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Beyond STDP — towards diverse and functionally relevant plasticity rules

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Synaptic plasticity, induced by the close temporal association of two neural signals, supports associative forms of learning. However, the millisecond timescales for association often do not match the much longer delays for behaviorally relevant signals that supervise learning. In particular, information about the behavioral outcome of neural activity can be delayed, leading to a problem of temporal credit assignment. Recent studies suggest that synaptic plasticity can have temporal rules that not only accommodate the delays relevant to the circuit, but also be precisely tuned to the behavior the circuit supports. These discoveries highlight the diversity of plasticity rules, whose temporal requirements may depend on circuit delays and the contingencies of behavior.

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Introduction

Synapses are capable of long-lasting plastic changes in strength, in response to specific patterns of neural input. The rules that determine that some input patterns, and not others, result in synaptic plasticity have been the subject of extensive research, as well as much debate. It is important to understand these rules because synaptic plasticity supports behavioral learning, and is a critical part of how the brain encodes a modified behavior. Recent discoveries suggest that rather than having universal rules for plasticity, there may be a diversity of rules, and that this diversity may be determined by the function of the neural circuit that each synapse is a part of.

The search for plasticity rules has long been based on Hebb's postulate that when a neuron repeatedly drives the activity of another, the connection between them is strengthened [1]. Hebbian plasticity addressed the question of *causality* in plasticity, but the discovery of spike timing-dependent plasticity (STDP) provided a framework for *order dependence* as well as causality. To elaborate, the STDP rule stated that if presynaptic activity preceded postsynaptic activity within a few tens of milliseconds, it resulted in the strengthening of the connecting synapse, while the converse temporal order resulted in the weakening of the synapse [2,3] (Figure 1a). STDP-like learning rules, in which the precise timing between presynaptic and postsynaptic neural activity is the critical determinant of the direction and degree of synaptic plasticity, are beautiful in their simplicity and have been supported by many studies, both in *ex vivo* preparations and *in vivo*, in different brain regions and in different species [4–11]. However, the necessity for postsynaptic action potentials remains controversial [12–15] and plasticity may be mediated by other depolarizing events in the postsynaptic cell [16]. In this review, therefore, plasticity rules requiring order-dependent, close temporal correlation of neural signals are referred to as STDP-like. These rules have been extensively reviewed elsewhere [17,18], and form a fundamental core of our understanding of associative plasticity at synapses [7,19–26].

Beyond STDP rules

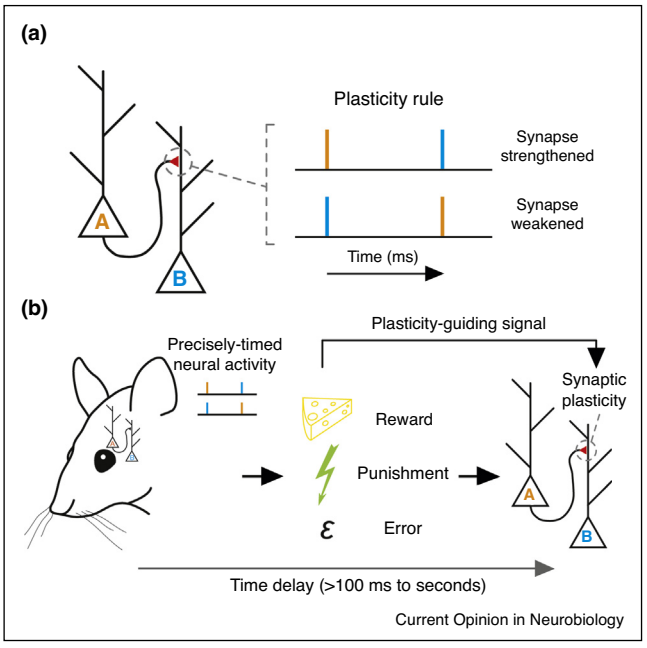
Relevance of plasticity to learning signals

One key difficulty with invoking STDP-like plasticity rules to support all forms of associative learning is the difference in timescale between plasticity rules, at the scale of tens of milliseconds, and the contingencies of behavioral learning, often on the timescale of minutes. Although STDP-like rules can vary between brain regions [19], this variability is not sufficient to directly bridge longer behavioral timescales. It has, however, been possible to reconcile these differences in timescale; for example, in hippocampal place cells, the timescale of hundreds of milliseconds can be compressed into the millisecond timescales relevant for STDP-type rules, in the presence of inhibition-driven theta oscillations and asymmetric excitation [27].

