Available online at www.sciencedirect.com
SCIENCE DIRECT®
Brain Research Reviews 44 (2004) 103–116
BRAIN RESEARCH REVIEWS
www.elsevier.com/locate/brainresrev

Reviews

Cerebellar aminergic neuromodulation: towards a functional understanding

Nicolas Schweighofer[a,*], Kenji Doya[a,b], Shinya Kuroda[c]

[a] *CREST, Japan Science and Technology Agency, ATR, 2-2-2, Hikaridai, Keihanna Science City, Kyoto 619-0288, Japan*
[b] *ATR Computational Neuroscience Laboratories, 2-2-2, Hikaridai, Kyoto 619-0288, Japan*
[c] *Undergraduate Program for Bioinformatics and Systems Biology, Graduate School of Information Science and Technology, PRESTO, Japan Science and Technology Agency, University of Tokyo, 7-3-1 Hongo, Bunkyo, Tokyo 113-0033, Japan*

Accepted 14 October 2003

Abstract

Although a number of neuromodulators influence the cerebellar circuitry, their functions remain largely unknown. By reviewing and combining results from data-driven and theory-driven studies, we attempt to provide an integrated systems view of cerebellar neuromodulation. First, we review the short- and long-term effects of neuromodulators on the cerebellar circuitry. Second, we review recent theories of the cerebellum and show that a number of modulatory signals are needed for powerful cerebellar learning and control. Finally, we attempt to match each theoretically derived modulatory signal with a specific neuromodulator. In particular, we propose that serotonin controls the 'responsibility' of each cerebellar unit (or microcomplex) in cerebellar learning and control; norepinephrine gates unsupervised learning in the cerebellar cortex; dopamine enhances goal-oriented cerebellar learning; and, finally, acetylcholine controls the speed of supervised learning in Purkinje cells.

Theme: Motor system and sensory motor integration
Topic: Cerebellum

Keywords: Feedback error learning; Granule cell; Hebbian plasticity; Internal neural model; Long-term depression; Rebound potentiation

Contents

* Corresponding author. Tel.: +81-774-95-1073; fax: +81-774-95-1259.
E-mail address: nicolas@atr.co.jp (N. Schweighofer).

0165-0173/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainresrev.2003.10.004

1. Introduction

Neuromodulation, as defined by chemical communication between neurons that is either not fast, not point-to-point, or not simply excitation or inhibition [57], influences the cerebellum circuitry in various ways. Its functions remain, however, largely unknown. Here, by reviewing and combining both data driven, i.e., bottom-up, and theory-driven, i.e., top-down, studies, we attempt to provide an integrated system view of the role of cerebellar extrinsic neuromodulation.

The neural circuitry in the cerebellar cortex is very uniform and can be analyzed in terms of small structural and functional units, or microcomplexes [50], inserted into various extracerebellar systems. A microcomplex consists of a microzone, a narrow sagitally oriented band of cerebellar cortex (100–200 μm width) [94], a small region of the inferior olive (IO), and small portion of the deep nucleus (Fig. 1). Each microcomplex receives two kinds of fast-acting inputs: mossy fibers (MFs) and climbing fibers (CFs)—the axons of the IO neurons (see Fig. 1 for a diagram of the cerebellar circuitry). The set of MF inputs is relayed to the cerebellar cortex by the granule cells (GCs). The ascending branch of GC axons make several synaptic connections with the overlying Purkinje cells (PCs) before bifurcating into the parallel fiber (PF), which reach PCs as far as several millimeters away. As PCs have inhibitory action upon deep nuclear cells (while collaterals of some MFs excite the nuclear cells), the signal flow from the nuclear cells is modulated by the microzone action. In contrast to the numerous GC inputs to a PC (up to 10^6 in man), there is only one CF per PC in the adult. The CFs are known to carry error signals that reflect error in movement performance [67,69,119]. When simultaneously activated with the PFs, the CF input modifies GC–PC synapses by long-term depression (LTD) [25,51,52,72]. The involvement of the cerebellum in error-driven learning behaviors, such as eye-movement control and conditioned eye blinking, has been experimentally demonstrated [50,121].

Traditionally, the cerebellum has been thought to receive only serotonergic and noradrenergic neuromodulatory afferents (e.g., Refs. [50,55]). Besides these two major projections, however, there are less prominent projections from the other long-range neuromodulatory groups: dopamine, acetylcholine, and histamine. In this paper, we first review the sources, the effects on the different cerebellar cell types, and the known behavioral effects for each of these neuromodulators.[1] We then review cerebellar learning theories and see that recent theories use several neuromodulator-like diffuse signals. We finally suggest a system view of the possible roles of the neuromodulators in cerebellar functions. Specifically, we propose that serotonin controls the 'responsibility' of each microcomplex in cerebellar learning and control, norepinephrine gates unsupervised learning in the cerebellar cortex, dopamine allows goal-oriented cerebellar learning, and acetylcholine controls the speed of memory update in PCs.

2. Cerebellar neuromodulation

2.1. Serotonin (5-HT; 5-hydroxytryptamine)

The serotonergic fiber input to the cerebellum is the third in size after the mossy fiber and climbing fiber input

[1] We restrict our discussion to neuromodulation in the mature cerebellum; that is, we will not study the role of neuromodulation in the developing cerebellum.

