergo potentiation or depression (Chistiakova and Volgushev 2009; Volgushev and others 1997; Volgushev and others 2000). Weak synaptic inputs with low release probability, for example, because they underwent depression in the past, have a stronger predisposition for potentiation. Strong synapses with high release probability, such as those recently potentiated, have higher predisposition for depression. The notion of predisposition of synapses for plastic changes is closely related to the ideas of sliding threshold between

depression and potentiation in the BCM rule (Bienenstock and others 1982; Yeung and others 2004) and metaplasticity—history dependent changes of the abilities of synapses to undergo potentiation or depression (Abraham and Bear 1996). One further parallel to properties of homosynaptic plasticity is the dependence of the magnitude of plastic changes induced by intracellular tetanization on initial paired-pulse ratio, which is indicative of initial synaptic weight. Weight dependence of synaptic plasticity has been suggested and analyzed in a theoretical study by Oja (1982). In this learning rule, the magnitude of potentiation is larger when synaptic weight is small, but decreases, eventually reaching zero, for stronger synapses. Weight-dependence of potentiation has been also reported for tetanization or pairing induced LTP in the hippocampus and neocortex (Hardingham and others 2007; Sjöström and others 2001; Van Rossum and others 2000; also our data—see Fig. 7). Further evidence for heterosynaptic plasticity is discussed below, in the sections on induction and mechanisms of heterosynaptic plasticity.

To summarize, heterosynaptic plasticity induced by intracellular tetanization expresses properties that are well suited for serving as a robust mechanism of normalization of synaptic weights: (a) it depresses strong and potentiates weak synapses thus preventing runaway dynamics of synaptic weights, (b) it can be induced at non-active synapses, and (c) it operates on the same time scale as homosynaptic plasticity. As we will discuss below, heterosynaptic plasticity with these properties can also support synaptic competition.

Plasticity of Intrinsic Excitability and Homeostatic Scaling

Two further forms of heterosynaptic changes have been described and well documented: changes of excitability and homeostatic plasticity. Changes of global or local dendritic excitability can be both of homeostatic nature, decreasing excitability after prolonged strong activity but increasing it after activity suppression (Zhang and Linden 2003), but also may enhance or amplify effects of potentiation by increasing excitability of the dendrites at which tetanized synapses are located (Fink and O'Dell 2009; Frick and others 2004). The excitability changes may dramatically affect neuronal responses; however, as changes of excitability do not change synaptic transmission as such, this type of plasticity is not discussed further in this review.

Homeostatic plasticity mediates compensatory scaling of synaptic weights counteracting prolonged dramatic changes of activity. Synaptic weights scale up after hours/days of activity blockade by TTX (Turrigiano and others 1998) or hyperpolarization of neurons caused by expression of inwardly rectifying potassium channels (Burrone and others 2002), and scaled down after prolonged increases of activity by blockade of inhibition (Turrigiano and others 1998). Homeostatic plasticity and its effects, cell-wide or compartmentalized, have been extensively reviewed recently (Rabinowitch and Segev 2008; Turrigiano 2008; Vitureira and others 2012). Homeostatic plasticity differs from the heterosynaptic plasticity described above in two important aspects. First, homeostatic plasticity requires nonspecific dramatic changes of neuronal activity over prolonged periods, which are unlikely to happen during everyday life and learning. Second, it operates on a very long time scale, hours and days, and thus cannot counteract runaway dynamics induced within seconds and minutes by Hebbian-type learning rules (Zenke and others 2013).

Computational Properties of Plasticity Induced by Intracellular Tetanization

We used computer models to test the hypothesis that heterosynaptic plasticity observed in intracellular tetanization experiments can prevent runaway dynamics of synaptic weights and activity (Chen and others 2013b). The model neuron consisted of two compartments, axosomatic and dendritic, and received synaptic inputs from 100 simulated presynaptic neurons (Fig. 4A). Each presynaptic neuron fired action potentials at average frequency of 1 Hz, with Poisson distributed interspike intervals. Activity of presynaptic neurons was mildly correlated, with averaged cross-correlation between pairs of spike trains 0.35 ± 0.05. This input led to the firing of the postsynaptic model neuron at ~1.8 Hz. With symmetrical STDP learning rule (Fig. 4A) synaptic weights showed runaway dynamics (Fig. 4B). By the end of the simulation, all synaptic weights were saturated at the maximal value, leading to a dramatic increase of the postsynaptic firing rate from ~1.8 Hz during the first 10 seconds of simulation, to ~6.3 Hz during the last 10 s of simulation. Implementing in the model heterosynaptic plasticity with experimentally observed properties effectively prevented runaway dynamics of synaptic weights and activity (Fig. 4C). In the model with both STDP and heterosynaptic plasticity, synaptic weights slightly increased, but did not saturate and formed a normal distribution around the new mean value, within the operation range of synapses. Firing rate of the postsynaptic neuron slightly increased from ~1.8 Hz to ~2.6 Hz. Further simulations demonstrated that the stabilizing effect of heterosynaptic plasticity on synaptic weights is long-lasting and robust to variations in the patterns of presynaptic activity, changes of calcium threshold for plasticity induction, and changes of parameters of STDP learning rules over a broad range of values. The latter point is demonstrated in Figure 5. To explore effects of STDP parameters, we fixed the depression window of STDP ($a- = 0.001$ mS/cm^2, $\tau- = 20$ ms), but changed systematically the amplitude and the time constant of the potentiation window (Fig. 5A). The range of tested STDP rules included those strongly dominated by depression, as well as those dominated by potentiation. The STDP-only model expressed nonsaturating behavior only with a very limited set of STDP rules, specifically those dominated by depression (Fig. 5B). As soon as the potentiation window of STDP rule was ~75% of the depression window or stronger, synaptic weights and postsynaptic firing invariably expressed runaway dynamics (Fig. 5B). Addition of heterosynaptic plasticity to the model robustly prevented runaway dynamics and led to the stable and physiological synaptic weight distribution. The model equipped with heterosynaptic plasticity expressed stable behavior with all STDP windows tested—from almost exclusively depressing STDP rules, to those strongly dominated by potentiation (Fig. 5C).

