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Modulation of spike-timing dependent plasticity: towards the inclusion of a third factor in computational models

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Author contribution statement

AF and AM participate to the writing of the neuromodulators part; JJ, HB and KB wrote the "Molecular pathway-based computational models of STDP " part; SV wrote the "Modulation of STDP by astrocytes: the forgotten third factor " part; LV wrote the introduction, neuromodulators and conclusion parts; all authors have edited and corrected the ms.

Keywords

spike-timing dependent plasticity (STDP), Dopamine, noradrenaline, Astrocytes, Acetylcholine, BDNF, Hebbian plasticity, computational model, GABA Modulators, Eligibility Traces, third factor, credit assignment

Abstract

Word count: 267

In spike-timing dependent plasticity (STDP) change in synaptic strength depends on the timing of pre- versus postsynaptic spiking activity. Since STDP is in compliance with Hebb's postulate, it is considered one of the major mechanisms of memory storage and recall. STDP comprises a system of two coincidence detectors with NMDA receptor activation often posited as one of the main components. Numerous studies have unveiled a third component of this coincidence detection system, namely neuromodulation and glia activity shaping STDP. Even though dopaminergic control of STDP has most often been reported, acetylcholine, noradrenaline, nitric oxide, BDNF or GABA also has been shown to effectively modulate STDP. Furthermore, it has been demonstrated that astrocytes, via the release or uptake of glutamate, gate STDP expression. At the most fundamental level, the timing properties of STDP are expected to depend on the spatiotemporal dynamics of the underlying signaling pathways. However in most cases, due to technical limitations experiments grant only indirect access to these pathways. Computational models carefully constrained by experiments, allow for a better qualitative understanding of the molecular basis of STDP and its regulation by neuromodulators. Recently, computational models of calcium dynamics and signaling pathway molecules have started to explore STDP emergence in ex and in vivo-like conditions. These models are expected to reproduce better at least part of the complex modulation of STDP as an emergent property of the underlying molecular pathways. Elucidation of the mechanisms underlying STDP modulation and its consequences on network dynamics is of critical importance and will allow better understanding of the major mechanisms of memory storage and recall both in health and disease.

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Modulation of spike-timing dependent plasticity: towards the inclusion of a third factor in computational models

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25 **Abstract**

26

27 In spike-timing dependent plasticity (STDP) change in synaptic strength depends on the
28 timing of pre- *versus* postsynaptic spiking activity. Since STDP is in compliance with Hebb's
29 postulate, it is considered one of the major mechanisms of memory storage and recall. STDP
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31 posited as one of the main components. Numerous studies have unveiled a third component
32 of this coincidence detection system, namely neuromodulation and glia activity shaping
33 STDP. Even though dopaminergic control of STDP has most often been reported,
34 acetylcholine, noradrenaline, nitric oxide, BDNF or GABA also has been shown to
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36 release or uptake of glutamate, gate STDP expression. At the most fundamental level, the
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39 experiments grant only indirect access to these pathways. Computational models carefully
40 constrained by experiments, allow for a better qualitative understanding of the molecular
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47 major mechanisms of memory storage and recall both in health and disease.

48

49 **Running title:** Modulation of STDP

50

51 **Keywords:** STDP, third factor, dopamine, acetylcholine, noradrenaline, astrocytes, eligibility
52 traces, Hebbian plasticity, computational models

53

54 INTRODUCTION

55 Most computational and experimental studies of synaptic plasticity focus on
56 variations of Hebb's rule in which the change in synaptic strength is caused by direct
57 association of two factors, *i.e.* two inputs (or activity patterns), one on the presynaptic and
58 one on the postsynaptic side. Thus, when neural circuits adjust their synaptic weights
59 depending on the frequency or timing of the pre-synaptic and post-synaptic firing patterns,
60 Hebb's postulate is fulfilled. In addition, a third factor (for example neuromodulators or
61 astrocytes) stabilizes or modulates the expression of synaptic plasticity and, thus, ultimately
62 learning (Kempster et al., 1998; Pawlak et al., 2010; Lisman et al., 2011; Frémaux and
63 Gerstner, 2015; Edelman et al., 2017; Kusmierz et al., 2017; Gerstner et al., 2018). The
64 inclusion of this third factor with two-factor Hebbian plasticity rule is called neoHebbian
65 plasticity (Lisman et al., 2011), and is infrequent in computational models of STDP. In this
66 review, we focus on spike-timing-dependent plasticity (STDP) (Sjöström et al., 2008;
67 Feldman, 2012), a synaptic Hebbian learning rule, and its control by the third factor:
68 neuromodulation (*via* the action of dopamine, acetylcholine, noradrenaline and others) or
69 astrocyte activity. Our goal is to highlight aspects of STDP that should be taken into account
70 in future computational models of STDP.

71 Since its discovery, STDP has attracted considerable interest in experimental and
72 computational neuroscience because it avoids implausibly high firing frequencies and instead
73 relies on spike correlation. STDP has emerged as a candidate mechanism for experience- and
74 activity-dependent changes in neural circuits, including map plasticity (Abbott and Nelson,
75 2000; Dan and Poo, 2006; Morrison et al., 2008; Sjöström et al., 2008; Feldman, 2012;
76 Froemke, 2015). Experiments in different brain regions and in diverse neuronal types have
77 revealed a plethora of STDP forms that vary in plasticity direction, temporal dependence and
78 the involvement of signaling pathways (Sjöström et al., 2008; Feldman, 2012; Korte and
79 Schmitz, 2016). Experimental protocols that investigate STDP use pairing of a presynaptic
80 stimulation with a postsynaptic spike, with the pre- and postsynaptic stimulations separated
81 by a fixed interval Δt_{STDP} (spike timing). In most of the studies, the spike timing is computed
82 as $\Delta t_{\text{STDP}} = t_{\text{post}} - t_{\text{pre}}$, where t_{post} and t_{pre} are the times of emission of the postsynaptic spike and
83 that of the presynaptic stimulation, respectively. If the postsynaptic stimulation occurs before
84 the presynaptic, $\Delta t_{\text{STDP}} < 0$ (post-pre pairings), whereas $\Delta t_{\text{STDP}} > 0$ when the presynaptic
85 stimulation occurs before the postsynaptic one (pre-post pairings). The same pairing pattern
86 is then repeated between 50 and 200 times at a constant frequency (typically between 0.1 and

87 5Hz). The canonical STDP is bidirectional (able to generate potentiation and depression
88 depending on the value of Δt_{STDP}) and Hebbian, *i.e.* post-pre pairings ($\Delta t_{\text{STDP}} < 0$) yield timing-
89 dependent long-term depression (tLTD) and pre-post pairings ($\Delta t_{\text{STDP}} > 0$) give rise to timing-
90 dependent long-term potentiation (tLTP). For most STDP forms, the expression of plasticity
91 is restricted to a narrow temporal window ($|\Delta t_{\text{STDP}}| < 80\text{ms}$); thus, when pre- and postsynaptic
92 activities are separated by a large Δt_{STDP} , long-term synaptic changes are not observed (Bi
93 and Poo, 1998; Markram et al., 1997).

94 The predominant form of STDP is Hebbian, and has been observed in the neocortex
95 (Feldman, 2000; Markram et al., 1997; Nevian and Sakmann, 2006; Sjöström et al., 2001;
96 Froemke et al., 2005), the hippocampus (Debanne et al., 1997; Debanne et al., 1998; Bi and
97 Poo, 1998; Nishiyama et al., 2000; Wittenberg and Wang, 2006), and the striatum (Shen et
98 al., 2008; Pawlak and Kerr, 2008; Fino et al., 2008; Fino et al., 2009). In contrast to Hebbian
99 STDP, bidirectional anti-Hebbian STDP expresses tLTP for $\Delta t_{\text{STDP}} < 0$ and tLTD for $\Delta t_{\text{STDP}} > 0$.
100 Anti-Hebbian STDP was first reported in the cerebellum-like structure of electrical fish (Bell
101 et al., 1997). More recently, bidirectional anti-Hebbian STDP has been observed in mammals
102 and in various structures including the striatum (Fino et al., 2005; Fino et al., 2010; Schulz et
103 al., 2010; Paillé et al., 2013; Valtcheva et al., 2017) and the somatosensory cortex (Letzkus et
104 al., 2006). Unidirectional anti-Hebbian forms of STDP inducing tLTD for both $\Delta t_{\text{STDP}} < 0$ and
105 $\Delta t_{\text{STDP}} > 0$, have been observed in the cerebellum (Han et al., 2000; Safo and Regehr, 2008),
106 the neocortex (Egger et al., 1999; Lu et al., 2007), the dorsal cochlear nucleus (Tzounopoulos
107 et al., 2004), and the hippocampus (Wittenberg and Wang; 2006). Recently, a unidirectional
108 Hebbian STDP where tLTP was observed for both post-pre and pre-post pairings, has been
109 reported in hippocampus (Mishra et al., 2016). The mechanisms that produce these diverse
110 forms of STDP are not completely understood, though could involve a third factor, such as
111 neuromodulators (such as dopamine or acetylcholine) (for reviews see Pawlak et al., 2010;
112 Edelman et al., 2017) or astrocytes.

113 All the forms of STDP described so far depend on one of three main systems of
114 coincidence detectors (Feldman, 2012; Korte and Schmitz, 2016). The first system comprises
115 the NMDA receptor (NMDAR) as the unique coincidence detector for both tLTP and tLTD,
116 though voltage-sensitive calcium channels may play a role in coincidence detection. This
117 form of plasticity has been reported in hippocampal CA1 neurons (Nishiyama et al., 2000),
118 neocortical layer 2/3 pyramidal cells (Froemke et al., 2005), striatal output neurons (Pawlak
119 and Kerr, 2008), and striatal GABAergic interneurons (Fino et al, 2008). The second system

120 combines NMDAR-dependent tLTP with tLTD which depends on metabotropic glutamate
121 receptor (mGluR)- and/or cannabinoid type-1 receptor (CB₁R)-activation. Though the tLTD
122 is independent of postsynaptic NMDARs, the activation of presynaptic NMDARs can be
123 implicated (Sjöström et al., 2003; Bender et al., 2006b; Corlew et al., 2007; Rodríguez-
124 Moreno and Paulsen, 2008). This form of plasticity has been observed in the visual (layer
125 2/3) and somatosensory (layer 5) cortex (Sjöström et al., 2003; Bender et al., 2006; Nevian
126 and Sakmann, 2006; Corlew et al., 2007; Rodríguez-Moreno and Paulsen, 2008), cholinergic
127 striatal interneurons (Fino et al., 2008) or striatal output neurons (Fino et al., 2010). Recently
128 in striatal output neurons, a third system has been reported, in which the tLTD is CB₁R-
129 dependent, whereas the molecular dependence of tLTP is governed by the number of
130 pairings: a small number of pairings (~10) produces a CB₁R-mediated tLTP, whereas greater
131 number of pairings yields an NMDAR-mediated tLTP (Cui et al., 2015; Cui et al., 2016).

132 The molecular mechanisms accounting for these various forms of STDP are not yet
133 fully understood, despite a substantial number of studies focusing on STDP. For the
134 NMDAR-dependent tLTP and tLTD, calcium amplitude seems to partly determine plasticity
135 direction (Nevian and Sakmann, 2006). For $\Delta t_{\text{STDP}} > 0$, when the presynaptic activity precedes
136 the back-propagating action potential, the excitatory post-synaptic potential coincides with
137 the back-propagating action potential resulting in high and more prolonged calcium influx
138 through the NMDAR and voltage-sensitive calcium channels, which leads to tLTP. For
139 $\Delta t_{\text{STDP}} < 0$, calcium influx through the NMDARs and voltage-sensitive calcium channels is
140 lower and as a result induces tLTD (Magee and Johnston, 1997; Koester and Sakmann, 1998;
141 Nevian and Sakmann, 2006; Pawlak and Kerr, 2008). These different calcium dynamics
142 produce different directions of plasticity by recruiting different downstream signaling
143 molecules. Several computational models have used a description of neuronal calcium
144 dynamics and/or the kinetics of downstream signaling pathways as a proxy to predict the
145 direction of plasticity (tLTP or tLTD). These computational models investigate the impact of
146 different STDP timings or of modulators on STDP by integrating their effects on calcium
147 dynamics or downstream signaling pathways. Therefore computational models based on the
148 kinetics of the implicated molecular pathways are promising avenues to integrate the third
149 factor in Hebbian plasticity and will be the main focus of the present review.

150

151 NEUROMODULATORS AFFECTING THE EXPRESSION, POLARITY AND 152 SHAPE OF STDP

153 Neuromodulators and neurotransmitters play an important, but often unappreciated,
154 role in the control of STDP induction and maintenance (for reviews see Pawlak et al., 2010;
155 Edelman et al., 2017). The skepticism about neuromodulation stems from the apparent
156 discrepancy between the time scale of neuromodulation and the coincidence detection timing
157 inherent to STDP. The former is on the scale of seconds or more, whereas the latter is on the
158 scale of milliseconds. However, this apparent discrepancy becomes less important after
159 considering STDP from the perspective of a learning system that needs to link recorded
160 information (memory) with a value scale (reward). Indeed, an individual acting on its
161 environment needs to learn to discriminate actions leading to reward from those leading to
162 punishment, both possibly occurring seconds, minutes or even hours after the taken action. A
163 system of memory and learning based only on the timescale of STDP would miss this
164 essential information. Thus, one role of neuromodulation is to link STDP and the reward
165 system. In this context, we demonstrate below how a third factor, comprised of
166 neuromodulators and/or astrocytes, modulates the timing dependence of STDP. Note that the
167 modulation of timing dependence depends on brain region and cell type; thus future
168 computational models will need to incorporate region and cell type specific modulation. In
169 this section, we detail STDP protocols used in experimental studies because depending on the
170 activity patterns neuromodulatory systems are differentially recruited. Therefore, the apparent
171 contradiction between several of the experimental reports on STDP could depend on the
172 activity patterns or neuromodulatory activation that were used. This knowledge might help
173 the building of computational models, by taking into account the different regimes of action
174 of neuromodulators in shaping STDP.

