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Spike timing-dependent plasticity and memory

Dominique Debanne¹ & Yanis Inglebert²

¹UNIS, UMR-1072, INSERM, Aix-Marseille Université, Marseille, France

²McGill University, Montreal, Canada

Correspondence should be addressed to Dominique Debanne

dominique.debanne@inserm.fr

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22 pages, 112 references

52 **Abstract**

53 Spike timing-dependent plasticity (STDP) is a bidirectional form of synaptic plasticity
54 discovered about 30 years ago and based on the relative timing of pre- and post-synaptic
55 spiking activity with a millisecond precision. STDP is thought to be involved in the formation of
56 memory but the millisecond-precision spike-timing required for STDP is difficult to reconcile
57 with the much slower timescales of behavioral learning. This review therefore aims to expose
58 and discuss recent findings about i) the multiple STDP learning rules at both excitatory and
59 inhibitory synapses *in vitro*, ii) the contribution of STDP-like synaptic plasticity in the formation
60 of memory *in vivo* and iii) the implementation of STDP rules in artificial neural networks and
61 memristive devices.

62 **Introduction: memory formation, associative learning and synaptic plasticity**

63 Memory is usually defined as the ability to use past experience to adapt and optimize the
64 behavior for present and future events. Formation of internal representation in the form of
65 memory take places in several steps; acquisition, encoding and retrieval. The formation of the
66 memory trace (i.e. the engram) and retrieval of memory has been reviewed recently [1] [2].
67 Encoding of memory is thought to be principally achieved through persistent modifications in
68 both excitatory and inhibitory synaptic transmission [3] [4] in conjunction with modulation of
69 intrinsic neuronal excitability [5]. In associative learning such as Pavlovian conditioning, a form
70 of Hebbian plasticity [6], storage of new information relies on the occurrence of a specific event
71 that can be an automatic behavioral response (salivation) to an unconditioned stimulus (meat
72 in Pavlov experiment). In neurobiological terms, this stimulus is thought to produce a strong
73 response, i.e. a neuronal discharge of action potentials (APs). The temporal association of this
74 stimulus with a neutral stimulus (bell ring) causing initially no behavioral response leads after
75 a few repetitions to the acquisition of a new behavior (salivation) in response to the neutral
76 stimulus (bell ring). The temporal contiguity between the two stimuli is important as the
77 dissociation or the random presentation of the two stimuli does not induce any learning.

78 Temporal synchrony of neural events is critical for sensory perception of visual scenes
79 or auditory stimuli [7]. This temporal binding is thought to be mediated by both network
80 properties [8] and axonal sodium channels that read and transmit levels of input synchrony in
81 local brain circuits [9]•. But according to the Hebb law, repeated temporal synchrony between
82 pre- and post-synaptic activity may also lead to reinforcement of excitatory inputs.

83 Here we review recent findings devoted to spike timing-dependent synaptic plasticity
84 (STDP) both *in vitro* and *in vivo*. In a first section, this review will establish the definition and
85 history of STDP. Then, the multiplicity of STDP learning rules at excitatory synapses and
86 inhibitory synapses will be discussed. Next, the mechanisms underlying STDP will be
87 dissected and the involvement of STDP-like plasticity in the formation of place field in the
88 hippocampus *in vivo* will be debated. Finally, the implementation of STDP rule in artificial
89 neural networks will be mentioned.

90

91 **Definition and brief history of STDP**

92 STDP is a form of long-term synaptic modification that is induced by the relative order of pre-
93 and post-synaptic spiking activity [10] [11] [12]. Originally derived from classical conditioning
94 [13] and Hebbian synaptic plasticity [14] [15], the concept of STDP emerged during the 1990's
95 with the discovery of the importance of timing in the polarity of long-lasting synaptic changes
96 [16] [17] [18] [19] [20]. Following the Hebbian principle, timing-dependent long-term synaptic
97 potentiation (t-LTP) results from the positive temporal correlation between an excitatory post-
98 synaptic potential (EPSP) followed a few milliseconds later by one or more postsynaptic APs
99 [15] [19] [20]. In contrast, timing-dependent long-term synaptic depression (t-LTD) results from
100 negative temporal correlation between an EPSP preceded by one or more postsynaptic APs
101 [16] [19] [20]. Thus, STDP is classically characterized by an asymmetric learning rule that
102 defines a causality relation [21] (**Figure 1A**). STDP is a general learning rule as it has been
103 reported in insects [22], and mammals including humans [23] [24,25]. It should be noted that
104 the spike number used to induce synaptic plasticity determines the extent of the t-LTP and t-
105 LTD windows, since the larger the number of spikes, the larger the temporal windows [16] [19]
106 (**Figure 1B**). t-LTD requires a higher number of association than t-LTP. In fact, while 3-6
107 pairings are sufficient to induce t-LTP with positive delays, this number is not sufficient to
108 induce t-LTD [26]. Similar conclusion has been drawn by another group using 20 pairings [27].