Thus, heterosynaptic plasticity makes a broad range of STDP parameters compatible with stable operation of neurons and neuronal networks. This is an important feature because experimental evidence indeed shows wide variations of STDP windows for potentiation and depression and of their relative strength in neurons of different types (Abbott and Nelson 2000; Caporale and Dan 2008; Feldman 2009; Froemke and others 2005; Haas and others 2006; Nishiyama and others 2000; Sjöström and others 2001; Zhou and others 2005).

Notably, despite its strong stabilizing effect on synaptic weights, heterosynaptic plasticity does not prevent synaptic competition and segregation of synaptic weights. Figure 6 shows results of simulations in which inputs to the model neuron were segregated in two groups. In one group of synapses, presynaptic firing was weakly correlated, with averaged correlation between spike trains 0.34 ± 0.02. In the other, smaller group, correlation of presynaptic firing was higher (0.61 ± 0.05). All presynaptic neurons fired at averaged frequency of ~1 Hz. In STDP-only model, strongly correlated inputs were rapidly potentiated and saturated at the maximum value, whereas distribution of the weakly correlated inputs changed little (Fig. 6A, B). In the model with both STDP and heterosynaptic plasticity, no inputs were saturated, but the groups of weakly and strongly correlated inputs formed two clearly separate distributions, both within the operation range of synaptic weights (Fig. 6C, D). Similarly, segregation was observed when the two groups of synaptic inputs differed by their average firing frequency rather than by the level of correlation. Results from Figure 6D illustrate one further notable feature introduced by heterosynaptic plasticity: the final distribution of synaptic weights is determined by the balance between STDP, or any other mechanisms that govern homosynaptic changes, and heterosynaptic plasticity.

Thus, heterosynaptic plasticity does not prevent segregation of groups of synaptic inputs exhibiting activity patterns that differ by the degree of correlation or by firing frequency. Moreover, it helps preserve the ability of a neuron with plastic synapses for further learning: unsaturated synapses have higher potential for further changes than those potentiated to the maximum or depressed to zero by STDP-only learning rules.

Functional Roles for Heterosynaptic Plasticity

Heterosynaptic plasticity with experimentally observed properties can play several important roles in learning systems equipped with plastic synapses.

First, it can play a stabilizing role by effectively counteracting positive feedback introduced by Hebbian-type learning rules, and thus prevent runaway dynamics of synaptic weight and neuronal firing. One consequence of this robust stabilization is that it makes a broad variety of learning rules and input activity patterns compatible with normal, unsaturated operation of learning networks. Another consequence is that weight-dependent heterosynaptic plasticity endorses any excessive activity in the system with stabilizing effect. Because only a fraction of synaptic inputs to a cell needs to be activated to induce firing, only this fraction of inputs will be subject to the positive feedback of the Hebbian learning. All other synapses, actually the majority of them, will be subject to stabilizing effect of heterosynaptic plasticity. Finally, by preventing saturation of synaptic weights, heterosynaptic plasticity keeps synapses within their operation range, susceptible to further changes, and thus keeps the system susceptible to new learning.

Second, heterosynaptic plasticity can support and facilitate synaptic competition by introducing an additional force driving synaptic weights toward equilibrium. Indeed, the weight of a synapse is determined by the balance between homosynaptic plasticity, for example, STDP, and heterosynaptic plasticity, with STDP pressing toward one of the extremes, and heterosynaptic plasticity pressing toward its own equilibrium. If STDP is not operating at a synapse, say, because it is not activated presynaptically, its weight will be

shifted toward the heterosynaptic plasticity equilibrium and thus away from the STDP-extreme. This will result in a more robust segregation of synaptic weights of competing synapses. Moreover, such a mechanism could underlie refinement of already learned patterns by decreasing weights of erroneously potentiated synapses, and in a limit would allow re-learning.

Induction of Input-Specific and Heterosynaptic Plasticity: Similarity of Mechanisms

Properties of heterosynaptic plasticity described above were derived from results of intracellular tetanization experiments. However, intracellular tetanization, though a useful tool to study plasticity that does not require presynaptic stimulation for its induction, is artificial in a way that in vivo, strong depolarization and firing of a neuron necessary for plasticity induction are produced by synaptic activity. This poses a question, whether a pairing procedure, conventionally used to induce STDP, can also induce heterosynaptic plasticity with the above properties? To address this question, we recorded synaptic responses in layer 2/3 pyramidal neurons from rat neocortex and induced STDP by pairing one of the test inputs with bursts of 5 postsynaptic action potentials. During pairing, the first spike in a burst was generated ~10 ms after the EPSP onset. Fifty pairings induced robust potentiation of EPSP amplitude to 137 ± 5.5% of the control (mean ± SEM, N = 81). The magnitude of EPSP change was significantly correlated with initial paired-pulse ratio (Fig. 7, magenta, diamond symbols; $r = 0.40$, $P < 0.001$). Importantly, the pairing procedure also induced plasticity in the inputs that were recorded in the same experiments but were not stimulated during the pairing procedure. The properties of this heterosynaptic plasticity were very similar to plasticity induced by intracellular tetanization. First, heterosynaptic changes in unpaired inputs occurred in both directions: 15 out of 50 inputs (30%) showed significant potentiation, and 12 more (24%) showed significant depression. Intracellular tetanization (data from Fig. 3) induced significant potentiation in 44 out of 136 inputs (32%) and depression in 49 inputs (36%). Second, the amplitude of EPSP changes was correlated with initial paired-pulse ratio (Fig. 7, cyan, square symbols, $r = 0.39$, $P < 0.001$; compare to $r = 0.43$, $P < 0.001$ for intracellular tetanization, pale blue). Third, although individual inputs did express significant potentiation and depression, there was no significant change of the averaged response amplitude (105.7 ± 4.7% of control, N = 50, compare to 106.8 ± 4.0% of control, N = 136, after intracellular tetanization).