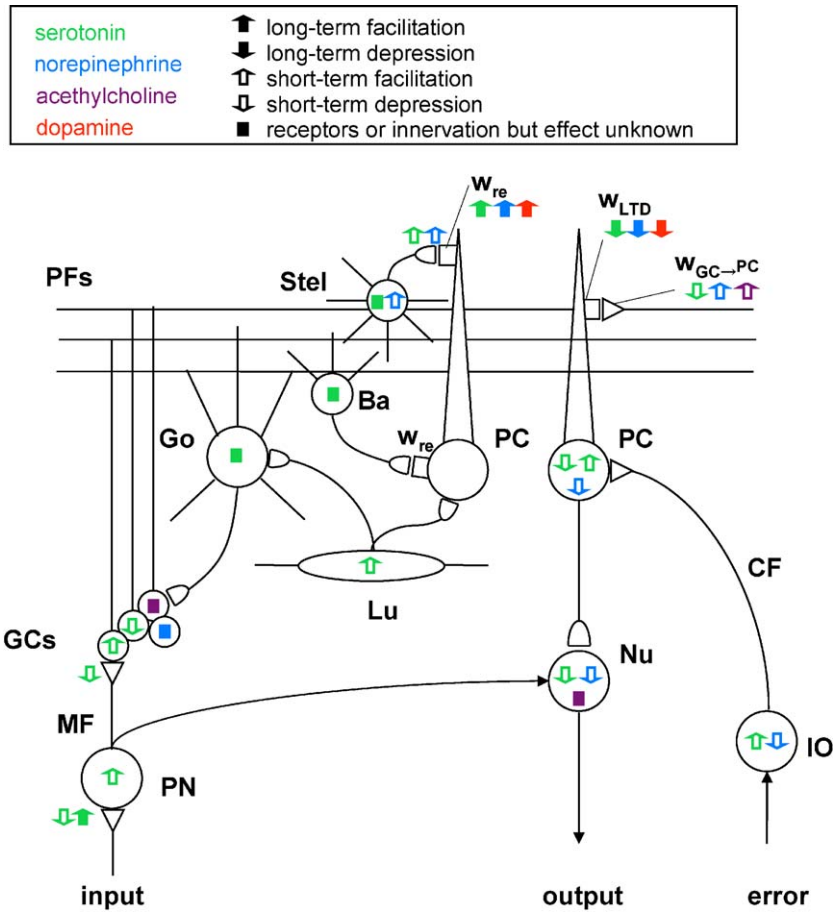

Fig. 1. Schematic cerebellar circuitry and neuromodulation. PN: pontine nucleus. MF: mossy fibers. GCs: granule cells. PFs: parallel fibers. Go: Golgi cell. Stel: stellate cell. Ba: basket cell. Lu: Lugaro cell. Note that the Lugaro cells receive only serotonergic inputs. PC: Purkine cell. w_{re}: Postsynaptic GABAergic inputs from stellate cells and basket cells to Purkinje cells, locus of a form of plasticity called rebound potentiation (the effects of neuromodulators are only indicated for the stellate cells synapses, but it is believed that basket cell synapses are under the same neuromodulatory effects). $w_{GC \rightarrow PC}$: presynaptic granule cell inputs to Purkinje cell. w_{LTD}: postsynaptic inputs from granule cells to Purkinje cells, locus of a form of plasticity called long-term depression. Nu: Nuclear cell. IO: Inferior olive cell. CF: Climbing fiber cell. Lines terminated by triangles represent excitatory connections, and lines terminated by semi-ovals represent inhibitory connections. The rectangle on each PC dendritic trees represents a spine. See color legend for meanings of other symbols.

and affects all parts of the cerebellar circuitry (see Fig. 1 and Table 1) via a number of serotonergic receptors: 5-HT1 [63] as well as 5-HT2A, 5-HT3, 5-HT5A, and 5-HT7 [38].

2.1.1. Sources

The serotonin input to the cerebellum arises from a fairly restricted nuclei in the medullary and pontine reticular formation [62]. The majority of the inputs arise from serotonergic neurons in the medullary reticular formation [15]. Inputs from the raphe nuclei have also been identified [129,130], but these raphe inputs may not be serotonergic [16].

All the components of the cerebellar system are innervated by serotonergic inputs.

- At the input level, the pontine nuclei, the main source of cerebellar mossy fibers, receives serotonergic inputs from the medullary and pontine reticular formation [86].
- In the cerebellar cortex, serotonergic fibers form a dense plexus that is present throughout the GC and PC layers. Combined retrograde tracing and 5-HT immunochemistry studies have shown that in any region of the brain stem that sends mossy fibers, a small percentage of cells are serotonergic [11,15,16]. Thus, the mossy fiber input to the cerebellar cortex is accompanied by a 5-HT input that is local and that has the same topographical organization as the mossy fibers.
- Within all the cerebellar nuclei, there is a dense uniform plexus of serotonergic fibers [62,68]. All three cerebellar nuclei receive 5-HT afferents from a variety of brainstem nuclei. However, the 5-HT projections to the cerebellar nuclei do not appear to be the collaterals of those projecting to the cortex [68].
- Finally, the IO is richly innervated by serotonergic fibers [131], which originate from wide areas on the medullary raphe nuclei. It is of interest that the input to these serotonergic neurons and to IO cells arises from common

Table 1
Summary of the known effects of the four neuromodulators serotonin, norepinephrine, acetylcholine, and dopamine on the different cerebellar cell types and synapses

	5-HT	NE	ACh	DA
inp → PN	−, ++ [90]			
PN	+ [90]			
MF → GC	− [80,120]	receptors [30,91]		
GC	variable [6,81]		receptors [40]	
Go	5-HT2A receptors [38]			
Lugaro	+ (trigger) [27,29]			
BA/Stel	5-HT5A receptors [38]	+ [87,102,103]		
PC	preferred rate [63,116,127]	− [13]	receptors [40]	receptors [8]
GC → PC	− [26,73, 79,115], −− LTD [22,33,99]	+ [36], −− LTD [20,96]	+ [4]	−− LTD [3]
GABA–PC	+, ++ [87,88]	+, ++ [56,58,87,88]		++ [59]
NUC	− [19,24]	− GABA [39]	innervation [53]	
IO	+ [75,111,117]	− [75,97]		

+: short-term facilitation; ++: long-term facilitation. −: short-term depression; −−: long-term depression.

descending fibers from the nucleus parafascicularis in the thalamus and the para-thalamic zona incerta [17,113].