109 While t-LTP is due to the activation of postsynaptic NMDA receptor (NMDAR) by the
110 back-propagated AP in the dendrite [19] [20], some forms of t-LTD has been shown to involve
111 presynaptic NMDAR and postsynaptic endocannabinoid (eCB) signaling [28] [29].
112 Experimentally, APs are triggered by a depolarizing step of current, naturally, however, they
113 are produced by a strong excitatory input as in the case of Pavlovian conditioning. Post-
114 synaptic spiking is not required in all the cases. Strong synaptic depolarization has been shown
115 to be more effective than back-propagated action potentials during induction of t-LTP in CA1
116 neurons [30]. In addition, subthreshold mossy fiber EPSPs are able to provide sufficient
117 depolarization to induce STDP at recurrent excitatory input in CA3 neurons [31]. Dendritic

118 NMDA spikes initially found in neocortical basal dendrites [32] has been shown to be critical in
119 STDP induction at hippocampal CA3-CA3 synapses [33] [34] and at olfactory bulb inputs in
120 the piriform cortex [35]. In addition, theoretical studies indicate that NMDA spikes promotes
121 cooperativity among synapses and lowers plasticity threshold [36].

122

123 **Multiple STDP rules at excitatory synapses**

124 While early papers reported classical asymmetric STDP curves at synapses formed by pairs
125 of CA3-CA3 pyramidal neurons [19], recent findings indicate a symmetric STDP curve with t-
126 LTP only (i.e. a lack of t-LTD) at recurrent excitatory synapses of CA3 pyramidal neurons [37]
127 (**Figure 1C**). A similar symmetric STDP curve has been observed at Schaffer collateral inputs
128 to CA1 pyramidal neurons in adult but not in young mice [38]•. Importantly, the absence of t-
129 LTD for negative correlation (post- before pre-) in adults involves release from astrocytes since
130 calcium chelation of the astrocyte cytosol prevents t-LTP and restores classical t-LTD.

131 Concurrent STDP rules for thalamic and cortical inputs have been observed in layer 2-
132 3 neurons of the barrel cortex during postnatal development [39]. The emergence of t-LTD is
133 related to the emergence of eCB signaling and may account for the transition from network
134 formation to the emergence of the critical period [40]. In the striatum, the thalamo-striatal inputs
135 that contribute to the initiation of movement, display a conventional asymmetric STDP curve
136 whereas cortico-striatal inputs display an inverted asymmetric curve [41] (**Figure 1C**). In
137 addition, cortico-striatal inputs express different learning rules as a function of the position in
138 the striatum. Symmetric STDP curve in the dorsolateral striatum but a t-LTD-only curve in the
139 dorsomedial striatum [42] (**Figure 1C**). Interestingly, t-LTP depends on eCB signaling in this
140 brain region [43].

141 STDP rule depends also on the cooperativity among dendritic spines in CA1 pyramidal
142 neurons [44]. Whereas t-LTP and t-LTD are observed at single dendritic spines, t-LTP but not
143 t-LTD occurs at clustered dendritic spines [45]•. The suppression of t-LTD has been recently
144 reported in the anterior cingulate cortex following induction of neuropathic pain [46]. In this

145 case, t-LTD impairment is mediated by the exclusion of GluN2B-containing NMDAR from the
146 postsynaptic site.

147

148 **STDP in inhibitory circuits**

149 STDP at glutamatergic synapses of GABAergic interneurons has been studied. For instance,
150 eCB-dependent t-LTD has also been reported at excitatory synapses on hippocampal
151 GABAergic interneurons [47] [48]. However, no t-LTP is found at excitatory inputs of fast
152 spiking (FS) interneurons [49] except if adrenergic receptors are co-stimulated [50].

153 Early studies showed that STDP at inhibitory synapses generally obeys anti-Hebbian
154 rule (i.e., t-LTP for negative correlation and t-LTD for positive correlation, **Figure 2A**) [51]. At
155 hippocampal inhibitory synapses, a symmetrical STDP curve with t-LTP only has been
156 reported, however [52]. This discrepancy among studies results in fact from different
157 developmental stages. In the auditory cortex, the GABAergic synapse established by FS
158 interneurons onto layer 4 glutamatergic neurons undergoes asymmetric anti-Hebbian STDP
159 during the critical period (**Figure 2A**) [53]●●. However, in mature animals the STDP rules
160 becomes symmetric with time-dependent LTP of inhibition (t-LTPi) only (**Figure 2A**). t-LTPi
161 depends of retrograde brain-derived factor (BDNF) signaling whereas time-dependent LTD of
162 inhibition (t-LTDi) involves GABA_B receptors [53]●●. Interestingly, sound exposure during the
163 critical period converts t-LTDi into t-LTPi while genetic deletion of GABA_BR prevents auditory
164 critical period plasticity. The asymmetric anti-Hebbian STDP curve for inhibitory synapses
165 during the critical period suggests that coordinated plasticity occurs between excitatory and
166 inhibitory plasticity at least during development (**Figure 2B**). In computational networks, the
167 symmetric plasticity rule with t-LTPi only described at inhibitory synapses of the auditory cortex
168 [54] [53]●● or at glycinergic synapses of the medial superior olive [55] allows the generation of
169 novelty responses [56].

