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Novel presynaptic mechanisms for coincidence detection in synaptic plasticity

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Long-term plasticity typically relies on postsynaptic NMDA receptors to detect the coincidence of pre- and postsynaptic activity. Recent studies, however, have revealed forms of plasticity that depend on coincidence detection by presynaptic NMDA receptors. In the amygdala, cortical afferent associative presynaptic long-term potentiation (LTP) requires activation of presynaptic NMDA receptors by simultaneous thalamic and cortical afferents. Surprisingly, both types of afferent can also undergo postsynaptically induced NMDA-receptor-dependent LTP. In the neocortex, spike-timing-dependent long-term depression (LTD) requires simultaneous activation of presynaptic NMDA autoreceptors and retrograde signalling by endocannabinoids. In cerebellar LTD, presynaptic NMDA receptor activation suggests that similar presynaptic mechanisms may exist. Recent studies also indicate the existence of presynaptic coincidence detection that is independent of NMDA receptors, suggesting that such mechanisms have a widespread role in plasticity.

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Introduction

One of the most central concepts in neuroscience is the notion that changes in synaptic strength underlie learning and memory. In this concept, repeated correlated activity in connected neurons results in both synaptic modification and the formation of a memory trace. The Hebbian postulate [1] and the subsequent discovery of long-term potentiation (LTP) in the hippocampus [2] have inspired hundreds of studies [3,4]. In the classical hippocampal CA1 model of LTP [3–5], correlated high-frequency pre- and postsynaptic activity results in presynaptic release of glutamate and postsynaptic depolarization, such that postsynaptic glutamate-bound NMDA receptors (NMDARs) are relieved from Mg^{2+} block [6,7] and mediate Ca^{2+} ion flux [8,9], which in turn results in large, brief spine Ca^{2+} transients and in LTP induction [3–5,10].

Similarly, relatively weak and more prolonged increases in Ca^{2+} owing to low-frequency activity evoke long-term depression (LTD) that typically depends on the activation of postsynaptic NMDARs [3,10–12]. More recent studies have emphasized the temporal order of excitatory postsynaptic potentials and action potentials in postsynaptic Ca^{2+} signalling [13] and in synaptic plasticity [14–18,19••], a concept that is termed 'spike-timing-dependent plasticity' (STDP) [10,20]. In this model, either LTP or LTD is evoked, depending on the relative millisecond timing of pre- and postsynaptic spikes [10,20]. Nevertheless, the postsynaptic NMDAR has remained the canonical coincidence detector in synaptic plasticity.

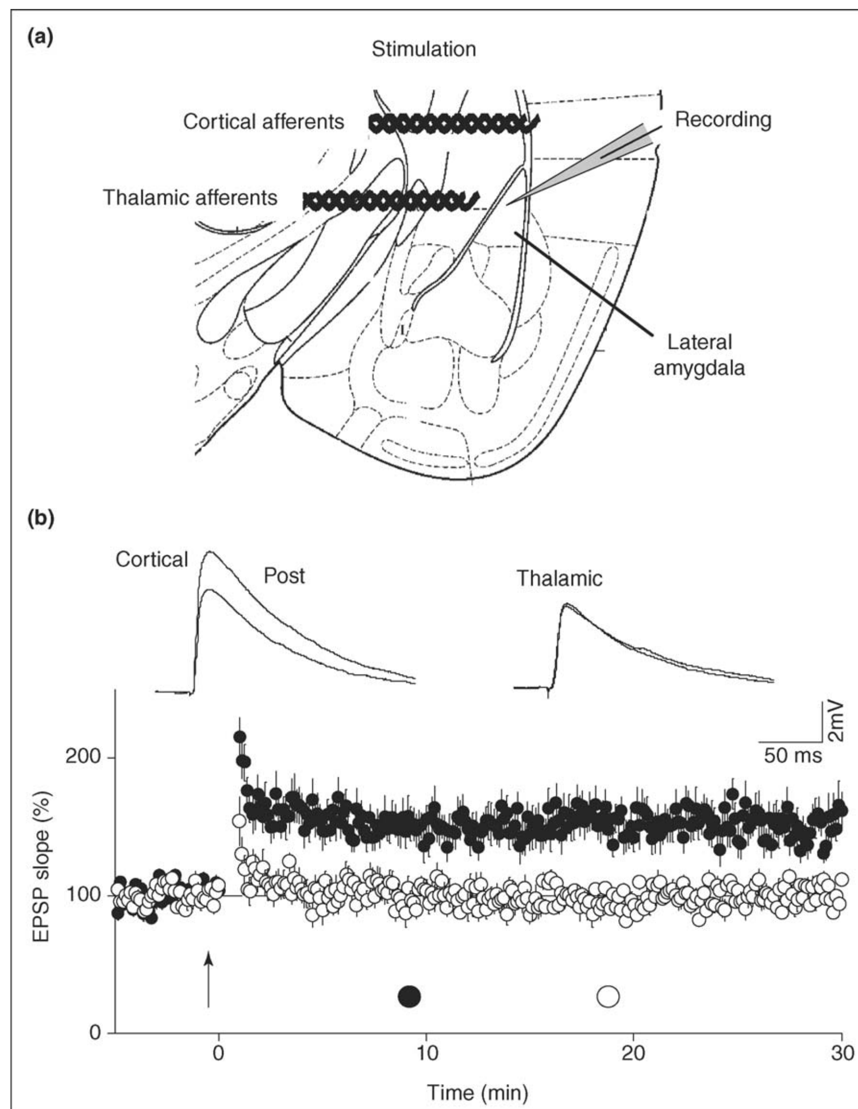
In recent years, a more pluralistic view of plasticity has emerged. Although the classical hippocampal CA1 model of LTP will undoubtedly prevail as a standard in the field of synaptic plasticity, it is increasingly clear that plasticity induction and expression mechanisms vary markedly according to factors such as brain region, cell and synapse type, animal age and induction protocol [10,19••,20,21]. Intriguingly, functional [22,23] and anatomical evidence [24,25] for presynaptic NMDARs imply the possible existence of presynaptic plasticity induction mechanisms. In fact, several recent studies have shown that synaptic plasticity at various central synapses depends on such presynaptically located NMDARs [26–28]. In this review, we discuss developments over the past couple of years and highlight studies pertaining to mechanisms of presynaptic coincidence detection in synaptic plasticity.

Presynaptic coincidence detection in associative LTP and fear conditioning

Some of the best evidence for the involvement of long-term plasticity in learning comes from Pavlovian fear conditioning, a learning model that involves the amygdala [29,30]. In auditory fear conditioning, for example, the repeated pairing of a tone with a foot shock leads to a freezing response when the tone is presented alone. This model of behavioural learning requires both the amygdala itself and projections from the auditory cortex and the auditory medial geniculate body of the thalamus to the basolateral amygdala [29,30].

Projection neurons of the lateral nucleus of the amygdala (LA) receive converging excitatory inputs from the

Figure 1



Associative LTP at cortical afferents to the LA depends on a mechanism of coincidence detection by presynaptic NMDARs. **(a)** Recording configuration: whole-cell recordings are made in the LA after extracellular stimulation in the thalamus and in the neocortex. **(b)** Normalized mean excitatory postsynaptic potential slope before and after simultaneous 30-Hz stimulation (arrow) of cortical (filled circles) and thalamic (open circles) afferents. Simultaneous stimulation results in the induction of NMDAR-dependent LTP at cortical, but not thalamic, afferent synapses. This form of associative LTP does not require postsynaptic NMDAR activation, or Ca^{2+} influx or activity. Scale bars: 2 mV (vertical), 50 ms (horizontal). Reproduced, with permission, from [28].

thalamus and cortex. Anatomical evidence for NMDARs has been found postsynaptically in both cortical [31] and thalamic [32] afferent synapses. Indeed, there are also postsynaptically induced forms of homosynaptic LTP at both cortical [33] and thalamic [19••] inputs to LA projection neurons.