2.1.2. Neuronal effects

2.1.2.1. Pontine nucleus. Serotonin affects the neurons in the pontine nucleus, the main source of mossy fibers, by increasing the neurons' excitability and decreasing the synaptic transmission on them [90]. However, serotonin simultaneously facilitates high-frequency inputs. Thus, the role of serotonin in the pontine nucleus could act as a high-pass filter: it increases the transmission of high-frequency inputs compared to that of low frequencies [90].

2.1.2.2. Granule cells. Serotonin modulates the MF–GC glutamate transmission in rat cerebellar slices, possibly by modulation of the release of glutamate by 5-HT through receptors situated on glutamate terminals [80]. The effect is inhibitory [120] and thus may further play a role in filtering of information. Further, serotonin modulates GC spontaneous activity in the rat cerebellum with variable effects [6]. This variability may be due to the presence of both 5-HT1/5-HT2 receptors in the cerebellar cortex [81].

2.1.2.3. Inhibitory interneurons. Serotonin triggers the firing of an inhibitory interneuron, the Lugaro cell, a cell presynaptic to Golgi cells [29] and Purkinje cells [27]. Because a Lugaro cell contacts more than 100 Golgi cells, it has been proposed that serotonin modulation of Lugaro cells may constitute a switch that through double inhibition release GC activity [29]. However, because the Lugaro cells also inhibit PCs [27], it is probable that it has a role similar to that in the pontine nucleus, i.e., filtering relevant information. Further, PC inhibition would result in enhancement of nuclear cells activity, de facto enhancing cerebellar output in those cerebellar microzones that receive strong serotonin inputs. Direct effect of serotonin on Golgi cell is unknown, but these cells are known to contain 5-HT2A receptors [38]. Similarly, direct effects of serotonin on basket and stellate cells are unknown, but these cells are known to contain 5-HT5A receptors [38].

2.1.2.4. Purkinje cells. Serotonin decrease PC activity [63] in several ways. First, short- and long-term increase in GABAergic transmission critically involves serotonin [87,88], via 5-HT1A receptors. The increase in long-term facilitation—called rebound potentiation [56,58]—of cerebellar GABAergic transmission [88] is via an increase in cAMP by serotonin. Second, serotonin may set PCs at a preferred firing rate [116], possibly by modulation of the transient outward h current [127]. Third, 5-HT has inhibitory effects on glutamatergic PF–PC synaptic transmission [73,115], presumably both pre- and postsynaptically [26,79]. One form of these long-term cerebellar effects is the possible modulation of postsynaptic induction of LTD by serotonin: several types of serotonin receptors including type 2A and 2B have been shown to be expressed in cerebellar Purkinje cells [22,33,76]. These types of serotonin receptors are known to activate phospholipase C [99], resulting in production of IP_3. In our recent detailed kinetics simulation model of Ca^{2+} (Doi et al., in preparation), we proposed that inositol-3 trisphosphate (IP_3) can regulate the threshold of regenerative cycles of Ca^{2+} elevation, known as supralinear Ca^{2+} signal. This indicates that the temporal window of cerebellar LTD induction depends on the timing of IP_3 production; the higher level of IP_3 extends the temporal window of LTD induction. Therefore, 5-HT can potentially facilitate cerebellar LTD.

2.1.2.5. Nuclear cells. Serotonin has a fast modulatory effect on all deep cerebellar nuclei, with the majority of responsive cells showing an inhibitory response with latency less than 30 ms [19]. 5-HT induced inhibition of deep nuclear neurons may be due to 5-HT2/1C receptor subtypes, possibly via activation of GABAergic interneurons [24].

In sum, the net effect of serotonin on PC is a decrease in responsiveness to its inputs. Because of the inhibitory nature of PCs on nuclear neurons, a decrease in PC activity by serotonin will lead to disinhibition of deep nuclear neurons and thence an increase in cerebellar output. As the projections to the cerebellar nuclei do not appear to be collaterals of those projecting to the cerebellar cortex, the nuclear neurons inhibited by serotonin will probably not correspond to those innervated by PC with reduced activity.

2.1.2.6. Inferior olive. Serotonin increases IO cell excitability presumably by shifting the inactivation curve of the somatic calcium current to a more positive potential level [75] and by reducing the anomalous rectification h current [117]. Simulations [111] showed that IO cells could be exquisitely sensitive to serotonin as relatively small changes in ionic conductances in the low threshold calcium current and the h current bring IO cells into spontaneous rhythmic firing modes.

2.1.3. Behavioral effects

Voltametric and microdialysis studies have shown that the level of cerebellar serotonin in the freely moving rat correlates with motor activity [18,84]. These results are in agreement with recordings of serotonergic neurons in medullary raphe nuclei [125,126], which are maximally activated during motor activity [125].

Evidence linking cerebellar serotonin dysfunction to behavioral deficits is scant, but this should not undermine the importance of serotonin, as disturbance to the serotonergic cerebellar input has been linked to cerebellar ataxia [123].

2.2. Norepinephrine (noradrenaline; NE)

The NE input to the cerebellum is the second largest modulatory input and distributes to all part of the cerebellar cortex with a patchy innervation pattern.

2.2.1. Sources

The cerebellar noradrenergic fibers project to all parts of the cerebellar cortex and originate from the dorsal and ventral parts of the locus coeruleus [64]. These fibers are found both around the glomeruli, making close contacts with GC dendrites, and around the PC dendrites [65].

2.2.2. Neuronal effects

Because of the difficulty to record from the tiny GCs, there is to our knowledge no study on the direct effect of NE upon GCs. However, it is known that cultured cerebellar GCs express adrenergic receptors [30]. Further, NE has been shown to lead in GCs, as well as astrocytes, to an increase in cyclic GMP, an important intracellular messenger of neuronal plasticity [91].

