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Timing in synaptic plasticity: from detection to integration

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Timing of cellular and subcellular events contributes to spiking-induced modification of synapses in a variety of ways. Initially, the timing of presynaptic and postsynaptic action potentials must be translated into signals that can initiate intracellular processes. Recent experimental and computational findings suggest that the spatiotemporal details of such signals, in particular the time courses and locations of postsynaptic Ca^{2+} transients, might themselves be crucial for driving potentiation and depression modules that interact in a time-dependent way to determine plasticity outcomes. On longer timescales, the effects of multiple spikes are integrated in a nonlinear manner, yielding non-intuitive plasticity results that are likely to be sensitive to local conditions and, finally, additional elements must be called into action to stabilize changes in synaptic strengths. This review is part of the *TINS Synaptic Connectivity series*.

Introduction

In the beginning, there was timing. Hebb's postulate on synaptic plasticity emphasized that changes in synaptic efficacy would take place when a presynaptic cell participated in firing a postsynaptic cell [1,2], which implies a quantitative temporal relationship between the outputs of the two cells. As the experimental study of long-term synaptic plasticity has expanded over the past decades, temporal correlation, defined with varying degrees of specificity across different studies, has remained as one of the fundamental components of this concept [3–5].

Recently, a more sensitive dependence on the precise details of presynaptic and postsynaptic spike timing has emerged, in the context of spike-timing dependent plasticity (STDP) [4–8]. As the 'S' in STDP indicates, this form of synaptic plasticity places an emphasis on spikes, or action potentials, that serve as the basic signal packets for communication between neurons [9]. The essence of STDP is that the precise timing of presynaptic and postsynaptic spikes determines the sign and magnitude of synaptic modifications [10–21]. Spikes are an efficient means for network-level information processing, but synaptic modification is effected by components that operate at the subcellular level and, hence, requires the transduction of spikes into intracellular events. More specifically, when a presynaptic spike and a postsynaptic spike occur with a certain temporal relationship, and this is repeated sufficiently many times, these spikes induce an intracellular response that must somehow represent the precise details of the spike timings to lead to corresponding plasticity outcomes.

In this review, we consider recent experimental and theoretical observations regarding the role of postsynaptic Ca^{2+} as an intracellular signal responsible for encoding spike timing, and we discuss how this signal could be used to orchestrate the enzymatic reactions that lead to synaptic changes. Findings suggest that in the early stages of STDP induction, different synaptic modules could detect different features in the detailed time course of Ca^{2+} influx induced by the precise timings of presynaptic and postsynaptic spikes. The dynamic interaction of these modules would in turn compute the resulting synaptic modification. According to this view, various protocols induce long-term plasticity by harnessing common intracellular mechanisms, with particular plasticity outcomes that could depend crucially on local conditions, in addition to details of membrane and synaptic dynamics.

Translating spike timing into Ca^{2+} signals – promise and problems

We start with a disclaimer: the exact mechanisms underlying STDP are still far from definitively known. Many molecular candidates have been implicated in the translation of neuronal activity patterns into synaptic plasticity outcomes, but how they actually interact with one another has not been fully understood [3,5,8,22]. Further, it is probable that multiple mechanisms contribute to this process, and that the set of mechanisms involved varies across organisms, across brain areas within an organism, across synaptic sites on a neuron, and even across experimental methods applied at a single neuronal site.

A starting point for elucidating the mechanisms underlying STDP derives from results illuminating the cellular basis of conventional long-term potentiation (LTP) and long-term depression (LTD), although several key issues there are still debated [23]. In particular, postsynaptic intracellular Ca^{2+} has been established as a central messenger in most forms of LTP and LTD [3,24]. Ca^{2+} enters dendrites and dendritic spines via Ca^{2+}-permeable receptors, such as NMDA receptors and voltage-gated

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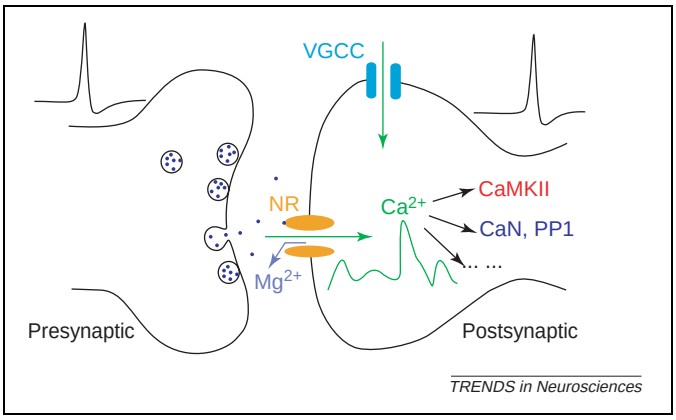

