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Two opposing plasticity mechanisms pulling a single synapse

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Homeostatic synaptic plasticity (HSP) has been suggested to act as a negative feedback mechanism responsible for globally and uniformly scaling (up or down) the strength of all synapses in the neuron, in compensation for chronically aberrant (too low or too high) levels of activity. Such global scaling preserves the relative strengths of synapses and thus keeps 'Hebbian-like' memory traces (long-term potentiations, LTP, or depressions, LTD). However, new experimental findings demonstrate that HSP can operate locally, controlling each synapse individually. Seemingly, this finding implies that HSP can abolish any modification of synaptic strength (erase LTP/LTD). We propose that dendrites offer an inherent solution to this 'paradox' and that in fact local HSP might confer upon the neuron several surprising benefits, which are demonstrated using computer simulations.

Introduction

The function and dynamics of neuronal networks are strongly dependent on the strengths of the synapses connecting neurons in the network. These connections are subject to continuous change and modification by various mechanisms of synaptic plasticity, affording remarkable adaptability and versatility to the neuronal network. Currently known plasticity mechanisms are highly diverse in their dynamics in terms of timescale, direction of change and spatial resolution. Thus, Hebbian long-term potentiation or depression (LTP/LTD) [1] operates at a short timescale of several seconds to several minutes (the time it takes for LTP/LTD to be elicited), in a positive feedback manner (already strong excitatory synapses, which tend to activate the postsynaptic neuron, tend to be further strengthened and vice versa) and at the spatial resolution of almost a single synapse (each synapse is modified individually; but see Ref. [2]). By contrast, homeostatic synaptic plasticity (HSP) [3–5] is a negative feedback mechanism (persistent overactivation of the neuron results in compensatory weakening of synapses and vice versa) operating at a substantially slower timescale on the order of hours to days. As for the spatial resolution of HSP, it is widely regarded as a global mechanism [3,4] that proportionally scales all synapses of a given neuron up or down (Figure 1a, top) and can thus maintain the relative strengths of all synaptic inputs into the neuron, conserving the neuron's optimal operating regime while presumably still preserving memory traces (the relative synaptic strengths) [3,6]. Therefore, under HSP, all synapses in a neuron are predicted to change in unison according to a cell-wide global signal.

New experimental results [7–11] demonstrate, however, that, in certain systems, HSP, like LTP/LTD, is endowed with synapse-specific resolution, individually controlling each synapse's strength according to the local level of activity at the site of the synapse (Figure 1a, bottom). Seemingly, this finding implies that HSP will detrimentally erase any modification of synaptic strength such as produced by LTP or LTD, and thus abolish any change that the neuron's synapses might undergo. We offer a solution to this 'paradox' and propose that a synapse-specific HSP mechanism has many advantages over global HSP in regulating neuronal activity, such as supporting dendritic compartmentalization and selecting which spatial patterns of synaptic potentiation and depression will endure and which will be eliminated.

New experimental evidence supporting local HSP

The prevailing experimental paradigm for eliciting HSP has been the exposure of the entire neuron to a chronic uniform global increase or decrease in activity (e.g. by blocking overall excitatory or inhibitory synaptic input with neurotransmitter receptor antagonists; Figure 1b). The typical result obtained in such experiments has been a uniform scaling (up or down) of all synaptic strengths, leading to the conclusion that HSP is a global scaling mechanism [3]. However, under such experimental conditions, similar results could be expected also if the mechanism underlying HSP were synapse specific, making it very hard to distinguish between the two options [12]. In addition, Stellwagen and Malenka [13] recently found that homeostatic synaptic upscaling is mediated by the cytokine tumor necrosis factor α (TNF-α) secreted by glial cells following global silencing of activity. The surprising role of the ubiquitous glia in eliciting HSP could be interpreted as a clear manifestation of global scaling. However, because glia are known to strongly associate and interact with individual synapses [14], a glia-induced mechanism for HSP could still act locally at the level of the single synapse.