Norepinephrine inhibits spontaneous PC discharge [13] possibly through both presynaptic adrenergic receptors on basket cells [87,103] and enhancement of spontaneous spike firing of basket cells [102]. Similar to serotonin, NE has been shown to be involved in short- and long-term modulation of GABAergic transmission [87,88]. However, unlike serotonin, and relative to the change in spontaneous activity, norepinephrine increases the responsiveness of the PC to its afferent excitatory inputs [36].

Norepinephrine exerts two types of long-term influence on PCs. First, activation of the beta-adrenergic receptor would result in a rise in intracellular levels of cyclic AMP, which in turn results in the increase of cyclic AMP-dependent protein kinase activity [20]. This action of NE suggests that it can enhance rebound potentiation, which requires elevation of intracellular cAMP level [56], and antagonize the suppression of rebound potentiation, which requires the suppression of cAMP level [58]. Second, NE increases the expression of immediate-early genes, such as c-*fos* and Jun-B, in the PCs [96]. Induction of immediate-early genes could then represent a mechanism by which sustained inputs are transformed into long-term biochemical changes that are required for the maintenance of cerebellar long-term plasticity, such as LTD.

NE receptors have also been found in the cerebellar nuclei, and NE modulates the GABAergic neurons inhibition of deep cerebellar neurons [39].

Noradrenergic fibers project to the IO [97]. In IO cells, NE has been shown to have an effect opposite to that of serotonin, as bathing IO neurons with NE stops oscillations previously induced by serotonin [75].

2.2.3. Behavioral effects

The level of NE has been related to cerebellar learning. First, exposure to an environment rich in new sensory-motor associations to learn increases NE content significantly in the cerebellum [92]. Second, there is a significant correlation between the loss of the neuromodulatory actions of NE in the cerebellar cortex and the rate of learning a novel motor task in rats [12]. Finally, NE depletion impairs acquisition of a new locomotor task [128] and suppresses the adaptive capacity of the vestibulospinal and vestibulo-ocular reflexes [96]. Note, however, that evidence from the eye-blink conditioning paradigm demonstrates that lesions of the locus of coeruleus (which result in decreased level cerebellar NE) do not affect acquisition of conditioned responses. However, in these animals, extinction of conditioned responses was disrupted [83].

2.3. Acetylcholine

The cholinergic input to the cerebellum, although sparser than to the forebrain and midbrain area, is nonnegligible. The cholinergic input makes a diffuse plexus of beaded fibers in the cerebellar cortex and cerebellar nuclei [9,10],[2] which originate in the pedunculopontine tegmental nucleus (PPTN), the lateral paragigantocellular nucleus, and, to a lesser extent, in various raphe nuclei [53].[3]

Application of ACh produces a strong and long-lasting increase of glutamate response of PCs [4]. Thus, ACh appears to potentiate GC–PC synapses, presumably via muscarinic acetylcholine receptors [4]. The other receptor

[2] A subpopulation of MFs ending in the flocculo-nodular lobe uses ACh as a transmitter; here, we only consider the diffuse system, which is the only one that can be considered 'neuromodulatory'.

[3] These projections show large interspecies variability, but also heterogeneity between cerebellar lobules in the same species [53].

type, nicotinic acetylcholine receptors, may also be involved in the modulation of cerebellar activity: most PCs, the GC layers in the deep nucleus, possess this receptor type [40]. In the cerebellar nuclei, the ACh fibers form a moderately dense network and could have a significant, but yet unknown, effect on neuronal activity [53].

2.4. Dopamine

Although the dopaminergic projections to the basal ganglia and cerebral cortex are well known, there are also dopaminergic projections to the cerebellum, although sparse. In particular, the ventral tegmental area, containing the A10 dopaminergic cell group, sends projection fibers to the cerebellar cortex [45].

In the cerebellar cortex, Purkinje neurons show the most dopamine receptor protein immunoreactivity [8]. Dopamine can influence plasticity in Purkinje cells in two ways. First, DARPP-32, a dopamine and adenosine 3′ :5′ -monophosphate (cAMP) regulated phosphoprotein of M(r) 32 kDa, which is expressed in PCs [3], may play a role in regulation of cerebellar LTD. Second, DARPP-32 has been shown to be required for the expression of rebound potentiation [59]. Taken together, it is likely that dopamine acts on PCs through cAMP and DARPP-32 cascades and regulates the responsiveness of PCs to GABA via the expression of rebound potentiation.

2.5. Histamine

Histamine, which is thought to be important in regulating the level of behavioral arousal, is found in nerve cell bodies of the tuberomammillary nucleus in the mammalian brain and has been shown to send projections to the cerebellar cortex [95] to both the PC layer and in the granular cell layer [132]. Histamine exerts an effect via both H1 and N2 receptors on the GCs [74] and an excitatory on the PCs via H2 receptors [122].

3. Learning theories of the cerebellum[4]

3.1. Supervised learning of internal models

In contrast to the numerous GC inputs to a PC (up to 10^6 in man), there is only one CF per PC in the adult. This peculiar architecture has led Marr [78], Albus [2], and Ito [50] to propose that each PCs acts as a one-layer supervised neural device: the GCs provide a sensorimotor context to the PCs and the CFs carry the error signal necessary for modifying GC–PC synapses in a supervised manner. Thus, the IO transmits the error E_i, and the changes in GC–PC synaptic strength are regulated by LTD. In its most simple form, LTD is modeled as a fraction of the product of the error term and the GC activity.[5]

Further, extending the supervised learning paradigm to powerful sensorimotor control schemes, several cerebellar theories postulate that the cerebellum provides neural internal models of the physical system to control movements accurately [60,85]. There are two major classes of internal models: inverse and forward. An inverse model is a neural circuit that can produce the appropriate motor commands according to the desired movement. An example is to predict what arm motor command is necessary to realize desired acceleration under current position and velocity. Inverse models allow, thanks to their feed-forward mode of operation, for fast movement control in the face of the long conduction delays that are omnipresent in the nervous system. A forward model is a neural circuit that can predict the sensory consequence of the motor commands sent to the muscles. An example is to predict how the arm would respond to a neural command, given its current position and velocity. Forward models allow, thanks to their predictive capabilities, for planning and delay compensation.