Thus, induction of homosynaptic plasticity by a pairing procedure typically used in STDP studies is accompanied by the induction of heterosynaptic plasticity in unpaired inputs. This heterosynaptic plasticity has properties similar to those of plasticity induced by intracellular tetanization, and thus can play a role in stabilizing synaptic weights and supporting synaptic competition.

This conclusion stays in apparent contradiction to the notion of input specificity of pairing-induced plasticity and to the wealth of publications reporting no changes in unpaired or control inputs. A solution to this contradiction may be the fact that heterosynaptic changes are bidirectional but balanced, as the results from Figure 7 show. To test this conjecture, we

reanalyzed results published in several STDP studies. For this analysis we have selected results of 35 experimental series from 8 studies of STDP, which stated the mean, the SD or SEM, and the number of observations contributing to the reported changes of response amplitude (Birtoli and Ulrich 2004; Feldman 2000; Hardingham and others 2007; Letzkus and others 2006; Nevian and Sakmann 2006; Sjöström and others 2001; Watt and others 2004; our data from Fig. 7). All these papers present clear cases of STDP of excitatory inputs to layer 2/3 or layer 5 pyramidal neurons in slices from somatosensory, visual, or auditory areas of rat neocortex. Figure 8 shows results of this analysis. Each bar shows the averaged after-pairing change of response amplitude (diamond symbol) and the range covered by ±2 SD. This range includes 95% of normally distributed values. Note that number of inputs contributing to each experimental series from published papers (Fig. 8, a-g) ranged between N = 4 and N = 20, and thus actually measured values have not necessary covered the whole ±2 SD range. Figure 8 illustrates several important points. First, ranges of response amplitude changes after most LTP and LTD protocols overlap, and typically include changes of the opposite signs (Fig. 8, magenta and green). LTP protocols, alongside with—by design—increase of the averaged amplitude, lead to highly variable effects, typically including amplitude decreases (in 8 out of 11 LTP protocols shown). This indicates that factors other than timing, such as synaptic predispositions for plasticity, contributed to the final change of response amplitude. Second, the ranges of response amplitudes in “No change or unpaired” groups (Fig. 8, blue), typically express substantial overlap with LTP and LTD ranges, and thus show evidence for heterosynaptic changes. However, most probably because heterosynaptic potentiation and depression were balanced, the average was not significantly different from zero. Third, the ranges of amplitude changes after AP bursts only protocols (Fig. 8, d, e, and our data in h) clearly include cases of potentiation and depression, though the average is not significantly different from zero, probably because of balanced LTP and LTD. Notably, Hardingham and others (2007) found that potentiation and depression can be induced by the same protocol, whereby the direction of the EPSP amplitude change was correlated with initial release probability. The LTP and LTD data from this article represent cases selected by the direction of the change. The third bar in this group (Fig. 8, g) shows LTP and LTD data pooled together. Finally, the range of amplitude changes of unpaired inputs is typically smaller than the range of amplitude changes induced by spike burst-only protocols (Fig. 8, d, e, and h). This may indicate that plastic synapses compete for limited resources. In this scenario, pairing may facilitate access to resources for paired inputs via mechanism of synaptic tagging (Fonseca and others 2004; Frey and Morris 1997) or a similar process, which would leave fewer resources available for heterosynaptic changes at unpaired inputs. Spikes-only protocols leave more resources available for heterosynaptic changes, and thus induce heterosynaptic plasticity of larger amplitude.

The above analysis demonstrates that although amplitude changes induced in unpaired inputs or by spike bursts-only protocols were not significant when averaged across the inputs, these groups might have included cases of potentiation and depression of individual inputs in most of the data shown in Figure 8. The reason for the absence of significant change of group-averages might be the balanced nature of heterosynaptic plasticity. It is also important to note that in articles specifically aimed at investigating heterosynaptic plasticity, it was readily induced by regular pairing (Arami and others 2013; Huang and others 2008;

Nishiyama and others 2000), afferent tetanization (Bauer and LeDoux 2004; Chevalyre and others 2003; Cummings and others 1996; Nugent and others 2007; Pascual and others 2005; Royer and Paré 2003; Staubli and Ji 1996; Wöhrl and others 2007), or purely postsynaptic protocols (e.g., Christofi and others 1993; Cummings and others 1996; Pockett and others 1990). This analysis substantiates our conclusion that induction of homosynaptic plasticity by a typical pairing procedure used in STDP studies is accompanied by induction of heterosynaptic plasticity in unpaired inputs.

Mechanisms of Heterosynaptic Plasticity

Rise of intracellular calcium concentration is an obvious candidate for triggering heterosynaptic plasticity. Indeed, the rise of $[Ca^{2+}]_{in}$ is sufficient to induce plasticity (Neveu and Zucker 1996; Yang and others 1999). Induction of long-term heterosynaptic plasticity by intracellular tetanization and other protocols was impaired or blocked by chelation of intracellular calcium with EGTA (Arami and others 2013; Bright and Brickley 2008; Han and Heinemann 2013; Lee and others 2012; Nugent and others 2007). Substantial rise of $[Ca^{2+}]_{in}$ is produced by bursts of back-propagating action potentials activating voltage-dependent calcium channels (Miyakawa and others 1992; Petrozzino and Connor 1994; Schiller and others 1995; Schiller and others 1998; Yuste and Denk 1995), and can be further amplified by calcium release from internal stores (Berridge 1998; Fagni and others 2000; Nakamura and others 1999). Because this $[Ca^{2+}]_{in}$ rise depends on backpropagating spikes, it can be induced cell-wide, including dendrites with no recently activated synapses. The profile of the $[Ca^{2+}]_{in}$ rise in nonactive dendrites will be determined by their ability to support backpropagation and by the number and frequency of action potentials (Golding and others 2002; Larkum and others 1999; Lisman and Spruston 2005; Spruston and others 1995). For example, bursts of action potentials can invade dendrites of layer 5 pyramidal neurons more reliably than single spikes (Kampa and others 2006; Sjöström and Häusser 2006). The resulting profile of $[Ca^{2+}]_{in}$ may promote induction of heterosynaptic LTP at sites of strong calcium rise, and LTD at sites of more moderate rise. However, the final outcome, LTP or LTD, might be also strongly influenced by predispositions of synapses for plasticity, because both potentiation and depression could be induced at synapses presumably located at similar distances and thus experiencing similar calcium rises (Lee and others 2012).