However, even under a global blockade paradigm of all excitatory AMPA receptors throughout the neuron, Thiagarajan *et al.* [11] managed to demonstrate nonuniform

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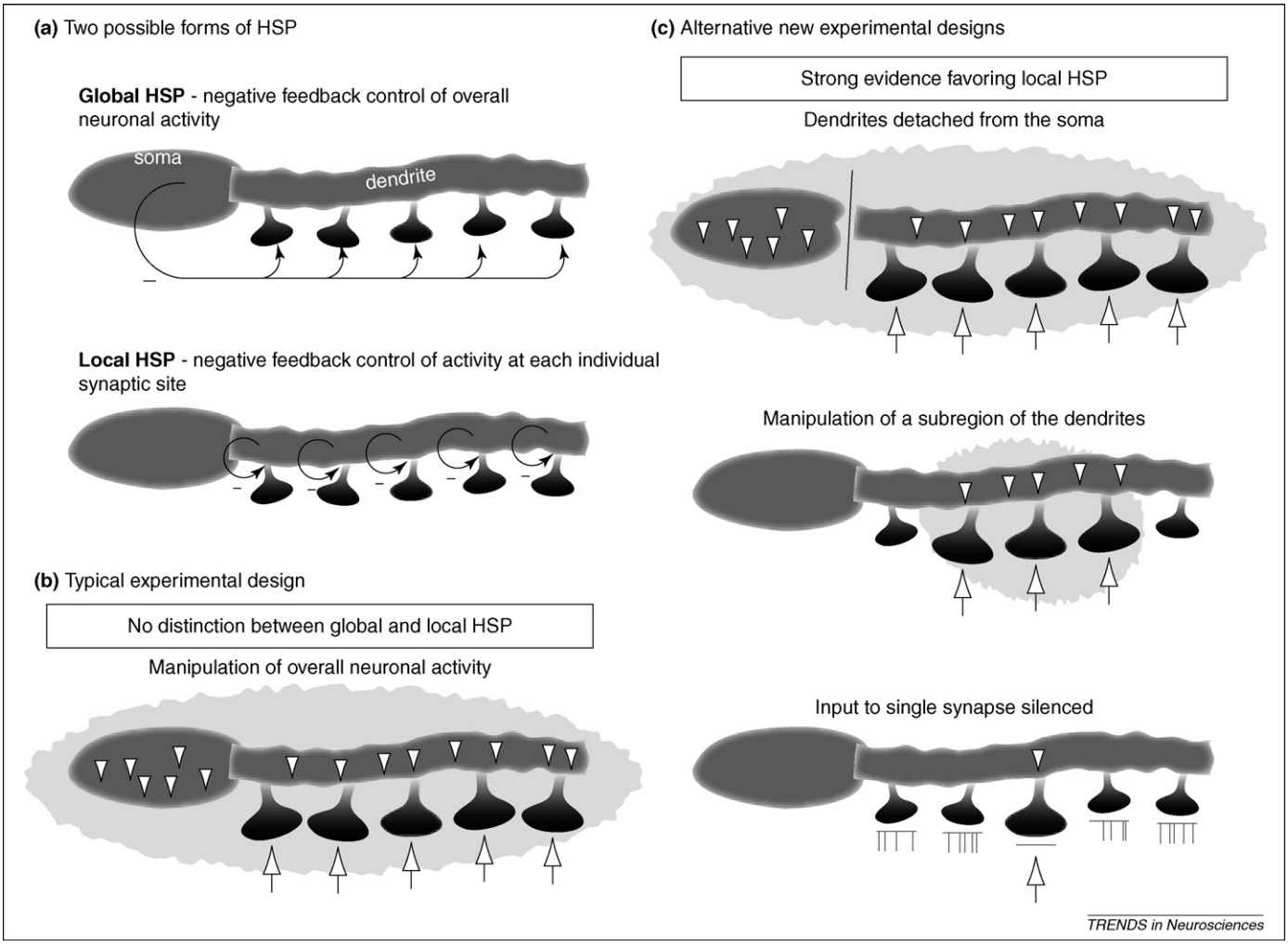

Figure 1. New experiments reveal that HSP operates locally at individual synapses. **(a)** The HSP negative feedback mechanism could either be global (top), controlling the overall level of activity of the entire neuron by modifying all synapses in unison, or local (bottom), controlling activity at each individual synaptic site. **(b)** Most experiments performed on HSP are designed to alter the overall activity of the neuron (e.g. pharmacologically decreasing activity, illustrated by downward-pointing arrowheads), and therefore cannot determine whether the HSP mechanism is local or global (because under these conditions, both types of mechanisms modify the strengths of all synapses, e.g. increasing all synaptic strengths, illustrated by upward-pointing arrows). **(c)** Several recent experiments with alternative designs strongly support the local hypothesis. Top: HSP occurs even when the dendrites are detached from the soma [8]. Middle: when activity in just a subregion of the dendrites is altered, only synapses in that subregion seem to undergo HSP [10]. Bottom: when input to a single synapse out of many others is silenced, that specific synapse alone increases its strength in compensation for the locally reduced activity [7].