170 Inhibitory STDP plays an essential role in the formation and maintenance of functional
171 cortical circuitry as its introduction in modelled recurrent networks provides a homeostatic

172 mechanism leading to asynchronous irregular network states [57]. In addition, inhibitory STDP
173 concurs to balance excitatory and inhibitory inputs in a model of feed-forward inhibition [58].

174

175 **Mechanisms of STDP: mitochondria, potassium channel & calcium levels**

176 Calcium (Ca^{2+}) influx is an essential trigger of STDP since most if not all forms of STDP
177 reported so far depends on NMDAR activation, voltage-gated calcium channels or the
178 mobilization of intracellular calcium stores [12].

179 Another player recently came into play: dendritic mitochondria. In fact, during period of
180 enhanced neuronal activity, cytosolic Ca^{2+} elevations propagate into the mitochondrial matrix
181 that subsequently accelerate ATP production. Mitochondrial activity is critical for local protein
182 synthesis in the dendrites [59] and synaptic plasticity [60]. Using a mitochondria-specific Ca^{2+}
183 probe, the group of Fleidervish recently showed that mitochondrial Ca^{2+} is elevated during
184 coincident EPSP and AP, but not during an EPSP or an AP alone [61]•. Importantly,
185 mitochondrial Ca^{2+} also decodes spike frequency and spike number. This study thus points to
186 the role of mitochondria in STDP induction.

187 NMDAR and metabotropic glutamate receptor (mGluR) have been both implicated in
188 synaptic plasticity. While postsynaptic NMDAR is necessary for the induction of t-LTP at many
189 different synapses, the primary role of presynaptic NMDAR for the induction of t-LTD in the
190 cortex [29] and hippocampus [62] has been revealed recently. mGluR acts as a coincidence
191 detector at synapses where NMDAR is not involved in plasticity induction [63]. Hippocampal t-
192 LTD and t-LTP induced by negative correlation at different ages require activation of mGluR5
193 [38,62]. Voltage-gated channels are also involved in STDP control. In fact, calcium-activated
194 small conductance K^+ (SK) channels shunt calcium influx through NMDARs [64] and mGluR
195 has a negative action on SK channels [65] [66]. Moreover, large conductance calcium-
196 activated K^+ (BK) channels activation reduces EPSP amplitude at neocortical synapses with
197 small head volume [67], suggesting their possible involvement in the control of synaptic
198 plasticity [68]. Other potassium channels gate induction of STDP. The adrenergic-gating of t-
199 LTP in hippocampal CA1 neurons is mediated by Kv1 channels [69]. Mild stress down-

200 regulates postsynaptic Kv4.2 channels through the PIK3, leading to the up-regulation of t-LTP
201 in neurons from nucleus accumbens [70].

202 The external calcium concentration varies in the brain between 1.1 and 1.5 mM [71,72].
203 However, all the *in vitro* work devoted to STDP uses much higher calcium concentration (i.e.
204 2.0 to 3.0 mM). The large variability of STDP curves reviewed here can be explained by
205 fluctuations in postsynaptic calcium as showed theoretically by Graupner and Brunel [73].
206 Based on this theoretical work, Inglebert & co-workers showed indeed that physiological
207 calcium has a profound impact on STDP curve [74]●●. While in high external calcium (3 mM),
208 a conventional asymmetric curve is reported, in 1.8 mM only t-LTD is observed and in 1.3 mM,
209 no synaptic plasticity is found (**Figure 3A**). In physiological calcium (1.3 mM), plasticity could
210 be restored by increasing the frequency of stimulation (t-LTP) or increasing the number of
211 postsynaptic spikes used during induction (t-LTD) [74]●●. Similarly, in the neocortex,
212 physiological calcium concentration reduces or abolishes t-LTP and t-LTD [75]●. Both plasticity
213 can, however, be restored with higher frequency stimulation.

