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Depressed by learning – heterogeneity of the plasticity rules at parallel fiber synapses onto Purkinje cells

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Abstract

Climbing fiber-driven long-term depression (LTD) of parallel fiber synapses onto cerebellar Purkinje cells has long been investigated as a putative mechanism of motor learning. We recently discovered that the rules governing the induction of LTD at these synapses vary across different regions of the cerebellum. Here, we discuss the design of LTD induction protocols in light of this heterogeneity in plasticity rules. The analytical advantages of the cerebellum provide an opportunity to develop a deeper understanding of how the specific plasticity rules at synapses support the implementation of learning.

Main text

Nearly half a century ago, Marr, Albus, and Ito proposed a model of cerebellum-dependent learning, wherein Climbing fibers carry instructive signals that guide plasticity at the parallel fiber synapses onto Purkinje cells [1–3]. A decade later, Ito and colleagues demonstrated that Climbing fiber activation could trigger long-term depression (LTD) at conjunctively activated parallel-fiber synapses [4,5]. Since then, the idea that the cerebellum learns by sculpting away synapses that cause errors through this anti-Hebbian form of synaptic plasticity has had a powerful influence on the cerebellar field. LTD and its links to cerebellum-dependent learning have been extensively investigated, yet there is still much disagreement about whether and how LTD at parallel fiber-to-Purkinje cell synapses contributes to learning [6,7,16–25,8,26–30,9–15]. Here, we review findings that suggest a path toward a Clearer and more sophisticated understanding of the contribution of LTD to cerebellum-dependent learning.

A variety of recording, stimulation and perturbation approaches have yielded considerable, convergent evidence for a role of LTD in learning [10,11,37–46,15,18,31–36] but also yielded results that call into question the necessity of parallel fiber-to-Purkinje cell LTD for

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learning [13,40,41,47–49]. One of the most widely used experimental approaches has been to employ pharmacological or molecular-genetic techniques to perturb LTD, and then test the effects on one or more cerebellum-dependent learning tasks. Results obtained with this approach have been mixed in their support for a role of LTD in learning. There are a number of potential reasons for the lack of consistent findings on the link between LTD and learning, including potential off-target effects of the manipulations used to perturb LTD (see discussion in Schonewille et al., 2011), compensation for LTD deficits by other forms of plasticity [8], and selective contribution of LTD to certain cerebellar leaning tasks and not others [7,40,41,50]. Here, we focus on one specific challenge in connecting *in vitro* LTD results and *in vivo* learning results, which was highlighted by two recent studies [51,52], namely the lack of a single, definitive protocol for studying LTD *in vitro*, and our rudimentary understanding of the sensitivity of LTD to variations in the protocols used to induce LTD.

Over the years, LTD at parallel fiber-to-Purkinje cell synapses has been studied using a wide range of induction protocols (see Table 1 for a representative sample of LTD protocols), which have generally been treated as equivalent. However, a recent study [51, see also 53] demonstrated that the measurement of LTD impairments can be highly sensitive to the parameters used for LTD induction. Four different LTD induction protocols, which all induced significant LTD in wild type mice, were used to study two lines of mice that had previously been reported as having normal cerebellum-dependent learning despite a lack of LTD [13]. When tested with different LTD induction protocols, the same line of mice could exhibit everything from considerable sparing of LTD to near-total perturbation of LTD. The demonstration that one can get different answers about whether and how much LTD is impaired, depending on the protocol used to study LTD makes it tempting to ask what is the “correct”, “physiological”, or “behaviorally relevant” protocol for testing LTD. However, another recent study illustrates that this question is unlikely to have a single or straightforward answer.

