Distributed synergistic plasticity and cerebellar learning

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Abstract | Studies on synaptic plasticity in the context of learning have been dominated by the view that a single, particular type of plasticity forms the underlying mechanism for a particular type of learning. However, emerging evidence shows that many forms of synaptic and intrinsic plasticity at different sites are induced conjunctively during procedural memory formation in the cerebellum. Here, we review the main forms of long-term plasticity in the cerebellar cortex that underlie motor learning. We propose that the different forms of plasticity in the granular layer and the molecular layer operate synergistically in a temporally and spatially distributed manner, so as to ultimately create optimal output for behaviour.

Intrinsic plasticity
Modification of a neuron's intrinsic electrical properties through changes in ion channel expression and properties in the neuron membrane. It can be induced by either neuronal spiking activity or synaptic inputs.

Motor performance
Baseline performance of movements. It corresponds to the absolute amplitude (gain) and timing (phase) values of the movements before any training paradigm has taken place.

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Historically, declarative and procedural memory formations in cortical structures have been proposed to be predominantly mediated by a specific form of plasticity. Long-term potentiation (LTP) at synapses of CA3 axons onto CA1 pyramidal cells was originally considered the sole substrate for hippocampal learning[1], whereas long-term depression (LTD) at the parallel fibre–Purkinje cell synapse has been proposed to be the dominant type of plasticity for cerebellar learning[2]. However, different forms of plasticity can occur at multiple synaptic and extrasynaptic sites within the same network and serve complementary or overlapping functions. For example, evidence is now emerging that LTD in the hippocampus and intrinsic plasticity in the cerebral cortex are likely to contribute to particular components of spatial and visual learning[3–8]. Likewise, procedural memory formation, which underlies the coordination of movements, may be mediated by multiple forms of plasticity, including those occurring in the cerebellum[9–12].

Neurons in the cerebellar cortex and neurons in cerebellar and vestibular nuclei show various forms of synaptic and intrinsic plasticity[13–15], and neurons in both regions are innervated by axons from the mossy fibre and climbing fibre system (BOX 1). This raises the possibility that the various forms of plasticity induced in the cerebellar cortex and nuclei are not independent but are finely regulated in a coordinated manner[16,17], and that some of the memories that are formed in the cerebellar cortex are also ultimately consolidated and stored in the cerebellar and vestibular nuclei[17–19]. Cerebellar research has benefited from discoveries of cell-specific promoters for the neurons that form the main chain of information through the different layers in the cerebellar cortex. These include both the promoter for the GABA type A ($GABA_A$) receptor α_6 subunit, which is specific for cerebellar granule cells[20] and the protein PCP2 promoter L7, which is specific for Purkinje cells[21]. These tools have enabled the creation of transgenic animals with cell-specific deletions in the granular or molecular layer. As a result, one can specifically and directly manipulate the output of the granule cells and Purkinje cells themselves[22–24]. Moreover, by manipulating postsynaptic receptors and/or second messenger systems inside these cells, one can in effect also make a specific interruption of the output of presynaptic interneurons involved[25].

Here, we review the main forms of plasticity that have been described for neurons in the granular and molecular layers of the cerebellar cortex and address their potential roles in motor performance, motor learning and motor consolidation, which have been deduced from phenotypic analyses of mouse mutants. We focus mainly on forms of long-term synaptic and intrinsic plasticity, as the evidence for their role in cerebellar motor learning is relatively robust; the various forms of short-term presynaptic plasticity that occur in the cerebellar cortex may also contribute to learning[26], but direct correlations between the two remain to be shown, and we therefore restrict ourselves in most cases to listing their characteristics (TABLE 1). We use compensatory eye movements — specifically, the control of the amplitude (that is, gain) and the timing (that is, phase) of the vestibulo-ocular reflex (VOR) — as the main model system to discuss the functional implications of different forms of plasticity, as this is the system in which cerebellar genetics, cell physiology, systems electrophysiology and behavioural studies have been extensively combined[23,27,28].

Motor learning
Adaptation of the amplitude (gain) and/or timing (phase) of movements following a training paradigm; typical forms of cerebellar motor learning paradigms include adaptation of the vestibulo-ocular reflex and eyeblink conditioning.

Plasticity in the granule cell network

Mossy fibre–granule cell synapses. Mossy fibres are derived from various brainstem nuclei[29]. A single mossy fibre can divide across different folia into multiple branches, each of which provides multiple rosettes; a single mossy fibre rosette provides excitatory input to tens of granule cells within a glomerulus[30]. In addition to short-term plasticity (TABLE 1), the mossy fibre–granule cell synapse undergoes both LTP and LTD. Mossy fibre–granule cell LTP is presynaptic, is dependent on activation of postsynaptic NMDA receptors (NMDARs) and metabotropic glutamate receptors (mGluRs) and can be reversed by presynaptic LTD[31,32]. LTP and LTD both depend on persistent presynaptic activity and subsequent Ca^{2+} influx in the postsynaptic granule cell[33] (FIG. 1). Activation of α7 nicotinic acetylcholine receptors

Box 1 | Layered character of the cerebellum and its position in the brain

Although voluntary and involuntary movements can be initiated without a cerebellum, the proper execution of movements as well as their adaptive modification and possibly cognitive preparation require an intact cerebellum[16]. This accords with the position and connectivity of the cerebellum: it is superimposed on, but not an essential part of, the brain systems that are required for the initiation and occurrence of movements (see the figure, part **a**). The cerebellum itself is composed of layered networks (see the figure, part **b**): first, the cerebellar cortex is superimposed on cerebellar and vestibular nuclei, to which it projects and via which it exerts all its effects; second, the granular layer of the cerebellar cortex contains the mossy fibre (MF)–granule cell (GrC) pathway on which Golgi cells (GoCs) and unipolar brush cells (UBCs) (both interneurons) are superimposed[158]; third, in the molecular layer, another group of interneurons (molecular layer interneurons (MLIs)), which is formed by stellate cells and basket cells, is superimposed on Purkinje cells (PCs)[159]; and last, the cerebellar cortex contains a type of interneuron, the Lugaro cell (LC), which is superimposed on all other types of interneurons in both the granular and molecular layers[158]. Because of the layered character of its networks, the cerebellar cortex is well suited to be dissected into cellular components so that their individual functional contributions within the networks can be analysed. Such an approach follows the concept that during CNS evolution the implementation of new functions involves imposing new networks onto existing circuitries and/or expanding existing circuitries[160,161]. Specific functions may thus be attributed to separate network layers in the cerebellar cortex and their target neurons in cerebellar and vestibular nuclei. In part **a**, pathways directly involved in olivocerebellar processing are shown in individual colours, and other pathways are indicated in dark grey. MFs (brown) and climbing fibres (CFs) (yellow) convey their input to both the nuclei and cortex of the cerebellum. PCs in turn project from the cerebellar cortex to the cerebellar and vestibular nuclei (blue). From these nuclei, projections are provided to the inferior olive for inhibitory feedback (red) and to other extracerebellar sites for control of motor behaviour and/or cognitive functions (green). The direct projections in the figure from the cerebellar and vestibular nuclei to the motor nuclei reflect the direct projections towards the oculomotor nuclei; direct connections to other motor nuclei have so far not been identified. In part **b**, excitatory and inhibitory synaptic connections are indicated by '+' and '–', respectively. The cerebellar cortex has many potential sites for synaptic plasticity at both excitatory and inhibitory terminals, but it may also regulate plasticity downstream in the cerebellar and vestibular nuclei. In general, deficits in motor consolidation, motor learning and motor performance result from mild, mediocre and severe problems in cerebellar function, respectively[16]. Thus, the larger the number of sites of synaptic plasticity are affected in the cerebellar circuitry, the more severe the impairment in motor function. PF, parallel fibre.

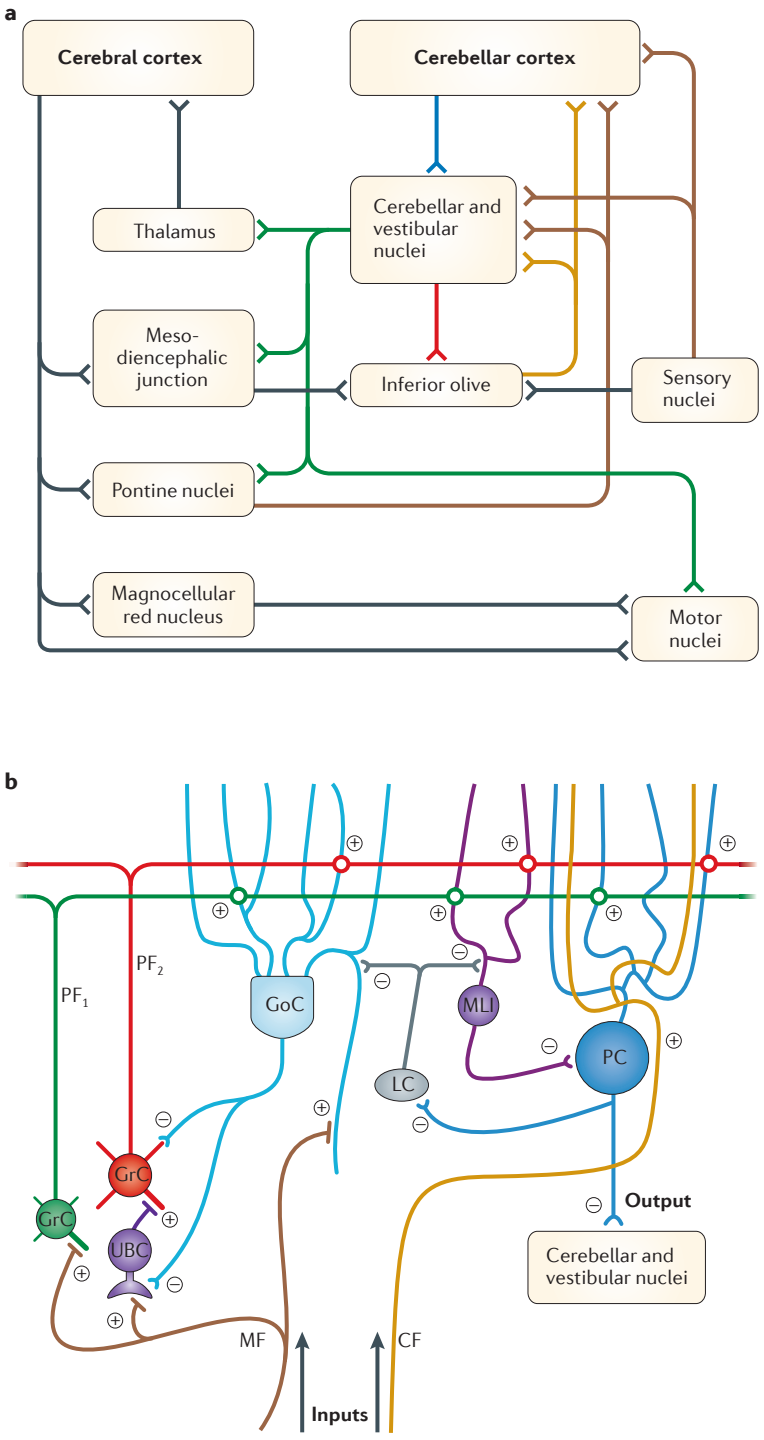


Table 1 | **Summary of all forms of short-term and long-term plasticity in cerebellar cortex**