214

215 **STDP-based plasticity and memory formation**

216 CA1 place fields can emerge from a initially unresponsive neuron when spontaneously
217 occurring dendritic plateau potential is triggered during the exploration [76]●. In this case, a
218 single postsynaptic depolarization triggering multiple spikes is paired with putative presynaptic
219 activity may lead to the reinforcement of excitatory synapses that were initially silent or to the
220 silence of inhibitory inputs that were initially active. More recently, the same group showed that
221 when the dendritic plateau potential occurs a few seconds before the place field-evoked a new
222 place field appears at the detriment of the old place field [77]●● (**Figure 4**). This finding
223 rehabilitates the use of a burst of APs that induces large LTD window found in early studies
224 [16] [17] as well as the use of single dendritic events to induce synaptic plasticity [78] [76]●.

225 Dopamine and serotonin are important neuromodulators of synaptic plasticity that are
226 respectively linked to positive or negative reward during learning. In hippocampal and
227 neocortical neurons, dopamine renders the STDP rule symmetric with t-LTP only [79,80] while

228 serotonin promotes t-LTD only [81]. A mathematical model shows that the interplay of
229 dopamine and serotonin improves hippocampal learning [82]. Similarly, noradrenaline
230 facilitates induction of t-LTP in the visual cortex [81], and stimulation of noradrenergic or
231 serotonergic system during visual stimulation respectively promotes reinforcement or
232 depression of visual cortical responses and can rescue deficits induced by monocular
233 deprivation [83,84]•. A fundamental problem in neuroscience is how the brain associates and
234 encodes events that are separated in time. Postsynaptic burst reactivation of hippocampal
235 neurons during dopaminergic stimulation has recently shown to enable associative plasticity
236 of temporally dis-contiguous inputs [85].

237 Memory is particularly altered in Alzheimer disease (AD) with a higher predisposition to
238 develop the disease for women. Classical LTP induced by presynaptic high-frequency
239 stimulation is impaired in mouse models of AD (see [86] for recent review). Interestingly, STDP
240 is also altered in murine models of AD. t-LTP is impaired at CA1 pyramidal neurons that are
241 proximal to the amyloid- β plaque but not at CA1 neurons that are distal ($>200\ \mu\text{m}$) [87].
242 Similarly, t-LTP is altered at excitatory synapses on cortical layer 2/3 (L2/3) pyramidal cells
243 because soluble amyloid- β protein reduces the opening of AMPAR [88]. At L5 cortical neurons,
244 t-LTP is also impaired in a mouse model of AD [89]. STDP-like forms of plasticity induced by
245 transcranial magnetic stimulation are impaired in AD patients [90]. Matrix metalloproteinases
246 (MMP) play a crucial role in the pathogenesis of AD and induction of t-LTP in the barrel cortex
247 requires normal activity of MMP-9 [91]. In addition, the predisposition of females to AD has
248 been confirmed experimentally by showing that in a mouse model of AD, t-LTP shows a faster
249 decay in females compared to males [92].

250 STDP-like mechanisms are also involved in neuropsychiatric diseases such as
251 depression induced by chronic stress. The lateral habenula has recently emerged as a key
252 brain region in the pathophysiology of depression. Elevated neuronal activity in the lateral
253 habenula is a sign of depression [93]. Potentiating hypothalamic to lateral habenula inputs by
254 an EPSP-burst pairing leads to lasting changes of emotional status similar to the depression
255 [94]. Moreover, endocannabinoid-dependent t-LTD is reduced following induction of social

256 defeat stress in neurons of the nucleus accumbens [95], another brain region involved in
257 reward and depressive disorders. In the same brain region, chronic unpredictable mild stress
258 enhances t-LTP [70], thus indicating that a general increase in synaptic excitation is induced
259 by stress in nucleus accumbens.

260

261 **Implementation of STDP in artificial neural networks and memristive devices**

262 Many synaptic plasticity rules found in natural circuits have been incorporated in artificial neural
263 networks. For instance, incorporation in artificial neural networks of the back-propagating t-
264 LTP found in hippocampal circuits [96], reduces the computational cost without affecting the
265 accuracy of the artificial circuits [97]. This indicates that self-back-propagating plasticity
266 produces coordinated modifications across neuronal layers. Temporally symmetric STDP rule
267 reported in CA3 neurons [37] has been shown to be essential in a network model of area CA3
268 for proper sequence replay in both forward and backward directions [98]. Sequential spiking
269 activity reflecting previous experience is considered as a hallmark of learning. However, the
270 way cortical circuits avoid the opposite problem, i.e. producing spurious sequences that are
271 not relevant to learning, was not clearly established. This problem has been theoretically and
272 experimentally solved recently. In fact, STDP in cortical circuits containing excitatory and
273 inhibitory neurons eliminates spurious sequences of action potentials [99]. In addition,
274 responses to artificial stimuli measured in the visual cortex of awake ferret initially includes
275 spurious sequences which diminished over extended exposure [99].