Surprisingly, Humeau *et al.* [28] discovered an associative form of cortical afferent LTP that does not require postsynaptic Ca^{2+} influx or activity, but is still dependent on NMDARs. This type of LTP was induced by repeated coincident 30-Hz stimulation of thalamic and cortical afferents onto LA projection neurons, which induced LTP of cortical but not thalamic inputs (Figure 1). Stimulation at 30 Hz of either pathway alone evoked no plasticity, demonstrating the associative nature of the cortical afferent LTP. Intriguingly, intracellular blockade of postsynaptic NMDARs with the antagonist MK-801 had no effect, suggesting that the NMDARs required for associative cortical afferent LTP must be located elsewhere. Immuno-electron microscopy evidence indicates the existence of presynaptic NMDARs in the LA [25]; thus, the most straightforward explanation is that the NMDARs relevant for this form of LTP are located at

or near the terminals of cortical afferent axons. In agreement with this hypothesis, high-frequency activation of thalamic afferents was found to result in a brief presynaptic increase in cortical afferent neurotransmission that was abolished by NMDAR blockade. Furthermore, Humeau *et al.* [28] found that the induction of associative LTP of cortical inputs resulted in changes in short-term plasticity and coefficient of variation consistent with a presynaptic locus of expression.

The existence of a presynaptically induced, presynaptically expressed, heterosynaptic form of LTP at cortical afferents [28] is all the more intriguing, given the recent evidence for a postsynaptically induced, postsynaptically expressed, homosynaptic form of LTP at the thalamic inputs [19••]. Interestingly, plasticity could be evoked by a standard STDP protocol at thalamic but not cortical afferents [19••]. Importantly, these two types of synapse showed specific morphological and mechanistic differences: spines of thalamic inputs were larger, displayed bigger action-potential-evoked Ca^{2+} transients, and expressed R-type Ca^{2+} channels [19••], consistent with the need for strong postsynaptic increases in Ca^{2+} in the postsynaptically induced forms of LTP in the LA [19••,33]. These differences potentially help to explain the differing forms of plasticity in the thalamic and cortical pathways.

These distinct forms of plasticity in separate pathways onto the LA projection neurons are likely to have evolved specifically for particular and disparate purposes. What function might the presynaptically induced cortical afferent LTP serve? Because it does not rely on postsynaptic suprathreshold activity, it is possible that it might potentiate and thereby 'prime' individual, relatively weak cortical inputs for subsequent potentiation through the homosynaptic form of LTP [33], which requires stronger postsynaptic activation and larger postsynaptic increases in Ca^{2+} [19••]. In keeping with this possibility, postsynaptic hyperpolarization *in vivo* reduces but does not abolish fear conditioning [34], suggesting that LTP in the absence of postsynaptic suprathreshold activity also occurs *in vivo*, presumably through the presynaptic coincidence detection mechanism discovered by Humeau *et al.* [28]. Although the work of Humeau *et al.* [28] nicely illustrates the importance of presynaptic coincidence detection in both plasticity and learning, the information carried by thalamic and cortical afferents to the LA in fear conditioning remains unknown [30]. A better understanding of the nature of this information would help to explain the existence of these distinct forms of plasticity in the LA.

In addition to the LA, the central nucleus of the amygdala is also likely to be important for fear conditioning [30,35]. In a recent study, Samson and Paré [36•] discovered a presynaptically expressed form of homosynaptic LTP at thalamic afferents onto medial sector neurons in the central nucleus. The magnitude of LTP was significantly reduced by global NMDAR antagonism, but internal blockade of postsynaptic NMDARs had no effect, suggesting that the crucial NMDARs are localized presynaptically. In agreement, postsynaptic hyperpolarization or Ca^{2+} chelation did not reduce LTP. Although it is clear that these presynaptic NMDARs are crucial for this form of LTP in the central nucleus of the amygdala [36•], whether or not they are involved in a mechanism of presynaptic coincidence detection remains unknown.

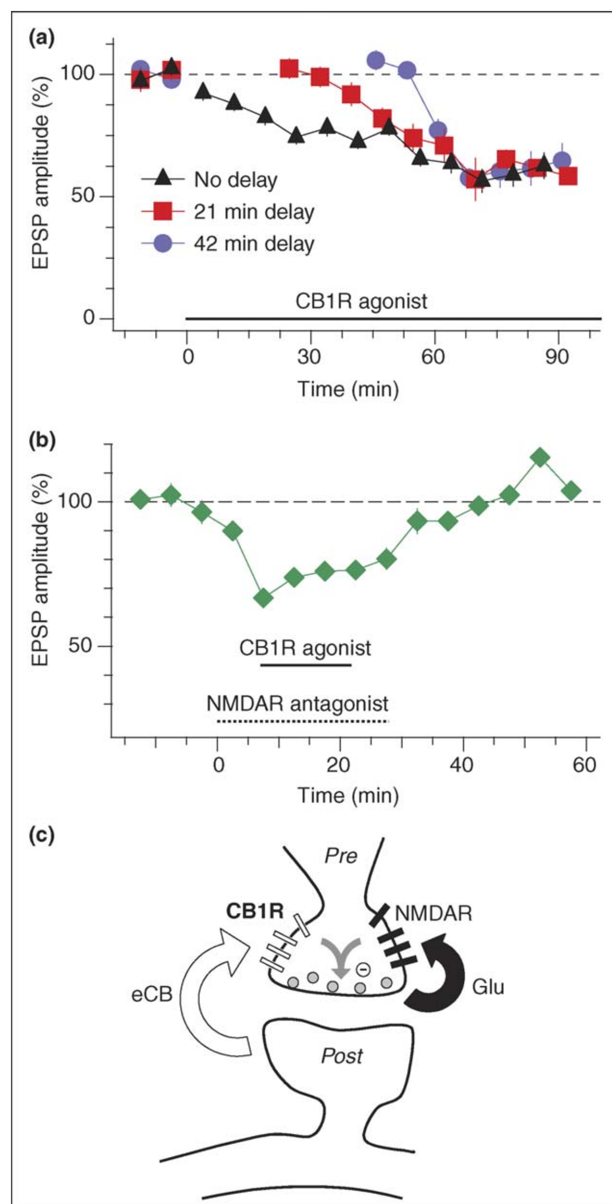
Presynaptic coincidence detection in neocortical spike-timing-dependent LTD

Although early studies investigated the role of timing in plasticity [37–39], the acute sensitivity of synaptic plasticity to the relative timing of pre- and postsynaptic spikes was perhaps fully appreciated first in the study of Markram *et al.* [14] on monosynaptically connected neocortical layer 5 (L5) pyramidal pairs. Sjöström *et al.* [16] subsequently found that L5 plasticity was determined not only by timing, but also by rate and cooperativity, thereby demonstrating the existence of complex nonlinear interactions between pre- and postsynaptic spikes in STDP, reminiscent of those discovered later in hippocampus and neocortical layers 2 and 3 (L2/3) [40,41].

More recently, Sjöström *et al.* [27] investigated the mechanisms underlying spike-timing-dependent LTD (tLTD). Like LTP at L5-to-L5 synapses [42], tLTD results in changes in short-term depression consistent with a presynaptic locus of expression. Given that tLTD requires both pre- and postsynaptic spiking [14,16,27,43•], this finding implies the need for a retrograde messenger. In basal ganglia, in the amygdala, and at inhibitory synapses of the hippocampus [44], retrograde signalling in LTD is mediated by endocannabinoids. Similarly, in the cerebellum, hippocampus and neocortex, the short-term regulation of presynaptic release via depolarization-induced suppression of inhibition and excitation depends on retrograde endocannabinoid signalling [45].