Strong local activation produces $[Ca^{2+}]_{in}$ rise that is not restricted to the activated synapses, and thus can trigger local heterosynaptic plasticity at nearby sites. Indeed, profile of $[Ca^{2+}]_{in}$ rise around the activation site can explain the Mexican-hat type profile of potentiation and depression induced along the activated dendrite (Royer and Paré 2003). Calcium release from internal stores may facilitate induction of this local heterosynaptic plasticity (Daw and others 2002; Dudman and others 2007; Nagase and others 2013; Nishiyama and others 2000; Royer and Paré 2003).

Plasticity induced by intracellular tetanization involves presynaptic components, implying retrograde signaling (Lee and others 2012; Volgushev and others 1997; Volgushev and others 2000). One candidate retrograde messenger is nitric oxide (NO). It is involved in mediating local heterosynaptic plasticity of both excitatory and inhibitory transmission (Lange and

others 2012; Nugent and others 2007; Schuman and Madison 1994). These effects could be due to diffusion of NO produced at activated synapses (Böhme and others 1991; Gally and others 1990; Hardingham and others 2013; Hölscher and others 1997; O'Dell and Alger, 1991). Disrupting NO signaling by NO-synthase inhibitors and NO-scavengers abolished the dependence of plasticity induced by intracellular tetanization on initial paired-pulse ratio (Lee and others 2012; Volgushev and others 2000). Weaker intracellular tetanization also induced plasticity that was not correlated with initial paired-pulse ratio, suggesting that NO signaling required strong postsynaptic activity (Volgushev and others 2000). Consistent with this suggestion are results demonstrating that the NO-dependent presynaptic component of homosynaptic plasticity was observed only after strong induction protocol, but not after a weaker protocol (Phillips and others 2008).

Disruption of NO signaling in intracellular tetanization experiments did not completely abolish presynaptic changes, implying involvement of additional retrograde signaling systems (Lee and others 2012; Volgushev and others 2000). Activation of metabotropic glutamate receptors (mGluRs) can trigger the production, release, and retrograde action of endocannabinoids, including heterosynaptic LTD at inhibitory synapses (Chevaleyre and Castillo 2003; Chevaleyre and others 2006; Chiu and others 2010; Maejima and others 2001; Pan and others 2008). The spread of retrograde signal to heterosynaptic sites was suggested to be due either to spillover of glutamate acting on local mGluR1/5-Rs (Chevaleyre and Castillo 2003; Yang and Calakos 2013), or the diffusion of endocannabinoids produced at active synapses (Yasuda and others 2008).

Heterosynaptic depression can be also mediated by activity-dependent release of ATP and adenosine from neurons (Lovatt and others 2012) and astrocytes (Chen and others 2013a; Pascual and others 2005; Serrano and others 2006; Zhang and others 2003). This depression was A1 receptor dependent: it was abolished by the A1 receptor antagonist DPCPX (Lovatt and others 2012; Pascual and others 2005) and was absent in mice with impaired adenosine tone and diminished A1 receptor activation (Pascual and others 2005).

Thus, multiple mechanisms mediate heterosynaptic plasticity. Most of these mechanisms overlap with those mediating homosynaptic plasticity, as indicated by at least partial occlusion between homo- and heterosynaptic plastic changes (Cummings and others 1996; Kuhnt and others 1994; Neveu and Zucker 1996; Volgushev and others 1999; Yang and others 1999). Heterosynaptic changes could be local, mediated by the spread of plasticity inducing factors, such as intracellular or extracellular messengers including retrograde signals, around the activated synapses. The spread involving glial cells may cover glial islets and thus reach several hundreds of dendrites (up to 600; Halassa and others 2007) arising from potentially large pool of distinct neurons, with thousands of synapses. In addition, heterosynaptic changes can be induced by cell-wide signals, such as $[Ca^{2+}]_{in}$ rises produced by backpropagating action potentials. Although heterosynaptic plasticity in its simplest sense does not demand associative activation of presynaptic sites, the physiological induction of heterosynaptic plasticity is almost certainly shaped by these signals.

Conclusion: A Multifaceted Picture of Plasticity

The emerging picture of long-term regulation of synaptic transmission includes an increasing number of forms and mechanisms of plasticity mediated by a variety of biochemical cascades. This multifaceted picture includes both mechanisms that mediate changes necessary for learning new behaviors, as well as those securing stability of the system by mediating compensatory changes to counteract positive feedback imposed by associative learning rules. The first task is best served by input-specific, associative Hebbian-type homosynaptic plasticity. It is mediated by mechanisms that require local synaptic activity and modify efficacy of activated synapses, such as canonical NMDA-receptor mediated plasticity. The second task, of achieving stability, requires balancing of synaptic weights within populations of synapses and depends on modifications at nonactivated synapses—heterosynaptic plasticity. Mechanisms mediating heterosynaptic plasticity overlap with those of homosynaptic plasticity, as indicated by the partial occlusion of effects of these two plasticity forms. Heterosynaptic plasticity can be local, mediated by the spread of a signal that induces changes at nearby active synapses. For example, short-range spread of NO may mediate distributed potentiation, which actually amplifies the effect of input-specific potentiation. The profile of $[Ca^{2+}]_{in}$ rise along a dendrite after a strong local stimulation may underlie the Mexican-hat profile of potentiation and depression, which balances the effect of the input-specific LTP or LTD. The spread of that kind of local heterosynaptic plasticity may be enhanced by intracellular mechanisms, such as activation of Ca^{2+} release from endoplasmic reticulum, or extracellular pathways, for example, involving glial cells. The latter pathway may cover glial islets and thus reach several hundreds of dendrites with thousands of synapses. Candidate trigger for inducing cell-wide heterosynaptic plasticity is $[Ca^{2+}]_{in}$ rise produced by back-propagating action potentials, eventually amplified by calcium-dependent calcium release from internal stores. At dendritic locations far away from the activity site, pre-dispositions of synapses for potentiation or depression may play a stronger role in determining plastic changes because local resources are not depleted by privileged-access activated synapses.

