

Submitted to Neuron as a Review

## Neuromodulation of Spike-Timing-Dependent Plasticity: Past, Present and Future

Zuzanna Brzosko<sup>1,2</sup>, Susanna B. Mierau<sup>1</sup> and Ole Paulsen\*

Department of Physiology, Development and Neuroscience,  
University of Cambridge, Cambridge CB2 3EG, UK.

Number of pages: 49

Number of words: Abstract: 91  
Body text: 11,079  
Figure legends: 509

References: 229

Number of figures: 4

<sup>1</sup>Contributed equally.

<sup>2</sup>Present address: Sixfold Bioscience Ltd, Translation and Innovation Hub, London W12 0BZ, UK.

\*Correspondence: [op210@cam.ac.uk](mailto:op210@cam.ac.uk)

### In Brief:

Spike timing-dependent synaptic plasticity (STDP) is a leading cellular model for behavioral learning and memory. Brzosko et al. discuss recent advances in our understanding of the mechanisms and functions of the neuromodulatory control of STDP in health and disease.

## **Abstract**

Spike timing-dependent synaptic plasticity (STDP) is a leading cellular model for behavioral learning and memory with rich computational properties. However, the relationship between the millisecond-precision spike timing required for STDP and the much slower time scales of behavioral learning is not well understood. Neuromodulation offers an attractive mechanism to connect these different time scales, and there is now strong experimental evidence that STDP is under neuromodulatory control by acetylcholine, monoamines and other signaling molecules. Here, we review neuromodulation of STDP, the underlying mechanisms, functional implications and possible involvement in brain disorders.

## **Keywords**

Long-term depression, Long-term potentiation, Neuromodulation, Spike timing-dependent plasticity, Synaptic plasticity.

## **1. Introduction**

Synaptic plasticity and neuromodulation are two brain mechanisms that together allow animals to adapt to environmental demands. However, these two mechanisms operate at different time scales. Whereas synaptic plasticity is the ability to make experience-dependent long-lasting changes in the strength of neuronal connections, neuromodulation refers to reversible changes in the functional properties of neurons and synapses, induced by the momentary release of specific signalling molecules, such as acetylcholine or monoamines. Thus, with its rapid induction and long duration, synaptic plasticity is a strong candidate to mediate synaptic remodelling during development, learning and memory. Conversely, neuromodulation can adjust the neural circuits to accommodate immediate behavioral requirements. Neuromodulation also sets the conditions for induction of synaptic plasticity; thus these mechanisms act in concert to flexibly respond to behavioral demands.

Synaptic plasticity enables adaptive experience-based brain development, learning and memory as well as response to brain injury and neurologic disease. Much research into synaptic plasticity is inspired by the ideas formulated by Donald Hebb. He postulated that 'When an axon of cell A [...] repeatedly or persistently takes part in firing [cell B], some growth process or

metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased' (Hebb, 1949). Experimental support for Hebbian plasticity is strong. Repeated activation of a presynaptic cell A immediately *before* spikes in a postsynaptic cell B induces synaptic strengthening, known as timing-dependent long-term potentiation (t-LTP). Hebb did not explicitly propose a rule for the reverse spike ordering, but experiments indicate that, at many synapses, repeated activation of a presynaptic cell A immediately *after* a postsynaptic cell B leads to timing-dependent long-term depression (t-LTD). Together, these synaptic learning rules are known as spike timing-dependent plasticity (STDP; Figure 1; Bi and Poo, 1998; Debanne et al., 1998; Markram et al., 1997; Song et al., 2000). Such STDP is "Hebbian" because synaptic inputs that contribute to postsynaptic firing are strengthened. Hence, STDP captures the concept of causality in determining the direction of synaptic modification (Bi and Poo, 1998; Masuda and Kori, 2007; Vogt and Hofmann, 2012). The temporal order of spiking activity is significant, as it provides a mechanism for storing sequences of neuronal activity and for creating and stabilizing activity patterns in neural assemblies and regulating total levels of synaptic drive (Paulsen and Sejnowski, 2000; Song et al., 2000). Spike timing-dependent plasticity is now widely considered a biologically plausible model for synaptic modifications occurring *in vivo* (Caporale and Dan, 2008).

In its classic form, STDP is local in nature, involving only the presynaptic and postsynaptic neurons (and possibly supporting glial cells), detecting the timing of arrival of presynaptic action potentials at the bouton and backpropagating postsynaptic action potentials in the dendrite (Stuart and Sakmann, 1994), making it a computationally elegant model for investigating plasticity during naturally occurring behaviors. Indeed, STDP can be observed in response to natural patterns of spiking activity (Paulsen and Sejnowski, 2000; Froemke and Dan, 2002). STDP has been demonstrated *in vitro* and *ex vivo* at both excitatory (Markram et al., 1997; Bi and Poo, 1998; Debanne et al., 1998) and inhibitory synapses (Ormond and Woodin, 2009; Ahumada et al., 2013; Takkala and Woodin, 2013) across different brain regions in a range of species, from locust and *Xenopus* through rodents to non-human primates and humans (Zhang et al., 1998; Meredith et al., 2003; Testa-Silva et al., 2010; Huang et al., 2014; Verhoog et al., 2016). Moreover, its physiological relevance has been assessed *in vivo* (Zhang et al., 1998; Yao and Dan, 2001; Meliza and Dan, 2006; Jacob et al., 2007; Dahmen et al., 2008; Schulz et al., 2010; Cui et al., 2018). Beyond the initial characterization of the Hebbian STDP time windows, it has emerged that the quantitative rules governing STDP vary; synapses with anti-Hebbian STDP (where the sign of plasticity is reversed in comparison to Hebbian STDP) and with

symmetric STDP (where the sign of plasticity is uniform across the entire STDP time window) have also been reported (Bell et al., 1997; Egger et al., 1999; Wang et al., 2000; Fino et al., 2005; Letzkus et al., 2006; Tzounopoulos et al., 2007; Mishra et al., 2016). Thus, STDP is a versatile mechanism with diverse properties allowing for flexible synapse-specific learning rules (Fino et al., 2008, 2010; Tzounopoulos et al., 2004, 2007).

However, the local nature and millisecond timescales for association of pre- and postsynaptic spikes in STDP raise two fundamental problems in understanding its relation to behavior. First, how can neural events preceding and following the plasticity-inducing event influence the outcome of synaptic plasticity, and, secondly, how can the millisecond timescales of STDP be reconciled with the much longer delays of behaviorally relevant signals? Neuromodulation offers an attractive solution to both these problems. Neuromodulator activity is different in sleep and wake, and different in different stages of sleep and different levels of vigilance in wakefulness (Lee and Dan, 2012). Moreover, the specific release of neuromodulators occurs in a wide range of behavioral situations, including during attention and arousal (Aston-Jones and Bloom, 1981; Aston-Jones and Cohen, 2005; Chamberlain and Robbins, 2013), exposure to novelty (Wilson and Rolls, 1990), and when an unexpected reward is encountered (Schultz et al., 1993, 1997). Moreover, there is strong experimental evidence that STDP is under neuromodulatory control (Seol et al., 2007; Pawlak et al., 2010). An important reason why neuromodulation may be able to span the time scales is that modulation of STDP occurs not only during induction of plasticity, but may precede it (act prospectively) or follow the induction period (act retrospectively).

Here, we review experimental evidence on the neuromodulation of STDP, the underlying mechanisms and the possible functional and clinical relevance. We will restrict ourselves to reviewing neuromodulation of STDP and not other forms of plasticity, such as high-frequency and low-frequency stimulation-induced LTP and LTD, respectively (Bliss and Lomo, 1973; Dudek and Bear, 1992; Mulkey and Malenka, 1992), or various forms of homeostatic plasticity (Turrigiano et al., 1998). We will argue that STDP is controlled not only by the neuromodulatory state during spiking activity of pre- and postsynaptic neurons, but also by neuromodulation prior to or after the plasticity-inducing event. This places constraints on the possible underlying mechanisms. The striking versatility and state dependence of STDP rules make them particularly attractive synaptic mechanisms for learning and memory and may help explain synaptic dysfunction in neuropsychiatric, neurodevelopmental and neurodegenerative disorders (Figure 2).

## 2. Neuromodulation of STDP

Spike timing-dependent plasticity is shaped by various intrinsic and extrinsic factors including the history of activity at the synapse (Larsen et al., 2014), dendritic location (Froemke et al., 2005; Letzkus et al., 2006; Sjöström and Häusser, 2006), astrocytes (Valtcheva and Venance, 2016), activity at adjacent synapses (Harvey and Svoboda, 2007) and availability of neuromodulators (Seol et al., 2007). Although local signaling molecules, such as endocannabinoids (Sjöström et al., 2003; Bender et al., 2006; Tzounopoulos et al., 2007; Fino and Venance, 2010; Cui et al., 2015, 2016) and brain-derived neurotrophic factor (Edelmann et al., 2014, 2015; Lu et al., 2014), as well as blood-borne steroid hormones, can influence plasticity, here we focus on the neuromodulation of STDP by long-range neural projections, whose activity is associated with distinct behavioral states *in vivo* and play a pivotal role in mediating higher cognitive functions (Pawlak et al., 2010). These include the cholinergic, dopaminergic, noradrenergic, serotonergic and histaminergic systems, mediated by neurons with cell bodies located in specific subcortical nuclei and with diffuse projections to the thalamus and cerebral cortex (Gu, 2002). Several of these neurons show co-transmission with glutamate (Trudeau and El Mestikawy, 2018) or GABA (Granger et al., 2016). The computational advantages of using neuromodulation as a third, global factor in Hebbian plasticity have recently been reviewed (Frémaux and Gerstner, 2015; Pedrosa and Clopath, 2016; Foncelle et al., 2018; Gerstner et al., 2018) and will not be explicitly discussed here.

