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1 **Robustness of STDP to spike timing jitter**

2
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15 **ABSTRACT**

16 In Hebbian plasticity, neural circuits adjust their synaptic weights depending on patterned
17 firing. Spike-timing-dependent plasticity (STDP), a synaptic Hebbian learning rule, relies on
18 the order and timing of the paired activities in pre- and postsynaptic neurons. Classically, in
19 *ex vivo* experiments, STDP is assessed with deterministic (constant) spike timings and time
20 intervals between successive pairings, thus exhibiting a regularity that differs from biological
21 variability. Hence, STDP emergence from noisy inputs as occurring in *in vivo*-like firing
22 remains unresolved. Here, we used noisy STDP pairings where the spike timing and/or
23 interval between pairings were jittered. We explored with electrophysiology and
24 mathematical modeling, the impact of jitter on three forms of STDP at corticostriatal
25 synapses: NMDAR-LTP, endocannabinoid-LTD and endocannabinoid-LTP. We found that
26 NMDAR-LTP was highly fragile to jitter, whereas endocannabinoid-plasticity appeared more
27 resistant. When the frequency or number of pairings was increased, NMDAR-LTP became
28 more robust and could be expressed despite strong jittering. Our results identify
29 endocannabinoid-plasticity as a robust form of STDP, whereas the sensitivity to jitter of
30 NMDAR-LTP varies with activity frequency. This provides new insights into the mechanisms
31 at play during the different phases of learning and memory and the emergence of Hebbian
32 plasticity in *in vivo*-like activity.

33 INTRODUCTION

34 Long-term changes in synaptic efficacy between neurons are thought to underlie learning and
35 memory¹ and can be assessed with a synaptic Hebbian paradigm such as spike timing-
36 dependent plasticity (STDP)²⁻⁸. In STDP, the occurrence of timing-dependent-long-term
37 potentiation (tLTP) or -depression (tLTD) is the result of three factors. The two first ones are
38 the two coincident activity patterns on either side of the synapse, which depends on 1) the
39 relative timing between pre- and postsynaptic spikes (Δt_{STDP})^{4,8}, 2) the dendritic and axonal
40 propagation delays⁹, 3) the number of paired spikes (N_{pairings})¹⁰⁻¹³, 4) the frequency of the
41 paired spikes (F_{pairings})^{6,7,10,11,14} and 5) membrane depolarization^{14,15}; the third factor involves
42 in STDP expression mainly refers to neuromodulators^{16,17} and glial cells¹⁸.

43 STDP has been attracting a lot of interest in computational and experimental neurosciences
44 because it relies on spike correlation and has emerged as a candidate mechanism for
45 experience-dependent changes in neural circuits, including map plasticity^{8,19-23}. STDP is
46 classically investigated using regular repetitions of the same spike timing and fixed intervals
47 between successive paired stimulations. A typical experimental protocol consists in pairing
48 pre- and postsynaptic stimulations with a fixed Δt_{STDP} (ranging from -30 to +30ms for
49 plasticity induction); $\Delta t_{\text{STDP}} < 0$ when the postsynaptic stimulation occurs before the paired
50 presynaptic one (post-pre pairings), whereas $\Delta t_{\text{STDP}} > 0$ when the presynaptic stimulation
51 occurs before the postsynaptic one (pre-post pairings). These pairings are then repeated
52 between 15 and 200 times (between 0.1 and 5Hz) with the spike timing and the time interval
53 between successive pairings being kept constant.

54 Regular stimulation paradigms produce patterns of activity that are likely to differ from the
55 variability expected in *in vivo*-like firing. *In vivo* paired natural visual stimulations with
56 postsynaptic action potential lead to Hebbian STDP with specific characteristics when
57 compared to *ex vivo* STDP (broader membrane potential changes and STDP window), which

58 can be explained by jittered presynaptic inputs occurring *in vivo*²². A theoretical study has
59 started to explore naturalistic stimulations and showed that when neurons fire irregularly, the
60 impact of spike timing in plasticity becomes weaker than the influence of the firing rate²⁴.
61 However, whether STDP emergence and maintenance is robust against biological variability
62 remains to be investigated. To address this question, it is important to take into account
63 various forms of STDP, involving distinct intracellular signal transduction pathways, i.e.
64 NMDAR-, mGluR- or endocannabinoid(eCB)-mediated STDP²⁵⁻²⁹ (for reviews see^{8,30,31}). It
65 is thus expected that those various STDP forms might exhibit different robustness to spike
66 train variability.

67 Here, we show with patch-clamp recordings and mathematical modeling that corticostriatal
68 NMDAR- and eCB-STDP do not exhibit the same sensitivity to noisy spike timings: eCB-
69 plasticity (eCB-tLTD and eCB-tLTP) appeared robust to jittering whereas NMDAR-tLTP was
70 fragile. However, increasing the number or frequency of pairings improved NMDAR-tLTP
71 robustness. Our results further indicate that the robustness of NMDAR-tLTP to jitter is also
72 strengthened by the irregularity of the spike-train stimulations.

73 RESULTS

74 Corticostriatal synapses exhibit a bidirectional STDP in which NMDAR-tLTP, eCB-
75 tLTD^{29,32-34} or eCB-tLTP^{12,13} are induced depending on the number of pairings (N_{pairings}) and
76 the spike timing (Δt_{STDP}). While STDP is classically investigated using fixed Δt_{STDP} , we
77 examine here the effect of noisy Δt_{STDP} , closer to *in vivo*-like firing. Here, we define the Inter-
78 Pairing-Interval (IPI) as the time interval between two consecutive presynaptic stimulations,
79 whereas Δt_{STDP} is the time interval between the post- and the presynaptic stimulation times
80 within a given paired stimulation (in a “standard” STDP protocol both IPIs and Δt_{STDP} are
81 constant).

82

83 NMDAR- and eCB-mediated STDP triggered with fixed Δt_{STDP}

84 We observed bidirectional asymmetric STDP in MSNs (Fig. 1a): 100 post-pre pairings
85 ($\Delta t_{\text{STDP}} < 0$) induced tLTP whereas 100 pre-post pairings ($\Delta t_{\text{STDP}} > 0$) induced tLTD. An
86 example of the tLTP induced by 100 post-pre pairings with fixed Δt_{STDP} (Fig. 1b) is illustrated
87 in Figure 1c1. The input resistance R_i remained stable over this period. Although we fixed the
88 values of Δt_{STDP} , they slightly vary from one pairing to another (Fig. 1b). This low jitter can
89 be written formally as $\Delta t_{\text{STDP}} = m_{\Delta t} + \xi_{\Delta t}$, where $m_{\Delta t}$ is the mean spike timing and $\xi_{\Delta t}$ is a
90 random variable with mean 0 and standard deviation $\sigma_{\Delta t}$. Overall, 100 post-pre pairings
91 induced tLTP (mean EPSC amplitude recorded 60 min after protocol induction: $149 \pm 13\%$ of
92 baseline, $p = 0.0028$, $n = 13$) (Fig. 1c2). $\sigma_{\Delta t}$ was 1.4 ± 0.2 ms (Fig. 1c3). This tLTP was NMDAR-
93 mediated since prevented by D-AP5 (50 μM), a NMDAR antagonist, ($88 \pm 12\%$, $p = 0.375$, $n = 5$;
94 $p < 0.0001$ when compared with tLTP in control) (Fig. 1c2). Conversely, pre-post pairings
95 induced tLTD, as shown in the example in Figure 1d1. Overall, 100 pre-post pairings induced
96 tLTD ($76 \pm 7\%$, $p = 0.0070$, $n = 10$) (Fig. 1d2). $\sigma_{\Delta t}$ was 1.4 ± 0.2 ms (Fig. 1d3). This tLTD was

97 CB₁R-mediated since prevented by AM251 (3μM), a CB₁R specific inhibitor (99±2%,
98 $p=0.816$, $n=5$; $p<0.0001$ when compared with tLTD in control) (Fig. 1d2). We thus find an
99 anti-Hebbian polarity for corticostriatal STDP. We previously showed that GABA operates as
100 a Hebbian/anti-Hebbian switch at corticostriatal synapses^{34,35} and corticostriatal STDP
101 polarity depends on the presence^{32,33} or the absence^{12,29,36,37} of GABA_A receptor antagonists.
102 Besides this bidirectional STDP (NMDAR-tLTP and eCB-tLTD) induced for 100 pairings,
103 we reported that low numbers of pairings ($N_{\text{pairings}}=5-15$) induce an eCB-tLTP, dependent on
104 the activation of CB₁R^{12,13}. Figure 1e1 shows an example of tLTP induced by 10 post-pre
105 pairings. Overall, 10 post-pre STDP pairings induced tLTP (145±9%, $p=0.0005$, $n=15$), which
106 was prevented by AM251 (3μM) (76±10%, $p=0.080$, $n=4$; $p<0.0001$ when compared with
107 tLTP in control) (Fig. 1e2) as recently reported¹². $\sigma_{\Delta t}$ for 10 post-pre pairings STDP was
108 1.8±0.3ms ($n=15$) (Fig. 1e3). Note that there was no difference between the $\sigma_{\Delta t}$ measured for
109 NMDAR-tLTP, eCB-tLTD and eCB-tLTP (one way ANOVA, $p=0.4094$).

110

111 **A computer model emulates NMDAR- and eCB-mediated STDP**

112 To help interpret our experimental results, we used a mathematical model of the signaling
113 pathways implicated in corticostriatal STDP, including NMDAR- and CB₁R-plasticity^{12,29,32,33}
114 (Fig. 1f1). The model is detailed in S1 Text, with parameter values listed in S1 and S2 Tables.
115 We include in the Supporting Information a thorough description of the mechanisms by which
116 eCB- and NDMAR-plasticity are expressed in the model when STDP protocol ($N_{\text{pairings}}=100$)
117 is applied (S3 Text). Figure 1f2 shows the value of the total synaptic weight (W_{total}) predicted
118 by the model with various N_{pairings} and Δt_{STDP} . In agreement with the experimental data, with
119 small $\sigma_{\Delta t}$ (3ms), the model features three main plasticity regions: tLTD was observed for
120 short pre-post pairings ($0<\Delta t_{\text{STDP}}<+30\text{ms}$), whereas short post-pre pairings ($-30<\Delta t_{\text{STDP}}<0\text{ms}$)

121 induced a first tLTP region for low numbers of pairings ($3 < N_{\text{pairings}} < 25$) and a second tLTP
122 region emerging for $N_{\text{pairings}} > 50$. Blocking the NMDAR-CaMKII pathway in the model (Fig.
123 1f3) suppresses the second tLTP region whereas blocking CB₁R activation (Fig. 1f4) prevents
124 the expression of tLTD and of the first tLTP region. Therefore, the model emulates both
125 CB₁R-tLTD and -tLTP, in agreement with the eCB-tLTD and eCB-tLTP illustrated in the
126 experimental data of Figure 1d and 1e, respectively. The model also faithfully emulates the
127 appearance of NMDAR-tLTP for $N_{\text{pairings}} > 50$.

128

129 **Predicting the effects of jittered STDP with a mathematical model**

130 The small jitter observed in the above experiments was the result of biological variability
131 inherent to the experimental setup. Our next goal was to extend this study to larger jitters
132 ($3 < \sigma_{\Delta t} < 10\text{ms}$) that we controlled experimentally. We first used constant intervals between
133 two consecutive pairings (Inter-Pairing Interval, IPI) and used the same definition as above
134 for jittered Δt_{STDP} (*Methods*): $\Delta t_{\text{STDP}} = m_{\Delta t} + \xi_{\Delta t}$, where $\xi_{\Delta t}$ is a random variable with zero
135 mean and $m_{\Delta t}$ is the expected value of the spike timing Δt_{STDP} over the N_{pairings} . Next, we
136 adjusted the probability distribution function and the variance of $\xi_{\Delta t}$ to perform a parametric
137 exploration of the impact of jitter.

138 In Figure 2, the jitter $\xi_{\Delta t}$ was sampled from a uniform distribution in $[-\sigma_{\Delta t}, +\sigma_{\Delta t}]$ (Fig. 2a1).
139 STDP in the model was globally not robust to jitter, since the three forms of plasticity
140 vanished when $\sigma_{\Delta t}$ was large enough (Fig. 2a2). However, the model delivered the prediction
141 that the three forms of plasticity do not display the same sensitivity to jitter. In particular,
142 NMDAR-tLTP is predicted to be very fragile when subjected to $\sigma_{\Delta t}$: its amplitude decreases
143 as soon as $\sigma_{\Delta t} > 2\text{ms}$ and completely vanishes for $\sigma_{\Delta t} > 4\text{ms}$ (Fig. 2a2 and 2b2). In contrast,

144 eCB-plasticity is much less sensitive: eCB-tLTP is still present for jitters as large as 7-8ms
145 and eCB-tLTD is still expressed with $\sigma_{\Delta t} = 10\text{ms}$ (Fig. 2b3).

146 We next evaluated the validity of this prediction when the probability distribution function of
147 the jitter changes. Figure 2 illustrates the results we obtained with Gaussian (Fig. 2c) or
148 triangular (Fig. 2d) distributions of $\sigma_{\Delta t}$ (see *Methods*). In both cases, the profiles of the
149 robustness curves (Fig. 2c2 and 2d2) are almost identical to each other and similar to the
150 robustness curves obtained with a uniform distribution (Fig. 2a2). In Figure 2e, we combined
151 a triangular distribution for $\sigma_{\Delta t}$ with random IPIs, i.e. in this case, stochasticity is applied not
152 only to the timing between the two stimulations of a given pairing, but also to the time
153 interval between two consecutive pairings: IPI distribution was Poisson with refractory period
154 τ_r and rate λ (see *Methods*). Despite this increased stochasticity, we found that eCB-tLTD
155 was again more robust, tolerating jitters up to 6-7ms (eCB-tLTP) or 10ms (eCB-tLTD)
156 whereas NMDAR-tLTP was fragile, vanishing for $\sigma_{\Delta t} > 4\text{ms}$ (Fig. 2e2). Therefore, according
157 to our model, the observation that eCB-STDP is more robust to jitter than NMDAR-tLTP
158 could be a general property of the response of the signaling pathways to noisy paired
159 stimulations.

160

161 **Differential effect of jitter on NMDAR- and eCB-mediated plasticity**

162 Based on the model predictions, we next investigated experimentally the sensitivity to jitter of
163 NMDAR-tLTP induced by 100 post-pre pairings (Fig. 3a), using stochastic Δt_{STDP} , distributed
164 according to Figure 2c1. As aforementioned, NMDAR-tLTP can be induced with a $\sigma_{\Delta t} < 3\text{ms}$
165 (Fig. 1c3). Increasing $\sigma_{\Delta t}$ beyond 3ms was sufficient to obliterate tLTP for 100 post-pre
166 pairings. As exemplified (Fig. 3b and c1), 100 post-pre pairings with $\sigma_{\Delta t} = 7.9\text{ms}$ and centered
167 on $m_{\Delta t} = -18\text{ms}$ failed to induce plasticity. Overall, we did not observe tLTP expression for

168 $\sigma_{\Delta t} > 3\text{ms}$ ($92 \pm 2\%$, $p = 0.560$, $n = 7$; $p < 0.0001$ when compared with tLTP observed without
169 jitter) (Fig. 3c2 and c3) in agreement with the model prediction (Fig. 2c2).

170 We next investigated the robustness of the eCB-tLTD to the variability of Δt_{STDP} . We
171 observed potent tLTD even with large values of $\sigma_{\Delta t}$. As shown in Figure 3d1, 100 pre-post
172 pairings with $\sigma_{\Delta t} = 7.0\text{ms}$ centered on $m_{\Delta t} = +18\text{ms}$ induced a large tLTD. Overall, we observed
173 that tLTD was still induced for 100 pre-post pairings with $3 < \sigma_{\Delta t} < 10\text{ms}$ ($70 \pm 6\%$, $p < 0.0001$,
174 $n = 14$; $p = 0.1661$ when compared with tLTD observed without jitter) (Fig. 3d2 and d3). The
175 mean value of tLTD, observed for $3 < \sigma_{\Delta t} < 10\text{ms}$, was not different from the one observed in
176 control, i.e. for $0 < \sigma_{\Delta t} < 3\text{ms}$ ($p = 0.400$).

177 Finally, we investigated the robustness of the eCB-tLTP to the variability of Δt_{STDP} and
178 observed potent tLTP even with large values of jitter, i.e. up to $\sigma_{\Delta t} \sim 8\text{ms}$. An example of tLTP
179 induced by 10 post-pre pairings with $\sigma_{\Delta t} = 6.4\text{ms}$ centered on $m_{\Delta t} = -21\text{ms}$ is illustrated in
180 Figure 3e1. In summary, tLTP could be induced even for $\sigma_{\Delta t} = 8\text{ms}$ ($160 \pm 12\%$, $p = 0.0021$, $n = 9$;
181 $p = 0.0732$ when compared with tLTP observed without jitter) (Fig. 3e2 and e3); the mean
182 value of tLTP was not different from the one observed in control ($p = 0.1660$).