Cell type	Synapse	Main receptors	Short-term plasticity	Key cascades	Selective refs	Long-term plasticity	Pre- or post-synaptic?	Typical protocol	Key cascades	Selective refs
Granule cell (GrC)	Golgi–GrC	$GABA_A$	Depression	$GABA_B$, mGluR	162	NA	NA	NA	NA	NA
	MF–GrC	AMPA, NMDA	Depression	$GABA_B$, mGluR	163–166	↑LTP, ↓LTD	Pre	MF burst, long	NMDAR, PKA	167
	UBC–GrC	AMPA, NMDA	NA	NA	NA	NA	Pre	MF burst, short	NMDAR, PKA	31,33
	Intrinsic excitability		NA	NA	NA	↑IP	NA	MF burst	NMDAR, PKA	37
Golgi cell (GoC)	PF–GoC	AMPA, NMDA, kainate	No PTP	NA	168	↓LTD	Post	100 Hz PF	PKA, mGluR2	42
	MF–GoC	AMPA, NMDA	NA	NA	NA	NA	NA	NA	NA	NA
	CF–GoC	mGluR2	NA	NA	NA	NA	NA	NA	NA	NA
	Lugaro–GoC	$GABA_A$, glycine	NA	NA	NA	NA	NA	NA	NA	NA
	GoC–GoC	$GABA_A$	NA	NA	NA	NA	NA	NA	NA	NA
	Intrinsic excitability		NA	NA	NA	NA	NA	NA	NA	NA
Unipolar brush cell (UBC)	GoC–UBC	$GABA_A$, glycine	NA	NA	NA	NA	NA	NA	NA	NA
	MF–UBC	AMPA, NMDA	PPF, PPD	NA	64	NA	NA	NA	NA	NA
Purkinje cell (PC)	PF–PC	AMPA	SSE, DSE	eCB	169,170	↑LTP	Pre	4–8 Hz PF	cAMP, PKA	12
						↓LTD	Pre	4 Hz PF	CB1R, NMDA	11
						↑LTP	Post	1 Hz PF	PP, NSF, NO	76, 77
						↓LTD	Post	1 Hz PF+CF	PKC, PICK1, PKA, PKG, CaMKII, CRF NMDAR, mGluR	2,84,93, 96,99, 171,172
	MLI–PC	$GABA_A$	DSI	eCB	173,174	↑RP	Post	CF stimu, PF depo	CaMKII	125,126
						↓LTD	NA	1 Hz MLI+CF	NA	175
						↑DPI	Pre	CF stimu, PC depo	NMDAR	176
	CF–PC	AMPA, NMDA	DSE	eCB	169,177	↑LTP, ↓LTD	Pre	5 Hz CF	Post Ca^{2+}	23
						↑LTP	Post	PC+CF	Post Ca^{2+}	178
						↓LTD	Post	5 Hz CF	mGluR, PKA, PKC, CRF	179
	Intrinsic excitability		NA	NA	NA	↑IP	NA	1–100 Hz PF	PKA, SK, CK2, PP2B	9,180
Molecular layer interneuron (MLI)	MLI–MLI	$GABA_A$	NA	NA	NA	↑LTP	Pre	100 Hz PF	NMDAR, PKA	181
	PF–MLI	AMPA, NMDA	SSE, DSE	eCB	122, 170	↑LTP	Pre	8 Hz PF	PKA, cAMP	111
						↓LTD	Pre	30 Hz PF	mGluR1, CB1R	113
						↑LTP, ↓LTD	Post	2–4 Hz PF	NO, mGluR, cAMP	112
	Lugaro–MLI	$GABA_A$	NA	NA	NA	NA	NA	NA	NA	NA
	Intrinsic excitability		NA	NA	NA	NA	NA	NA	NA	NA

CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; cAMP, cyclic AMP; CB1R, cannabinoid 1 receptor; CF, climbing fibre; CK2, casein kinase 2; CRF, corticotropin-releasing factor; depo, depolarization; DSE, depolarization-induced suppression of excitation; DSI, depolarization-induced suppression of inhibition; eCB, endocannabinoid; $GABA_A$, GABA type A; $GABA_B$, GABA type B; IP, intrinsic plasticity; LTD, long-term depression; LTP, long-term potentiation; MF, mossy fibre; mGluR, metabotropic glutamate receptor; NA,not applicable; NMDAR, NMDA receptor; NO, nitric oxide; NSF, *N*-ethylmaleimide-sensitive factor; PICK1, protein-interacting with C kinase 1; PKA, cAMP-dependent protein kinase; PKC, protein kinase C; PKG, cyclic guanylate monophosphate-dependent protein kinase; PF, parallel fibre; PP, protein phosphatase; PP2B, protein phosphatase 2B; PPD, pair-pulse depression; PPF, pair-pulse facilitation; PTP, post-tetanic potentiation; RP, rebound potentiation; SK, small conductance Ca^{2+}-activated K^+ channel; SSE, eCB-dependent synaptically evoked suppression of excitation; stimu, stimulation. Arrows up or down indicate final effect on synaptic strength or excitability.

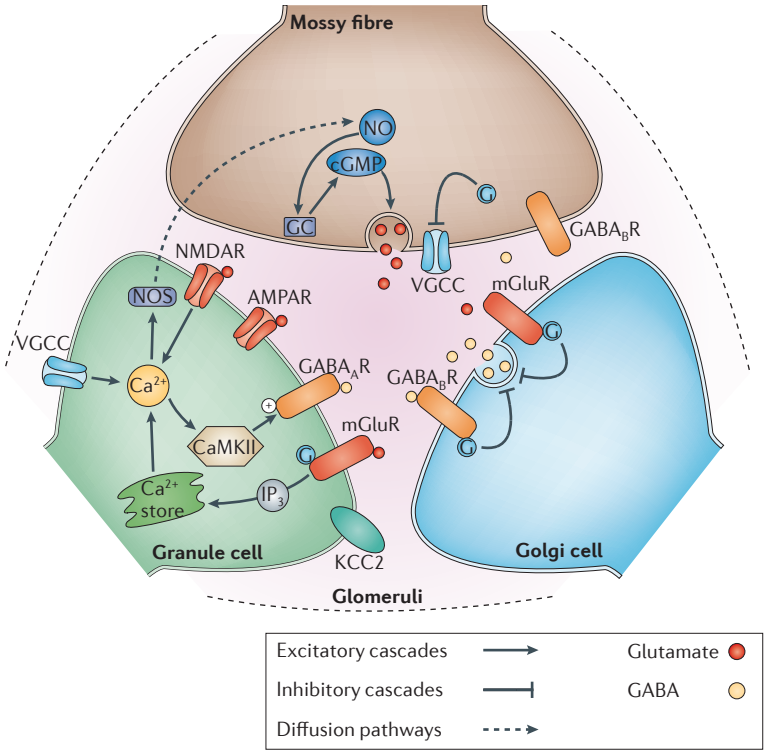


Figure 1 | **Molecular mechanisms underlying plasticity in granule cells.** Glutamate release from mossy fibre terminals and GABA release from Golgi cell terminals trigger various signalling cascades inside the 'mossy fibre glomerulus' (pink area). Glutamate release evokes an increase in Ca^{2+} levels in the granule cell as a result of Ca^{2+} influx through NMDA receptors (NMDARs) and voltage-gated Ca^{2+} channels (VGCCs) and through Ca^{2+} release from internal Ca^{2+} stores. The increase in Ca^{2+} triggers retrograde nitric oxide (NO) transport into the mossy fibre terminal, which facilitates a presynaptic form of long-term potentiation via guanylyl cyclase (GC) and cyclic guanylate monophosphate (cGMP) pathways. In addition, the increase in Ca^{2+} activates Ca^{2+}/calmodulin activated kinase II (CaMKII) in the granule cell and thereby facilitates the response of GABA type A receptors ($GABA_A$Rs) to GABA released from Golgi cells. Within the glomerulus, GABA spillover can suppress transmitter release presynaptically via activation of GABA type B receptor ($GABA_B$R)-mediated pathways. AMPAR, AMPA receptor; IP_3, inositol trisphosphate; KCC2, K^+-Cl^- co-transporter 2; mGluR, metabotropic glutamate receptor; NOS, NO synthase.

(α7nAchRs) on the mossy fibre terminals and granule cell dendrites enhances the postsynaptic Ca^{2+} influx, which can be sufficiently potent to turn LTD into LTP and saturate this plasticity for hours, thereby providing a neuromodulatory gating mechanism[34].

Mice lacking the NR2A (also known as GluN2A) subunit of NMDARs (*Nr2a*$^{-/-}$ mice) show impaired induction of mossy fibre LTP and a reduced ability to induce synaptic excitation in granule cells, whereas the basic output of mossy fibres is unaffected[35]. Both *Nr2a*$^{-/-}$ mutants and mice in which the C terminus of the NR2A subunit is selectively truncated (*Nr2a*$^{\Delta C/\Delta C}$ mice) have mild, but significant, deficits in phase reversal adaptation of the VOR, whereas their basic eye movement performance and ability for gain decrease learning is similar to that of controls[35]. In wild-type mice, phase reversal of the VOR occurs following several days of visuovestibular mismatch training, during which a visual stimulus is constantly given in-phase (that is, simultaneously in the same direction) with vestibular stimulation but at a gradually greater amplitude (BOX 2). This mismatch training forces the mouse to make a compensatory eye movement during vestibular stimulation in the dark that is opposite in direction to that before the training because the error signals of retinal slip during the training in the light are reversed in direction. In line with the deficits in VOR phase reversal adaptation in *Nr2a*$^{-/-}$ mice and *Nr2a*$^{\Delta C/\Delta C}$ mice, local microperfusion of α7nAchR agonists into the granular layer of the flocculus, which is the main cerebellar lobule for controlling compensatory eye movements, affects VOR gain decrease adaptation[34]. This form of VOR adaptation also occurs when a visual stimulus is constantly given in-phase with vestibular stimulation but at constant amplitudes. Together, these results suggest that NMDAR-mediated potentiation at the mossy fibre–granule cell synapse may contribute to vestibulocerebellar learning but not to basic motor performance. Interestingly, the number of mossy fibre filopodia in the granular layer may correlate with the strength of cued fear conditioning[36], which raises the possibility that presynaptic LTP at mossy fibre terminals has a morphological substrate.