276 Incorporation of unsupervised STDP learning rule in artificial neural networks has
277 revealed a remarkable ability for object and digit recognition [100●,101]. Moreover, in an
278 artificial saccadic system under the control of a cerebellar-like artificial spiking network
279 incorporating STDP rules at the parallel fiber-Purkinje cell synapse, accuracy and speed of
280 simulated saccadic eye movements are improved through synaptic plasticity [102].

281 Increasingly large computing needs at a low energy cost have led to the development
282 of new nanometric memory media based on the properties of brain synapses. Memristors (or
283 memristive devices) are memory resistors, i.e. electrical resistance switches that can retain a

284 state of internal resistance based on the recently applied voltage and current. Functionally,
285 memristors are able to mimic synapse function and thus correspond to tunable electronic
286 synapses. Physically, they are based on ionic motion and are made of a layer of metal oxide
287 sandwiched between two metal electrodes [103]. STDP rules have been successfully
288 implemented in memristors [104] [105] [106] [107]. For instance, a network of memristors
289 including STDP rules is able to robustly detect the coincidence by selectively increasing
290 synaptic efficacy of synchronized inputs [104]. Furthermore, memristors are able to capture
291 natural synapses properties as frequency dependent plasticity and temporal integration of
292 plasticity induced by triplets of pre- and post-synaptic spikes [105]. However, memristors are
293 not limited to mimicking real brain synapses, and self-powered, second-order memristors are
294 able to emulate functional properties of visual cortical neurons such as orientation selectivity
295 [108,109]. This research field is extremely dynamic and there are good reasons to believe that
296 the implementation of STDP in artificial synapses will lead to tremendous improvements in
297 computing power at a low energy cost.

298

299 **Conclusion and perspectives**

300 Impressive progresses have been achieved these last 30 years in the understanding of STDP
301 rules at excitatory and inhibitory synapses, in different cortical layers, in various brain regions
302 and during learning. Initially reported *in vitro*, STDP is now clearly demonstrated *in vivo*.
303 However, some questions remain unanswered. First, a large part of our knowledge on the role
304 of STDP in learning and memory comes from modelling studies that present the advantage to
305 be largely predictive but these models are often too simplistic to account for the complexity of
306 the mechanisms occurring in the real brain.

307 STDP rules at excitatory inputs described for ages with abnormally elevated external
308 calcium are in fact profoundly altered in physiological extracellular calcium [74]●●. It is possible
309 that the symmetric STDP curve (i.e., LTP only) observed at both CA3 recurrent excitatory
310 synapses [37] and in mature CA3-CA1 synapses [38]● could become asymmetric (i.e.,
311 LTD/LTP) in physiological calcium.

312 In addition, the STDP rules in physiological calcium are still unknown at inhibitory
313 synapses on pyramidal neurons and on interneurons. In particular, the developmental
314 transition from a t-LTPi/t-LTDi plasticity rule to a uniform t-LTPi rule [53]●● could perhaps not
315 be preserved in physiological calcium. In addition, STDP at inhibitory synapses may obey
316 different learning rules depending on the nature of the presynaptic interneuron and the
317 projection sites. Therefore, the use of paired-recording (or optogenetic tools) must be
318 generalized to unambiguously characterize the presynaptic interneuron [53]●● [110,111].

319 Another set of questions are related to the induction of STDP *in vivo*: what triggers
320 dendritic spikes in hippocampal pyramidal neurons during spatial exploration *in vivo* [76]●
321 [77]●●? This may result from a selective and massive dendritic disinhibition together with a
322 sudden and massive synaptic and intrinsic excitation. What triggers this abrupt disinhibition?
323 Disinhibition is classically mediated by the selective activation of inhibitory interneuron-
324 targeting GABAergic cells such as vasoactive intestinal polypeptide- (VIP) expressing
325 interneurons. While to date the contribution of VIP interneurons to STDP remains unknown, a
326 recent study shows that associative LTP is possible upon activation of VIP interneurons [112]●.
327 Further studies will certainly provide answers to all these pending questions.

