

# Functional consequences of pre- and postsynaptic expression of synaptic plasticity

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## Abstract

Experimental evidence has shown that both homeostatic and Hebbian synaptic plasticity can be expressed presynaptically as well as postsynaptically. In this review, we discuss some of the functional consequences of this diversity in expression loci. In particular, using a biologically tuned model of spike-timing-dependent plasticity (STDP) we show that a combination of both pre- and postsynaptic components leads to 1) more reliable receptive fields, 2) rapid recovery of forgotten information, 3) and reduced response latencies, compared to a model with postsynaptic expression only. The diversity of expression of synaptic plasticity thus has important functional consequences. We propose that a considerable research effort is needed to better elucidate how the specific locus of expression of homeostatic and Hebbian plasticity alters network computations.

## 27 Introduction

28 Synapses shape the computations of the nervous system. The combination of thousands of exci-  
29 tatory and inhibitory synaptic inputs determine whether a neuron fires or not. Furthermore, the  
30 synapse is known to be a key site of information storage in the brain, although not the only one  
31 [1]. Changes in the synapses are hypothesized to allow neuronal networks to change function and to  
32 adapt through Hebbian and Hebbian-like mechanisms. At the same time, large perturbations in ac-  
33 tivity levels such as those occurring during synaptogenesis or eye-opening require negative feedback  
34 so that the network can keep its activity level within reasonable bounds and continue performing its  
35 computational tasks properly [2]. Such homeostatic control of neuronal activity can occur through  
36 changes in intrinsic neuronal properties such as control of dendrite excitability [3, 4], somatic ex-  
37 citability [5, 1] and movement of the axon hillock relative to the soma [6]. However, in this review  
38 we focus on homeostatic processes at the synapse such as synaptic scaling, which provides a form of  
39 negative feedback to counter changes in the activity levels, while providing synaptic normalisation  
40 and competition among inputs [7].

41 As we explain in detail in this review, irrespective of whether synaptic plasticity is Hebbian or  
42 homeostatic, the expression locus of plasticity matters. A fundamental distinction is whether the  
43 change is pre- or postsynaptic. Changes in the number of postsynaptic receptors typically only  
44 modify the synaptic gain. However, long-term changes in the presynaptic release probability al-  
45 ter the short-term dynamics of the synapse [8, 9, 10, 11, 12, 13, 14]. Synaptic dynamics such as  
46 short-term depression and facilitation describe how the synaptic efficacy changes during repeated  
47 stimulation of the synapse over a time course of hundreds of milliseconds [11, 15, 16, 17]. These  
48 short-term modifications of synaptic efficacy (reviewed in [17]) have been proposed to underlie com-  
49 putations like gain control [18], redundancy reduction [19] and adaptive filtering [20]. In the context  
50 of a recurrent neuronal network, they can affect the activity dynamics and allow the formation and  
51 switching among attractor states [21, 22], and have been proposed as the basis for working memory  
52 [23].

53 Synaptic plasticity can thus affect network dynamics, but this poses several questions: What  
54 are the functional implications of expressing long-term plasticity pre- or postsynaptically? What  
55 are the underlying expression mechanisms? Why is there such a large diversity in the expression?  
56 And why is there sometimes both pre- and postsynaptic expression? In this review, we begin  
57 by discussing pre- and postsynaptic components of Hebbian and homeostatic synaptic plasticity.  
58 Then we examine some of the consequences of the variability of the expression locus of synaptic  
59 plasticity, including those that we recently identified using a biologically tuned computational model  
60 of neocortical spike-timing-dependent plasticity (STDP) [14].