183 We ensured that the $m_{\Delta t}$ absolute values were not different in control and jittered conditions
184 for 100 post-pre pairings ($18 \pm 2\text{ms}$, $n = 13$, vs $21 \pm 3\text{ms}$, $n = 7$, $p = 0.4711$), 100 pre-post pairings
185 ($21 \pm 2\text{ms}$, $n = 10$, vs $21 \pm 2\text{ms}$, $n = 14$, $p = 0.8984$), 10 post-pre pairings ($17 \pm 2\text{ms}$, $n = 15$, vs
186 $20 \pm 2\text{ms}$, $n = 9$, $p = 0.2297$) or between these different STDP protocols (one-way ANOVA:
187 $p = 0.4851$) (Supplementary Fig. 1).

188 In conclusion, in agreement with our model prediction, whereas NMDAR-mediated tLTP
189 appears fragile against the variability of Δt_{STDP} , eCB-plasticity (eCB-tLTD as well as eCB-
190 tLTP) exhibits a large robustness for the temporal imprecision of Δt_{STDP} .

191

192 **Model-based analysis of the effects of jittering**

193 The above experimental results provide us with a validation of our mathematical model. We
194 next used this validated model as a tool to investigate the molecular mechanisms behind these
195 differences of robustness.

196 We have shown in a previous study that eCB-tLTP was expressed when the amount of eCBs
197 produced was large enough that the fraction of activated CB₁R, y_{CB1R} , overcomes a threshold
198 θ_{LTP}^{start} ¹³. In the absence of added noise, $\sigma_{\Delta t} = 0$, our experimental data shows that as few as 5
199 pairings at 1Hz and $\Delta t_{STDP} = -15ms$ are enough to trigger eCB-tLTP¹². Accordingly, our model
200 produces large amounts of eCBs in the first 5-10 pre-post pairings so that y_{CB1R} reaches θ_{LTP}^{start}
201 after as few as 5 pairings (Fig. 4a1). When $\sigma_{\Delta t} = 5ms$ jitter was added to $m_{\Delta t} = -15ms$,
202 some of the pairings failed to deliver y_{CB1R} transients of maximal amplitude (Fig. 4a2). But
203 for $\sigma_{\Delta t} < 7-8ms$, a number of y_{CB1R} transients still had sufficient amplitude to overcome θ_{LTP}^{start} ,
204 which was enough to trigger eCB-tLTP (Fig. 4a2). When $\sigma_{\Delta t}$ was large though (e.g. 10ms),
205 the y_{CB1R} transients failed to reach the LTP zone and eCB-tLTP was not expressed (Fig. 4a3).

206 In experiments without added jitter, eCB-tLTD progressively accumulates when $N_{pairings}$
207 increases and starts to be significant for $N_{pairings} > 25$ ¹². In the model with $m_{\Delta t} = +20ms$ and
208 $\sigma_{\Delta t} = 0$, the y_{CB1R} transients remain in the LTD area for the most part of the STDP pairings
209 (Fig. 4a3). To account for the progressive accumulation of eCB-tLTP with $N_{pairings}$, each
210 transient in the model contributes a small decrease of the synaptic weight. Even with large
211 amounts of jitter (see e.g. $\sigma_{\Delta t} = 5$ or 10ms in Figure 4a2-a3) y_{CB1R} transients remain mostly
212 inside LTD area so eCB-tLTD remains expressed even with large jitter.

213

214 **The robustness of NMDAR-tLTP is predicted to be frequency-dependent**

215 Experimentally, NMDAR-tLTP ($m_{\Delta t} = -15\text{ms}$ and $\sigma_{\Delta t} = 0$) was observed at $F_{\text{pairings}}=1\text{Hz}$
216 when $N_{\text{pairings}}>50$, beyond which its amplitude did not depend much on N_{pairings} ¹³. To account
217 for this feature, the steady-state concentration of activated CaMKII, that sets W_{post} in the
218 model, is bistable: 45 min after the stimulation, CaMKII was either almost fully inactivated
219 ("no plasticity" state) or almost fully activated ("LTP" state)^{13,38}. When the frequency of post-
220 pre pairings ($-30<\Delta t_{\text{STDP}}<0\text{ms}$) was large enough (i.e. $F_{\text{pairings}}\geq 1\text{Hz}$), the IPI was smaller than
221 the decay time of the CaMKII activation transient triggered by each post-pre pairings (Fig.
222 4b1). As a result, in the absence of added noise ($\sigma_{\Delta t} = 0$), the CaMKII activation transients
223 progressively built up on top of each other. The accumulated CaMKII activation overcomes
224 the threshold between the "no plasticity" and the "LTP" states only for $N_{\text{pairings}}>50$ (Fig.
225 4b1)¹³. With jitter (e.g. $\sigma_{\Delta t} = 5\text{ms}$ in Fig. 4b2 or 10ms in Fig. 4b3), many of the IPIs were
226 either too long or too short to trigger maximal amplitude transients of activated CaMKII. As a
227 result, CaMKII activation never reached the threshold, thus explaining the fragility of
228 NMDAR-tLTP with respect to jittering (at 1Hz).

229 A major indication from the above analysis is the importance of the IPI frequency for the
230 robustness of NMDAR-tLTP to jitter. Figure 5 compares the robustness to jitter for constant
231 IPI with $F_{\text{pairings}}=1\text{Hz}$ (Fig. 5a) and 1.05Hz (Fig. 5b). The size of the green area that locates
232 eCB-tLTD on Figure 5a2-b2 was not much altered by the increase of the pairing frequency.
233 Likewise, the size of the red area that locates eCB-tLTP in Figure 5a1-b1 did not vary much
234 when the frequency was increased. However, the size of the red area locating NMDAR-tLTP
235 increased drastically with frequency (Fig. 5a2-b2). Therefore, our model predicts that
236 NMDAR-tLTP should become more robust to jitter at larger frequencies, whereas eCB-tLTP
237 and eCB-tLTD are not significantly changed.

238 Several aspects of glutamate signaling at the corticostriatal synapse are known to display
239 complex frequency-dependence³⁹. Our model is calibrated with experimental data at 1Hz and
240 features none of the above frequency dependencies. Therefore, we cannot expect a precise
241 quantitative match between experiments and model when frequency is varied below or above
242 1Hz. However, the model still yields correct predictions of the main qualitative trends
243 observed in the experiments, since the effects of a small change of F_{pairings} in the model (1.00
244 to 1.05Hz) were similar to the effects of larger changes (1 to 3Hz) in the experiments¹³.
245 Therefore, in the experiments, we expect to observe a change of robustness pattern similar to
246 Figure 5b, around $F_{\text{pairings}}=3\text{Hz}$ rather than 1.05Hz.

247

248 **Increasing F_{pairings} and N_{pairings} stabilized NMDAR-tLTP against jitter**

249 We next tested experimentally whether an increase from 1 to 3Hz of STDP pairings would
250 protect the NMDAR-tLTP against jitter, as predicted by the model. As shown in Figure 6a1,
251 100 post-pre pairings at 3Hz with $\sigma_{\Delta t}=9\text{ms}$ and centered on $m_{\Delta t}=-22\text{ms}$ induced tLTP.
252 Overall, we observed tLTP for 100 post-pre pairings applied at 3Hz with $4<\sigma_{\Delta t}<9\text{ms}$
253 ($181\pm 30\%$, $p=0.0274$, $n=9$) (Fig. 6a2 and a3); the mean value of these tLTP observed at 3Hz
254 with $4<\sigma_{\Delta t}<9\text{ms}$ were not significantly different from the one observed with stimulation-
255 related $\sigma_{\Delta t}<3\text{ms}$ at 1Hz ($p=0.520$). When we plotted the magnitude of plasticity against $\sigma_{\Delta t}$
256 for 100 post-pre pairings at 3Hz, we observed that tLTP was still induced even for $\sigma_{\Delta t}=9\text{ms}$
257 (Fig. 6a3). We observed different synaptic efficacy changes following 100 post-pre pairings at
258 1Hz with and without jitter and at 3Hz with jitter (ANOVA, $p<0.0001$). The NMDAR-tLTP
259 thus acquires certain robustness to the variability of Δt_{STDP} with increasing frequency of
260 pairings.

261 We next investigated whether a higher N_{pairings} would secure the expression of NMDAR-tLTP
262 even with $\sigma_{\Delta t} > 3\text{ms}$ (Fig. 6b). When we doubled N_{pairings} we did not observe expression of
263 significant tLTP. Indeed, 200 post-pre pairings ($-30 < m_{\Delta t} < 0\text{ms}$ with $3 < \sigma_{\Delta t} < 10\text{ms}$) did not
264 induce plasticity ($112 \pm 9\%$, $p=0.236$, $n=6$; Fig. 6b3) but when we increased N_{pairings} up to 250-
265 300, tLTP was reliably observed with $\sigma_{\Delta t} > 3\text{ms}$. Figure 6b1 shows an example of tLTP
266 induced by 250 pairings with $\sigma_{\Delta t} = 5\text{ms}$ and centered on -20ms . Overall, 250-300 post-pre
267 STDP pairings ($-30 < m_{\Delta t} < 0\text{ms}$ with $3 < \sigma_{\Delta t} < 10\text{ms}$) induced tLTP ($170 \pm 10\%$, $p=0.0012$, $n=6$;
268 Fig. 6b2 and b3); the mean values of these tLTP observed for $N_{\text{pairings}} = 250-300$ at 1Hz with
269 $4 < \sigma_{\Delta t} < 9\text{ms}$ were not different compared to tLTP induced with 100 post-pre pairings at 1Hz
270 with $\sigma_{\Delta t} < 3\text{ms}$ ($p=0.1952$). We observed different synaptic efficacy changes following 100,
271 200 and 250-300 post-pre pairings (ANOVA, $p < 0.0001$).

272

273 **Transitions from spike-timing- to frequency-dependent plasticity**

274 We next tested with our mathematical model whether the robustness of STDP to jitter of the
275 spike timing depends on the regularity of the spike train. In Figure 2e, we show an example of
276 the combination of stochastic spike timings (triangular distribution) with stochastic IPIs
277 (Poisson distributed) with a constant and relatively large refractory period τ_r (see *Methods-*
278 *Mathematical model, Protocol 4*). However, when τ_r decreases, short IPIs are more
279 frequently sampled and the train of presynaptic stimulation becomes more irregular.
280 Therefore, through variations of the refractory period τ_r , the presynaptic stimulation can be
281 progressively switched from highly irregular to regular spike trains.

282 Figure 7 shows model predictions for the alteration of the robustness curves when τ_r varies.
283 With high refractory period, *i.e.* when $\tau_r \approx F_{\text{pairings}}$, the IPIs are weakly noisy, so one
284 recovers the robustness curves of Figure 2e, with eCB-STDP being more robust than

285 NMDAR-tLTP. However, when τ_r is 70% of F_{pairings} , the robustness of both eCB-tLTP and
286 NMDAR-tLTP increases and both exhibit similar robustness. With even smaller values of τ_r ,
287 NMDAR-tLTP becomes more robust than eCB-tLTP. Moreover, eCB-tLTD ($F_{\text{pairings}}=1\text{Hz}$,
288 $m_{\Delta t} = +20\text{ms}$, $N_{\text{pairings}}=100$) progressively stops triggering LTD when τ_r decreases, even
289 inducing LTP for very low τ_r . Hence, when the presynaptic spike train is progressively
290 switched from regular to very irregular spike trains, two main changes occur: (i) the three
291 plasticity forms (NMDAR-tLTP, eCB-tLTD and eCB-tLTP) become increasingly robust to
292 jittering (at the limit of highly irregular spike trains, jittering hardly affects plasticity
293 amplitudes), and (ii) eCB-tLTD is progressively changed to LTP, so that highly irregular
294 paired stimulations with $F_{\text{pairings}}=1\text{Hz}$ only produce LTP regardless of the sign of the spike
295 timing.

296 **DISCUSSION**

297 Here, we have introduced jittered STDP protocols as noisy variants of STDP protocols where
298 the spike timing, *i.e.* the delay between a presynaptic and paired postsynaptic stimulation (or
299 vice-versa), is a random variable. Our results show that the magnitude of variability that
300 STDP can tolerate varies depending on the pairing frequency and on the STDP form, *i.e.*
301 NMDAR-tLTP, eCB-tLTP or eCB-tLTD. At 1Hz pairing frequency, eCB-STDP (eCB-tLTD
302 and eCB-tLTP) is much more robust than NMDAR-dependent tLTP. However, this
303 robustness depends on the number and frequency of pairings. Indeed, increasing the average
304 pairing frequency to 3Hz improved the robustness of NMDAR-tLTP. We observed a similar
305 improvement of the robustness of NMDAR-tLTP to jitter when the number of pairings
306 increased more than two folds.

307 These results have wide-ranging implications for STDP expression in *in vivo*-like firing. They
308 indicate that eCB-STDP could be more likely responsible for fast learning involving few trials
309 (eCB-tLTP) or for learning at lower activity frequency than NMDAR-STDP. NMDAR-STDP
310 could however take part in learning for larger frequencies or when the same spike timing
311 recurs a large number of times during sustained activity. It also implies that in synapses where
312 NMDAR is the main coincidence detector for tLTD or tLTP^{3,5,6,40-42}, a high degree of
313 precision of the spike timing, and/or an increased number or frequency of pairings, are
314 required for the emergence of the NMDAR-mediated plasticity. This can be viewed as a
315 mechanism preventing the occurrence of spurious plasticity for noisy neural network activity.
316 At synapses in which NMDAR and endocannabinoids are both involved in STDP
317 expression^{12,13,25-27,33,43} and in which eCB-LTP can occur, as it is the case in the striatum^{12,13},
318 the hippocampus⁴⁴⁻⁴⁸ or the neocortex⁴⁹ the emergence of STDP would be possible even in
319 noisy conditions and could thus serve subsequently as a priming for the subsequent
320 expression of NMDAR-tLTP.

321 In the present study, we explored the robustness of STDP when noise affects not only the
322 spike timing but also the inter-pairing interval (IPI), i.e. the delay between two successive
323 pairings. In the absence of jitter of the spike timing, our model predicts that IPI irregularity
324 tends to consolidate tLTP at the expense of tLTD. This prediction that irregular IPIs
325 strengthen tLTP when the spike timing is constant confirms the result obtained independently
326 and with different mathematical models^{7,19,22,24}. When IPIs are regular, adding jitter of the
327 spike timing in our model progressively suppresses STDP. However, with more irregular IPIs
328 our model predicts that the three STDP forms should exhibit larger robustness to noise.
329 Therefore our result suggests that jittering of the spike timing has larger impact on STDP
330 when the IPIs are regular, but that jittering has much less consequence with irregular IPIs.
331 Experimental testing of this model prediction would greatly improve our understanding of the
332 induction and maintenance of STDP in *in vivo*-like firing.

333 Subthreshold postsynaptic depolarization is a key factor in the induction of plasticity⁵⁰. The
334 existence of plasticity induced by STDP-like protocols without postsynaptic spikes
335 (subthreshold-depolarization-dependent plasticity, SDDP) has been reported in the
336 neocortex⁵¹, striatum⁵² and hippocampus⁵³. In the striatum, SDDP differs from STDP on two
337 aspects: (i) SDDP was induced in a larger temporal window ($-100 < \Delta t_{\text{STDP}} < +100\text{ms}$) and (ii)
338 tLTP and tLTD were induced regardless of the spike timing. Therefore, the action potential
339 would not be necessary for plasticity induction, but determinant for the STDP polarity and the
340 width of the Δt_{STDP} . The effects of jitter remain to be determined on SDDP, *i.e.* subthreshold
341 events.

342 The polarity of plasticity depends greatly on the frequency of stimulus presentation. Indeed,
343 prolonged firing activity at low and high frequency promote LTD and LTP, respectively, at
344 the same synapses in hippocampus⁵⁴⁻⁵⁶. However, alteration of a regular low-frequency
345 stimulation (900 stimulations at 1Hz) with Poisson-distributed interstimulus intervals (as an

346 approximation of naturalistic patterns) prevents LTD expression in the neocortex⁵⁷.
347 Interestingly, this LTD induced with regular low-frequency stimulation has been reported to
348 be NMDAR-mediated⁵⁸, and we show here that NMDAR-plasticity is fragile to jitter
349 especially for low firing rate (1Hz). It remains thus to investigate in a rate-based paradigm
350 whether Poisson stimulation would erase LTD induced by higher firing rate (3-5Hz⁵⁴).
351 Various forms of naturalistic patterns as an attempt to mimic *in vivo* activity have been
352 experimentally tested for plasticity expression: from single burst of dendritic spikes, which
353 induced NMDAR-LTP in hippocampus⁵⁹ and NMDAR-LTD in neocortex⁶⁰, to noisy STDP-
354 like protocols^{7,19,20,22} and burst-timing-dependent plasticity paradigms⁶¹. Based on data
355 harvested in the neocortex, a phenomenological computer modeling showed that for constant
356 frequencies but random spiking, LTP wins over LTD with increasing frequency⁷. Activity
357 patterns recorded *in vivo* during specific behavioral tasks have been replayed *ex vivo* to test
358 their ability to induce plasticity^{19,56,62}. When sequences of spike trains recorded *in vivo* from
359 visual cortex of the anaesthetized cat in response to natural scenes were replayed *ex vivo* in
360 layer 2/3 pyramidal cells of rat visual cortex, both LTP and LTD was observed
361 experimentally and modeling suggested the importance of suppressive interactions between
362 spikes¹⁹. In the dentate gyrus, *in vivo* patterns recorded in granule cell during a task of delayed
363 nonmatch-to-sample were able in most of the cases to induce LTP at mossy fibers⁵⁶.
364 Similarly, when hippocampal place cells activity recorded *in vivo* were replayed *ex vivo*,
365 NMDAR-LTP (also dependent on cholinergic tone) was observed⁶². Natural stimuli recruit
366 various neuronal circuits leading to presynaptic jitter, which can have important physiological
367 consequences. Indeed, *in vivo* visually driven presynaptic inputs induce presynaptic jitter
368 leading to broader membrane potential events, and can consequently promote a spatial
369 reorganization of the responses of neurons to neighboring stimuli within a receptive field, as
370 demonstrated in the rat visual cortex²².