Suvrathan and colleagues discovered that the requirements for the induction of plasticity at the parallel fiber-to-Purkinje cell synapses can vary across regions of cerebellum, and even between nearby Purkinje cells within a region [52]. More specifically, there is heterogeneity in the optimal parallel fiber – Climbing fiber pairing interval for inducing LTD at parallel fiber synapses onto Purkinje cells in different regions of the cerebellum. The timing requirements for inducing LTD in the flocculus, the region of the cerebellum that supports oculomotor learning, are strikingly different from the timing requirements in the well-studied vermis. In the flocculus, LTD is only induced if the delay between parallel fiber and Climbing fiber activation is matched to the feedback delay for Climbing fibers to signal errors *in vivo* during oculomotor learning, which is approximately 120 ms (Fig. 1) [52,54,55]. Moreover, this delay must be precise to within a few tens of milliseconds to be effective in driving LTD. The 120-ms feedback delay in the flocculus is relatively long, because the error signals are visual, and visual processing is slow compared to other sensory modalities such as somatosensation. Crucially, in the vermis, which supports different behaviors and thus receives error signals from the Climbing fibers of different modalities and different delays, the associative synaptic depression has different timing requirements. An important direction for future research will be to test the match between the feedback

delays and the timing requirements for LTD in different Purkinje cells of the vermis. Mechanistically, there are known molecular differences between Purkinje cells [56], which could potentially support the tuning of plasticity to the appropriate Climbing fiber delay, however the molecular mechanism for the temporal tuning of LTD has not yet been identified. These findings demonstrate that the rules governing the induction of LTD are not uniform across all parallel fiber-to-Purkinje cell synapses, but rather appear to be locally tuned to the functional requirements of the circuit for a specific behavior. Conversely, a single LTD induction protocol can vary in its effectiveness for inducing LTD in different cerebellar regions [57].

The demonstration of heterogeneity in the optimal pairing interval for LTD of parallel fiber-to-Purkinje cell synapses in different regions of the cerebellum opens up the possibility that there may be heterogeneity in other aspects of the LTD learning rule as well. Might there also be regional tuning of the LTD rule to the typical patterns of parallel fiber activation, Climbing fiber activation, or the inhibitory or neuromodulatory tone in different cerebellar microcircuits? In a “standard” LTD experiment, the slice physiologist must make choices related to all of these factors (Table 1). Below, we consider some of the findings that can inform these decisions about experimental design (Fig. 2).

Biologically plausible variations that may influence the induction of LTD

Parallel fiber activation

In vitro, LTD can be induced by pairing Climbing fiber stimulation with either a single stimulus to the parallel fibers, or a brief, high frequency train of parallel fiber activation (Table 1). Many influential studies have used single parallel fiber stimulation during LTD induction [13,31,58–62]. Yet, there is evidence that metabotropic glutamate receptors (mGluRs) contribute to motor learning and to LTD [46,63,64], and mGluR activation requires multiple parallel fiber stimuli at high frequency [65,66]. Also, stimulation of parallel fibers either in larger numbers or at a higher frequency can overcome the necessity for Climbing fiber co-activation [67,68].

The *in vivo* data currently available do not provide strong guidance for the *in vitro* physiologist’s choice of parallel fiber stimulation parameters for studying LTD. Our knowledge about the natural patterns of activity in the parallel fibers *in vivo* during learning is extremely limited, because of technical difficulties in recording from the small, densely packed granule cells, whose axons form the parallel fibers. In anesthetized animals, granule cells were reported to be largely silent, and emit brief, high-frequency bursts of spikes in response to a punctate whisker stimulus [69,70], whereas a study in decerebrate animals found more sustained granule cell spiking in response to a more sustained somatosensory stimulus (cutaneous forepaw stimulus; [71]). In the vestibulocerebellum, granule cells exhibit a range of responses to vestibular stimuli, including high-frequency bursts of spikes, sustained firing with smooth firing rate modulation in response to the vestibular stimulus, or, in some granule cells, a combination of both response types [72]. Likewise, calcium imaging studies suggest that many granule cells have high levels of sustained activity in awake behaving animals [73–75], although this approach does not provide spike-level resolution of granule cell activity.