The temporal credit assignment problem

During some forms of associative learning, an animal associates a neural event with information about its behavioral effect. The valence of such a signal can vary — reward, punishment and error signals all drive associative learning.

Figure 1



The short timescales of spike timing-dependent plasticity (STDP) are difficult to reconcile with the long timescales of associative learning where information about outcome is delayed. **(a)** Spike timing-dependent plasticity is induced when neuron A activates neuron B repeatedly. When A fires up to a few tens of milliseconds before B, the synapse between A and B is strengthened. If B fires up to a few tens of milliseconds before A, the synapse is weakened. **(b)** Neural activity (left) leads to an outcome (middle), for example, a reward, a punishment, or a motor error. Information about the outcome is conveyed back to the neurons whose activity caused the outcome, but it comes at a long delay relative to the original, precisely timed, neural activity.

For the neural circuits where such associations are made, the delayed signal about the outcome results in a problem of temporal credit assignment. How does the signal about the outcome of an action, occurring long after the relevant synaptic activity that drove the action, identify the appropriate synapses to modify (Figure 1b)? It is possible to invoke STDP-like synaptic learning rules by bridging gaps in time, for example, with a synaptic eligibility trace which tags synapses for plasticity in response to a delayed reward signal, a cascade of plasticity events, or sustained responses to a stimulus [28–31,32•]. However, recent studies demonstrate that the association of neural signals temporally spaced much farther apart than STDP-like processes, are nevertheless capable of inducing synaptic plasticity. These studies describe plasticity rules that extend beyond millisecond timescales, to longer timescales that are behaviorally and physiologically relevant [33••,34••].

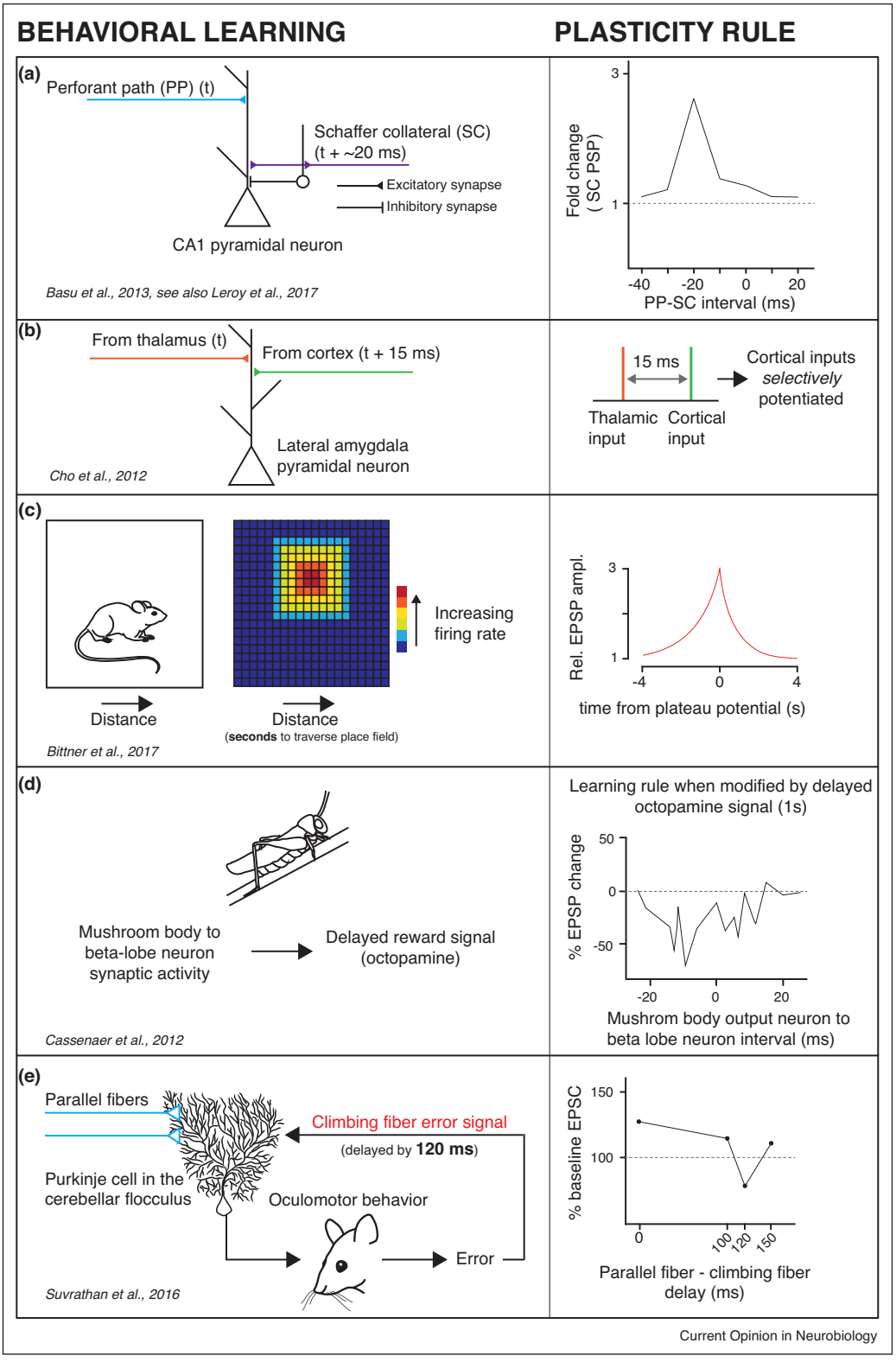
Synaptic plasticity on functionally relevant timescales