175

176 **Dopamine**

177 The action of dopamine is mediated by the metabotropic dopaminergic receptors that
178 functionally modulate other receptor systems and/or ion channels without inducing large
179 postsynaptic currents. Dopaminergic receptors belong to two groups based on their G-protein
180 coupling: the D₁-class receptors (D₁R and D₅R) are coupled to G_s- or G_{o1f}-proteins and the
181 D₂-class receptors (D₂R, D₃R and D₄R) to G_{i/o}-proteins (Neve et al., 2004). D₁- and D₂-class
182 receptors have opposite action on the cAMP second messenger pathway and the protein
183 kinase A (Fig. 1a).

184 Dopamine is released by midbrain dopaminergic neurons in response to both reward
185 and the reward prediction error (Schultz, 2007). In the hippocampus, tLTD, which is
186 observed in control conditions for negative Δt_{STDP} , is converted to tLTP by dopamine
187 addition during STDP pairings or immediately after STDP pairings (aiming at mimicking a
188 retroactive effect) (Zhang et al., 2009; Brzosko et al., 2015) (Fig. 1b). Dopamine addition
189 during STDP induction leads to the enlargement of the temporal window of tLTP expression
190 (Fig. 1b). However the effects of dopamine disappear when dopamine is added long after
191 STDP pairings, since dopamine addition 10 and 30 minutes after pairings results in an
192 absence of plasticity and a recovery of tLTD observed in control conditions, respectively
193 (Brzosko et al., 2015) (Fig. 1b). This dopaminergic modulation, which converts bidirectional
194 STDP to unidirectional tLTP, is D_1R - but not D_2R -mediated (Zhang et al., 2009; Brzosko et
195 al., 2015). Acetylcholine (classically associated with arousal and exploratory behavior; Ma et
196 al., 2018) transforms bidirectional Hebbian hippocampal STDP into unidirectional tLTD
197 (Brzosko et al., 2017). However, the effect of acetylcholine is reverted by dopamine addition
198 1 second after STDP pairings, which allows recovering tLTP (Fig. 1b). Although these results
199 constitute an important step for the experimental demonstration of a retroactive action of
200 dopamine on Hebbian plasticity, the molecular mechanisms underlying dopamine interactions
201 with the coincidence detectors were not characterized. In addition, more distal action of
202 dopamine from STDP protocol remains to be investigated to fully explore the temporal
203 credit-assignment problem (Sutton and Barto, 1998; Schultz, 2007; Izhikevich, 2007;
204 Gerstner et al., 2018).

205 Additional evidence supports the role of dopamine for promoting hippocampal tLTP.
206 Conditions that lower basal dopamine during the preparation of brain slices prevent the
207 induction of tLTP at synapses between Shaffer collaterals and CA1 pyramidal cells
208 (Edelmann and Lesmann, 2011). Subsequent addition of dopamine rescues tLTP, through a
209 D_1R -mediated mechanism (Edelmann and Lesmann, 2011; Edelmann and Lesmann, 2013).
210 In addition, D_1 - and D_5R -activations are important for the induction of tLTP at the synapses
211 between the medial perforant pathway and dentate gyrus neurons (Yang and Dani, 2014). The
212 mechanism here includes a change in cell excitability: inactivation of the transient A-type
213 potassium current by D_1R and D_5R increases the excitability of dentate gyrus neurons and the
214 amplitude of their back-propagating action potentials (Yang and Dani, 2014).

215 Beyond the hippocampus, the importance of dopamine modulation of STDP also is attested in
216 the basal ganglia, where dopamine plays a crucial role in motor control, action selection and

217 reinforcement learning (Yin and Knowlton, 2006; Schultz, 2007). Given the importance of
218 dopamine, it is not surprising that dopamine is required for STDP in the striatum, both *ex vivo*
219 (Shen et al., 2008; Pawlak and Kerr, 2008) and *in vivo* (Schulz et al., 2010; Fisher et al.,
220 2017). However, the situation is complicated by the diversity in dopamine receptors. In
221 rodents, striatal output neurons belong either to the direct or the indirect trans-striatal
222 pathways and show different dopaminergic receptor expression, D₁- and D₂-class receptors,
223 respectively (Calabresi et al., 2014). *In vivo* in anesthetized rodents, negative and positive
224 pairing STDP protocol both result in tLTD at corticostriatal synapses, and bidirectional STDP
225 can be elicited only with phasic dopaminergic release obtained by electrical stimulation of
226 midbrain dopaminergic neurons (Schulz et al., 2010) or pharmacological manipulation of
227 dopaminergic transmission (together with GABAergic and adenosine transmissions) (Fisher
228 et al., 2017). These results are consistent with *ex vivo* studies, which showed that application
229 of dopamine either simultaneously, or 0.6 sec after glutamate allows dendritic spine
230 enlargement and calcium increase (Yagishita et al., 2014). Moreover, this study demonstrated
231 the existence of synaptic eligibility traces, which can be revealed by subsequent dopamine
232 release after Hebbian learning (see section “Monoamines transform eligibility traces into
233 plasticity” below). *Ex vivo*, conflicting results have been reported regarding STDP
234 modulation by dopamine: according to Pawlak and Kerr (2008) both tLTD and tLTP requires
235 D₁R- but not D₂R-activation (D₂R-activation affecting only plasticity kinetics: tLTP and
236 tLTD onset is shortened and delayed, respectively), whereas Shen et al. (2008) reported that
237 D₂R-activation is required for tLTD expression in striatal neurons belonging to the indirect
238 pathway and D₁R-activation is necessary for tLTP in striatal neurons belonging to the direct
239 pathway. There are methodological differences between these two studies which could
240 account for this discrepancy in results: for post-pre and pre-post pairings the same STDP
241 protocol (*i.e.* 100 pairings at 0.1Hz) was applied by Pawlak and Kerr (2008), whereas two
242 distinct STDP-like protocols (theta bursts 3:3 for tLTP and 1:3 for tLTD) were utilized by
243 Shen et al. (2008). Depending on the activity patterns, D₁- and D₂-class receptors could be
244 differentially activated. The effects of dopamine in the striatum via D₂R receptors would
245 result from a D₂R-mediated attenuation of both synaptic- and back-propagating action
246 potential-evoked calcium influx into dendritic spines *via* the inhibition of protein kinase A-
247 dependent regulation of NMDARs (Higley and Sabatini, 2010) (Fig. 1). This mechanism also
248 is supported by the demonstration that dopamine depletion enhances calcium influx in
249 dendrites of the D₂R-expressing striatal neurons belonging to the indirect pathway (Day et al.,
250 2008). Future development of detailed computational models of the signaling pathways will

251 be useful for fully exploring the involvement of dopaminergic receptors in various forms of
252 STDP (see section “Molecular pathway-based computational models of STDP”).

253 The role of dopamine has been demonstrated in two other brain regions, the prefrontal
254 cortex and the amygdala. In the prefrontal cortex (at layer 5 pyramidal cells) an STDP
255 protocol such as 60 pairings ($\Delta t_{\text{STDP}} = +10\text{ms}$) at 0.1Hz fails to produce plasticity, while
256 dopamine application during the STDP pairings permits the induction of Hebbian tLTP
257 ($\Delta t_{\text{STDP}} = +10\text{ms}$) (Xu and Yao, 2010) and anti-Hebbian tLTP ($\Delta t_{\text{STDP}} = -30\text{ms}$) (Ruan et al.,
258 2014) (Fig. 1b). Both Hebbian and anti-Hebbian tLTP directly depends upon D_1R -activation
259 in the postsynaptic neuron whereas the Hebbian tLTP depends also indirectly upon the
260 activation of D_2R expressed by GABAergic interneurons. D_2R activation blocks the
261 inhibition exerted by GABAergic interneurons and permits the expression of Hebbian tLTP
262 ($\Delta t_{\text{STDP}} < +10\text{ms}$). By combining D_1R - and D_2R -activation, the temporal window of tLTP is
263 extended up to $\Delta t_{\text{STDP}} = +30\text{ms}$ (Xu and Yao, 2010) (Fig. 1c). This suggests that in prefrontal
264 cortex, the physiological form of STDP is the anti-Hebbian tLTP since the expression of
265 Hebbian tLTP is disfavored by GABAergic network activity. In the lateral nucleus of the
266 amygdala tLTP requires the activation of D_2R located on neighboring GABAergic
267 interneurons (Bissière et al., 2003). Since dopamine is released in the amygdala in response
268 to stress (Inglis et al., 1999), dopaminergic neuromodulation of inhibitory synaptic
269 transmission appears to be a crucial mechanism underlying the acquisition of fear
270 conditioning.

271 In summary, these results show that dopamine is a key neuromodulator of STDP and
272 constitutes the third factor required for the temporal credit-assignment. Overall, the effects of
273 dopamine seem to conform to a simple general scheme: the activation of G_s/G_{olf} -coupled D_1R
274 tends to promote tLTP whereas the activation of G_i -coupled D_2R favors tLTD. However, the
275 effects exerted by dopamine strongly depend on the brain area: dopamine either can be
276 mandatory for STDP induction and/or maintenance or modulate STDP properties (width of
277 the Δt_{STDP} window, polarity of the STDP or magnitude of the plasticity). Moreover, network
278 effects can add complexity to the picture, since the expression of dopamine receptors is not
279 restricted to the examined neuron but can affect the response to *e.g.* local interneurons.

280

281 **Noradrenaline**

282 Noradrenaline interacts with G-protein–coupled receptors of three families: α 2-, α 1-
283 and β 1-3-adrenergic receptors (by order of decreasing affinity) (Ramos et al., 2007). α 2-
284 adrenergic receptors are Gi/Go-coupled and lead to cAMP decrease. α 1-adrenergic receptors
285 are Gq- coupled, and activate phospholipase C β , resulting in intracellular calcium release via
286 inositol 1,4,5-triphosphate. β -adrenergic receptors are Gs-coupled and yield cAMP increase
287 (Fig. 2a).

288 In several brain regions, activation of adrenergic receptors modifies the shape of the
289 STDP curve (Fig. 2b). In the hippocampus, activation of β -adrenergic receptors enlarges the
290 range of Δt_{STDP} for Hebbian tLTP expression by increasing the excitability of CA1 pyramidal
291 cells (Lin et al., 2003). In the visual cortex, whereas paired stimulations of layer 4 afferents
292 with postsynaptic action potential bursts does not produce plasticity, the concomitant
293 activation of adrenergic receptors (with both α 1- and β -adrenergic receptor agonists) allows
294 the emergence of bidirectional Hebbian STDP in pyramidal cells of layer 2/3 (in rodents: Guo
295 et al., 2012; in primates: Huang et al., 2014) (Fig. 2b) as well as in fast-spiking interneurons
296 and non-fast-spiking somatostatin-positive interneurons (Huang et al., 2013). Note that α 1-
297 adrenergic receptor agonists alone (or agonists of M₁-class mAChRs, see section below; Seol
298 et al., 2007) trigger a tLTD-only (*i.e.* unidirectional anti-Hebbian STDP), whereas β -
299 adrenergic receptor agonists alone induce the expression of a tLTP-only (*i.e.* unidirectional
300 Hebbian STDP) (Seol et al., 2007; Guo et al., 2012; Huang et al., 2013) (Fig. 2b). The
301 affinity for noradrenaline of α 1-adrenergic receptors exceeds that of β -adrenergic receptors,
302 and unidirectional anti-hebbian STDP (tLTD-only) is observed in low noradrenaline, whereas
303 bidirectional Hebbian STDP can be induced with higher noradrenaline concentration
304 (Salgado et al., 2012) (Fig. 2b and 2c).

305 Taken together, those studies show that adrenergic receptors play an important role in
306 shaping STDP, mostly by enlarging Δt_{STDP} and controlling STDP polarity, but also, similarly
307 to dopamine, by acting subsequently to the stimulation to promote plasticity. Overall, a
308 pattern emerges from the effects of noradrenaline: the activation of Gs-coupled β -adrenergic
309 receptors tends to promote tLTP, whereas the activation of Gq-coupled α 1-adrenergic
310 receptors tends to favor tLTD.

311

312 **Monoamines transform eligibility traces into plasticity**

313 One of the fundamental questions in reward learning is the temporal credit-
314 assignment problem: how are the correct actions learned given that delivery of a reward or
315 punishment occurs significantly later than the key actions that promoted the outcome
316 (Schultz, 2007). In an attempt to solve the temporal credit-assignment problem, some
317 computational studies addressed the question of the retroactive effect of dopamine on cortical
318 and hippocampal STDP (Sutton and Barto, 1998; Izhikevich, 2007; Gerstner et al., 2018).
319 From a cellular perspective, the temporal credit-assignment problem translates into the
320 following question: if dopamine (and more broadly monoamines) modulates STDP, is there a
321 dependence of this modulation on the time elapsed between the stimulus (STDP pairings) and
322 the reward (release of monoamines)? This question adds a supplementary temporal
323 dimension to the modulation by the third-factor monoamine.