328

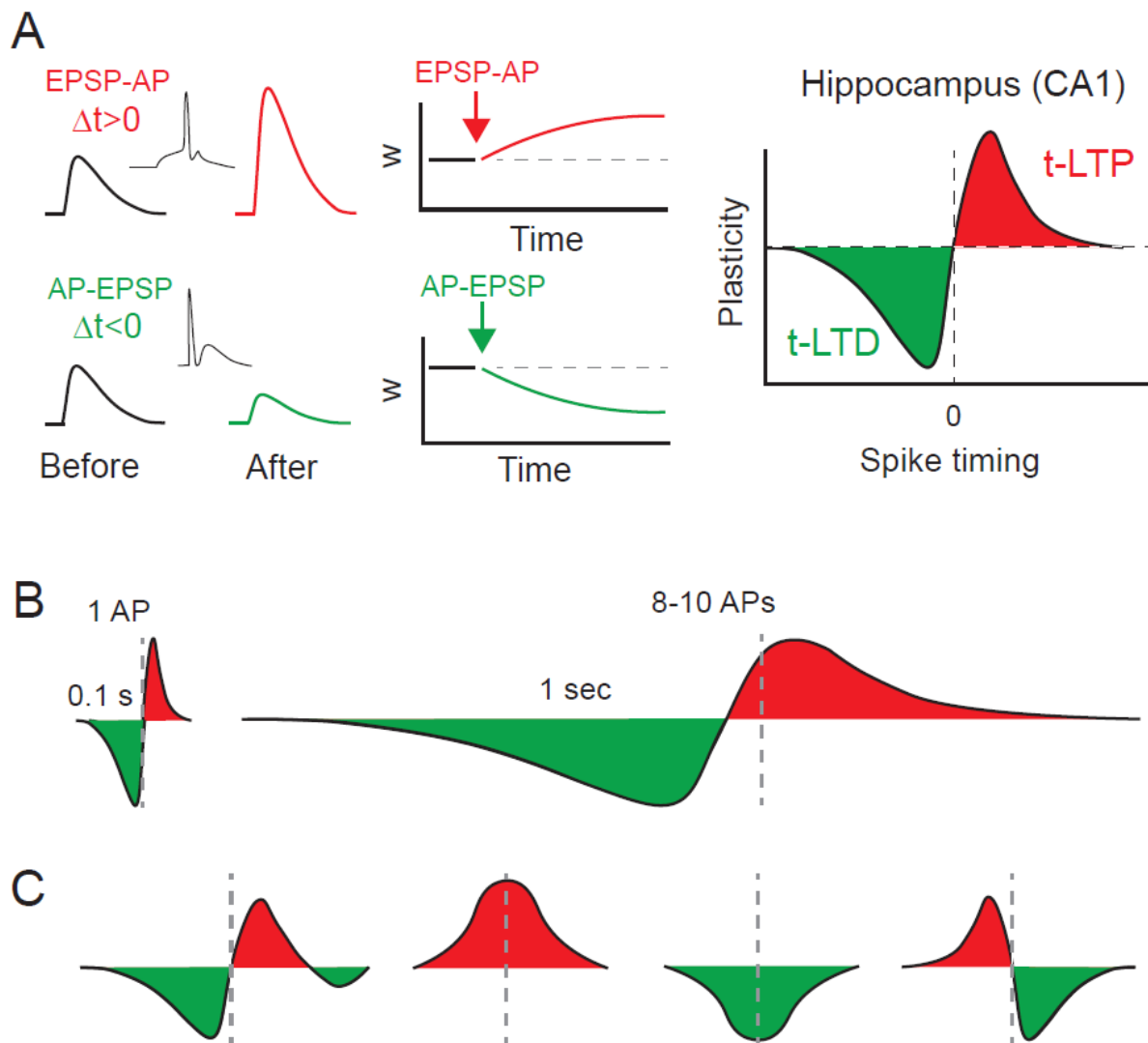
329 **Conflict of interest statement**

330 The authors declare no conflict of interest.

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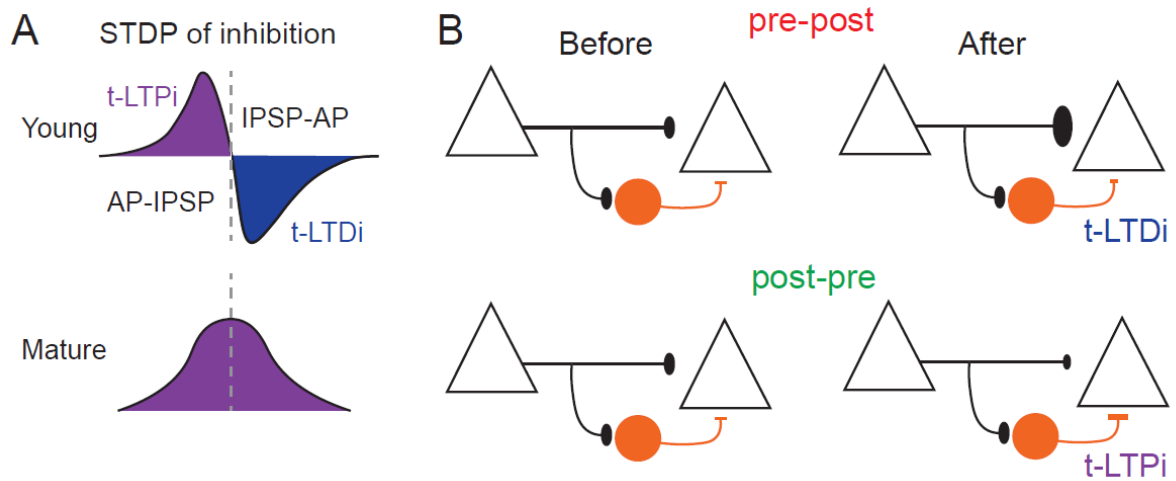
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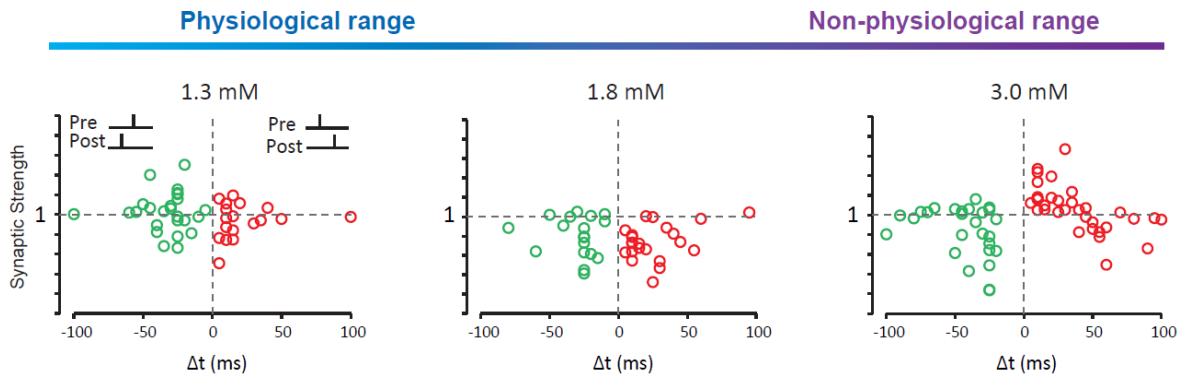
341 **Figure 1.** Spike timing-dependent plasticity (STDP) at excitatory inputs. A. Asymmetric STDP
 342 curve. Left, enhancement of synaptic transmission (t-LTP) following repeated EPSP-AP
 343 sequences and depression of synaptic transmission (t-LTD) following repeated AP-EPSP
 344 sequences. Middle, time-course of t-LTP (top) and t-LTD (bottom). Right, plasticity as a
 345 function of spike timing. For positive correlation (EPSP-AP, $\Delta t > 0$) t-LTP is observed (red)
 346 whereas for negative correlation (AP-EPSP, $\Delta t < 0$) induces t-LTD. B. Time windows for t-LTP
 347 and t-LTD depends on the spike number. For 1 postsynaptic AP, the time window is small
 348 (~ 0.1 s) whereas for a large number of postsynaptic AP (8-10), the time window is larger (~ 1
 349 sec; adapted from [16,19]). C. Variability of STDP curves at excitatory inputs. Left, asymmetric
 350 STDP curve with a second t-LTD window. Middle, t-LTP only and t-LTD only. Right, anti-
 351 Hebbian asymmetric curve.