An inverse model of a body part dynamics (e.g., eye, arm,. . .) can be learned by feedback error learning [60], with the help of a feedback controller. In this scheme, the IO input to the cerebellum transmits the feedback error, which approximates the directions and magnitudes of the necessary modifications to the inverse neural model. After learning, the motor command is mostly generated in a feed-forward manner by the cerebellum, and the feedback loop only ensures robustness in the face of perturbation and noise. Feedback error learning is compatible with the facts that the IO carries error signals (see above), LTD, and the precise one-to-one anatomical correspondence between each microzone, a small portion of the deep nucleus, a small region of the IO, and a motor network [60]. Simulations have shown that learned cerebellar inverse models can increase the accuracy of saccadic movements by compensating for the nonlinearity of the eye ball [107,108] or increase the accuracy of fast arm reaching movements by compensating for interaction torques [109,110]. The feedback error learning of inverse models is supported by PC recordings in the ventral paraflocculus during ocular following response: a class of PCs has been shown to carry signals that can be accurately reconstructed with an inverse dynamics model [114].

A forward model can be simply learned by self-generated movements. The error between the real sensory input and the predicted sensory input, presumably carried by IO neurons, is used to train the model in the cerebellum. Although there is no definitive evidence yet that parts of the cerebellum act as forward models, there is a number of supporting evidence, from functional imaging [37,49,54], clinical [28,93], and simulation studies [85].

[4] We limit here our discussion to the role of the cerebellum in sensorimotor control.

[5] Note that a LTP term, which can be implemented by synaptic weight normalization, is necessary to ensure that all the synaptic efficacies do not become zero (see Ref. [112]).

3.2. Modular modulation

3.2.1. Multiple internal models

Although the nervous system could potentially learn a single forward and a single inverse models, a general purpose internal model can be advantageously replaced by a modular system that include multiple internal forward and inverse models for the following three reasons [61]. First, the environment is essentially modular, as individuals interact with multiple qualitatively different objects and environment. Second, the use of multiple models allows individual models to participate in learning without affecting the motor behavior already learned by other models. Third, by combining the output of multiple modules, a very large repertoire of behaviors can be generated. Schemes for motor learning and control based on multiple pairs of internal models and controllers have been proposed and shown to be able to control complex systems [32,42].

The multiple internal model hypothesis has received recent experimental support. Using a computer mouse with rotated pointing directions, Imamizu et al. [46] showed that subjects could learn how to manipulate two different kinds of unusual computer mouse and, after learning, could quickly switch between the two. Further, two different sets of activation spots were found in the lateral cerebellum, which were interpreted as correlates of two internal models [47]. In light of these data, we assume that each cerebellar microzone acquires an internal model. This can be achieved by the precise one-to-one anatomical correspondence between each microzone, a small region of the IO, a small portion of the deep nucleus, and a motor network [60].

3.2.2. Modular responsibility signals

Crucial to the multiple internal model schemes are the 'responsibility signals' that are used both for weighting the model outputs and for gating the learning of the internal models [32,42]. Multiple internal model control schemes always require the learning of multiple forward models. The prediction error E_i for each model is given by the difference between the forward model output and the sensory input.[6]

Each responsibility signal gives the relative goodness of the predictions of multiple forward models, i.e., if the model output is 'far' from the present dynamics of the environment (the environment can be an arm for instance), its responsibility signal will be small, and vice versa. How could these responsibility signals be computed in the central nervous system? A responsibility signal is specific to one internal model, but must be diffused to all the neurons making the internal model. It has both short-term gating effect on the output of the model and long-term learning effects. Furthermore, computation of a responsibility signal requires the prediction error between the forward model and the sensory input. Finally, a responsibility signal is normalized by the prediction errors of all models. Such a responsibility signal λ_i can be implemented with a soft-max function[7].

Table 2
The four theoretically derived cerebellar 'diffuse signals', their functions, desired spatial extent, and effects duration

Signal function	Spatial extent	Effects	
		Fast	Slow
Responsibility signal λ_i	modular	○	○
Error-based unsupervised learning gating signal g	global		○
Performance-based learning rate signal α	global	○	
Reward-based signal δ	global		○

Note that the learning rate signal is modulated rapidly but induces long-term effects (synaptic strength change).

These requirements are best fulfilled by a modular neuromodulator signal, which would be specific to each microcomplex. This modular neuromodulator would have both short-term effects (for control) and long-term effects (for learning) on the neurons of the microcomplex. We call this responsibility signal diffuse signal 1 (Table 2).

3.3. Global modulation

3.3.1. Error-based modulation of unsupervised and supervised learning in the granule cell layer

Learning highly nonlinear internal models with neural networks requires powerful learning techniques such as back-propagation: the error signals from the output layer of the neural network are 'back-propagated' to the intermediate layers. As it is unlikely that such precise back-propagation of the error signals from the PCs to the GCs can take place, how can the cerebellum learn internal models efficiently?

Marr [78] and Albus [2] proposed that supervised learning in the PCs is facilitated if the GCs act from a 'sparse code' in which MF inputs are recoded onto highly dissimilar patterns by the GCs and thus are easily learnable by the PCs. We further proposed that learning 'good' GC sparse codes requires three activity-dependent plastic processes: GC firing homeostasis, Hebbian MF–GC synapses—see Ref. [5] for supporting evidence—and anti-Hebbian GO–GC synapses [112].

In a continuous reaching movement task, these unsupervised learning rules greatly facilitated learning of an inverse model of the arm [112]. However, if prolonged periods of inaction alternate with short periods of activity, the GCs eventually learn to respond only to the arm's position, the only variable represented in MFs during inaction [124].