## 61 **The biological underpinnings of pre- and postsynaptic expression of plasticity**

62 As old as the field of long-term synaptic plasticity itself is the question of how precisely informa-  
63 tion is stored in neuronal circuits. Historically, Donald Hebb and Jerzy Konorski argued for the  
64 strengthening of already existing connections between neurons as a means for information storage,  
65 whereas Santiago Ramon y Cajal favoured the growth of new connections [24]. Several relatively  
66 recent studies have found evidence that the formation of new synapses is important for long-term  
67 information storage in neuronal circuits [25, 26, 27, 28]. Indeed, there is strong evidence both in  
68 mammals and in the sea slug *Aplysia* that structural plasticity via formation of new afferent inputs  
69 is essential for protein-synthesis dependent long-term memories [29]. The creation of new afferents  
70 would correspond to an increase in the number of release sites (see Box 1: Methods), but it should  
71 be noted that the number of release sites might be different from the number of anatomical contacts  
72 [e.g. 30].

73 With already existing connections between neurons, there are essentially only two possible ways  
74 of increasing synaptic strength: either presynaptic release is increased, or postsynaptic receptor  
75 channels are upregulated [31, 32]. Both can be achieved in a number of ways. The presynaptic  
76 release probability is controlled by various factors, such as the number and sensitivity of presynaptic  
77 calcium channels, as well as other presynaptic ion channels that can modulate neurotransmitter  
78 release (such as the epithelial sodium channel ENaC in case of synaptic scaling at the *Drosophila*  
79 neuromuscular junction [33, 34]), the setpoint of presynaptic calcium sensors involved in eliciting  
80 neurotransmitter release, e.g. the synaptotagmins 1, 2 and 9 [35], and the size of the pool of readily  
81 releasable vesicles as well as its replenishment rate (in case of homeostasis, see [36, 37]) [11, 35].

82 The postsynaptic contribution to the synaptic response is determined by the number and location  
83 of postsynaptic receptors, as well as their properties (e.g. conformational state [38] and subunit  
84 composition [39, 40]). In addition, the geometry of the extracellular space and the apposition of the  
85 release sites have also been suggested as important determinants of the response amplitude [41, 42].

86 Experimentally, determination of the expression locus is far from trivial and a battery of tech-  
87 niques has been applied (see Box 1). In long-term potentiation (LTP) experiments, evidence for  
88 most of the above mechanisms has been found. The historic pre versus post controversy is now typ-  
89 ically interpreted as a reflection of the diversity of LTP phenomena, which we now know depends on  
90 multiple factors such as age, synapse state, neuromodulation, synapse type, and induction protocol  
91 [31, 43, 44, 45, 46, 47, 48, 49, 50] (but see [51]). A combination of pre- and postsynaptic expression  
92 is also possible [31].

93 A similar pre- or postsynaptic expression question exists for synaptic homeostasis. While most  
94 studies have focused on postsynaptic expression, also here a wide variety in expression, including  
95 presynaptic expression [52, 53, 54], has been observed, and for instance whether the expression is  
96 pre- or postsynaptic appears to depend on developmental stage [55, 56]. Sometimes diversity in  
97 mechanisms can even be observed within one system. For instance, in homeostatic plasticity experi-

98 ments in the hippocampus both pre- and postsynaptic expression was observed, while some CA3-CA3  
99 connections were unexpectedly *reduced* after activity deprivation, other connections strengthened  
100 as expected, perhaps to prevent network instability [57]. Also some forms of synaptic scaling at the  
101 *Drosophila* and mammalian neuromuscular junction (NMJ) are presynaptic: loss of postsynaptic  
102 receptors is compensated by increased transmitter release, which restores the mean amplitude of  
103 evoked EPSPs [34, 58]. A presynaptic locus of expression of homeostatic plasticity at the NMJ  
104 is perhaps to be expected, given that the postsynaptic partner — the muscle myotube — does  
105 not integrate its inputs like a neuron does, but rather serves to fire in response to activation at the  
106 synaptic input. The pre- and postsynaptic components of the NMJ are therefore tightly co-regulated  
107 in synaptogenesis and after damage to ensure proper activation of the muscle [59], so when postsy-  
108 naptic NMJ sensitivity is reduced, it is in this context not entirely surprising that the presynaptic  
109 machinery compensates accordingly by upscaling neurotransmitter release. This example illustrates  
110 how the locus of expression must be understood in the context of function of the synapse type at  
111 hand.