This interacting network of complementary plasticity mechanisms introduces several forces that drive synaptic weight changes in opposite directions (Fig. 9). Homosynaptic plasticity is induced by specific patterns of input activity such as high-frequency tetanization for LTP or prolonged low-frequency stimulation for LTD, or specific timing relative to postsynaptic spikes for STDP. Homosynaptic changes mediate associative learning, but they also drive synaptic weights to the extreme values, bringing the system out of balance. Heterosynaptic plasticity is not restricted to activated synapses, thus making any synapse a potential target for modification by episodes of strong postsynaptic activity. Because of the weight-dependence of the direction of heterosynaptic changes, LTP for weak synapses but LTD for strong synapses, it introduces two forces that drive synaptic weights away from the extremes, toward an equilibrium within the operation range. Relative effectiveness of these opposite forces can possibly change as a function of brain state (e.g., sleep vs. wakefulness), thus opening possibility for promoting either local stimulus specific changes or global homeostatic scaling. Because all four forces operate on the same time scale, they can effectively balance each other. The weight of a synapse is determined by the balance

between the homosynaptic and heterosynaptic plasticity forces. The combined action of these forces on synaptic weights allows neuronal networks to sustain the ability for associative synaptic changes while preserving secure balance around a stable operating point.

Outlook and Open Questions

The complementary nature of homosynaptic and heterosynaptic plasticity stresses the need for understanding the interaction between these forms of plasticity in governing synaptic changes. What determines the balance between homosynaptic and heterosynaptic plasticity at individual synapses and in neuronal networks? What are synapse-specific, cell type-specific, and structure-specific mechanisms of maintaining this balance? How is the balance between homosynaptic and heterosynaptic plasticity regulated, and what factors may disturb it? Revealing these factors may have important implications to understanding emergence of pathological states of the brain, such as posttraumatic stress disorder. Shifting the balance toward homosynaptic plasticity, for example, during traumatizing experiences, may lead to runaway potentiation and/or depression of selected populations of synapses, resulting in the restriction of future activity routing to the few deeply carved pathways.

How is the balance between homosynaptic and heterosynaptic plasticity regulated during development? During formation of sensory representations, runaway dynamics may be a useful process contributing to elimination of excessive connections while preserving the “correct” synapses. After the representations have been established, however, the balance might shift so that the stabilizing effect of heterosynaptic plasticity becomes capable to counteract runaway dynamics imposed by associative learning rules.

What determines the predispositions of synapses for potentiation and depression, and what are mechanisms of weight-dependence of both homosynaptic and heterosynaptic plasticity? Finally, how is long-term stability of connections mediating life-long memory traces achieved in the face of the multitude of plasticity mechanisms driving homosynaptic and heterosynaptic changes? How can some synapses escape the drive for modifications imposed by these forces? Answering these questions will advance our understanding of multifacet roles of synaptic plasticity: how it mediates learning of adaptive behaviors, but also may lead to pathological brain states.

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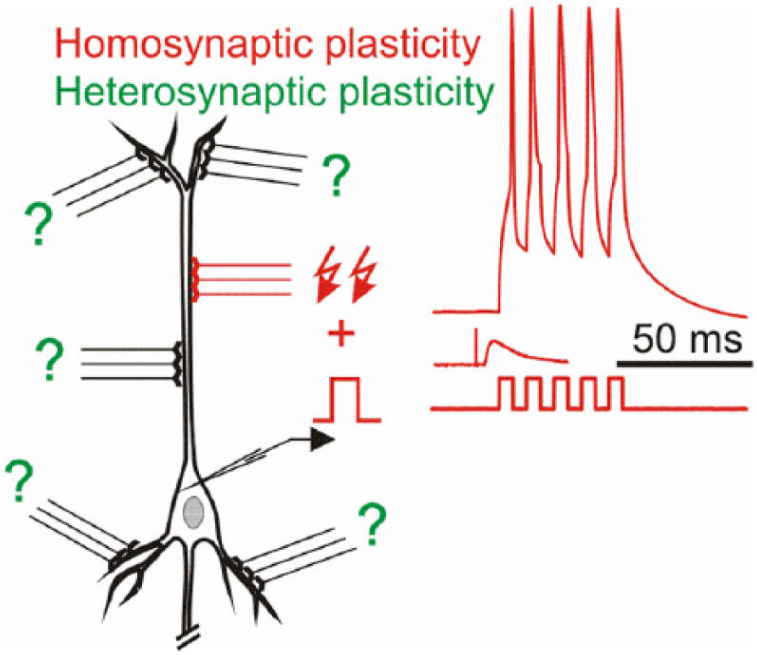

Figure 1.

Homosynaptic and heterosynaptic plasticity. In a typical plasticity experiment, a set of inputs to a neuron is stimulated to induce plasticity, for example, at high frequency to induce potentiation, or a low frequency to induce depression, or paired with bursts of postsynaptic spikes. *Homosynaptic plasticity* refers to changes of transmission at synapses that were activated during the induction (red inputs). *Heterosynaptic plasticity*—changes at synapses that were not active during the induction (black inputs, green question marks).