The alignment of timing rules to the function of the local circuit was recently demonstrated in the hippocampus [35]. Pairing of entorhinal perforant path and hippocampal Schaffer collateral inputs to hippocampal CA1 pyramidal neurons resulted in an enhancement of Schaffer collateral-driven postsynaptic potentials, which arises in part from the long-term depression of feedforward inhibition onto CA1 neurons. This reduction in feedforward inhibition was localized to reduced GABA release from cholecystokinin-expressing interneurons via endocannabinoid signaling [35,36]. During such input-timing-dependent plasticity (ITDP), pairing of the perforant path input 20 ms prior to the Schaffer collateral inputs induced heterosynaptic plasticity. Interestingly, the 20 ms delay matches both the delay caused by the neural circuit architecture as well as the period of the gamma oscillation. ITDP has also been demonstrated at CA2 pyramidal neurons, albeit with less precise tuning to the 20 ms delay. In the CA2, ITDP is mediated by depression of feedforward inhibition from parvalbumin-expressing interneurons via activation of δ-opioid receptors [37•] (Figure 2a).

Another recent study that highlights the relevance of precise timing rules to circuit delays considers input-timing-dependent plasticity in the amygdala, where coincidence of thalamic and cortical inputs to the lateral amygdala causes selective LTP of the cortico-amygdala pathway, but only when the thalamic–amygdala synapses are stimulated 15 ms before the cortico-amygdala synapses [38]. Behaviorally, the amygdala supports fear conditioning, during which information about the auditory conditioned stimulus arrives via the thalamic inputs before the cortical ones, at approximately the same 15 ms delay (Figure 2b).

The circuit-specific timing rules discussed thus far show modifications to the STDP rule, adapted to relevant local circuit delays. However, these rules still act on the timescale of tens of milliseconds. Recently, a learning rule that itself spans a seconds-long timescale has been discovered in the hippocampus [34••,39] (Figure 2c). During the formation of place fields, ramp-like depolarization of CA1 neurons caused by plateau potentials led to place field firing on subsequent trials. The plasticity rule at synapses onto CA1 neurons was tested in the slice preparation, where trains of synaptic activation were paired with a postsynaptic plateau potential. The temporal interval between the two signals that was effective in driving plasticity extended asymmetrically out to seconds in both directions (Figure 2c). This learning rule contradicts Hebb's original postulate, as potentiated inputs were not causal for postsynaptic spiking. A key difference from STDP-like rules is that repeated pairing was not necessary for the induction of plasticity; just five pairings were sufficient. Critically, this novel form of plasticity can account for the rapid formation of place fields over the seconds it takes for an animal to cross a novel arena. In addition, very few trials (~1.4) with a plateau potential