Another variable in studies of LTD that is not well constrained by *in vivo* data is the number of co-activated parallel fiber inputs to a given Purkinje cell. A prominent and compelling theory proposes sparse coding of information by granule cells [76–79]. However, recent imaging studies challenge the hypothesis that activation of the granule cell population is sparse in behaving animals [73,74,80,81]. *In vitro*, the number of co-activated parallel fibers, which can be controlled by the strength of parallel fiber stimulation, can influence whether LTD is induced or not [67,68], suggesting that cooperativity at parallel fiber synapses is an important consideration. However, the mechanisms underlying LTD induced by stimulation of multiple parallel fiber inputs vs. a few inputs may be different [82]. Distant parallel fiber synapses that are not activated during LTD induction, do not undergo modification [4,83–86]. LTD does seem to spread to nearby synapses [61,67,87], however, LTD at synapses that were not paired with Climbing fiber stimulation appears to involve different mechanisms [88,89].

Thus, *in vivo*, during learning, there may be considerable heterogeneity in the patterning and overall rate of firing in individual granule cells, from mostly silent with an occasional burst of spikes, to tonically firing [75,90–92]. Likewise, there may be heterogeneity in the level of parallel fiber co-activation. This heterogeneity of parallel fiber activity patterns could influence the likelihood of LTD induction at parallel fiber synapses in different cerebellar regions. Alternatively, the parallel fiber activation requirements for LTD in different cerebellar regions may be *tuned* to the relevant patterns of parallel fiber activity, as observed for the parallel fiber-Climbing fiber pairing interval [52].

Climbing fiber activation

A spike in a Climbing fiber triggers a characteristic “complex spike” in its Purkinje cell targets, which is associated with a prolonged calcium transient [93–98]. Historically, the Climbing fiber-triggered calcium transient in the Purkinje cell was considered a binary, all-or-none error signal, and many of the seminal studies of LTD used depolarization of the Purkinje cell and the resulting calcium entry through voltage-gated calcium channels as a substitute for Climbing fiber-induced calcium entry (Table 1). However, more recent studies have suggested that the calcium transient produced by the Climbing fiber and its efficacy at inducing LTD is graded. The efficacy of LTD induction is strongly correlated with the amount of calcium influx during induction [11,82,99–102]. In slice preparations, the number of spikes in a Climbing fiber burst affects the likelihood of LTD induction [103]. Moreover, *in vivo*, the duration of the Climbing fiber-triggered complex spike in a Purkinje cell is correlated with the amount of single-trial plasticity [104]. Thus, the choice of Climbing fiber stimulation parameters for studying LTD is a critical one, and, like the parameters of parallel fiber activity, can vary *in vivo*, even from trial to trial in the same cell.

Number and frequency of parallel fiber-Climbing fiber pairings

The number and frequency of parallel fiber-Climbing fiber pairings have varied across studies of cerebellar LTD, but a common choice is 300 pairings at 1 Hz (Table 1). This choice has similarities and differences with the number and frequency of behavioral training trials typically used to induce cerebellum-dependent learning, which develops over hundreds of training trials. For example, a typical oculomotor learning experiment might pair 1 Hz

sinusoidal vestibular and visual stimuli, with learning developing over 30–60 min of training, for a total of approximately 2000–3000 stimulus cycles, or "trials" [7,13,35,37,105,106]. An eyeblink conditioning procedure may include 100 trials per session, with learning developing over 5–10 sessions, delivered over multiple days, for a total of about 1000 trials [107,108]. Thus, the number of pairings used in a typical LTD experiment is on the low end of the number of behavioral pairings used to induce cerebellum-dependent learning, and, not surprisingly, a greater number of pairings is more effective at inducing LTD [85]. In terms of the spacing between pairings, the 1 Hz frequency typical in LTD experiments is in the range used in oculomotor learning, but the inter-trial interval used in eyeblink conditioning is typically much longer, in the range of tens of seconds between trials within a session and 24 hours between sessions.