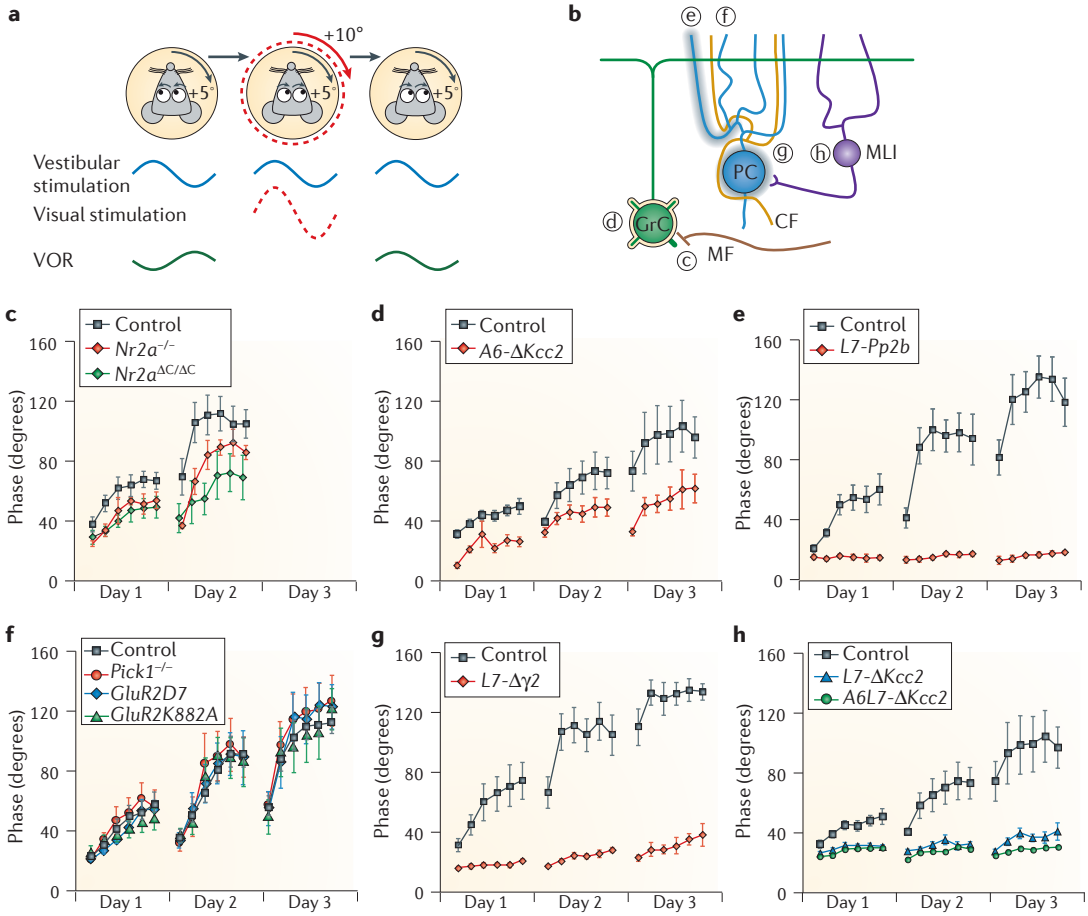
Intrinsic plasticity of granule cells. Cerebellar granule cells are the smallest neurons in the brain and have on average only four short dendrites[30]. Each dendrite receives a single, excitatory mossy fibre input and some of the dendrites also receive inhibitory input from a Golgi cell terminal (FIGS 1,2). Theta bursts of mossy fibre stimulation not only induce presynaptic LTP but also lead to enhanced intrinsic excitability of the granule cell[37] (TABLE 1). The enhanced excitability results from an increased input resistance and lowered spike threshold, which enhances excitatory postsynaptic potentials (EPSPs) and facilitates spike output. Further modification of spike output may be due to changes in intrinsic excitability resulting from NMDAR and GABA receptor activation in granule cells[24,38,39] (FIG. 1). Thus, although granule cells have low background firing rates owing to tonic inhibition by Golgi cells, sensory activation can cause bursting in granule cells, such that mossy fibre input is transmitted with high reliability, yet in a modifiable manner, to Purkinje cells[40].

Intrinsic plasticity of granule cells may have a specific role in cerebellar motor learning. Granule cells in which the K^+-Cl^- co-transporter (KCC2; also known as SLC12A5) is ablated have increased excitability because their resting potential is constitutively depolarized owing to a resting Cl^- conductance through $GABA_A$ and glycine receptors[24]. Mice lacking KCC2 specifically in granule cells (*A6-ΔKcc2* mice) show a moderate impairment in phase reversal learning of the VOR and a virtually absent consolidation of this long-term phase learning, whereas baseline performance, short-term gain decrease learning and gain consolidation of the VOR remain relatively intact[24] (BOX 2). Hence, setting an appropriate level of granule cell excitability appears to be particularly relevant for phase learning and consolidation.

Motor consolidation
Preservation of the level of adaptation of the amplitude and/or timing of movements overnight.

Vestibulo-ocular reflex
(VOR). Reflex movement of the eyes elicited by vestibular stimulation, whereby the eyes move in a direction opposite to that of the head to ensure that the retinal image is kept stable; the reflex is under the control of the vestibulocerebellum.

Box 2 | **Phase reversal of vestibulo-ocular reflex in mice with deficits in cerebellar plasticity**



Phase reversal of the vestibulo-ocular reflex (VOR) occurs when a surrounding visual stimulus is given in-phase (that is, simultaneously and in the same direction) with vestibular stimulation but at a greater amplitude (see the figure, part **a**; the yellow platforms and black arrows indicate the turntable and vestibular stimulation, respectively, and the dashed red circle and larger red arrow indicate the visual screen and visual stimulation, respectively, during the training). This mismatch training, during which the retinal slip reverses in direction, will force the mouse to make compensatory eye movements during vestibular stimulation in the dark that are opposite in direction to those before the training (see the figure, part **a**; compare the green line on the right, which reflects the VOR after learning, with that on the left, which reflects the VOR before learning). As the retinal slip signals are mediated by climbing fibres (CFs)[25], and as the presence and absence of CF activity influence most forms of plasticity (for example, see sites e, f, g and h in the figure, part **b**), the most prominent deficits in VOR phase reversal would be expected to occur in mouse mutants in which multiple forms of CF-dependent plasticity are affected simultaneously (reducing the capacity for compensation). The deficits in motor learning that have been observed in mutant mice are in line with this prediction. Altering the granule cell (GrC) network by changing long-term potentiation (LTP) at the mossy fibre (MF)–GrC synapse (in mice lacking the NMDA receptor subtype 2A subunit (*Nr2a*$^{-/-}$ mice) and mice in which the C terminus of the NR2A subunit is selectively truncated (*Nr2a*$^{\Delta C/\Delta C}$ mice))[35] or the intrinsic excitability of GrCs (in mice lacking the K^+-Cl^- co-transporter 2 (KCC2) specifically in GrCs (*A6-ΔKcc2* mice))[24] causes a relatively mild deficit in phase reversal learning (see the figure, parts **c** and **d**). Blocking parallel fibre–Purkinje cell (PC) LTP and the intrinsic plasticity of PCs simultaneously (by deleting protein phosphatase 2B (PP2B) in a PC-specific manner (*L7-Pp2b* mice)[23]) causes a prominent phenotype in phase reversal learning (see the figure, part **e**). Altering long-term depression (LTD) at the parallel fibre–PC synapse selectively at the level of the AMPA receptors or their insertion (in mice with a mutant form of the GluR2 AMPA receptor subunit lacking the last seven amino acids (*GluR2D7* mice), mice with a mutant form of GluR2 designed to prevent PKCα-mediated phosphorylation at Ser-880 (*GluR2K882A* mice) or mice lacking protein-interacting with C kinase 1 (*Pick1*$^{-/-}$ mice))[28] and thereby probably allowing compensation at other sites in the PC network has no effect (see the figure, part **f**). Lastly, in effect deleting plasticity at the parallel fibre–molecular-layer interneuron (MLI) synapse and at the MLI–PC synapse (by deleting the GABA receptor γ2 subunit (*L7-Δγ2*) or the KCC2 channel specifically in PCs (*L7-ΔKcc2* mice)[24,25] or in both PCs and GrCs (*A6L7-ΔKcc2* mice)[24]) induces a prominent change in phase reversal learning (see the figure, parts **g** and **h**). Panel **c** is modified, with permission, from REF. 35 © (2011) Elsevier. Panel **d** and **h** are modified, with permission, from REF. 24 © (2012) Macmillan Publishers Ltd. All rights reserved. Panel **e** is modified, with permission, from REF. 23 © (2010) Elsevier. Panel **f** is reproduced, with permission, from REF. 28 © (2011) Elsevier. Panel **g** is modified, with permission, from REF. 25 © (2009) Macmillan Publishers Ltd. All rights reserved.