112 Further indication that the exact expression locus is functionally important comes from the  
113 fact that both short-term plasticity [60] and long-term plasticity [50] can be expressed in a synapse  
114 specific manner. In the case of short-term plasticity, connections from the same presynaptic neurons  
115 onto different cells can short-term depress or facilitate depending on the target cell type [61, 62].  
116 Similarly, while spike-timing-dependent plasticity (STDP) exists at both horizontal and vertical  
117 excitatory inputs to visual cortex layer-2/3 pyramidal cells, the mechanistic underpinnings as well  
118 as the precise temporal requirements for induction are different [63]. Such specificity suggests that  
119 the specific locus of expression of long-term plasticity at a given synapse type is meaningful for the  
120 proper functioning of microcircuits in the brain, as otherwise tight regulation of expression locus  
121 would not have arisen during the evolution of the brain.

## 122 **BOX1: Methods to determine the locus of plasticity**

123 [Note, this section is proposed to be a separate text box (as in TINS)]

124 The properties of synaptic release can be used to determine the locus of synaptic plasticity by  
125 a variety of methods. Among these there are methods for studying vesicle release, such as FM1-43  
126 dye labelling to explore changes presynaptic release [64], glutamate uncaging to explore changes  
127 in postsynaptic responsiveness or spine size [65, 66], measuring NMDA:AMPA ratio to look for  
128 insertion of postsynaptic receptors [67, 46], employing the use-dependent NMDA receptor blocker  
129 MK-801 to look for changes in glutamate release [68, 69], or exploring changes in paired-pulse ratio  
130 suggesting a change in probability of release [13, 46] (although see [70]).

131 It is also common to employ spontaneous release as a metric of the locus of expression, as each  
132 spontaneously released vesicle gives rise to a well-defined single postsynaptic quantal response known  
133 as a miniPSC. This approach is often used in studies of homeostatic plasticity (e.g. [71]), because

134 here it is important to measure synaptic changes globally across a majority of inputs to a cell, but  
135 this method has also been used to explore Hebbian plasticity [72, 67]. An increase in miniPSC  
136 frequency in the absence of a change in miniPSC amplitude is typically interpreted as indicating  
137 higher release probability or an increase in the number of synaptic contacts, while an increased  
138 miniPSC amplitude is most often thought to reflect an increase in postsynaptic responsiveness  
139 due to more efficacious postsynaptic receptors. Alternative interpretations of spontaneous release  
140 experiments are, however, also possible, for example in the case of AMPA-fication of silent synapses,  
141 which leads to an apparent change in release probability even though unsilencing is a postsynaptic  
142 process [72].

143 In the scenario where individual synapses are monitored, it is possible to employ methods that  
144 rely on the response variability. One such method is non-stationary noise analysis [73], which has  
145 been used to determine the effect of homeostasis on inhibitory connections [74], although this method  
146 can be unreliable for dendritic synapses [75]. In the related coefficient of variation (CV) analysis,  
147 the peak synaptic response is modelled as a binomial process. The process has as parameters the  
148 release probability  $Pr$ , the number of release sites  $N$ , and the response to each vesicle, the quantal  
149 amplitude  $q$ . The CV — which is experimentally quantified as the response standard deviation over  
150 the mean — is independent of  $q$ , namely  $CV = \sqrt{\frac{1-Pr}{PrN}}$ , and therefore an increase in the mean  
151 without an increase in CV can be interpreted as a postsynaptic increase of  $q$  [76]. Conversely, if  
152 plasticity is presynaptically expressed, then a change in CV is expected, since the CV is a measure  
153 of noise and since the chief source of noise in neurotransmission is the presynaptic stochasticity of  
154 vesicle release. The CV analysis method does, however, come with several caveats. In particular,  
155 accidental loss or gain of afferent fibers in extracellular stimulation experiments, or unsilencing or  
156 growth of new synapses will confuse the results [76]. It is also not obvious that release is independent  
157 at different sites, in which case the binomial model is not suitable [76]. By assuming that one of  
158 the parameters does not change during the experiment (e.g. fixed  $N$  as is reasonable to assume in  
159 some plasticity experiments [77, 78]) the variance and mean of postsynaptic responses can be used  
160 to estimate  $Pr = \frac{mean}{Nq}$  and  $q = \frac{variance}{mean} + \frac{mean}{N}$  [31, 79, 14].