324 To solve the temporal credit-assignment or the distal reward problem, it has been
325 proposed that synaptic eligibility traces could constitute synaptic tags that are set by
326 Hebbian learning and that will be transformed subsequently into synaptic plasticity by
327 neuromodulators, bridging the learning sequence with reward (Sutton and Barto, 1998;
328 Izhikevich, 2007; Gerstner et al., 2018). In other words, eligibility traces would be induced
329 by Hebbian learning but would remain silent in terms of synaptic efficacy changes, unless a
330 neuromodulator released subsequently transforms them for plasticity. Synaptic eligibility
331 traces would allow the synapse to keep a trace from the stimulus until getting the reward, the
332 latter of which is represented by monoamines. We can distinguish two cases: the subsequent
333 release of neuromodulator shapes an existing plasticity (Cassenaer and Laurent, 2012;
334 Brzosko et al., 2015; Brzosko et al., 2017; Shindou et al., 2018) or allows the plasticity
335 expression (Yagishita et al., 2014; He et al., 2015).

336 Octopamine, the equivalent of noradrenaline in insects, changes the bidirectional
337 Hebbian STDP at synapses of Kenyon cells in the locust, critical for the associative learning
338 of odors, into a unidirectional STDP (tLTD-only) even in a retroactive manner when applied
339 seconds after the relevant pairing (Cassenaer and Laurent, 2012). In a similar way, in rodents,
340 when dopamine is applied just after STDP pairings, it converts tLTD into tLTP in
341 hippocampus (Brzosko et al., 2015; Brzosko et al., 2017) or in striatum (Shindou et al., 2018).

342 In striatum, dopamine induces spine enlargement exclusively when opto-stimulation
343 of dopaminergic terminals occur between 0.3 to 2 seconds after Hebbian learning (*i.e.* STDP
344 pairings) (Yagishita et al., 2014). In the visual cortex and in the medial prefrontal cortex,
345 release of noradrenaline and serotonin, just after the whole set of pairings or just after every

346 pairing, allows the expression of tLTP and tLTD for pre-post and post-pre pairings,
347 respectively (He et al., 2015); the STDP pairings *per se* did not induce plasticity (Fig. 2c). He
348 et al. (2015) observed that the eligibility traces are short-lived since the monoamines need to
349 be release 5 to 10 sec after learning to promote plasticity (He et al., 2015). The fact that a
350 couple of monoamines (or third factors) is at play for distinct induction plasticity (tLTP vs
351 tLTD) could allow an efficient stabilization of learning and avoid synaptic saturation.

352

353 **Acetylcholine**

354 Acetylcholine acts on two types of muscarinic receptors (mAChRs): the M₁- (M₁, M₃
355 and M₅) and M₂- (M₂ and M₄) class receptors (Thiele, 2013), and the ionotropic (cationic)
356 nicotinic receptors (nAChRs) (Albuquerque et al., 2009). M₁-class mAChRs are Gq/G11-
357 coupled leading to inositol 1,4,5-triphosphate and diacylglycerol production (*via*
358 phospholipase C β activation), subsequent increase of intracellular calcium and activation of
359 protein kinase C (Fig. 2a); M₂-class mAChRs are Gi/Go-coupled, leading to inhibition of
360 adenylate cyclase, and a reduction of cAMP and thus protein kinase A activity.

361 Unlike STDP experiments with noradrenaline and dopamine, experiments to
362 characterize the effect of acetylcholine have not carefully delineated M₁-class vs M₂-class
363 effects; thus experimental results are more diverse. At hippocampal CA1 pyramidal cells,
364 bidirectional Hebbian STDP is converted into unidirectional tLTP after enhancement of
365 acetylcholine (Brzosko et al., 2017) (Fig. 1b), whereas inhibition of mAChRs prevents post-
366 pre tLTD and converts pre-post tLTP into tLTD (Sugisaki et al., 2011; Sugisaki et al., 2016).
367 When excitatory and inhibitory post-synaptic currents were examined at synapses of CA1
368 pyramidal neurons, pre-post pairings induce tLTP of excitatory pathway while it triggers
369 tLTD at inhibitory pathways via the co-activation of mAChRs and CB₁R (Ahumada et al.,
370 2013). Thus, Hebbian STDP in CA1 pyramidal neurons depends on the excitation/inhibition
371 balance, which is tightly regulated by mAChRs expressed in GABAergic interneurons and
372 pyramidal cells (Ahumada et al., 2013; Sugisaki et al., 2011; Takkala and Woodin, 2013;
373 Sugisaki et al., 2016).

374 Though acetylcholine alone seems to promote unidirectional plasticity (tLTP- or
375 tLTD-only), co-activation of mAChRs and Gs coupled pathways (either D1/D5 dopaminergic
376 receptors in the hippocampus CA1 pyramidal cells (Brzosko et al., 2017) or β -adrenergic

377 receptors in visual cortex layer 2/3 pyramidal cells (Seol et al., 2007)) promotes bidirectional
378 plasticity by restoring Hebbian tLTP for $\Delta t_{\text{STDP}} > 0$ (Fig. 2b).

379 The effects of acetylcholine *via* nAChR-activation are expected to include
380 depolarization and possibly increased calcium influx (Jones et al., 2012), but they also can
381 exert a more subtle influence on STDP by regulating the magnitude of STDP rather than its
382 polarity or expression (Sugisaki et al., 2016). Nicotine increases the threshold for the
383 induction of Hebbian tLTP at excitatory synapses of pyramidal cells of the prefrontal cortex
384 (Couey et al., 2007). However, note that nicotine when applied at a high concentration
385 ($\sim 10\mu\text{M}$) can exert a more drastic effect on STDP since it converts tLTP into tLTD (Couey et
386 al., 2007). Interestingly, in the medial prefrontal cortex, after nicotine treatment in juvenile
387 rats, opposing effects are obtained depending on the developmental stage: tLTP magnitude
388 was reduced in juvenile whereas it was increased in adult rats (Goriounova and Mansvelder,
389 2012).

390

391 Taken together, the above results reveal a general principle whereby the
392 neuromodulatory effects exerted on STDP by monoamines (dopamine or noradrenaline) or
393 acetylcholine are for a large part guided by the type of G-protein activated (regardless of the
394 agonist): Gi/o-coupled and Gq/11-coupled receptor activation facilitates tLTD (D_2 -class, $\alpha 1$ -
395 adrenergic, M_1 -class), whereas Gs- and Golf-coupled receptor activation rather leads to the
396 expression of tLTP (D_1 R-class, β -adrenergic receptors). However the validity of this general
397 principle needs further investigation in other brain areas and neuronal subtypes.

398

399 **Brain-derived neurotrophic factor (BDNF)**

400 The neurotrophic factor BDNF binds to the tyrosine receptor kinase B, which induces
401 tyrosine receptor kinase B dimerization and the autophosphorylation of tyrosine residues in
402 the cytoplasmic kinase domain. This process induces the activation of three main signaling
403 pathways: phospholipase $C\gamma$, phosphoinositide 3-kinase and extracellular signal-regulated
404 protein kinases cascades. Notably, the phosphoinositide 3-kinase signaling pathway plays an
405 important role in the regulation of mRNA translation, which impacts protein synthesis and
406 putatively BDNF-dependent plasticity. Numerous studies have shown the role of BDNF in
407 modulating synaptic transmission and plasticity (for reviews see Park and Poo, 2013;
408 Edelman et al., 2014).

409 Concerning STDP, pairings of glutamate release and postsynaptic spiking at 1Hz are
410 sufficient to release BDNF from the postsynaptic dendrites in a spike-timing-dependent
411 manner (for $0 < \Delta t_{\text{STDP}} \leq +20\text{ms}$; for $\Delta t_{\text{STDP}} > 20\text{ms}$ BDNF release was not detected) (Lu et al.,
412 2014). This spike-timing-dependent BDNF release is dependent on the activation of NMDA
413 receptors. In hippocampal neurons, the tLTP part of the observed bidirectional Hebbian
414 STDP depends on BDNF (Bi and Poo, 1998; Lu et al., 2014). Interestingly, depending of the
415 activity pattern during STDP pairings, the BDNF dependence of the observed plasticity is
416 different. Indeed, hippocampal tLTP induced with presynaptic activation paired with
417 postsynaptic bursts of four back-propagating action potentials (1:4 pairings repeated 30 times
418 at 0.5 Hz) is BDNF and tyrosine receptor kinase B-mediated, whereas canonical STDP
419 pairings (1:1 pairings repeated 100 times at 0.5 Hz) induced a tyrosine receptor kinase B-
420 independent tLTP at the same synapses (Edelmann et al., 2015). Genetic impairment of
421 BDNF synthesis has led to alteration of STDP in the prefrontal cortex. Disruption of one of
422 the promoters involved in BDNF transcription (promoter IV mutant mice) leads to the
423 aberrant induction of tLTP, which is absent in wild-type mice, for 50 pairings (Sakata et al.,
424 2009). In the infralimbic medial prefrontal cortex, STDP is absent in a rodent model (BDNF-
425 Met/Met mice) of the human BDNF Val66Met polymorphism (leading to severe cognitive
426 dysfunction and anxiety disorders) in which the BDNF release is impacted; STDP is
427 recovered after exogenous BDNF application (Pattwell et al., 2012).

428

429 **Nitric oxide (NO)**

430 NO, an intercellular messenger, is generated by the enzyme NO synthase and activates
431 soluble guanylyl cyclase leading to cGMP formation. In turn, cGMP-activated protein
432 kinases regulate multiple substrates such as DARPP-32 and G-substrate, which inhibits
433 phosphatases that are involved, among other effects, in synaptic plasticity expression (for
434 review see: Hardingham et al., 2013). Concerning STDP, in the somatosensory cortex of
435 mice, Hebbian tLTP depends both on the AMPAR-subunit-1 and a NO-dependent
436 presynaptic component (Hardingham and Fox, 2006). Similarly, glutamate afferents to
437 serotonergic neurons of the dorsal raphe nucleus exhibit tLTP for pre-post pairings, which
438 is NO-dependent, involving the cGMP-activated protein kinase signaling cascade (Haj-
439 Dahmane et al., 2017). In retinal ganglion cells of tadpoles, STDP can be induced by natural
440 visual stimulation (*e.g.* moving bar) or by electrical stimulation of the retina and in both
441 cases, NO is required for tLTD while BDNF is required for tLTP (Mu and Poo, 2006).

442

443 **GABA**

444 In the dorsal striatum, anti-Hebbian STDP as observed in control conditions in striatal output
445 neurons is shifted to Hebbian STDP under pharmacological blockade of GABA_AR receptors
446 (Fino et al., 2010; Paillé et al., 2013; Valtcheva et al., 2017) (Fig. 3a). This effect applies
447 equally at D₁R-class striatopallidal (direct pathway) and D₂R-class striatonigral (indirect
448 pathway) neurons of juvenile and adult rodents. Although the molecular mechanisms
449 underneath this reversal of polarity by GABA are not fully elucidated, a computational model
450 suggests that depolarizing effects of GABA at distal dendrites would reverse calcium influx
451 by modifying the balance between calcium influxes from NMDAR *vs* voltage-sensitive
452 calcium channels (Paillé et al. 2013). Although GABA increases calcium influxes in both
453 NMDAR and voltage-sensitive calcium channels, *via* its depolarizing effect in striatal output
454 neurons (due to the relative values of the chloride reversal and membrane potential), the
455 depolarizing effect of GABA would impact differentially NMDAR and voltage-sensitive
456 calcium channels depending on the order of pairings (post-pre *vs* pre-post). GABA would
457 favor calcium influx via voltage-sensitive calcium channels for post-pre pairings (promoting
458 tLTP), whereas it would favor calcium influx via NMDARs for pre-post pairings (promoting
459 tLTD) in control conditions, leading to anti-Hebbian STDP (Paillé et al., 2013). Under
460 GABA blockade, this balance between calcium influxes is shifted and Hebbian STDP can be
461 observed. Change in GABAergic signaling during striatal development (*i.e.* the onset of the
462 tonic GABAergic signaling around P₁₄; Ade et al., 2008) appears to be a key factor for
463 shaping of striatal STDP. Indeed, in young rats (P₇₋₁₀) corticostriatal STDP is unidirectional
464 and Hebbian (tLTD with post-pre pairings, no plasticity with pre-post pairings) but
465 bidirectional and anti-Hebbian in adult rodents (Valtcheva et al., 2017) (Fig. 3a). GABA
466 signaling is also at play with the control of CB₁R-dependent tLTP which expression shifts
467 from post-pre to pre-post stimulation when ionotropic GABA_A transmission is blocked (Cui
468 et al., 2015). GABA is not involved in the induction of STDP *per se*, nor its magnitude, but
469 controls STDP polarity, *i.e.* the association between the sign of the pairing (pre-post or post-
470 pre) and the plasticity outcome (tLTP or tLTD). The tonic GABAergic component plays a
471 major role in the emergence of the anti-Hebbian striatal STDP in juvenile and adult rodents
472 (Valtcheva et al., 2017) (Fig. 3a). Thus, the pathological deregulation of tonic GABAergic
473 signaling may affect the polarity and occurrence of striatal plasticity and alter procedural

474 learning and memory. It remains to be seen whether the neuromodulator role of GABA for
475 STDP emergence and/or polarity constitutes a general rule in the brain.