Figure 2



Examples of synaptic plasticity tuned to the temporal requirements of the circuit and behavior. Left column: illustration of behavioral or circuit-level delays, from the studies listed on the bottom left of each row. Right column: Schematized plasticity rule based on each study, highlighting the alignment of the timing of the plasticity rule to the temporal constraint in the left column. **(a)** Input-timing-dependent heterosynaptic plasticity at CA1 neurons is tuned to the 20 ms circuit delay between direct perforant path inputs from the entorhinal cortex and delayed Schaffer collateral inputs [35].

were sufficient to induce a place field *in vivo*, which is also in contrast to Hebb's postulate of repeated pairings being necessary for modification of synaptic strength. The timing requirements of such behavioral time scale plasticity (BTSP) fit well with the function of the hippocampal circuit, demonstrating that the synaptic plasticity rule itself can account for long timescales relevant for behavioral learning. It is possible, however, that more than one plasticity mechanism is recruited during the formation of place fields [40,41].

More than twenty years ago, a similarly long timescale (hundreds of milliseconds to over a second) for induction of associative synaptic plasticity was demonstrated in the hippocampus, albeit depression rather than potentiation [42]. In this study, the usual STDP-like pre-post order of synaptic events was inverted: depolarization of the postsynaptic CA1 cell, followed by synaptic activation hundreds of milliseconds later, resulted in synaptic depression. This investigation forms part of an early set of studies describing timing rules for plasticity, often with longer timescales for association [43–45].

Dealing with delays: neuromodulators and plasticity rules

Associative learning is often guided by signals that indicate the outcome of an action, such as reward signals. In such cases, learning may be supervised by a neuromodulatory signal rather than by synaptic activity. The timing rules for such supervised learning follow timescales whose behavioral significance is easier to understand. For example, dopamine signals evoked by stimulation of the ventral tegmental area (VTA) can modulate the cortical representation of a tone paired with it, with the tone preceding VTA stimulation by hundreds of milliseconds [46]. The number and duration of pairings with a behaviorally relevant stimulus can be significantly different from those in STDP-like rules, or BTSP, extending to hundreds of pairings, over 20–25 days [47]. Indeed, such long timescales, both for the interstimulus interval of one pairing, and for the number of pairings itself, are likely to be relevant to the contingencies of behavioral learning. Moreover, it brings into question the relevance of precise spike timing for neural circuits where learning is supervised by delayed and temporally more diffuse neuromodulatory signals.

However, not only can neuromodulators signal relevance or reward to directly drive plasticity, they can also change the temporal requirements of precise spike timing necessary for inducing synaptic plasticity. Neuromodulatory signals encoding reward, delayed in time relative to the neural activity that caused it, have been demonstrated to interact with plasticity rules to modify the appropriate synapses [48••,49]. In locusts, where the reward signal is the neuromodulator octopamine, a local STDP rule is modified by the delayed (by one second) application of octopamine [50••]. Kenyon cell to beta-lobe neurons follow a Hebbian STDP rule that, along with lateral inhibition, is thought to regulate the spiking response of beta-lobe neurons. This timing rule identifies the presynaptic and postsynaptic components of the synapse to be modified — if a delayed global reward signal occurs, it interacts with the eligibility trace created by precisely timed prior synaptic activity in order to modify the appropriate synapses. Remarkably, the delayed reward modifies the plasticity rule (the curve relating synaptic plasticity to inter-event time) (Figure 2d). The ability of modulatory inputs to affect plasticity has been demonstrated in several different contexts. It can play a gating role [51–54] or can change the shape of the plasticity rule itself [32•,55–58].