Figure 1. Central role of postsynaptic Ca^{2+} in induction of activity-dependent long-term synaptic plasticity. Ca^{2+} enters the postsynaptic compartment through multiple sources, including NMDA receptors (NR) and voltage-gated Ca^{2+} channels (VGCCs). When an action potential arrives at the presynaptic terminal, it triggers release of the neurotransmitter glutamate (blue dots), which in turn binds to postsynaptic NMDA receptors that will open and allow Ca^{2+} influx, if the Mg^{2+} block to the receptors is removed by postsynaptic depolarization. Meanwhile, postsynaptic depolarization itself opens VGCCs to allow Ca^{2+} entry. The resulting Ca^{2+} signal, depending on its spatiotemporal pattern, can activate enzymes that lead to synaptic modification, such as Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), the Ca^{2+}/calmodulin-dependent protein phosphatase calcineurin (CaN) and protein phosphatase 1 (PP1), or other molecules. Additional Ca^{2+} sources that could be involved in plasticity, such as intracellular stores, are omitted here.

Ca^{2+} channels (VGCCs), and there it can initiate molecular processes leading to synaptic plasticity (Figure 1). The fact that STDP can be abolished or altered by manipulation of NMDA receptors and L-type VGCCs [11,14,18] indicates that Ca^{2+} might have a similarly central role in STDP [5,8].

The classical framework, casting postsynaptic Ca^{2+} as a central element in signaling certain forms of synaptic plasticity (Figure 1), would imply that, no matter how many different molecules and modules were involved in implementing the corresponding synaptic changes, the activity of each would be a function of some aspect of Ca^{2+} concentration in the postsynaptic compartment. Under this assumption, if two different spike combinations lead to different plasticity outcomes, then there must be something different about the Ca^{2+} signals they generate, producing different behaviors of the relevant cellular machinery.

To explore this idea further, let us begin with the long-standing hypothesis that peak postsynaptic Ca^{2+} levels can be translated into plasticity outcomes [25–27], with sufficiently high Ca^{2+} levels yielding LTP and moderate Ca^{2+} levels giving rise to LTD. Biochemically, this picture of Ca^{2+}-level-determinism is based on the differential activation thresholds of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and phosphatase (calcineurin), with kinase dominance at high Ca^{2+} levels (Figure 1). This explanation fits well with the results from classical LTP and LTD and, on the surface, it appears to offer a qualitative resolution of the temporal asymmetry that is the main feature of STDP [27]. Intuitively, presynaptic–postsynaptic (pre–post) spike pairing leads to LTP because it highly activates NMDA receptors, allowing high Ca^{2+} influx, whereas post–pre pairing leads to LTD because it allows a moderate Ca^{2+} influx via postsynaptic VGCCs, as well as only subthreshold activation of NMDA receptors [7,8].

However, level-based models necessarily run into a fundamental difficulty. Suppose that you are driving your car at 40 miles per hour (mph) and you apply the brakes, gradually coming to a stop. Without question, at some moment before you stopped, you were going exactly 20 mph, because your speed varied continuously from 40 mph down to 0 mph. Similarly, suppose we assume a model for STDP based on Ca^{2+} levels in which a presynaptic spike that occurs ~10 ms before a postsynaptic spike causes LTP. Correspondingly, such a pairing must induce a high Ca^{2+} level. When a postsynaptic spike occurs a sufficiently long time after a presynaptic spike, there is no change in synaptic strength, and correspondingly the Ca^{2+} level must be low. Thus, there must be a range of pre–post spike timing intervals that induce Ca^{2+} levels in the LTD range, implying a zone of pre–post LTD. In fact, Nishyama *et al.* did observe a form of pre–post LTD [18] in the CA1 area of hippocampal slices, but this could stem from feedforward inhibition in the circuitry [28].

Another problem with the Ca^{2+}-level hypothesis arises from complex scenarios of presynaptic and postsynaptic activity. In cultured hippocampal neurons, in contrast to the LTP induced by repeated pre–post spike pairs [14], no LTP was induced by repeated pre–post–pre spike triplets [29,30]. This is particularly perplexing because the triplets presumably could trigger more Ca^{2+} influx (through NMDA receptors) than that given by pre–post pairings alone. By contrast, LTP was indeed induced by post–pre–post spike triplets [29,30]. Therefore, it is unlikely that Ca^{2+} level by itself is sufficient to translate spike timing into STDP.