### 2.1. Prospective neuromodulation of STDP by prior neuronal activity

STDP is a powerful mechanism for computation and information processing in the brain, in part because of the variation in induction requirements for STDP at different synapses on to the same cell, between different brain regions, and over postnatal development. Experience-induced plasticity during development as well as in the adult depends not only on the patterns of afferent input, but also on modulatory signals related to the behavioral and emotional state of the animal (Bear and Singer, 1986; Kilgard and Merzenich, 1998; Gu, 2002; Conner et al., 2003; Hu et al., 2007). Both previous synaptic activity and neuromodulatory events may influence subsequent induction of plasticity. This is known as “metaplasticity” (i.e., the plasticity of synaptic plasticity; Abraham and Bear, 1996), or priming of synaptic plasticity (Seol et al., 2007). Indeed, neuromodulatory inputs can prime synapses for the induction and expression of STDP

(Seol et al., 2007; Edelmann and Lessmann, 2011; Sugisaki et al., 2011), and both cholinergic and adrenergic mechanisms have been reported to prime synaptic plasticity. The cholinergic agonist McN, acting on muscarinic acetylcholine receptors (mAChRs), was able to prime timing-dependent LTD, an effect that lasted for 30 minutes (Seol et al., 2007). The activation of nicotinic acetylcholine receptors (nAChRs) also leads to priming effects on STDP. While acute nAChRs activation in the medial prefrontal cortex (mPFC) of adolescent rats decreases the ability of layer (L)2/3 synapses to exhibit t-LTP shortly after nicotine exposure (Couey et al., 2007; Goriounova and Mansvelder, 2012), it facilitates t-LTP in adult rats that received nicotine treatment during adolescence (Goriounova and Mansvelder, 2012). Thus, nicotine's effect on the ability of cortical synapses to undergo subsequent plasticity depends on the time after exposure (Goriounova and Mansvelder, 2012). The beta-adrenergic receptor ( $\beta$ -AR) agonist isoproterenol similarly primes induction of timing-dependent LTP, an effect that lasts for at least 40-50 minutes (Seol et al., 2007). Conversely, in L2/3 of visual cortex, transient activation of  $\alpha$ - and  $\beta$ -adrenergic receptors can suppress respectively LTP and LTD for up to an hour, leading to a push-pull mechanism for modulation of STDP, in which  $\alpha$ -adrenergic receptor ( $\alpha$ -AR) activation promotes subsequent induction of t-LTD and suppresses t-LTP, while  $\beta$ -AR activation promotes t-LTP and suppresses t-LTD (Huang et al., 2012). Thus, prior neuromodulatory events may enable or disable subsequent timing-dependent plasticity with a duration that can vary from short experience-dependent modulation (Huang et al., 2012) to lasting changes that occur during development (Banerjee et al., 2009; Goriounova and Mansvelder, 2012).

## 2.2 Concurrent neuromodulation of STDP

Activation of neuromodulatory inputs at the time of presynaptic and postsynaptic spiking activity can strongly influence plasticity. Thus, both the induction requirements and the polarity of plasticity are controlled by neuromodulation.

### 2.2.1 Neuromodulatory control of the induction requirements of STDP

The cholinergic system affects the induction of STDP via activation of ionotropic nAChRs and metabotropic mAChRs. In layer (L)5 pyramidal neurons of mouse mPFC, nicotine, a cholinergic agonist acting on nAChRs, elevates the threshold for STDP induction by increasing the amount of postsynaptic activity necessary to induce plasticity. This effect is likely mediated by activation of nAChRs on GABAergic interneurons (Couey et al., 2007). Activation of muscarinic  $M_1$

receptors promotes t-LTD and suppresses t-LTP in slices from visual cortex (Seol et al., 2007) and the CA1 region of the hippocampus (Brzosko et al., 2017) and prevents the induction of postsynaptic disinhibition-mediated t-LTP (Ormond and Woodin, 2009; Takkala and Woodin, 2013). mAChRs are required for t-LTD at inhibitory GABAergic synapses (Ahumada et al., 2013). However, mAChRs have also been reported to facilitate t-LTP (Sugisaki et al., 2016) and other types of potentiation, e.g. that induced by theta burst stimulation (Buchanan et al., 2010).

In contrast, noradrenaline (NA) promotes t-LTP in the hippocampus. Activation of  $\beta_2$ -ARs widens the time window for t-LTP induction in both CA1 hippocampal neurons (Lin et al. 2003; Liu et al. 2017) and L2/3 pyramidal cells of the rodent and primate visual cortex (Seol et al. 2007; Huang et al. 2012; Huang et al. 2014) as well as cortical interneurons (Huang et al. 2013). Moreover, since endogenous NA can act on both  $\alpha$ - and  $\beta$ -ARs, with different affinities for NA, the outcome of such neuromodulation may be concentration-dependent. While a high concentration of NA has been found to enable bidirectional STDP, a low concentration leads to a depression-only state (Salgado et al. 2012).

Endogenous dopamine acting on type 1 dopamine receptors ( $D_1$ Rs) is required for t-LTP at Schaffer collateral–CA1 synapses in acute hippocampal slices from juvenile rats (Edelmann and Lessmann, 2011). Evidence from dissociated hippocampal cell cultures suggests that the effect of dopamine on t-LTP may be due to a reduction in the threshold for induction of plasticity, as activation of  $D_1$ Rs reduced the number of spike pairings needed to induce t-LTP (Zhang et al., 2009). These effects appear to be specific to dopamine as activation of  $\beta$ -ARs, although acting via the same signaling cascade as  $D_1$ Rs (cAMP/PKA), could not restore t-LTP after dopamine depletion (Edelmann and Lessmann, 2011). Dopamine also dramatically widens the time window for detecting coincident spiking in the pre- and postsynaptic cells, facilitating the induction of t-LTP. Thus,  $D_1$ R activation in both L5 of the prefrontal cortex (Ruan et al., 2014; Xu and Yao, 2010) and hippocampal cultures (Zhang et al., 2009) allows t-LTP induction at substantially longer, normally ineffective, spike-timing intervals. In the prefrontal cortex, however, this  $D_1$ R-mediated effect occurs only at pharmacologically-isolated excitatory synapses, and the cooperation between  $D_1$ -like and  $D_2$ -like receptors, acting in separate glutamatergic and inhibitory circuits, is needed to effectively broaden t-LTP window under intact inhibition (Xu and Yao, 2010). Dopamine, acting via  $D_2$ Rs, suppresses feed-forward inhibition to enable successful t-LTP induction in L5 of the prefrontal cortex (Xu and Yao, 2010). A similar mechanism was reported in the amygdala (Bissière et al., 2003). Also in the amygdala, at the

synapses between the lateral nucleus and dorsal intercalated cell mass (ITC), t-LTD requires the activation of, most likely presynaptic, D<sub>4</sub>Rs and a concomitant increase in inhibition from dorsal ITC neurons (Kwon et al., 2015).

In the striatum the effect of dopamine is independent of GABAergic transmission (Pawlak and Kerr, 2008; Shen et al., 2008). In dorsal striatum under GABA<sub>A</sub> receptor blockade, inhibiting D<sub>1</sub>Rs prevents t-LTP as well as t-LTD (Pawlak and Kerr, 2008). While blocking D<sub>2</sub>Rs hastens the onset of the potentiation (Pawlak and Kerr, 2008), D<sub>2</sub>Rs on cortical terminals are required for endocannabinoid-dependent (eCB)-t-LTP expression induced by few coincident pre- and postsynaptic spikes (~5 to 15 pairings; Xu et al., 2018). In the ventral tegmental area (VTA), endogenous dopamine acts via D<sub>1</sub>-like receptors (most likely of the D<sub>5</sub> subtype) to permit t-LTP in the dopaminergic cells (Argilli et al., 2008).

### 2.2.2 Neuromodulatory control of the polarity of STDP

Perhaps the most striking demonstration of the effect of neuromodulation on STDP is how the neuromodulatory state can change whether the same timing between the activity of the pre- and postsynaptic neurons strengthens or weakens the synaptic weights. This reversal in the sign of plasticity can be seen in dissociated hippocampal cell cultures, where application of exogenous dopamine during STDP induction leads to robust t-LTP with spike timing that would induce t-LTD in control conditions. This effect was mediated by D<sub>1</sub>Rs, but not D<sub>2</sub>Rs (Zhang et al., 2009). Similarly, in the CA1 region of murine acute hippocampal slices, endogenous dopamine, presumably released during the plasticity-inducing event, as well as exogenous dopamine applied during pairings of postsynaptic action potentials before presynaptic action potentials (post-before-pre pairing) also induced t-LTP rather than t-LTD (Brzosko et al., 2015). In the dentate gyrus, during inhibition of D<sub>1</sub>Rs, both narrow post-before-pre and pre-before-post spike-timing intervals induced t-LTD, while activation of D<sub>1</sub>Rs with the same pairing protocols induced t-LTP instead (Yang and Dani, 2014). A similar effect was observed in L5 of the prefrontal cortex, where dopamine application enabled t-LTP with spiking timing that would otherwise induce t-LTD (Ruan et al., 2014). Unlike dopamine-enabled t-LTP with a pre-before-post protocol (Xu and Yao, 2010), this dopamine-enabled t-LTP with post-before-pre pairings occurred under intact inhibitory transmission and only required D<sub>1</sub>R activation in the excitatory prefrontal circuitry (Ruan et al., 2014). In contrast, inhibition of D<sub>2</sub>Rs, but not D<sub>1</sub>Rs, during a



protocol for induction of eCB-dependent t-LTP at synapses on striatal medium-sized spiny neurons resulted in t-LTD instead (Cui et al., 2015).