modification of synaptic strength. They showed that the coefficient of variation of the amplitude of miniature excitatory postsynaptic currents (mEPSC) could change substantially following HSP, indicating that what HSP modifies is not just the magnitude of mEPSCs but also their distribution. This finding sharply contradicts a global HSP scenario whereby the ratio between synaptic weights is assumed to remain fixed. Moulder *et al.* [9] also reported a nonuniform HSP change. In their study, neurons were subjected to a prolonged mild depolarization (by moderately increasing the extracellular K^+ concentration). This resulted in a bimodal presynaptic HSP response: a subgroup of synapses became completely inactive and the remaining synapses maintained on average their original strengths, thus questioning the notion that HSP scales all synapses uniformly.

Moreover, new evidence has emerged in direct support of an alternative local synapse-specific HSP mechanism. Ju *et al.* [8] used a combination of ReAsH-EDT(2) and FlAsH-EDT(2) staining to monitor AMPA receptor subunit synthesis and trafficking in dendrites. Their study demonstrated that HSP could enhance dendritic synthesis of the AMPA receptor subunit GluR1 (but not GluR2) even in neurons in which the soma was physically detached from the dendrites (Figure 1c, top), suggesting that similar to LTP (which was also tested in that study) both the sensing of altered levels of activity and the response to it could well be taking place locally in the dendrites. Sutton *et al.* [10] continuously blocked mEPSCs in only a restricted subregion of the dendrites by local perfusion of an NMDA receptor antagonist (Figure 1c, middle) while globally inhibiting action potentials in the background with TTX, a sodium channel blocker. This resulted in a compensatory enhanced synthesis and surface expression of GluR1 (and consistent with Ref. [8], not GluR2) AMPA receptor subunits exclusively in the affected subregion. These changes, which were attributed specifically to the experimentally abolished miniature postsynaptic potentials, were produced by local dendritic protein synthesis within a relatively short timescale of less than an hour. Most recently,

the Turrigiano group performed a similar local perfusion experiment whereby TTX was continuously applied selectively to a small dendritic subregion and the surface expression of GluR2 was measured [15]. Unlike global or soma-specific application of TTX, which resulted in a homeostatic increase in GluR2 expression, the local treatment did not show any effect. The reason for the discrepancy between these results and the results obtained by Sutton *et al.* could lie in the use of different preparations (see below) and the measurement of GluR2 expression as opposed to GluR1. Although a previous work showed that GluR2 changed in proportion to GluR1 following chronic TTX application [16], it should be interesting to repeat the experiment measuring GluR1 expression to make it more comparable with the previous results.

Very recently, evidence favoring a local HSP mechanism gained an important confirmation in an elegant study by Hou *et al.* [7], who suppressed a small fraction of a neuron's presynaptic partners by transfecting these presynaptic neurons with the Kir2.1 inward rectifying potassium channel. This caused a selective silencing of single synapses out of all of the synapses converging onto the postsynaptic neuron (Figure 1c, bottom). The results showed a very clear local HSP response observed within 2 days of transfection. Out of all synapses impinging onto the postsynaptic neuron, only the specific silenced synapses underwent HSP modification, expressed by a selective increase in the abundance of postsynaptic GluR1 as well as GluR2/3 receptors in the silenced synapse in compensation for the loss of input.

Noticeably, whereas HSP has been found to operate in numerous neuron types and brain regions, all of the above-cited experiments that reveal HSP's local nature have been conducted exclusively on cultured hippocampal pyramidal neurons. Indeed, the sole indication that HSP might not be local was found in dissociated visual cortex cultured neurons [15]. It remains to be seen whether HSP is a local or global mechanism in other cell types and brain regions.

The paradox of oblivion and its solution

The possibility of HSP being a local mechanism has been repeatedly rejected on the basis that it would lead to a seeming paradox [3,15,17]: on the one hand, it is widely assumed that the whole point of (e.g. Hebbian) synaptic plasticity is to introduce long-lived changes in neurons and in the way that they (and the network they are part of) function (Figure 2a). On the other hand, HSP acting locally on specific synapses will presumably counteract and eventually erase any such changes in the strength of these particular synapses, ultimately driving all synapses back to their homeostatic setpoint (Figure 2b), as phrased by