The timing requirements for the action of a neuromodulatory signal have also been investigated in the context of dopamine's modulation of plasticity of spine structure in medium spiny neurons in the striatum, showing that dopamine needs to be timed 0.3–2 s after glutamatergic stimulation [59]. During such supervised learning, an eligibility trace is created, which can then be converted by neuromodulators into long-term plasticity [60,61]. However, further investigation is needed into the timing requirements for delayed reward signals in different brain regions, and in the underlying mechanisms that can support synaptic eligibility traces and their interaction with modulatory signals. The timing of the reward signal itself can be learned [62,63], leading to the possibility of plasticity in the timing of the learning rule.

Synaptic plasticity tuned to behaviorally relevant delays

In the cerebellum, a plasticity rule which is broadly tuned to associations was thought to account for long circuit delays in a manner similar to rules in the hippocampus [33••], although on the much shorter timescales relevant to the behavior the cerebellum supports (hundreds of milliseconds instead of seconds) [64]. By contrast, we recently showed that a plasticity rule in the cerebellum can not only account for long delays, but that it can be

(Figure 2 Legend Continued) A similar timing rule exists at CA2 pyramidal neurons [37•]. (SC PSP: Schaffer collateral postsynaptic potential. PP before SC is negative.) **(b)** Synaptic plasticity at cortical synapses onto lateral amygdala inputs is selectively induced when thalamic and cortical inputs are separated by 15 ms, which matches the delay between inputs *in vivo* [38]. **(c)** Hippocampal CA1 place cells follow a rule for rapid induction of plasticity at synaptic inputs activated within seconds of a plateau potential, which matches the timescale of place field formation [34••]. **(d)** The STDP-like plasticity rule underlying olfactory conditioning in locusts is modified by the delayed occurrence of a reward signal [50••]. **(e)** Synaptic plasticity in the flocculus of the cerebellum is tuned to the 120 ms delay in climbing fiber error signal during oculomotor learning [33••].

precisely tuned to a specific, long delay appropriate to behavioral function [33••].

Cerebellar learning is guided by errors in motor performance. Within the cerebellar cortex, the teaching signal for plasticity is therefore an error signal carried by climbing fibers, synapsing onto Purkinje cells. The original Marr-Albus theory postulated that climbing fiber error signals drive plasticity of correlated parallel fiber-to-Purkinje cell synapses [65,66]. This form of error-signal driven heterosynaptic plasticity is anti-Hebbian in nature, in that it causes long-term depression (LTD) at the parallel fiber synapses which contributed to the error, similar to plasticity in other cerebellum-like structures [67].

We demonstrated that the plasticity rules that guide climbing fiber-driven LTD at parallel fiber-to-Purkinje cell synapses within a small, functionally homogenous region of the cerebellum, the flocculus, are different from the rules in the well-studied cerebellar vermis [33••]. In particular, plasticity was tuned to a long delay in climbing fiber error signal, which exactly matched the delay for error signals during learning *in vivo*. Specifically, LTD was induced at parallel fiber-to-Purkinje cell synapses in the flocculus if climbing fiber stimulation was repeatedly paired with parallel fiber stimulation, with the climbing fibers delayed 120 ms relative to the parallel fibers. LTD was not induced if the delay was varied by a few tens of milliseconds in either direction, suggesting the timing rule for plasticity has the precision of STDP in the cortex or the hippocampus (Figure 2e).

The flocculus of the cerebellum supports forms of oculomotor learning, where the relevant error signal during learning is a slip of images on the retina. Retinal slip error signals reach the flocculus with an ~120 ms delay, and therefore the timing rule for plasticity is tuned to the signals present during learning. The tuning of Purkinje cells within the flocculus to a specific and behaviorally relevant timing rule suggests that plasticity rules themselves can vary to account for the properties of the circuit and behavior. This is in contrast to previous theories where synaptic plasticity follows uniform, coincidence-based rules, and circuit properties account for the temporal contingencies of the relevant behavioral output.

One timing to rule them all, and in the synapses bind them?

In addition to LTD, single-trial climbing fiber-driven plasticity in the flocculus, which may provide a substrate for trial-by-trial motor learning, was also tuned to the same 120 ms error signal delay [33••]. By contrast, the tuning of single-trial plasticity in the cerebellar vermis varied. Different cells appeared to be tuned to different climbing fiber delays, which would match the diversity of error signal modalities related to the different motor tasks supported by the vermis.