161 An alternative way to determine whether synaptic changes correspond to alterations of release  
162 probability or of quantal response amplitude is to examine the postsynaptic response to a pair or a  
163 train of presynaptic stimuli. The idea is that when the release probability is high, the vesicle pool  
164 will be depleted more quickly, leading to a more strongly depressing train of postsynaptic responses.  
165 When combined with CV analysis, this method can be used to measure all three parameters —  $Pr$ ,  
166  $N$ , and  $q$  — of the binomial release model [80]. By fitting these phenomenological models before and  
167 after plasticity induction, one can determine which combination of parameters were changed due to  
168 plasticity. It should be noted that experimental results from paired-pulse experiments should also  
169 be treated with caution. For example, unsilencing or specific postsynaptic upregulation of release  
170 sites with quite different release probability may lead to changes in short-term dynamics that could

171 erroneously be interpreted as presynaptic in origin, even though the actual site of expression is  
172 postsynaptic [70]. There are also postsynaptic contributions to synaptic short-term dynamics [81,  
173 82, 83], that can complicate the interpretation of experiments. It is therefore better to employ several  
174 methods in parallel in the same study — such as CV analysis, paired-pulse ratio, NMDA:AMPA  
175 ratio, and spontaneous release [13, 46] — to independently verify the locus of expression.

176 Recently, inference methods of short-term plasticity and quantal parameters have been intro-  
177 duced [84, 85, 86]. The sampling method of [84] is particularly well suited to deal with the strong  
178 correlation and uncertainty in the synapse parameters. Based on this method we revealed interest-  
179 ing variations between different neuronal connections and proposed more informative experimental  
180 protocols based on irregular spike-trains, which would be promising to apply in plasticity experi-  
181 ments.

182 END BOX1

### 183 **Consequences of diversity in locus of plasticity**

184 While the diverse pathways of plasticity induction and expression are increasingly unravelled, their  
185 functional roles are still largely an open question. We have already mentioned that different plas-  
186 ticity expression sites have different effects on short-term synaptic dynamics and therefore on the  
187 network dynamics, but the “embarrassment of riches” in the possible expression sites of plasticity  
188 [45], paralleled in many other biological systems, has a number of other important consequences as  
189 well:

- 190 • It provides robustness to the system and multiple ways to maintain the capacity for plasticity,  
191 despite internal or external disruption. Evolutionarily this can be advantageous, as the pop-  
192 ulation can be functionally similar but diverse in mechanism, thus allowing better adaptation  
193 to novel circumstances [87].
- 194 • It provides flexibility to local circuits, so that, via synapse-type-specific plasticity, different  
195 microcircuit components can be independently regulated [50]. For example, long-term de-  
196 pression (LTD) at layer 4 to layer 2/3 connections, but not at layer 2/3 to 2/3 synapses,  
197 is more readily induced during the critical period [88, 89], while thalamocortical LTP is al-  
198 ready strongly diminished before the critical period has begun [90]. The locus of expression  
199 of long-term plasticity at these different synapse types also differs.
- 200 • Different plasticity protocols are affected by distinct forms of neuromodulation and these  
201 neuromodulators can specifically control forms of STDP that express, for example, postsy-  
202 naptically [91, 92, 93], providing a potential link between behaviourally relevant behaviours  
203 and expression loci.
- 204 • The different plasticity sites can differ in stability properties: some changes might be quick to

205 induce, but hard to stabilise and vice versa. This in turn can provide neuronal networks with  
206 the necessary flexibility to quickly adapt to environmental changes (see below).

207 • The locus of expression of plasticity will change the trial-to-trial variability of the synaptic  
208 response and overall reliability of neurotransmission (see below).