476 Change of STDP polarity induced by GABAergic transmission has also been observed in
477 hippocampus. In hippocampal CA1 pyramidal cells, blockade of GABA_ARs converts
478 unidirectional tLTD to bidirectional Hebbian STDP (with 80 pairings at 5Hz) (Sugisaki et al.,
479 2016) (Fig. 3b). The modulatory effects of GABA_A and GABA_B receptors can also combine.
480 Indeed, at Schaffer collateral-CA1 excitatory synapses of the rat hippocampus, plasticity
481 relies on postsynaptic GABA_A receptors to set the spike-timing dependency and also depends
482 on presynaptic GABA_B receptors for its frequency dependence (Nishiyama et al., 2010) (Fig.
483 3b). Specifically, postsynaptic GABA_A receptors regulate the timing dependence of tLTD at
484 5Hz pairings (in the theta frequency band), whereas presynaptic GABA_B receptors control the
485 frequency dependence of tLTD at 25Hz (alpha and beta frequencies) and also accounts for
486 the expression of tLTP for 5Hz and 50Hz (gamma frequencies) (Nishiyama et al., 2010). In
487 addition, STDP can be expressed at GABAergic interneurons, where it modulates the strength
488 of GABAergic inhibition since STDP pairings alters the activity of potassium-chloride
489 cotransporter-2, resulting in changes in the reversal potential of GABAergic synaptic currents
490 (Woodin et al., 2003).

491

492 Taken together, the above results indicate that the spectrum of the third factor of STDP is
493 very large since in addition to neuromodulators it can be extended to BDNF, NO and
494 neurotransmitters acting as neuromodulators such as GABA. STDP synaptic plasticity is thus
495 modulated, whether in its induction, its direction or its temporal window. Though
496 neuromodulation of STDP has been investigated for the early phase of plasticity (within the
497 first hour, *i.e.* the induction phase), the effects of neuromodulators remain to be investigated
498 for the late phases of plasticity in which the third factor is expected to have a crucial role for
499 the maintenance of memory (Lisman et al., 2011).

500

501 **Modulation of STDP by astrocytes: the forgotten third factor**

502 Many forms of excitatory STDP rely on either pre- or postsynaptic glutamate
503 receptors (Sjöström et al., 2008; Feldman, 2012; Korte and Schmitz, 2016). Therefore, STDP
504 is expected to be tightly controlled by glutamate dynamics. Specifically, the spatiotemporal

505 profile of glutamate may define the extent and location of recruited glutamate receptors,
506 which are involved in the induction of tLTP or tLTD.

507 An overriding question is how coincident synaptic activity in the millisecond range
508 can be integrated over a longer timescale during the iteration of pre- and postsynaptic
509 pairings to allow STDP induction, while keeping sharp sensitivity to timing during individual
510 pairing episodes. A potential solution to this problem could be that (1) glutamate should be
511 released in a delayed manner to allow integration of pre- and postsynaptic activity over the
512 time course of minutes; and (2) synaptically released glutamate during neuronal activity
513 needs to be reliably cleared from the extracellular space to allow high fidelity sampling of
514 coincident pre- and postsynaptic activity during STDP pairings. Astrocytes help solve this
515 problem of controlling extracellular glutamate dynamics and have been shown to play an
516 important role in synaptic transmission, as well as short- and long-term memory (Chung et
517 al., 2015; Oliveira et al., 2015). This role of astrocytes has led to the concept of the tripartite
518 synapse, comprised of the pre- and postsynaptic neuronal elements as well as the astrocytes.
519 Indeed, a substantial part of central synapses are contacted by astrocytes (Bernardinelli et al.,
520 2014). Notably, astrocytes are able to release glutamate *via* exocytosis in response to
521 neuronal activity (Araque et al., 2014; Sahlender et al., 2014; Verkhratsky et al., 2016) and to
522 efficiently clear glutamate from the extracellular space on a submillisecond timescale *via*
523 high-affinity glutamate transporters (Danbolt, 2001). Therefore, astrocytes can both detect
524 and control neuronal activity *via* the release and reuptake of glutamate.

525 Astrocytes can integrate the coincident neuronal activity during STDP pairings and
526 participate in the induction of tLTD (Min and Nevian, 2012). Excitatory tLTD induced by
527 post-pre pairings at layer 4 onto layer 2/3 synapses in the rat barrel cortex relies on the
528 release of endocannabinoids by the postsynaptic element through the activation of astrocytic
529 CB₁Rs. In turn, glutamate released by astrocytes activates presynaptic NMDARs which are
530 required for tLTD induction (Rodríguez-Moreno and Paulsen, 2008). Astrocytes are able to
531 sense postsynaptic endocannabinoid release by gradually increasing their calcium waves
532 exclusively during repetitive post-pre pairings within a narrow temporal window of $\Delta t_{\text{STDP}} = -$
533 25 ms which is eligible for tLTD induction. Indeed, pre-post pairings at $\Delta t_{\text{STDP}} = +25$ ms and
534 post-pre pairings at $\Delta t_{\text{STDP}} = -250$ ms, which induce tLTP and no plasticity, respectively, do
535 not trigger any changes in calcium dynamics. Therefore, astrocytes are selective to a unique
536 temporal pattern, which both generates calcium dynamics to promote glutamate release and
537 imposes a threshold for tLTD induction. Astrocytes can thus act as a time buffer by

538 integrating coincident pre- and postsynaptic activity over the time course of minutes and
539 enabling tLTD by delayed release of glutamate.

540 Astrocytes also are crucial for the gating of both tLTP and tLTD in the dorsal striatum
541 *via* the uptake of glutamate (Valtcheva and Venance, 2016). Physiological activity of the
542 astrocytic glutamate transporter, called the excitatory amino acid transporter-2 (EAAT2),
543 allows the expression of bidirectional anti-Hebbian STDP induced in a narrow temporal
544 window $-30 < \Delta t_{\text{STDP}} < +30$ ms (Fino et al., 2010; Paillé et al., 2013; Valtcheva and Venance,
545 2016). When EAAT2 is blocked, a form of LTP that does not rely on coincident detection can
546 be induced by uncorrelated activation of pre- and postsynaptic elements. This non-Hebbian
547 LTP requires postsynaptic back-propagating action potentials and extrasynaptic GluN2B-
548 containing NMDARs, which are activated by glutamate spillover. In contrast, the
549 overexpression of EAAT2 prevents the expression of striatal STDP (Valtcheva and Venance,
550 2016) possibly by restricting glutamate availability for both the NMDARs and mGluRs
551 required for striatal STDP (Fino et al., 2010; Shen et al., 2008). Thus, preserving the optimal
552 temporal contingency between pre- and postsynaptic activity required for STDP depends on
553 astrocytic glutamate uptake. Astrocytes gate tLTP and tLTD by a subtle regulation of the
554 extracellular glutamate levels and, therefore, a precisely tuned range of EAAT2 activity
555 allows the emergence of STDP. Computational models have begun to explore interactions
556 between glutamatergic synapses and astrocytes (De Pitta et al, 2011; De Pitta and Brunel
557 2016; see also De Pitta et al 2012 for a review), but investigating the role of astrocytic
558 glutamate control requires transforming the binary glutamate release event typically used in
559 STPD models into glutamate diffusion and uptake mechanisms.

560 Astrocytes can release various other neurotransmitters and factors besides glutamate
561 (Araque et al., 2014; Sahlender et al., 2014; Verkhratsky et al., 2016) including the NMDAR
562 co-agonist D-serine which regulates different forms of synaptic plasticity. The release of D-
563 serine is necessary for frequency-dependent LTD and LTP in the hippocampus (Henneberger
564 et al., 2010; Zhang et al., 2008) and prefrontal cortex (Fossat et al., 2011). Moreover,
565 experience-dependent changes in the degree of synaptic enwrapment by astrocytes governs
566 the level of D-serine availability and subsequently controls the expression of NMDAR-
567 dependent LTP and LTD in the supraoptic nucleus of the hypothalamus of lactating rats
568 (Panatier et al., 2006). The NMDARs implicated in STDP can be situated at both pre- or
569 postsynaptic sites (Feldman, 2012; Korte and Schmitz, 2016) and thus may be affected to
570 different extents by gliotransmission. D-serine has a permissive role for the induction of

571 NMDAR-dependent tLTP at mossy fiber-CA1 hippocampal synapses (Rebola et al., 2011),
572 although its glial origin has not been investigated. In the developing hippocampus a
573 presynaptic tLTD at CA3-CA1 synapses requires D-serine signaling possibly released from
574 astrocytes (Andrade-Talavera et al., 2016). Interestingly, the same STDP pairing protocol
575 induces tLTP at later developmental stages suggesting the possibility that astrocytic coverage
576 of neurons and modulation of STDP by gliotransmission may be developmentally regulated.

577 Another important gliotransmitter is ATP, which is enzymatically converted to
578 adenosine in the extracellular space and can act on pre- and postsynaptic adenosine receptors
579 situated on neurons. Glial release of ATP controls the magnitude of hippocampal LTP
580 induced with high-frequency stimulation (Pascual et al., 2005) and blockade of postsynaptic
581 adenosine A2a receptor increases the amplitude of low-frequency stimulation-dependent
582 LTD in the striatum (Lerner et al., 2010). Adenosine also mediates striatal tLTP *via*
583 postsynaptic adenosine A2a receptors both *in vitro* (Shen et al., 2008) and *in vivo* when the
584 STDP paradigm is coupled with dopamine pairing (Fisher et al., 2017). In addition,
585 presynaptic adenosine A1 receptors modulate the amplitude of tLTP in the visual cortex
586 (Bannon et al., 2017). However, evidence directly implicating astrocytes in the purinergic
587 control of STDP is still lacking. Computational models of signaling pathways underlying
588 STDP have begun to include adenosine A2a receptors (see below), but investigation of
589 interaction between pre-synaptic NMDA and adenosine A1 receptors requires modeling of
590 mechanisms controlling pre-synaptic vesicle release.

591 Finally, astrocytes are involved in the GABAergic modulation of both the polarity
592 (Fino et al., 2010; Paillé et al., 2013; Valtcheva et al., 2017) and threshold for induction
593 (Groen et al., 2014) of excitatory STDP. Astrocytes regulate basal and transient inhibitory
594 tone *via* GABAergic transporters (Scimemi, 2014). Non-specific blockade of both neuronal
595 and astrocytic GABA transporters in the developing striatum has a permissive role for the
596 induction of tLTD (Valtcheva et al., 2017) but the particular contribution of astrocytic GABA
597 clearance in STDP remains to be explored.

598

599 **MOLECULAR PATHWAY-BASED COMPUTATIONAL MODELS OF STDP**

600 In an attempt to better understand the mechanisms governing learning and memory
601 and determine which mechanisms control input-dependent plasticity, modeling efforts have
602 focused on biophysical and biochemical models that utilize a kinetic description of the

603 molecular pathways implicated in STDP. These models range in molecular complexity from
604 single ion (*i.e.* calcium) to complicated signaling pathways, and in spatial complexity from
605 single-compartment (Fig. 4a1) to multi-compartment (Fig. 4a2). An overview of this
606 literature can be found in several review articles (see *e.g.* Graupner and Brunel, 2010; Griffith
607 et al., 2015). In the following, we focus on the articles published after 2010, though include
608 the most influential contributions published before that date. Moreover, in the following, we
609 subdivide the models into two types: those evaluating the control of plasticity from calcium
610 dynamics alone, and those that add one or more downstream signaling pathway molecules. In
611 addition, we try to distinguish single-compartment models from those that add some degree
612 of spatial structure to the postsynaptic neuron. We acknowledge that in both of these
613 dimensions the classification is not binary and some models bridge the divide.

614 **Simplified calcium dynamics and two-threshold rules**

615 Models of calcium dynamics in response to STDP stimuli are the most common type
616 of models, and are justified both by the critical role of calcium in plasticity and also by the
617 stimulation protocol in which neuromodulator release does not change. The only difference
618 between STDP protocols that produce tLTP and STDP protocols that produce tLTD is the
619 timing between the presynaptic stimulation and the postsynaptic action potential, Δt_{STDP} ; thus
620 the number and frequency of presynaptic stimulations does not differ between tLTP and
621 tLTD. This implies that presynaptic release of neuromodulators does not differ so it must be
622 postsynaptic molecules activated by calcium dynamics that determine the polarity of
623 plasticity.

624 Calcium predicting the direction of synaptic plasticity is one of the ideas that are
625 popular among theoreticians and experimentalists. In the simplest form the peak calcium (or
626 indeed the amplitude of the current through the calcium permeable, NMDA subtype of the
627 glutamate receptor) controls the direction of plasticity (for reviews see: Evans and Blackwell
628 2015; Graupner and Brunel, 2010; Griffith et al., 2015). This is known as the “two-threshold”
629 rule: if calcium (either peak or integrated) is above the higher, potentiation threshold, tLTP is
630 induced, whereas if calcium is larger than the lower LTD threshold but lower than the LTP
631 threshold, tLTD occurs (Fig. 4c1). Pre-post pairings produce a large calcium influx through
632 the NMDA receptor channel with calcium concentration above the LTP threshold, whereas
633 post-pre pairings produce a moderate calcium influx with calcium concentration between the
634 LTD and LTP thresholds. One of the first models of NMDAR-dependent synaptic plasticity
635 was proposed by Shouval et al. (2002). This model, using simplified calcium dynamics inside

636 a dendritic spine, accounted for a diverse range of stimulation protocols such as STDP and
637 classical rate-based plasticity; however it predicted depression for long positive Δt_{STDP} , a
638 model prediction which is not confirmed by experiments (but see Nishiyama et al., 2000;
639 Wittenberg and Wang, 2006; Nishiyama et al., 2010). In the dorsal striatum, a model of
640 calcium dynamics (Evans et al. 2012) evaluated the role of NMDAR subunit (2A and 2B
641 subunits) in shaping the sensitivity to timing dependence, and correctly predicted that
642 NMDAR-2A would require a small Δt_{STDP} , whereas NMDAR-2B can support tLTP with a
643 large Δt_{STDP} . Several extensions or modifications to the basic model have been made both to
644 account for results with spike triplets (*i.e.*, when either two presynaptic stimuli or two
645 postsynaptic action potentials are generated) and to minimize the tLTD window for long
646 positive spike-timings. Adding another coincidence detection of presynaptic NMDA
647 receptors with endocannabinoids is one mechanism utilized in a neuromorphic
648 implementation of calcium based synaptic plasticity (Rachmuth et al., 2011). Alternatively,
649 incorporating short term depression of transmitter release or AP back-propagation (Shouval
650 and Kalantzis, 2005, Bush and Jin, 2012) minimizes the tLTD seen with long positive Δt_{STDP}
651 and can account for other experimental results; however, a more broadly applicable study
652 (Rubin et al. 2005) showed that plasticity rules that use calcium amplitude alone cannot
653 completely avoid predicting tLTD for long positive timings.