371 The debate about the nature of the neural coding, i.e. rate versus time codes⁶³⁻⁶⁵, is prominent
372 when studying STDP. It remains to be tested with mathematical models and experiments
373 whether activity patterns of various vigilance states differently result in the emergence of
374 spike- or rate-coding plasticity. At most of the synapses both rate and time codes co-exist; for
375 example at CA1 synapses, stimuli induced LTD at 2-3Hz, no plasticity at 10Hz and LTP at 50
376 Hz demonstrating a rate code⁵⁴, and time codes are also supported as illustrated by the
377 expression of various forms of STDP at the same synapse¹¹. An answer to this debate could
378 be that both rate and time codes work together for plasticity expression, as recently shown in
379 the somatosensory cortex⁶⁶, but their relative contribution *in vivo* would depend on the
380 ongoing activity (low or high), the cerebral structures, the noise level, the neuromodulatory
381 systems at play and the signaling pathways involved in plasticity expression (as shown in the
382 present study). Briefly, it appears that STDP can emerge from low frequency activity whereas
383 rate codes would take over for higher frequency ranges^{7,19,20,22}.

384 A major conclusion from our present work is that the robustness of STDP to jitter depends on
385 the underlying signaling pathways. For instance, the robustness of NMDAR-tLTP in our
386 model is dependent on the amplitude of the activated CaMKII transients triggered by each
387 post-pre pairings or on alterations of the ratio between the decay time of these transients and
388 the IPIs. The robustness of STDP to jitter could be similarly controlled by quantitative
389 variations in the underlying pathways. Such variations are expected to occur between two
390 neuronal subtypes or brain regions but also as a result of the activation of a neuromodulatory
391 pathway. Therefore, our work suggests that the expression of STDP in *in vivo*-like firing
392 might appear or disappear as a result of modulations of its robustness to jitter, depending on
393 the properties of the incoming patterns (reflecting for example fast learning or heavy
394 training), but also on the brain region and, more transiently, on the activation of
395 neuromodulatory pathways.

396 **METHODS**

397 *Animals and brain slice preparation*

398 OFA (Oncins France Strain A) rats (Charles River, L'Arbresle, France) were used at postnatal
399 day 25-32 for brain slice electrophysiology. All experiments were performed in accordance
400 with the guidelines of the local animal welfare committee (Center for Interdisciplinary
401 Research in Biology Ethics Committee) and the EU (directive 2010/63/EU). The experimental
402 protocol (ref. 2017-02 N° 2016120110255176) was approved by the Ethics Committee in
403 Charge of Animal Experimentation (Paris Centre et Sud). Every precaution was taken to
404 minimize stress and the number of animals used in each series of experiments. Animals were
405 housed in standard 12 hours light/dark cycles and food and water were available *ad libitum*.
406 Horizontal brain slices containing the somatosensory cortical area and the corresponding
407 corticostriatal projection field were prepared as previously described³⁶. Corticostriatal
408 connections (between somatosensory cortex layer 5 and the dorso-lateral striatum) are
409 preserved in the horizontal plane. Brain slices (330µm-thick) were prepared with a vibrating
410 blade microtome (VT1200S, Leica Microsystems, Nussloch, Germany). Brains were sliced in
411 an ice-cold cutting solution (125mM NaCl, 2.5mM KCl, 25mM glucose 25mM NaHCO₃,
412 1.25mM NaH₂PO₄, 2mM CaCl₂, 1mM MgCl₂, 1mM pyruvic acid) through which 95% O₂/5%
413 CO₂ was bubbled. The slices were transferred to the same solution at 34°C for one hour and
414 then to room temperature.

415

416 *Patch-clamp recordings*

417 Patch-clamp recordings were performed as previously described^{12,18}. Briefly, for whole-cell
418 recordings in borosilicate glass pipettes of 5-7 MΩ resistance were filled with (in mM): 122
419 K-gluconate, 13 KCl, 10 HEPES, 10 phosphocreatine, 4 Mg-ATP, 0.3 Na-GTP, 0.3 EGTA

420 (adjusted to pH 7.35 with KOH). The composition of the extracellular solution was (mM):
421 125 NaCl, 2.5 KCl, 25 glucose, 25 NaHCO₃, 1.25 NaH₂PO₄, 2 CaCl₂, 1 MgCl₂, 10 μM
422 pyruvic acid bubbled with 95% O₂ and 5% CO₂. Signals were amplified using EPC10-2
423 amplifiers (HEKA Elektronik, Lambrecht, Germany). All recordings were performed at 34°C
424 (Bath-controller V, Luigs&Neumann, Ratingen, Germany) and slices were continuously
425 superfused with extracellular solution, at a rate of 2 ml/min. Slices were visualized under
426 microscope (BX51WI Olympus, Rungis, France), with a 4x/0.13 objective for the placement
427 of the stimulating electrode and a 40x/0.80 water-immersion objective for the localization of
428 cells for whole-cell recordings. Current- and voltage-clamp recordings were filtered at 5 kHz
429 and sampled at 10 kHz, with the Patchmaster v2x32 program (HEKA Elektronik).

430

431 ***Spike timing-dependent plasticity protocols: regular and jittered patterns***

432 Electrical stimulations were performed with a concentric bipolar electrode (Phymep, Paris,
433 France) placed in layer 5 of the somatosensory cortex. Electrical stimulation was monophasic,
434 at constant current (ISO-Flex stimulator, AMPI, Jerusalem, Israel). Cortical stimulations
435 evoked glutamatergic excitatory postsynaptic currents (EPSCs) (inhibited by CNQX 10μM
436 and D-AP5 50μM, n=6) and not significantly affected by GABAergic events; Indeed,
437 blocking GABA_ARs with picrotoxin (50μM) did not significantly affect EPSC amplitude at
438 corticostriatal synapses (123±31pA before and 118±26pA after picrotoxin, $p=0.500$, n=5).
439 MSNs were kept at their resting membrane potential (-74.6±0.6 mV, n=90) and repetitive
440 control stimuli were applied at 0.1Hz. Currents were adjusted to evoke 50-200 pA EPSCs.
441 STDP protocols consisted of pairings of pre- and postsynaptic stimulations (at 1Hz) separated
442 by a specific time interval (Δt_{STDP}). The paired stimulations were applied at 1Hz throughout
443 the study except in Figure 6a1 and 6a2 in which 3Hz stimulations were tested. Presynaptic
444 stimulations corresponded to cortical stimulations and the postsynaptic stimulation of an

445 action potential evoked by a depolarizing current step (30ms duration) in MSNs. $\Delta t_{\text{STDP}} < 0\text{ms}$
446 for post-before-pre pairings, and $\Delta t_{\text{STDP}} > 0\text{ms}$ for pre-before-post pairings. Neuronal
447 recordings on neurons were made over a period of 10 minutes at baseline, and for at least 60
448 minutes after the STDP protocols. EPSC baseline stability was assessed by comparing the
449 average of the EPSC magnitude of the two first and the two last minutes of baseline; if the
450 variation of amplitude exceeded 10%, the experiment was discarded⁴. Recordings were
451 stopped if the injected current was larger than 50 or 100-150 pA during the baseline and after
452 pairings, respectively. We individually measured and averaged the amplitude of 60 successive
453 EPSCs from both baseline and 45-55 minutes after STDP protocol, in which the latter was
454 normalized by the former to calculate long-term synaptic efficacy changes. Neuron recordings
455 were made in voltage-clamp mode during baseline and for the 60 minutes of recording after
456 the STDP protocol, and in current-clamp mode during STDP protocol. Experiments were
457 excluded if the input resistance (R_i), measured every 10 sec all along the experiment, varied
458 by more than 20% during the very same time period where the EPSC amplitude were
459 measured for plasticity assessment: 10 minutes of baseline and the 10 last minutes of the
460 recording (generally 45-55 minutes after pairings). After recording of 10 min control baseline,
461 drugs were applied in the bath. A new baseline with drugs was recorded after a time lapse of
462 10 min (to allow the drug to be fully perfused) for 10 min before the STDP protocol. Drugs
463 were present until the end of the recording. All chemicals were purchased from Tocris
464 (Ellisville, MO, USA), except for picrotoxin (Sigma). DL-2-amino-5-phosphono-pentanoic
465 acid (D-AP5; 50 μM) and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX; 10 μM) were
466 dissolved directly in the extracellular solution and bath applied. N-(piperidin-1-yl)-5-(4-
467 iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide (AM251; 3 μM)
468 and picrotoxin (50 μM) were dissolved in ethanol and added to the external solution, such that
469 the final concentration of ethanol was 0.01-0.1%.

470 For the jittered Δt_{STDP} patterns, we used the following algorithm (see Protocol 2, below). We
471 note t_{pre_i} and t_{post_i} the times of the presynaptic and postsynaptic stimulations in the paired
472 stimulation number i , respectively. To set them, we first fixed the times of each presynaptic
473 stimulation using the pairing frequency, i.e. $t_{\text{pre}_i} = \frac{i}{F_{\text{pairings}}}$. The postsynaptic times were
474 then chosen randomly according to $t_{\text{post}_i} = t_{\text{pre}_i} + m_{\Delta t} + \xi_{\Delta t, i}$ where $m_{\Delta t}$ is the average
475 spike timing and $\xi_{\Delta t}$ is a random variable with mean 0 and variance $\sigma_{\Delta t}^2$. We defined the
476 Inter-Pairing-Interval (IPI) as the time interval between the presynaptic stimulation times of
477 two consecutive paired stimulations ($\text{IPI}_i = t_{\text{pre}_{i+1}} - t_{\text{pre}_i}$), whereas the spike timing Δt is
478 the time interval between the postsynaptic and the presynaptic stimulation times within a
479 given paired stimulation ($\Delta t_{\text{STDP}_i} = t_{\text{post}_i} - t_{\text{pre}_i}$). In a standard STDP protocol both the
480 spike timing and the IPI are constant. The above algorithm yields constant IPIs and stochastic
481 spike timings.

482

483 ***Electrophysiological data analysis***

484 Off-line analysis was performed with Fitmaster (Heka Elektronik) and Igor-Pro 6.0.3
485 (Wavemetrics). Statistical analysis was performed with Prism 5.02 software. In all cases “n”
486 refers to an experiment on a single cell from a single slice. All results are expressed as mean \pm
487 SEM in the text and as mean \pm SD in the figures. Statistical significance was assessed in
488 unpaired t tests, one way ANOVA, or in one-sample t tests, as appropriate, using the indicated
489 significance threshold (p).

490

491 **Mathematical model**

492 **Jittered STDP protocols.** In the model, we define the spike timing as $\Delta t_{\text{STDP}_i} = t_{\text{post}_i} -$
 493 $t_{\text{pre}_i} + \delta$ where δ accounts for the time elapsed between the onset of the postsynaptic step
 494 current and the action potential it triggers ($\sim 3\text{ms}$ in MSNs). In agreement with the experiment
 495 protocol above, we introduced stochasticity of the spike timing by adding a random jitter $\xi_{\Delta t}$
 496 to the spike timing: $\Delta t_{\text{STDP}} = m_{\Delta t} + \xi_{\Delta t}$, where $m_{\Delta t}$ is the average spike timing and $\xi_{\Delta t}$ is a
 497 random variable whose distribution is given by the STDP protocol. Here, we explored five
 498 STDP protocols:

499 1) *Protocol 0* consisted of pairings with no jittering, i.e. $\text{IPI}_i = \frac{1}{F_{\text{pairings}}}$ and $\xi_{\Delta t} = 0$.

500 2) *Protocol 1* consisted of deterministic IPIs and uniformly distributed spike timings (Fig.
 501 2a1), i.e. $\text{IPI}_i = \frac{1}{F_{\text{pairings}}}, \forall i$, and the probability distribution function of the jitter is given by

$$502 \quad P(\xi_{\Delta t}) = \begin{cases} \frac{1}{2\sigma_{\Delta t}} & \text{if } |\xi_{\Delta t}| < \sigma_{\Delta t}, \\ 0 & \text{otherwise} \end{cases} \quad (1)$$

503 In eq. (1), $\sigma_{\Delta t}$ defines the maximal jitter amplitude *i.e.* the level of noise in the protocol. To
 504 simulate *Protocol 1*, we first set each presynaptic stimulation time using $t_{\text{pre}_i} = \frac{i}{F_{\text{pairings}}}$.
 505 Postsynaptic times were then fixed by $t_{\text{post}_i} = t_{\text{pre}_i} + m_{\Delta t} + \xi_{\Delta t,i} - \delta$.

506 3) *Protocol 2* (Fig. 2c1) shared the same definition as Protocol 1, except that the jitter
 507 followed a normal distribution with zero mean and variance $\sigma_{\Delta t}^2$: $P(\xi_{\Delta t}) = \mathcal{N}(0, \sigma_{\Delta t}^2)$.

508 4) For *Protocol 3* (Fig. 2d1), we used a triangular distribution of the jitter by adding
 509 uniformly distributed jitter to both presynaptic and postsynaptic times. We set $t_{\text{pre}_i} =$
 510 $\frac{i}{F_{\text{pairings}}} + \zeta_{\text{pre},i}$ and $t_{\text{post}_i} = \frac{i}{F_{\text{pairings}}} + m_{\Delta t} + \zeta_{\text{post},i} - \delta$, where ζ_{pre} and ζ_{post} are i.i.d.

511 random variables with the uniform distribution of eq. (1). The resulting spike timing is
 512 $\Delta t_{\text{STDP}} = m_{\Delta t} + \xi_{\Delta t}$ where $\xi_{\Delta t} = \zeta_{\text{post}} - \zeta_{\text{pre}}$ has a triangular distribution. Note that in this
 513 case, one still has $\text{IPI}_i \approx \frac{1}{F_{\text{pairings}}} \forall i$ as long as $2|m_{\Delta t}|F_{\text{pairings}} \ll 1$, which can safely be
 514 assumed here since we used $|m_{\Delta t}| < 50\text{ms}$ and $F_{\text{pairings}} < 2\text{Hz}$.

515 5) *Protocol 4* includes both a stochastic spike timing and stochastic IPIs (Fig. 2e1). We first
 516 sampled N_{pairings} IPIs according to an exponential distribution with rate λ and refractory
 517 period τ_r : $P(\text{IPI}) = \Theta(\text{IPI} - \tau_r)\lambda\exp(-\lambda(\text{IPI} - \tau_r))$, where $\Theta(x)$ is the Heaviside function
 518 $\Theta(x)=1$ if $x \geq 0$; 0 otherwise. The spike trains defined with protocol 4 are thus Poisson
 519 process. We used these IPIs to fix the stimulation times, adding a triangularly distributed jitter
 520 as in Protocol 3 above: $t_{\text{pre}_i} = \sum_{j<i} \text{IPI}_j + \zeta_{\text{pre},i}$ and $t_{\text{post}_i} = \sum_{j<i} \text{IPI}_j + m_{\Delta t} + \zeta_{\text{post},i} - \delta$.
 521 To keep the average stimulation frequency at $1/F_{\text{pairings}}$, we constrained the value of the rate
 522 λ as $\lambda = (1/F_{\text{pairings}} - \tau_r)^{-1}$.

523
 524 **Stimulations.** A detailed account of our mathematical model can be found in S1 Text. We
 525 modeled glutamate concentration in the synaptic cleft, $G(t)$, as a train of exponentially-
 526 decaying impulses triggered by presynaptic stimuli at time t_{pre_i} . We modeled the electrical
 527 response to these stimulations in a postsynaptic element considered as a single isopotential
 528 compartment with AMPAR, NMDAR, VSCC and TRPV1 conductances:

$$529 \quad C_m \frac{dV}{dt} = -g_L(V - V_L) - I_{\text{AMPAR}}(V, G(t)) - I_{\text{NMDAR}}(V, G(t)) \quad (2)$$

$$-I_{\text{VSCC}}(V) - I_{\text{TRPV1}}(V, AEA) - I_{\text{action}}(t)$$

530 where V is membrane potential; g_L and V_L are leak conductance and reversal potential
 531 respectively; I_{AMPAR} , I_{NMDAR} , I_{VSCC} and I_{TRPV1} are currents through AMPAR, NMDAR, L-
 532 type VSCC (v1.3) and TRPV1 respectively. I_{action} is the action current resulting from the

533 postsynaptic stimulation (backpropagating action potential on top of a 30ms depolarization).
534 Details about the analytical expressions of these currents are given in S1 Text.