Notably, plasticity at parallel fiber-to-Purkinje cell synapses can be triggered not only by repeated parallel fiber-Climbing fiber pairings, as discussed above, but also by the extreme case of a single parallel fiber-Climbing fiber pairing [52], and similar single-trial plasticity has been observed *in vivo* [20,41,104,109,110]. In the flocculus, the properties of short-term, single-trial associative synaptic depression has striking parallels with those of LTD, including tight tuning for the functionally relevant Climbing fiber delay [52]. The molecular mechanisms of short-term associative depression induced by one or a few pairings are not well understood, and may be different from those of LTD [111].

Inhibition and other heterosynaptic modulatory influences

In order to isolate plasticity at the parallel fiber-to-Purkinje cell synapses from plasticity occurring at the synapses of inhibitory interneurons, most investigations of LTD are performed with GABAergic transmission blocked. However, there are some notable exceptions (see Table 1, seventh column). Whereas some studies [83,88,89] suggest that LTD can only be induced in the absence of GABAergic inhibition, successful LTD induction has been reported without a block of GABAergic inhibition (Table 1, [4,60,82,112]). Some investigators have suggested that the study of LTD with inhibition blocked is "unphysiological", however, another interpretation is that *in vivo*, the induction of LTD requires a transient reduction in the level of inhibitory input to the Purkinje cell from the molecular layer interneurons. Moreover, there could be additional factors gating the induction of LTD by paired activation of parallel fibers and Climbing fibers [41,113]. Neuromodulators, such as acetylcholine and norepinephrine, which are known to influence associative synaptic plasticity in other brain areas [114–117], are also present in the cerebellum

Implications for future research

For years, the study of synaptic plasticity *in vitro*, in the cerebellum and other brain areas, focused on uncovering the cellular-molecular mechanisms. Driven by this goal, the protocols for inducing plasticity were selected mainly to optimize their reliability at inducing synaptic changes, and thereby facilitate the analysis of underlying cellular-molecular processes. More recently, there has been renewed effort to establish more direct, causal links between specific synaptic plasticity mechanisms and learning. In the cerebellar field, this has prompted

consideration of how to design studies of LTD *in vitro* to facilitate this goal. The synaptic physiologist must make many choices, as outlined above. There have been attempts to make choices that recreate some of the specific conditions that are present *in vivo* [52,68,112]. However, our lack of knowledge about what exactly these conditions are during learning remains a challenge. Moreover, the conditions *in vitro* will always, by definition, differ in certain respects from those *in vivo* (let's not forget that we are removing a piece of a neural circuit from the brain, and that the strength of reduced preparations is the ability to create simplified and more controlled conditions). The vexed question of which protocol, within the intimidatingly large parameter space, to use for induction of LTD is further complicated by heterogeneity in the plasticity rules operating at different parallel fiber-to-Purkinje cell synapses [51], and the possibility that there could be multiple heterosynaptic influences that govern the induction of LTD, in addition to the patterns of parallel fiber and Climbing fiber activation. Hence, there is no single, straightforward answer to the question of the most appropriate way to conduct LTD experiments in slice—there is no one-size-fits-all "standard" protocol. Nor is it possible for every study to explore the relevant parameter space. This represents both a significant challenge and a major opportunity.

The complexity and heterogeneity of learning rules identified at the parallel fiber-to-Purkinje cell synapses in the cerebellum may reflect a broader principle of how learning is implemented throughout the brain. The cerebellum is described as having the most uniform, "crystalline" cytoarchitecture in the mammalian brain. If there is heterogeneity of synaptic learning rules in this context, it seems likely that this is a more widespread property of synaptic plasticity, and there are already suggestions of this in other brain areas [118–121]. Exploration of the large parameter space and potential interactions between parameters governing the induction of plasticity at any type of synapse in the brain represents a major undertaking that will take years of effort by multiple labs. The cerebellum, with its relatively simple circuit architecture and its support of a number of simple and analytically tractable behaviors, offers unique opportunities to make sense of this newly recognized complexity of synaptic plasticity rules [51, 52], and to establish how the brain utilizes this complexity in the service of learning. The discovery of the tuning of LTD for different parallel fiber-Climbing fiber intervals illustrates how existing knowledge of the broader circuits supporting simple cerebellum-dependent forms of learning can be leveraged to inform experimental manipulations *in vitro* that can uncover new features of synaptic learning rules. Moreover, we can draw on a vast literature on the molecular mechanisms that support parallel fiber-to-Purkinje cell LTD [10,11,38,39,44,106,122,18,31–37], and on the heterogeneity of Purkinje cells [123,124,133–137,125–132]. Thus, studies of plasticity at the cerebellar Purkinje cells' synapses offers unique insights and opportunities to move beyond broad concepts of Hebbian and anti-Hebbian plasticity to a more sophisticated understanding of the complex rules governing plasticity at synapses in a behaving animal undergoing learning.