654 An extension of the two-threshold rule states that the duration of calcium elevation is
655 equally important in determining direction of plasticity (Fig. 4c2). Several models of STDP
656 explicitly take into account both the amplitude and the duration of calcium in predicting
657 plasticity outcome (Kumar and Mehta, 2011; Graupner and Brunel, 2012). Including a
658 duration threshold or integrating the total calcium response allows correctly predicting
659 experimental outcomes for both traditional STDP curves and STDP curves produced by spike
660 triplets. Another extension of the Shouval et al., (2002) model, Standage et al. (2014),
661 implements a calcium-dependent, sigmoid-shaped time constant of calcium decay, which
662 represents saturation of calcium extrusion from the spines. This model shows that saturation
663 of calcium extrusion might be responsible for the dependence of tLTP on the (theta-
664 frequency like) inter-spike interval for triplet stimulation protocols. Including the duration of
665 calcium does not exclude consideration of presynaptic release probability on STDP. Indeed,
666 gliotransmission may change the shape of the STDP curve depending on whether
667 gliotransmitters increase or decrease presynaptic release (De Pitta and Brunel 2016).

668 **Threshold rules based on detailed calcium dynamics**

669 Most of the aforementioned models use simplified calcium dynamics instead of
670 explicitly implementing the mechanisms underlying control of calcium (Fig. 4b), which
671 might improve predictions of synaptic plasticity. In other words, the next set of models used
672 neither single time constant of decay nor summation of independent pre- and postsynaptic
673 components for calcium dynamics. Though not explicitly implementing a STDP rule, Griffith
674 et al., (2016) indirectly consider the effect of calcium duration by using calcium-bound
675 calmodulin to assess how back-propagating action potential timing influences calcium
676 concentration. Using a 3-dimensional, deterministic reaction-diffusion model of calcium
677 interactions with calmodulin and other calcium binding proteins within a dendritic spine,
678 Griffith et al. (2016) show that calcium-bound calmodulin is a more sensitive indicator of
679 spike timing than free calcium. They further demonstrate the role of neuromodulators in
680 regulating synaptic plasticity through their activation or inhibition of calcium dependent
681 potassium channels during an STDP protocol, which greatly modulates calmodulin
682 activation.

683 Several studies explicitly investigate how the dendritic location and inhibitory inputs
684 shape the local calcium-based plasticity rules (Bar-Ilan et al., 2013; Jędrzejewska-Szmek et
685 al. 2016). Bar-Ilan et al. (2013) showed that inhibition shapes the spatial profile of dendritic
686 calcium concentration in neocortical pyramidal neurons. Depending on the location of the
687 excitatory and inhibitory inputs on the dendritic tree (Fig. 4a2), tLTP may be blocked,
688 transformed to tLTD, or the synapse may undergo no plasticity. Similarly, Jędrzejewska-
689 Szmek et al. (2016) developed a computational model of the major neuron type in the
690 striatum, the striatal output neurons, including both electrical activity and calcium dynamics.
691 They demonstrated that calcium amplitude and duration together (Fig. 4c2) can predict a
692 wide range of experimental plasticity outcomes, and further demonstrated a distance
693 dependence of STDP caused by the back-propagating action potential. In both of these
694 models, the distance dependent decreases in back-propagating action potential amplitude
695 reduces calcium influx through NMDA receptors for more distant synapses. This reduced
696 calcium influx can convert tLTP into either tLTD or no plasticity. These publications
697 demonstrate that by modeling mechanisms controlling calcium dynamics, including
698 diffusion, buffers and pumps, and by considering calcium duration, the LTD window for long
699 positive Δ_{STDP} is avoided.

700 An aspect of calcium dynamics often ignored in modeling studies is calcium release
701 from intracellular stores. This has been shown to contribute to tLTP under some conditions

702 (Plotkin et al., 2013; Cui et al, 2016). Thus, Nakano et al., (2013) included calcium release
703 from stores in their multi-compartmental model of a direct pathway spiny projection neuron.
704 In addition, though not explicitly including other signaling pathways, they evaluated the
705 effect of dopaminergic modulation of calcium, potassium and NMDAR channels. The main
706 result of their simulations showed that dopaminergic input preceding a back-propagating
707 action potential induced higher calcium responses than dopamine input following a back-
708 propagating action potential. This study also predicted that the timing dependence of calcium
709 responses between the up- and down-states was similar.

710 **Models of signaling pathway to explain synaptic plasticity**

711 Beyond calcium, several models add on simplified or abstract version of downstream
712 signaling molecules. Rubin et al., 2005 propose a three detector system, loosely based on
713 pathways resembling the opposing CaMKII – protein phosphatase signaling pathways. In
714 brief, three calcium-sensitive detectors are implemented: high, transient calcium levels
715 activate the tLTP detector; low calcium elevations activate the tLTD detector; and
716 intermediate calcium levels activate a “Veto” detector. Another variable integrates both the
717 tLTD detector and the Veto detector (called a double filter), such that intermediate calcium
718 levels decrease the double filter value; thus the double filter detects the uninterrupted
719 duration of calcium at low values yet suppresses the development of tLTD should calcium
720 spend some time at intermediate values, such as occurs with long positive Δt_{STDP} . Using the
721 three calcium detector system of Rubin et al. (2005), Cutsuridis (2011) showed that single
722 GABAergic inhibitory inputs can sharpen the shape of the STDP curve: narrowing the
723 temporal window that supports tLTD, whereas a train of GABAergic inputs both sharpens the
724 tLTD window and reduces the tLTP amplitude. A follow-up study (Cutsuridis, 2012)
725 extended the model to burst stimulation, and predicted that GABAergic inputs would expose
726 a tLTD window for long positive Δt_{STDP} . The timing of the GABA inputs determined whether
727 the effect was predominantly depression or potentiation.

728 Several models (Graupner and Brunel, 2007; Carlson and Giordano, 2011; Graupner
729 and Brunel, 2012; Mihalas, 2012; Saurdargiene and Graham, 2015; Pi and Lisman, 2008; Cui
730 et al, 2016; for reviews see: Graupner and Brunel, 2010; Evans and Blackwell, 2015; Griffith
731 et al., 2015) have implemented even more realistic representations of signaling pathway
732 kinetics, including the calcium activated phosphatase calcineurin, the calcium activated
733 kinase, CaMKII, and the Gs-activated adenylyl cyclase, the latter of which produces cAMP to
734 activate protein kinase A (Fig. 5). Additional pathways, such as protein kinase C (resulting

735 from activation of Gq-coupled receptors such as M₁R and mGluR) and ERK (downstream of
736 protein kinases A, C and tyrosine receptor kinase B) are also involved. Several advantages
737 accrue from these models, including the ability to produce experimentally testable predictions
738 regarding the role of specific molecules. Another key advantage of simulating signaling
739 molecules is that the tLTD window for long positive Δt_{STDP} is eliminated without arbitrarily
740 assuming the existence of a dedicated calcium concentration range that does not elicit
741 synaptic plasticity, *i.e.*, a separate range between the tLTD-inducing calcium range and the
742 tLTP range. Again these models vary in complexity, such as the number of different signaling
743 pathways included, and whether spatial aspects are included. Several models of these
744 signaling molecules have been applied to STDP protocols in the cortex, hippocampus and
745 striatum.

746 One of the earliest models, the single-compartment electric model of Graupner and
747 Brunel, (2007), couples membrane potential with a biochemical reaction model *via* calcium
748 dynamics. Phosphorylation state of CaMKII serves as the models readout, *i.e.* the level of
749 phosphorylated CaMKII serves as a proxy of the synaptic weight. Short positive intervals can
750 switch the CaMKII to a highly phosphorylated state; whereas negative intervals (but not long
751 positive intervals) switch the CaMKII to a low phosphorylated state. Critical to success of
752 this model is adjustment of calcium dependence of protein kinase A and calcineurin activity
753 against inhibitor 1, which controls the level of free protein phosphatase 1. A high-level of
754 protein phosphatase 1 will dephosphorylate CaMKII to prevent its persistent activation.
755 Indeed, in this model (Fig. 5): (i) the protein phosphatase-1/CaMKII activation ratio dictates
756 plasticity; LTD is expressed when protein phosphatase-1 activation overcomes CaMKII,
757 whereas LTP occurs when CaMKII activation is larger than protein phosphatase-1 activation,
758 and (ii) protein phosphatase-1 activity is maximal at intermediate calcium levels whereas
759 CaMKII activation needs larger calcium levels. Short negative Δt_{STDP} yield intermediate but
760 long lasting calcium levels, which efficiently activate protein phosphatase-1 but are not large
761 enough to activate CaMKII, thus triggering LTD. Short positive Δt_{STDP} yield sharp calcium
762 peaks that are large enough to activate CaMKII but do not persist long enough around
763 intermediate values to activate protein phosphatase-1 significantly; this leads to LTP. Finally,
764 the calcium levels triggered by long positive Δt_{STDP} are too weak to activate CaMKII but do
765 not stay long enough around intermediate values to activate protein phosphatase-1. Long
766 positive Δt_{STDP} therefore fail to activate either the protein phosphatase-1 or CaMKII, which in
767 effect rules out the expression of tLTD. This molecular system therefore exhibits dynamics

768 similar to the "Veto" detector proposed by Rubin et al. (2005) to eliminate tLTD at long
769 positive spike timings (see above).

770 Subsequent models either enhance the electrical activity model, or add AMPA
771 receptors as a model readout. Urakubo et al. (2008) develop a multi-compartment, multi-ion
772 channel model of visual cortex pyramidal neurons to activate a biochemical reaction model.
773 In contrast to Graupner and Brunel (2007), the timing dependence of tLTD cannot be
774 reproduced unless calcium-bound calmodulin allosterically inhibits NMDARs. Both Carlson
775 and Giordano (2011) and Saurdargiene and Graham (2015) used a model of AMPAR
776 insertion controlled by the CaMKII/protein phosphatase-2A switch. Carlson and Giordano
777 (2011) used a single-compartment model of calcium dynamics (from Shouval et al. 2002) to
778 activate the biochemical network model of Pi and Lisman, (2008). This single-compartment
779 model can explain STDP and does not predict tLTD for long positive Δt_{STDP} . Voltage-
780 sensitive calcium channels are critical for the latter effect, as blocking voltage-sensitive
781 calcium channels allow tLTD to emerge for long positive Δt_{STDP} . Saudargiene and Graham
782 (2015) incorporated spatial aspects of calcium dynamics by using a detailed compartmental
783 model of pyramidal CA1 neuron (Poirazi et al, 2003) to activate a biochemical network
784 model derived from two earlier models (Pi and Lisman, 2008; Graupner and Brunel, 2007).
785 Saudargiene and Graham (2015) showed, by monitoring AMPAR phosphorylation by the
786 CaMKII/protein phosphatase-2A switch, that tLTD is indeed induced by lower calcium levels
787 than tLTP, and that tLTD also requires many more repetitions of this lower calcium (which is
788 consistent with experimental results). Saudargiene and Graham (2015) also investigated the
789 influence of particular timings of inhibition associated with excitatory inputs, showing that
790 inhibition affects tLTD more than tLTP, because tLTD occurs for moderate calcium levels
791 and is thus more vulnerable to any reduction in peak calcium.

792 Whereas spatial models of calcium dynamics typically include dendritic branching or
793 explicit spines (microdomains), many signaling molecules are anchored *via* structural
794 proteins into multi-protein complexes, effectively creating nanodomains of molecule
795 interactions. One method for evaluating the effect of nanodomains (without explicitly
796 creating a spatial model) is to couple different sources of calcium to different downstream
797 signaling molecules. This approach was utilized by Mihalas (2011) who coupled three
798 different calcium sources to three different signaling molecules: NMDAR to CaMKII,
799 voltage-sensitive calcium channels to calcineurin, and phosphodiesterase to calcium release.
800 Adenylyl cyclase was coupled to both voltage-sensitive calcium channels and NMDAR. The

801 change in synaptic weight was calculated from kinase (tLTP) and phosphatase (tLTD)
802 activity. This model investigated the role of cAMP degradation in triplet-based STDP, and
803 showed that, if cAMP activity is spatially restricted to the membrane, the STDP profile is
804 similar to that observed in cortical layer 2/3 slices. The STDP profile for spatially diffuse
805 cAMP activity was consistent with that observed in hippocampal cell culture.