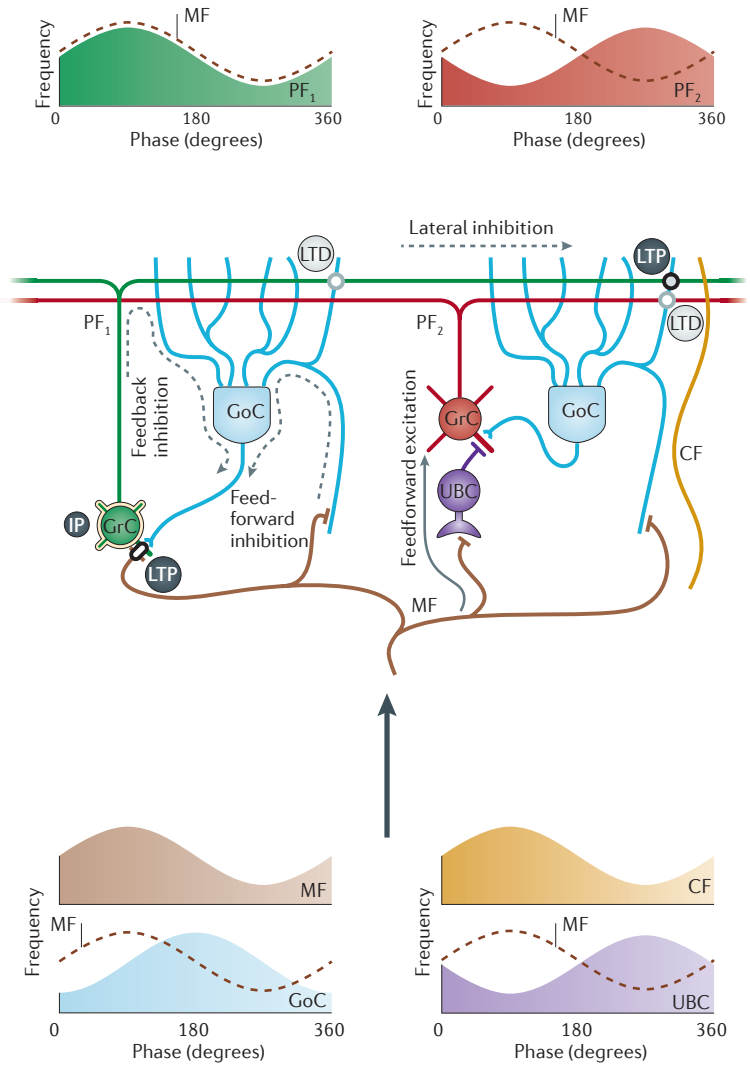


Figure 2 | **Spreading diversity and setting time windows in the granule cell network.** A simplified connectivity model of diversity spreading in the granule cell (GrC) network without and with unipolar brush cell (UBC) input to the GrC. During visual or vestibular sinusoidal stimulation, the mossy fibre (MF) and the climbing fibre (CF) inputs to the vestibulocerebellum show periodic activity with a limited range of phase values (example periodic spiking activities of in-phase MF and CF inputs carrying visual information are represented in brown and yellow, respectively, at the bottom; phase refers to the periodicity of the activity relative to that of the stimulus). The GrCs and their parallel fibres (PF_1 and PF_2) show a variety in periodicity of firing that is greater than the variety of signals carried by the MFs; this is due to the diversity in periodicity of the firing inputs that the GrCs receive from UBCs (purple sinus in the right bottom panel) and Golgi cells (GoCs; blue sinus in the left bottom panel) and to the additional delays in activity that the UBCs can impose onto GrCs via feedforward excitation (grey solid arrow, see REF. 71). In addition, only about half of all GrCs receive input from one or more serially connected UBCs. We therefore predict that the temporal coding of the corresponding parallel fibres ranges from purely in-phase with that of the MFs (for example, PF_1; green sinus) to completely out-of-phase (for example, with PF_2; red sinus). Thus, the activity phase of the different GrCs and their PFs can be pluriform, even when the MF input is relatively uniform (for variety in vestibular MF inputs to GrCs, see REF. 75). The presence or absence of CF activity may influence the activity of the GoCs by inducing long-term potentiation (LTP) or allowing long-term depression (LTD), respectively, at the PF–GoC synapse. The GoCs can provide inhibition onto the GrCs in a feedforward manner through their input from the MFs and in a feedback and lateral manner through their input from the PFs (grey dashed arrows). Note that the phase and amplitude of the activity of the fibres and (inter)neurons in this scheme are simplified for clarity of presentation.

Granule cell–Golgi cell synapses. Golgi cells form a heterogeneous group of GABAergic and/or glycinergic interneurons in the granular layer[41]. Their dendrites arborize in both the granular and molecular layers (BOX 1; FIG. 2). Golgi cells receive most of their inputs from parallel fibres, which are all derived from granule cells[30]. High-frequency parallel fibre burst stimulation results in mGluR2- and cyclic AMP (cAMP)-dependent protein kinase (PKA)-dependent, but NMDAR-independent, LTD that is expressed postsynaptically[42]. Whether this form of homosynaptic LTD is sufficiently potent to modulate the spiking output of Golgi cells and is functionally relevant *in vivo* is unclear, especially as the efficacy of parallel fibre–Golgi cell input is already relatively weak at its baseline level[43]. It is more likely that climbing fibre activity has a potentiating effect on the spike rate of Golgi cells during peripheral activation[44]. Indeed, the inhibitory component of the often biphasic excitatory–inhibitory response of Golgi cells in crus I/II to peripheral stimulation is strongly attenuated by conjunctive climbing fibre activation. The mechanism by which climbing fibres impose these effects onto Golgi cells might be heterosynaptic potentiation of the parallel fibre–Golgi cell synapse, similar to that described for the parallel fibre–molecular layer interneuron synapse (see below)[45].

Notwithstanding the weak parallel fibre input to Golgi cells, there is indirect evidence that plasticity at this synapse might be relevant for cerebellar motor learning. Mice in which 70% of granule cells lack P/Q-type voltage-gated Ca^{2+} channels (*A6-ΔCacna1a* mice) have granule cells that show deficits in transmission at parallel fibre synapses[46], and the mutation also results in deficits in gain increase learning and consolidation of both gain and phase during phase reversal adaptation of the VOR (BOX 2). Likewise, selectively blocking neurotransmission of parallel fibre terminals in an acute and reversible manner using tetanus toxin (reversible neurotransmission blocking mice) abolishes eyeblink conditioning in a dose-dependent manner[47]. These findings raise the possibility that plasticity at the granule cell–Golgi cell synapse contributes to some aspects of cerebellar motor learning.

Golgi cell–granule cell synapses. Single axons of Golgi cells innervate hundreds of granule cells and, in the vestibulocerebellum, also tens of unipolar brush cells (UBCs)[41]. The terminals of their axonal tree end predominantly in the periphery of glomeruli in the granular layer[30]. Two-thirds of Golgi cell axons use both GABA and glycine as their neurotransmitter and the rest use either GABA or glycine[48]. Golgi cell inhibition of granule cells is mediated by GABA receptors, whereas that of UBCs is dominated by glycinergic currents[49], suggesting that postsynaptic selection of co-released transmitters is used to achieve target-specific signalling[41]. The granule cell dendrites express different combinations of $GABA_A$ receptor subunits at different locations with putatively different functions[50,51]. The receptors with α_1 subunits are primarily localized in the synaptic cleft and might determine the amplitude of the phasic inhibition exerted by Golgi cells, whereas those with α_6 subunits,

Homosynaptic
Pertaining to the same synapse. Homosynaptic plasticity is a form of synaptic plasticity in which activity of a particular group of synapses results in synaptic plasticity of the same group of synapses; it can be induced at a single-synapse level.

Heterosynaptic
Pertaining to a different synapse. Heterosynaptic plasticity is a form of synaptic plasticity in which activity of a particular group of synapses results in synaptic plasticity of another group of synapses of the same neuron.

Vestibulocerebellum
The part of the cerebellum that receives direct or indirect vestibular input and controls eye and body reflexes following vestibular input.

Granule cell network
Circuitry consisting of granule cells and interneurons (that is, unipolar brush cells and Golgi cells), which share common mossy fibre inputs and/or are connected through parallel fibres.

Diversity spreading
Expansion of signal coding in the spatial and temporal domain; the granule cell network in the cerebellar cortex is well designed to mediate this process.

Feedforward inhibition
When external inputs excite both a principal neuron and an inhibitory interneuron that inhibits the principal neuron. This phenomenon sharpens the time window during which the principal neuron can fire.

Feedback inhibition
When a principal neuron activates downstream interneurons that inhibit the principal neuron, thereby regulating the subsequent activity of the principal neuron.

First-spike delay
The time interval between the onset of an excitatory input and the generation of the first action potential in a neuron; this interval depends, in part, on the intrinsic excitability of the neuron.

which are more sensitive to GABA, are distributed both inside and outside postsynaptic densities and could thus determine the strength of tonic inhibition following spillover of GABA released from either Golgi cells[52–56] or astrocytes[57]. In effect, Golgi cell inhibition of granule cells may downregulate the level of LTP induction at the mossy fibre–granule cell synapse discussed above[58,59].

Apart from the VOR studies on the *A6-ΔKcc2* mutants described above, in which the output of Golgi cells is affected indirectly by manipulating the intracellular Cl^- concentration of granule cells[24], few studies have aimed to relate activity or plasticity of Golgi cells to cerebellar adaptation of eye movements (for a role in eyeblink conditioning and locomotion training, see REFS 39,60). One study[61] showed that during adaptation of saccadic eye movements the responses of Golgi cells in the oculomotor vermis do not correlate strongly with changes in eye saccade metrics or the direction of movement during motor learning, whereas the mossy fibre discharges in the same region correlate linearly with eye saccade metrics and timing. Thus, as Golgi cells are probably innervated by the same set of mossy fibres that will provide a changing input as soon as the amplitude of the eye movements starts to change (BOX 1; FIG. 2), it is possible that plasticity at the parallel fibre–Golgi cell input serves to stabilize firing frequency of the Golgi cells during learning, which in turn may control plasticity at the granule cell inputs.

Mossy fibre–unipolar brush cell synapses. UBCs are excitatory interneurons that are prominently distributed in the granular layer of the vermis and the flocculonodular lobe[62]. They have a single brush-like dendrite, which receives input from, in most cases, a single mossy fibre terminal. In turn, UBCs give rise to intrinsic mossy fibres that contact both granule cells and other UBCs[63] (BOX 1). Owing to the large three-dimensional space of the mossy fibre–UBC synapse, glutamate released from mossy fibre terminals can become entrapped inside the synaptic cleft, resulting in long-lasting, repetitive postsynaptic activation[64]. Activation of the mossy fibre input to UBCs can evoke excitatory responses in the UBC that are mediated by AMPA receptors, kainate receptors and NMDARs[65,66] or inhibitory responses through activation of group 2 mGluRs[67]. Various forms of plasticity may further fine-tune and divert the duration of sustained activity in each individual UBC. The fast AMPA and kainate receptor-mediated responses show depression at short inter-stimulus intervals, whereas the responses of the other, slower, 'steady-state' currents can be both facilitated and depressed, depending on the duration of inter-stimulus intervals[64,66] (TABLE 1).

So far, no UBC-specific mouse mutants have been created that allow us to test the potential role of UBCs in phase reversal learning of compensatory eye movements. However, the modifiable elements of the UBC network appear to be well-designed to provide feedforward excitation and to thereby impose precisely determined, prolonged activity in granule cells over time courses varying from hundreds to thousands of milliseconds following activation by the extrinsic mossy fibres[54,55].