209 Finally, it is noteworthy that by the diversity of expression mechanisms, LTD is not necessarily the  
210 opposite of LTP. In other words, contrary to what is assumed in virtually all computational models,  
211 LTP induction followed by LTD induction might leave the synapse in a different state, despite the  
212 apparent synaptic weight being the same.

213 Recently, we have started exploring some of these consequences using computational models.

## 214 **Pre- and postsynaptic expression of STDP**

215 In STDP experiments, where spikes from the presynaptic neuron are paired with millisecond preci-  
216 sion with postsynaptic ones, the question of pre- versus postsynaptic expression has been extensively  
217 examined as well. Depending on factors such as synapse type, brain area and experimental condi-  
218 tions, there is evidence for both pre- and postsynaptic changes [13, 46, 94, 95, 63, 96]. Because of the  
219 synapse-type specificity of STDP [50], we tuned a computational model to STDP data using only  
220 connections between visual cortex layer-5 pyramidal cells [97, 13, 46]. At this synapse it has been  
221 observed that using STDP induction protocols potentiation has both pre- and postsynaptic compo-  
222 nents [46], while LTD is expressed presynaptically only [13]. Presynaptic-only time-dependent LTD  
223 has also been found in other synapse-types and brain areas [94, 96].

224 Our model of STDP allows for distinct pre- and postsynaptic expression, Fig.1a. This phe-  
225 nomenological model relies on three dynamic variables, one which tracks past presynaptic activity  
226  $x_+(t)$ , and two that track postsynaptic activity,  $y_+(t)$  and  $y_-(t)$ . These traces increase with every  
227 spike and decay exponentially between spikes. The plasticity is expressed as a function of the traces,  
228 but in contrast to traditional STDP models where just the synaptic weight changes as a function of  
229 them [98], here both the release probability and the quantal amplitude are independently modified.  
230 In our model, we assume that the number of release sites  $N$  is fixed and that it does not change on  
231 the time-scale of the experiments, consistent with experimental observations [77, 78]. However, the  
232 model could be straightforwardly generalised to also include changes in  $N$ .

233 Even though we model the observed phenomenology rather than the biophysical or mechanistic  
234 details, with caution the components of the model can be interpreted to correspond specific phys-  
235 iological components. The presynaptic trace ( $x_+$ ), for example, could represent glutamate binding  
236 to postsynaptic NMDA receptors, which when depolarised by postsynaptic spikes unblocks NMDA  
237 receptors, leading to classical postsynaptic LTP [32]. Similarly, the postsynaptic trace  $y_+$  can  
238 be interpreted as retrograde nitric oxide (NO) signalling, which is read out by presynaptic spikes  
239 and leads to presynaptically expressed LTP [46]. Finally, the postsynaptic trace  $y_-$  can be linked

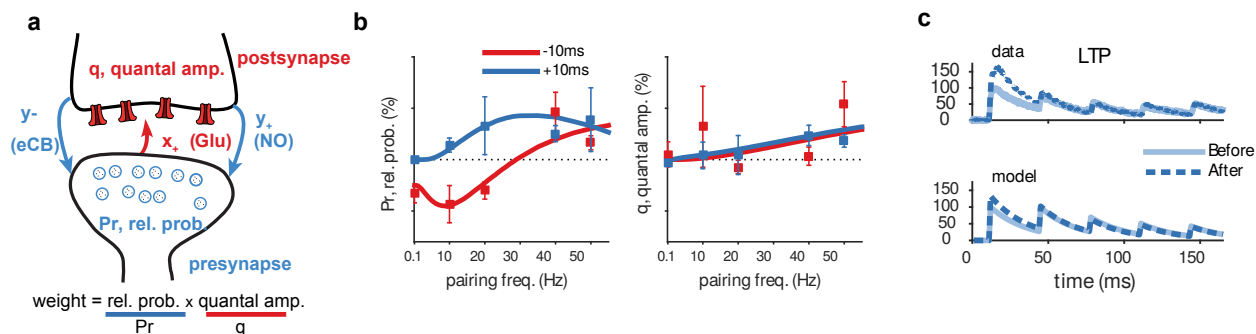


Figure 1: A schematic of our biologically tuned STDP model with pre- and postsynaptic expression. a) The synaptic weight is the product of the release probability  $P$  and the quantal amplitude  $q$ . Changes in these parameters due to STDP are modelled as functions of presynaptic activity trace  $x_+$  and postsynaptic activity traces  $y_+$  and  $y_-$ .