In summary, recent findings on novel features of the rules governing synaptic plasticity in the cerebellum force us to consider the role of heterogeneity in the properties of LTD at parallel fiber-to-Purkinje cell synapses. This heterogeneity has been observed in the sensitivity to one key parameter of the protocols that induce LTD, the pairing interval; however, there are other relevant variables that may also show heterogeneous properties.

Rather than considering this explosion of parameter space as a problem, we suggest that it may provide an opportunity, given the unique properties of the cerebellum and cerebellum-dependent behavior, to better understand the logic of how the recruitment of synaptic plasticity is precisely controlled during learning.

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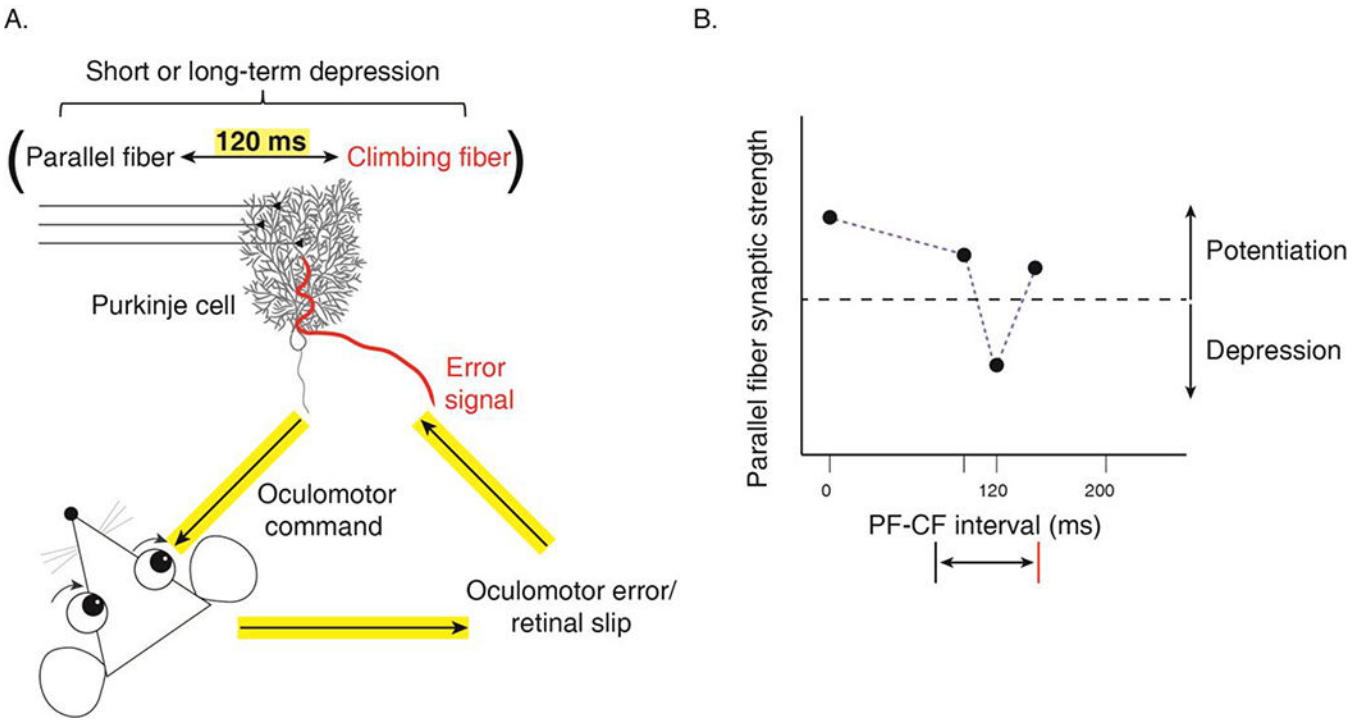