Granule cell network: spreading diversity and setting time windows. Several trends emerge from behavioural analyses of mice injected with α7nAchR agonists (affecting mossy fibre LTP) into the floccular granular layer[34] and of mutant mice in which plasticity in the granule cell network is altered, such as *Nr2a*$^{-/-}$, *Nr2a*$^{\Delta C/\Delta C}$, *A6-ΔKcc2* and *A6-ΔCacna1a* mice[24,35,46]. First, the effect of alterations in any form of long-term plasticity in the granule cell network on gain learning and phase reversal learning is consistently relatively mild but present (BOX 2, TABLE 1); second, the most robust deficits are apparent in consolidation of gain and/or phase over consecutive days of training; and third, none of the learning and/or consolidation deficits in the mutant mice results in permanent impairments in motor performance. So what is the precise contribution of the granule cell network to cerebellar motor learning and how could it work?

The structure of the granular layer network and its mossy fibre inputs is well suited for spreading diverse sets of information (referred to here as 'diversity spreading'). The mossy fibres themselves are derived from many different sources and individual fibres cover large parts of the cerebellar lobules, innervating many different granule cells. The granule cells in turn provide numerous parallel fibre inputs to large parts of the molecular layer. The Golgi cells, which form a very heterogeneous group of interneurons that are superimposed on the granule cells[48], may serve to further enhance this coding diversity. For example, the combination of feedforward inhibition and feedback inhibition by Golgi cells enables the granular layer to control first-spike delay, to increase the firing rate for specific short periods, to induce delays in firing rate changes and to generate prolonged periods of increased firing[38]. It has been proposed that the various forms of plasticity in the granule cell network serve to fine-tune and preserve these spiking patterns[38] (FIG. 2). For example, the level of LTP at the mossy fibre–granule cell synapse may have a prominent effect on the time at which the first granule cell spike occurs in response to a particular mossy fibre input (that is, first-spike delay). By controlling first-spike delay, this form of LTP may allow spikes to fall within the window that is set by the feedforward inhibition provided by Golgi cells, whereas LTD at the mossy fibre–granule cell synapse may drive the granule cell response beyond this window. By controlling the exact onset of a time window and the number of spikes that occur within a time window, such fine-tuning may modify the mossy fibre patterns that enter the granule cell network[37,50]. Indeed, as the Golgi cells in the flocculus of the vestibulocerebellum carry relatively strong eye-position signals during visuovestibular stimulation (at least during non-adaptation paradigms; C.I.D.Z and B.J.v.B, unpublished observations), they may influence both the timing and amplitude of the eye-velocity signals carried by the mossy fibres during the phase reversal paradigm (FIG. 2). The feedback inhibition provided by Golgi cells, in turn, might control the offset of a time window as well as the duration of the silent period following granule cell

spiking activity. In addition, plasticity at the parallel fibre–Golgi cell synapse, which may be homosynaptic LTD[42] and/or heterosynaptic LTP driven by climbing fibres[44], can provide a mechanism to manipulate feedback inhibition and thereby to manipulate the duration of silent intervals in granule cell activity (FIG. 2). As potentiation of intrinsic excitability can be achieved at a relatively low threshold in granule cells, this potentiation may help to maintain their readiness for generating action potentials in conditions of strong synaptic inhibition and/or weak synaptic excitation[68,69]. Thus, if the synergistic roles of synaptic and intrinsic plasticity in the granular cell network are fully exploited, this network may operate as a flexible device for expanding and redistributing spiking information. As phase reversal learning and consolidation probably require a substantial temporal expansion of spike coding that exceeds the duration of information with hundreds of milliseconds, this network may be especially useful for this type of learning.

However, the relatively mild phenotypes in phase reversal learning observed in mutant mice in which mossy fibre–granule cell plasticity or intrinsic granule cell plasticity is affected (BOX 2) suggest that part of the diversity spreading is embedded in the hardware connections rather than mediated by plasticity. UBCs may form an essential link in this respect. The extent of diversity spreading and the processing time window will be more prominent when the circuitry is enriched by the feedforward excitation exerted by UBCs, which are inserted into the granule cell network in a serial fashion, either as single or as multiple, consecutively ordered elements[62]. Even without plasticity, these superimposed elements in the network allow the granular layer to induce delays in changes of firing rate for periods of hundreds of milliseconds[70,71] and to generate prolonged periods of increased firing that can vary from hundreds to even thousands of milliseconds[62,64,66,72]. Thus, these capabilities expand the diversity of coding tremendously, especially in the temporal domain. As UBCs are particularly prominently distributed in the vestibulocerebellum, which controls relatively slow compensatory eye and head movements[73], the long timescales of UBC operations may optimize the control of these types of movements. We therefore propose that UBCs are essential for shifting and converting the phase of mossy fibre activity that relays information from the vestibular apparatus, eyes or neck (FIG. 2), and that their characteristic cellular properties are particularly relevant for controlling and consolidating motor learning in paradigms such as VOR phase reversal. Owing to the diversity of delays imposed by UBCs[71], mossy fibre signals that enter the granular layer with a relatively uniform electrophysiological identity, such as a typical type 1 phase or type 2 phase relative to the vestibular stimulus[74,75], will become pluriform at the level of the granule cell activity (in awake behaving subjects) and some of them may even encode a phase that is opposite to that of the original mossy fibre input[70]. As approximately half of the granule cells in the vestibulocerebellum are innervated by UBCs, which themselves form a heterogeneous population[62,63], the result will be a huge diversity of phase coding in the parallel fibre pathways (FIG. 2). This coding diversity, which is created and supplied by the granule cell network, is exactly what Purkinje cells and molecular layer interneurons would need to select the appropriate signals that are required to adjust behaviour in a particular learning paradigm.

Plasticity in the Purkinje cell network

Parallel fibre–Purkinje cell synapses. Purkinje cells receive their input from granule cells via thousands of parallel fibre varicosities[30]. All four forms of long-term plasticity that can occur at a synapse — postsynaptic LTD[10], postsynaptic LTP[11,76], presynaptic LTP[12] and presynaptic LTD[77] — have been described for the parallel fibre–Purkinje cell contacts. Whereas the functional relevance of the presynaptic forms of plasticity largely remains to be demonstrated at the behavioural level[26,78] (TABLE 1), the postsynaptic forms of plasticity have been implicated in learning.

Postsynaptic LTD at the parallel fibre–Purkinje cell synapse is typically induced by paired stimulation of parallel fibres and climbing fibres (TABLE 1). This combined stimulation induces a large Ca^{2+} influx and activates both AMPA and mGluR1 receptors (FIG. 3), which in turn facilitate phospholipase C to produce inositol-1,4,5-triphosphate (IP_3)[79–81]. Boosted by IP_3- and Ca^{2+}-mediated Ca^{2+} release from the endoplasmic reticulum, the postsynaptic Ca^{2+} transient becomes supralinear[82], and this in turn activates protein kinase Cα (PKCα; also known as PRKCA)[83] and α-Ca^{2+}/calmodulin-dependent protein kinase II (αCaMKII)[84]. Ultimately, PKCα phosphorylates serine-880 (S880) of the GluR2 subunit[85], which causes dissociation of GluR2 subunit-containing AMPA receptors from GluR-interacting protein (GRIP)[86] and facilitates their interaction with protein-interacting with C kinase 1 (PICK1)[87], allowing receptor internalization via a clathrin-dependent process[87,88]. In addition to this general pathway, several factors, such as GluRδ2 receptors[89,90], nitric oxide (NO) and cyclic guanylate monophosphate (cGMP)-dependent protein kinase (PKG)[91], endocannabinoids[92], corticotropin-releasing factor[93,94] and possibly short transient receptor potential channel 3 (REF. 95) and NMDARs[96], may have a facilitating or permissive role in the induction of postsynaptic LTD (FIG. 3). Studies aimed at elucidating the effect of postsynaptic LTD at the parallel fibre–Purkinje cell synapse on behaviour have received a lot of attention[2]. Purkinje cell-specific and global (that is, brain-wide) manipulation of cytosolic enzymes such as PKC, PKG, αCaMKII or CaMKIV induce impairments in both LTD induction in Purkinje cells and VOR adaptation[22,84,97,98]. However, in more recent studies in which the expression of parallel fibre LTD was blocked by modifying AMPA receptors (mice with a mutant form of the GluR2 AMPA receptor subunit lacking the last seven amino acids (*GluR2D7* mice) and mice with a mutant form of GluR2 designed to prevent PKCα-mediated phosphorylation at S880 (*GluR2K882A* mice) or their endocytosis downstream of the molecular cytosolic pathway at