b) The fitted model captures the estimated changes in release probability (left) and quantal amplitude (right) for both positive timing (presynaptic spikes 10 ms before postsynaptic ones; blue) and negative timing (presynaptic spikes 10 ms after postsynaptic ones; red), as a function of the frequency of STDP pairings. Symbols indicate data, while lines denote the model fit.

c) After LTP, the release probability is enhanced, which leads to stronger short-term depression. The change in short-term synaptic dynamics in the model (bottom) mimics the data (top).

Panels b and c are reproduced from [14].

240 to endocannabinoid (eCB) retrograde release, which triggers presynaptically expressed LTD when  
 241 coincident with presynaptic spikes [13, 94, 96].

242 As mentioned above, we fitted our model to experimental data of one synapse type only (layer-  
 243 5 pyramidal cells onto layer-5 pyramidal cells in the visual cortex) [97, 13, 46], across different  
 244 frequencies and timings. To ensure the biological realism of the model, we further constrained the  
 245 model fitting by using data from NO and eCB pharmacological blockade experiments in which either  
 246 presynaptic LTD or LTP expression alone was abolished [46]. Furthermore, we verified that our  
 247 model captured the expected interaction of short and long-term plasticity correctly (see Fig.1c),  
 248 which permits the exploration of the functional implications of changes in short-dynamics due to  
 249 the induction of long-term plasticity.

## 250 Functional consequences of pre- and postsynaptic expression

251 The model reveals several functional implications of expressing synaptic plasticity pre- as well as  
 252 postsynaptically. First, by increasing the release probability, trial-to-trial reliability from synaptic  
 253 transmission can be increased. Thus, joint pre- and postsynaptic plasticity can lead to a larger  
 254 increase in the signal-to-noise ratio (SNR) than postsynaptic modification alone (Fig.2a). The  
 255 functional impact on SNR of this joint modification is consistent with improved sensory perception  
 256 and its electrophysiological correlates observed in auditory cortex [99].