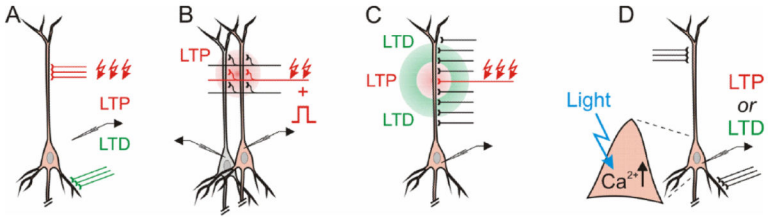

Figure 2. Experimental evidence for heterosynaptic plasticity

(**A**) Heterosynaptic LTD in the hippocampus (Lynch and others 1977, field potential recording). Induction of LTP at Schaffer collateral-commissural inputs to apical dendrites of CA1 pyramidal neurons was accompanied by an LTD at commissural inputs to basal dendrites that were not stimulated during the induction. And vice versa, induction of LTP at inputs to basal dendrites was accompanied by LTD of inputs to the apical dendrites. (**B**) Distributed plasticity and breakage of input specificity at short distances (Bonhoeffer and others 1989; Engert and Bonhoeffer 1997; Kossel and others 1990; Schuman and Madison 1994). After pairing of one input to a CA1 neuron, synapses formed by nearby fibers on that cell and even on nearby neurons were potentiated too (pink circle). (**C**) Mexican hat profile of plasticity (Royer and Paré 2003; White and others 1990). In structures with regular organization of the inputs, such as the hippocampus or amygdala, induction of LTP was accompanied by a weaker LTP at nearby inputs (pink circle) and heterosynaptic LTD at more distant inputs (green annulus), with the amplitude of LTD decreasing with distance. Symmetrical profile was observed around the site of LTD induction. This resulted in a Mexican hat profile of plasticity, with balanced potentiation and depression (Royer and Paré 2003). (**D**) Long-term plastic changes can be induced by rises of intracellular calcium concentration produced by photolysis of caged calcium (Neveu and Zucker 1996; Yang and others 1999). LTP could be induced by large increases of intracellular calcium, and LTD by smaller amplitude prolonged increases.

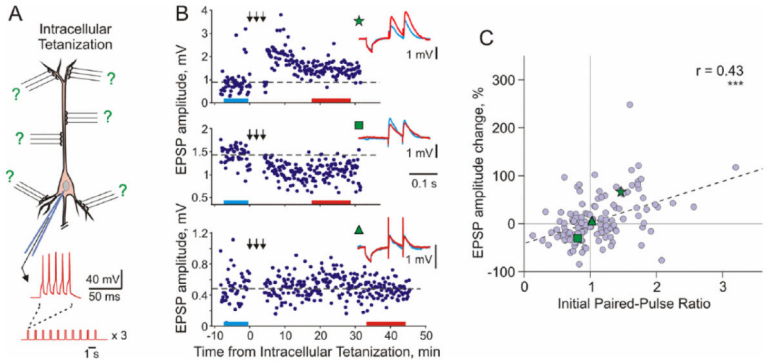

Figure 3.

Long-term synaptic plasticity induced by intracellular tetanization. (**A**) A scheme of intracellular tetanization experiment. Bursts of short depolarizing pulses (5 pulses at 100 Hz; 10 bursts at 1 Hz, 3 trains of 10 bursts) were applied through the recording electrode without presynaptic stimulation to induce bursts of action potentials. Synaptic responses were recorded before and after the intracellular tetanization. Because no inputs were stimulated during the induction, plasticity at all synapses can be considered heterosynaptic. (**B**) Examples of inputs that underwent potentiation (top), depression (middle), or did not change after intracellular tetanization. Time courses of amplitudes of EPSPs evoked by the first pulse in a paired-pulse paradigm. The timing of intracellular tetanization is indicated by the arrows above each plot. Insets show averaged responses to paired pulse stimuli before and after intracellular tetanization, from color-coded time intervals. In this example, LTP and LTD were induced simultaneously at two inputs to the same neuron. Note that input resistance of neurons measured by responses to small hyperpolarizing pulses applied before synaptic stimuli remained unchanged. (**C**) Correlation between changes of EPSP amplitude after intracellular tetanization and initial paired-pulse ratio. Data for N = 136 inputs to pyramidal neurons in slices of visual cortex (N = 60 inputs) and auditory cortex (N = 76 inputs). Green symbols (star, square, and triangle) refer to the example inputs from **B** (Modified, with permission, from Chen and others 2013b).

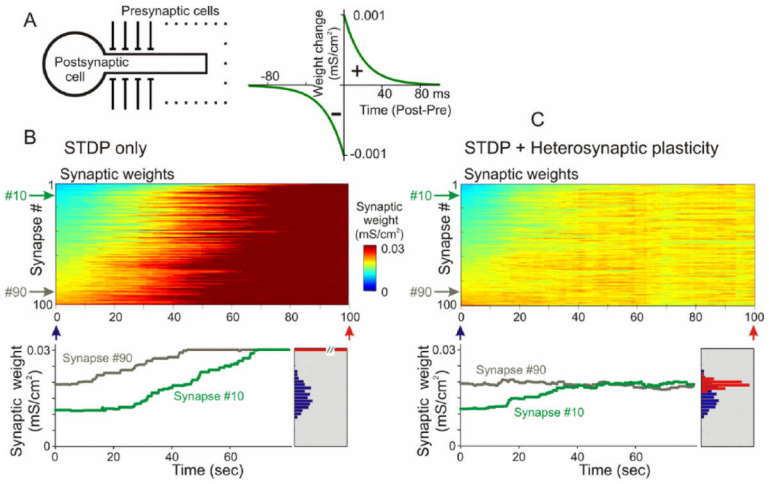

Figure 4.