806 In the striatum, endocannabinoid production and activation of CB₁Rs are required for
807 most forms of tLTD (Mathur and Lovinger, 2012); thus, Cui et al. (2016) extended the
808 signaling pathways from Graupner and Brunel (2007) with 2-arachidonoylglycerol (the main
809 endocannabinoid) production via mGluR- and M₁R activation. Cui et al. (2016) utilized a
810 single-compartment model of electrical activity of a spiny projection neuron for calcium
811 dynamics, coupled with a model of signaling pathways underlying STDP in striatum,
812 including calcium-induced calcium release from internal stores. This model used a combined
813 2-arachidonoylglycerol- and CaMKII-based plasticity rule, where the direction of plasticity
814 (LTP or LTD) was determined by the product of the presynaptic weight (2-
815 arachidonoylglycerol-based) and postsynaptic weight (CaMKII based). The strength of this
816 model is the ability to show the mechanism whereby decreasing the number of pairings
817 converts NMDAR-dependent tLTP to an endocannabinoid-dependent tLTP, which was
818 confirmed experimentally (Fig. 5) (Cui et al., 2015; Cui et al., 2016). The underlying
819 hypothesis of this model (that was confirmed experimentally) is that moderate activation of
820 CB₁R caused endocannabinoid-mediated tLTD whereas large CB₁R activation leads to tLTP.
821 In the model, 10-20 negative pairings trigger large endocannabinoid transients that result in
822 endocannabinoid-mediated tLTP. However, CB₁R desensitization and partial depletion of
823 calcium in the endoplasmic reticulum starts to be significant after 20 pairings, so that CB₁R
824 activation is in fact smaller with more than 20 pairings than with 10-20 pairings. As a result,
825 the expression of endocannabinoid-mediated tLTP is restricted to 10-20 negative pairings, in
826 agreement with experimental observations (Cui et al., 2015; Cui et al., 2016). On the other
827 hand, as in the original model by Graupner and Brunel (2007), calcium levels become large
828 enough to activate significant amounts of CaMKII only after 40-50 negative pairings, thus
829 restricting the expression of NMDAR-dependent tLTP to this range of pairings. As a result,
830 this model successfully reproduces the experimental observation that the endocannabinoid-
831 mediated tLTP expressed at 10-20 positive pairings disappears, to be replaced by NMDAR-
832 dependent tLTP after 50 pairings (Fig.5). The addition of presynaptic dopamine signaling to

833 the model correctly predicted that the CB₁R-dependent tLTP observed with 10-20 pairings is
834 also under the control of presynaptic D₂R (Fig. 5).

835

836 **Exploring *in vivo*-like conditions**

837 One benefit of computational modeling is the ability to isolate a specific aspect of
838 STDP and address the impact of this very aspect at the level of networks and/or learning *in*
839 *vivo*. For instance, Kempter et al., (1998) used spike-based models to explore how the pulse
840 structure of neuronal signals and events on a millisecond scale influenced learning rules.
841 Clopath et al. (2010) utilized a voltage-based plasticity rule, consistent with a wide body of
842 experimental data, to study the emergence from plasticity of connectivity patterns in a
843 cortical network. Along the same line, variants of the classical computational STDP rule have
844 been devised that yield broad synaptic weight distributions matching the available
845 experimental observations (Gilson and Fukai, 2011).

846 However, one major detractor of STDP is its deterministic and constant spike timing
847 (interval between spikes within a pairing) and inter-stimulation interval (interval between
848 consecutive pairings), which diverge highly from biological variability. One of the most
849 pressing questions of learning and memory is which stimuli resemble *in vivo*-like conditions
850 best. Gjorgjieva et al. (2011) showed that a triplet model of STDP, depending on the
851 interactions of three precisely timed spikes, described plasticity experiments closer to natural
852 stimuli measured in the brain. Graupner et al., (2016) compared *in silico* plasticity outcomes
853 to several types of irregular, *in vivo*-like, firing patterns to investigate the influence of firing
854 rate and spike timing on synaptic plasticity. They showed that sensitivity of plasticity to
855 spike-timing is reduced by adding jitter (irregularity) to spike-pairs. Using physiological
856 firing patterns recorded in awake behaving macaque monkeys, Graupner et al, (2016) further
857 showed that moderate variation of firing rate, without any timing constraints, could reproduce
858 synaptic changes induced by spike timing. This result offers a different view on the central
859 role played by spike timing in long-term synaptic plasticity.

860 Most computational models of STDP indicate that plasticity disappears when the
861 timing between pre and postsynaptic pairings loses its regularity. However, it is not clear
862 what amount of noise can be tolerated for STDP or ITDP to be expressed (robustness) and
863 whether this amount depends on the signaling pathway supporting the plasticity. This
864 question has recently been tackled both experimentally and in a computational model, using

865 noisy STDP stimulations where the timing between the pre- and the postsynaptic stimulations
866 was jittered (Cui et al. 2018). As stated above, in striatum three forms of STDP are observed:
867 NMDAR-tLTP, endocannabinoid-tLTD and endocannabinoid-tLTP (Cui et al., 2015; 2016).
868 These three forms do not show similar sensitivity to jittered spike timing: NMDAR-tLTP
869 appeared poorly resistant whereas endocannabinoid-plasticity (tLTD and tLTP) appeared
870 more robust (Cui et al. 2018). Moreover, increasing the average pairing frequency or the
871 number of pairings reinforces NMDAR-tLTP and increases resistance to jittered spike timing.
872 These results suggest that the probability to observe the various forms of STDP *in vivo* is a
873 multivariate function of the mean spike timing, the number of pairings, the frequency of
874 pairings and also the variability of the spike timing. The shape of this multivariate function is
875 thus more complex than *e.g.* a monotonic decay with increasing variability of the spike
876 timing, and could reveal a functional specialization of each of these STDP forms to sub-
877 regions of the stimulation train parameters.

878

879 **Conclusions and future directions**

880 In addition to the pre- and postsynaptic firing patterns, a third factor for STDP control
881 comprises not only the classical neuromodulators (dopamine, noradrenaline or acetylcholine
882 to name a few) but also neuropeptides (BDNF), unconventional neurotransmitters (NO) and
883 astrocytes surrounding neurons, which can uptake or release neurotransmitters and
884 neuromodulators. The spectrum of the third factor of STDP is even larger since it can be
885 extended to neurotransmitters acting as neuromodulators such as GABA and glutamate (*via*
886 their tonic component) and endocannabinoids. Here, we reviewed the main effects of the
887 third factor on STDP: from the emergence of STDP, to the shaping of STDP *i.e.* the
888 dependence on Δt_{STDP} , and the magnitude and polarity of plasticity.

889 Beyond the time scale of Δt_{STDP} that is consistently in the ~ 80 ms range, the studies
890 that explored STDP properties have used a large variety of pairing protocols to induce STDP.
891 This diversity in stimulation protocol renders the comparison between studies exceedingly
892 difficult. As described above, beside its dependence on Δt_{STDP} , STDP expression is highly
893 affected by varying the structure of STDP pairings (1:1, 1:2, ... n:n or theta bursts)
894 (Edelmann et al., 2015), or the number and/or frequency of pairings (Sjöström et al., 2001;
895 Cui et al., 2016) (for review see Sjöström et al., 2008; Feldman, 2012; Edelmann et al.,

896 2017). It is thus expected that the effect of neuromodulation also would strongly depend on
897 the STDP activity pattern (as an example see Edelmann et al., 2015).

898 How the local interneuron networks (GABAergic or cholinergic) or the
899 neuromodulatory afferents are recruited and impact STDP, depends on the activity patterns of
900 the two main inputs. *I.e.*, the third factor effect may vary with or depend on a triplet of
901 characteristics: Δt_{STDP} , number of pairings, frequency of pairings. Optogenetics will most
902 certainly be a key method to induce neuromodulator release in a more time-controlled
903 manner to mimic for example phasic activity or explore precisely the retroactive action of
904 neuromodulation on STDP properties.

905 The number of experimental studies investigating the signaling pathways underlying
906 the STDP expression and their modulation by a third factor is still limited and needs further
907 consideration. The signaling pathways underlying frequency-dependent plasticity (triggered
908 by high- or low-frequency stimulations) have been more thoroughly explored, but need to be
909 fully address in STDP. Signaling through G-protein coupled receptors is far more complex
910 than the static view of the list of proteins that compose each signaling pathways. For instance,
911 G-protein coupled receptors exhibit the "biased agonism", *i.e.* the notion that a given agonist
912 of a signaling pathway activates only a subset of all the signaling pathways associated with
913 its receptor (Kenakin and Christopoulos, 2013). In other words, two agonists of the same
914 signaling pathway, even of the same receptor, activate different subsets of reactions, thus
915 yielding different biological effects. One potential mechanism explaining biased agonism is
916 the interplay between differential ligand-binding kinetics and the kinetics associated with
917 different cell signaling processes (Klein Herenbrink et al., 2016). In this context, the subsets
918 of signaling processes effectively activated by STDP pairings could differ from those
919 activated by the stronger protocols employed in frequency-dependent plasticity.

920 The complexity of G-protein coupled receptor signaling also has consequences on
921 STDP modulation. The available experimental data surveyed above point to a general rule
922 according to which neuromodulation by monoamines or acetylcholine is mostly controlled by
923 the type of G-protein coupled receptors activated: regardless of the agonist, G_i -coupled and
924 $G_{q/11}$ -coupled receptors favor tLTD, whereas G_s - and G_{olf} -coupled receptor activation leads
925 to tLTP. One might therefore erroneously conclude that two modulators would have the same
926 effect by activating the same signaling pathway. This would of course be at odds with the
927 concept that different neuromodulators exhibit different biological effects, due to different
928 receptor affinities, different receptor locations, co-localization of diverse downstream

929 signaling molecules, and the ability of phosphorylated receptors to switch their coupling to
930 different G proteins. Hence, dopamine signaling *via* D₁R may display different biological
931 effects from noradrenaline signaling *via* β -adrenergic receptors, although both activate the
932 G_s/G_{olf} signaling pathway. Future computational models of STDP modulation should aim to
933 reconcile the general scheme of the above rule with the specificity of neuromodulators,
934 probably through variants of biased agonism.

935 Because of the complexity of the mode of action of neuromodulators, most of the
936 studies have investigated the role of only a small number of neuromodulators one by one (the
937 neuromodulator systems have mostly been activated or inhibited one-at-a-time), but the
938 crosstalk between neuromodulators is critical, as demonstrated in only a few studies: for
939 dopamine and acetylcholine (Brzoko et al., 2017), dopamine and GABA (Xu and Yao, 2010),
940 dopamine and noradrenaline (Seol et al., 2007) or dopamine and endocannabinoids (Cui et
941 al., 2015). The effects of other neurotransmitters/neuromodulators (such as adenosine,
942 serotonin or endocannabinoids), or neuropeptides (substance P, enkephalins, oxytocin), fatty
943 acids (arachidonic acid, cholesterol, omega-3), hormones or the role of other non-neuronal
944 cells (astrocytes, oligodendrocytes, microglia, pericytes, ependymal cells or endothelial cells)
945 remain to be investigated in STDP expression; Indeed, most of these actors are known to
946 modulate rate-dependent plasticity. Furthermore, the effects of neuromodulators in STDP
947 maintenance remain to be determined and not only for the induction phase of STDP. It has
948 been shown in a rate-coded plasticity at CA1 hippocampal synapses that D₁-like-receptor
949 inhibition blocks late-phase LTP (Huang and Kandel, 1995), impedes consolidation of
950 memory and accelerates its erasure (Wang et al., 2010; Lisman et al., 2011). Similarly, the
951 third factor effect should be evaluated in the late phase of STDP (maintenance and potentially
952 erasure).

953 By fully taking into account the third factor, *i.e.* a multicomponent learning rule, the
954 computational power of neural networks might be considerably improved (as reviewed in
955 Kusmierz et al., 2017). Up to now, the third factor has usually been considered in isolation
956 from the pre- and postsynaptic firing patterns. This experimental convenience might well
957 disguise more complex network-level properties. In this regard, the fact that the level of tonic
958 GABA in the local network can switch STDP from Hebbian to anti-Hebbian may have
959 important consequences in dendritic computation and in a network context (Hiratani and
960 Fukai, 2017). The interplay between changes of the firing rate of some of the network
961 neurons due to Hebbian STDP and resulting changes in tonic GABA could give rise to abrupt

962 STDP shifts locally from Hebbian to anti-Hebbian. Such local STDP shifts may provide the
963 network with self-organizing properties that would not be predicted easily when the third
964 factor is considered in isolation. Added to the fact that different synapse types in the network
965 can have different STDP rules (and possibly, different modulation by the third factor), the
966 complexity and variety of the resulting network dynamics would considerably increase. Note
967 that here again, computational models will be instrumental to explore the potential impact of
968 these mechanisms on the dynamics and functional properties of neural networks.

969 A fair criticism of the physiological relevance of STDP has been raised by Lisman et
970 al. (2010) since *in vivo* the back-propagating action potential is obviously not triggered with a
971 somatic current injection in the postsynaptic neuron (as classically performed in STDP
972 experiments) but rather with the dynamic integration of synaptic inputs whose build-up
973 would eventually reach the action potential threshold. Input-timing-dependent plasticity
974 (ITDP), a form of heterosynaptic plasticity, consists in paired activation of presynaptic inputs
975 separated by an interval Δt_{ITDP} , leading to sub- or suprathreshold activity in the postsynaptic
976 neuron (Dudman et al., 2007; Williams et al., 2007). Therefore, ITDP could be viewed as an
977 attractive naturalistic upgrade of STDP, not only for experimental studies (Dudman et al.,
978 2007; Cho et al., 2012; Mehaffey and Doupe, 2015; Brandalise et al., 2016; Leroy et al.,
979 2017) but also for computational models (Shim et al., 2016). ITDP has been reported in
980 amygdala following activation of thalamic and cortical inputs (Humeau et al., 2003; Cho et
981 al., 2012), in hippocampal CA1 (Dudman et al., 2007), CA2 (Leroy et al., 2017) or CA3
982 (Brandalise et al., 2016) pyramidal cells and in avian basal ganglia (Mehaffey and Doupe,
983 2015). Interestingly, GABA and enkephalin have been shown to modulate CA2 hippocampal
984 ITDP (Leroy et al., 2017), which paves the way for future studies investigating the role of the
985 third factor in ITDP properties.