Indeed, pharmacological blockade of the endocannabinoid CB1 receptor (CB1R) abolishes tLTD in L5, suggesting that the retrograde messenger is an endocannabinoid [27]. Conversely, application of CB1R agonists results in presynaptically expressed LTD that requires high-frequency presynaptic but not postsynaptic firing (Figure 2a). Intriguingly, like tLTD, the CB1R-agonist-induced LTD is abolished by NMDAR antagonists (Figure 2b), suggesting that the requirement for presynaptic activity arises from a need for presynaptic NMDAR activation. In fact, anatomical evidence for both presynaptic CB1Rs [46] and presynaptic NMDARs [24] has been found in L5 of visual cortex. In addition,

Figure 2



Spike-timing-dependent LTD in neocortical L5 pyramidal neurons is induced by the coincident activation of presynaptic NMDARs and CB1Rs. **(a)** Application of a CB1R agonist (unbroken line) results in depression that requires pre- but not postsynaptic activity [27]. **(b)** Depression induced by application of a CB1R agonist (unbroken line) is abolished by application of an NMDAR antagonist (broken line) [27], which, along with the data in (a), suggests that these NMDARs are located presynaptically. These data also suggest that these NMDARs are sensors for presynaptic activity, because application of the NMDAR blocker itself results in reversible suppression of neurotransmission [27], consistent with a presynaptic location of these NMDARs. **(c)** Model of tLTD induction. Postsynaptic spiking releases endocannabinoids [43•], which diffuses retrogradely (open arrow) to activate presynaptic CB1Rs; by contrast, presynaptic spiking results in glutamate release (filled arrow), which activates presynaptic NMDARs [27]. The simultaneous activation of presynaptic CB1Rs and NMDA autoreceptors results in LTD of glutamate release (grey arrow) by an unknown downstream molecular pathway. Adapted, with permission, from [27].

electrophysiological data suggest that presynaptic NMDARs exist in L5 of entorhinal cortex [23].

In the most parsimonious model consistent with these findings (Figure 2c), the coincident activation of presynaptic CB1Rs and NMDA autoreceptors results in long-term reduction of neurotransmitter release. These presynaptic CB1Rs thus detect postsynaptic activity, whereas presynaptic NMDARs are sensors for presynaptic spiking. The details of the downstream molecular mechanisms, however, remain unknown. Functionally, this mechanism of coincidence detection might impart synapse specificity to endocannabinoid signalling [27]. Endocannabinoid release induced by postsynaptic activity is often relatively global [47]; thus, without the tLTD presynaptic coincidence requirement (Figure 2c), all inputs might depress. In addition, because prolonging postsynaptic activity [27,43•] or reducing endocannabinoid breakdown [27] increases the duration of the temporal window of tLTD, this mechanism (Figure 2c) might help to explain the timing requirements of tLTD [27].

The role of NMDARs in the model of tLTD in L5 (Figure 2c) is unorthodox: the well-known dual requirement of NMDARs for glutamate-binding and depolarization [6,7] does not appear to underlie this mechanism of presynaptic coincidence detection. In fact, the tLTD model (Figure 2c) suggests that very low-frequency tLTD should not be possible, because — at inter-spike intervals much longer than the NMDAR glutamate dissociation time constant — presynaptic NMDARs become glutamate-bound only after the presynaptic spike has ended. Yet, tLTD is readily evoked at low frequencies [27]. LTD induced by CB1R agonists, however, displays the kind of frequency dependence predicted by the model [27] (Figure 2c). Thus, the tLTD model is incomplete. A direct amplifying action of endocannabinoids on NMDAR-mediated Ca^{2+} responses [48], or an additional, unknown retrograde signal would explain this discrepancy. The retrograde messenger could transiently depolarize presynaptic NMDARs; alternatively, postsynaptically released glutamate [49,50•] could provide the missing retrograde signal, because it would ensure that presynaptic NMDARs are glutamate-bound at the time of the presynaptic action potential. Additional experiments are required to find this missing piece of the tLTD puzzle.

Postsynaptic NMDARs at many central synapses undergo a gradual developmental switch from NR2B to a combination of NR2A and NR2B subunits [51,52]. Unlike postsynaptic NMDARs at L5 to L5 synapses [52], however, presynaptic NMDARs have not undergone the developmental switch from the NR2B to the NR2A subunit at an age of 2–3 weeks. This implies that presynaptically induced tLTD, but not postsynaptically induced LTP, requires NR2B-containing NMDARs. In

agreement with this idea, blockade of NR2B-containing NMDARs specifically abolishes LTD without any appreciable effect on LTP [27]. This specific expression of presynaptic NR2B-containing NMDARs is similar to that found in L2/3 and L5 of entorhinal cortex [23,53•], although a role for entorhinal presynaptic NMDARs and coincidence detection in plasticity has not been demonstrated. At presynaptic terminals in entorhinal cortex, NR2B-containing presynaptic NMDARs are downregulated at a mature stage [53•]. Interestingly, this developmental transition is reversed in a chronic epileptic condition [53•], suggesting that presynaptic NMDARs and, as a corollary, presynaptic coincidence detection mechanisms may have a role in epileptogenesis.

Why is the coincidence detector for LTD presynaptic (Figure 2c), when that for LTP is postsynaptic [14,27]? To account for the typical existence of a single LTD temporal window in STDP [10], computer modelling has predicted the need for separate coincidence detectors in LTP and LTD [54]. Interestingly, evidence for separate coincidence detectors in classical rate-dependent LTP and LTD has been recently found in the hippocampus [55] and perirhinal cortex [56]. Similar to STDP in neocortical L5 [27], the coincidence detector for LTD is based on NR2B-containing NMDARs, whereas that for LTP requires NMDARs containing the NR2A subunit [55,56]. However because of the specificity of the pharmacological agents used, results such as these [55,56] should be interpreted with care [57,58]. Curiously, in both perirhinal cortex and hippocampus, the coincidence detectors for LTP and LTD are postsynaptic [55,56]. Recent results suggest that the faster kinetics of NR2A- versus NR2B-containing NMDARs ensures that the former contribute more to LTP and the latter more to LTD [59], although it remains possible that the two types of NMDAR simply link to distinct downstream signalling cascades. The existence of separate coincidence detectors for LTP and LTD [27,55,56,58,60•] might turn out to be a general principle in synaptic plasticity, although the reasons why are unclear. Obviously, one way of having such a division of coincidence detectors is to put one presynaptically.

At many synapses, LTD can be induced by protocols other than STDP, such as low-frequency stimulation [61] or pairing of presynaptic spikes with subthreshold postsynaptic depolarization (‘dLTD’) [62]. At some synapses, the type of LTD induced depends on the induction protocol used [10,21]. In a recent study, Sjöström *et al.* [43•] investigated the mechanisms of low-frequency stimulation and dLTD in neocortical L5 pairs. Surprisingly, low-frequency stimulation resulted in no plasticity, perhaps because these unitary synapses are weak [63] and might not sufficiently activate postsynaptic NMDARs [61]. Induction of dLTD, however, was robust [43•], consistent with earlier findings at the same synapse [16]. As assessed by the change in short-term plasticity and coefficient of variation, dLTD, like tLTD, was presynaptically expressed [27]. In addition, their identical dependence on NR2B and time course of expression along with occlusion suggest that dLTD and tLTD rely on the same mechanism of presynaptic coincidence detection (Figure 2c), which suggests, paradoxically, that tLTD does not require postsynaptic spiking.

A puzzling aspect of this dLTD mechanism is that endocannabinoid production is known to require micromolar increases in Ca^{2+} in some cell types, such as Purkinje cells [64]. How, then, can subthreshold depolarization evoke postsynaptic Ca^{2+} influx sufficient to stimulate endocannabinoid production? Perhaps low-threshold Ca^{2+} channels, which are known to exist in L5 neurons [65], are activated during the induction of dLTD. Alternatively, there might be many pathways of endocannabinoid production, some of which might require little or no Ca^{2+} influx [66]. Indeed, Ronesi and Lovinger [67•] have recently discovered a novel form of endocannabinoid-dependent striatal LTD that does not require postsynaptic depolarization or Ca^{2+} influx.