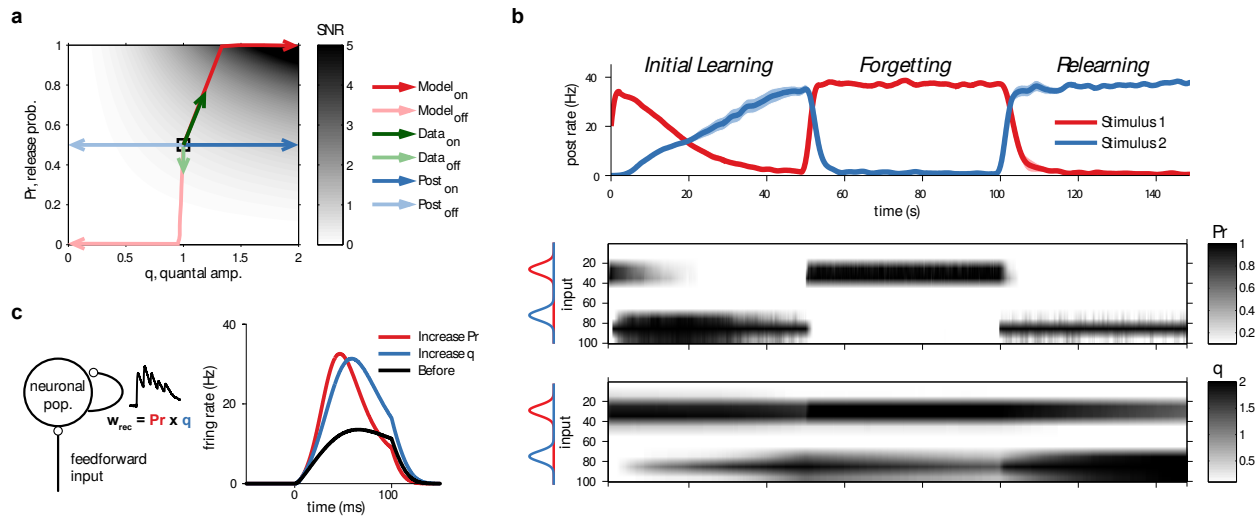


Figure 2: STDP with pre- and postsynaptic expression improves sensory perception, enables memory savings and shortens response latencies compared to postsynaptic expression alone.

a) Joint pre- and postsynaptic expression improves the signal-to-noise ratio (SNR) after LTP more than with postsynaptic changes alone. Inputs that were stimulated (“on”) obtain high signal-to-noise ratio (“SNR”) for postsynaptic-only potentiation (dark blue arrows), but combining pre- and postsynaptic potentiation yields considerably better SNR (dark red arrows). Weakly stimulated inputs (“off”) obtain lower SNR in either condition (light blue and light red arrows). Our modelling results are in keeping with modifications of *in-vivo* synaptic responses to a tone from on and off receptive field positions (dark and light green arrows) [99].

b) Rapid relearning and memory savings with asymmetrically combined pre- and postsynaptic expression of long-term plasticity. Top: A network initially learns the blue stimulus. This initial learning is slow because the changes in  $q$  are slow. After learning, the memory is overwritten with the red stimulus. When switching back to the initial blue stimulus, the relearning is more rapid compared to the first exposure. Middle: Presynaptically, LTP and LTD can reverse each other completely. Bottom: LTP has a postsynaptic component that does not reverse quickly, which means a postsynaptic trace is left behind after overwriting with novel information. This hidden trace enables rapid relearning of previously learnt but overwritten information.

c) Schematic of a firing-rate model with feedforward and feedback connections as described in [20] (left). In this network, recurrent synapses are short-term depressing. Changing release probability  $Pr$  affects the short-term dynamics, while changing the postsynaptic amplitude  $q$  only scales the postsynaptic response. Comparison of changes in the response dynamics in a recurrent network model when the recurrent synapses are subject to changes in  $Pr$  or  $q$ . Increases in the release probability shorten the latency more than increases in the postsynaptic amplitude (right).

Panels a and b were reproduced from [14].

257 Secondly, the pre- and postsynaptic components may evolve on different timescales. Using a  
258 simple receptive field development simulation, we propose that this might enable a form of memory  
259 savings. Memory savings is a concept introduced by Hermann Ebbinghaus and means that repeated  
260 learning of information is easier, even if the initially learned information appears to have been for-  
261 gotten [100]. In the data we saw no evidence for any decrease in the postsynaptic component  $q$ ,  
262 perhaps because its decrease maybe very slow. For completeness, we assumed that a slow homeo-  
263 static process could decrease  $q$ , but its presence is not essential to our arguments. When memories  
264 were overwritten, the presynaptic component of the old memory was erased quickly but the post-  
265 synaptic component stayed largely intact. As a result, information that was initially learned but  
266 subsequently overwritten could rapidly be recovered upon relearning, provided that the postsynaptic  
267 component had not yet decayed completely (Fig. 2b). This mechanism could thus enable the brain  
268 to adapt quickly to different environments or to different tasks without fully forgetting previous  
269 learned information. This effect mirrors that of monocular deprivation experiments showing lasting  
270 postsynaptic structural effects on spine density that enable more rapid visual cortex plasticity after  
271 repeated monocular deprivation [101, 102].