986 The vast majority of STDP studies investigating the third factor have been achieved
987 *ex vivo* (cell cultures or acute brain slices), although few studies have addressed
988 neuromodulation of STDP *in vivo* (Mu and Poo, 2006; Cassenaer and Laurent, 2012; Schulz
989 et al., 2010; Yagishita et al., 2014; Fisher et al., 2017). In *ex vivo* studies, neuromodulators
990 (dopamine, acetylcholine) are typically applied exogenously because of their very low levels
991 when compared to *in vivo*. Neuromodulators are released in tonic and phasic modes *in vivo*
992 and therefore *ex vivo* bath-applications of neuromodulators or specific agonists hardly mimic
993 such complexity of the neuromodulation. It would be important to explore the *in vivo*
994 neuromodulation needed to stabilize STDP or ITDP, by transforming eligibility traces into

995 plasticity, and thus allowing an activity pattern sequence to be pertinent for the engram. Thus,
996 there is a need to collect data *in vivo* in awake and behaving animals and model *in vivo*-like
997 plasticity rules and stimulation patterns to fully understand the action of the third factor in
998 Hebbian learning and information storage and recall.

999 **Figure Legends**

1000 **Figure 1: Dopamine and acetylcholine shape STDP in hippocampus and prefrontal** 1001 **cortex.**

1002 (a) Generic schematics of the main signaling pathways activated in STDP in response to
1003 dopamine, acetylcholine and glutamate. Full and tee-shaped arrows denote activation and
1004 inhibition, respectively. G_x: G-protein coupled receptor signaling x subclass, PKA: Protein
1005 kinase A, MEK-ERK (activation of MAPK), PP1: Protein Phosphatase-1, CaMKII: Calcium-
1006 calmodulin dependent kinase I α , DAG: diacylglycerol, PLC: phospholipase C. (b) In
1007 hippocampus, bidirectional Hebbian STDP observed in control conditions is converted to
1008 tLTP when dopamine is applied during the STDP pairings or just after it. When dopamine is
1009 applied 10 and 30 minutes after STDP pairings, an absence of plasticity and tLTD are
1010 observed, respectively. Adapted from Zhang et al. (2009) and Brzosko et al. (2015).
1011 Acetylcholine, applied during STDP pairings, converts bidirectional Hebbian STDP to
1012 unidirectional tLTD for both post-pre and pre-post pairings. Dopamine applied just after
1013 STDP pairings with acetylcholine during STDP pairings can rescue pre-post tLTP. Adapted
1014 from Brzosko et al., 2017. (c) In the prefrontal cortex, addition of dopamine or D₁- plus D₂-
1015 class receptor agonists to a pairing protocol that does not induce STDP promotes a
1016 unidirectional tLTP. The inhibition of GABA_A receptors or application of agonists of D₂-
1017 class receptors allows the expression of tLTP for pre-post pairings. Conversely, application of
1018 agonists of D₁-class receptors allows the expression of tLTP for post-pre pairings. Activation
1019 of D₂R expressed by GABAergic interneurons (or their direct inhibition by GABA_A receptor
1020 inhibitors) decreases activity of these interneurons uncovering tLTP for pre-post pairings. For
1021 post-pre pairings induction relies on D₁-class receptor (located on the postsynaptic neuron)
1022 activation. Adapted from Ruan et al. (2014) and Xu and Yao (2010), with no permission
1023 required.

1024

1025 **Figure 2: Noradrenaline and acetylcholine shape STDP in the visual cortex.**

1026 (a) Generic schematic of the main signaling pathways activated in STDP in response to
1027 noradrenaline, acetylcholine and glutamate. Abbreviations are those of Figure 1a. (b) In layer

1028 2/3 of the visual cortex, STDP protocols consisting of 120 to 200 pairings at 1Hz do not
1029 produce STDP in control conditions. When α 1- and β -adrenergic receptor agonists (1) or
1030 when muscarinic M_1R and β -adrenergic receptor agonists (3) are applied, then bidirectional
1031 Hebbian STDP can be observed. Unidirectional anti-Hebbian tLTD and unidirectional
1032 Hebbian tLTP are induced after α 1- and β -adrenergic receptor agonist application,
1033 respectively (2); M_1R agonist promotes unidirectional anti-Hebbian tLTD (3). Low and high
1034 concentration of noradrenaline promote unidirectional anti-Hebbian tLTD (2) and
1035 bidirectional Hebbian STDP (1), respectively. (c) Monoamines transform eligibility traces
1036 into plasticity. Hebbian pairings (200 pairings at 10 Hz) induce post-pre tLTD and pre-post
1037 tLTP only if serotonin and noradrenaline are released 5-10 seconds after STDP pairings.
1038 Adapted from Seol et al. (2007), Salgado et al. (2012), Guo et al. (2012), Huang et al. (2013)
1039 and Huang et al. (2014), He et al. (2015) with no permission required.

1040

1041 **Figure 3: GABA_A and GABA_B receptor activation shapes STDP in dorsal striatum and**
1042 **hippocampus.**

1043 (a) Modulation of striatal synaptic plasticity by GABAergic signaling at different post-natal
1044 ages. Schematic view of the impact of GABAergic signaling on corticostriatal STDP
1045 throughout development. Left, at P₇₋₁₀, inhibition of GABAergic signaling turns Hebbian
1046 tLTD into bidirectional Hebbian STDP. Selective activation of tonic GABAergic signaling
1047 converts Hebbian tLTD into bidirectional anti-Hebbian STDP (as observed at P₂₅₋₃₀). Adapted
1048 from Valtcheva et al. (2017). Right, at P₂₅₋₃₀, inhibition of GABAergic signaling shifts
1049 bidirectional anti-Hebbian STDP into bidirectional Hebbian STDP. Selective inhibition of
1050 tonic GABAergic converts bidirectional anti-Hebbian STDP into Hebbian tLTD (as observed
1051 at P₇₋₁₀). Adapted from Paillé et al. (2013) and Valtcheva et al. (2017). (b) In hippocampus,
1052 depending on the frequency of STDP pairings (5, 25 and 50Hz), inhibition of GABA_A or
1053 GABA_B receptors shape differently STDP expression and polarity. GABA_A receptors
1054 modulate the timing dependence of tLTD whereas GABA_B receptors control STDP frequency
1055 dependence. Adapted from Nishiyama et al. (2010) and Sugisaki et al. (2016), with no
1056 permission required.

1057

1058 **Figure 4: Computational models for predicting the direction of STDP have a wide range of**
1059 **complexity. (a) Models differ in morphological complexity, from single-compartment (a1) to**
1060 **multi-compartment models (a2). Top traces show that the back-propagating action potential**
1061 **decreases in amplitude, initiates later and broadens as it propagates distally in multi-**

1062 compartmental models. Bottom traces show that distal synapses may produce higher calcium
1063 elevations than proximal synapses due to higher local input resistance. **(b)** Models differ in
1064 the mechanisms used to control calcium dynamics, from single time constant of decay, to
1065 biophysical/biochemical models of diffusion (red arrows), pumps (such as the plasma
1066 membrane ATPase: PMCA) that extrude calcium (yellow arrow), buffers (such as
1067 calmodulin, calbindin, or immobile buffers) that bind to free calcium (gray arrows), and
1068 calcium release (not shown). All models include influx through the NMDA receptors (blue
1069 arrows). **(c)** The prediction of plasticity from calcium often uses two amplitude thresholds
1070 **(c1)**, but sometimes include duration thresholds **(c2)** or other measures of calcium duration.
1071 T_{LTP} : tLTP amplitude threshold, T_{LTD} : tLTD amplitude threshold, D_{LTD} : threshold on the
1072 duration of the calcium elevation.

1073

1074 **Figure 5: Main predictions of the model of Cui et al. (2016).** **(a)** Scheme of the signaling
1075 pathways that are considered in the model. The postsynaptic weight is set by the amount of
1076 phosphorylated CaMKII whereas the presynaptic weight is controlled by the activation of
1077 CB_1R . Abbreviations: PIP2: phosphatidylinositol 4,5-bisphosphate; DAG: diacylglycerol; IP3:
1078 inositol-1,4,5-triphosphate; $PLC\beta/\delta$: phospholipase-C β/δ ; $DAGL\alpha$: diacylglycerol lipase α ;
1079 2-AG: 2-arachidonoylglycerol; AEA: anandamide; TRPV1: transient receptor potential cation
1080 channel subfamily V member 1; IP3R: IP3-receptor channel; SERCA:
1081 sarcoplasmic/endoplasmic reticulum calcium ATPase; Ca_{ER} : calcium in the endoplasmic
1082 reticulum; $(Ca)_4CaM$: fully bound calmodulin; CaN: calcineurin aka PP2B; PKA: protein
1083 kinase A; I1p/I1: phosphorylated/unphosphorylated protein phosphatase-1 inhibitor 1
1084 (DARPP-32 in striatal output neurons); PP1: protein phosphatase 1; CaMKII:
1085 Ca^{2+} /calmodulin-dependent protein kinase II. **(b)** Prediction of the evolution of the total
1086 synaptic weight (product of the pre- and postsynaptic weights) when the spike timing and the
1087 number of pairing varies. tLTP progressively emerges at positive Δt_{STDP} , whereas for
1088 negative Δt_{STDP} , the model correctly predicts two domains of tLTP, one around 10-20
1089 pairings and another emerging after 50 pairings. **(c)** When CB_1R are blocked in the model,
1090 both the tLTD and the tLTP for low pairing numbers disappear. **(d)** Adding presynaptic D_2Rs
1091 in the model, correctly predicts that tLTP for low pairing numbers is also controlled by
1092 dopamine. Adapted from Cui et al. (2016) with no permission required.

1093

1094

1095 **Author contributions**

1096 AF and AM participated in the writing of the neuromodulators section; JJ, HB and KB wrote
1097 the "Molecular pathway-based computational models of STDP " section; SV wrote the
1098 "Modulation of STDP by astrocytes: the forgotten third factor " section; LV wrote the
1099 introduction, neuromodulators and conclusion sections; all authors have edited and corrected
1100 the manuscript.

1101

1102 **Abbreviations**

1103 STDP: spike-timing dependent plasticity; NMDAR: N-methyl-D-aspartate receptor; BDNF:
1104 brain-derived neurotrophic factor; GABA: gamma-aminobutyric acid; tLTD: timing-
1105 dependent long term depression; tLTP: timing-dependent long term potentiation; CB₁R:
1106 cannabinoid type-1 receptor; D_xR: dopaminergic type-X receptor; M_x: muscarinic type-X
1107 receptor; cAMP: cyclic adenosine monophosphate; nAChRs: Nicotinic acetylcholine
1108 receptors; mAChRs: Muscarinic acetylcholine receptors; NO: nitric oxide; cGMP: cyclic
1109 guanosine monophosphate; DARP-32: dopamine- and cAMP-regulated phosphoprotein, Mr
1110 32 kDa; AMPAR: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor ;
1111 EAAT2: excitatory amino acid transporter-2; mGluR: metabotropic glutamatergic receptor;
1112 ATP: adenosine triphosphate; CaMKII: Ca²⁺/calmodulin-dependent protein kinase-II; ERK:
1113 extracellular signal-regulated kinase; ITDP: input-timing dependent plasticity.

1114

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1119

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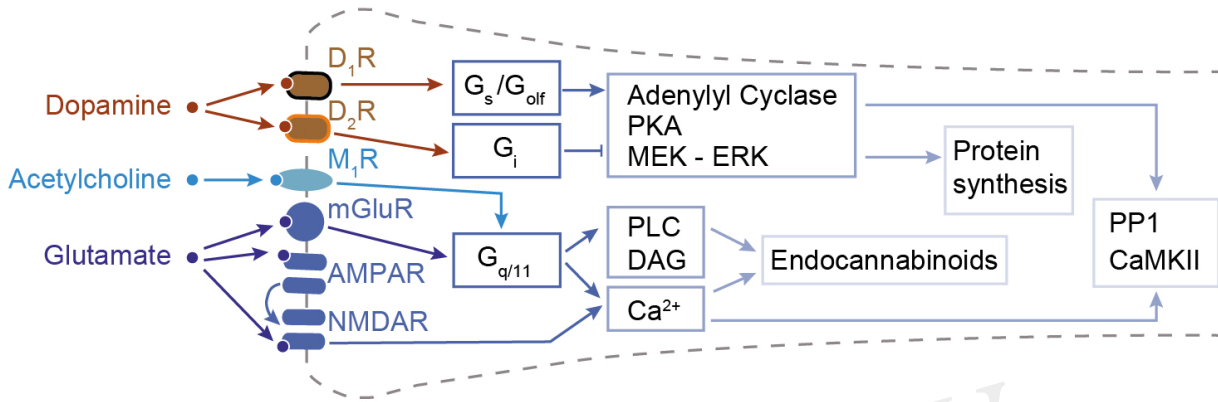
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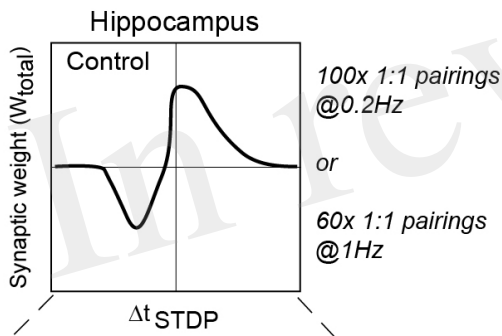
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Figure 1.JPEG

a

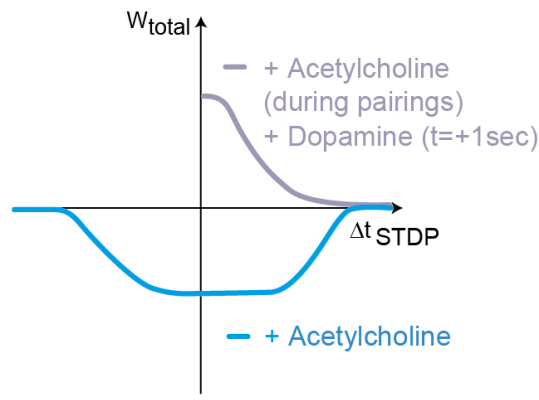
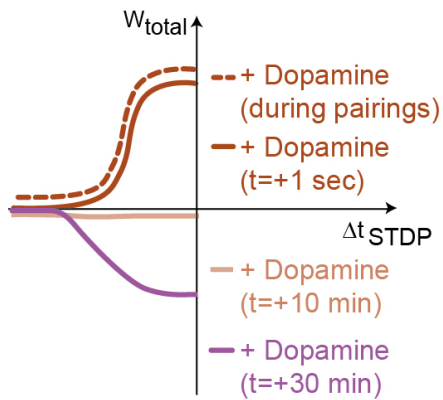