Figure 1.

A. The optimal parallel fiber – Climbing fiber (PF-CF) pairing interval for induction of plasticity at parallel fiber-to-Purkinje cell synapses in the cerebellar flocculus is 120 ms, which is the feedback delay for Climbing fibers to signal an error during oculomotor learning. B. Schematic illustrating the tuning of LTD at parallel fiber-to-Purkinje cell synapses in the flocculus to a Climbing fiber delay of 120 ms (Schematic adapted from Suvrathan et al., *Neuron*, 2016).

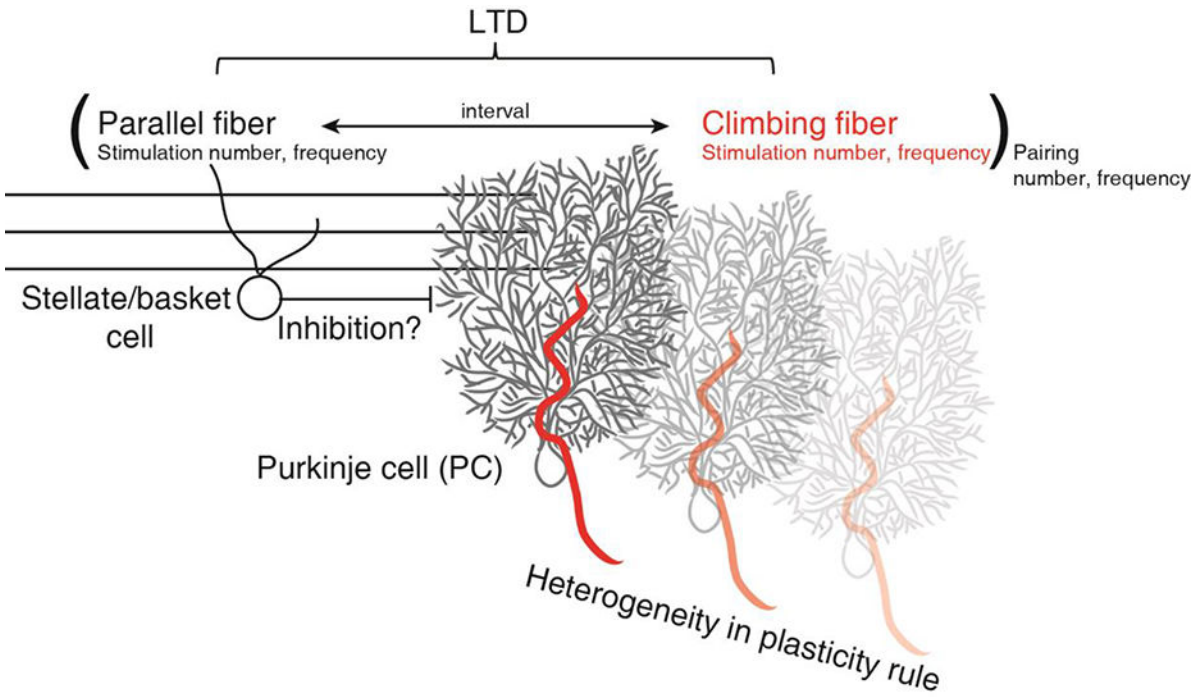

Figure 2.