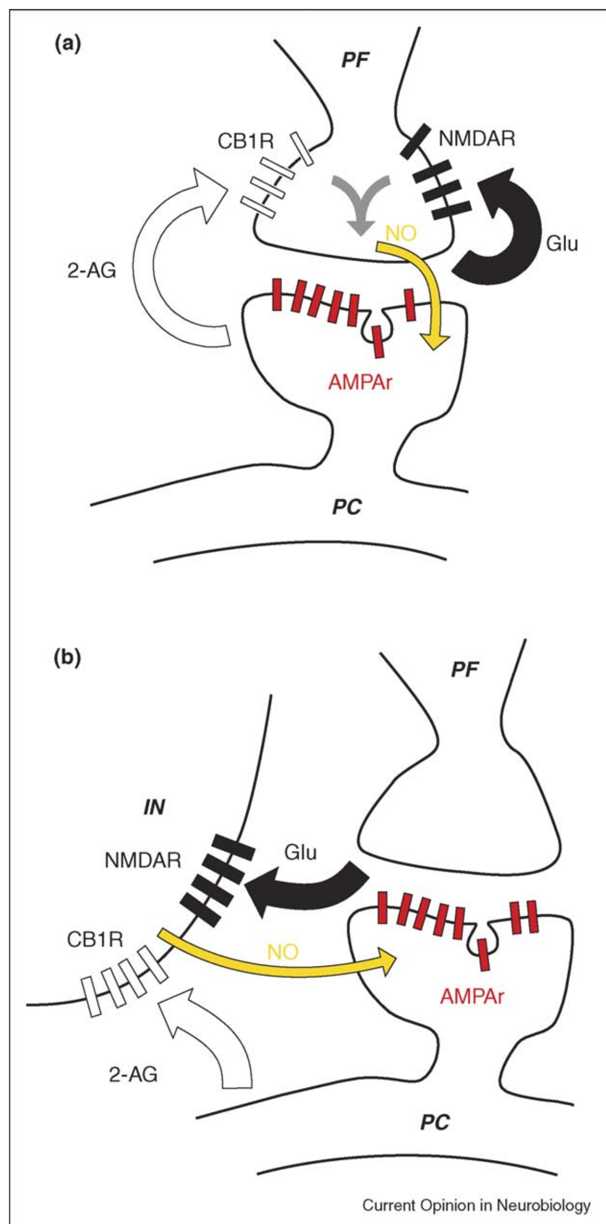
Finally, although it seems unlikely that postsynaptic NMDARs are involved in inducing LTD when they are hyperpolarized [27] or at resting membrane potential [27,43•], the possibility that postsynaptic NMDARs participate in L5 tLTD cannot be excluded at present. In fact, postsynaptically induced and expressed forms of LTD are known to exist in L5 neurons [68,69] and spike-mediated suppression of postsynaptic NMDARs has been recently proposed to underlie STDP in neocortical L2/3 [15]. Future experiments will be required to investigate the possible involvement of postsynaptic coincidence detection in L5 tLTD.

Presynaptic coincidence detection in cerebellar LTD?

Cerebellar LTD at the parallel fibre to Purkinje cell synapse is thought to underlie several forms of associative learning [70] and depends on the relative timing of parallel fibre and climbing fibre inputs [71,72]. In contrast to other synapses that show Ca^{2+}-dependent associative plasticity, however, parallel fibre synapses lack postsynaptic NMDARs [73], and thus rely on alternative signalling pathways for coincidence detection [72]. The locus of parallel fibre LTD expression has been firmly established as postsynaptic, requiring phosphorylation of AMPA receptors and clathrin-mediated endocytosis [74].

A study by Casado *et al.* [26] has suggested, however, that presynaptic NMDARs might have a crucial role in the induction of parallel fibre LTD. The authors found that parallel fibre LTD induced by conjunctive parallel fibre stimulation and Purkinje cell depolarization at 1 Hz was abolished by NMDAR blockade [26]. Because Purkinje

Figure 3



Hypothetical models of parallel fibre LTD. **(a)** Conjunctive stimulation of parallel fibres and postsynaptic activity release the endocannabinoid 2-AG [47,77••] and glutamate [26], which act on presynaptic CB1Rs and NMDARs, respectively, to induce parallel fibre LTD. NMDARs present on parallel fibre terminals function as presynaptic coincidence detectors, requiring simultaneous glutamate binding and depolarization for activation [26], whereas activation of CB1R promotes the release of NO by an unknown pathway [77••]. In a hypothetical model, these two independent pathways might converge at the presynaptic terminal to create a novel form of presynaptic coincidence detection at the synapses between parallel fibres and Purkinje cells, perhaps similar to that observed in LTD in L5 [27] (Figure 2c).
(b) Recent work suggests that signalling cascades involved in the induction of parallel fibre LTD might in fact be localized to interneurons [78•]. As in (a), conjunctive parallel fibre stimulation and postsynaptic activity release 2-AG [47,77••] and glutamate, which might act on CB1Rs and NMDARs located on molecular layer interneurons [22,50•,78•,79–81,99] to induce cerebellar LTD. The models in (a) and (b), although hypothetical, are based on published data [26,77••,78•]. Abbreviations: PF, parallel fibre; IN, interneuron; PC, Purkinje cell.

cells do not possess functional NMDARs at this age [73,75], the need for NMDAR activation in parallel fibre LTD suggests that the relevant NMDARs might be situated not on the postsynaptic side, but presynaptically on parallel fibre terminals. In this view, presynaptic NMDAR activation initiates nitric oxide (NO) production in the parallel fibre terminal [76], and NO subsequently triggers parallel fibre LTD in Purkinje cells [26] (Figure 3a). In keeping with a need for presynaptic NMDAR activation, which requires simultaneous glutamate binding and depolarization, parallel fibre LTD was evoked only when parallel fibre doublet stimuli were paired with Purkinje cell depolarization, and not when single parallel fibre stimuli were used. Moreover, recordings from pairs of synaptically connected granule cells and Purkinje cells also displayed NMDAR-dependent LTD, indicating that NMDARs present on or near parallel fibre terminals function as coincidence detectors during the induction of parallel fibre LTD [26] (Figure 3a).

Intriguingly, endocannabinoids have recently been implicated in the induction of parallel fibre LTD [77••]. The most compelling evidence for the involvement of endocannabinoids arises from experiments conducted in CB1R-deficient mice, in which conjunctive parallel fibre and climbing fibre stimulation was ineffective at inducing parallel fibre LTD [77••]. Although presynaptic NMDARs and CB1Rs might induce parallel fibre LTD independently, it is possible that parallel fibre LTD induction requires the coincident activation of both types of receptor. Such a mechanism would be similar to that observed in LTD in neocortical L5 (Figures 3a and 2c) [27], although the postsynaptic release of endocannabinoids from Purkinje cells might additionally require the activation of a postsynaptic coincidence detection mechanism (Figure 3) [47].

Although presynaptic NMDARs seem to be involved in the induction of parallel fibre LTD [26], controversy surrounds their exact location and function. Shin and Linden [78•] recently reported that the NMDAR/NO cascade involved in cerebellar LTD might be localized at interneuron axon terminals rather than at parallel fibre terminals. Their proposed mechanism involves the spillover of glutamate from active parallel fibre terminals to adjacent interneuron axon terminals, which have been shown to possess functional NMDARs [22,50•,79,80]. The resultant NMDAR-mediated influx of Ca^{2+} would activate neuronal NO synthase — which is expressed in abundance in interneuron axon terminals [81] — thereby releasing NO [78•] (Figure 3b). Interestingly, one untested possibility is that direct parallel fibre stimulation of molecular layer interneurons results in the activation of

extrasynaptic NMDARs [82], which would induce the Ca^{2+}-dependent release of NO. Recent results show that even a single pulse of extracellular stimulation can evoke a burst of parallel fibre action potentials [83]. Such a burst of parallel fibre spikes might be sufficient to recruit extrasynaptic NMDARs on interneurons [82] or to drive the generation of action potentials in interneurons, thereby releasing NO. So far, however, no direct link between the production of NO by interneurons and the induction of parallel fibre LTD has been established. These apparently conflicting reports illustrate the difficulties involved in identifying the exact location of the mechanisms underlying the induction of synaptic plasticity.

Presynaptic NMDARs and synaptic plasticity without coincidence detection

In the classical view, activation of NMDARs requires simultaneous glutamate binding and sufficient depolarization to relieve the ion channels of Mg^{2+} blockade [6,7]. In recent years, however, it has been established that the composition of NMDAR subunits has important implications for the biophysical properties of the receptor: in some instances, glutamate binding alone is sufficient for activation [22,75,84]. Indeed, several studies have shown that NMDARs containing the NR2C and NR2D subunits have reduced sensitivity to Mg^{2+} [80,85–90]. In the cerebellum, presynaptic NMDARs present on interneuron axon terminals [22,50•,79,80] have a pivotal role in the induction of depolarization-induced potentiation of inhibition (DPI) [50•]. This potentiation of inhibition is evoked by repeated postsynaptic depolarization in a manner reminiscent of depolarization-induced suppression of inhibition and excitation [45,47,77••]. In contrast to the mechanism of Casado *et al.* [26] for inducing presynaptic NMDAR-dependent parallel fibre LTD (Figure 3a), DPI does not require coincident presynaptic bursting, even though presynaptic NMDAR activation is necessary [22,50•,80]. In conclusion, even though the NMDAR is often viewed as a coincidence detector, not all presynaptic NMDARs function as coincidence detectors in synaptic plasticity.