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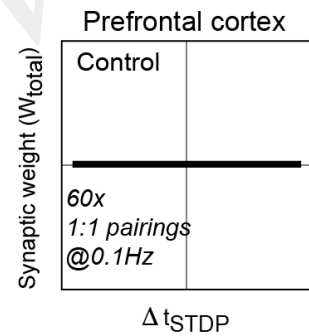


(1)

(2)



c



(1)

(2)

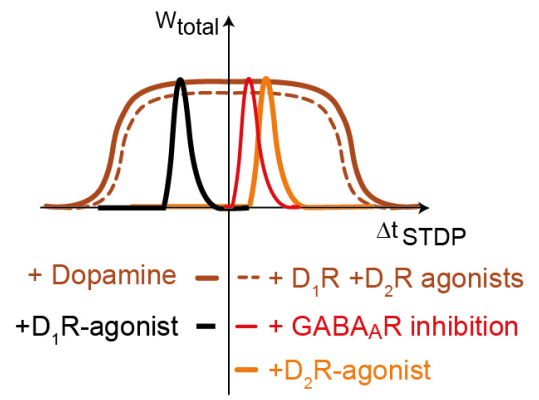


Figure 2.JPEG

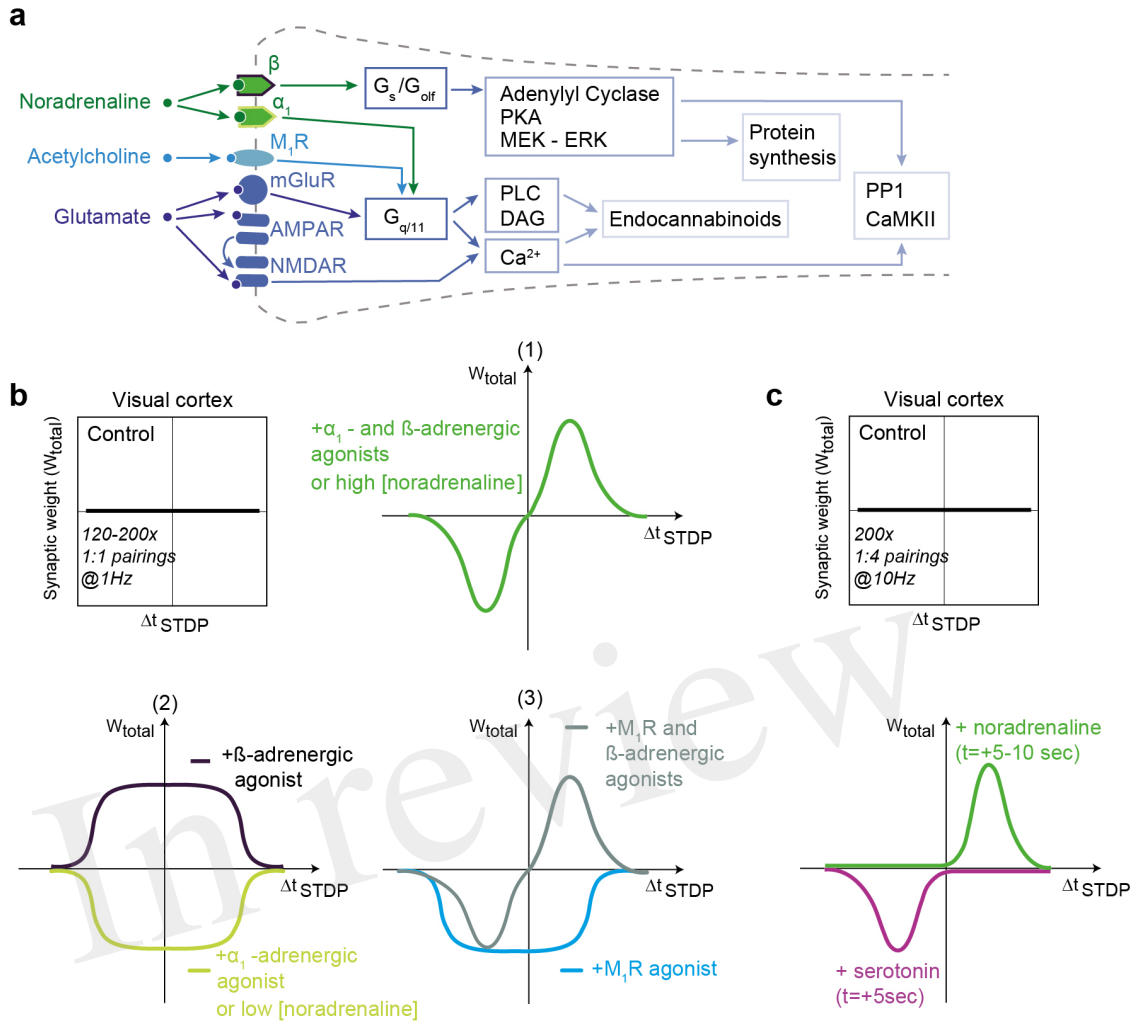


Figure 3.JPEG

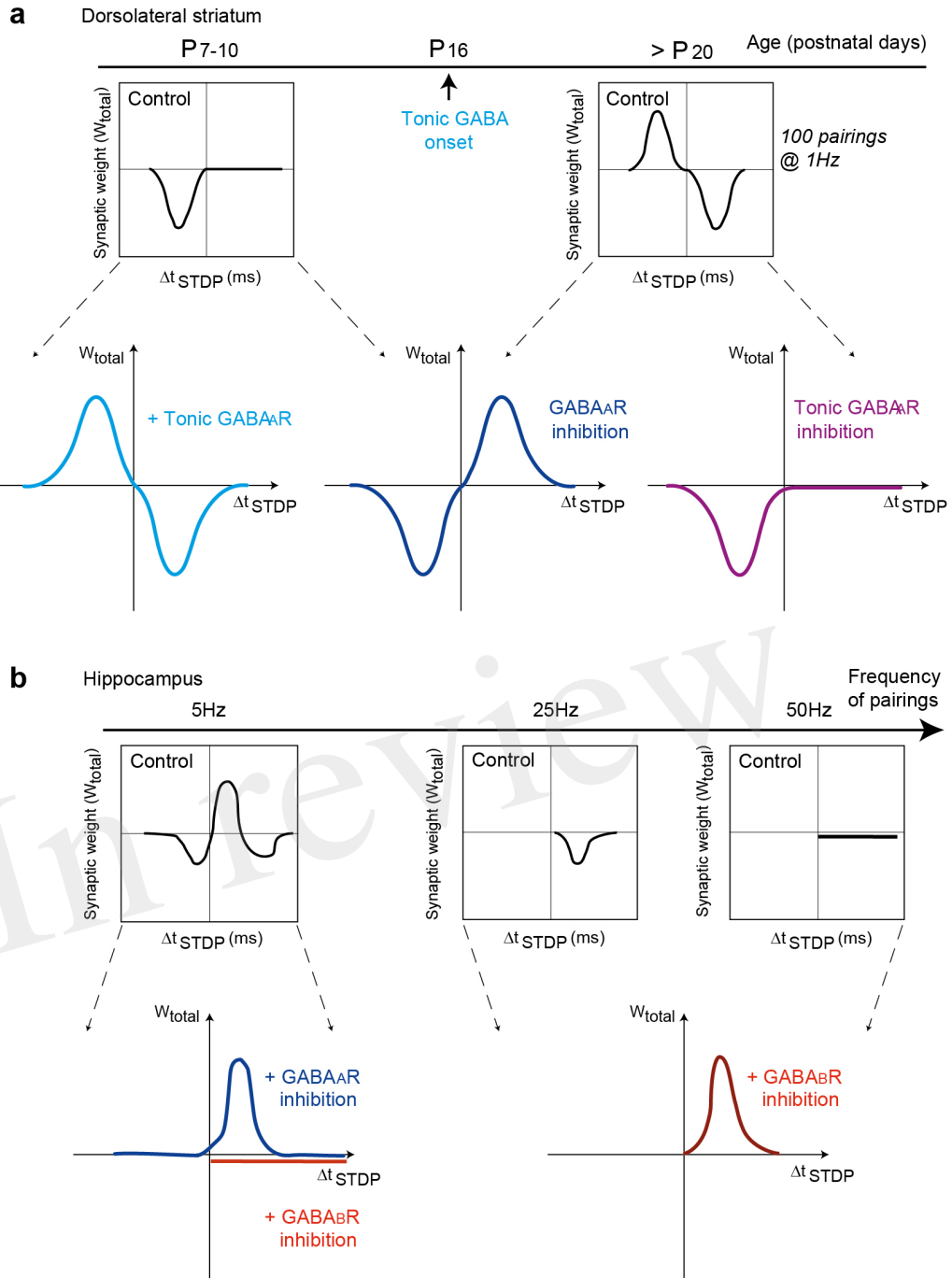


Figure 4.JPEG

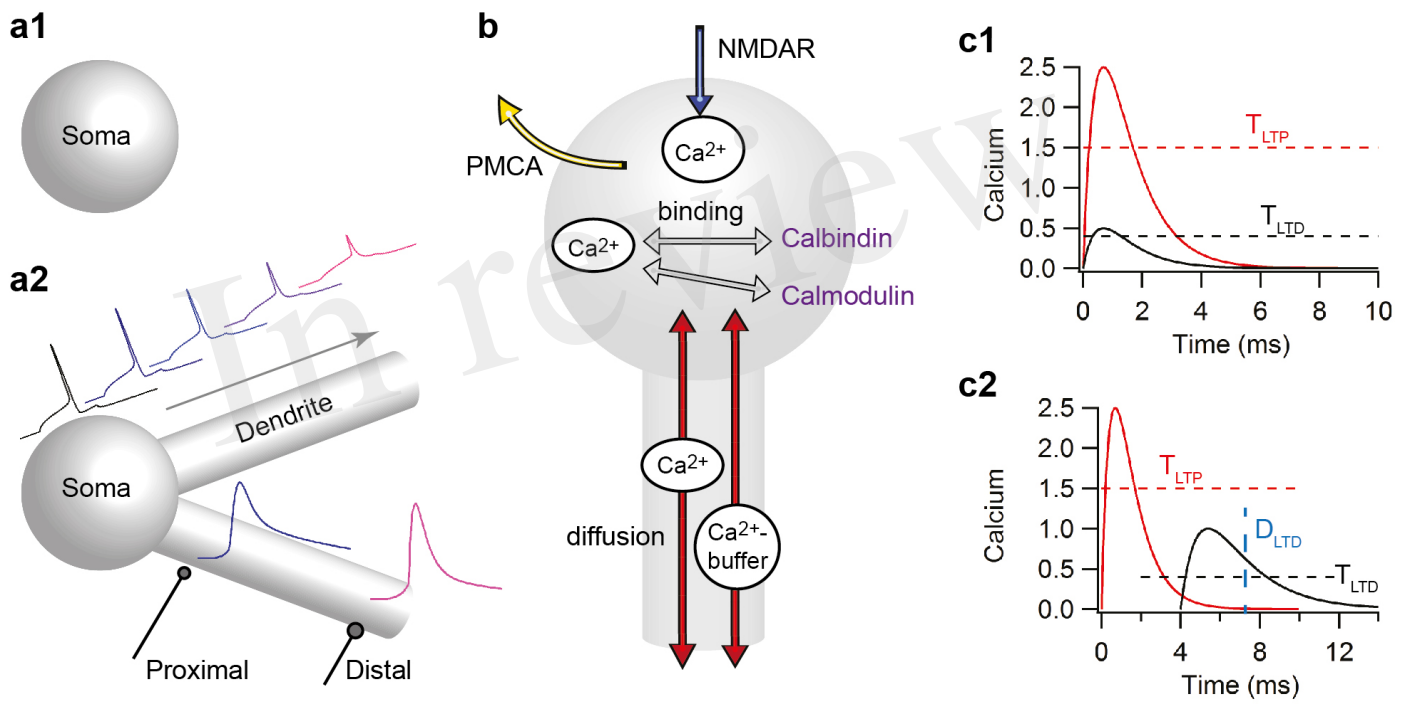


Figure 5.JPEG