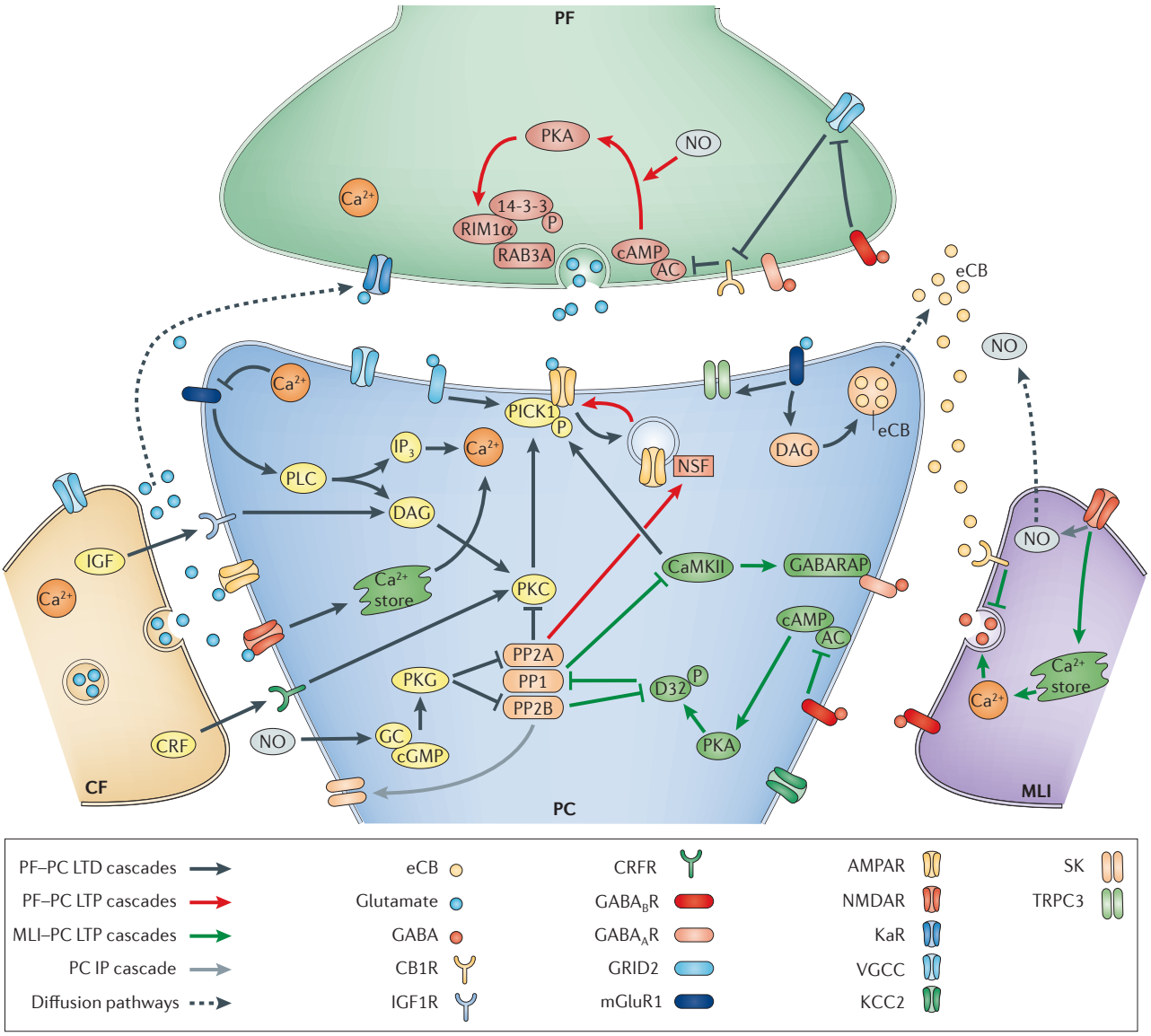


Figure 3 | **Molecular mechanisms underlying plasticity in Purkinje cells.** The schematic drawing presents the main molecules and pathways involved in the various forms of synaptic plasticity that can occur at synapses between parallel fibres (PFs), climbing fibres (CFs) or molecular layer interneurons (MLIs) and Purkinje cells (PCs). Pathways involved in long-term depression (LTD) at PF–PC synapses are marked in black, and pathways involved in long-term potentiation (LTP) at PF–PC synapses are marked in red. Green arrows indicate pathways involved in LTP at MLI–PC synapses and the grey arrow indicates the molecular cascade for intrinsic plasticity (IP). Freely diffusing messenger pathways are marked in dashed arrows. AC, adenylyl cyclase; AMPAR, AMPA receptor; CaMKII, Ca^{2+}/calmodulin-activated kinase II; cAMP, cyclic AMP; CB1R, cannabinoid receptor 1; cGMP, cyclic guanylate monophosphate; CRF, corticotropin-releasing factor; CRFR, CRF receptor; D32, DARPP32; DAG, diacylglycerol; eCB, endocannabinoid; $GABA_A$, GABA type A receptor; $GABA_B$, GABA type B receptor; GABARAP, $GABA_A$R-associated protein; GC, guanylyl cyclase; Glu, glutamate; GluRδ2, glutamate receptor δ2 (GRID2); IGF1, insulin-like growth factor 1; IGF1R, insulin-like growth factor 1 receptor; IP_3, inositol trisphosphate; KaR, kainate receptor; KCC2, K^+-Cl^- co-transporter 2; mGluR1, metabotropic glutamate receptor 1; NMDAR, NMDA receptor; NO, nitric oxide; NSF, *N*-ethylmaleimide-sensitive factor; PICK1, protein interacting with C kinase 1; PKA, cAMP-dependent protein kinase; PKC, protein kinase C; PKG, cGMP-dependent protein kinase; PLC, phospholipase C; PP1, protein phosphatase 1; PP2A, protein phosphatase 2A; PP2B, protein phosphatase 2B; RAB3A; RAS-related protein RAB3A; RIM1α, RAB3-interacting molecule 1α; SK, small conductance Ca^{2+}-activated K^+ channel; TRPC3, short transient receptor potential channel 3; VGCC, voltage-gated Ca^{2+} channel.

Type 1 phase
Positive rate modulation of the mossy fibres when the vestibular stimulus moves in the ipsilateral direction.

Type 2 phase
Negative rate modulation of the mossy fibres when the vestibular stimulus moves in the ipsilateral direction.

the level of the membranes (mice lacking *Pick1* (*Pick1*$^{-/-}$ mice))[99], mice did not show deficits in learning, at least not during low-frequency gain increase, gain decrease and phase reversal learning[28] (BOX 2). These results suggest that the behavioural phenotypes that have been obtained by manipulating the LTD pathway upstream result at least in part from deficits in cell physiological processes other than LTD.

Postsynaptic LTP can be reliably induced by low-frequency parallel fibre stimulation without climbing fibre stimulation[11,76] (TABLE 1). Induction of postsynaptic LTP requires a postsynaptic Ca^{2+} transient that is relatively small compared to that for LTD induction[76,100]. Following such a transient, Ca^{2+}/calmodulin-activated protein phosphatase 2B (PP2B) activates protein phosphatase 1 (PP1) by releasing the block of PP1 by DARPP32 (also known as PPP1R1B), which itself is under control of PP2B and cAMP-activated PKA (FIG. 3). Indeed, selective inhibition of phosphatases PP1, PP2A or PP2B prevents postsynaptic LTP[101]. The trafficking of AMPA receptors to the synapse — the structural correlate of LTP expression — is controlled by Ca^{2+}-sensitive *N*-ethylmaleimide-sensitive factor[102,103]. As climbing fibre activity can reverse the induction of postsynaptic LTP into LTD and at the same time alter postsynaptic Ca^{2+} transients[76], these transients may have an important role in determining the direction of plasticity at the parallel fibre–Purkinje cell synapse. Further evidence that Ca^{2+}-sensitive phosphatases and kinases act together to control postsynaptic plasticity is provided by analyses of mice with a global knockout of βCaMKII (*Camk2b*$^{-/-}$ mice)[104]. In such mice, LTP and LTD stimulation protocols induce LTD and LTP, respectively, which can be normalized by inhibiting the pathways involved (that is, kinases and phosphatases). LTP induction at the parallel fibre–Purkinje cell synapse may contribute to cerebellar motor learning. This is supported by the finding that *Camk2b*$^{-/-}$ mice are ataxic and show deficits in the acquisition of new motor tasks[104]. In addition, mutant mice in which LTP induction is blocked by deleting PP2B specifically in Purkinje cells (*L7-Pp2b* mice) show pronounced deficits in motor coordination. These mice show abnormalities in: motor performance during both VOR and optokinetic reflex; VOR gain decrease and gain increase learning; and VOR phase reversal[23] (BOX 2). Finally, natural changes in VOR learning capabilities during the oestrous cycle in female mice can be correlated with the level of LTP induction at the parallel fibre–Purkinje cell synapse[105].

At the presynaptic site, plasticity at the parallel fibre–Purkinje cell synapse is dominated by potentiation and the control thereof by endocannabinoids[26]. Presynaptic LTP, which is independent of postsynaptic activity, can be elicited by a relatively short period of activity in parallel fibres[12] (TABLE 1). This induces a presynaptic Ca^{2+} influx that activates a pathway involving Ca^{2+}/calmodulin-sensitive adenylyl cyclase, which in turn leads to a rise in cAMP and subsequent activation of cAMP-dependent PKA[12,106]. PKA activation may further increase the number and size of presynaptic Ca^{2+} transients, thereby probably further strengthening the potentiation[77]. In addition, nitric oxide (NO) released from other synapses may contribute, through diffusion, to the induction of presynaptic LTP in non-activated parallel fibre terminals. This NO release might be initiated by activation of NMDARs at sites other than parallel fibres[77,107]. It is possible that a short-lasting form of presynaptic potentiation, which can be induced by a periodic burst pattern of homosynaptic stimulation of parallel fibres, can facilitate the initiation of presynaptic LTP at the parallel fibre–Purkinje cell synapse[108]. By contrast, activation of cannabinoid 1 (CB1) receptors following climbing fibre-evoked release of endocannabinoids suppresses adenylyl cyclase 1, and thereby attenuates cAMP-dependent PKA activity and induction of presynaptic LTP[109]. A recent study[77] reported a form of presynaptic LTD that is expressed at the parallel fibres. Strikingly, this type of plasticity — which is most efficiently induced using a parallel fibre stimulation protocol that is similar to that for presynaptic LTP (TABLE 1) — can only be revealed when presynaptic LTP is pharmacologically prevented by inhibiting PKA or NO. It requires activation of CB1 receptors in an NMDAR, but not mGluR1, dependent fashion. Thus, in principle, bidirectional plasticity mechanisms exist for both postsynaptic and presynaptic plasticity at the parallel fibre–Purkinje cell synapse, but it remains to be shown whether presynaptic LTD has a behaviourally relevant function. The potential impact of presynaptic LTP at parallel fibre–Purkinje cell synapses during cerebellar learning may be indirectly assessed by evaluating granule cell-specific *A6-ΔCacna1a* mutant mice, in which synaptic transmission of most parallel fibre–Purkinje cell synapses is impaired[46]. As indicated above, these mutants show specific deficits in VOR learning and consolidation[46].

Parallel fibre–molecular layer interneuron synapses. Both types of molecular layer interneuron, that is, stellate cells and basket cells, are innervated by parallel fibres[30]. Considering that there are functional differences in activity among different Purkinje cell (micro) zones[110], it is possible that the ultrastructure of the parallel fibre–molecular layer interneuron synapse is not homogeneous throughout the molecular layer. The types of plasticity at this synapse include postsynaptic LTD, postsynaptic LTP and presynaptic LTP[111,112].

Postsynaptic LTD can be induced by low-frequency stimulation of parallel fibres alone[96]. It can be further facilitated by high-frequency parallel fibre stimulation, which promotes Ca^{2+} entry through Ca^{2+}-permeable AMPA receptors and thereby activates mGluR1 receptors and CB1 receptors[113] (TABLE 1). Because most of the Ca^{2+} is quickly removed through buffering mechanisms, LTD expression is restricted to activated synapses, resulting in high input specificity. Enhanced Ca^{2+} entry not only changes the efficacy of synaptic transmission, it also drives the replacement of Ca^{2+}-permeable AMPA receptors with GluR2-containing, Ca^{2+}-impermeable AMPA receptors[114]. Thus, postsynaptic LTD at the parallel fibre–molecular layer interneuron synapse is a form of self-limiting plasticity. The switch in AMPA receptors requires PKC activation and interaction with GRIP and PICK1, suggesting that insertion of GluR2-containing receptors and removal of GluR2-lacking receptors at the synapse are mediated by exocytosis and endocytosis, respectively[115–117]. The finding that a single fear-inducing stimulus *in vivo* can increase a noradrenaline-dependent incorporation of GluR2-containing AMPA receptors in stellate cells supports the possibility that this form of LTD contributes to learning[118]. However, the finding that

Motor coordination
A combination of motor performance, motor learning and motor consolidation.