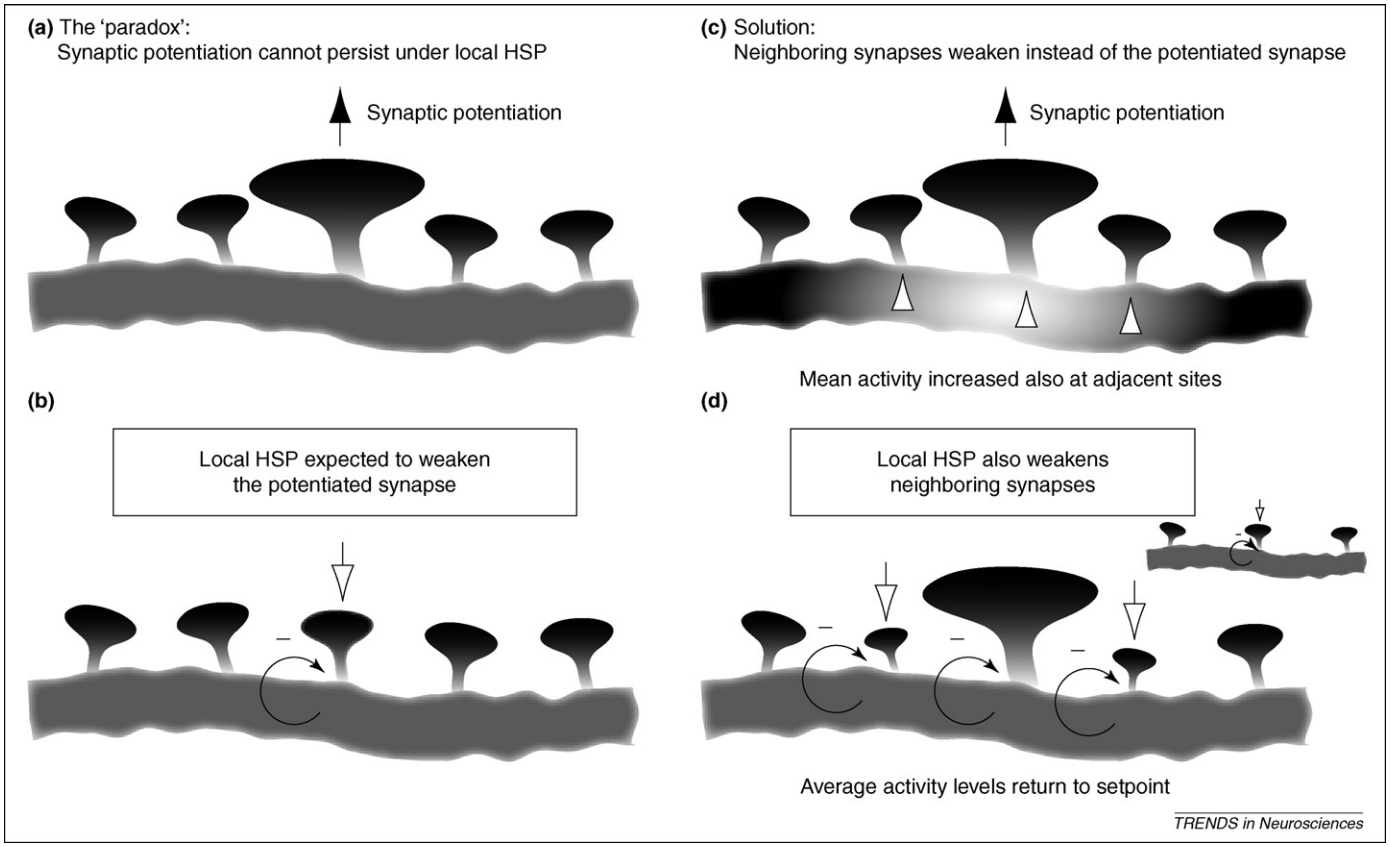

Figure 2. A solution to the seeming 'paradox' of local HSP erasing Hebbian-like synaptic plasticity. **(a,b)** The paradox: when a certain synapse is potentiated as in LTP ([a], upward-pointing black arrow), local HSP is expected to weaken that synapse so that the original potentiation is wiped out ([b], downward-pointing white arrow). **(c,d)** A solution to this paradox takes into account the spatial interactions occurring along the dendritic branch. When a synapse is potentiated, this causes an increase in the average level of activity not only at the site of the potentiated synapse but also at adjacent synaptic sites ([c], upward-pointing white arrowheads). As a result, local HSP is predicted to start weakening not just the potentiated synapse but also its close neighbors ([d], downward-pointing white arrows) so that the elevated levels of activity are balanced out, and thus a long-lasting change at the potentiated synapse can persist in spite of local HSP. Inset: in order for LTP to last under local HSP, there must be a substantial number of synapses adjacent to the potentiated synapse that can weaken in compensation for the enhanced activity. If not enough adjacent synapses are available (e.g. as in a typical neuron culture preparation such as in Ref. [7]), then the synaptic potentiations/depressions will not endure under HSP.