Both adrenergic and cholinergic stimulation can also change the sign of STDP. Application of a  $\beta$ -AR agonist restored the classical STDP window by changing pre-before-post pairing-induced t-LTD into t-LTP in L2/3 of the prefrontal cortex (Zaitsev and Anwyl, 2012). Conversely, activation of nAChRs using nicotine during STDP induction changed t-LTP into t-LTD in L5 of prefrontal cortex (Couey et al., 2007). A similar effect occurs with activation of mAChRs in the dorsal cochlear nucleus; synaptic or pharmacological activation of postsynaptic M<sub>1</sub>/M<sub>3</sub> mAChRs changes postsynaptic Hebbian t-LTP to presynaptic anti-Hebbian t-LTD (Zhao and Tzounopoulos, 2011). Activation of mAChRs also changes pre-before-post spike pairing-induced t-LTP into t-LTD at the Schaffer collateral–CA1 synapses in mouse hippocampus (Brzosko et al., 2017). Remarkably, activation of mAChR (Adams et al., 2004; Sugisaki et al., 2011, 2016), or nAChR (Sugisaki et al., 2016), can also change t-LTD into t-LTP at the Schaffer collateral–CA1 synapses in rat hippocampus (Sugisaki et al., 2016), as in L2/3 of the rat prefrontal cortex (Zaitsev and Anwyl, 2012). Thus, cholinergic stimulation appears to be capable of bidirectional modulation of plasticity at CA3-CA1 hippocampal synapses.

Layer-specific cholinergic modulation is seen in neocortical STDP. Brief light-evoked cholinergic signals prevent t-LTP in L2/3 while facilitating t-LTP in L6 in mice (Verhoog et al., 2016). Interestingly, similar cholinergic modulation of STDP was also observed in human neocortex from surgically resected brain tissue from epilepsy patients (Verhoog et al., 2016). The bidirectional effects of cholinergic modulation on STDP depends on the concentration of agonist and the specific cholinergic receptor subtypes activated (Auerbach and Segal, 1996; Sugisaki et al., 2011; Dennis et al., 2016). Cholinergic modulation of STDP also exhibits a remarkable temporal precision (Ge and Dani, 2005; Gu and Yakel, 2011). Single pulses of the septal cholinergic input can directly induce either potentiation or depression of the Schaffer collateral–CA1 synaptic plasticity depending on the millisecond-range timing of cholinergic input relative to the Schaffer collateral input (Gu and Yakel, 2011). Thus, the precise timing of neuromodulator action can be critical for the action of neuromodulators on STDP.

### 2.3 Retrospective neuromodulation of STDP

One of the challenges to understanding learning at the cellular scale is that mechanisms for inducing changes in synaptic weights depend on spike-timing in milliseconds, while the change in synaptic weights occurs more slowly (over minutes to tens of minutes) and may need to be modified based on further information, for example behavioral outcome evaluation. Dendritic plateau potentials can extend the time window of activity between pre- and postsynaptic neurons to a few seconds (Bittner et al., 2017), but behavioral outcomes are often not available until several seconds or minutes after the initial experience. Neuromodulation provides a mechanism for making adjustments to the synaptic weights up to minutes after the STDP-inducing event (Figure 3). This may be particularly important for biological reinforcement learning (Section 4.2).

Neuromodulators acting within a delay time window of up to two seconds can affect timing-dependent plasticity, as first described in locust (Cassenaer and Laurent, 2012), and later in rats (Fisher et al., 2017) and mice (Yagishita et al., 2014; Shindou et al., 2019). In locust, at the synapses between the Kenyon cells and the  $\beta$ -lobe, delivery of a brief injection of the reinforcement signal octopamine after spike pairings alters the outcome of STDP such that the synapses invariably become weaker, even under conditions in which they would normally have grown stronger. Crucially, the action of octopamine was shown to be specific to synapses that had undergone associative changes, even though its release is diffuse and delayed relative to the conditioned stimuli (Cassenaer and Laurent, 2012). Similarly, a recent study in mouse striatal medium spiny neurons tested the effects of a physiologically-relevant phasic release of dopamine induced by the optogenetic stimulation of dopaminergic fibers from the VTA. The authors found that dopamine promotes robust spine enlargement when acting immediately after the induction of STDP (Yagishita et al., 2014).

STDP is modulated *in vivo* by physiologically-relevant, visually-evoked activation of afferent networks following a pairing protocol with a delay of 0.25 seconds in striatal neurons (Schulz et al., 2010). Similarly, sensory experience (light flash to a rat's contralateral eye) applied one second after STDP pairings, followed by electrical stimulation in substantia nigra pars compacta after a further one second, resulted in significant bidirectional corticostriatal synaptic plasticity. Pre-before-post pairings followed by conditioned light stimulus induced synaptic potentiation while post-before-pre pairings followed by the same reinforcement protocol induced synaptic depression. Conditioned light was shown to modulate STDP via dopamine ( $D_1$ ) and adenosine ( $A_{2A}$ ) receptors (Fisher et al., 2017). Phasic dopamine release at different time points before and

after the STDP protocol induced t-LTP, even up to two seconds after the cessation of presynaptic cortical and postsynaptic striatal pairing activity given a period free of glutamatergic excitation (Shindou et al., 2019). In the mPFC—another important projection area of the dopaminergic system, which is involved in detecting reward—dopamine induced synaptic potentiation within a delay on the scale of seconds following the normally ineffective pre-before-post pairing protocol at L2/3 synapses (He et al., 2015). STDP can also be retrospectively modulated by other neuromodulators. At L2/3 synapses in the visual and prefrontal cortices, the application of distinct and specific monoamine neuromodulators following normally ineffective STDP pairing protocols results in robust t-LTP or t-LTD (He et al., 2015). While noradrenaline retrospectively enables the pre-before-post-conditioned pathway to express t-LTP, serotonin enables the post-before-pre-conditioned pathway to express t-LTD with otherwise ineffective pairing protocols (He et al., 2015).

The timing rules for modulation vary depending on neuromodulator, brain region and species. The narrow temporal detection window of up to 2 seconds (Yagishita et al., 2014; Fisher et al., 2017) cannot account for behavioral studies of response acquisition with an extended reinforcement delay of 1-40 seconds in rats and pigeons (Lattal and Gleeson, 1990; Sutphin et al., 1998), rhesus monkeys (Galuska and Woods, 2005) and humans (Okouchi, 2009). Longer delays, in the order of minutes, however, were effective for dopamine in the hippocampus. It was demonstrated that dopamine can retroactively modulate STDP with an extended delay of at least one minute (Brzosko et al., 2015). In the CA1 of acute hippocampal slices, activation of DARs after the pairing protocol converted both conventional t-LTD (post-before-pre pairing; (Brzosko et al., 2015) and acetylcholine-facilitated LTD (pre-before-post pairing protocol; (Brzosko et al., 2017) into synaptic potentiation. This conversion of t-LTD into t-LTP was dependent on afferent synaptic activity, suggesting that the conversion can occur only at synapses that are reactivated following the initial pairing event (Brzosko et al., 2015).

Almost everything we know about neuromodulation of STDP originates from *in vitro* and *ex vivo* experiments. What will be important in the future is to investigate in what neuromodulatory state synapses are in the intact brain during different behavioral states. This is now possible due to the development of new techniques, in particular optogenetics, which enables cell type-specific activation of afferent input to individual cells *in vivo* (González-Rueda et al., 2018).

### **3. Mechanisms of neuromodulation**

Multiple mechanisms contribute to the control of STDP by neuromodulation. First, at the network level, neuromodulation alters the excitability and spiking dynamics of neural circuits, thus determining whether the pre- and postsynaptic spiking requirements for inducing STDP are met or not. Secondly, at the synaptic level, neuromodulation gates the synaptic activation of glutamate receptors, including NMDA receptors, which are crucial for both timing-dependent potentiation and depression. Thirdly, at the intracellular signaling level, neuromodulation directly activates, inhibits or regulates intracellular signaling cascades involved in synaptic plasticity (Figure 3).

### 3.1. Excitability and spiking dynamics

Neuromodulation controls the network states of thalamocortical and hippocampal networks. Neuromodulation is involved both in setting a global network state, such as regulating sleep and wakefulness, and in controlling local circuit activity, such as during selective attention. Acetylcholine, for example, is important for shifting network dynamics from sharp wave-ripples to theta-gamma oscillations in the hippocampus and from slow oscillations to desynchronized states in the neocortex (Alger et al., 2014). Some effects on cortical networks are mediated indirectly through changes in thalamic networks, which are also strongly influenced by neuromodulators and show dramatically different activity during sleep and awake states (McCormick, 1992). The mechanisms of neuromodulation involve both changes in intrinsic membrane properties of individual cells and changes in synaptic transmission (Lee and Dan, 2012; Nadim and Bucher, 2014). In general, both acetylcholine and monoamines increase the excitability of principal neurons by modulating various ion channels, particularly through changing the phosphorylation state of potassium channels or associated proteins (Nicoll, 1988; Storm, 1990). They also alter excitability in GABAergic interneurons, which may control action potential timing in principal cells (Cobb et al., 1995), and shift the excitability of different subclasses of interneurons (Bacci et al., 2005), thus changing the balance between somatic and dendritic targeting interneurons. Dendritic inhibition is important for controlling the extent of dendritic backpropagation of action potentials (Meredith et al., 2003) and was recently shown to control branch-specific dendritic responses during development (Yaeger et al., 2019).

### 3.2. Synaptic gating of plasticity

NMDA receptors are crucial for both t-LTD and t-LTP (Shipton and Paulsen, 2014). Modulation of NMDA receptors can therefore gate plasticity at individual synapses. The activation of NMDA receptors requires synaptically released glutamate and membrane depolarization to relieve the NMDA receptor channel of its voltage-dependent  $Mg^{2+}$  block (Bliss and Collingridge, 1993). Thus, both presynaptic release probability and membrane excitability can modulate the activation of NMDA receptors during pre- and postsynaptic spiking. In addition, NMDA receptor activation requires binding of a co-agonist, either glycine or D-serine. Although the co-agonist site of the NMDA receptor was initially assumed to be saturated *in vivo*, there is now strong evidence it is not, and this opens the possibility for an interesting neuromodulatory gating mechanism of plasticity (Johnson and Ascher, 1987; Schell et al., 1995; Henneberger et al., 2010).