Dynamic detection of Ca^{2+} time courses

Clearly, peak Ca^{2+} level is only one aspect of the Ca^{2+} signal. On millisecond and nanometer scales, Ca^{2+} influx during synaptic activation can have rich spatiotemporal dynamics, as revealed by detailed simulations [31,32]. When caged Ca^{2+} experiments showed that similar Ca^{2+} levels could induce different plasticity outcomes [33,34], the Ca^{2+} time course was proposed as a more sophisticated postsynaptic plasticity signal [34–38]. The Ca^{2+} time course includes such features as rate of rise, rate of decay, duration of time spent at various levels, and relative timings of periods spent at different levels, all of which could depend on the details of various experimental plasticity protocols. Although biochemical assays often measure the steady-state activation of Ca^{2+}-dependent enzymes, the actual activation process by spike-induced Ca^{2+} transients in a living cell can be highly dynamic. Could these elements form a detector system that is sufficiently sensitive to translate differences in precise details of the Ca^{2+} time course, directly as they arise, into observed plasticity outcomes?

Building from Ca^{2+}-imaging experiments, a variety of recent efforts have aimed to develop biophysically detailed models of Ca^{2+} dynamics in spines or other dendritic compartments. These have incorporated, at very least, Ca^{2+} influxes resulting from evoked postsynaptic potentials and backpropagating action potentials, with an eye

towards implications for plasticity [31,32,37–39]. The prevailing view in these studies is that STDP and classical forms of LTP and LTD are produced by common underlying machinery, harnessed in different ways by different experiments. The features necessary to translate postsynaptic Ca^{2+} time courses into plasticity outcomes can then be elucidated by simulations across induction paradigms known to produce different plasticity results. For example, simulations of an experimentally calibrated, multi-compartment CA1 pyramidal cell model [40], with experimentally based Ca^{2+} [36,41–43] and synaptic [44,45] dynamics, showed that four fundamental detector properties would suffice to distinguish spike pair and triplet STDP results as well as to reproduce results from certain classical LTP and LTD protocols [38] (Figure 2). These properties were induction of LTP by Ca^{2+} levels above a high threshold, reminiscent of earlier, level-based models; induction of LTD by Ca^{2+} levels above a low threshold for a sufficiently long, continuous time period (i.e. a width detector; see also Ref. [35]); a veto of depression components, triggered independently from LTP by moderate Ca^{2+} levels; and a competition between LTP and LTD components to influence the final readout. It is important to note that because of this competition, the relative timings and durations with which different Ca^{2+} levels are achieved influence plasticity outcomes in this model. Further, the idea of a veto that suppresses LTD appears to be crucial, both for reproducing STDP results incorporating multiple spikes and for elimination of the LTD at the long positive timings already discussed.

Simulation studies of STDP based on Ca^{2+} time course predict that small variations in parameters, such as neuronal excitability, can qualitatively alter plasticity outcomes [38]. This sensitivity suggests that if timing-dependent plasticity was induced by postsynaptic Ca^{2+} signals alone, then its details would necessarily vary across systems and synapses [20,21,30,46]. In this context, it is also important to note that, although plasticity results from pairing protocols in computational models can show robustness to spike timing jitter [38], the general effects of noise in Ca^{2+} signals and detection elements on STDP outcomes remain to be explored.

In most computational models, it is assumed for mathematical simplicity that Ca^{2+} is well-mixed within each of a set of postsynaptic compartments, with Ca^{2+} influx from all sources contributing to a unified Ca^{2+} signal in each. Accumulating evidence suggests, however, that a high degree of spatial specificity exists in postsynaptic signaling. Particularly revealing are recent experiments indicating that conventional LTP requires NMDA receptors with NR2A subunits, whereas the presence of NR2B subunits is necessary for LTD [47,48]. It will be important to determine whether similar specificity exists in the induction of STDP. If this is the case, it will suggest that a single spike pattern yields multiple, spatially localized postsynaptic signals with distinct temporal signatures, which could activate different detection modules or could interact after spatial propagation and associated temporal delay. Spatial organization of detection modules, with multiple detection elements at different proximities to different Ca^{2+} sources within and near the postsynaptic density [49–51], could in principle enhance the capacity of the system to distinguish robustly the details of Ca^{2+} dynamics [7,8,32]. Although the idea that distinct Ca^{2+} sources could have different roles in inducing STDP has been implemented phenomenologically in a computational model [52], the details of how such a system would work await further investigation.