535 **Biochemical signaling.** We modeled the kinetics of the biochemical pathways activated by
536 the above electrical stimulations using the model of ref[13]. We give below a quick overview
537 of this model and refer to S1 Text for the details. Free cytosolic calcium is one of the main
538 signaling actors in the model. To model its dynamics, we assumed calcium can be transferred
539 from/to two main sources: (i) extracellular calcium, via the plasma membrane channels of eq.
540 (3) above and (ii) the endoplasmic reticulum (ER), via the IP3-dependent calcium-induced
541 calcium release system. These calcium transients activated a network of biochemical
542 pathways that collectively set the synaptic weight. Hence, in this model, the synaptic weight
543 is entirely fixed by the underlying biochemical signaling network¹³. More precisely, we
544 assumed that the total synaptic weight is the product of a pre- and a postsynaptic contribution
545 $W_{\text{total}} = W_{\text{pre}}W_{\text{post}}$. Postsynaptic plasticity was based on the activation by calcium of
546 calmodulin and CaMKII^{67,68}. We assumed that postsynaptic plasticity is directly proportional
547 to the calcium-dependent activation of CaMKII:

$$548 \quad W_{\text{post}} = 1 + 3.5 \frac{\text{CaMKII}^*}{\text{CaMKII}_{\text{max}}^*} \quad (5)$$

549 where CaMKII^* and $\text{CaMKII}_{\text{max}}^*$ are the current concentration of activated (phosphorylated)
550 CaMKII and its maximum value.

551 Our model also accounts for the biochemical pathways leading to the production of the
552 endocannabinoids 2-arachidonoylglycerol (2-AG) and AEA, and their subsequent activation
553 of CB₁R (see S1 Text for further details). In our model, CB₁R activation (y_{CB1R}) controls the
554 presynaptic weight W_{pre} according to the following rule:

$$555 \quad \Omega(y_{CB1R}) = \begin{cases} 1 - A_{LTD} & \text{if } \theta_{LTD}^{start} < y_{CB1R} < \theta_{LTD}^{stop} \\ 1 + A_{LTP} & \text{if } \theta_{LTP}^{start} < y_{CB1R} \\ 1 & \text{otherwise} \end{cases} \quad (7)$$

$$556 \quad \text{and } dW_{pre}/dt = (\Omega(y_{CB1R}) - W_{pre})/\tau_{W_{pre}} \quad (8)$$

557 Details about model implementation and numerics are given in the supplementary
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564

565 **Author contribution:**

566 L.V. and H.B. designed the study; Y.C. and A.M. performed electrophysiological experiments
567 and analysis; H.B. carried out the conception and the design of the mathematical model; H.B.
568 and I.P. performed the acquisition and analysis of data from the mathematical model; H.B.
569 and L.V. wrote the manuscript and all authors have edited and corrected the manuscript; L.V.
570 supervised the whole study.

571

572 **Competing financial interest:**

573 The authors declare no competing interests.

574

575 **Figure Legends**

576 **Figure 1: NMDAR- and eCB-mediated STDP induced with fixed Δt_{STDP}**

577 (a) STDP protocol: a single postsynaptic spike was paired with a single cortical stimulation,
578 10 or 100 times at 1Hz. (b) Example of 5 successive pairings (#4-8, from c1) exhibiting
579 relatively fixed Δt_{STDP} (#4-8: -8.0, -7.8, -7.4, -8.8 and -8.0ms). Plotting the successive Δt_{STDP}
580 illustrates their low variance $\sigma_{\Delta t}$ (2.6ms). (c) Corticostriatal NMDAR-mediated tLTP induced
581 by 100 post-pre pairings with fixed Δt_{STDP} . (c1) Example of tLTP induced by 100 post-pre
582 pairings ($m_{\Delta t}=-9\text{ms}$, $\sigma_{\Delta t}=2.6\text{ms}$). The mean baseline EPSC amplitude, $95\pm 3\text{pA}$, increased by
583 77% to $168\pm 6\text{pA}$ 45 minutes after pairings. Upper panel, time course of R_i (baseline:
584 $172\pm 2\text{M}\Omega$ and 35-45 min after pairings: $170\pm 3\text{M}\Omega$; change of 1%) and holding current (I_{hold}).
585 Inset: distribution of the 100 Δt_{STDP} . (c2) Averaged time-courses of tLTP induced by 100
586 post-pre pairings; this tLTP was NMDAR-mediated because prevented by D-AP5 ($50\mu\text{M}$).
587 (c3) Relationship between the STDP magnitude and the STDP jitter for each of the recorded
588 neurons. (d) Corticostriatal eCB-mediated t-LTD induced by 100 pre-post pairings with fixed
589 Δt_{STDP} . (d1) Example of tLTD induced by 100 pre-post pairings ($m_{\Delta t}=+21\text{ms}$, $\sigma_{\Delta t}=2.1\text{ms}$);
590 the mean baseline EPSC amplitude, $206\pm 4\text{pA}$, decreased by 25%, to $154\pm 8\text{pA}$, 45 minutes
591 after pairings. Upper panel, time course of R_i (baseline: $195\pm 1\text{M}\Omega$ and 45-55 min after
592 pairings: $196\pm 2\text{M}\Omega$; change $<1\%$) and I_{hold} . Inset: distribution of the 100 Δt_{STDP} . (d2)
593 Averaged time-courses of tLTD induced by 100 pre-post pairings; this tLTD was CB₁R-
594 mediated because prevented by AM251 ($3\mu\text{M}$). (d3) Relationship between the STDP
595 magnitude and the jitter. (e) Corticostriatal eCB-mediated tLTP induced by 10 post-pre
596 pairings with fixed Δt_{STDP} . (e1) Example of tLTP induced by 10 post-pre pairings ($m_{\Delta t}=-$
597 11ms , $\sigma_{\Delta t}=3.1\text{ms}$); the mean baseline EPSC amplitude, $147\pm 3\text{pA}$, increased by 43% to
598 $209\pm 9\text{pA}$ 45 minutes after pairings. Upper panel, time course of R_i (baseline: $227\pm 2\text{M}\Omega$ and
599 45-55 min after pairings: $239\pm 2\text{M}\Omega$; change of 5%) and I_{hold} . Inset: distribution of the 10

600 Δt_{STDP} . **(e2)** Averaged time-courses of tLTP induced by 10 post-pre pairings; this tLTP was
601 CB₁R-mediated because prevented by AM251. **(e3)** Relationship between the STDP
602 magnitude and the jitter. **(c1-d1-e1)** Insets: average of 12 successive EPSC amplitude at
603 baseline (black traces) and at 40-50 min after pairings (grey traces). **(f)** Predictions of the
604 mathematical model in the absence of added jitter. The model expresses the biochemical
605 pathways schematized in **(f1)**. **(f2)** Changes of W_{total} with various Δt_{STDP} and N_{pairings} . **(f3)**
606 Removing NMDAR/CaMKII signaling suppresses the tLTP observed for $\Delta t_{\text{STDP}} > 0$ and
607 $N_{\text{pairings}} > 50$. **(f4)** Removing CB₁R suppresses the tLTP observed for $\Delta t_{\text{STDP}} > 0$ and $N_{\text{pairings}} < 20$
608 and the tLTD observed for $\Delta t_{\text{STDP}} < 0$.

609

610 **Figure 2: The mathematical model predicts that NMDAR-tLTP is less robust to jitter**
611 **than eCB-tLTP and eCB-tLTD.**

612 **(a)** Using a jittered STDP protocol combining uniformly-distributed jitter of the spike timing
613 with deterministic IPIs at 1Hz **(a1)**, the amplitudes of NMDAR-tLTP, eCB-tLTD and eCB-
614 tLTP decrease with increasing jitter amplitudes $\sigma_{\Delta t}$ **(a2)**. eCB-tLTP (red full line) was
615 triggered with 10 pairings of average spike timing $m_{\Delta t} = -15\text{ms}$ and eCB-tLTD (blue full
616 line) with 100 pairings of $m_{\Delta t} = +20\text{ms}$. NMDAR-tLTP (red dashed line) corresponded to
617 100 pairings of $m_{\Delta t} = -15\text{ms}$. eCB-tLTD and eCB-tLTP are weakly affected by the jitter.
618 NMDAR-tLTP is less robust. Full and dashed lines show averages and light swaths show
619 $\pm 1\text{sem}$. **(b)** Evolution of NMDAR-tLTP, eCB-tLTD and eCB-tLTP domains for $\sigma_{\Delta t} = 0$ **(b1)**,
620 5 **(b2)** and 10ms **(b3)** for the STDP protocol of **(a)**. Note the persistence of the eCB-tLTD
621 domain (blue box) while eCB-tLTP (red box) and NMDAR-tLTP domain (red dashed box)
622 disappeared for 5 and 10ms, respectively. **(c-e)** Similar results are obtained with other jitter
623 distributions, including Gaussian-distributed jitter **(c)** and triangularly-distributed jitter **(d)**.
624 We also considered a combination of triangularly-distributed jitter with random IPIs

625 distributed according to an exponential distribution with refractory period $\tau_r=0.95$ s (see
626 *Methods*) in (e). The plots of the amplitude of NMDAR-tLTP, eCB-tLTD and eCB-tLTP for
627 increasing jitter amplitude $\sigma_{\Delta t}$ (**c2**, **d2**, **e2**) show similar profiles and are similar to panel (**a2**),
628 indicating that the model predictions are not qualitatively modified by the probability
629 distribution function of the jitter.

630

631 **Figure 3: Differential effect of jitter on NMDAR- and eCB-mediated plasticity.**

632 **(a)** STDP protocol; Δt_{STDP} indicates the time between pre- and postsynaptic stimulations.
633 $\Delta t_{\text{STDP}} < 0$ and $\Delta t_{\text{STDP}} > 0$ refer to post-pre and pre-post pairings, respectively. **(b)** Example of 5
634 successive pairings (#5-9, from c1) exhibiting jittered values of Δt_{STDP} (#5-9: -10.3, -15.2, -
635 30.5, -20.7 and -17.3ms); these pairings are indicated with the grey frame within the 100
636 pairings displaying jittered Δt_{STDP} . The distribution of the successive Δt_{STDP} illustrate their
637 standard deviation $\sigma_{\Delta t}=7.9$ ms. **(c)** NMDAR-tLTP is prevented with $\sigma_{\Delta t}>3$ ms. **(c1)** Example
638 of the absence of plasticity after 100 post-pre pairings with $m_{\Delta t}=-18$ ms and $\sigma_{\Delta t}=7.9$ ms; the
639 mean baseline EPSC amplitude, 194 ± 3 pA, did not show significant change 45 minutes after
640 pairing, 186 ± 4 pA. Upper panel, time course of R_i (baseline: 198 ± 2 M Ω and 45-55 min after
641 pairings: 194 ± 2 M Ω ; change of 2%) and holding current (I_{hold}). Inset: distribution of the 100
642 Δt_{STDP} . **(c2)** Averaged time-courses of the absence of plasticity after 100 post-pre pairings
643 with $3<\sigma_{\Delta t}<10$ ms. **(c3)** Relationship between the STDP magnitude and the jitter. **(d)** eCB-
644 mediated t-LTD is not affected by $3<\sigma_{\Delta t}<10$ ms. **(d1)** Example of tLTD induced by 100 pre-
645 post pairings with $m_{\Delta t}=+18$ ms and $\sigma_{\Delta t}=7.1$ ms; the mean baseline EPSC amplitude,
646 160 ± 3 pA, decreased by 50%, to 81 ± 5 pA, 45 minutes after pairings. Upper panel, time course
647 of R_i (baseline: 112 ± 1 M Ω and 35-45 min after pairings: 118 ± 1 M Ω ; change of 5%) and I_{hold} .
648 Inset: distribution of the 100 Δt_{STDP} . **(d2)** Averaged time-courses of tLTD induced by 100 pre-
649 post pairings with $3<\sigma_{\Delta t}<10$ ms. **(d3)** Relationship between the STDP magnitude and the

650 jitter. (e) eCB-mediated tLTP is not affected by $3 < \sigma_{\Delta t} < 10$ ms. (e1) Example of tLTP induced
651 by 10 post-pre pairings with $m_{\Delta t} = -21$ ms and $\sigma_{\Delta t} = 6.4$ ms; the mean baseline EPSC amplitude,
652 113 ± 2 pA, increased by 115% to 243 ± 6 pA 45 minutes after pairings. Upper panel, time
653 course of R_i (baseline: 185 ± 1 M Ω and 45-55 min after pairings: 197 ± 2 M Ω ; change of 6%)
654 and I_{hold} . Inset: distribution of the 10 Δt_{STDP} . (e2) Averaged time-courses of tLTP induced by
655 10 post-pre pairings with $3 < \sigma_{\Delta t} < 10$ ms. (e3) Relationship between the STDP magnitude and
656 the jitter.
657 Insets: average of 12 successive EPSC amplitude at baseline (black trace) and at 40-50 min
658 after STDP pairings (grey trace). Error bars represent the SEM.

659

660 **Figure 4: Model-based analysis of the effects of jittering.**

661 Model-predicted time-courses of (a) y_{CB1R} activation and (b) the concentration of active
662 CaMKII during a protocol with jitter amplitude $\sigma_{\Delta t} = 0$ (a1-b1), 5 (a2-b2) or 10 (a3-b3) ms.
663 The STDP protocol was the same as Figure 2a1 *i.e.* uniformly-distributed jitter of the spike
664 timing and deterministic IPIs at 1Hz. eCB-tLTP (a, red full line) and NMDAR-tLTP (b, red
665 dashed line) were triggered with average spike timing $m_{\Delta t} = -15$ ms and eCB-tLTD (a, blue
666 full line) with $m_{\Delta t} = +20$ ms. In (a) the shaded boxes locate the areas where y_{CB1R} triggers
667 eCB-tLTP or eCB-tLTD. Those areas are defined by the thresholds $\theta_{\text{LTP}}^{\text{start}}$ and $(\theta_{\text{LTD}}^{\text{start}}, \theta_{\text{LTD}}^{\text{stop}})$,
668 respectively (see *Methods*). For $m_{\Delta t} = -15$ ms (red), increasing jitter amplitudes
669 progressively hinders the build up of the y_{CB1R} transients. y_{CB1R} still reaches the LTP area for
670 5-25 pairings with $\sigma_{\Delta t} = 0$ (a1) and 5ms (a2) thus triggering eCB-tLTP but fails to do so for
671 $\sigma_{\Delta t} = 10$ ms (a3). Conversely, eCB-tLTD is robust to jitter because y_{CB1R} remains in the LTD
672 region for most of the pairings with $m_{\Delta t} = +20$ ms (blue), for all tested jitter amplitudes. In
673 (b), with $m_{\Delta t} = -15$ ms (red) the switch from the low activation to the high activation state

674 of CaMKII is obtained in the absence of jittering $\sigma_{\Delta t} = 0\text{ms}$ (**b1**). The progressive build up of
675 activated CaMKII is efficiently suppressed as soon as $\sigma_{\Delta t} = 5\text{ms}$ (**b2**) thus effectively
676 suppressing NMDAR-tLTP (**b3**).

677

678 **Figure 5: Model-based analysis of the change of robustness with frequency.**

679 **(a)** Summary of the robustness of the model plasticity at 1Hz. The jittered STDP protocol
680 combined uniformly-distributed jitter of the spike timing and constant IPIs at 1Hz. Two-
681 dimensional maps show alterations of the plasticity obtained with 10 (**a1**) or 100 (**a2**)
682 pairings, when the average spike timing $m_{\Delta t}$ and the jitter amplitude $\sigma_{\Delta t}$ are changed. The
683 locations of the plasticity blotches are indicated with horizontal lines: full red for eCB-tLTP,
684 full blue for eCB-tLTD and dashed red for NMDAR-tLTP. The length of each of these
685 blotches along the y-axis reflects their robustness to jitter. **(a3)** A cross-section along the
686 dashed and full horizontal lines of (**a1-a2**) illustrates the robustness of NMDAR-tLTP, eCB-
687 tLTD and eCB-tLTP. **(b)** Robustness of the model with larger frequency (1.05Hz) and same
688 jittered STDP protocol as in **(a)**. Note the distortion between the pairing frequency in the
689 model and in the experiments. The behavior of the model for $F_{\text{pairings}}=1.05\text{Hz}$ corresponds to
690 experimental results with $F_{\text{pairings}} \approx 3\text{Hz}$ ¹³. The two-dimensional maps for 10 (**b1**) or 100 (**b2**)
691 pairings as well as the cross-sections (**b3**) predict that for frequencies larger than 1Hz, the
692 robustness changes, with NMDAR-tLTP becoming more robust.