Astrocytes may mediate some of the gating functions of neuromodulation. In addition to the pre- and postsynaptic neuronal elements, astrocytes are an integral part of the 'tripartite synapse' (Araque et al., 1999) and appear to be important for both t-LTP (Yang et al., 2003) and t-LTD (Min and Nevian, 2012). They are therefore in a prime position to mediate neuromodulation of STDP. However, although  $Ca^{2+}$  signaling in astrocytes is required for several forms of LTP and LTD (Henneberger et al., 2010; Min and Nevian, 2012), the mechanism of astrocytic regulation of STDP is not clear. They have been suggested to supply glutamate for mGluR-dependent presynaptic potentiation in the hippocampus (Perea and Araque, 2007) and NMDA receptor-dependent presynaptic depression in the neocortex (Min and Nevian, 2012). They have also been suggested to supply the co-agonist at NMDA receptors during hippocampal LTP (Yang et al., 2003; Henneberger et al., 2010) and t-LTD (Andrade-Talavera et al., 2016); however, the identity and source of this co-agonist remain controversial, and might be different between synaptic and extrasynaptic receptors (Papouin et al., 2012), different at different synapses (Le Bail et al., 2015) and vary with NMDA receptor subunit composition (Papouin et al., 2012; Le Bail et al., 2015) and synaptic activity level (Li et al., 2013). In particular, it is currently unclear whether D-serine originates from neurons and/or glia (Wolosker et al., 2016; Mothet et al., 2019). Nevertheless, irrespective of the origin of the co-agonist, there is good evidence that long-range neuromodulators mediate some of their effects through local astroglia, for example, acetylcholine requires astroglial  $\alpha 7$  nicotinic receptors for controlling synaptic D-serine levels (Papouin et al., 2017). In addition to this external modulation of NMDA receptor activity, the NMDA receptor itself is also subject to direct neuromodulation by phosphorylation (Chen and Roche, 2007).

### 3.3. Intracellular signaling pathways

Whereas priming and concurrent neuromodulation of STDP could be explained by changes in spike patterns and synaptic gating, retrospective effects are more likely to involve modulation of the intracellular signaling pathways that mediate plasticity. There is strong evidence that synaptic potentiation is mediated by postsynaptic  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase II (CaMKII), and at least some forms of LTD rely on a signaling pathway in which the  $\text{Ca}^{2+}$ /calmodulin-dependent phosphatase calcineurin dephosphorylates and inactivates inhibitor-1, which in turn increases protein phosphatase 1 activity (Mulkey et al., 1994). This establishes a push-pull mechanism of kinase-phosphatase activity which ultimately controls the trafficking of postsynaptic AMPA receptors (Diering and Huganir, 2018). However, presynaptic forms of t-LTD have also been reported (Bouvier et al., 2018). A key insight from the specific receptor subtypes involved in neuromodulation of STDP reviewed in Section 2 is that neuromodulators affect STDP induction and expression by acting on distinct signaling cascades involved in synaptic potentiation and depression (PKA pathway activated by stimulation of Gs-coupled receptors including  $\text{D}_1\text{Rs}$  and  $\beta\text{-ARs}$ , and PLC pathway activated by stimulation of Gq-coupled receptors including mAChRs and  $\alpha 1\text{-ARs}$ ). A still unresolved question is whether both potentiation and depression occur at the same synapses or at distinct ones. A detailed discussion of signaling pathways involved in neuromodulation of LTP and LTD is beyond the scope of this review, but a simple model to explain retrospective modulation of STDP is illustrated in Figure 4A.

## 4. Functional implications

The release of neuromodulators occurs in a wide range of behavioral situations. Hence, the neuromodulatory influence on STDP can be associated with an equally extensive range of behavioral processes, including attention (Couey et al., 2007; Sugisaki et al., 2011; Sabec et al., 2018), reward-based learning (Pawlak and Kerr, 2008; Zhang et al., 2009; Hamilton et al., 2010; Xu and Yao, 2010; Ruan et al., 2014; Yang and Dani, 2014; Brzosko et al., 2015), fear-conditioning (Bissière et al., 2003), as well as pathological states (Shen et al., 2008), such as addictive behaviors (Argilli et al., 2008). Despite the conceptual attractiveness of a link between behaviorally-relevant neuromodulatory inputs and the cellular process of STDP, there is a

scarcity of experimental data directly testing the relationship between neuromodulated-STDP and behavior. Here we briefly discuss some examples of how neuromodulation of STDP may relate to specific cognitive processes.

#### 4.1. Attention

Attention can refer to level of alertness, or vigilance, as well as the ability to focus on a particular stimulus or task, termed selective attention (Lee and Dan, 2012). Acetylcholine is essential for both vigilance and selective attention, and the release of acetylcholine is dynamically modulated to improve performance on tasks requiring sustained attention (Hasselmo, 2006; Wallace and Bertrand, 2013). One of the key features of selective attention is the ability to filter stimuli based on their relevance (Kirszenblat and van Swinderen, 2015). While behaviorally we associate improved performance due to selective attention with increased sensitivity to salient stimuli, this is achieved at the circuit-level by suppressing activity from non-relevant stimuli (Kirszenblat and van Swinderen, 2015). This suppression of response to irrelevant stimuli can occur through modulating neuronal firing rates in target areas (Herrero et al., 2008) and decreasing the correlation of firing from non-salient stimuli (Kirszenblat and van Swinderen, 2015; Lee and Dan, 2012).

Early studies of cholinergic modulation of hippocampal LTP using frequency-based induction protocols suggested that acetylcholine may improve performance by facilitating LTP (Boddeke et al., 1992; Huerta and Lisman, 1995; Ovsepian et al., 2004; Shinoe et al., 2005; Buchanan et al., 2010; Connor et al., 2012; Digby et al., 2012; Dennis et al., 2016). However, STDP studies (reviewed in Section 2) revealed that activation of cholinergic receptors may instead play a role in suppressing the response to non-relevant stimuli, critical for selective attention. Acetylcholine biases neocortical and hippocampal STDP towards t-LTD (Seol et al., 2007; Brzosko et al., 2015); thus, providing a mechanism for enhancing the signal-to-noise ratio in cortical information processing and improving task-specific performance (Couey et al., 2007).

The prospective and concurrent effects of cholinergic modulation on STDP may be particularly relevant for understanding how selective attention improves performance on memory tasks. Firstly, the pattern of acetylcholine release is finely tuned to specific aspects of learning and memory. Tonic levels of acetylcholine, coordinated between the prefrontal cortex and hippocampus, are maximal during training on a rewarded working memory task, while phasic acetylcholine release occurs only during retrieval and is localized to reward delivery areas

without being contingent on trial outcome (Teles-Grilo Ruivo et al., 2017). Secondly, the polarity of acetylcholine-modulated plasticity can also depend on the concentration and specific cholinergic receptor subtype activated (Müller et al., 1988; Auerbach and Segal, 1996; Dennis et al., 2016). Distinct functions of nAChR subtypes, for example, allow bidirectional modulation of STDP at hippocampal-prefrontal synapses during different stages of long-term associative recognition memory tasks. Activation of  $\alpha 7$  nAChRs, which gate t-LTP, is required for encoding of associative recognition memory, while activation of  $\alpha 4\beta 2$  nAChRs, which gate t-LTD, is critical for memory retrieval (Sabec et al., 2018). Thirdly, the synaptic depression bias induced by acetylcholine can also be modulated retroactively. Subsequent application of dopamine after acetylcholine-induced t-LTD can retroactively convert synaptic depression into potentiation (Brzosko et al., 2017). This sequential neuromodulation of STDP may yield flexible learning, surpassing the performance of other reward-modulated plasticity rules (Zannone et al., 2018).

Noradrenergic neurons from locus coeruleus also play a key role in vigilance, attention and emotional arousal, with low firing rates during drowsiness and slow-wave sleep, regular firing at quiet wakefulness, and burst-firing in response to arousing stimuli (Aston-Jones and Bloom, 1981). Hence, the finding that adrenergic signaling biases STDP towards t-LTP (Seol et al., 2007) and increases dendritic excitability to facilitate t-LTP induction (Liu et al., 2017) may provide an additional mechanism for how arousal facilitates learning.

Neuromodulation of STDP also provides a paradigm for future studies of cellular and circuit mechanisms underlying improved performance with attention. In particular, further *in vivo* STDP studies are needed in rodent models to examine the state-dependent cholinergic and adrenergic modulation of t-LTP and t-LTD. Using head-fixed rodents within virtual reality environments, it may also be possible to directly test the possible role of attention in neuromodulation of STDP for task performance.

#### 4.2. Reinforcement learning

By connecting the different time scales of the induction of plasticity (milliseconds) and behavioral outcomes (seconds or longer), studies of neuromodulation of STDP may also yield new insights into the cellular basis of learning, in particular biological reinforcement learning, which depends on the activity of reward-linked neuromodulators, in particular dopamine (Schultz et al., 1997; Suri and Schultz, 1999; Pan et al., 2005). One of the key outstanding questions—at the cellular level—is how neural networks, despite the temporal gap, identify which past network



activities led to reward and which are irrelevant. This problem is referred to as the *distal reward problem* (Hull, 1943; Izhikevich, 2007) or *credit assignment problem* as it is known in machine learning literature (Minsky, 1963; Sutton and Barto, 1998). Reinforcement learning theory postulates the existence of a slowly decaying eligibility trace (Klopf, 1982) marking the memory parameters associated with an event or episode as eligible to undergo learning changes (Sutton and Barto, 1998). Neuromodulators including dopamine may then act on this eligibility trace produced by the spiking activity. Most studies on the effect of dopamine on STDP manipulated dopamine during the entire experiment (Pawlak and Kerr, 2008; Shen et al., 2008) or during the induction of STDP (Zhang et al., 2009), and did not investigate the effect of dopaminergic modulation on pre-existing synaptic plasticity. The finding that dopamine can retroactively convert depression to potentiation in the hippocampus provides evidence for dopamine as a positive reinforcement signal (Brzosko et al., 2015). Additionally, the effects on STDP of neuromodulators other than dopamine (e.g., noradrenaline and serotonin) suggest the existence of distinct eligibility traces for LTP and LTD in the cerebellum (Wang et al., 2000; Sarkisov and Wang, 2008) and cortex (He et al., 2015). The difference observed in the maximum time delay between the STDP induction protocol and the application of the neuromodulators for modulation to occur (5 seconds for t-LTP and 10 seconds for t-LTD) may impact the temporal dynamics and play a role in generating stable learning (He et al., 2015).