272 Finally, while the effects reported in [14] considered feedforward networks, the changes in release  
273 probability under STDP also has consequences for recurrent networks. Excitation-dominated re-  
274 current networks connected through strong short-term depressing synapses can have long response  
275 latencies, that are governed by the synaptic dynamics. We used the model presented in [20] to  
276 examine the effect of different expression loci in recurrent network. Fig. 2c illustrates the response  
277 of a firing-rate model when the release probability  $Pr$  is increased, versus a case in which the  
278 quantal amplitude  $q$  is increased. The pre- and postsynaptic modifications were set such that the  
279 peak responses were identical. In both cases the response latency was shortened, but when release  
280 probability was allowed to increase due to LTP, response latency shortened about twice as much  
281 compared to the case where only postsynaptic plasticity was enabled.

## 282 Discussion

283 To model the impact of synaptic plasticity on circuit computations, it is important to know how  
284 synapses change during Hebbian and homeostatic plasticity. Here, we have discussed several  
285 possible expression sites of synaptic plasticity. We have demonstrated three candidate effects in  
286 a model where both pre- and postsynaptic components are modified: 1) a change in the release  
287 probability can improve the SNR in the circuit, 2) the difference in the time scales of modification  
288 can lead to the formation of hidden memory traces, and 3) as a result of changes in synaptic  
289 dynamics, the response latency in recurrent networks can be shortened with plasticity. The possible  
290 functional impact of combining pre- and postsynaptic plasticity is certainly not restricted to the  
291 three findings we illustrate here. We have rather just scratched the surface of what is likely an  
292 emerging field of study.

293 There is a large range of open issues. For instance, it has long been argued that the stability of  
294 memory in spite of continuous molecular turn-over is a quite remarkable problem for nature to solve  
295 [103, 104]. How synapses maintain stable information storage while staying plastic still remains  
296 unclear. The diversity of plasticity expression mechanisms could allow for a staged process by  
297 which initial changes are presynaptic, but later changes are consolidated structurally and distributed  
298 across pre- and postsynaptic compartments. It is, however, not unlikely that multiple expression  
299 mechanisms are active in tandem. How these pre- and postsynaptic alterations are coordinated to  
300 ensure the long-term fidelity of information storage will require extensive further research.

301 Another important issue is the weight dependence of long-term plasticity — LTP is hard to  
302 induce at synapses that are already strong [105, 106, 107, 97] — which has important implications  
303 for the synaptic weight distribution, memory stability [108] and information capacity [109]. It has  
304 been shown that presynaptic modifications strongly depend on the initial release probability [31],  
305 which is expected as release probability is bounded between 0 and 1. This demonstrates that the  
306 weight-dependence can stem from presynaptic considerations. However, postsynaptic mechanisms  
307 such as compartmentalisation of calcium signals may also explain this weight dependence, as it leads  
308 to large spines with long necks being “write protected” [110, 111, 112, 113]. This finding together  
309 with the fact that spine volume is proportional to the expression of AMPA receptors [114] implies  
310 that small spines should be more prone to LTP, which is consistent with experimental observations  
311 [66]. Such pre- and postsynaptic mechanisms are of course not mutually exclusive and both may  
312 contribute to the weight dependence of plasticity [106].

313 Long-term synaptic plasticity and homeostatic plasticity have been fruitful modelling topics that  
314 have clarified the role of plasticity in biological neuronal networks as well as inspired applications  
315 using artificial neuronal networks. Yet, despite experimental evidence for presynaptic components in  
316 both Hebbian plasticity and synaptic homeostasis, in the overwhelming majority of computational  
317 models presynaptic contributions have been ignored (for an exception, see [115]), or the models are  
318 agnostic about the expression and only adjust the synaptic weight. However, as we have seen, this  
319 is not a neutral assumption, and may affect the outcome of the plasticity on network function.

320 Our discussion has been restricted to the plasticity of excitatory synapses. Inhibitory neurons,  
321 in all their diversity [116, 117, 118], bring yet another level of complexity as differential short-  
322 term dynamics of excitatory and inhibitory synapses yields considerably richer dynamics [119, 120,  
323 84, 60]. We suspect that only a small fraction of the richness and variety of the experimentally  
324 observed plasticity phenomena are understood and only a few computational models include them.  
325 A continued dialogue between theory and experiment should hopefully advance our understanding.

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