Optokinetic reflex
Reflex movement of the eyes in response to visual input, whereby the eyes follow the direction of moving objects to stabilize the retinal image.

Bidirectional plasticity
A form of plasticity that can show both depression and potentiation, depending on the presence or absence of a guiding signal; various sites in the Purkinje cell network show bidirectional plasticity guided by the climbing fibres.

LTD-deficient, *Pick1*$^{-/-}$ mice do not show any deficits in cerebellar learning (including phase reversal learning) suggests that its role is not crucial for learning[28,116], either by itself or in combination with parallel fibre–Purkinje cell LTD.

Postsynaptic LTP at parallel fibre–molecular layer interneuron synapses can be induced by parallel fibre stimulation combined with stellate cell depolarization (TABLE 1), which in turn may be mediated, through spillover, by climbing fibre activation[112,119]. This form of LTP depends on NO and/or cAMP[112]. *In vivo*, it may underlie the changes in the size of the cutaneous receptive fields of stellate cells that can be observed following combined parallel fibre and climbing fibre stimulation[45,120]. Whereas parallel fibre burst stimulation alone leads to a long-lasting decrease in size of the receptive fields of interneurons, conjunctive parallel fibre and climbing fibre stimulation leads to an increase of the parallel fibre input to stellate cells with a resulting increase in receptive fields.

Presynaptic LTP at parallel fibre–molecular layer interneuron synapses can be induced by parallel fibre stimulation alone[111]. GABA release from molecular layer interneurons can activate $GABA_A$ receptors on parallel fibres, which in turn can increase the release probability at parallel fibre–molecular layer interneuron synapses[121]. Thus, here LTP implicates a positive feedback mechanism whereby transmission from granule cells to molecular layer interneurons is strengthened during granule cell spike bursts. It will be interesting to find out to what extent this form of LTP can be facilitated by climbing fibre activation of molecular layer interneurons and to what extent stellate cells, basket cells and Golgi cells differ in this respect. Importantly, the parallel fibre–basket cell synapse, but not the parallel fibre–stellate cell synapse, shows a form of short-term depression that causes transient inhibition of the Purkinje cell soma during high-frequency stimulation of granule cells, while inhibition at the dendrites persists[122] (TABLE 1). Similar to the parallel fibre–Purkinje cell synapse, the limitations of the impact of presynaptic plasticity at parallel fibre–molecular layer interneuron synapses during VOR learning and consolidation may be assessed by evaluating granule cell-specific *A6-ΔCacna1a* mutant mice in which synaptic transmission of most of the parallel fibre–molecular layer interneuron synapses is impaired[46].

Molecular layer interneuron–Purkinje cell synapses. In addition to recurrent collaterals and GABA release from Bergmann glia, Purkinje cells receive inhibitory input from molecular layer interneurons[25,30,57]; stellate cells inhibit Purkinje cell dendrites, whereas basket cells provide inhibition to the Purkinje cell soma[30]. Although climbing fibre activity directly suppresses GABA release from molecular layer interneurons at their synaptic input to Purkinje cells through glutamate spillover[123,124], activation of Purkinje cells by climbing fibres can potentiate the amplitude of spontaneous inhibitory postsynaptic currents (IPSCs) and of IPSCs evoked by activation of molecular layer interneurons[125–127] (TABLE 1). This long-lasting potentiation, which is also called rebound potentiation, is caused by a Ca^{2+}-dependent upregulation of $GABA_A$ receptor activity on Purkinje cells[125,126,128]. The transient increase in intracellular Ca^{2+} in Purkinje cells, which is due to activation of voltage-gated Ca^{2+} channels and IP_3-mediated Ca^{2+} release from internal stores[129], activates CaMKII, which in turn regulates transmission at $GABA_A$ receptors[125] (FIG. 3). The binding of $GABA_A$ receptor γ_2 subunit with $GABA_A$ receptor-associated protein (GABARAP) is probably crucial for both the induction and maintenance of rebound potentiation[128]. Future studies will have to further elucidate to what extent rebound potentiation can be expressed in a synapse-specific or global manner[127,130].

Plasticity at the molecular layer interneuron–Purkinje cell synapse may be relevant for cerebellar learning. The Purkinje cell-specific deletion of $GABA_A$ receptor γ_2 subunits (*L7-Δγ2* mice) or KCC2 (*L7-ΔKcc2* mice) — which removes virtually all inhibition, specifically in Purkinje cells — affects both phase reversal learning and gain and phase consolidation of the VOR, even though these mutants are not ataxic[24,25] (BOX 2). Likewise, deleting CaMKII or PP2B in Purkinje cells, which may influence the molecular layer interneuron–Purkinje cell synapse more indirectly (FIG. 3), also affects both gain increase and gain decrease in VOR learning[23,84]. Thus, plasticity at molecular layer interneuron–Purkinje cell synapses might have a role in cerebellar learning but is probably not essential for normal motor performance.

Intrinsic plasticity of Purkinje cells. Purkinje cell excitability can be enhanced by somatic current injections or by parallel fibre stimulation[9,23] (TABLE 1). Analogous to parallel fibre LTP, Purkinje cell intrinsic plasticity requires postsynaptic Ca^{2+} signalling followed by activation of PP1, PP2A and PP2B[9] (FIG. 3). Activation of PKA and casein kinase 2 is essential for LTP expression, which ultimately leads to a downregulation of small conductance Ca^{2+}-activated K^+ channel-mediated conductances[9]. Intrinsic plasticity of Purkinje cells is promoted by parallel fibre LTP, but in turn has a negative impact on the expression of parallel fibre LTP[9]. Thus, LTP at activated parallel fibres could inhibit the induction of parallel fibre LTP at neighbouring non-potentiated dendrites through intrinsic plasticity of Purkinje cells. Ultimately, enhanced excitability of a Purkinje cell (or parts of its dendritic tree) could lead to an increase in firing frequency *in vivo* during spontaneous activity and/or during particular patterns of activation by parallel fibres and/or molecular layer interneurons.

Mice that lack PP2B specifically in Purkinje cells (*L7-Pp2b* mice) show not only impaired induction of LTP at parallel fibre–Purkinje cell synapses, but also impaired intrinsic plasticity[23]. Therefore, it is possible that the prominent impairments in motor performance and motor learning of the compensatory eye movements in *L7-Pp2b* mutants[23] described above reflect, in part, deficits in intrinsic plasticity.

Purkinje cell network: creating output by selecting input. The behavioural phenotypes of mice in which one or more forms of plasticity and/or

Purkinje cell network
Circuitry consisting of Purkinje cells and molecular layer interneurons, which share common parallel fibre and/or (extra)synaptic climbing fibre inputs.

signal processing in the molecular layer have been manipulated range from no phenotype (*GluR2D7*, *GluR2K882A* and *Pick1*$^{-/-}$ mice) and moderate phenotypes that predominantly affect consolidation (*L7-Δγ2* and *L7-ΔKcc2* mutants) to severe deficits in motor learning and motor performance (*L7-Pp2b* and *Camk2b*$^{-/-}$ mice) (BOX 2). This range of phenotypes is greater than the range of phenotypes observed in mice in which plasticity in the granular layer was manipulated. This observation is in line with the fact that the number of potential sites for plasticity in the molecular layer exceeds that in the granular layer. On the one hand, this implies that the Purkinje cell network provides ample room for compensation in plasticity mechanisms, but on the other hand, it suggests that the molecular layer has the main, yet not exclusive, role in cerebellar motor learning. So, how does the Purkinje cell network contribute to motor learning?

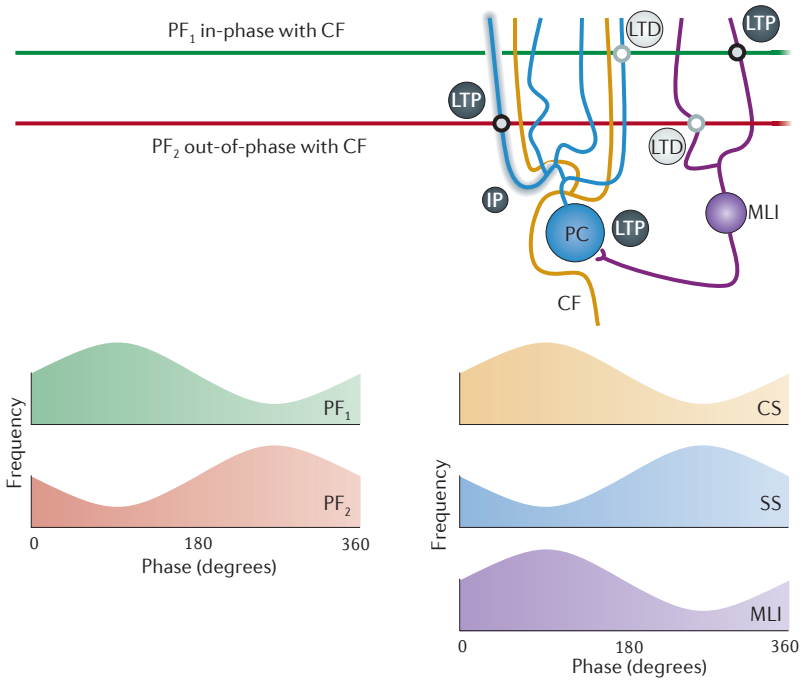


Figure 4 | **Creating output by selecting input in the Purkinje cell network.** By controlling the direction of plasticity at multiple synapses, climbing fibre (CF) activity links the parallel fibre (PF) that has the appropriate phase to the desired target. When CF activity is in-phase with PF activity (PF_1), it will promote long-term potentiation (LTP) at the PF–molecular layer interneuron (MLI) synapse, long-term depression (LTD) at the PF–Purkinje cell (PC) synapse and rebound potentiation at the MLI–PC synapse (for simplicity the rebound potentiation is here also indicated as LTP). Conversely, when CF activity is absent (that is, out-of-phase with PF activity (PF_2)), LTD is induced at the PF–MLI synapse, whereas LTP is induced at the PF–PC synapse together with intrinsic plasticity (IP) in the PC (which is depicted as a 'halo' around the dendritic membrane). Thus, because the inductions of these forms of plasticity are dependent on the direction of the periodic CF stimuli, CF activity can induce opposite phases in the MLI versus the PC. As a result of the above mechanisms, simple-spike (SS) activity in PCs is determined directly by excitatory inputs from out-of-phase PFs (PF_2) and by suppression from in-phase PFs (PF_1), and the SS output of PCs will thus be out-of-phase with CF activity (indicated as complex spikes (CSs)). As the route of information in PF_1 and PF_2 through the MLIs is parallel to the direct route through the PCs, we predict that the various forms of plasticity in either one of these routes can compensate at least in part for deficits in the other route.