[6] The prediction error E_i for each model is formally given by $E_i = (\hat{x}_i(t) - x(t))^2$, where $\hat{x}_i(t)$ is the output of the ith forward model and $x(t)$ is the true value given by the sensory input.

[7] The responsibility signal, λ_i results from a competition implemented by a soft-max function $\lambda_i = e^{(-(E_i/\sigma)^2)} / \sum_j e^{(-(E_j/\sigma)^2)}$, where E_i is the prediction error of the forward model. The sum in the denominator is over all the forward internal models and makes λ_i sum up to 1. σ controls the overlap between models or the 'sharpness' of the response.

Because learning the inverse dynamic models for arm control requires position, velocity, and acceleration inputs, performance becomes poor during movement. To solve this stability–plasticity problem, we earlier proposed that a diffuse gating signal turns on plastic processes in the GC layer only when movement is generated, thus stabilizing unsupervised learning rules, regardless of the frequency of motor activity [112].

Replacing this simple binary gating signal (movement on or off) by a slightly more complex signal can dramatically improve learning performance. The unsupervised learning rules listed above, although creating desirable sparse code from an information theoretic standpoint, do not take into account the goal of the microcomplex, i.e., learning an internal model. Because LTD is the result of correlation between GC and IO inputs, the usefulness of the GC code resides in preparing goal-directed inputs to the PCs (here, 'goal' refers to the goal of the microcomplex, not that of the animal—see below). Consequently, it is desirable that the GC code possesses an adaptive resolution, thereby providing the PC with fine inputs where they need to learn to compensate for large movement errors. This is achieved if the gating signal is related to the error in performance [34]. We [112] modeled these global gating signals the sum of the absolute values of individual model errors.[8] Simulations showed that adaptive resolution does not lead to large improvements in learning performance (plasticity), but also maintains performance during rest (stability).

Although we did not implement it in our model, such neuromodulatory gating of both rebound potentiation of the GABA–PC and of LTD of the GC–PC synapses would be very useful in the real cerebellum. The IO cells are known to have a background activity relatively high compared to their maximum rate. If LTD could be induced at all times, it is probable that the synapses that were adapted during movement errors would soon be "erased"—the PC would soon lose its functional input output mapping so crucial in learning the internal models. Thus, the gating signal g could allow LTD and rebound potentiation only during errors in movement.

3.3.2. Performance-based modulation of supervised learning

To respond rapidly to changes in the environment, the learning rates of the modifiable cerebellar synapses should be adequate to allow fast learning at the system level. Overly large learning rates are not desirable in adaptive neural networks as they can induce oscillations in the patterning of synaptic weights and even divergence [44]. Conversely, excessively small learning rates slow down the system's learning. For quick and accurate learning, the learning rate should be initially set large but gradually decreased. Doya [31] proposed a theory of the roles of neuromodulators in terms of setting the meta-parameters; in particular, a diffuse signal controls the learning rate values in time in a feed-forward manner. Since the performance of the cerebellar networks is crucial to the setting of the PC synaptic learning rate, we propose that it is set by a neuromodulator.

3.3.3. Reward-based modulation of supervised learning

In the cerebellum, there are only a few thousands microcomplexes—and thus as many possible internal models. An organism, however, must focus on forming effective models of the external environment only when the behavior enhance the wellness of the animal, i.e., when the behavior increase the chances to get any reward.

In the multiple internal model schemes described above, learning is not related to the goal of the animal—every experience it encounters is learned. We propose here that the experiences most relevant to the wellness of the animal, i.e., those that are associated with rewards, lead to largest internal model updating by modulating the supervised learning rule. Note that unlike the above feed-forward modulation of supervised learning, this modulation is based on feedback information given by rewards. This reward-dependent signal is a global signal that is sent to all the internal models.

In Table 2, we summarize the four 'diffuse signals', their functions, and desired spatial extent. We now review the different cerebellar extrinsic neuromodulators and their multiple effects on the cerebellar circuitry.

4. A theory of cerebellar neuromodulation

We are now ready to give a theoretically motivated account of the data regarding the different neuromodulators reviewed above (summarized in Table 3).

4.1. Serotonin: responsibility signals

We propose here that serotonin fibers carry the responsibility signals λ_i necessary for learning and controlling appropriate internal models. For serotonin to carry responsibility signals, five conditions need to be met: (1) modularity of the projections, (2) short-term role in internal model

Table 3
The four theoretically derived 'diffuse signals' with their putative biological counterparts

Signal function	Spatial extent	Putative neuromodulator
Responsibility signal λ_i	modular	serotonin
Error-based unsupervised learning gating signal g	global	norepinephrine
Performance-based learning rate signal α	global	acetylcholine
Reward-based signal δ	global	dopamine

[8] We modeled these global gating signals the sum of the absolute values of individual model errors: $g = \sum_i |E_i|$, where i is the index of the model and E_i is the error of for each internal model.

selection, (3) long-term role in internal model learning, (4) activity correlating with the error in internal forward model predictions, and (5) cross-talk between the responsibility signal to perform the normalization (the sum of all the responsibility signal is equal to 1) necessary to compute the responsibility signals. We now propose that all these conditions have biological plausibility.

4.1.1. Modularity

As reviewed above, serotonin fiber projections are topographically organized; thus, it is conceivable that each microcomplex has its own private serotonin projection that carries λ_i. We do not propose that the cerebellum acts like one large controller with thousands of internal models working together. Instead, we propose that there are multiple subsystems working in parallel (such systems could be the arm control system, the locomotion system, etc...). The cerebellar input–output projections, including the serotonergic subnuclei in the brainstem, define the number and the extent of these systems. For one system, there may be dozens of microzones each controlled by its own responsibility signal.