Recently, presynaptic NMDAR-mediated enhancement of synaptic transmission has been implicated in the developmental maturation of the inhibitory neural network of the cerebellar cortex [80], where it might modulate the interplay between excitation and inhibition. Whether this effect of presynaptic NMDARs is trophic or homeostatic, however, remains unclear. Nevertheless, this study suggests that there is a morphological correlate to DPI [80] and points to the developmental regulation of both presynaptic NMDAR-dependent plasticity and DPI [50•].

Conclusions and future directions

In the classical view of long-term plasticity, coincidence detection occurs postsynaptically, typically through the activation of NMDARs [3–5]. This view currently dominates neuroscience, not only because postsynaptic coincidence detection is unequivocally a key feature of synaptic plasticity, but perhaps also because postsynaptic manipulations are easier to achieve than presynaptic ones. For example, the absence of a postsynaptic effect of a drug manipulation, such as Ca^{2+} chelation or internal NMDAR blockade, does not prove that the locus of a mechanism is presynaptic — in principle, the mechanism could be located elsewhere, as is suggested in cerebellar parallel fibre LTD [78•] (Figure 3). The conclusive elucidation of presynaptic mechanisms therefore requires a combination of direct approaches, such as paired recordings [26,27], presynaptic Ca^{2+} imaging [78•], immunological [24,25,46], molecular [4] or genetic tools [4,77••], or electrophysiological recordings from presynaptic boutons [80].

Although this list might seem daunting, it also means encouragingly that the field is essentially wide open. The number of identified presynaptic coincidence detection mechanisms will no doubt grow, in particular because mechanisms of presynaptic coincidence detection [28] might coexist at synapses with more classical mechanisms of postsynaptic induction [33]. Furthermore, the downstream molecular mechanisms involved in presynaptic coincidence detectors remain largely unexplored [26–28]. In addition, recent studies have shown that presynaptic NMDARs regulate neurotransmitter release at several types of synapse, such as at spinal cord primary afferents [91], in entorhinal cortex [53•], and at the Schaffer collaterals and CA1 pathway of the hippocampus [92,93]. Yet, the potential involvement of these presynaptic NMDARs in long-term plasticity has not been investigated.

As illustrated throughout this review, presynaptic coincidence detection offers several functional advantages. In the amygdala, it provides an associative learning rule that persists even in the absence of postsynaptic activity [28] and that might prime relatively weak cortical inputs for subsequent strengthening by other mechanisms [33]. At neocortical L5 to L5 synapses, the dual need for CB1R and NMDAR activation might endow tLTD with a degree of synapse specificity to ensure that only active inputs are depressed by endocannabinoid retrograde signalling [27]. In addition, the presynaptic coincidence detection of tLTD in L5 might be a way of partitioning LTD from LTP induction mechanisms [55,56,58,60•], which might help to provide the temporal asymmetry that is typical of STDP learning rules [10,20,54].

Although we have focused on NMDAR-based presynaptic mechanisms for coincidence detection, we are not suggesting that mechanisms of presynaptic coincidence detection need to rely on NMDARs. After all, postsynaptic coincidence detection can be based on NMDAR-

independent mechanisms, such as buffer saturation [94], inositol 1,4,5-trisphosphate (IP_3) receptors [72] and dendritic voltage-dependent ion channels [95,96]. Indeed, evidence indicates that there might be a presynaptic coincidence detector based on the glutamate receptor mGluR7 at mossy fibre synapses onto hippocampal CA3 interneurons [97]. Similarly, an NMDAR-independent presynaptic coincidence detector in striatal LTD has been proposed [98•]. In principle, any form of presynaptically expressed plasticity that requires simultaneous activation of the postsynaptic neuron [27] or other cells [28] is likely to rely, at least in part, on a presynaptic coincidence detection mechanism. Unlike the plasticity induction mechanisms themselves, this is no coincidence.

Update

In a recently published study, Lien *et al.* [100••] demonstrated that light stimuli or theta burst stimulation of the optic nerve in the developing *Xenopus* retinotectal system induced LTP of glutamatergic inputs but LTD of GABAergic inputs to the same tectal neuron. Although both forms of plasticity were abolished by bath application of the NMDAR antagonist D-APV — thus indicating a pivotal role for NMDARs during plasticity induction — only LTP of excitatory afferents was abolished after infusing the tectal cell with the antagonist MK-801, which selectively blocks postsynaptic NMDARs. Similarly, postsynaptic hyperpolarization or postsynaptic loading of the rapid Ca^{2+} chelator BAPTA-AM prevented the induction of excitatory LTP but had no effect on LTD at inhibitory synapses. The authors conclude that high-frequency theta burst stimulation results in spillover of glutamate onto NMDARs on adjacent interneuron axon terminals, and that coincident high-frequency interneuron firing activates these presynaptic NMDARs, which triggers the induction of GABAergic LTD.

This elegantly executed study provides the first *in vivo* evidence for the involvement of presynaptic NMDARs in coincidence detection and synaptic plasticity. In addition, Lien *et al.* [100••] propose that these presynaptic NMDARs play an important role in the developmental fine-tuning of the retinotectal system: the activation of presynaptic NMDARs serves to locally dampen inhibitory synaptic input, which facilitates Hebbian plasticity at excitatory inputs and which might lead to a 'winner-takes-all' form of competition among retinotectal afferents.

In another recent paper, Bender *et al.* [60•] study STDP in L2/3 neurons using extracellular stimulation in layer 4. They find that presynaptically expressed tLTD requires the activation of putatively presynaptic NMDARs and CB1Rs, because postsynaptic hyperpolarization or loading with the NMDAR antagonist MK801 does not abolish tLTD. At first glance, this mechanism appears similar to that proposed for tLTD at unitary L5-to-L5 connections (Figure 2c) [27], but Bender *et al.* [60•] found that NMDAR blockade only abolished L2/3 tLTD if it began 10 minutes or more prior to the induction stimulus (cf. Figure 2b) [27]. In addition, CB1 agonist application evoked LTD in L2/3 neurons regardless of presynaptic frequency, an observation that was not made in L5 neurons [27]. Perhaps the L2/3 presynaptic NMDARs have reduced Mg^{2+} blockade and do not require depolarization for activation (cf. [50•]). Regardless, the L2/3 and L5 tLTD induction mechanisms thus appear to be dissimilar [27].

Bender *et al.* [60•] also provide evidence for a postsynaptic coincidence detection mechanism for L2/3 tLTD, which relies on IP_3 receptors to detect the simultaneous activation of mGluR5s and voltage-dependent calcium channels. Although in principle this postsynaptic mechanism for tLTD induction does not preclude the co-existence of a presynaptic coincidence detection mechanism, it does seem to be at odds with an earlier study implicating postsynaptic NMDARs in L2/3 tLTD [15].

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Hebb DO: *The Organization of Behavior*. New York: Wiley; 1949.
2. Bliss TV, Lømo T: **Plasticity in a monosynaptic cortical pathway**. *J Physiol* 1970, **207**:61P.
3. Malenka RC, Nicoll RA: **Long-term potentiation — a decade of progress?** *Science* 1999, **285**:1870-1874.
4. Lynch MA: **Long-term potentiation and memory**. *Physiol Rev* 2004, **84**:87-136.
5. Bliss TV, Collingridge GL: **A synaptic model of memory: long-term potentiation in the hippocampus**. *Nature* 1993, **361**:31-39.
6. Nowak L, Bregestovski P, Ascher P, Herbet A, Prochiantz A: **Magnesium gates glutamate-activated channels in mouse central neurones**. *Nature* 1984, **307**:462-465.
7. Mayer ML, Westbrook GL, Guthrie PB: **Voltage-dependent block by Mg^{2+} of NMDA responses in spinal cord neurones**. *Nature* 1984, **309**:261-263.
8. Ascher P, Nowak L: **The role of divalent cations in the *N*-methyl-D-aspartate responses of mouse central neurones in culture**. *J Physiol* 1988, **399**:247-266.
9. MacDermott AB, Mayer ML, Westbrook GL, Smith SJ, Barker JL: **NMDA-receptor activation increases cytoplasmic calcium concentration in cultured spinal cord neurones**. *Nature* 1986, **321**:519-522.
10. Sjöström PJ, Nelson SB: **Spike timing, calcium signals and synaptic plasticity**. *Curr Opin Neurobiol* 2002, **12**:305-314.