The activity dependence of the retroactive modulation of STDP is interesting in terms of credit assignment to the relevant synapses. In this scenario, it is not enough for the synapse to have been active during the behavioral episode, but the synaptic weights are updated only if the neurons are reactivated following the event (Brzosko et al., 2015). Interestingly, the reward signal dopamine does not only update the synaptic weights following reactivation of the synapse, but it also increases the frequency of reactivation events themselves, making them an interesting biological solution to the credit assignment problem. In the hippocampus, the signature of a reactivation event is the sharp-wave ripple, during which event-related spike sequences are replayed in forward or reverse order (O'Neill et al., 2010; Foster, 2017). Both reward itself (Singer and Frank, 2009), and optogenetic activation of dopaminergic neurons in the VTA (McNamara et al., 2014), which project to the hippocampus, increase reactivation events. Interestingly, reward appears to selectively increase reverse order replay events (Ambrose et al., 2016), thus specifically potentiating those synapses that have undergone t-LTD during previous behavior. In this way, the combination of dopamine and reactivation may strengthen a trace of multiple synapses in a network if a reward is encountered, possibly

converting a repeller network induced by cholinergic depression, which would favor exploration, into an attractor induced by dopaminergic potentiation, which would favor exploitation (Figure 4B). A next step could be to investigate whether retrospective modulation of STDP can alter the synaptic efficacy based on behavioral outcome *in vivo*. It would be interesting to test whether the combination of reactivation and dopamine release could switch the polarity of synaptic plasticity only at synapses relevant to the previous few minutes of experience.

#### 4.3. Memory consolidation

Sleep is critical for memory consolidation (Kandel, 2014; Dudai et al., 2015); however, the precise mechanisms remain unknown. Consolidation can be considered at the synaptic and systems levels, and there is debate as to what plasticity rules underlie memory consolidation in the sleeping brain (Timofeev and Chauvette, 2017; Tononi and Cirelli, 2019). Sleep is under neuromodulatory control and is classified into different stages. During slow-wave sleep (SWS) the levels of ACh and monoamines are low, whereas rapid eye movement (REM) sleep is characterized by an increased level of ACh, which may explain the characteristic brain rhythms seen in different sleep stages (Krishnan et al., 2016). Neural reactivations, assumed to be important for memory consolidation during sleep, are seen primarily during SWS (Kudrimoti et al., 1999; Dudai et al., 2015). Since the neuromodulatory state is different in sleep and during wake, and different in different stages of sleep, one may expect the rules of synaptic plasticity to differ as well. Unfortunately, there are very few studies on STDP during sleep. SWS has been suggested to be associated with enhanced synaptic potentiation (Timofeev and Chauvette, 2017). On the other hand, a seminal study found evidence for net synaptic potentiation in wake, whereas synaptic strength, on average, appears to decrease during sleep in the cortex and hippocampus *in vivo* (Vyazovskiy et al., 2008). Whereas the wake potentiation has generally been attributed to Hebbian plasticity, the sleep-related synaptic depression could be due to global, homeostatic downscaling (Turrigiano et al., 1998), or specific activity-dependent synaptic depression, as recently reviewed (Tononi and Cirelli, 2019). A recent study in urethane-anesthetized mice revealed that cortical plasticity rules during slow-wave-sleep-like activity vary based on whether the pre- and postsynaptic activity occurs during Up-states or Down-states. Whereas conventional STDP was seen during Down-states, Up-states were biased toward depression such that presynaptic stimulation alone led to synaptic depression, while connections contributing to postsynaptic spiking were protected against this synaptic weakening (González-Rueda et al., 2018). Alternatively, the latter result has been considered as a potential

mechanism for anesthesia-induced amnesia, and not sleep-related plasticity (Timofeev and Chauvette, 2018). However, recent *in vitro* recordings in entorhinal cortex slices, without the addition of drugs, also showed weakening of subthreshold synaptic inputs during Up-states (Bartram et al., 2017). In the latter study, pairing synaptic input with postsynaptic spike bursts during Up-states induced synaptic potentiation, suggesting that postsynaptic bursting activity may have special significance for synaptic potentiation (Lisman, 1997; Pike et al., 1999), and supporting the idea that both potentiation and depression may occur during SWS. The activity-dependent and input-specific downscaling mechanism discussed here offers two important computational advantages over global downscaling: improved signal-to-noise ratio and preservation of previously stored information (González-Rueda et al., 2018). A similar role was recently suggested for hippocampal sharp-wave ripples in downscaling of synaptic weights during SWS (Norimoto et al., 2018). This down-regulation of synaptic weights was input-specific and NMDA receptor-dependent, as in the neocortex, and could serve as a mechanism for refining memories and reducing responses to irrelevant activity (Norimoto et al., 2018). An important next step will be to investigate the plasticity rules and effects of neuromodulation during natural sleep *in vivo*.

## **5. Neuromodulation of STDP in disease models**

Neuromodulation and STDP are two cellular mechanisms that enable adaptation to our environment; however, there is growing evidence that these mechanisms may also play an important role in the pathogenesis of brain disorders, as well as provide novel pharmacologic targets for developing new therapies (Figure 2). Alterations in the conditions for LTP and LTD have been identified in animal models of multiple neurologic and psychiatric disorders; however, most studies have used non-physiological stimuli for inducing plasticity such as high- or low-frequency or theta-burst stimulation protocols. Thus, further studies using STDP protocols may reveal how neuromodulation of STDP before, during and after the plasticity-inducing event is altered in these disorders and provide insight into how synaptic deficits lead to the cognitive dysfunction. One of the main challenges in studying STDP in neurologic and psychiatric disorders is the availability of animal models that share a common pathogenesis with the human disorder. This is particularly true for common psychiatric disorders including depression, schizophrenia, and obsessive-compulsive disorder, in which neither the genes nor the underlying neurobiology are known. There is growing evidence of deficits in STDP, however, from monogenic disorders of neurodevelopment and familial forms of neurodegenerative

diseases, in which mouse models have been made with the human disease mutation that replicate many of the anatomical and behavioral features of the disorders. This section will review possible roles for altered neuromodulation of STDP in the pathology of neurologic and psychiatric disorders and the potential to use neuromodulation as therapeutic target for neuropsychiatric disorders. It should be noted that neuromodulation is often used with a different meaning in clinical neuroscience, namely the alteration of neural activity through delivery of electromagnetic or chemical stimulation with a therapeutic aim. Here we discuss the involvement of physiological neuromodulation through long-range neural projections.

## 5.1. Addiction and Obsessive-Compulsive Disorder (OCD)

### 5.1.1. Role for disruption of neuromodulation of STDP in addiction

Drugs of abuse increase dopamine in the VTA, and its projections, leading to lasting changes in synaptic transmission (Lüscher and Malenka, 2011). Based on the studies of dopaminergic modulation of STDP, stimulants such as cocaine, which inhibits the reuptake of dopamine, would be predicted to lead to a pathological over-strengthening of synaptic connections by “hijacking” the adaptive mechanisms for experience-dependent plasticity. Thus, mechanisms of cocaine addiction may directly involve alteration of the requirements for STDP. In the VTA, activation of D<sub>5</sub>R is required for t-LTP (Argilli et al., 2008); thus, higher dopamine levels may increase the likelihood of potentiating inputs. Likewise in prefrontal cortex, activation of D<sub>1</sub>R increases the time window for t-LTP (Xu and Yao, 2010). Thus, pathological dopaminergic stimulation would be predicted to allow t-LTP at normally ineffective spike-timing intervals. Increased dopamine in drug abuse would also be predicted to impair t-LTD, as blocking D<sub>2</sub>R is necessary in the striatum (Shen et al., 2008). Further understanding of the net effect of dopamine on different circuits is needed to fully understand of the relationship of cocaine use and possible pathological neuromodulation of STDP, however, due to variation in the region-, layer-, and cell-type-specific effects of dopamine on STDP.

There is growing evidence for neuromodulation of STDP in the pathogenesis of drug addiction from rodent models. A single injection of cocaine potentiates dopaminergic cells in the VTA, occluding t-LTP in rats (Ho et al., 2012) suggesting that cocaine is acting through neuromodulation to promote t-LTP. Chronic, intermittent exposure extends the time window for t-LTP induction in L5 of the prefrontal cortex (Ruan and Yao, 2017) and D<sub>1</sub>R-expressing medial

spiny neurons of the nucleus accumbens, consistent with our prediction, while inhibiting t-LTP induction in D<sub>2</sub>R-expressing medial spiny neurons (Ji et al., 2017). These effects of cocaine on STDP likely act not only through direct modulation of the induction by altering the behavioral state, but also as a form of metaplasticity, as prior exposure to cocaine use has lasting effects on the regulation of synaptic plasticity in rodent models (Lee and Dong, 2011). Interestingly, this hijacking of normal STDP mechanisms by cocaine may also act through factors necessary for the maintenance of STDP. Cocaine facilitation of t-LTP requires a brain specific isoform of protein kinase C—protein kinase M $\zeta$  (PKM $\zeta$ )—which is critical for LTP maintenance (Ho et al., 2012). Administration of PKM $\zeta$  inhibitor, myristoylated zeta inhibitory peptide (ZIP), restores t-LTP in cocaine-treated rats (with no effect on t-LTP in saline-treated rats) suggesting that cocaine may upregulate PKM $\zeta$  synthesis after induction leading to a pathological maintenance of cocaine-induced potentiation (Ho et al., 2012). Thus, the alteration in STDP rules may shift the balance of excitation and inhibition in these circuits contributing to the persistence of addictive behaviors.