Temporal integration of STDP

The modular structure proposed in the theoretical literature on STDP consists of one set of detector agents working together as an LTP module and another set forming an LTD module [38,52–55]. In most models, these computational modules are activated independently and can subsequently interact to reproduce experimental pre–post or post–pre STDP results. Biologically, although the exact mechanisms are not yet fully understood, it has been shown in various systems that the activation of certain kinase or phosphatase signaling pathways is indeed highly specific to the temporal dynamics or the source of a Ca^{2+} concentration increase [32,56,57]. Consistent with results from studies of conventional LTP and LTD [58], recent experiments further indicate that pre–post spike pairs might selectively activate a potentiation module that requires CaMKII, whereas post–pre spike pairs activate a calcineurin-dependent depression module [30]. In addition, these modules appear to be activated together by more complex spike patterns such as triplets, because blocking one module can unmask the effects of the other (Table 1). An interesting question is: how would such modules interact to induce synaptic modification, particularly when a complex series of presynaptic and postsynaptic spikes occur?

In most computational models, the modules combine linearly to influence a plasticity variable [37,52–55]. However, such interaction can be nonlinear owing to dynamic competition between components [38]. Several recent experimental studies have indicated that the interaction between the modules is indeed nonlinear (Table 1). In layer 2/3 of the visual cortex, an initial pairing event can suppress the effects of later events in a time-dependent manner [21]. In layer 5 of the same cortical area, however, a 'potentiation-dominating' rule was observed [20], which could be promoted by a weakened A-type K^+ current [38,59]. In cultured hippocampal neurons, depression appears to cancel previously activated potentiation, whereas potentiation tends to override previously activated depression [29,30]; this seems to be opposite to the first-pair dominance observed in cortical layer 2/3. One possible explanation for this disparity is that layer 2/3 neurons could feature additional mechanisms, such as strong short-term depression in both synaptic transmission and backpropagation of action potentials, also acting on the timescale of tens of milliseconds [21]. Such factors would suppress the ability of later spikes to elicit Ca^{2+} influx and thereby ensure the priority of initial signals. Alternatively, differences in cellular signaling machinery, such as the threshold and time constant of a veto system that blocks depression, might account for different integration results in the two systems.

A strongly nonlinear interaction between potentiation and depression on the millisecond timescale suggests that