11. Hansel C, Artola A, Singer W: **Relation between dendritic Ca^{2+} levels and the polarity of synaptic long-term modifications in rat visual cortex neurons**. *Eur J Neurosci* 1997, **9**:2309-2322.

12. Cummings JA, Mulkey RM, Nicoll RA, Malenka RC: **Ca^{2+} signaling requirements for long-term depression in the hippocampus**. *Neuron* 1996, **16**:825-833.

13. Koester HJ, Sakmann B: **Calcium dynamics in single spines during coincident pre- and postsynaptic activity depend on relative timing of back-propagating action potentials and subthreshold excitatory postsynaptic potentials**. *Proc Natl Acad Sci USA* 1998, **95**:9596-9601.

14. Markram H, Lübke J, Frotscher M, Sakmann B: **Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs**. *Science* 1997, **275**:213-215.

15. Froemke RC, Poo MM, Dan Y: **Spike-timing-dependent synaptic plasticity depends on dendritic location**. *Nature* 2005, **434**:221-225.

16. Sjöström PJ, Turrigiano GG, Nelson SB: **Rate, timing, and cooperativity jointly determine cortical synaptic plasticity**. *Neuron* 2001, **32**:1149-1164.

17. Feldman DE: **Timing-based LTP and LTD at vertical inputs to layer II/III pyramidal cells in rat barrel cortex**. *Neuron* 2000, **27**:45-56.

18. Zhang LI, Tao HW, Holt CE, Harris WA, Poo M: **A critical window for cooperation and competition among developing retinotectal synapses**. *Nature* 1998, **395**:37-44.

19. Humeau Y, Herry C, Kemp N, Shaban H, Fourcaudot E, Bissière S,
•• Lüthi A: **Dendritic spine heterogeneity determines afferent-specific hebbian plasticity in the amygdala**. *Neuron* 2005, **45**:119-131.

In projection neurons of the lateral nucleus of the amygdala (LA), thalamic inputs readily undergo classical spike-timing-dependent plasticity, whereas cortical afferents show a higher threshold for plasticity. The authors find that, as a morphological correlate, spines contacted by thalamic afferents are larger, have greater Ca^{2+} signals evoked by action potentials, and preferentially express R-type Ca^{2+} channels. Importantly, an earlier study [28] demonstrated the existence of an associative form of LTP at cortical inputs to the LA that is induced by presynaptic NMDAR-based coincidence detection of simultaneous thalamic and cortical input activation. This shows that pre- and postsynaptic coincidence detection mechanisms may coexist and are specific to particular synapses and activity patterns.

20. Abbott LF, Nelson SB: **Synaptic plasticity: taming the beast**. *Nat Neurosci* 2000, **3**:1178-1183.

21. Malenka RC, Bear MF: **LTP and LTD: an embarrassment of riches**. *Neuron* 2004, **44**:5-21.

22. Glitsch M, Marty A: **Presynaptic effects of NMDA in cerebellar Purkinje cells and interneurons**. *J Neurosci* 1999, **19**:511-519.

23. Berretta N, Jones RS: **Tonic facilitation of glutamate release by presynaptic *N*-methyl-D-aspartate autoreceptors in the entorhinal cortex**. *Neuroscience* 1996, **75**:339-344.

24. Aoki C, Venkatesan C, Go CG, Mong JA, Dawson TM: **Cellular and subcellular localization of NMDA-R1 subunit immunoreactivity in the visual cortex of adult and neonatal rats**. *J Neurosci* 1994, **14**:5202-5222.

25. Farb CR, Aoki C, LeDoux JE: **Differential localization of NMDA and AMPA receptor subunits in the lateral and basal nuclei of the amygdala: a light and electron microscopic study**. *J Comp Neurol* 1995, **362**:86-108.

26. Casado M, Isope P, Ascher P: **Involvement of presynaptic N-methyl-D-aspartate receptors in cerebellar long-term depression**. *Neuron* 2002, **33**:123-130.

27. Sjöström PJ, Turrigiano GG, Nelson SB: **Neocortical LTD via coincident activation of presynaptic NMDA and cannabinoid receptors**. *Neuron* 2003, **39**:641-654.

28. Humeau Y, Shaban H, Bissière S, Lüthi A: **Presynaptic induction of heterosynaptic associative plasticity in the mammalian brain**. *Nature* 2003, **426**:841-845.

29. Maren S: **Neurobiology of Pavlovian fear conditioning**. *Annu Rev Neurosci* 2001, **24**:897-931.

30. Maren S: **Synaptic mechanisms of associative memory in the amygdala**. *Neuron* 2005, **47**:783-786.

31. Farb CR, LeDoux JE: **Afferents from rat temporal cortex synapse on lateral amygdala neurons that express NMDA and AMPA receptors**. *Synapse* 1999, **33**:218-229.

32. Farb CR, LeDoux JE: **NMDA and AMPA receptors in the lateral nucleus of the amygdala are postsynaptic to auditory thalamic afferents**. *Synapse* 1997, **27**:106-121.

33. Huang YY, Kandel ER: **Postsynaptic induction and PKA-dependent expression of LTP in the lateral amygdala**. *Neuron* 1998, **21**:169-178.

34. Rosenkranz JA, Grace AA: **Dopamine-mediated modulation of odour-evoked amygdala potentials during pavlovian conditioning**. *Nature* 2002, **417**:282-287.

35. Paré D, Quirk GJ, LeDoux JE: **New vistas on amygdala networks in conditioned fear**. *J Neurophysiol* 2004, **92**:1-9.

36. Samson RD, Paré D: **Activity-dependent synaptic plasticity**
• **in the central nucleus of the amygdala**. *J Neurosci* 2005, **25**:1847-1855.

LTP of thalamic afferents to the central nucleus of the amygdala is dependent on NMDARs, but is not blocked by postsynaptic hyperpolarization, Ca^{2+} chelation or internal postsynaptic NMDAR blockade. This suggests that induction depends on presynaptic NMDAR activation [28]. Furthermore, LTP results in changes in short-term plasticity, arguing that its expression has a presynaptic locus.

37. Levy WB, Steward O: **Temporal contiguity requirements for long-term associative potentiation/depression in the hippocampus**. *Neuroscience* 1983, **8**:791-797.

38. Gustafsson B, Wigström H, Abraham WC, Huang YY: **Long-term potentiation in the hippocampus using depolarizing current pulses as the conditioning stimulus to single volley synaptic potentials**. *J Neurosci* 1987, **7**:774-780.

39. Debanne D, Gähwiler BH, Thompson SM: **Asynchronous pre- and postsynaptic activity induces associative long-term depression in area CA1 of the rat hippocampus *in vitro***. *Proc Natl Acad Sci USA* 1994, **91**:1148-1152.

40. Bi GQ, Rubin J: **Timing in synaptic plasticity: from detection to integration**. *Trends Neurosci* 2005, **28**:222-228.

41. Froemke RC, Tsay IA, Raad M, Long JD, Dan Y: **Contribution of individual spikes in burst-induced long-term synaptic modification**. *J Neurophysiol* 2006, **95**:1620-1629.

42. Markram H, Tsodyks M: **Redistribution of synaptic efficacy between neocortical pyramidal neurons**. *Nature* 1996, **382**:807-810.

43. Sjöström PJ, Turrigiano GG, Nelson SB: **Endocannabinoid-**
• **dependent neocortical layer-5 LTD in the absence of postsynaptic spiking**. *J Neurophysiol* 2004, **92**:3338-3343.