693

694 **Figure 6: Increasing frequency and N_{pairings} stabilized NMDAR-tLTP against jitter.**

695 **(a)** 100 post-pre pairings at 3Hz induced a tLTP, which is not affected by $3 < \sigma_{\Delta t} < 10\text{ms}$. **(a1)**
696 Example of tLTP induced by 100 post-pre pairings at 3Hz with $m_{\Delta t} = -22\text{ms}$ and $\sigma_{\Delta t} = 9\text{ms}$;
697 the mean baseline EPSC amplitude, $194 \pm 4\text{pA}$, increased by 212%, to $606 \pm 7\text{pA}$, 45 min after
698 pairings. Upper panel, time course of Ri (baseline: $123 \pm 1\text{M}\Omega$ and 45-55 min after pairings:

699 $138 \pm 1 \text{M}\Omega$; change of 12%) and I_{hold} for this cell. Inset: distribution of Δt_{STDP} for the 100
700 pairings. **(a2)** Averaged time-courses of tLTP induced by 100 post-pre pairings at 3Hz with
701 $3 < \sigma_{\Delta t} < 10 \text{ms}$. **(a3)** Relationship between the STDP magnitude and the jitter for each of the
702 recorded neurons after 100 pairings at 1Hz (n=7; blue circles) or at 3Hz (n=10; red circles).
703 **(b)** 250-300 post-pre pairings induced tLTP, which is not affected by $3 < \sigma_{\Delta t} < 10 \text{ms}$. **(b1)**
704 Example of tLTP induced by 250 post-pre pairings with $m_{\Delta t} = -20 \text{ms}$ and $\sigma_{\Delta t} = 5 \text{ms}$; the mean
705 baseline EPSC amplitude, $126 \pm 3 \text{pA}$, increased by 57% to $198 \pm 4 \text{pA}$ 45 minutes after pairings.
706 Upper panel, time course of R_i (baseline: $65 \pm 1 \text{M}\Omega$ and 45-55 min after pairings: $65 \pm 2 \text{M}\Omega$;
707 change $< 1\%$) and I_{hold} . Inset: distribution of Δt_{STDP} for the 250 pairings. **(b2)** Averaged time-
708 courses of tLTP induced by 250-300 post-pre pairings with $3 < \sigma_{\Delta t} < 10 \text{ms}$. **(b3)** Relationship
709 between the STDP magnitude and the jitter for each of the recorded neurons after 100 (n=7;
710 blue circles), 200 (n=6; black circles) or 250-300 (n=7; red circles) post-pre pairings.
711 Insets: average of 12 successive EPSC amplitude at baseline (black trace) and at 40-50 min
712 after STDP pairings (grey trace). Error bars represent the SEM.

713

714 **Figure 7: The robustness of plasticity depends on the regularity of the presynaptic spike**
715 **train.**

716 The figure shows the robustness of the model plasticity (eCB-tLTP with red, eCB-tLTD with
717 blue and NMDAR-tLTP with dashed red) with the jittered STDP protocol of figure 2e1, *i.e.*
718 exponentially-distributed IPIs with refractory period τ_r and triangularly-distributed jitter $\xi_{\Delta t}$.
719 From right to left, the refractory period τ_r is gradually decreased. When $\tau_r \rightarrow 1/F_{\text{pairings}}$
720 where $F_{\text{pairings}} = 1 \text{Hz}$ is the average pairings frequency, one gets regular presynaptic spike
721 trains, similar to classical STDP protocols. In this case (see e.g. $\tau_r = 0.95/F_{\text{pairings}}$), the
722 robustness pattern is similar to the previous observations at 1Hz: eCB-STDP is robust,
723 whereas NMDAR-tLTP is fragile. However, when $\tau_r \rightarrow 0$, the presynaptic spike train

724 becomes highly irregular. In this case, the robustness patterns changes totally, with NMDAR-
725 LTP becoming the most robust, and eCB-tLTD turning into a LTP. Hence, irregular
726 presynaptic spike trains are predicted to produce robust LTP at the expense of LTD.

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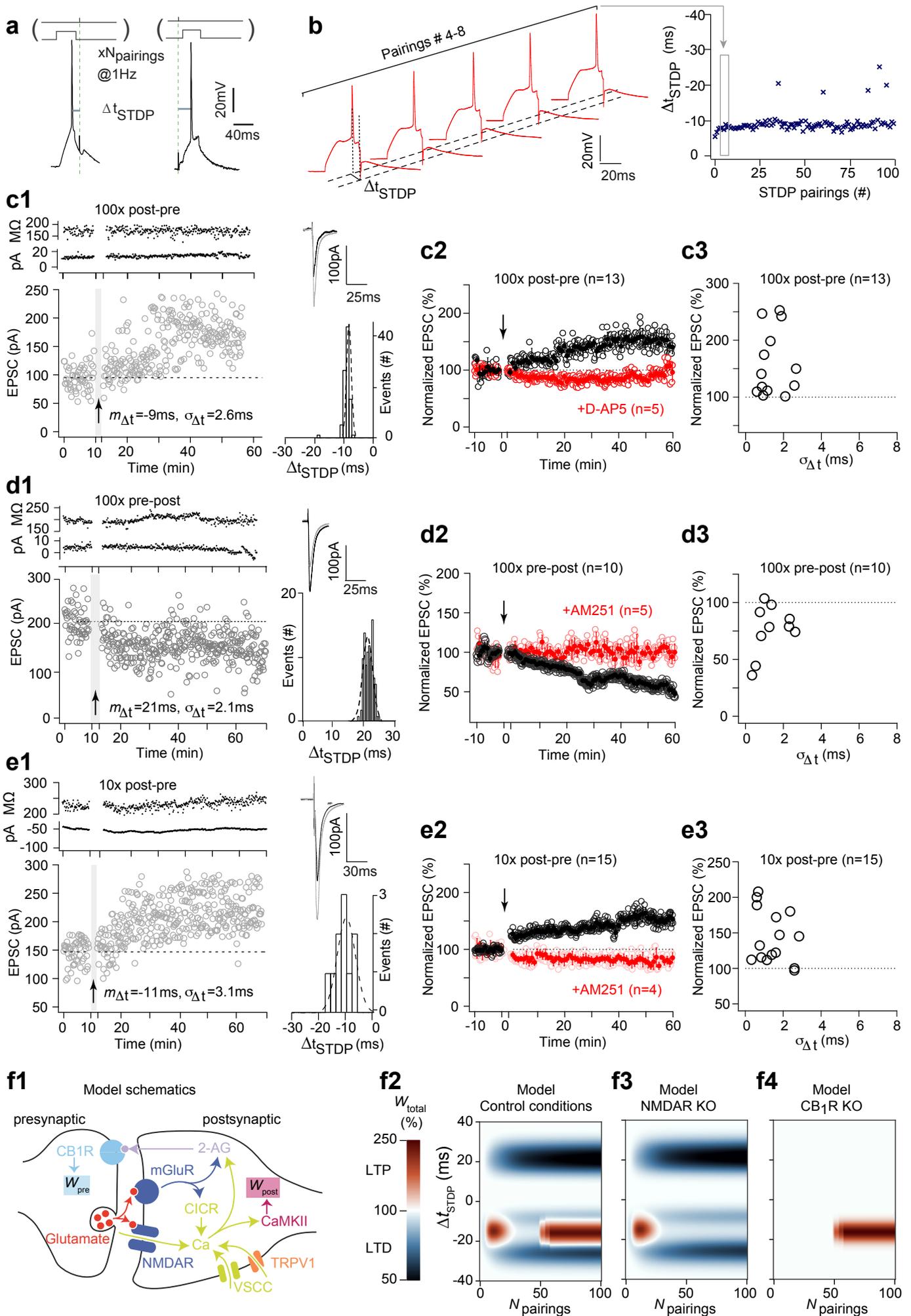
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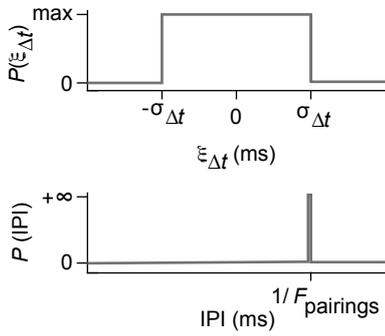
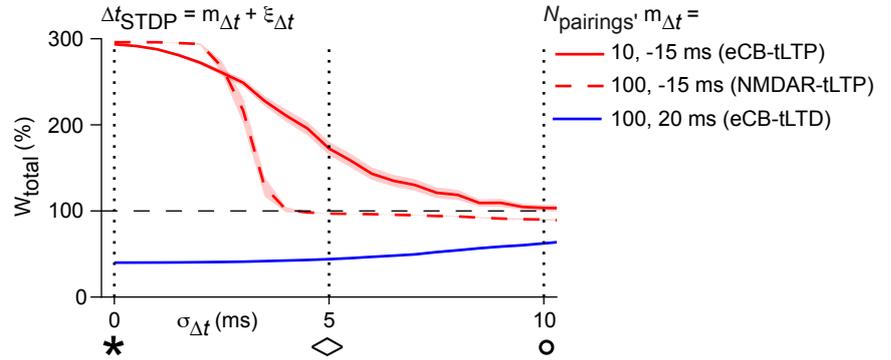
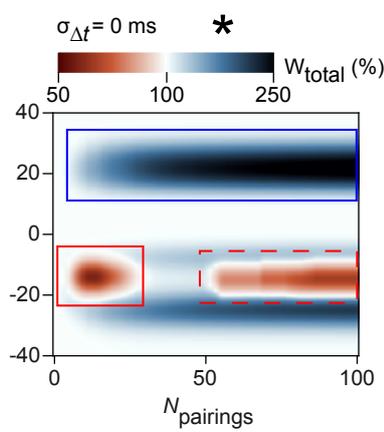
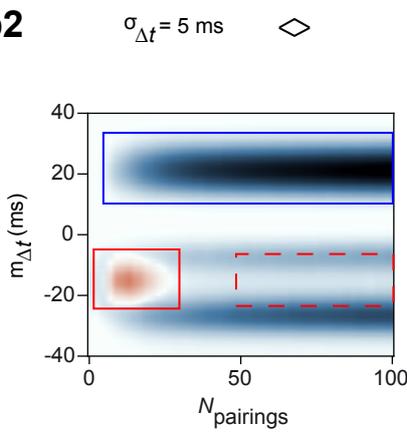
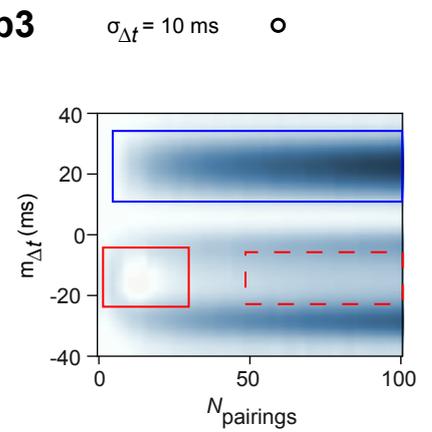
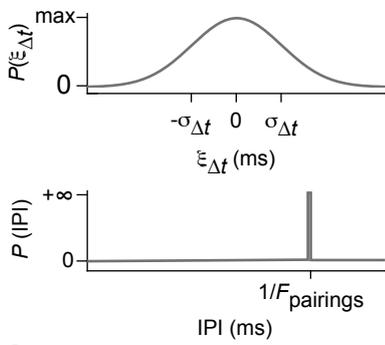
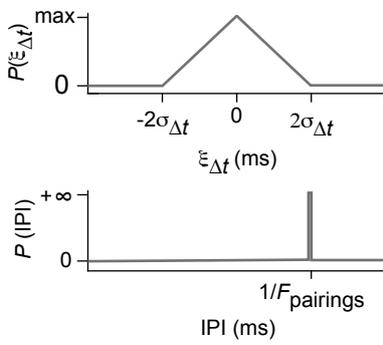
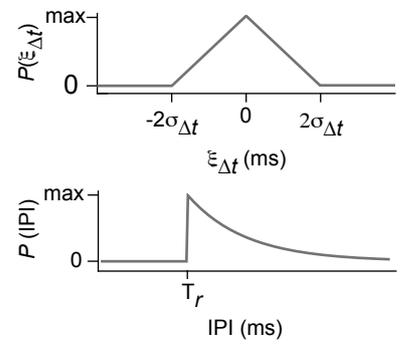
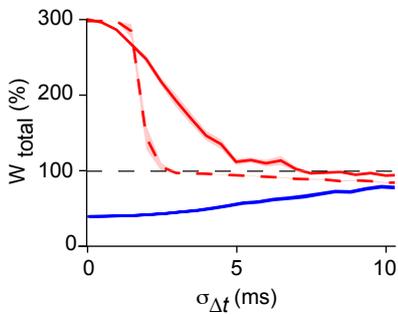
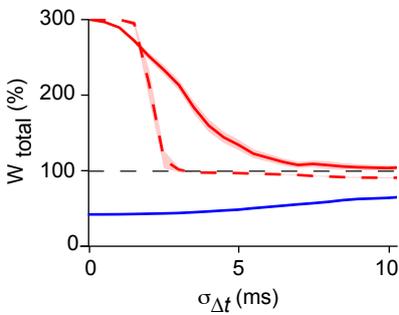
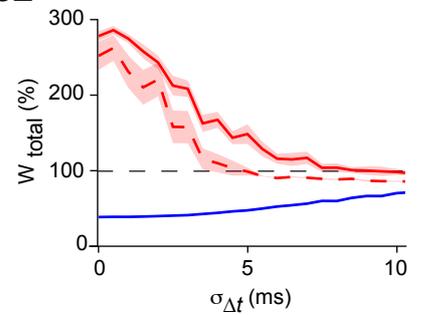
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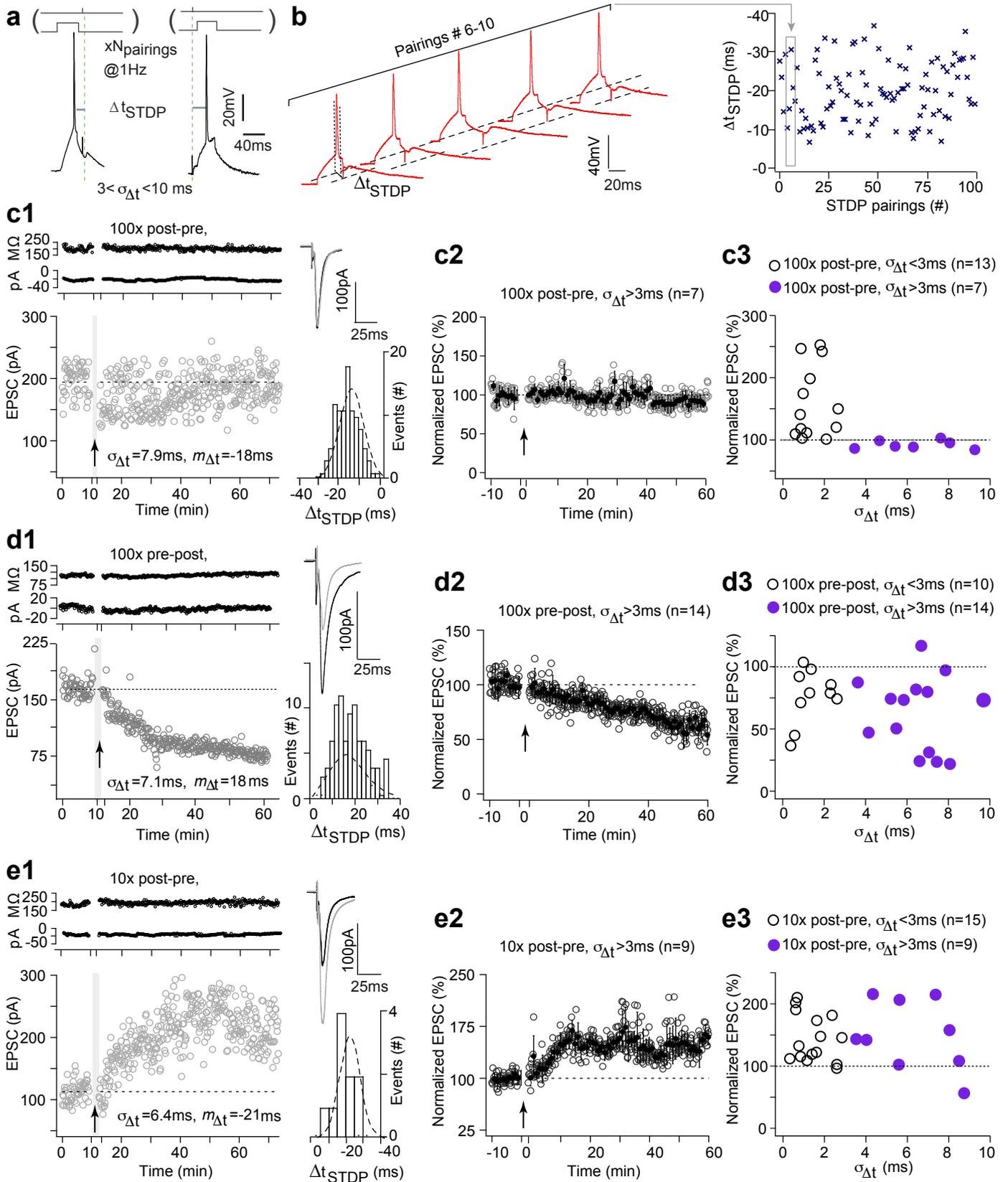
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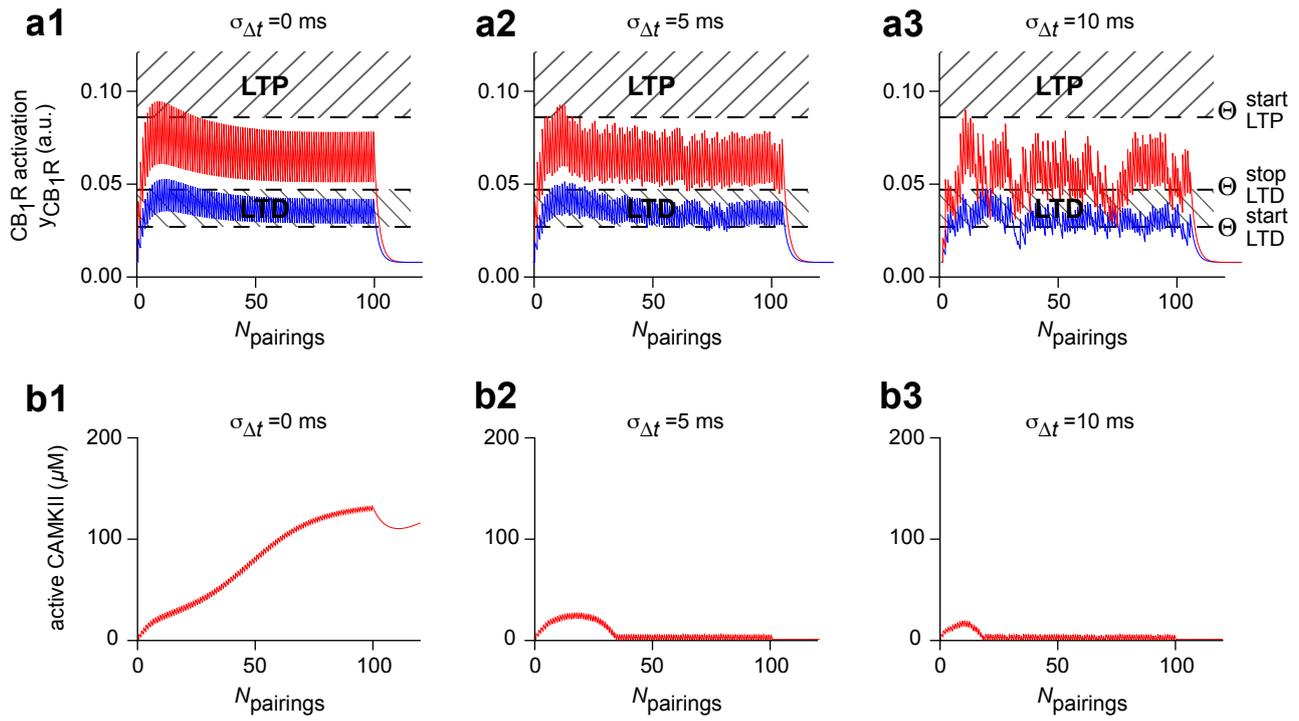
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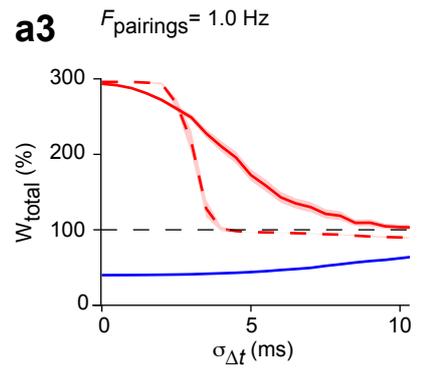
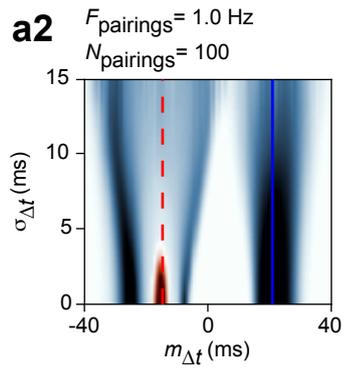
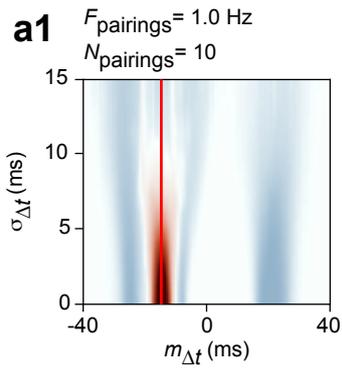
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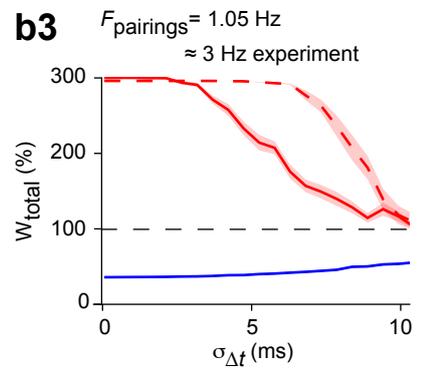
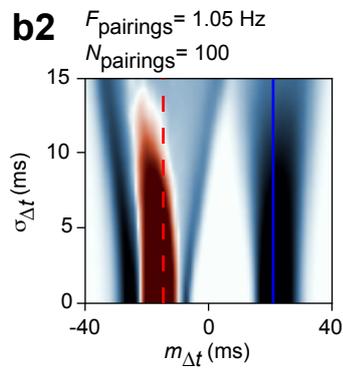
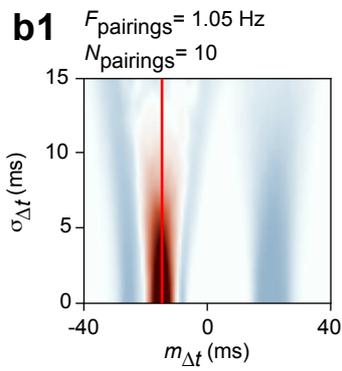
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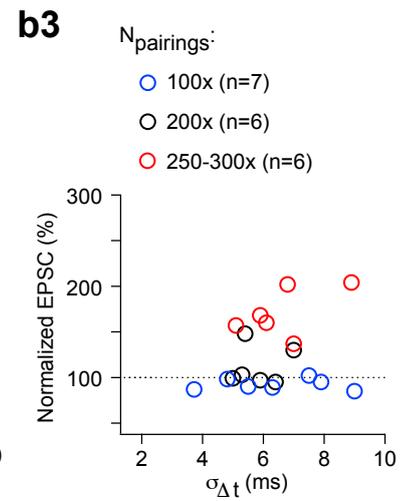
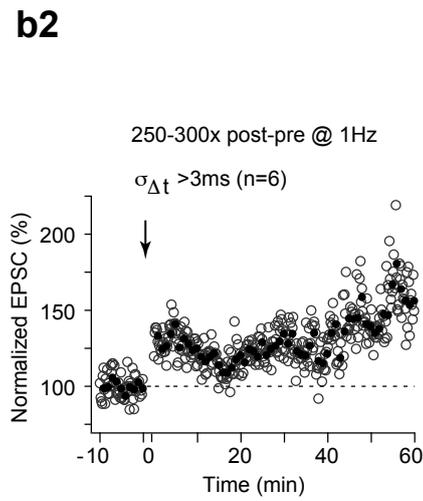
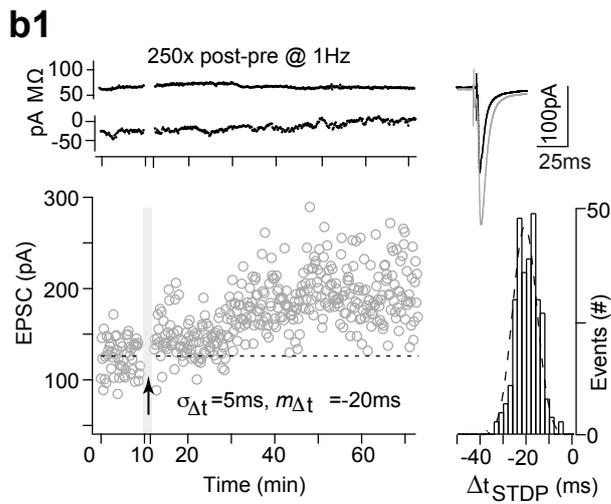
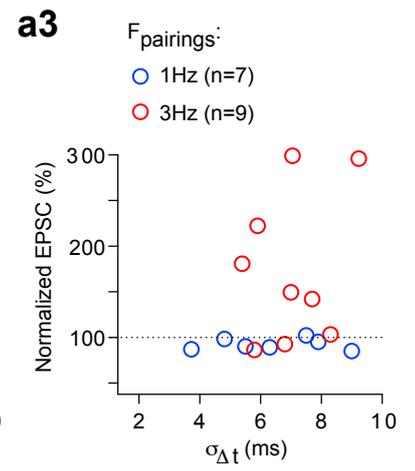
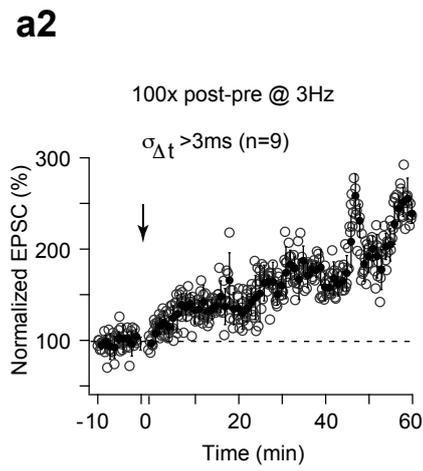
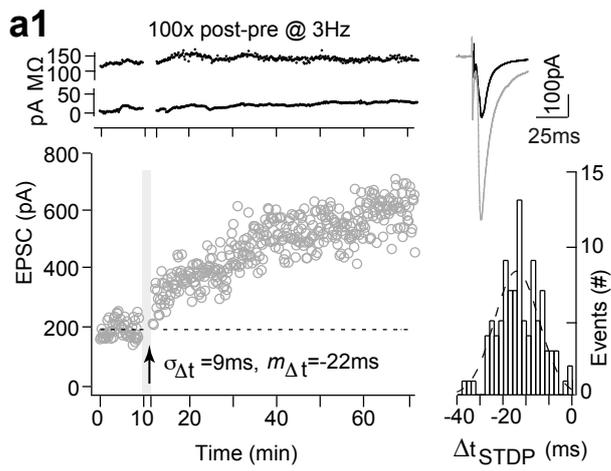