Hou *et al.* [7]: "Given the existence of homeostasis suggested by the present work, how the two types of plasticity [Hebbian and HSP] cross-talk remains an intriguing and important question. A possible prediction is that any 'long-term' synaptic plasticity might actually be short-lived because of a reversal by homeostatic mechanisms."

A possible solution to this paradox could lie in the highly distinct induction mechanisms underlying LTP/LTD and HSP, the former based on brief calcium transients entering through NMDA receptors, and the latter relying on temporal and spatial integration of calcium influx through L-type calcium channels [18]. However, although the induction of LTP/LTD and HSP is quite disparate, there seems to be substantial overlap in their expression. Both LTP/LTD and HSP involve postsynaptic modifications in the expression of at least the AMPA receptor subunit GluR1, and presynaptic modifications in vesicle turnover rate [18]. Furthermore, because LTP/LTD and HSP have never been studied together in a single experiment, it is hard to tell how these two separately explored mechanisms actually interact (e.g. can HSP completely abolish LTP/LTD-induced changes? Can one mechanism override the other?). Until these issues are resolved, we are limited to considering only the net influence of LTP/LTD and HSP on the efficacy of the synapse, and in this respect the paradox of local HSP erasing LTP/LTD seems to hold.

We argue, however, that there is a simple solution to the paradox and, in effect, neurons can sustain changes in the strength of their synapses (a mechanism that is assumed to support memory and learning processes) even in the face of local HSP. The key to the solution requires one to realize that neighboring synapses on a dendritic branch are not isolated one from the other. Instead, there is a significant degree of cooperation between adjacent synapses, mediated by spatial electrical interactions and corresponding calcium fluctuations (e.g. via L-type voltage-sensitive calcium channels [11]). When a certain excitatory synapse is potentiated, for example, this causes an increase in activity (larger depolarization) not only at the site of the potentiated synapse but also at neighboring synapses (Figure 2c). Consequently, in response to the strengthening of a particular synapse, a local HSP mechanism will weaken not only the potentiated synapse but also its neighbors (Figure 2d). Such weakening in strength of a group of adjacent synapses in a dendritic branch will entail a local decrease in activity, opposing the initial increase brought about by the potentiation of the synapse. Thus, a new (homeostatic) balance can be obtained in which the initially potentiated synapse can maintain a significant fraction of its potentiation with the support of its neighboring nonpotentiated synapses that become weaker, forming a 'Mexican hat'-like stable configuration of synaptic strength that is resistant to the canceling efforts of local HSP (Figure 2d).

To appreciate this effect, we designed a computer simulation of a realistic CA1 pyramidal neuron (Figure 3a) with multiple synapses, each generating occasional local postsynaptic potentials and undergoing slow modifications according to a local HSP rule (see Box 1) [19]. A representative synapse was 'potentiated' by increasing its peak conductance by 50% (Figure 3b, left) and the simulation was run until it reached steady state. At steady state the potentiated synapse (Figure 3b, right, black arrow) indeed maintained most of its initial potentiation (its peak conductance remained ~40% greater than before potentiation) at the expense of its neighboring synapses that lost some of their strength in a distance-dependent manner (Figure 3b, right, white arrow). Thus, with the help of its adjoining synapses, the strength of a potentiated synapse can endure in spite of the opposing effect of local HSP operating on that same synapse.

One should note that the same principle also applies for synaptic depression. Therefore, if a synapse undergoes LTD, implying a local decrease in activity which will also affect neighboring synapses, then the ensuing effect of local HSP would be to increase the strength of the neighboring (nondepressed) synapses and to thus restore activity at that dendritic branch to its setpoint, hence permitting the depressed synapse to retain a large portion of its initial depression.