This study demonstrates that dLTD, which is induced by pairing presynaptic stimulation with postsynaptic subthreshold depolarization, relies on a mechanism that is indistinguishable from that of tLTD, which requires correlated pre- and postsynaptic spiking [27]. This mechanism is known to require simultaneous presynaptic NMDAR and CB1R activation, which suggests that tLTD does not actually require spiking and that the Ca^{2+} threshold for endocannabinoid production might be low in neocortical L5 pyramidal neurons.

44. Gerdeman GL, Lovinger DM: **Emerging roles for endocannabinoids in long-term synaptic plasticity**. *Br J Pharmacol* 2003, **140**:781-789.

45. Diana MA, Marty A: **Endocannabinoid-mediated short-term synaptic plasticity: depolarization-induced suppression of inhibition (DSI) and depolarization-induced suppression of excitation (DSE)**. *Br J Pharmacol* 2004, **142**:9-19.

46. Ong WY, Mackie K: **A light and electron microscopic study of the CB1 cannabinoid receptor in primate brain**. *Neuroscience* 1999, **92**:1177-1191.

47. Brenowitz SD, Regehr WG: **Associative short-term synaptic plasticity mediated by endocannabinoids**. *Neuron* 2005, **45**:419-431.

48. Hampson AJ, Bornheim LM, Scanziani M, Yost CS, Gray AT, Hansen BM, Leonoudakis DJ, Bickler PE: **Dual effects of anandamide on NMDA receptor-mediated responses and neurotransmission**. *J Neurochem* 1998, **70**:671-676.

49. Nedergaard M, Takano T, Hansen AJ: **Beyond the role of glutamate as a neurotransmitter**. *Nat Rev Neurosci* 2002, **3**:748-755.

50. • Duguid IC, Smart TG: **Retrograde activation of presynaptic NMDA receptors enhances GABA release at cerebellar interneuron–Purkinje cell synapses**. *Nat Neurosci* 2004, **7**:525-533.

In this study, postsynaptic depolarization induces a potentiation of inhibitory synaptic transmission at the synapse of interneuron axons and Purkinje cells, defined as 'depolarization-induced potentiation of inhibition'. This glutamate-mediated retrograde signalling pathway requires presynaptic NMDAR activation and subsequent Ca^{2+}-induced Ca^{2+} release from presynaptic ryanodine-sensitive stores, resulting in a sustained increase in inhibitory synaptic efficacy at the synapse of interneuron axons and Purkinje cells. Interestingly, these presynaptic NMDARs do not require simultaneous glutamate binding and depolarization, thus demonstrating the existence of presynaptic NMDAR-dependent synaptic plasticity in the absence of coincidence detection.

51. Sheng M, Cummings J, Roldan LA, Jan YN, Jan LY: **Changing subunit composition of heteromeric NMDA receptors during development of rat cortex**. *Nature* 1994, **368**:144-147.

52. Stocca G, Vicini S: **Increased contribution of NR2A subunit to synaptic NMDA receptors in developing rat cortical neurons**. *J Physiol* 1998, **507**:13-24.

53. • Yang J, Woodhall GL, Jones RS: **Tonic facilitation of glutamate release by presynaptic NR2B-containing NMDA receptors is increased in the entorhinal cortex of chronically epileptic rats**. *J Neurosci* 2006, **26**:406-410.

Presynaptic NR2B-subunit-containing NMDARs exist at excitatory terminals onto pyramidal neurons in entorhinal cortical layers L2/3 and L5. The effect of NR2B-specific NMDAR blockade is reduced during development, which suggests that autoreceptor function is downregulated in mature animals. In a model of chronic epilepsy, this downregulation is delayed, indicating that presynaptic NMDARs might have a possible role in epilepsy.

54. Karmarkar UR, Buonomano DV: **A model of spike-timing dependent plasticity: one or two coincidence detectors?** *J Neurophysiol* 2002, **88**:507-513.

55. Liu L, Wong TP, Pozza MF, Lingenhoehl K, Wang Y, Sheng M, Auberson YP, Wang YT: **Role of NMDA receptor subtypes in governing the direction of hippocampal synaptic plasticity**. *Science* 2004, **304**:1021-1024.

56. Massey PV, Johnson BE, Moult PR, Auberson YP, Brown MW, Molnar E, Collingridge GL, Bashir ZI: **Differential roles of NR2A and NR2B-containing NMDA receptors in cortical long-term potentiation and long-term depression**. *J Neurosci* 2004, **24**:7821-7828.

57. Neyton J, Paoletti P: **Relating NMDA receptor function to receptor subunit composition: limitations of the pharmacological approach**. *J Neurosci* 2006, **26**:1331-1333.

58. Hrabetova S, Serrano P, Blace N, Tse HW, Skifter DA, Jane DE, Monaghan DT, Sacktor TC: **Distinct NMDA receptor subpopulations contribute to long-term potentiation and long-term depression induction**. *J Neurosci* 2000, **20**:RC81.

59. Erreger K, Dravid SM, Banke TG, Wyllie DJ, Traynelis SF: **Subunit-specific gating controls rat NR1/NR2A and NR1/NR2B NMDA channel kinetics and synaptic signalling profiles**. *J Physiol* 2005, **563**:345-358.

60. • Bender VA, Bender KJ, Brasier DJ, Feldman DE: **Two coincidence detectors for spike timing-dependent plasticity in somatosensory cortex**. *J Neurosci* 2006, **26**:4166-4177.

The authors find two separate postsynaptic coincidence detectors for timing-dependent LTP and LTD. LTP relies on the classical postsynaptic NMDAR-based mechanism, as it is blocked by NMDAR antagonists and by postsynaptic Ca^{2+} chelation using BAPTA. LTD, however, required mGluR5 activation, IP_3 receptor signalling, and postsynaptic Ca^{2+} influx through voltage-dependent Ca^{2+} channels. Downstream of postsynaptic calcium, retrograde endocannabinoid signalling and presynaptic NMDARs were required for presynaptic LTD expression.

61. Kirkwood A, Bear MF: **Homosynaptic long-term depression in the visual cortex**. *J Neurosci* 1994, **14**:3404-3412.

62. Artola A, Bröcher S, Singer W: **Different voltage-dependent thresholds for inducing long-term depression and long-term potentiation in slices of rat visual cortex**. *Nature* 1990, **347**:69-72.

63. Song S, Sjöström PJ, Reigl M, Nelson S, Chklovskii DB: **Highly nonrandom features of synaptic connectivity in local cortical circuits**. *PLoS Biol* 2005, **3**:e68.

64. Brenowitz SD, Regehr WG: **Calcium dependence of retrograde inhibition by endocannabinoids at synapses onto Purkinje cells**. *J Neurosci* 2003, **23**:6373-6384.

65. Markram H, Sakmann B: **Calcium transients in dendrites of neocortical neurons evoked by single subthreshold excitatory postsynaptic potentials via low-voltage-activated calcium channels**. *Proc Natl Acad Sci USA* 1994, **91**:5207-5211.

66. Chevaleyre V, Castillo PE: **Heterosynaptic LTD of hippocampal GABAergic synapses: a novel role of endocannabinoids in regulating excitability**. *Neuron* 2003, **38**:461-472.

67. • Ronesi J, Lovinger DM: **Induction of striatal long-term synaptic depression by moderate frequency activation of cortical afferents in rat**. *J Physiol* 2005, **562**:245-256.

This study demonstrates that there are several ways of inducing striatal LTD and also suggests that endocannabinoid production might be evoked through many pathways [66,77••]. Intriguingly, for this particular protocol of LTD induction, the source of the endocannabinoid might not be the postsynaptic neuron.

68. Holthoff K, Kovalchuk Y, Yuste R, Konnerth A: **Single-shock LTD by local dendritic spikes in pyramidal neurons of mouse visual cortex**. *J Physiol* 2004, **560**:27-36.

69. Dodt H, Eder M, Frick A, Zieglgänsberger W: **Precisely localized LTD in the neocortex revealed by infrared-guided laser stimulation**. *Science* 1999, **286**:110-113.

70. Mauk MD, Garcia KS, Medina JF, Steele PM: **Does cerebellar LTD mediate motor learning? Toward a resolution without a smoking gun**. *Neuron* 1998, **20**:359-362.