Heterosynaptic plasticity prevents runaway dynamics of synaptic weights. (**A**) A scheme of a model neuron and STDP learning rule. The model neuron consisted of axosomatic and dendritic compartments, receiving 100 synaptic inputs from 100 presynaptic neurons. Each presynaptic neuron fired action potentials at ~1 Hz, with Poisson distributed interspike intervals. In simulations shown in this figure, firing of input neurons was mildly correlated (averaged cross-correlation 0.35 ± 0.05), and STDP learning rule had symmetrical potentiation and depression windows. (**B**) In a model with symmetrical STDP learning rule ($\tau^+ = \tau^- = 20$ ms; $a^+ = a^- = 0.001$ mS/cm^2) synaptic inputs express runaway dynamics, and saturate at maximal value. Color plot shows dynamics of changes of synaptic weights (color coded). Synapses were sorted by their weights at the beginning of experiment. Bottom: Time course of weight changes of synapses #10 and #90. Inset on the right shows distributions of synaptic weights at the beginning (red) and at the end of the simulation. At the end of the simulation, all inputs were potentiated to the maximum (red bar length is out of scale). (**C**) In a model with STDP and heterosynaptic plasticity implemented according to experimental data, same pattern of input activity did not lead to saturation of synaptic weights. Instead, synaptic weights reached a new balance and formed a normal distribution around a new mean. Conventions as in B (Modified, with permission, from Chen and others 2013b).

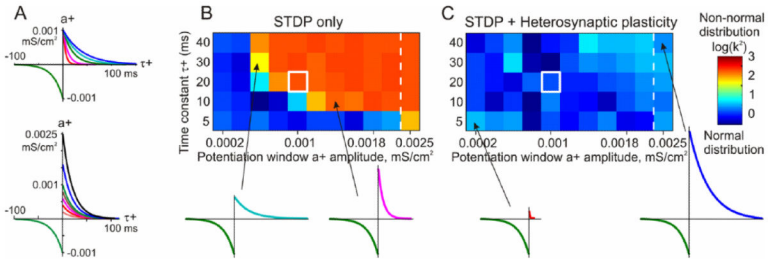

Figure 5.

Heterosynaptic plasticity makes a broad range of STDP parameters compatible with stable operation of neurons. (**A**) Examples of STDP rules with a constant depression window ($a^- = 0.001$ mS/cm^2, $\tau^- = 20$ ms), but changing the potentiation window time constant (top, $\tau^+ = 5$, 10, 20, 30, 40 ms) and amplitude (bottom, $a^+ = 0.2–2.5 \times 10^{-3}$ mS/cm^2). (**B**, **C**) Each box in the grids shows the D'Agostino-Pearson's K^2 test for normality of synaptic weight distribution after 100 seconds of simulations with different STDP potentiation windows, with a^+ and τ^+ as indicated on the *X* and *Y* axes. White square indicates symmetrical STDP learning rule. Synaptic weight distributions with high K^2 test values (>50) indicating deviation from normality, typically contain most of the weights saturated at maximal or minimal values. Note that in simulations with STDP only model (**B**), only few STDP rules, with strong bias toward depression, did not lead to runaway dynamics. Most STDP rules, including examples shown in the bottom, led to runaway dynamics of synaptic weights. In contrast, model with STDP and heterosynaptic plasticity (**C**) did not express runaway dynamics over the whole range of tested STDP rules, including those extremely unbalanced (insets, bottom) (Modified, with permission, from Chen and others 2013b).

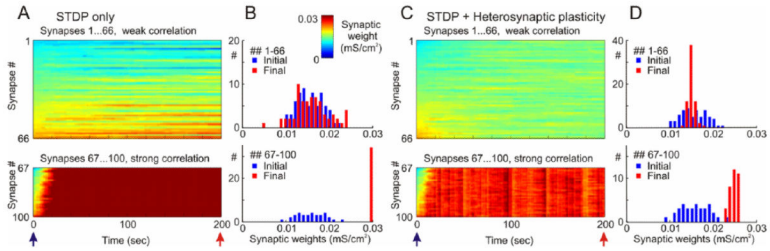

Figure 6.

Synaptic competition and segregation of synaptic weights of strongly versus weakly correlated inputs in the model with heterosynaptic plasticity. A model neuron received input from N = 100 presynaptic neurons firing at average frequency of 1 Hz. Spike trains of 66 presynaptic neurons (inputs ## 1 to 66) were weakly correlated (averaged cross-correlation 0.34 ± 0.02), spike trains of 34 presynaptic neurons (inputs ## 67 to 100) were strongly correlated (averaged cross-correlation 0.61 ± 0.05). Symmetrical STDP rule was used in the simulations, with $\tau^+ = \tau^- = 20$ ms; $a^+ = a^- = 0.001$ mS/cm^2. (**A**, **C**) Dynamics of synaptic weights of weakly correlated inputs (synapses ## 1 … 66) and strongly correlated inputs (synapses ## 67 … 100) in the model with STDP only (**A**) and the model with STDP and heterosynaptic plasticity (**C**). (**B**. **D**) Distributions of synaptic weights at the beginning (blue bars) and at the end (red) of simulations from A and C, respectively. Note runaway dynamics of synaptic weights and their saturation at the highest value (0.03 mS/cm^2) for the group of strongly correlated inputs in STDP-only simulation (Modified, with permission, from Chen and others 2013b).

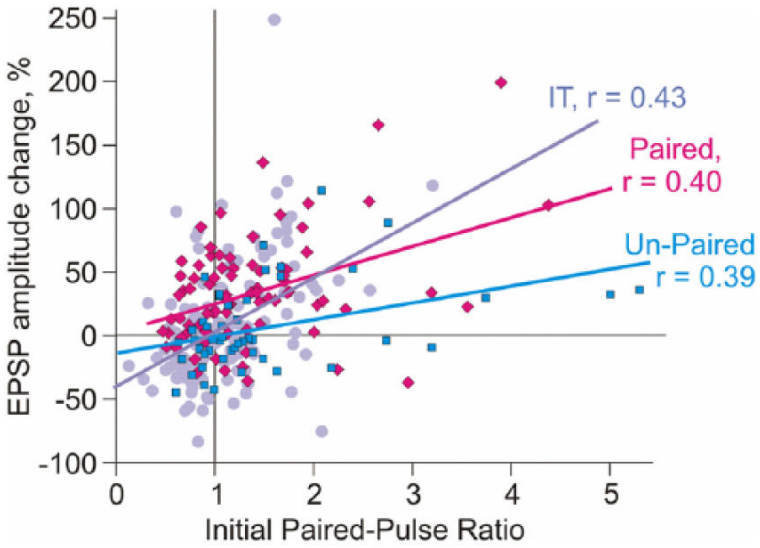

Figure 7.