The theoretically predicted emergence of a local HSP-resistant synaptic configuration comprising a potentiated synapse surrounded by weakened nonpotentiated neighbors requires experimental confirmation. However, this poses quite a technical challenge. First, the cell-culture preparation used for example in the Hou *et al.* study [7] is not ideal for such an experiment because the density of excitatory synapses in the dendrites of cultured neurons is an order of magnitude lower than in *in situ* grown neurons (~0.1–0.3 synapses per μm of dendritic branch length in culture [20] compared to ~1–7 synapses per μm in most accessible areas of CA1 pyramidal neurons from brain slice [21]). To support synaptic potentiation under local HSP, a relatively large number of neighboring nonpotentiated synapses per electrotonic space constant are required [19], otherwise the potentiated (or depressed) synapse will indeed lose its potentiation (depression) owing to local HSP (Figure 2d, inset). One possible way to circumvent this experimental problem could be to coculture the neurons with astroglia, the presence of which has been shown to increase synapse density in culture [22,23], or alternatively to use organotypic brain slices instead of dissociated cultures. Second, the weakening of neighboring synapses is not expected to be dramatic (e.g. Figure 3b, right, white arrow), and might thus be too small to be clearly detected, at least with an immunocytochemical approach, as was done, for example, in Ref. [7]. Therefore, perhaps other more quantitative methods should be applied, such as recording electrical and calcium responses in individual dendritic branches following local glutamate uncaging [24].

New roles for synapse-specific HSP

What are the potential benefits that a synapse-specific HSP mechanism could offer? The importance of a locally operating HSP mechanism was previously proposed in the context of Hebbian plasticity and local dendritic spikes. It was argued that without local regulation such as could be provided by local HSP, various dendritic subregions would become overdominant owing to the repeating firing of local dendritic spikes at these regions (giving rise to many very strong synapses via a spike timing-dependent plasticity