71. Ito M, Kano M: **Long-lasting depression of parallel fiber–Purkinje cell transmission induced by conjunctive stimulation of parallel fibers and climbing fibers in the cerebellar cortex**. *Neurosci Lett* 1982, **33**:253-258.

72. Wang SS, Denk W, Häusser M: **Coincidence detection in single dendritic spines mediated by calcium release**. *Nat Neurosci* 2000, **3**:1266-1273.

73. Rosenmund C, Legendre P, Westbrook GL: **Expression of NMDA channels on cerebellar Purkinje cells acutely dissociated from newborn rats**. *J Neurophysiol* 1992, **68**:1901-1905.

74. Ito M: **The molecular organization of cerebellar long-term depression**. *Nat Rev Neurosci* 2002, **3**:896-902.

75. Llano I, Marty A, Armstrong CM, Konnerth A: **Synaptic- and agonist-induced excitatory currents of Purkinje cells in rat cerebellar slices**. *J Physiol* 1991, **434**:183-213.

76. Bredt DS, Hwang PM, Snyder SH: **Localization of nitric oxide synthase indicating a neural role for nitric oxide**. *Nature* 1990, **347**:768-770.

77. •• Safo PK, Regehr WG: **Endocannabinoids control the induction of cerebellar LTD**. *Neuron* 2005, **48**:647-659.

The authors show that parallel fibre LTD, induced by conjunctive parallel fibre and climbing fibre stimulation, requires activation of CB1R. Parallel fibre LTD induction is blocked both by CB1R antagonists and by inhibiting the synthesis of the endocannabinoid 2-AG, and is absent in CB1R knockout mice.

78. • Shin JH, Linden DJ: **An NMDA receptor/nitric oxide cascade is involved in cerebellar LTD but is not localized to the parallel fiber terminal**. *J Neurophysiol* 2005, **94**:4281-4289.

The authors demonstrate that the NMDAR/NO cascade involved in the induction of parallel fibre LTD might be localized to interneuron axons rather than to parallel fibres. Exogenous NMDAR activation evokes Ca^{2+} transients and increases the frequency of miniature release from interneuron axon terminals; however, no such evidence is found for functional NMDARs on parallel fibre terminals. See also [80].

79. Huang H, Bordey A: **Glial glutamate transporters limit spillover activation of presynaptic NMDA receptors and influence synaptic inhibition of Purkinje neurons**. *J Neurosci* 2004, **24**:5659-5669.

80. Fiszman ML, Barberis A, Lu C, Fu Z, Erdelyi F, Szabo G, Vicini S: **NMDA receptors increase the size of GABAergic terminals and enhance GABA release**. *J Neurosci* 2005, **25**:2024-2031.

81. Rodrigo J, Alonso D, Fernandez AP, Serrano J, Richart A, Lopez JC, Santacana M, Martinez-Murillo R, Bentura ML, Ghiglione M *et al.*: **Neuronal and inducible nitric oxide synthase expression and protein nitration in rat cerebellum after oxygen and glucose deprivation**. *Brain Res* 2001, **909**:20-45.

82. Clark BA, Cull-Candy SG: **Activity-dependent recruitment of extrasynaptic NMDA receptor activation at an AMPA receptor-only synapse**. *J Neurosci* 2002, **22**:4428-4436.

83. Isope P, Franconville R, Barbour B, Ascher P: **Repetitive firing of rat cerebellar parallel fibres after a single stimulation**. *J Physiol* 2004, **554**:829-839.

84. Binshtok AM, Fleidervish IA, Sprengel R, Gutnick MJ: **NMDA receptors in layer 4 spiny stellate cells of the mouse barrel cortex contain the NR2C subunit**. *J Neurosci* 2006, **26**:708-715.

85. Kutsuwada T, Kashiwabuchi N, Mori H, Sakimura K, Kushiya E, Araki K, Meguro H, Masaki H, Kumanishi T, Arakawa M *et al.*: **Molecular diversity of the NMDA receptor channel**. *Nature* 1992, **358**:36-41.

86. Monyer H, Burnashev N, Laurie DJ, Sakmann B, Seeburg PH: **Developmental and regional expression in the rat brain and functional properties of four NMDA receptors**. *Neuron* 1994, **12**:529-540.

87. Monyer H, Sprengel R, Schoepfer R, Herb A, Higuchi M, Lomeli H, Burnashev N, Sakmann B, Seeburg PH: **Heteromeric NMDA receptors: molecular and functional distinction of subtypes**. *Science* 1992, **256**:1217-1221.

88. Ishii T, Moriyoshi K, Sugihara H, Sakurada K, Kadotani H, Yokoi M, Akazawa C, Shigemoto R, Mizuno N, Masu M *et al.*: **Molecular characterization of the family of the N-methyl-D-aspartate receptor subunits**. *J Biol Chem* 1993, **268**:2836-2843.

89. Kuner T, Schoepfer R: **Multiple structural elements determine subunit specificity of Mg2+ block in NMDA receptor channels**. *J Neurosci* 1996, **16**:3549-3558.

90. Casado M, Lopez-Guajardo A, Mellstrom B, Naranjo JR, Lerma J: **Functional N-methyl-D-aspartate receptors in clonal rat phaeochromocytoma cells**. *J Physiol* 1996, **490**:391-404.

91. Bardoni R, Torsney C, Tong CK, Prandini M, MacDermott AB: **Presynaptic NMDA receptors modulate glutamate release from primary sensory neurons in rat spinal cord dorsal horn**. *J Neurosci* 2004, **24**:2774-2781.

92. Mameli M, Carta M, Partridge LD, Valenzuela CF: **Neurosteroid-induced plasticity of immature synapses via retrograde modulation of presynaptic NMDA receptors**. *J Neurosci* 2005, **25**:2285-2294.

93. Suarez LM, Suarez F, Del Olmo N, Ruiz M, Gonzalez-Escalada JR, Solis JM: **Presynaptic NMDA autoreceptors facilitate axon excitability: a new molecular target for the anticonvulsant gabapentin**. *Eur J Neurosci* 2005, **21**:197-209.

94. Maeda H, Ellis-Davies GC, Ito K, Miyashita Y, Kasai H: **Supralinear Ca^{2+} signaling by cooperative and mobile Ca^{2+} buffering in Purkinje neurons**. *Neuron* 1999, **24**:989-1002.

95. Watanabe S, Hoffman DA, Migliore M, Johnston D: **Dendritic K^+ channels contribute to spike-timing dependent long-term potentiation in hippocampal pyramidal neurons**. *Proc Natl Acad Sci USA* 2002, **99**:8366-8371.

96. Stuart GJ, Häusser M: **Dendritic coincidence detection of EPSPs and action potentials**. *Nat Neurosci* 2001, **4**:63-71.

97. Pelkey KA, Lavezzari G, Racca C, Roche KW, McBain CJ: **mGluR7 is a metaplastic switch controlling bidirectional plasticity of feedforward inhibition**. *Neuron* 2005, **46**:89-102.

98. • Ronesi J, Gerdeman GL, Lovinger DM: **Disruption of endocannabinoid release and striatal long-term depression by postsynaptic blockade of endocannabinoid membrane transport**. *J Neurosci* 2004, **24**:1673-1679.
The authors show that, in the striatum, endocannabinoids might be released postsynaptically by anandamide membrane transporters. In addition, presynaptic CB1R activation is necessary but not sufficient for striatal LTD, suggesting the simultaneous need for another, unknown signal.

99. Takahashi KA, Linden DJ: **Cannabinoid receptor modulation of synapses received by cerebellar Purkinje cells**. *J Neurophysiol* 2000, **83**:1167-1180.

100. •• Lien CC, Mu Y, Vargas-Caballero M, Poo MM: **Visual stimuli-induced LTD of GABAergic synapses mediated by presynaptic NMDA receptors**. *Nat Neurosci* 2006, **9**:372-380.
The authors show that repetitive light stimuli or theta burst stimulation of the optic nerve in the developing *Xenopus* retinotectal system induces LTP of glutamatergic inputs but LTD of GABAergic inputs to the same tectal neuron. This presynaptically expressed form of LTD relies on presynaptic NMDARs to detect glutamate spillover from retinotectal afferents that is coincident with high frequency GABAergic afferent activity.