LTD is a function of the frequency and number of parallel fiber and Climbing fiber stimuli, the parallel fiber-Climbing fiber pairing interval, and the frequency and number of pairings: LTD(PF-to-PC) = f([PF(n)(ν) $\xrightarrow{t}$ CF(n)(ν)] (n)(ν)), where n = number of stimuli or pairings, ν = frequency, t = PF-to-CF time nterval. The role played by inhibition and neuromodulators remains unclear. There is also heterogeneity in the plasticity rules implemented at the parallel fiber synapses onto different Purkinje cells.

Table 1.

Representative stimulation protocols which have been used to induce long term depression at parallel fiber-to-Purkinje cell synapses. The pairing of parallel fibers (PF, black) and Climbing fibers (CF, red) is schematized in the first column, with each stimulus shown as a line. The time between stimuli is not drawn to scale. The following columns describe the parameters of the parallel fiber and Climbing fiber stimuli and the pairings between them, the region of the cerebellum where the investigation was conducted, and the presence or absence of blockers of inhibition [5,13,61,62,68,82–85,102,138,139,31,140–149,34,150,151,51,52,57–60].

Pairing protocol [1]	PF	CF	Pairing interval	Number and frequency of pairings	Location	$GABA_A$ block	Reference
PF CF	Single	Single	PF 250 ms before CF optimal	100 pairings at 1 Hz	Vermis	No,Yes [2]	Chen & Thompson, *Learn Memory*, 1995
PF CF	5 at 100 Hz	Single	PF 150 ms before CF	50 pairings at 0.5 Hz	Unspecified	No	Wang, Denk, Hausser, *Nat.Neurosc.*, 2000
PF CF	8 at 100 Hz	Single	PF 120-150 ms before CF	300 pairings at 1 Hz	Vermis	Yes	Piochon et al., *J.Neurosci.*, 2010
PF CF or	Single/ 5 at 100 Hz	Single	PF 120 ms before CF optimal	300 pairings at 1 Hz	Flocculus	Yes	Suvrathan et al., *Neuron*, 2016
PF CF	7 at 100 Hz	Single	Variable, ~80 ms PF-CF optimal	30 pairings at 0.1 Hz	Vermis	Yes	Safo & Regehr, *Neuropharmacology*, 2008
PF CF	10 at 100 Hz, single	2 at 20 Hz, single	PF before CF, coincident	30 pairings at 0.1 Hz, 300 pairings at 1Hz	Vermis	Yes	Safo & Regehr, *Neuron*, 2005
PF CF	8 at 100 Hz	3 at 20 Hz	CF at end of PF stim (80 ms from start of PF stim)	20 pairings at 0.025-0.033 Hz	Vermis	Yes	Schreurs et al., *J.Neurophysiol.*, 1996
PF CF	8 at 100 Hz	3 at 20 Hz	CF at end of PF stim.	20 pairings at 0.025-0.05 Hz	near Ipsilateral HVI	No	Schreurs et al., *J.Neurophysiol.*, 1997
PF CF	10 at 100 Hz	2 at 20 Hz	PF before CF	30 pairings, at 0.1 Hz	Vermis	Yes	Carey et al., *J.Neurophysiol.*, 2011
PF depol.	10 at 100 Hz	0mV for 100 ms	Coincident	60 pairings at 0.5 Hz	Vermis lbl. III, X	Yes	Wadiche & Jahr, *Nat.Neurosci.*, 2005
PF depol.	Single	0mV, 200 ms	Coincident	300 pairings at 1 Hz	Unspecified	Yes	Tanaka & Augustine, *Neuron*, 2008
PF depol.	900 at 1 Hz	Depol., 15 min	Coincident	15 min pairing	Vermis, lbl.IX, X	Yes	Crepel & Jaillard, *J.Physiol.*, 1991