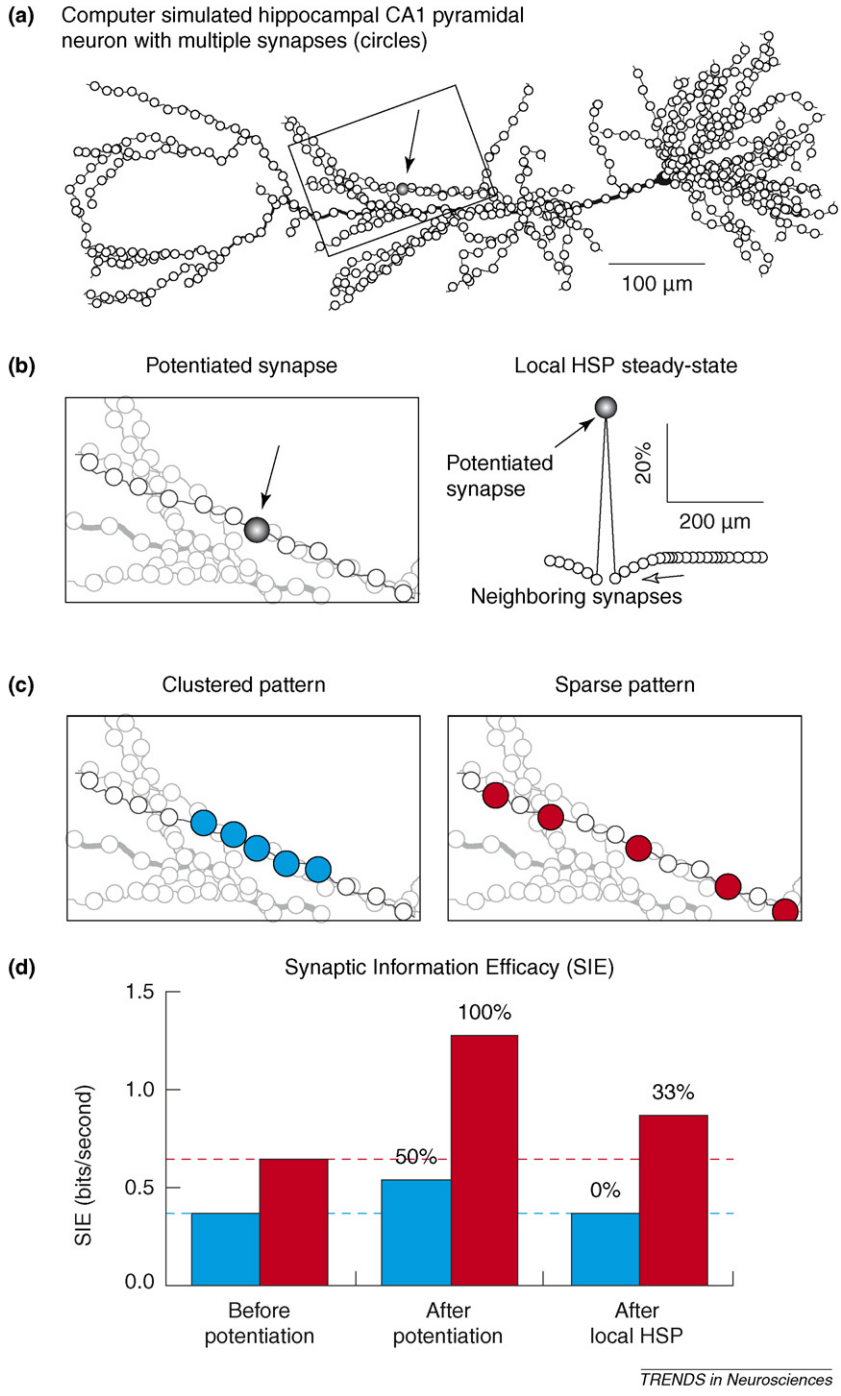

Figure 3. Hebbian LTP endurance and selectivity by local HSP in a computer-simulated neuron. **(a)** Reconstructed hippocampal CA1 pyramidal neuron (courtesy of N. Spruston) with hundreds of synaptic inputs randomly activated, and undergoing local HSP (for details, see Box 1 and Ref. [19]). Arrow points at the representative synapse potentiated in **(b)**. (b) Left: closer view of a representative synapse that was potentiated by increasing its peak synaptic conductance by 50%. The dendritic branch where the potentiated synapse is situated is emphasized. Right: peak synaptic conductance at local HSP steady state relative to peak synaptic conductance before the potentiation. The potentiated synapse (black arrow) maintained at steady state ~40% potentiation, in spite of local HSP, thanks to the weakening of its neighboring synapses (white arrow). **(c)** Five synapses were potentiated together in either a clustered spatial pattern (left, blue) or a sparse pattern (right, red). **(d)** Synaptic information efficacy (SIE) of the representative synapse in (b) within either a clustered (blue) or sparse (red) pattern of potentiation. Prior to potentiation, the sparse pattern shows higher synaptic efficacy. After an equal 50% potentiation of the peak synaptic conductance, the SIE in the clustered pattern increased by 50%, whereas in the sparse pattern it increased by 100%. Following local HSP, the efficacy in the clustered pattern returned to its pre-potentiation level (i.e. the potentiation was completely abolished), whereas the efficacy in the sparse pattern was 33% greater than before potentiation (i.e. the potentiation was sustained). Adapted from Ref. [19].

mechanism) at the expense of other degenerate subregions of dendrites (with very weak synapses) [25].

We have used computer simulations (see Box 1) to investigate in detail additional roles that local HSP might have in neuronal function [12,19,26]. To begin with, a defining property of many neurons and in particular hippocampal pyramidal neurons is the elaborate morphology of their dendrites [27], which naturally divides the dendritic tree into electrical [28–33] and biochemical [34] compartments. Various functional roles have been proposed for

Box 1. A model for local homeostatic synaptic plasticity

We designed a computer simulation for studying how local HSP can operate in the dendrites and how it affects synapses undergoing LTP/LTD [19]. The simulation consisted of a reconstructed hippocampal CA1 pyramidal neuron (see Figure 3a) with numerous model excitatory synapses delivering transient conductance changes to the dendrites at random intervals. Local HSP was implemented as a continuous and very slow change to the peak synaptic conductance $G_{syn,i}$ of each model synapse i, in proportion to the difference between the membrane potential, V_i, at the dendritic site of that synapse and an overall target membrane potential, V_{trg}, representing the desirable (homeostatic) average level of activity for the neuron. It is unknown whether HSP is directly controlling postsynaptic membrane potential, calcium concentration or some other component of the neuron's activity. We focused on membrane potential because its spread in dendrites has a well-established theoretical framework [26] and because it correlates quite well with fluctuations in calcium concentration. We assume for simplicity that V_{trg} is uniform throughout the dendrites. Thus, each synapse underwent a unique succession of small modifications throughout the simulation as formulated in Equation 1:

$$\tau_H \cdot \frac{dG_{syn,i}}{dt} = \frac{V_{trg} - V_i}{\kappa} \cdot G_{syn,i} \qquad [1]$$

where τ_H is the time constant for the HSP process, which is very large relative to the membrane time constant, and $\kappa = 1$, in voltage units, maintains $G_{syn,i}$ in units of conductance. Full details of the model can be found in Ref. [19].