Homosynaptic and heterosynaptic plasticity induced by pairing and by intracellular tetanization. Correlation between long-term changes of EPSP amplitude and initial paired-pulse ratio for three groups of inputs. First, paired inputs (N = 81, magenta, diamond symbols): plasticity was induced by 50 pairings (1/s) of EPSPs with bursts of 5 action potentials produced by injection of short depolarizing current steps (5 ms duration at 100 Hz). During pairing, first spike in the burst was generated ~10 ms after the onset of the EPSP. Second, unpaired inputs (N = 50, cyan, square symbols): simultaneously recorded inputs to the same cells, but no synaptic responses were evoked during the pairing procedure. Thus, the unpaired inputs experienced the same postsynaptic firing as the paired inputs, but were not active during the pairing procedure, so plastic changes in these inputs were heterosynaptic. For comparison, the third group of inputs shows results of intracellular tetanization experiments (data from Fig. 3C, N = 136, pale blue circle symbols).

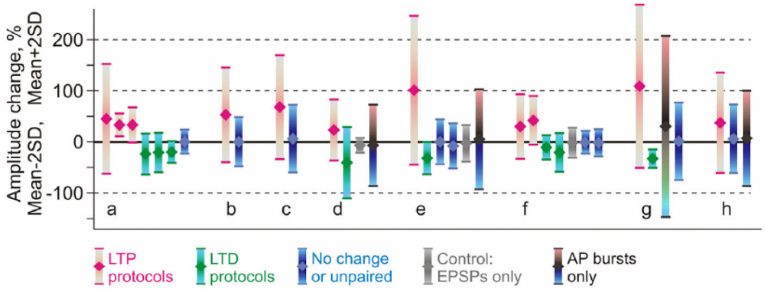

Figure 8.

Comparison of reported changes of response amplitude at inputs that were active during the induction (homosynaptic, input-specific) and those not active during the induction (heterosynaptic). The plot shows results of 35 experimental series (bars) from 8 articles (groups of bars) on pairing-induced long-term plasticity (STDP), in which the mean amplitude changes were reported together with the SD (or SEM) and number of observations. Each bar shows an average (diamond symbol) change of EPSP amplitude after pairing procedure ±2 SD. This range includes 95% of normally distributed values. *Magenta*: changes after potentiation-inducing protocols (post after pre). *Green*: changes after depression inducing protocols (pre after post). *Blue*: range of EPSP amplitudes after protocols that did not lead to significant changes of the averaged response (such as interval between pre and post spikes outside plasticity windows). *Gray*: range of EPSP amplitudes after presynaptic only stimulation without postsynaptic spikes. Black, bars from cyan to pink (in d, e, h): range of EPSP amplitudes after bursts of postsynaptic spikes only, without presynaptic stimulation. Data for excitatory inputs to L2/3 or L5 pyramidal neurons from somatosensory, visual, or auditory cortex, from the following articles: Feldman 2000 (a); Sjöström and others 2001 (b); Watt and others 2004 (c); Birtoli and Ulrich 2004 (d); Nevian and Sakmann 2006 (e); Letzkus and others 2006 (f); Hardingham and others 2007 (g); Our data from Figure 7 (h).

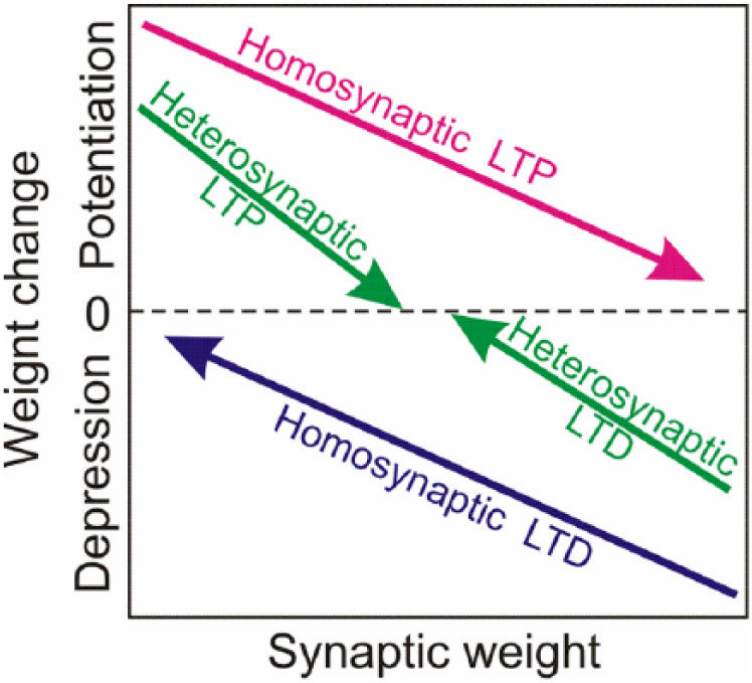

Figure 9.

Driving forces for homosynaptic and heterosynaptic weight changes. Homosynaptic plasticity, LTP or LTD, is induced only at synapses active during the induction, and requires specific activity patterns. Homosynaptic LTP leads to weight-dependent increase of synaptic weights: potentiation is stronger at initially weak than at initially strong synapses. Homosynaptic LTD leads to weight-dependent decrease of synaptic weights: depression of strong synapses is stronger than depression of the weak synapses. Heterosynaptic plasticity can be induced at any synapse during episodes of strong postsynaptic activity. Initially weak synapses are subject to weight-dependent heterosynaptic LTP. Initially strong synapses are subject to weight-dependent heterosynaptic LTD.