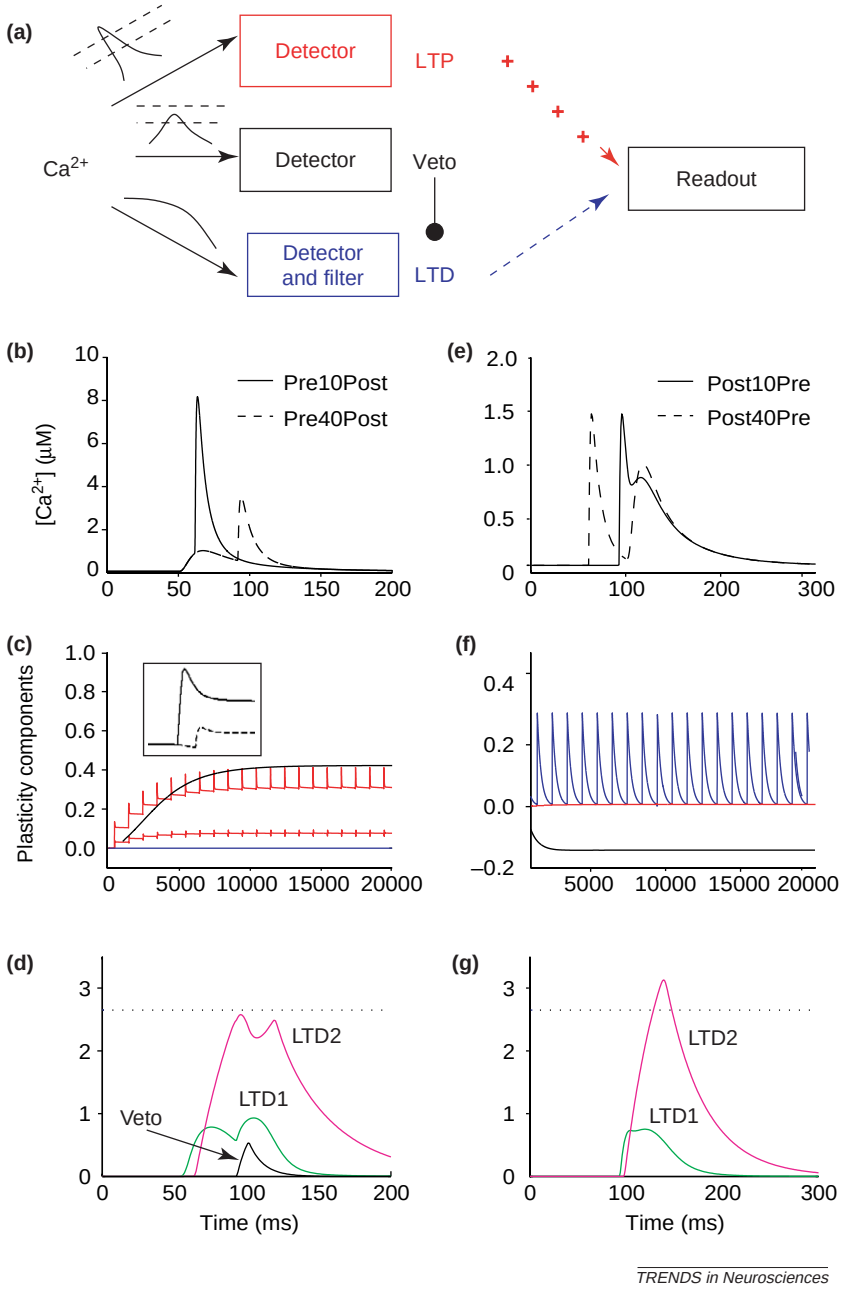

Figure 2. A Ca^{2+} detector system. **(a)** Different Ca^{2+} detectors drive LTP, veto and LTD components of the system. The detector for LTP responds to Ca^{2+} concentrations above a high threshold (upper broken line), the veto detector responds to Ca^{2+} concentrations above a moderate threshold (lower broken line) and the LTD detector responds to Ca^{2+} concentrations of a sufficient duration. The LTP component (crosses) and LTD component (blue broken line) compete to influence a readout variable, after temporal filtering in the LTD case; the readout is upregulated by the LTP agent and downregulated by the LTD agent. The veto suppresses LTD, if it is activated at an appropriate time and strength. The LTP and LTD components can also influence the dynamics of one another (not illustrated). **(b)** Postsynaptic Ca^{2+} time courses corresponding to a presynaptic spike followed by a postsynaptic spike, with interspike intervals of 10 ms (Pre10Post, solid line) or 40 ms (Pre40Post, broken line). **(c)** The upper red line shows the response of the LTP detector to a series of 20 pairings delivered at 1 Hz in the Pre10Post case, which drives potentiation (black). The LTD agent is not activated (blue), owing to the brief duration of the Ca^{2+} signal. The lower red line shows the weaker response of the LTP detector in the Pre40Post case. Inset: an expanded view of the LTP detector response to the first pairing (Pre10Post, solid line; Pre40Post, broken line). **(d)** In the Pre40Post case, the initial detector in the LTD component (LTD1) is activated somewhat by each spike pair, but activation of the veto adjusts its dynamics in a way that compromises its response. As a result, the filtered LTD signal (LTD2) can never reach the threshold (broken line) to induce LTD. **(e)** Ca^{2+} time courses corresponding to a postsynaptic spike followed by a presynaptic spike, with interspike intervals of 10 ms (Post10Pre, solid line) or 40 ms (Post40Pre, broken line). Note the different vertical scale from (b). **(f)** For each of 20 pairings delivered at 1 Hz in the Post10Pre case, the final LTD component (blue) is activated, leading to a net depression of the readout variable (black), whereas the LTP detector is not activated (red). **(g)** Each activation of the LTD component in (f) is driven by a sufficiently strong activation of LTD1, which allows LTD2 to cross the LTD threshold (dotted line). The veto is not activated in the Post10Pre case owing to the small amplitude of the peak in the Ca^{2+} signal, as shown in the solid curve in (e). The width of this Ca^{2+} signal is sufficient to activate the LTD detector, but this is not true in the Post40Pre case, where the valley between peaks, seen in the dotted curve in (e), breaks the Ca^{2+} signal into two narrower components. Adapted, with permission of The American Physiological Society, from Ref. [38].

the two modules reside within the same cellular compartment. However, these modules represent only the initial stages of plasticity signaling. Further, it has been suggested that in some systems, spike-timing-dependent potentiation occurs at the postsynaptic side whereas depression occurs at the presynaptic side. In visual cortex layer 5, for example, there is a presynaptic component to the induction and expression of timing-dependent LTD.