As explained above, the granule cell network provides enormous diversity in signal coding to Purkinje cell dendrites in the molecular layer[131], even when the mossy fibre input is relatively uniform[75]. The huge diversity of parallel fibre codings, which are widely distributed over the molecular layer, has the advantage that guiding signals (provided by climbing fibres) can select and sculpt those codings that are needed to improve behaviour as required in a particular spatiotemporal context[16]. The climbing fibres achieve this through the presence and absence of heterosynaptic effects, either directly or via spillover. Climbing fibre activity may not only reduce Purkinje cell activity by inducing LTD at the parallel fibre–Purkinje cell synapse but also by promoting potentiation at the parallel fibre–molecular layer interneuron synapse, the molecular layer interneuron–Purkinje cell synapse (FIG. 4) and probably even at the parallel fibre–Golgi cell synapse (FIG. 2). Conversely, the absence of climbing fibres can increase Purkinje cell activity by permitting LTP at the parallel fibre–Purkinje cell synapse, by increasing the intrinsic excitability of Purkinje cell dendrites and by promoting LTD at parallel fibre–interneuron synapses. For the VOR phase reversal learning paradigm, this implies that multiple forms and sites of plasticity will be actively involved once the direction of the retinal slip and thereby that of the climbing fibre modulation is reversed (BOX 2). For example, when retinal slip is reversed towards the left during training, a specific set of parallel fibre–Purkinje cell synapses is probably potentiated in the left flocculus, whereas the synapses of the same parallel fibres onto interneurons are depressed[23,27]. Conversely, when the retinal slip is moving towards the right a different set of parallel fibre synapses with the same Purkinje cells is subject to depression, whereas the synapses of these parallel fibres onto interneurons are potentiated. As these depressing and potentiating effects (which work in synergy) are all timing-dependent, in the sense that they all depend on whether climbing fibre activity coincides (within a particular time frame) with parallel fibre activity[76,82,132,133], it is crucial that parallel fibres carry sufficient variety in temporal coding. This variety allows the climbing fibres to shape the simple-spike modulation of the Purkinje cells in any direction, even to a phase that is opposite to that of the mossy fibres (FIGS 2,4). Interestingly, such an opposite phase in mossy fibre activity and Purkinje cell simple-spike activity is exactly what has been observed in various experiments. For example, during VOR most vestibular simple-spike responses of Purkinje cells in vertical axis zones of the floccular complex in primates show a phase that is opposite to that of most of the corresponding mossy fibre inputs[74,134,135]. Likewise, during smooth-pursuit eye movement the percentage of Purkinje cell simple-spike responses that are excited for rotation of the ipsilateral eye to the ipsilateral side of recording is higher than that of corresponding mossy fibre responses[74,134]. If the climbing fibres dominate the periodicity of the simple-spike activity by regulating multiple forms of plasticity in the molecular layer, one expects that selectively reversing the laterality of the climbing fibres from a contralateral

to an ipsilateral projection reverses the simple-spike modulation even when the laterality of the mossy fibre projection is unaffected; this prediction indeed holds[136]. Moreover, as VOR phase reversal learning in effect also reverses the climbing fibre modulation, one expects that manipulating simultaneously multiple forms of climbing fibre-mediated forms of plasticity induces the most prominent deficits in this paradigm (reversal of the phase of the climbing fibre signals induces potentiation at parallel fibre–Purkinje cell synapses and the parallel fibre synapses onto interneurons that were in a silent or depressed state before the reversal, and it depresses the parallel fibre–Purkinje cell and parallel fibre–interneuron synapses that were potentiated in the initial state); this prediction indeed also holds (BOX 2). We therefore argue that climbing fibre-guided selection in the molecular layer provides a powerful mechanism to create the appropriate Purkinje cell simple-spike output by simultaneously inducing several forms of plasticity.

Distributed synergistic plasticity

The data reviewed above indicate that distributed plasticity in both the granule cell network and the Purkinje cell network is required for motor learning and consolidation. Plasticity in the granule cell network may increase the diversity of coding, whereas plasticity in the Purkinje cell network may facilitate the selection of the appropriate coding and transfer it to the output domain that controls the appropriate movement. We refer to the combination of the different forms of plasticity in these networks during learning as distributed synergistic plasticity: distributed because it includes various types of synaptic and intrinsic plastic effects in various types of neurons and superimposed interneurons in both the granular and molecular layer under compatible induction protocols (TABLE 1); and synergistic because the different forms of long-term plasticity in the cerebellar cortex act synergistically. Forms of plasticity that occur in serial manner (that is, plasticity in granule cell network and plasticity in Purkinje cell network) and forms of plasticity that occur in parallel manner (that is, plasticity at parallel fibre–Purkinje cell synapses and that at parallel fibre–interneuron synapses) in effect enhance one another through precise and periodic timing in the climbing fibre system relative to the mossy fibre system (FIGS 2,4). This configuration implies that memory formation and storage in the olivocerebellar system is created in a distributed and synergistic fashion across the networks, allowing continuous expansion and fine-tuning to the changing bodily and environmental conditions.

The processes — such as plasticity at the mossy fibre–granule cell synapse or intrinsic plasticity of granule cells — that modify activity in the granule cell network and may serve to enhance, fine-tune and maintain diversity of parallel fibre coding probably depend predominantly on activity in the mossy fibres and Golgi cells (FIG. 2). By contrast, the processes that modify activity in the Purkinje cell network are mainly regulated by climbing fibre activity (FIG. 4). The climbing fibres have a crucial role in all of these processes by inducing various forms of heterosynaptic plasticity when they are active and by permitting various forms of homosynaptic plasticity when they are silent[136]. The various forms of climbing fibre-dependent plasticity are bidirectional (that is, they have depressing and potentiating effects) and are reinforcing in a parallel fashion, in the sense that the potentiating and depressing effects of climbing fibres at the inputs onto and output of superimposed interneurons act in synergy with the direct depressing and potentiating effects, respectively, of the climbing fibres at the parallel fibre inputs to the Purkinje cells. As the routes of information through the interneurons are parallel to the routes of information through the Purkinje cells, the various forms of plasticity in either one of these routes can compensate at least in part for deficits in the other route. We therefore also attribute major roles to plasticity at the input and output of interneurons.

Our conceptual model of distributed synergistic plasticity elaborates on concepts initiated by Marr, Albus, Ito and others[137–143]. We argue that potentiation of granule cells and potentiation of Purkinje cells are, at least initially, the dominant type of plasticity during visuovestibular learning (TABLE 1). LTD at the inputs to these cells might contribute at various levels during ongoing learning. Apart from its direct contribution, it might compensate for deficits in potentiation at synapses with opposite polarity and/or might avoid saturation of synapses by noise, preventing overexcitation[76,144]. However, LTD does not appear to be essential for visuovestibular motor learning (BOX 2; FIG. 4). By speculating that LTP and intrinsic changes in the excitability of granule cells and Purkinje cells are, initially, the fundamental mechanisms underlying procedural memory formation, we follow the notion that the cerebellum has an excessive number of granule cells and even more parallel fibre varicosities, most of which have been reported to be silent during rest[40,145,146] and therefore initially tend to be more sensitive to potentiation than depression[26]. By contrast, interneurons have been reported to be more active relative to granule cells during rest[70], and their inputs and outputs may therefore initially be more prone to depression. If potentiation of granule cells and Purkinje cells and depression of interneurons are indeed the main initial forms of plasticity underlying learning, one may predict that during the execution of learned motor skills the activity of granule cells increases, whereas that of interneurons decreases; this indeed turns out to be the case for locomotion (S. S. Wang, personal communication). However, as different cerebellar lobules and zones show different levels of intrinsic activity that may lead to different propensities for potentiation and depression[147], different learning behaviours controlled by different regions may show different propensities for plasticity. In this respect, it will be interesting to investigate the extent to which the concept of distributed synergistic plasticity applies to other forms of cerebellar learning, such as Pavlovian eyeblink conditioning, locomotion conditioning, fear conditioning and spatial navigation[148–151]. The similarities in the presence and absence of phenotypes of mouse mutants that have been subjected to multiple cerebellar learning tests suggest that Pavlovian conditioning is subject to the same principles as visuovestibular motor learning[23,28,47].

Owing to the abundance and distributed variety of different forms of plasticity in the cerebellar cortex and the room for compensation (FIG. 4), none of them is probably essential. Thus, the concept of distributed synergistic plasticity predicts that none of the individual forms of plasticity is absolutely essential, even though some forms of plasticity may be more efficient than their counterparts in the initial stages of various forms of cerebellar learning. In this respect, one could hypothesize that the superimposed interneurons, which may have arisen later in evolution than their target neurons (that is, the Purkinje cells and granule cells), have endowed the cerebellar cortex with a wide range of possibilities to compensate for potential deficits in one of the forms of plasticity in the target neurons themselves (BOX 2). This development would by itself emphasize how important the role of the cerebellar cortex in learning and consolidation has become during evolution. Thus, we propose that the options provided by distributed synergistic plasticity in the cerebellar cortex are sufficiently rich to modify phases of activity and behaviour in any direction, and that these acquired behaviours can be maintained for a lifetime in the sets of modified inputs to granule cells and Purkinje cells as well as their superimposed interneurons, even when failures at particular forms of plasticity occur. These memories may remain stored in the cerebellar cortex independently from the 'copy transfer' to the cerebellar and vestibular nuclei that may facilitate retrieval of the memories after consolidation[17–19,25].

The fact that a stored procedural memory or cognitive procedure should, in principle, be retrievable for the rest of one's life demands a mechanism that can last forever. In this respect, the molecular mechanisms underlying distributed synergistic plasticity in the cerebellar cortex may differ from those underlying plasticity in the hippocampus, which is required for declarative memory formation — a type of memory that is formed more rapidly, with more readily available options for extinction[152,153]. Procedural memories formed at a young age can indeed last forever[154], and the ability to form new procedural memories is affected by ageing[155]. It will be interesting to find out whether the capacity for modifying parallel fibre synapses both at Purkinje cells and interneurons is diminished over time and whether analogous changes in the capacity for plasticity can be observed in the hippocampus[3,156]. In particular, it will be interesting to investigate whether a change in capacity for synaptic plasticity is reflected in the amount of particular stabilizing receptor subunits at the end of life and whether there is a difference between the target neurons and interneurons in this respect[3,156,157].

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