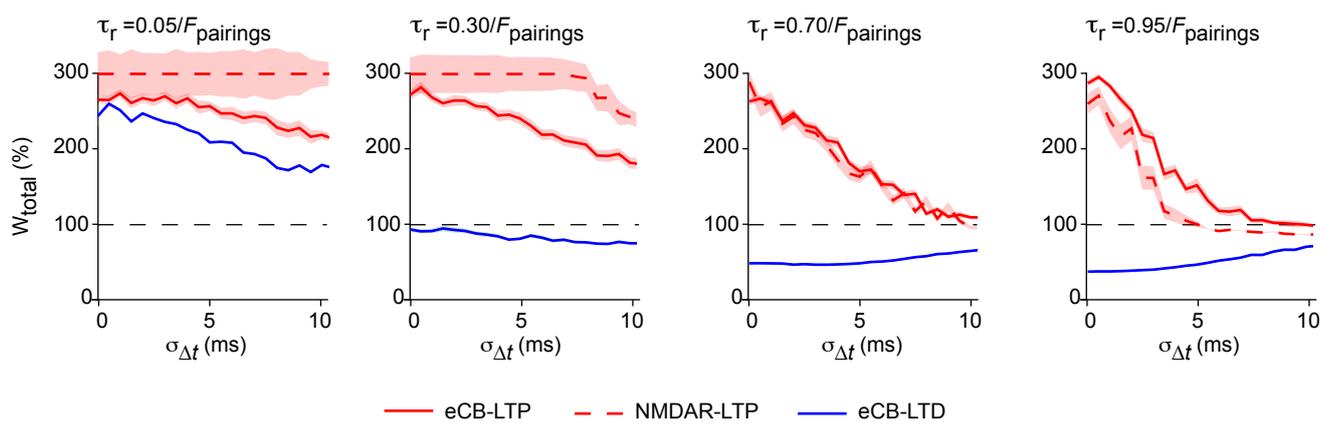


— eCB-LTP - - NMDAR-LTP — eCB-LTD





Presynaptic spike trains *Irregular* $\xrightarrow{\text{refractory period } \tau_r}$ *Regular*



Robustness of STDP to spike-timing jitter

Y. Cui, I. Prokin, A. Mendes, H. Berry, L. Venance

SUPPORTING INFORMATION

S1 Text - Description of the mathematical model

We describe here the mathematical model used to predict the outcome of STDP stimulations with spike timing jitter. We give here the information necessary to implement the model. Further detail and validation can be found in Cui et al (2016).

Stimulations. A STDP protocol consists in a series of N_{pairings} post- and presynaptic pairs of stimulations. We note t_{pre_i} the time at which the i^{th} presynaptic stimulation is delivered and t_{post_i} the onset time of the i^{th} postsynaptic step current stimulation, where $i = 1, \dots, N_{\text{pairings}}$. We modeled glutamate concentration in the synaptic cleft, $G(t)$, as a train of exponentially-decaying impulses triggered by presynaptic stimuli at time t_{pre_i} :

$$G(t) = G_{\text{max}} \sum_i \exp\left(-\frac{t-t_{\text{pre}_i}}{\tau_G}\right) \Theta\left(t - t_{\text{pre}_i}\right) \quad (\text{SI1})$$

where G_{max} is the peak glutamate concentrations and τ_G is the glutamate clearance rate. On the postsynaptic side, action currents resulting from postsynaptic stimulations were modeled according to

$$I_{\text{action}}(t) = -DC_{\text{max}} \sum_i R(t, t_{\text{post}_i}, DC_{\text{dur}}) - AP_{\text{max}} \sum_i \Theta(t - \delta - t_{\text{post}_i}) \exp\left(\frac{-t + \delta + t_{\text{post}_i}}{\tau_{\text{bAP}}}\right) \quad (\text{SI2})$$

where the rectangle function $R(t, a, l) = \Theta(t - a) - \Theta(t - a - l)$, DC_{max} and DC_{dur} are the amplitude and duration of step-current injected by the patch pipette in the postsynaptic soma, AP_{max} is the amplitude of the action current producing the bAP; and τ_{bAP} is the time scale for bAP decay.

We modeled the electrical response to these stimulations in a postsynaptic element considered as a single isopotential compartment with AMPAR, NMDAR, VSCC and TRPV1 conductances

$$C_m \frac{dV}{dt} = -g_L(V - V_L) - I_{\text{AMPA}}(V, G(t)) - I_{\text{NMDAR}}(V, G(t)) - I_{\text{VSCC}}(V) - I_{\text{TRPV1}}(V, \text{AEA}) - I_{\text{action}}(t) \quad (\text{SI3})$$

where V is membrane potential; g_L and V_L are leak conductance and reversal potential respectively; I_{AMPA} , I_{NMDAR} , I_{VSCC} and I_{TRPV1} are currents through AMPAR, NMDAR, L-type VSCC (v1.3) and TRPV1, respectively, and AEA stands for anandamide. NMDAR and AMPAR were modeled with two-state kinetic models and 1.0mM Mg^{2+} (Destexhe *et al.*, 1995) whereas the model and parameters for the $\text{Ca}_v1.3$ VSCC current was taken from Wolf *et al.* (2005). The TRPV1 current, including its dependence on AEA, was modeled as:

$$I_{\text{TRPV1}}(V, \text{AEA}) = g_{\text{TRPV1}} \cdot V \cdot P_{\text{TRPV1}}^{\text{open}}(V, \text{AEA}) \quad (\text{SI4})$$

where g_{TRPV1} is the maximal conductance of TRPV1 and the mathematical expression for the $P_{\text{TRPV1}}^{\text{open}}$ was taken from Matta and Ahern (2007).