4.1.2. Short-term role

All short-term effects of the serotonin in the cerebellar cortex (on inputs to MF, MF firing, MF–GC transmission, GC firing, Lugaro cell firing, PC membrane excitability, pre- and postsynaptic effects on glutamatergic PC synapses, short-term GABA modulation, NUC firing, and IO firing) point to a role in serotonin in the control of microzone activity. Furthermore, the strong, triggering effects on Lugaro cells can activate very large number of GCs and thus recruit selectively the microzones associated with a high responsibility signal.

Further, serotonin modulation of microcomplex outputs by fast inhibitory influence on deep nuclear cells can further sharpen the cerebellar output. As the 5-HT projections to the cerebellar nuclei are not collaterals of those projecting to the cortex, the modulatory effect of serotonin on these structures is different. Thus, we hypothesize that serotonin in the cerebellar nuclei blocks the outputs of the internal models with small responsibility signals—the models with high responsibility signals are not affected.

4.1.3. Long-term role

The long-term plastic effects associated with serotonin (via modulation of both GABAergic synapses rebound potentiation and LTD) are consistent with serotonin being a responsibility signal that modulates the learning of internal models. Finally, serotonin modulation of IO firing can make the IO cells sensitive to small errors in occurring when learning to compensate for small movement errors.

4.1.4. Error signals

Serotonin level in the cerebellar cortex is specifically and positively correlated to the level of motor activity of the animal [84]. Furthermore, because common fibers innervate both the IO and the serotonergic neurons [17,113], we propose that the serotonergic fibers carry errors between the real sensory input and the predicted sensory input from internal forward model. These errors can be computed, for instance, at the level of the zona incerta, which is known to receive inputs from the deep cerebellar nuclei [101].

4.1.5. Normalization

Although little is known about medullary serotonergic neurons, serotonergic neurons in the raphe contain large number of 5-HT1A autoreceptors. Furthermore, in the raphe nuclei, there are high levels of extracellular serotonin, which are controlled by intrinsic serotonergic mechanisms as well as afferent connection [1]. We make a parallel here for the medullary serotonergic neurons and assume that, within subsystems, serotonin neurons that are activated release extracellular serotonin locally. As in the cerebellar cortex, this extracellular serotonin diffuses to neighboring serotonergic cells and activates inhibitory 5H1A receptors in these cells. The resulting decrease of activity of all the neurons in a subsystem has in effect a normalization role.

4.2. Norepinephrine: error-based modulation of unsupervised and supervised learning

Noradrenergic neurons in the locus coeruleus are activated in urgent situations, in relation to novel stimuli, and are less active during sleep. In primates, high levels of LC discharge are related to decreased foveation, restlessness, and impaired task performance [7]. Further, locus coeruleus activation is associated with cortical processing mechanisms and in learning the significance of behaviorally important stimuli.

Thus, NE neurons seem to fire most strongly during large differences between internal model sensory predictions and actual sensory input. We therefore propose that the NE neuron response transmit the gating signal for the three forms of unsupervised learning in the GC layer (MF–GC Hebbian learning, GC–GO anti-Hebbian learning, and GC homeostatic process) for rebound potentiation at the GABA–PC synapses and LTD at the GC–PC synapses. The gating signal $\sum_i |E_i|$ could be computed in part via projections from the cerebellar nuclei to the locus coeruleus [21].

Our 'gating of learning' hypothesis of cerebellar NE is in agreement with the proposed role of neuromodulators (such as NE a and ACh) as switches of long-term potentiation [43]. It is also in agreement with most data reviewed above. First, NE has long-term effects on both GC neurons and inhibitory interneuron synapses, and NE could be the gate controlling the plastic processes of the MF–GC and GO–GC synapses and of the GC homeostatic process. Second, the GABA–PC rebound potentiation and the increase of the expression of immediate-early genes in PCs can potentially show that the gating function can be extended to all plastic

synapses in the cerebellar cortex. Finally, the reduction of the firing of the IO cells by NE—the opposite effect to that of serotonin—keeps the firing of the IO to a low level even in the face of large errors. Note that because the NE projections are, unlike those of serotonin, very diffuse, this gating signal is sent too all microcomplexes simultaneously: only in those that receive strong MFs input will induce significant plasticity. Further, note that we did not give an account of the data demonstrating that decrease of cerebellar NE in the eye-blink conditioning paradigm disrupts the extinction, but not in the acquisition, of conditioned responses.

4.3. Acetylcholine: performance-based modulation of supervised learning

Acetylcholine appears to control the balance between the storage and update of memory at the both cellular and circuit levels [43]. A number of methods for automatically tuning the learning rate parameter have been proposed. One of those, known as the delta-bar-delta [105,118] method, detects oscillations in the error signal, which means that the setting of the learning rate is too large. It has been proposed [31] that according to such a regulatory mechanism, frequent changes in the direction of the error would have an inhibitory effect on the learning rate represented by the cholinergic system.

Here we propose a similar function for cerebellar ACh, i.e., optimal global setting of learning rates at GC–PC synapses (Table 2). This is consistent with data showing that ACh potentiates the GC–PC synapses via muscarinic receptors.

A short-term effect of ACh on cerebellar output, via nicotinic receptors, is also possible. The cholinergic fibers arising in the PPTN could modulate the excitability of the cerebello-nuclear neurons in relation to sleep and arousal [53,82]. Further, as the PPTN has been linked to the motor performance [48], and specifically in relation to the attention or vigilance level of the animal [70], the ACh input could modulate the cerebellar on-line control of movements.

4.4. Dopamine: reward-based modulation of learning

Although there is to our knowledge no study of the behavioral effect of cerebellar dopamine, dopamine is traditionally seen as the signal for reward prediction [104]. Dopamine neurons respond to rewards early in learning, or when reward is given unexpectedly outside the task. After learning is completed, dopamine neurons respond to stimuli predicting the reward and do not respond to the reward itself. If the reward is omitted, dopamine neuron activity is depressed. Such changes in response closely resemble the behavior of the called temporal difference errors in models of reinforcement learning [104].