Heterogeneous plasticity rules were recently also demonstrated in Drosophila mushroom body output neurons that lie in functionally different compartments [68•,69]. Dopaminergic neurons signaling the valence of an odor innervate anatomically distinct compartments of the mushroom body lobes. Pairing an odor with activation of dopaminergic neurons in the γ1-pedc compartment leads to depression of mushroom body output neuron (MBON) firing in response to that odor. Inverted pairing, with the dopamine activation prior to the odor delivery did not result in plasticity, replicating the temporal order of sequence-dependent associative learning. Odor-dopamine pairing depresses the input to MBONs, that is, Kenyon cell-MBON synapses. Different MBON compartments are known to be behaviorally segregated, with activation of different compartments evoking contrasting behavioral responses, such as attraction or avoidance. Strikingly, the plasticity induced by pairing an odor with dopaminergic neuron activation had timing rules for induction which varied between compartments, suggesting behaviorally relevant plasticity rules. Here, postsynaptic spiking was not necessary for plasticity and hence the timing rules for plasticity relate to the timing of the dopaminergic input.

In addition to heterogeneity at synapses of the same type, plasticity rules also vary at and between different cell types, as has been discussed in more detail elsewhere [70]. Furthermore, emerging evidence suggests that there is an unexpected molecular heterogeneity even within what has previously been considered a single cell-type. For example, in the hippocampus, there are dorso-ventral gradients of gene expression in CA1 pyramidal cells. In addition, the variability in gene expression among CA1 pyramidal cells may correlate with the neural networks they connect to [71•]. Indeed, diverse learning rules at what has so far been considered a single type of synaptic connection [33••,68•] may arise because synaptic inputs arise from diverse cell populations and carry different information [72]. Thus, functionally and molecularly dissimilar cells may have been included as part of a single gross classification only because of the lack of tools to identify more fine-scaled heterogeneity.

Conclusions

With the discovery of STDP, neuroscientists had the long-hoped-for, single learning rule, which could be applied to any spike train to predict plasticity. Indeed, STDP-like learning rules have formed a core element of models of learning. However, recent studies suggest that the timing rules for synaptic plasticity can be aligned with the behavioral and functional requirements of a circuit, contradicting the concept of plasticity rules based only on close temporal correlations.

In neural circuits where plasticity is supervised by a reward or an error signal, or where the delays in neural activity are known, it has been possible to understand the relevance of precisely timed plasticity rules. More generally, arriving at the appropriate plasticity rule for a given synapse, in a given brain region, remains a challenging problem.

Timing is only part of the picture, since there are several other parameters that form a critical part of any plasticity rule, such as the rate of neuronal firing, number of repetitions, and the cooperativity of synapses, as well as integration of more than one pair of presynaptic and postsynaptic signals [11,13,73–75]. Indeed, with our focus on the timescales of pairing, the timescales over which the pairings are repeated is often ignored. With the noteworthy exception of the recently discovered BTSP, associative synaptic plasticity is usually induced by repeated pairings. The number of pairings influences the degree of plasticity induced [76], and continues on the order of minutes — a timescale which may be the most relevant one to behavioral learning. Moreover, synaptic plasticity is far from being the only form of plasticity in a neural circuit [70,77], and we do not even scratch the surface of how plasticity rules are shaped by the history of neural activity. In addition, synaptic plasticity that supports behavioral plasticity is likely to be distributed over more than one site in a neural circuit [78]. It is possible that the unifying link between plasticity rules at different synapses of a single neuron will be found by considering the intracellular mechanisms that support plasticity [79], or that learning rules can be best understood with more high-dimensional representations of plasticity that integrate all the forms of synaptic, intrinsic and homeostatic plasticity within a neural circuit with the dynamics of neural activity during learning.

In summary, coincidence-based rules for synaptic plasticity are no longer sufficient to explain the diversity of ways neural circuits can adapt and learn. The rules for plasticity can cover much longer timescales than previously thought and vary depending on the circuit they are embedded in, forcing both a reevaluation of the synaptic basis of learning rules as well as investigation into underlying mechanisms that can bridge long timescales.

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Conflict of interest statement

Nothing declared.

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