Biochemical signaling. Free cytosolic calcium is one of the main signaling actors in the model. To model its dynamics, we assumed it can be transferred from/to two main sources: (i) extracellular calcium, via the plasma membrane channels of eq. (SI3) above and (ii) the endoplasmic reticulum (ER), via the IP3-dependent Calcium-Induced Calcium Release (CICR) system. Hence, the concentration of free cytosolic calcium C was computed according to

$$T_C(C) \frac{dC}{dt} = J_{\text{IP3R}} - J_{\text{SERCA}} + J_{\text{leak}} + J_{\text{NMDAR}} + J_{\text{VSCC}} + J_{\text{TRPV1}} - \frac{C - C_b}{\tau_{C_b}} \quad (\text{SI5})$$

where the fluxes J_{IP3R} , J_{SERCA} , J_{leak} from and to the ER in the CICR system were taken from the model of De Pittà *et al.* (2009) - see also Cui *et al.* (2016) and J_{NMDAR} , J_{VSCC} and J_{TRPV1} are the calcium fluxes from the plasma membrane channels (eq. SI3), computed as $J_x = \xi_x \cdot I_x$ where the ξ_x are constants, $x \in \{\text{NMDAR}, \text{VSCC}, \text{TRPV1}\}$. C_b is the basal cytosolic calcium level resulting from equilibration with calcium diffusion out of the cell and τ_{C_b} is the corresponding time scale. The CICR model also includes the dynamics of the fraction of inactive IP3 (inositol triphosphate) receptor channels (IP3R), h

$$\frac{dh}{dt} = a_2 d_2 \frac{\text{IP3} + d_1}{\text{IP3} + d_3} (1 - h) - a_2 C h \quad (\text{SI6})$$

Likewise, the dynamics of C_{ER} , the calcium concentration in the endoplasmic reticulum (ER) was given by

$$T_{C_{ER}}(C_{ER}) \frac{dC_{ER}}{dt} = -\rho_{ER} (J_{IP_3R} - J_{SERCA} + J_{leak}) \quad (SI7)$$

where ρ_{ER} is the ER to cytoplasm volume ratio. In eq.(SI5) and (SI7), T_x , $x = C$ or C_{ER} , is a time scaling factor accounting for the presence of endogenous calcium buffers and expressed according to

$$T_x(x) = 1 + \frac{B_T}{K_{dB} (1 + x / K_{dB})^2} \quad (SI8)$$

Our model also accounts for the biochemical pathways leading to the production of the endocannabinoids 2-Arachidonoylglycerol (2-AG) and AEA, and their subsequent activation of cannabinoid receptors type-1, CB₁R. Principally, the model expresses the kinetics of the following enzymatic reactions: (i) synthesis of DAG (diacylglycerol) and IP₃ (inositol triphosphate) as a result of glutamate (G) binding of metabotropic glutamate receptors (mGluR) and subsequent activation of PLC β as well as Ca-dependent synthesis by PLC δ , (ii) transformation of DAG into 2-AG by DAG Lipase α and (iii) synthesis of AEA by calcium-dependent fatty acid amide hydrolase (FAAH). The dynamics of this system was modeled with the following equations:

$$\frac{dIP_3}{dt} = v_\beta \frac{G}{G + K_R + K_P C / (C + K_\pi)} + \frac{v_\delta}{1 + IP_3 / \kappa_d} \frac{C^2}{K_\delta^2 + C^2} - v_{3K} CaMKII * \frac{IP_3^{n_3}}{K_3^{n_3} + IP_3^{n_3}} - r_{5P} IP_3 \quad (SI9)$$

$$\frac{dDAG}{dt} = v_\beta \frac{G}{G + K_R + K_P C / (C + K_\pi)} + \frac{v_\delta}{1 + IP_3 / \kappa_d} \frac{C^2}{K_\delta^2 + C^2} - \frac{r_{DGL} \cdot DAGL \cdot \varphi_{DAGL} \cdot DAG}{DAG + K_{DAGL}} - r_{DAGK} \cdot DAG \quad (SI10)$$

$$\frac{d2AG}{dt} = \frac{r_{DGL} \cdot DAGL \cdot \varphi_{DAGL} \cdot DAG}{DAG + K_{DAGL}} - r_{MAGL} 2AG \quad (SI11)$$

$$\frac{d\varphi_{DAGL}}{dt} = r_k C^{n_c} (1 - \varphi_{DAGL}) - r_p \varphi_{DAGL} \quad (SI12)$$

$$\frac{dAEA}{dt} = v_{AT} C - r_{FAAH} \frac{AEA}{K_{FAAH} + AEA} \quad (SI13)$$

where $CaMKII^*$ is the amount of activated (phosphorylated) CaMKII (see below); φ_{DAGL} is the fraction of active DAG Lipase α and DAGL its total (activated+not activated) concentration. Eq. (SI9-SI11) account for IP3 degradation by IP3 3-kinase (3K) and inositol polyphosphate 5-phosphatase (5P), while DAG and 2AG are degraded by DAG kinase (DAGK) and monoacylglycerol lipase (MAGL), respectively.

2-AG and AEA are retrograde signaling molecules that are produced in the postsynaptic neuron but diffuse to the presynaptic cell, where they activate CB₁R. We modeled CB₁R activation by 2-AG and AEA using a simple three-state kinetic model: open (x_{CB1R}), desensitized (d_{CB1R}) and inactivated (i_{CB1R}):

$$\frac{dx_{CB1R}}{dt} = \alpha_{CB1R} \cdot eCB \cdot i_{CB1R} - (\beta_{CB1R} + \gamma_{CB1R}) x_{CB1R} \quad (SI14)$$

$$\frac{dd_{CB1R}}{dt} = -\epsilon_{CB1R} d_{CB1R} + \gamma_{CB1R} x_{CB1R} \quad (SI15)$$

where $eCB = 2-AG + 0.10 AEA$ and mass conservation implies $x_{CB1R} + d_{CB1R} + i_{CB1R} = 1$. The open fraction x_{CB1R} was then used to compute CB₁R activation as

$$y_{CB1R} = k_{CB1R} x_{CB1R} + C_1 \quad (SI16)$$

where C_1 is a constant that accounts for the modulation of presynaptic plasticity by other pathways and k_{CB1R} quantifies the strength of CB₁R activation on presynaptic plasticity.

In our model, CB₁R activation (y_{CB1R}) controls the presynaptic weight W_{pre} according to the following rule: W_{pre} decreases for intermediate values of y_{CB1R} , i.e. when y_{CB1R} is comprised between two tLTD thresholds ($\theta_{LTD}^{start} < y_{CB1R} < \theta_{LTD}^{stop}$) whereas W_{pre} increases when y_{CB1R} is larger than a tLTP threshold ($y_{CB1R} > \theta_{LTP}^{start}$). Following Cui et al. (2016), we implemented this rule as

$$\Omega(y_{CB1R}) = \begin{cases} 1 - A_{LTD} & \text{if } \theta_{LTD}^{start} < y_{CB1R} < \theta_{LTD}^{stop} \\ 1 + A_{LTP} & \text{if } \theta_{LTP}^{start} < y_{CB1R} \\ 1 & \text{otherwise} \end{cases} \quad (SI17)$$

and

$$\frac{dW_{\text{pre}}}{dt} = \frac{\Omega(y_{\text{CB1R}}) - W_{\text{pre}}}{\tau_{W_{\text{pre}}}(y_{\text{CB1R}} + C_2)} \quad (\text{SI18})$$

Here Ω determines the change of presynaptic plasticity, with a time scale $\tau_{W_{\text{pre}}}$ set to yield rapid changes of W_{pre} for large y_{CB1R} values and very slow changes at very low y_{CB1R} :

$$\tau_{W_{\text{pre}}}(x) = \frac{P_1}{P_2^{P_3} + x^{P_3}} + P_4 \quad (\text{SI19})$$

To account for experimental observation that the presynaptic weight ranges from about 50 to 300%, W_{pre} was clipped to 3.0 (hard bound).

Postsynaptic plasticity in the model was based on the activation by calcium of calmodulin and CaMKII and the regulation of this system by PKA, calcineurin and protein phosphatase 1 (PP1). The model of Cui et al (2016) for this subsection is based on the model proposed in Graupner & Brunel (2007). In this model the concentration of the calcium/calmodulin complex with four calcium ions bound (CaM) is considered at equilibrium and computed as:

$$CaM = \frac{CaMT}{1 + \sum_{i=1}^4 (C^i \cdot \prod_{j=5-i}^4 K_j)} \quad (\text{SI20})$$

where $CaMT$ is the total calmodulin concentration and K_i stands for the equilibrium constant of the binding of the i^{th} calcium ion to calmodulin. Each CaMKII enzyme consists of two subunits, each of which contains 6 phosphorylation sites, thus defining 14 phosphorylation states per subunit. Denoting y_i , $i=0 \dots 13$ the concentrations of subunit in phosphorylation state i , the model of Graupner & Brunel (2007) expresses their dynamics as:

$$\begin{aligned}
\frac{dy_1}{dt} &= 6k_6\gamma^2 y_0 - (4k_6\gamma^2 + k_7\gamma + k_{10})y_1 + 2k_{10}\sigma_2^4 \\
\frac{dy_2}{dt} &= (k_7\gamma + k_6\gamma^2)y_1 - (3k_6\gamma^2 + k_7\gamma + 2k_{10})y_2 + k_{10}(y_5 + \sigma_5^7) \\
\frac{dy_3}{dt} &= 2k_6\gamma^2 y_1 - 2(k_7\gamma + k_6\gamma^2 + k_{10})y_3 + k_{10}(\sigma_5^7 + 3y_8) \\
\frac{dy_4}{dt} &= k_6\gamma^2 y_1 - 2(k_7\gamma + k_6\gamma^2 + k_{10})y_4 + k_{10}(y_6 + y_7) \\
\frac{dy_5}{dt} &= k_7\gamma(\sigma_2^3 - y_5) + k_6\gamma^2(y_2 - 2y_5) + k_{10}(2y_9 + y_{10} - 3y_5) \\
\frac{dy_6}{dt} &= k_6\gamma^2(\sigma_2^3 - y_6) + k_7\gamma(2y_4 - 2y_6) + k_{10}(-3y_6 + \sigma_9^{11} + y_{11}) \\
\frac{dy_7}{dt} &= k_6\gamma^2(y_2 + 2y_4 - y_7) + k_7\gamma(y_3 - 2y_7) + k_{10}(-3y_7 + \sigma_9^{11} + y_{11}) \\
\frac{dy_8}{dt} &= k_6\gamma^2 y_3 - 3k_7\gamma y_8 + k_{10}(y_{10} - 3y_8) \\
\frac{dy_9}{dt} &= k_7\gamma(\sigma_5^7 - y_9) + k_6\gamma^2(y_5 - y_9) + k_{10}(-4y_9 + 2y_{12}) \\
\frac{dy_{10}}{dt} &= k_6\gamma^2 y_5 + k_6\gamma^2 y_6 + k_7\gamma(y_7 + 3y_8 - 2y_{10}) + k_{10}(2y_{12} - 4y_{10}) \\
\frac{dy_{11}}{dt} &= k_7\gamma(y_6 - 2y_{11}) + k_6\gamma^2 y_7 + k_{10}(y_{12} - 4y_{11}) \\
\frac{dy_{12}}{dt} &= k_6\gamma^2 y_9 + k_7\gamma(2\sigma_9^{11} - y_9 - y_{12}) + k_{10}(6y_{13} - 5y_{12}) \\
\frac{dy_{13}}{dt} &= k_7\gamma y_{12} - 6k_{10}y_{13}
\end{aligned} \tag{SI21}$$

where $\sigma_i^j = \sum_{k=i}^j y_k$ and mass conservation implies $y_0 = 2CaMKII_0 - \sigma_1^{13}$, where $CaMKII_0$ is the total CaMKII concentration. In eq. (SI21) above the probabilities that CaM binds to phosphorylated (γ) and dephosphorylated (γ^*) subunit of CaMKII are computed as $\gamma = CaM/(CaM + K_5)$ and $\gamma^* = CaM/(CaM + K_9)$. Moreover, the rate of subunit dephosphorylation (k_{10}) is given by $k_{10} = k_{12}PP1/(K_M + CaMKII^*)$ where K_M is a constant, $PP1$ is the concentration of PP1. $CaMKII^*$ is the total concentration of phosphorylated subunits of CaMKII computed accross all possible states of phosphorylation $CaMKII^* = \sum_{i=0}^{13} m_i y_i$ where m_i is the number of the phosphorylated subunits of CaMKII in state i and y_i .

Finally, the model of Graupner & Brunel (2007) assumes that, in addition to calcineurin (CaN), PKA activity depends on CaM according to a Hill-function activation:

$$v_x(CaM) = k_x^0 + \frac{k_x}{1+(K_x/CaM)^{n_x}} \tag{SI22}$$

where $x = CaN$ or PKA , The interaction between PP1 and I1 is then described as:

$$\begin{aligned}
\frac{dI1}{dt} &= \frac{dPP1}{dt} - v_{CaN}I1 + v_{PKA}I1_0 \\
\frac{dPP1}{dt} &= -k_{13}I1 \cdot PP1 + k_{-13}(PP1_0 - PP1)
\end{aligned} \tag{SI23}$$

where $PP1_0$ and $I1_0$ are total PP1 and I1 concentrations, respectively.

In agreement with Cui et al. (2016) and Graupner & Brunel (2007), we assumed that postsynaptic plasticity is directly proportional to the calcium-dependent activation of CaMKII and set:

$$W_{\text{post}} = 1 + 3.5 \frac{CaMKII^*}{CaMKII_{\text{max}}^*} \quad (\text{SI24})$$

where $CaMKII_{\text{max}}^*$ is the maximal concentration of activate (phosphorylated).

Finally, the total synaptic weight was taken as the product of the presynaptic and the postsynaptic contributions above:

$$W_{\text{total}} = W_{\text{pre}} W_{\text{post}} \quad (\text{SI25})$$

Model implementation and numerics. Our mathematical model comprises 36 ordinary differential equations and close to 150 parameters, among which more than one half is constrained by experimental data. Initial conditions were set to the steady-state of each variable in the absence of stimulation. Numerical solution was obtained with the LSODA solver from the ODEPACK fortran77 library with absolute and relative tolerances both equal to 10^{-7} . Initial conditions were set to the steady-state of each variable in the absence of stimulation. Numerical integration proceeded until the synaptic weights reach stable values (typically observed around $t \approx 5\text{min}$ after the stimulation protocol). We used the final values of the pre- and postsynaptic weights to compute the total synaptic weight change due to the stimulations. Importantly, with the exception of the stimulation protocols, *we have used the exact same equations and parameter values as in Cui et al. (2016)*. The list of parameters and their estimated values is given in S2 Table. The current study employs stochastic simulations since the stimulation protocol is stochastic (while the rest of the model is deterministic). Therefore, the model was calibrated using experimental data from deterministic stimulation

protocols (Cui et al., 2016) and we tested here whether it can make successful predictions when we applied stochastic stimulation protocols, for which the model was not calibrated. The results are thus averages over N_{trials} realizations. N_{trials} was varied from 30 to 500 depending on the smoothness of the averaged curves and values of SEM, but $N_{\text{trials}}=50$ in most of the simulations. The computer code of the model is available online from <https://github.com/iprokin/Cx-Str-STDP> and <https://senselab.med.yale.edu/modeldb/ShowModel.cshtml?model=187605>.

S2 Table – Parameter values

A. Intracellular dynamics

Description	Name	Values	Units	Reference
I _{NMDAR} to Ca flow conversion	ξ_{NMDAR}	98	$\mu\text{M/pCol}$	set to match Ca ²⁺ amplitudes in [1]
I _{VSCC} to Ca flow conversion	ξ_{VSCC}	140	$\mu\text{M/pCol}$	set to match Ca ²⁺ amplitudes in [2]
I _{TRPV1} to Ca flow conversion	ξ_{TRPV1}	290	$\mu\text{M/pCol}$	set to match Ca ²⁺ amplitudes in [1]
Total endogenous Ca buffer	B_T	4.5	μM	Estimated from our experimental data
Basal cytoplasmic [Ca]	C_b	0.1	μM	[1,3]
Time scale for Ca exit	τ_{cb}	0.007	s	Idem
Endogenous Ca buffer affinity	K_{dB}	0.5	μM	[3,4]
ER-to-cytosol volume ratio	ρ_{ER}	0.3	-	Adapted from [4]
IP3R binding rate (inactivation)	a_2	0.5	$\mu\text{M/s}$	Idem
Maximal SERCA pump rate	v_{ER}	8	$\mu\text{M/s}$	Idem
IP3R affinity for IP3	d_3	0.9434	μM	[5]
Maximal IP3R rate	r_C	4	1/s	Adapted from [5]
Basal [Ca] in the ER	$Ca_{ER,b}$	65	μM	[6]
Ca leak from the ER	r_l	0.1	1/s	[5]
IP3R affinity for Ca	d_5	0.12	μM	Adapted from [5]
IP3R dissociation constant	d_2	3.049	μM	Idem
SERCA pump affinity for Ca	K_{ER}	0.05	μM	[5]
IP3R affinity for IP3	d_1	0.13	μM	Idem
PLC δ product inhibition	κ_d	1.5	μM	Idem
PLC δ Ca-activation	K_δ	0.1	μM	Idem
5P-IP maximal rate	r_{5P}	0.2	1/s	Adapted from [5]
PI3K maximal rate	v_{3K}	0.001	$\mu\text{M/s}$	Idem
PI3K Ca-activation constant	K_D	1.5	μM	Idem
PLC δ maximal rate	v_δ	0.02	$\mu\text{M/s}$	[5]
PI3K affinity for IP3	K_3	1	μM	Idem
Glutamate affinity to mGluR	K_R	1.3	μM	Idem
regulation by PLC β termination	K_P	10	μM	Idem
PLC β maximal rate	v_β	0.8	$\mu\text{M/s}$	Adapted from [5]
PKC Ca-activation constant	K_π	0.6	μM	[5]
Total CaMKII α concentration	$CaMKII_0$	16.6	μM	[7]
Total Calmodulin concentration	$CaMT$	0.07085	μM	Adapted from [7]
PKA Hill number	n_{PKA}	3	-	Idem

Referenced articles: [1] Sabatini, B.L., Oertner, T.O. and Svoboda, K. (2002) *Neuron* 33(3):439-452 [2] Carter, A.G. and Sabatini, B.L. (2004) *Neuron* 44(3):483-493 [3] Jackson, M.B. and Redman, S.J. (2003) *J Neurosci* 23:1612–1621 [4] Nägerl, U.V. *et al.* (2000) *Biophys J* 79: 3009–3018 [5] De Pittà M. *et al.* (2009) *J Biol Phys* 35:383-411 [6] Solovyova, N. *et al.* (2002) *EMBO J* 21:622-630 [7] Graupner, M. and Brunel, N. (2007) *PLoS Comput Biol* 3:e221.