In contrast to the effects of cocaine, acute exposure to ethanol (5 mM to 50 mM) inhibited the induction of t-LTP at synapses onto medium spiny neurons in the nucleus accumbens in a concentration-dependent manner with no effect on t-LTD until a small increase was observed at higher concentrations (Ji et al., 2015). The loss of t-LTP may be due to an ethanol-induced enhancement of the large conductance calcium- and voltage-gated potassium (BK) channels on the medial spinal neurons (Ji et al., 2015). Chronic intermittent exposure to ethanol that induced dependency in mice, however, enhanced t-LTP in layer 5 pyramidal cells in orbitofrontal cortex, likely through the concomitant increase in the ratio of AMPA to NMDA receptors and the expression of GluA1/2-containing AMPA receptors (Nimitvilai et al., 2016). This highlights potential roles for STDP in both the acute depressive effects of ethanol as well as the addictive potential from repeated use.

#### 5.1.2. Neuromodulation of STDP as a potential therapeutic target in addiction

Maladaptive dopaminergic function is likely not only a key contributor to addictive behaviors, but may also provide an effective therapeutic target. A decrease in phasic release of striatal dopamine observed in rats that self-administered cocaine could be rescued with the indirect dopamine receptor agonist levodopa (L-DOPA; Willuhn et al., 2014). Treatment with L-DOPA increased dopamine release in the medial prefrontal cortex and decreased cocaine self-

administration in the rats (Antinori et al., 2018). Future therapeutics may also target cholinergic modulation to dampen the cocaine's potentiating effect on synaptic plasticity. Activation of nAChR in the prefrontal cortex increases the threshold for STDP in rodent models (Couey et al., 2007). Further studies will be necessary to identify the specific receptor subtypes and regions to target as drugs with broad cholinergic effects would likely also activate mAChRs, which has mixed effects on STDP (see Section 2). Serotonergic modulation may also hold potential as a future therapeutic, as activation of 5-HT<sub>4</sub> receptors promotes t-LTD in striatal neurons (Cavaccini et al., 2018) and activation of 5-HT<sub>1A</sub> receptors can reduce dopamine release and synthesis (Renard et al., 2017). Key to new therapeutics will be to identify drugs with receptor subunit specificity. For example, the anxiolytic drug cannabidiol, unlike delta-9-tetrahydrocannabinol (THC), has no known psychoactive or dependence-producing side effects and is thought to reduce the effects of dopaminergic modulation via 5-HT<sub>1A</sub> receptors (Renard et al., 2017).

### 5.1.3. Role for neuromodulation of STDP in OCD pathogenesis and treatment?

Obsessive-compulsive disorder is characterized by distressing repetitive thoughts, urges, or impulses and repetitive behaviors (or thoughts) that occur in response to the obsessions to reduce the distress (Hirschtritt et al., 2017; Richter and Ramos, 2018). Dysfunction of frontostriatal and frontotemporal circuits has been implicated, which is supported by the prevalence of OCD-like behaviors in neurodegenerative diseases including frontotemporal dementia, Huntington's disease and Parkinson's disease (Richter and Ramos, 2018). Drug-induced OCD-like behaviors are often seen with dopaminergic drugs suggesting both a role for dopaminergic modulation in the pathogenesis and as a potential therapeutic target. Activating or blocking dopaminergic receptor subtypes show different effects on STDP in these brain regions; thus, maladaptive neuromodulation of STDP and other factors affecting the balance of excitation and inhibition in these circuits may contribute to the symptoms. In particular, activation of D<sub>1</sub>Rs in the prefrontal cortex increases the time window for t-LTP, which could contribute to the pathological reinforcement of the intrusive thoughts and repetitive behaviors in these frontostriatal circuits.

Serotonergic dysfunction may also play a role. Serotonin gene variants have been the target of genetic studies in families with OCD (Sinopoli et al., 2017), and the first-line medications for OCD are selective serotonin reuptake inhibitors (SSRIs; Hirschtritt et al., 2017; Richter and

Ramos, 2018). STDP at thalamocortical synapses is regulated by serotonergic tone; for example, t-LTD requires decreased activation of 5-HT<sub>4</sub> receptors (Cavaccini et al., 2018). Serotonergic modulation of STDP may also act indirectly through its regulatory effects on other neuromodulatory systems and specific inhibitory cell-types within cortical circuits. There is also evidence from other SSRIs tested on frequency-based synaptic plasticity. Vortioxetine, which acts on multiple serotonin receptor subtypes enhances frequency-based LTP at hippocampal CA1 synapses (Dale et al., 2014). Chronic treatment with fluoxetine impaired both frequency-based LTP and LTD in CA1 from Schaffer collateral, but not perforant path, stimulation in the hippocampus (Rubio et al., 2013).

Atypical antipsychotics, many of which have mixed effects on dopamine receptors, are also used as adjunct therapy with SSRIs for OCD; however, the efficacy has not been supported in randomized-control trials (Hirschtritt et al., 2017; Richter and Ramos, 2018). Surgical approaches to OCD treatment have included ablation of the anterior cingulate cortex and/or internal capsule and, more recently, deep brain stimulation in the anterior limb of the internal capsule, nucleus accumbens, thalamus, or sub-thalamic nucleus (Hirschtritt et al., 2017). It is important to note that while clinically these surgical (and non-surgical approaches including transcranial magnetic stimulation) are often referred to as “neuromodulation” therapies, their mechanisms are unknown and may or may not affect the neuromodulatory tone in the relevant brain regions.

## 5.2. Neurodevelopmental disorders

### 5.2.1. Role for disruption of neuromodulation of STDP in neurodevelopmental disorders

Autism spectrum disorders (ASD) are characterized by childhood-onset, lifelong difficulties with social interaction, communication and sensory perception (Brugha et al., 2016). There is growing evidence that widespread disruption of synaptic function during early postnatal development may underlie the core deficits in autism (Meredith et al., 2012; Johnson et al., 2015). Many of the genes identified in ASD and related monogenic neurodevelopmental disorders affect synaptic proteins (Peça et al., 2011; Pinto et al., 2014). Developmental changes at the synapse, primarily in the receptor composition, and in the local circuit, through changes in inhibition, alter the conditions for the induction of synaptic plasticity in the cortex and hippocampus. Alteration of NMDA receptor expression and maturation in multiple mouse

models of autism and related disorders would predict perturbations of STDP rules, as NMDA receptors are critical for many forms of STDP throughout the brain (Shipton and Paulsen, 2014). Moreover, excitatory and inhibitory cell-types may have different STDP rules even in the same area of cortex (Huang et al., 2013). Thus, any alteration in STDP time windows, for example, may contribute to the imbalance of excitation and inhibition during early postnatal development (Gogolla et al., 2009). Disruption of neuromodulatory circuits has also been identified in multiple developmental disorders, including Rett syndrome. Rett syndrome is a severe neurodevelopmental disorder caused by loss-of-function mutations in *MECP2*, which codes for MeCP2, a chromatin remodeler (Chao et al., 2007; Cohen et al., 2011). Selective deletion of *Mecp2* in different neuromodulatory cell-types (dopaminergic, noradrenergic, or serotonergic) in mice reproduced different aspects of the clinical phenotype (Samaco et al., 2009). Thus loss of *Mecp2* would predict disruption of synapse- and region-specific rules for STDP, which may contribute to the cognitive decline. For example, loss or impairment of dopaminergic modulation in the cortex would predict a loss of flexibility in the refinement of STDP rules over development and may favor facilitation- or depression-only states.

Although there are limited studies of STDP in models of neurodevelopmental disorders, evidence for deficits in STDP has been identified in monogenic mouse models, including Fragile X syndrome (Meredith and Mansvelder, 2010). Loss of t-LTP occurs at L4/5-to-L5 synapses in primary somatosensory cortex (Desai et al., 2006), L2/3-to-L2/3 synapses in prefrontal cortex (Meredith et al., 2007), and medium spiny neuron synapses in the nucleus accumbens (Neuhofer et al., 2015). t-LTP is decreased in stratum-radiatum CA1 synapses in cultured hippocampal slices (Hu et al., 2008). The loss of t-LTP at multiple synapses in the *Fmr1* knock-out (KO) mice is likely due to an increase in the threshold for induction (Meredith et al., 2007) through impairments in AMPA receptor trafficking (Hu et al., 2008), altered spine morphology leading to a decrease in synaptic AMPA receptor expression (Meredith and Mansvelder, 2010), and, in the nucleus accumbens, a decrease in synaptic NMDA receptors (Neuhofer et al., 2015). Interestingly, t-LTD is preserved in the somatosensory cortex (Desai et al., 2006) and prefrontal cortex of *Fmr1*-KO mice (Meredith et al., 2007); moreover, mGluR5-mediated LTD is actually enhanced in mouse models of both Fragile X and Angelman syndromes (Meredith and Mansvelder, 2010). Thus, disrupted regulation of STDP may contribute to the excitatory-inhibitory imbalance underlying the cognitive dysfunction.



There is strong evidence that the balance of excitation and inhibition is altered by loss of *Mecp2*. NMDA receptor subunit composition is altered in homogenates of hippocampus (Asaka et al., 2006) and visual cortex (Durand et al., 2012). Importantly cell-type specific effects on the maturation of excitatory synaptic transmission in excitatory and inhibitory neurons (Mierau et al., 2016) may also affect the induction of STDP. The developmental delay of GluN2B to GluN2A subunit switch in pyramidal cells and the acceleration of the switch in parvalbumin-positive interneurons would predict deficits in NMDA receptor-dependent forms of STDP at the L4-to-L2/3 visual cortical synapses (Mierau et al., 2016). These deficits would be predicted to arise not only from the altered maturation of inhibition, but also from the NMDA receptor subunit composition, which affects the permissibility of STDP (Shipton and Paulsen, 2014). Although, notably, the only available study of STDP in *Mecp2*-deficient mice to date did not show any impairment of t-LTP at layer-5-to-layer-5 synapses in pyramidal cells in primary somatosensory cortex (Dani and Nelson, 2009), further studies of STDP in other cell-types, cortical layers and brain regions may reveal significant deficits in STDP that may be modulated in a receptor subtype- and region-specific manner.