dendritic compartmentalization [35], culminating in the recent discovery that dendritic branches can function as individual units of plasticity [24]. Thus, the question arises, how compatible is HSP with a compartmentalized organization of dendritic activity? A hypothetical global HSP mechanism, which by definition lacks the spatial resolution to discern dendritic compartments, could actually be harmful for dendritic compartmentalization. For example, if the activity in compartment *A* becomes chronically low, but in addition, activity throughout the rest of the dendrites is persistently high, global HSP will weaken all synapses including those in compartment *A*, and will thus only exacerbate the drop in activity in that already weak compartment, potentially silencing it altogether. By contrast, local HSP, even if it controls each synapse individually, will actually regard each dendritic compartment as a single functional subunit owing to strong interactions between synapses within each compartment and will regulate the activity in each compartment separately, thus maintaining all compartments fully balanced and functional [12].

An additional rather different and surprising function that local HSP can have is to select which spatial patterns of LTP/LTD will persist and which will perish [19]. According to our modeling analysis, synapses that are potentiated together in a spatially clustered pattern (e.g. Figure 3c, left, blue pattern) will lose much more of their potentiation under local HSP than synapses that are potentiated in a sparse pattern (e.g. Figure 3c, right, red pattern). The reason for this is that in the sparse case, for each potentiated synapse there are more adjacent nonpotentiated neighboring synapses that can compensate for the elevated activity. Is there any functional significance to preferring scattered configurations over clustered ones? To compare the functional value of the scattered versus clustered patterns, we used the synaptic information efficacy (SIE) measure [26,36]. This measure estimates how much information can be extracted from the input of a synapse about the output of the entire neuron. The more effective a synapse is the greater its influence on the overall neuron's output and hence the higher its SIE score should be. Applying the SIE measure to the same representative synapse once within a clustered pattern and once within a sparse one (Figure 3d, 'before potentiation') shows an inherent advantage to the latter even before any potentiation has occurred. This can be attributed to a reduced driving force and input resistance resulting from the close proximity of the synapses in the clustered case. Immediately following a 50% potentiation in synaptic conductance of the synapses in Figure 3c, an increase in SIE was detected in these synapses (Figure 3d, 'after potentiation'). However, although in both cases synaptic conductance was increased equally (by 50%), the potentiation in terms of synaptic efficacy was double in the sparse pattern compared to the clustered pattern (100% versus 50%, respectively). Finally, following local HSP (Figure 3d, 'after local HSP'), the SIE of synapses in the clustered pattern returned to what it was before LTP, so that effectively, no trace of the potentiation remained. By contrast, synapses in the sparse pattern showed an enduring and substantially (~33%) larger SIE than their SIE before LTP (Figure 3d, 'after local HSP,' red bar). Therefore, local HSP might have an important role of selecting between patterns of synaptic potentiation according to their spatial context, eliminating ineffective patterns and allowing the more effective ones to persist. Such pattern selectivity agrees very well with dendritic branch plasticity [24], which can selectively enhance the dendritic spike propagation in those branches that have been stimulated by a highly effective spatial pattern of inputs.

Conclusions

A key principle of the operation of neuronal networks is their ability to continuously and adaptively respond to the environment. One basic means for achieving this is implemented by the synapse – a miraculous device that connects between neurons and that is endowed with a rich collection of activity-dependent plasticity mechanisms. These mechanisms seem to operate at different timescales and spatial resolutions, and might even oppose each other in the direction of their effect. Some operate in a positive feedback manner (e.g. Hebbian-like LTP/LTD) and some as negative feedback (e.g. homeostatic synaptic plasticity; HSP). The recent findings that HSP operates locally at the spatial resolution of individual synapses seems at first to be counterintuitive and counterproductive, as it might erase any local changes that synapses undergo. Indeed, if each synapse experiences both Hebbian-like LTP/LTD changes and in parallel also an opposing HSP modification (assuming that eventually both mechanisms converge on the same target, e.g. the expression of AMPA receptors), then how can changes in synaptic strength endure? We propose a solution for this seeming paradox, showing that neighboring nonpotentiated synapses situated on a small dendritic branch could 'share the cost' of persistently enhanced (or reduced) activity at this branch with the potentiated (depressed) synapse and thus enable that synapse to main-

tain its potentiation (depression) even under local HSP. This theoretical result emphasizes the important role of the dendritic compartment, which is composed of many interacting synapses, as the functional unit for HSP. It also provides several predictions regarding the role of local HSP for selecting which potentiated/depressed synapses will persist and which will perish, which could be tested experimentally with the use of creative new molecular and optical techniques.

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