B. Electrophysiology

Description	Name	Values	Units	Reference
TRPV1R max. conductance	g_{TRPV1}	0.0003	nS	Estimated from our experimental data
Permeability of L-type VSCC	p_{VSCC}	0.00000102	$\mu\text{M/s}$	Value of [1], scaled to ~5,000 spines, radius 1 μm
AMPA maximal conductance	g_{AMPA}	5.1	nS	Estimated from our experimental data
AMPA closing rate constant	β_{AMPA}	190	1/s	Adapted from [2]
AMPA opening rate constant	α_{AMPA}	1.02	1/($\mu\text{M}\cdot\text{s}$)	Idem
NMDAR maximal conductance	g_{NMDAR}	1.53	nS	Estimated from our experimental data
Magnesium concentration	Mg	1	mM	Directly measured in our experiments
NMDAR opening rate constant	α_{NMDAR}	0.072	1/($\mu\text{M}\cdot\text{s}$)	Set to emulate the experimental kinetics of NMDAR-transported Ca in [3]
NMDAR closing rate constant	β_{NMDAR}	100	1/s	Idem
Resting membrane potential	V_L	-70	mV	Directly measured in our experiments
Leak conductance	g_L	10	nS	Idem
Membrane capacitance	C_m	0.1	nF	Idem
Extracellular Ca ²⁺ concentration	Ca_{out}	5000	μM	[1]
Duration of depolarization step	DC_{dur}	0.03	s	From the experimental stimulation protocol
Amplitude of depolarization step	DC_{max}	495	pA	Idem
Amplitude of action current	AP_{max}	7020	pA	[4]
Time constant of action current	τ_{bAP}	0.001	s	Idem
Glutamate peak concentration in the cleft	G_{max}	2000	μM	Estimated from our experimental data
Glutamate decay time constant in the cleft	τ_G	0.005	s	Estimated from our experimental data
Delay to bAP outset	δ	0.015	s	From the experimental stimulation protocol
Stimulation frequency	$F_{pairings}$	1	Hz	From the experimental stimulation protocol

Referenced articles: [1] Wolf, J.A. *et al.* (2005) *J Neurosci* 25(40):9080-9095 [2] Destexhe, A., Mainen, Z., and Sejnowski, T. (1994) *J Comput Neurosci* 1:195-230 [3] Sabatini, B.L., Oertner, T.O. and Svoboda, K. (2002) *Neuron* 33(3):439-452 [4] Fino, E., *et al.* (2010) *J Physiol* 588:3045-3062.

C. Endocannabinoid dynamics

Description	Name	Values	Units	Reference
Scaling factor for endocannabinoid contribution to plasticity	k_{CB1R}	3000	1/ μ M	Estimated from our experimental data
presynaptic plasticity time scale	P_1	1e-9	s	Set to yield rapid / slow changes of W_{pre} for high / low 2-AG values, respectively
presynaptic plasticity time scale	P_2	1e-5	-	Idem
presynaptic plasticity time scale	P_3	7	-	Idem
presynaptic plasticity time scale	P_4	2	s	Idem
The lower limit of LTD induction	θ_{LTD}^{start}	0.027	-	Estimated from our experimental data
The upper limit of LTD induction	θ_{LTD}^{stop}	0.047	-	Idem
The constant determining the rate of LTD induction	A_{LTD}	0.65	-	Idem
The lower limit of LTP induction	θ_{LTP}^{start}	0.087	-	Idem
The constant determining the rate of LTP induction	A_{LTP}	10.8	-	Idem
CB1R opening rate constant	α_{CB1R}	0.2402	1/(μ M.s)	Idem
CB1R closing rate constant	β_{CB1R}	11.072	1/s	Idem
CB1R desensitization rate constant	γ_{CB1R}	416.38	1/s	Idem
CB1R closing rate constant	ϵ_{CB1R}	0.047796	1/s	Idem
DAGL α affinity for DAG	K_{DAGL}	30	μ M	[1]
Maximal rate of MAG lipase	r_{MAGL}	0.5	μ M/s	Set for rapid turnover dynamics.
Maximal DAGL α rate	r_{DGL}	20000	μ M/s	Idem
DAG kinase rate	r_{DAGK}	2	s ⁻¹	Idem
Hill number for DAGL activation by Ca	n_c	6	-	Estimated from our experimental data
DAGL dephosphorylation rate	r_p	380	s ⁻¹	Idem
DAGL phosphorylation rate	r_K	50	μ M ⁻¹ .s ⁻¹	Idem
Total DAGL concentration	$DAGL$	1	μ M	Idem
N-acetyltransferase activity	v_{AT}	0.2	1/s	Idem
FAAH Michaelis-Menten constant	K_{FAAH}	1	μ M	[1]
FAAH enzyme activity	r_{FAAH}	4	μ M/s	Estimated from our experimental data

Referenced articles: [1] Okamoto, Y. et al. (2004) *J Biol Chem* 279:5298-5305.

S3 Text – Mechanisms of STDP expression in the model

We give here an overview of the mechanisms that give rise to the expression of eCB-tLTP, eCB-tLTD and NMDAR-tLTP in our mathematical model. All the examples given here concern regular (deterministic) STDP protocols with constant IPI and spike timings.

Our model combines the two signaling pathways involved in cortico-striatal STDP: a first signaling pathway leading from NMDAR to calmodulin and CaMKII with a second that couples mGluR and cytosolic calcium to eCB production and the resulting activation of CB₁R (see Fig. 1f1). In the model, we assume that the total synaptic weight (W_{Total}) is the product of presynaptic (W_{Pre}) and postsynaptic (W_{Post}) weights (see Supporting Information S1).

On the postsynaptic side, W_{Post} is proportional to the amount of CaMKII activated by the NMDAR pathway. CaMKII in our model forms a bistable system that settles at long times either on a "DOWN" state where CaMKII is mostly inactive (no plasticity) or on an "UP" state characterized by high levels of activated CaMKII (Fig. 2b1) (NMDAR-tLTP). In the example of the figure, the time needed for CaMKII dephosphorylation is larger than the interval between two successive pairings, so activated CaMKII accumulates with the number of pairings during the protocol. For a transition from the UP to the DOWN state to occur, the amount of activated CaMKII needs to overcome the separatrix between the two states. The separatrix is reached in the example of *Supplementary Figure S2* (in Supporting Information S4 below) for circa 50-60 post-pre pairings (with $\Delta t_{\text{STDP}} = -15$ ms) (Fig. S2a1). Therefore, in the conditions of Figure S2 (short post-pre pairings), W_{Post} converges to the UP state (potentiation) only when the STDP protocol comprises > 50 post-pre pairings. With pre-post pairings, the calcium released after each pairing activates less calmodulin than with post-pre protocols. As a result, activated CaMKII never reaches the threshold for the UP state (Fig. S2a2). To summarize, the model successfully reproduces the experimental observations that (i) NMDAR-dependent tLTP emerges after 50-75 short post-pre pairings and (ii) no NMDAR-dependent LTP is obtained with pre-post pairings (Cui et al., 2016).

When a stimulation protocol composed of 100 pairings is applied, the evolution of the amplitude of the triggered calcium peaks is biphasic (Fig. S2c): it increases up to 10-20 pairings and decreases afterwards to settle to constant amplitude after circa 50 pairings. For the first 10-20 stimulations, the iterated activation of mGluRs leads to the accumulation of IP₃, which contributes an extra influx of calcium from the endoplasmic reticulum through calcium-induced calcium release. This extra-boost of cytoplasmic calcium however vanishes when the number of pairings increases further because the concentration of calcium in the ER

decreases. This decay ER calcium eventually compensates the effect of IP3 accumulation on the calcium-induced calcium release, thus stabilizing the amplitude of the calcium peaks for $N_{\text{pairings}} > 50$. Moreover, since the width of the postsynaptic calcium peak in the model is larger with post-pre than pre-post pairings (Fig S2b), the fraction of calcium-activated DAGL α is much larger for post-pre pairings. As a result, the amplitude of eCB peaks and, ultimately, the amplitude of the fraction of activated CB $_1$ R ($y_{\text{CB}_1\text{R}}$), show a more pronounced biphasic profile (Fig S2d). The biphasic trend is further amplified at the level of CB $_1$ R activation because of CB $_1$ R receptor desensitization that amplifies the decay above 20 pairings (Fig S2d). The amplitude of the $y_{\text{CB}_1\text{R}}$ peaks increases sharply for the first 10-20 pairings, and progressively decays afterwards to converge to constant amplitude. As show in the figure, $y_{\text{CB}_1\text{R}}$ reaches large values only for short post-pre pairings (Δt_{STDP} around -15 ms) while even short pre-post pairings ($0 < \Delta t_{\text{STDP}} < 10$ ms) do not give rise to such large amplitude peaks.

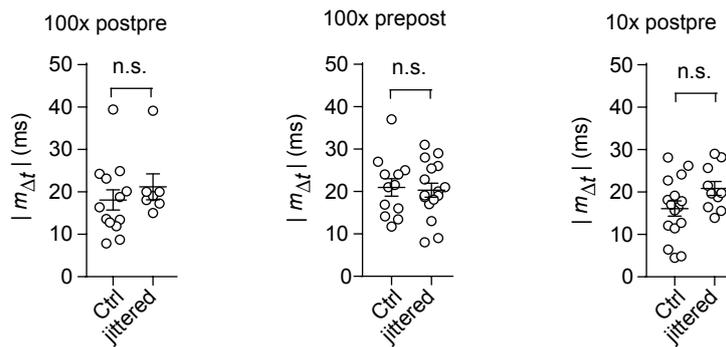
The dynamics of the level of $y_{\text{CB}_1\text{R}}$ is responsible for the emergence of eCB-dependent plasticity in the model. Indeed, in the model, W_{Pre} depends on $y_{\text{CB}_1\text{R}}$ with the piecewise constant function shown in Figure S2e and its 3 thresholds $\Theta_{\text{LTD}}^{\text{start}}$, $\Theta_{\text{LTD}}^{\text{stop}}$ and $\Theta_{\text{LTP}}^{\text{start}}$: if $y_{\text{CB}_1\text{R}}$ reaches moderate amounts, i.e. lies within $[\Theta_{\text{LTD}}^{\text{start}}, \Theta_{\text{LTD}}^{\text{stop}}]$, W_{Pre} decays (thus emulating eCB-tLTD); whereas W_{Pre} increases (eCB-tLTP) if $y_{\text{CB}_1\text{R}} > \Theta_{\text{LTP}}^{\text{start}}$ (see the dashed lines in Fig. S2d and summary in Fig. S2e). With short pre-post pairings ($10 < \Delta t_{\text{STDP}} < 40$ ms), $y_{\text{CB}_1\text{R}}$ enters the LTD range during most of protocol so each pairing contributes a increment of W_{Pre} reduction. Since W_{Post} is not changed with positive, pre-post pairings (Fig. S2a2), pre-post pairings globally lead to a progressive reduction of W_{Total} , i.e. the expression of eCB-tLTP. The situation is different for post-pre pairings. The amplitude of $y_{\text{CB}_1\text{R}}$ peaks overcomes $\Theta_{\text{LTP}}^{\text{start}}$ for ≈ 5 to 30 post-pre-pairings with short Δt_{STDP} (around -15 ms), yielding a strong increase of W_{Pre} . Given that more that 50 post-pre pairings are needed to alter W_{Post} (Fig. S2a1), the expansion of W_{Pre} leads to eCB-tLTP. However, when $N_{\text{pairings}} > 30$ post-pre pairings, $y_{\text{CB}_1\text{R}}$ amplitude gets back below $\Theta_{\text{LTP}}^{\text{start}}$ so that the initial increase of W_{Pre} does not continue beyond 30 post-pre pairings. This property of the model dynamics emulated the experimental observation that eCB-tLTP disappears when the number of pairings becomes larger than 25-30.

Therefore, the mechanisms that lead to the expression of eCB-dependent plasticity with regular deterministic stimulation protocols in our model can be summarized as follow. eCB-tLTD requires moderate levels of CB $_1$ R activation that are reached with pre-post but not pre-post pairings. The expression of eCB-tLTP however demands larger amounts of CB $_1$ R

activation, which are reached only during the first 5-30 post-pre pairings, where every component of the system contributes maximally to CB₁R activation. When the number of post-pre pairings becomes larger than 30, calcium efflux from the internal calcium stores decreases and CB₁R desensitization increases: CB₁R activation becomes insufficient to support such high values of CB₁R activation, so eCB-tLTP vanishes.

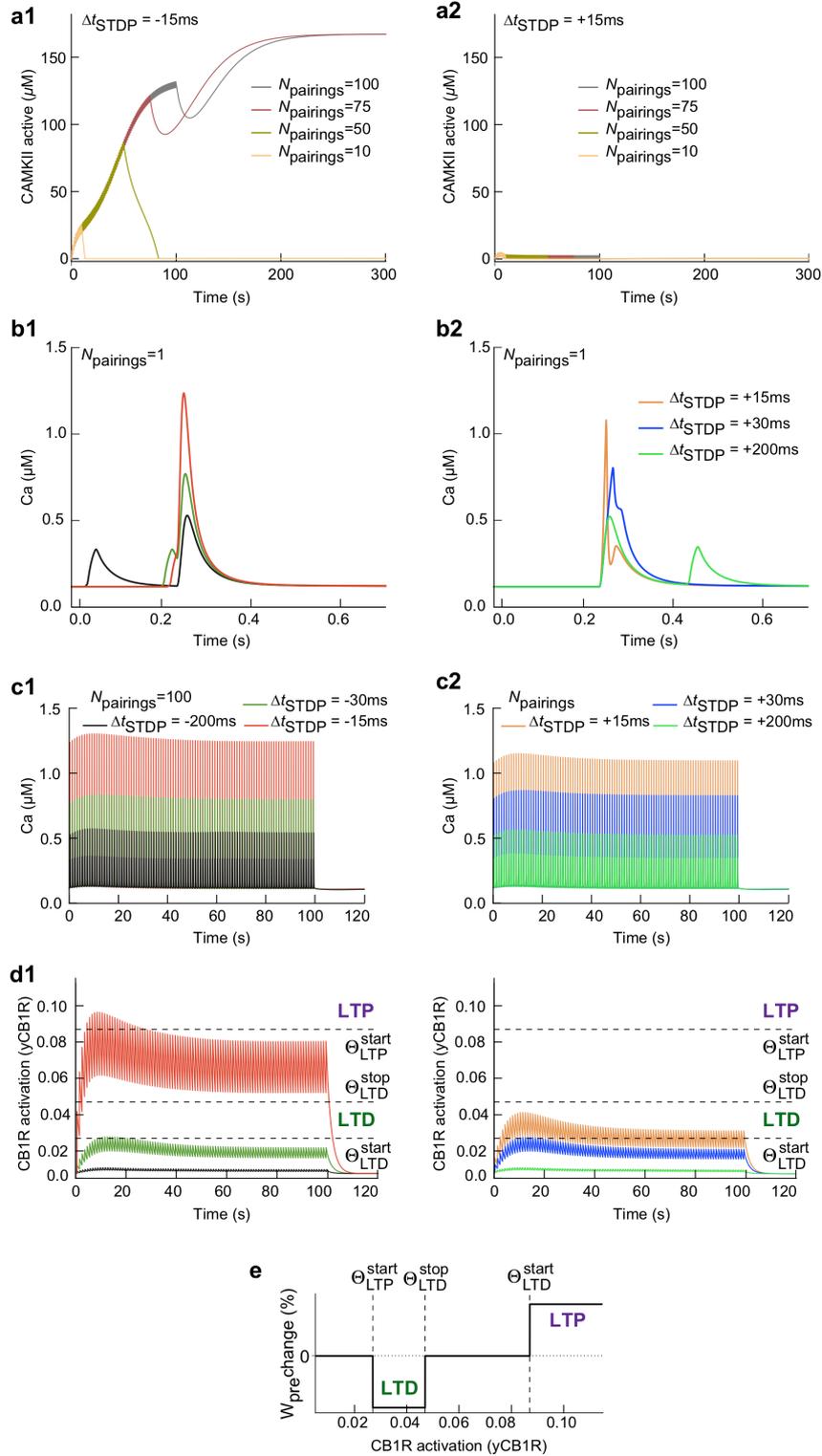
S4 Figure – Supplementary Figures

Figure S1



Supplementary Figure 1: $m_{\Delta t}$ values were not significantly different among STDP paradigms. $m_{\Delta t}$ were not significantly different in control and jittered conditions for 100 post-pre, 100 pre-post and 10 post-pre pairings (empty circles: individual neurons; black circle: average). Error bars represent the SEM. ns: not significant.

Figure S2



Supplementary Figure 2: Mechanisms of STDP expression in the model with deterministic stimulation protocols.

(a) Changes in the amount of active CaMKII starting from the down (non-activated) state. The number of pairings, N_{pairings} , is indicated for spike-timing $\Delta t_{STDP} = -15$ (a1) or $+15$ (a2) ms. (b) Intracellular calcium changes for the first pairing in post-pre (b1) or pre-post (b2) pairing protocols. (c) Predicted dynamics of the cytoplasmic calcium for 100 post-pre (c1) or 100 pre-post pairings (c2) and corresponding activation of CB1R, y_{CB1R} (d). The spike-timing Δt_{STDP} for each curve is indicated in the legend. (e) The presynaptic weight W_{pre} changes as a function of y_{CB1R} : it decreases (LTD) when y_{CB1R} reaches intermediate values and it increases (LTP) if y_{CB1R} overcomes the LTP threshold. The corresponding thresholds are reported in D as dashed lines. For all the simulations shown, the stimulation protocols were deterministic (regular) with a frequency of 1Hz.

SUPPLEMENTARY REFERENCES

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