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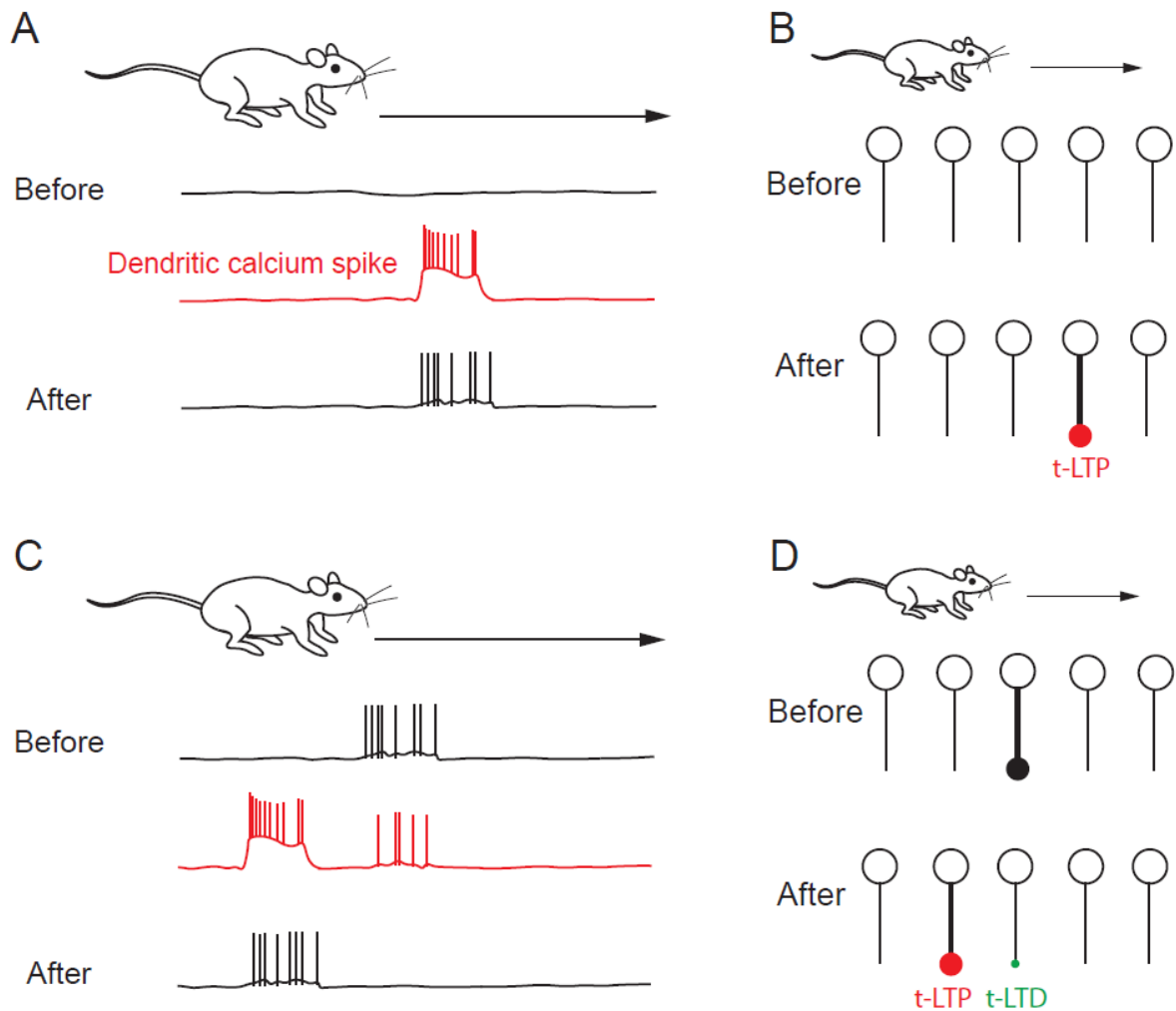
353 **Figure 2.** STDP at inhibitory synapses. A. Anti-Hebbian asymmetric curve observed at fast-
 354 spiking interneuron-pyramidal neuron in young mice becomes symmetric with age (adapted
 355 from [53]●●). B. Synergy between plasticity at excitatory and inhibitory synapses. Simplified
 356 circuit constituted of three neurons (2 pyramidal cells and 1 FS interneuron). Top, pre-post
 357 spiking activity leads to enhanced synaptic excitation and reduced synaptic inhibition (t-LTDi).
 358 Bottom, post-pre spiking activity reduces synaptic excitation and enhance synaptic inhibition
 359 (t-LTPi).

360



361

362 **Figure 3.** STDP under various external calcium concentrations in CA1 pyramidal neurons
 363 recorded in a whole-cell configuration. Pre-synaptic stimulation was evoked by a stimulation
 364 electrode placed in the Schaffer collaterals. These results were obtained with a simple 1:1
 365 protocol (i.e. 1 presynaptic and 1 postsynaptic action potential) with a low pairing frequency of
 366 0.3 Hz and 100 repetitions for t-LTP, and 150 repetitions for t-LTD. In 1.3 mM extracellular
 367 calcium, no plasticity is induced. In 1.8 mM extracellular calcium, pre-post and post-pre
 368 protocols leads to t-LTD. In 3 mM extracellular calcium, pre-post protocol leads to t-LTP and
 369 post-pre protocol leads to t-LTD. Adapted from [74]●●.



370

371 **Figure 4.** STDP-like plasticity induced by dendritic calcium spike in mouse CA1 hippocampal
 372 neurons during spatial exploration. A. & B. Emergence of a place field in a silent neuron. A.
 373 Voltage responses of a CA1 pyramidal neuron before and after the spontaneous occurrence
 374 of a dendritic spike (red trace). B. Interpretation of the plasticity. In initial conditions (Before),
 375 the neuron is silent during the exploration of the environment (A) indicating that presynaptic
 376 CA3 synapses are weak (B). After dendritic calcium spike (After), the CA3 input spatially
 377 corresponding to the animal position when the dendritic calcium spike occurred is strongly
 378 potentiated (symbolized by a big red terminal, B). C & D. Plasticity of an existing place field
 379 induced by dendritic calcium spike. C. The dendritic calcium spike precedes the place-field
 380 evoked discharge by a few hundred milliseconds. D. Interpretation of the changes. In initial
 381 conditions (Before), the CA3 input corresponding to the animal position in the place field is
 382 strong (big and black terminal). After dendritic calcium spike, this input weakens (green and
 383 small terminal) and the neighbor input is potentiated (red and big terminal). Adapted from [76]●
 384 [77]●●.

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