#### 5.2.2. Neuromodulation of STDP as a therapeutic target for neuropsychiatric disorders

Multiple mouse studies illustrate neuromodulation as a potential target to reverse the deficits observed in synaptic plasticity. In the *Fmr1*-KO mice, co-activation of serotonin (5-HT<sub>2B</sub>) and dopamine (D<sub>1</sub>) receptors restored frequency-based LTP in cultured slices from CA1 hippocampus (Lim et al., 2014). Based on these findings, pharmaceutical trials in Fragile X syndrome for the first disease-modifying therapy in a cognitive disorder are underway. In addition, activation of a different group of serotonin receptors (5-HT<sub>7</sub>R) with a novel agonist (LP-211) was able to reverse the abnormal enhancement of mGluR-LTD in CA1 hippocampal pyramidal neurons from the *Fmr1*-KO mice (Costa et al., 2012). Of note, increasing 5-HT<sub>7</sub> receptor activity may also be beneficial in Rett syndrome; LP-211 injections improved performance on several behavioral tests in *Mecp2*-deficient mice, although effects on synaptic plasticity have yet to be assessed (De Filippis et al., 2014). Modulating serotonergic release in the nucleus accumbens has also shown promise for ameliorating social deficits in the 16p11.2 autism mouse model (Walsh et al., 2018). Further studies of neuromodulation of STDP in ASD mouse are warranted to reveal a more detailed, synapse-specific mechanistic picture of how STDP is differentially disrupted in these disorders and may be targeted with novel synapse- or cell-type specific therapeutics.

### 5.2.3. Can neural circuits be modulated retrospectively?

Targeting defects in synaptic plasticity identified in genetic mouse models offers a strategy for developing new therapies for neurologic and psychiatric disorders. However, given the developmental constraints on synaptic plasticity rules, a key question is whether these synaptic defects can be corrected retrospectively. For neurodevelopmental disorders, in particular, many of the synaptic deficits occur early in postnatal development either before or during critical periods in sensory development. Thus, treatments targeting synaptic plasticity deficits would either require introduction before the onset of symptoms, or reopening of critical periods in early development in adulthood.

Critical periods for induction of specific types of STDP have been identified in animal models. In humans, critical periods exist in early postnatal life in which sensory experience is required for the normal development of skills including vision, hearing, and language. The visual cortex requires input from both eyes during early life in order to acquire binocular vision. Misalignment of eyes, if not corrected prior to 8 years-of-age, will prevent the development of depth perception and impair visual acuity in the amblyopic eye. Until recently, this deficit was thought to be permanent; however, new studies suggest that it may be possible to re-open critical periods in adulthood (Gervain et al., 2013).

Neuromodulation of synaptic plasticity may be key to correcting developmental deficits. Increased cholinergic transmission may re-open critical period plasticity in adult visual cortex. Loss of input from one eye—such as in monocular deprivation—shifts the response of neurons in the contralateral visual cortex to the ipsilateral eye in young animals but disappears by adulthood. Remarkably, this form of plasticity could be induced in adult mice through the deletion of *Lynx-1*, a molecular brake on critical period plasticity, which works through increased nicotinic cholinergic transmission (Morishita et al., 2010). Human trials are now underway to investigate whether acetylcholine esterase inhibitors, which also increase cholinergic transmission, might improve vision in the amblyopic eye in people over the age of 8 years (NIH Clinical Trial, NCT01584076). Serotonergic modulation may also allow modification of visual circuits later in development. Modulation of layer 1 5-HT<sub>3A</sub> receptor-positive inhibitory interneurons can reopen the critical period for tonotopic plasticity in auditory cortex (Takesian et al., 2018). The serotonin reuptake inhibitor, fluoxetine, also enables improvement in vision in

rats after monocular deprivation (Maya Vetencourt et al., 2008). Evidence in humans that re-opening critical periods may be possible comes from a recent study in which valproate, a common anti-epileptic medication that is thought to act as an epigenetic regulator, permitted perfect pitch learning in healthy adults (Gervain et al., 2013).

### 5.3. Neurodegenerative disorders

#### 5.3.1. Role for neuromodulation of STDP in neurodegenerative disorders.

Severe effects on neuromodulatory systems, in particular loss of cholinergic and dopaminergic cells, in neurodegenerative disorders including Alzheimer's and Parkinson's disease predict major deficits in the flexibility of learning rules for STDP. Moreover, neuronal hyperexcitability occurs in the early stages of Alzheimer's disease leading to a disruption of excitatory-inhibitory (E/I) balance in the cortex (Hall et al., 2015; Brown et al., 2018). Altered E/I balance could be caused, at least in part, by neuromodulatory effects on STDP and would also be expected to have further effects on STDP depending on behavioral state. Studies of STDP in animal models predict alterations in the induction requirements for STDP, as well as the polarity, due to loss of cholinergic tone. The net effect of reduced cholinergic modulation, however, may be difficult to deduce given the diverse actions on nicotinic and muscarinic receptors at different synapses and brain regions (Section 2). Decreased activation of nAChR, for example, may permit t-LTP in prefrontal cortex through lowering the threshold for induction and/or removing the inhibition of t-LTP by inhibitory interneurons (Couey et al., 2007). Decreased activation of mAChR, in contrast, might be predicted to favor t-LTD in prefrontal cortex and hippocampus from some studies (Adams et al., 2004; Zaitsev and Anwyl, 2012; Sugisaki et al., 2016) but equally could be predicted to reduce t-LTD based on other studies (Seol et al., 2007; Brzosko et al., 2015). These effects, particularly in the human temporal cortex, may be layer-specific, as reduced cholinergic tone would be predicted to favor t-LTP over t-LTD at integration layers (i.e., L2/3) while reducing the facilitation of t-LTP in output layers (i.e., layer 6; Verhoog et al., 2016).

Evidence for a disruption in the neuromodulation of STDP comes from studies in mouse models of human gene mutations found in familial forms of Alzheimer's disease. Loss of t-LTP occurred at L2/3-to-L5 cortical synapses in 5xFAD mice (Buskila et al., 2013) and L2/3-to-L2/3 synapses in APP-swe/PS1dE9 mice (Shemer et al., 2006). The loss of t-LTP was age-dependent (increasing from 3.5 to 7 months), and t-LTP could be abolished by the application of soluble A $\beta$

oligomers. Both studies suggest the proximal cause is a decrease in synaptic AMPA receptor expression; however, the loss of acetylcholine and other neuromodulatory deficits in Alzheimer's disease likely also contributes. The reduction in cholinergic tone likely also explains the reversal in the polarity of STDP observed at the L2/3-to-L5 synapses in the 5xFAD mice (Buskila et al., 2013).

Deficits in STDP were also observed in two mouse models of Parkinson's disease (Thiele et al., 2014). The 6-OHDA-lesioned mice replicate the slowing and difficulty with the initiation of movements, while the levodopa (L-DOPA)-induced dyskinesia mouse model recapitulates the unwanted increase of involuntary movements secondary to L-DOPA use. Consistent with animal studies of dopaminergic modulation of STDP (Section 2), t-LTP could only be induced in the indirect pathway and t-LTD in the direct pathway at corticostriatal synapses in the 6-OHDA-lesioned mouse model of Parkinson's disease, whereas both t-LTP and t-LTD could be induced in either pathway in wild-type mice. In contrast, in the L-DOPA-induced dyskinesia mouse model, t-LTP could only be induced in the direct pathway and t-LTD in the indirect pathway (Thiele et al., 2014). Thus, altered dopaminergic modulation likely leads to loss of bidirectional plasticity at corticostriatal synapses in these two contrasting mouse models. Notably, the treatment of motor symptoms in Parkinson's disease with drugs targeting the dopamine system has revealed a high prevalence of non-motor symptoms in people with Parkinson's disease, including dementia (Cheon et al., 2008). Thus, we would predict that alterations in other neuromodulatory systems (e.g., cholinergic) may also be affected with additional impacts on STDP outcomes, as in Alzheimer's disease.

### 5.3.2. Neuromodulation of STDP as a potential therapeutic target for neurodegenerative disorders

Testing the neuromodulatory effects on STDP in animal models of Alzheimer's and Parkinson's disease may yield further mechanistic insight into the cognitive decline and provide additional drug targets. In both Parkinson's and Alzheimer's disease, the loss of neurons affects many areas important for neuromodulation and would thus be expected to alter STDP rules in response to past history, behavioral state, and behavioral outcomes. While current therapies primarily target dopaminergic and cholinergic function, serotonergic modulation is an attractive target for future therapeutics. A new drug inhibiting serotonin receptor 6 (5-HT<sub>6</sub>R) improves cognitive function in Alzheimer's disease (Johnson et al., 2008) and a 5-HT<sub>6</sub>R receptor

antagonist blocks the attenuation of theta-burst-stimulation-induced LTP in CA1 of the hippocampus (West et al., 2009).

### 5.3.3. Can old synapses be made plastic again?

One problem in developing therapeutics for neurodegenerative disorders is whether deficits in synaptic plasticity can be reversed. Employing a similar strategy as that used in neurodevelopmental disorders, targeting perineuronal nets (PNNs), which maintain parvalbumin-positive inhibitory neurons in a mature state, in an Alzheimer's disease mouse model restored synaptic defects and improved memory on behavioral testing (Yang et al., 2015). Moreover, deletion of histone deacetylase 3 (HDAC3) in 18-month-old mice improved performance on hippocampal-dependent object learning memory tasks—which is typically impaired in aging mice—and restored the ability to induce LTP with theta-burst stimulation (Kwapis et al., 2018). Thus, further research is warranted to determine whether alterations in the neuromodulation of STDP in neurodegenerative disorders can also be reversed.