PF depol.	150 at 0.5 Hz	-10 mV Depol., 5 min	Coincident	5 min pairing	Unspecified	Yes	Mark et al., *J.Neurosci.*, 2015
PF depol.	60 at 1 Hz	Depol., 1 min + depol. steps	Coincident	2 pairings, 5 min apart	Vermis	Yes	Goossens et al., *J.Neurosci.*, 2001
Agonist CF	2-5 s GluR agonist	2 Hz, Inf.Olive	Coincident	Inf.Ol. for 5 s, 5 s off, for 4 min	Drsl. paraflocculus [3]	No	Kano & Kato, *Nature*, 1987
Glutamate depol.	Glutamate	0mV for 3 s	Coincident	6 pairings	Cell Culture	Yes	Linden, *J.Neurophysiol.*, 2012
PF CF	20 Hz, vest. nerve, glutamate	4 Hz, Inf.Olive	Coincident	Pairing for 25s	Flocculus [3]	No	Ito et al., *J.Physiol.*, 1982
PF CF or or coterminating trains	Single,40 at 100 Hz	Single,2 at10 Hz	PF 20/50 ms CF, CF 50 ms PF, Coterminating	120 pairings at 4 Hz, [4] 20 pairings at 0.017-0.033 Hz	Vermis	Yes, no	Schreurs & Alkon, *Brain Research*, 1993
PF CF	Single,5 at 100 Hz	Single, 5 at 100 Hz	Varied	300 pairings at 1 Hz effective	Vermis, lbl V	Yes	Karachot et al., *Neurosc. Res.*, 1994
PF CF	Single	Single	PF 1 ms before CF	100-300 pairings at 1 Hz	Vermis	Yes	Mittmann & Hausser, *J.Neurosci.*, 2007
PF CF	Single	Single	Coincident	300 pairings at 1 Hz	Vermis	Yes	Coesmans et al., *Neuron*, 2004
PF CF	Single	Single	Coincident	300 pairings at 1 Hz	Vermis	Yes	Hansel et al., *Neuron*, 2006
PF CF	Single	Single	Coincident	8 pairings at 1 Hz	Unspecified	No	Konnerth et al., *PNAS*, 1992
PF CF	Single	Single	Coincident	300 pairings at 1 Hz	Vermis	Yes	Reynolds & Hartell, *J.Physiol.*, 2000
PF CF	Single	Single	Coincident	300 pairings at 1 Hz	Vermis	Yes	Schonewille et al., *Neuron*, 2011
PF CF	Single	Single	Coincident	300 pairings at 1 Hz	Vermis	Yes	Belmeguenai et al., *J. Neurophysiol.*, 2008
PF CF	Single	Single	Coincident + 1ms (model)	300 pairings at 1 Hz	Vermis	Yes	Steuber et al., *Neuron*, 2007
PF CF or or or	Single, 2 at 20 Hz, 5 at 100 Hz	Single/50 ms depol.	Coincident, CF at end of PF stim	300/180 at 1 Hz, 90 at 0.5 Hz	Vermis	Yes	Yamaguchi et al., *PNAS*, 2016
PF CF	Single	Single	CF 5 to 12 ms before PF	120-480 pairings at 4 Hz	Post. vermis, [3] Drsl paraflocculus	No	Ito & Kano, *Neurosc. Lttrs.*, 1982
PF CF	Single	Single	CF 10 ms before PF	100 pairings at 4 Hz	Nodulus, uvula	Yes	Sakurai, *J.Physiol.*, 1987
PF CF	Single	Single	CF 20 ms before PF	960 pairings at 2 Hz	Drsl. paraflocculus [3]	No	Ekerot & Kano, *Brain Res.*, 1985
PF CF	Single	Single	Varied, CF before PF	960 at1 Hz/ 2 Hz, 240 at 4 Hz	Drsl. paraflocculus [3]	No	Ekerot & Kano, *Neurosc. Res.*, 1989

[1] In order of increasing PF-CF interval.

[2] 100 coincident pairings only effective with GABA block, 600 pairings effective at all tested intervals including CF before PF.

[3] Not in slice preparation.

[4] with trains unpaired stimulation causes LTD