Table 1. Modular detection and different rules of nonlinear integration of STDP

	Layer 5 visual cortical slices	Layer 2/3 visual cortical slices	Hippocampal culture	Hippocampal culture with CaMKII block[a]	Hippocampal culture with calcineurin block[b]
Pre–post–pre triplet[c]	↑	↑	N	↓	↑
Post–pre–post triplet	↑	↓	↑	↓	↑
Refs	[20]	[21]	[30]	[30]	[30]

[a]Experiment was performed in the presence of the CaMKII antagonist KN-62.
[b]Experiment was performed in the presence of calcineurin antagonist cyclosporin A or FK520.
[c]The spike timing for adjacent presynaptic and postsynaptic spikes in a triplet paradigm was chosen to be $\sim \pm 10$ ms (positive for pre–post timing, negative for post–pre timing) so that both potentiation and depression modules were engaged. Each triplet was repeated many times (e.g. 60) at low frequency (e.g. 1 Hz), similar to STDP experiments using spike pairs [14] to obtain significant potentiation (↑) or depression (↓). N indicates that no consistent or significant synaptic change was observed.

This LTD is at least partially mediated by retrograde endocannabinoid signaling and Ca^{2+} influx via presynaptic NMDA receptors [60], although LTP in the same synapses appears to be induced and expressed postsynaptically. These synapses might employ additional processes, perhaps on different timescales, to balance the opposite functional changes occurring across the synaptic cleft.

A basic assumption in many computational studies implementing STDP in network level models has been that STDP in response to complex spike trains progresses via the summation of a series of pair-wise interactions, each following the same experimentally defined first-order rule that describes the outcome of single spike pairings [61–65]. However, the strong nonlinearity in the interaction between potentiation and depression modules observed across different systems suggests the existence of a set of nontrivial second-order integration rules, going beyond summation of pair-wise interactions, that must also be defined experimentally for multi-spike interactions. The existence of multiple forms of such second-order rules, whether they correspond to differences in how a single molecular signaling system is harnessed under different conditions or to the recruitment of different signaling agents in different settings, suggests that STDP could be 'tuned' to serve specific functions in different circuits. With deeper knowledge about the details of the signaling modules and their interactions, it should be possible for future studies to deduce the essential framework of the Ca^{2+}-driven signaling system and to translate this into a unified set of biophysically based integration rules, encompassing a variety of paradigms leading to long-term plasticity.

The time beyond STDP

So far, we have focused on spiking events occurring on millisecond timescales and early cellular signaling processes that are activated and interact with similar time constants. The physical changes responsible for functional synaptic modification occur on many, mostly slower, timescales. Numerous intermediate processes of signaling (e.g. protein phosphorylation and gene regulation) and physical (re)construction (e.g. channel insertion or removal and new bouton formation) must be coordinated to ensure that the temporal information encoded in spike patterns is translated faithfully into memory engrams [3,66,67]. From this perspective, even a complete picture of spike-timing detection and subsequent integration for the induction of STDP would represent only an early step towards understanding synaptic plasticity.

In particular, several issues concerning different timescales must be addressed by future experimental and theoretical explorations. First, it takes time for STDP and some other forms of LTP and LTD to be expressed. In some cases, there appears to be a delay of as long as 10 min before potentiation or depression reaches a stable level [10,14,15], which is often neglected in computational studies. Such slow processes cannot quantitatively account for fast memory formation. Other synaptic, cellular or network mechanisms must fill in this gap. More importantly, such mechanisms must coordinate with the slower processes so that memory traces in distributed networks are not lost or altered.

Also on the longer timescale of minutes, Zhou and Poo found that in the presence of uncorrelated activity *in vivo,* STDP is easily reversed unless it is consolidated by temporally spaced stimuli [68]. In various systems, it also appears that reversal of LTP or LTD requires weaker stimulation than is needed to induce naïve LTD or LTP [69]. Similar fragility of LTP and LTD signals (on a shorter timescale) is implied by results from the triplet experiments, where potentiation and depression modules tend to cancel each other rather than summing linearly [30]. The cellular nature of the reversal and consolidation processes remains to be understood. Finally, on a still longer timescale, homeostatic control is in place to maintain synaptic and network stability [70]. Future studies should elucidate how homeostatic mechanisms interact with the signaling and expression systems of actively induced plasticity, such as STDP, to ensure an appropriate balance of synaptic stability and modification, leading to reliable network function.

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