### 5.4. Modulation of STDP as a therapeutic target for recovery from stroke and brain injury?

There is growing interest in enhancing the functional remapping in the brain after stroke or traumatic brain injury. Neuronal plasticity facilitates the cortical reorganization necessary to regain function in a weak or paralyzed limb; however, plasticity mechanisms post-stroke can also worsen function through increased inhibition of the affected hemisphere by the unaffected hemisphere (Bashir et al., 2010). Transcranial magnetic stimulation (TMS) has been used clinically to release the inhibition from the intact hemisphere (Bashir et al., 2010) and is also under investigation to improve motor symptoms in Parkinson's disease (Zhu et al., 2015). Attempts have been made to replicate *in vitro* synaptic plasticity induction protocols with TMS including “theta-burst” protocols (e.g. by applying bursts of 3 pulses at 50 Hz every 200 ms, which increased the amplitude of TMS-induced potentials in motor cortex for 20-30 minutes post-stimulation) and a combination of peripheral nerve stimulation with TMS of the motor cortex (Rodrigues et al., 2008; Zamir et al., 2012; Wessel et al., 2015; Casula et al., 2016; Foyzal et al., 2016). While it is tempting for authors to equate the latter to spike-timing-dependent plasticity, TMS lacks the spatial resolution to study synaptic plasticity. Moreover, modulation of cortical inhibition on a regional scale seems an equally likely contributor to the observed changes in TMS response for both protocols.

## 6. Conclusion

Neuromodulation of STDP to incorporate prior experience, current behavioral state, and feedback from learning outcomes allows the adaptation of synaptic plasticity to the different computational needs across brain regions and bridging the multiple timescales on which learning takes place. Neuromodulation also enables flexible adaptation to changes in the external environment and internal brain state. Basic science investigations into the parameters and mechanisms underlying STDP has also been translated to mouse models of neurologic and psychiatric disorders. The most pressing issues to address in future research are, firstly, whether the same plasticity rules operate *in vivo* as those found in *ex vivo* and *in vitro* preparations; secondly, how STDP is controlled by local spiking activity and neuromodulatory inputs; and, thirdly, the function of this plasticity in behavioral learning and memory and their involvement in different brain disorders. Further exploration of how the neuromodulation of STDP is altered in different behavioral and disease states is likely to reveal new mechanisms underlying the cognitive function and dysfunction in these disorders and may offer novel treatment strategies for improving cognition throughout the lifespan.

**Acknowledgments**

The authors' research is supported by the Biotechnology and Biological Sciences Research Council (U.K.). Z.B. held a Medical Research Council (U.K.) studentship. S.B.M. was supported by a Marie Skłodowska-Curie Individual Fellowship (E.C.).

**Author contributions**

All authors contributed to writing the paper.

**Declaration of Interests**

The authors declare no competing interests.

## Figure legends

**Figure 1. Induction and expression of spike-timing-dependent plasticity (STDP).** (A) After a stable baseline period, STDP is typically induced by repeated pairings of single presynaptic and postsynaptic spikes. In its classic form, STDP depends on the order and millisecond-precision timing of spikes: multiple pre-before-post spike pairings induce timing-dependent long-term potentiation (t-LTP), whereas post-before-pre pairings induce timing-dependent long-term depression (t-LTD). The magnitude of plasticity, as an indicator of synaptic change, is defined as a percentage change in synaptic weight from baseline. (B) The classic Hebbian STDP window: induction protocols with positive (pre-before-post) spike-timing intervals induce synaptic potentiation; protocols with negative (post-before-pre) spike-timing intervals induce synaptic depression. (C, D) The relative spike timing is not the sole determinant governing timing-dependent plasticity. Instead, STDP is malleable. Both the magnitude (C) and the temporal requirements for STDP (D) can be modulated.

**Figure 2. Neuromodulation of STDP in behavior and disease.** STDP (blue) can be conceptualized in three stages: the neuronal activity prior to the plasticity-inducing event, the spiking-timing event that induces plasticity, and the expression of plasticity seen as a long-lasting change in synaptic weights. Neuromodulation of STDP (orange) occurs at all three stages leading to priming of synaptic plasticity by prior experience (prospective neuromodulation), modulation of STDP rules at the time of induction (concurrent neuromodulation), and modification—or even reversal—of synaptic weights based on behavioral outcomes after the plasticity-inducing event (retrospective neuromodulation). Altered neuromodulation of STDP may play a key role in neurologic and psychiatric disorders (red) and may serve a target for developing new treatments.

**Figure 3. Cellular mechanisms underlying neuromodulation of STDP.** Neuromodulatory inputs at synapses can alter STDP rules via three classes of mechanisms: (1) alteration of neuronal excitability and spiking dynamics; (2) gating of synaptic function, including control of presynaptic glutamate release (2a), regulation of postsynaptic membrane potential via potassium channels (SK; 2b), and availability of co-agonist at NMDA receptors (2c); and (3) regulation of intracellular signaling cascades involved in synaptic plasticity.



**Figure 4. Retrospective modulation of STDP at the synaptic and behavioral level.** (A) Schematic of the dopamine-induced conversion of t-LTD into t-LTP. De-depression (left of dotted line): Activation of dopamine receptors (DAR) stimulates adenylyl cyclase (AC), increasing cAMP which activates protein kinase A (PKA). PKA phosphorylates inhibitor 1 (I-1), which reverses the PP1-induced dephosphorylation of synaptic AMPARs. Potentiation (right of dotted line): Activation of postsynaptic dopamine receptors stimulates AC, increasing cAMP which activates PKA. PKA enhances  $Ca^{2+}$  influx leading to the insertion of AMPA receptors via  $Ca^{2+}$ -calmodulin-dependent protein kinase II (CaMKII). Arrows indicate activation/phosphorylation, blunt-ended lines indicate inhibition/dephosphorylation. (B) Schematic of synaptic and behavioral timescales in reward-related learning. During exploration, the activity-dependent modification of synaptic strength due to STDP depends on the coordinated spiking between presynaptic and postsynaptic neurons on a millisecond time scale. The change in synaptic weights develops gradually on a scale of minutes. Increased cholinergic tone (ACh) during exploration facilitates synaptic depression. Reward, signaled by an increase in dopamine (DA), within a delay of seconds to minutes following exploration, converts synaptic depression into potentiation. Panel B modified from Brzosko et al., 2017.

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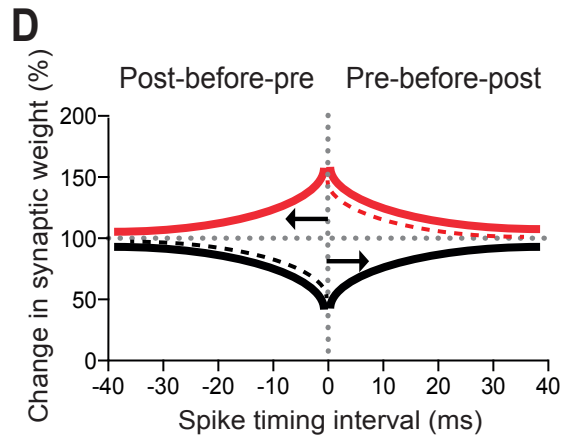
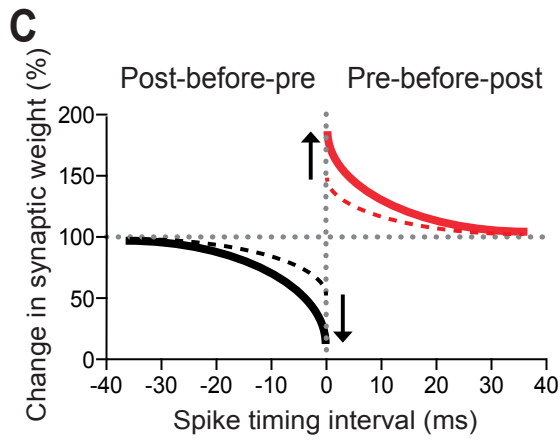
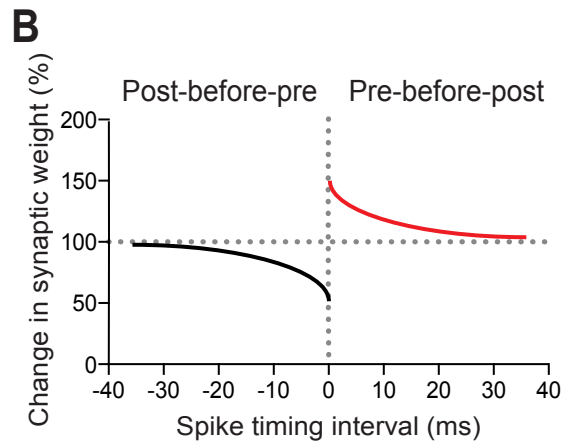
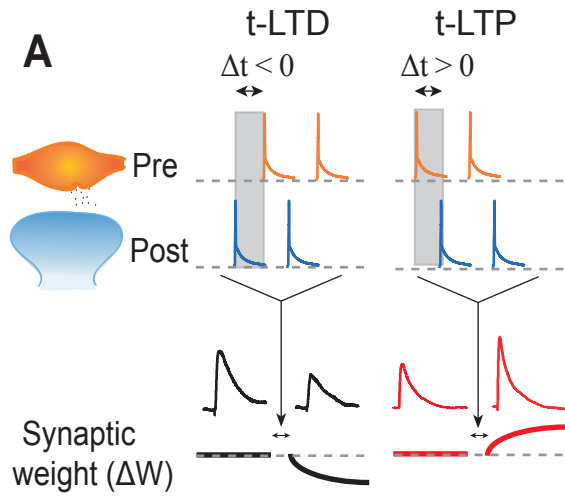
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**Spike-timing dependent plasticity (STDP)**