We propose here that dopamine fibers in the cerebellum carry a diffuse signal that gates learning of the internal models: only those forward models that are beneficial to the survival of the animal are learned. This hypothesis is consistent with the data regarding dopamine reviewed above, notably the possible dopamine modulation of cerebellar LTD. We speculate that LTD is then a monotonically increasing function of the dopamine level. Note that this type of three-way learning rule involving dopamine has been shown in the striatal neurons [100].

5. Conclusion

We reviewed the cerebellar neuromodulation and showed the multiple effects that neuromodulators have on the cerebellar circuitry. Then, we reviewed cerebellar learning theories and models and showed that several diffuse signals are needed for powerful cerebellar adaptive control. These top-down and bottom-up reviews allowed us to match each of the theory-derived diffuse signals with one neuromodulator, as given in Table 3. Incorporating neuromodulator function makes the current cerebellar learning models more powerful, realistic, and complementary. First, serotonin, by encoding the responsibility signals, allows the cerebellum to learn multiple internal models efficiently and switch between these models when needed. Second, norepinephrine allows the cerebellum to maintain sophisticated learning algorithm to acquire the internal models, notably in the granule cells. Third, acetylcholine allows the supervised learning update of the models to be directed by the attentional state of the animal. Finally, dopamine allows some degree of reward-dependent learning in the cerebellum and thus an optimal allocation of the neural resources as a function of the needs of the animal.

We gave an account of most known effects of the cerebellar extrinsic aminergic neuromodulators. However, we did not give an account of the following neuromodulatory functions.

(1) Short-term effects of norepinephrine and Ach.
(2) Role of histamine. Although histamine is involved in the wake–sleep cycle, and excite PCs, lack of data and general understanding of histamine functions do not allow us to make testable prediction regarding its role in cerebellar functions.

Besides the extrinsic aminergic neuromodulators reviewed above, the cerebellum is also endowed with other neuromodulators, for which we did not provide functional roles. In particular, corticotrophin release factor (CRF) functions as a cerebellar neuromodulator [66] and has been identified to be released by climbing fibers [14]. Infusions of CRF in the cerebellum alter firing responses in both Purkinje cells and neurons of the deep nucleus [14]. Further, CRF has been shown to suppress Purkinje cell afterhyperpolarization [35]. Finally, in slice, application of CRF antagonists blocks cerebellar LTD [89].

The cerebellum also contains several *intrinsic* neuromodulators, whose functions remain to be elucidated: GABA spillover in GC glomeruli (e.g., Ref. [41]), cannabinoids [71,133], and nitric oxide (e.g., Ref. [23]—but see possible function in Ref. [106]).

In the cerebellum, like in all other neural circuits, although the potential advantage of neuromodulation is flexibility, the drawback is that this potential must be accompanied by circuit designs that prevent overmodulation or loss of function [77]. In particular, it is critical that the neuromodulator levels must be controlled to their 'just' levels. Two types of control are possible: (1) control via external feedback loop and (2) local control. Regarding serotonin, we made the testable predictions that the regulation of serotonin is achieved both externally (via cerebellar inputs to the zona incerta, which then projects to the serotonergic neurons innervating the cerebellum) and locally at the level of the serotonergic neurons themselves (via the inhibitory effect of external serotonin). It is also possible that serotonin release is controlled locally in the cerebellar cortex via the level of the extrinsic neuromodulator nitric oxide [98], which itself can be modulated by local activity (e.g., Ref. [106]). Although the control of norepinephrine is less well defined, projections from the cerebellar nuclei to the locus coeruleus [21] could possibly control the norepinephrine level. In particular, these projections could participate in the computation of the proposed gating signal carried by norepinephrine. For dopamine, a closed loop pathway that has been identified is the closed loop pathway between the cerebellum and with dopamine neurons: the ventral tegmental area receives feedback projection fibers from the lateral and interpositus cerebellar nuclei [45]. New experiments designed to further elucidate these feedback pathways are crucial to better elucidate the systems view of cerebellar neuromodulation that we outlined here.

References

[1] A. Adell, P. Celada, M.T. Abellan, F. Artigas, Origin and functional role of the extracellular serotonin in the midbrain raphe nuclei, Brain Res. Brain Res. Rev. 39 (2002) 154–180.

[2] J.S. Albus, The theory of cerebellar function, Math Biosci. 10 (1971) 25–61.

[3] R. Alder, H. Barbas, Complementary distribution of the phosphoproteins DARPP-32 and I-1 in the cerebellar system, NeuroReport 6 (1995) 2368–2372.

[4] P. Andre, O. Pompeiano, S.R. White, Activation of muscarinic receptors induces a long-lasting enhancement of Purkinje cell responses to glutamate, Brain Res. 617 (1993) 28–36.

[5] S. Armano, P. Rossi, V. Taglietti, E. D'Angelo, Long-term potentiation of intrinsic excitability at the mossy fiber-granule cell synapse of rat cerebellum, J. Neurosci. 20 (2000) 5208–5216.

[6] D.L. Armstrong, M. Hay, D.M. Terrian, Modulation of cerebellar granule cell activity by iontophoretic application of serotonergic agents, Brain Res. Bull. 19 (1987) 699–704.

[7] G. Aston-Jones, C. Chiang, T. Alexinsky, Discharge of noradrenergic locus coeruleus neurons in behaving rats and monkeys suggests a role in vigilance, Prog. Brain Res. 88 (1991) 501–520.

[8] P. Barili, E. Bronzetti, A. Ricci, D. Zaccheo, F. Amenta, Microanatomical localization of dopamine receptor protein immunoreactivity in the rat cerebellar cortex, Brain Res. 854 (2000) 130–138.

[9] N.H. Barmack, R.W. Baughman, F.P. Eckenstein, Cholinergic innervation of the cerebellum of rat, rabbit, cat, and monkey as revealed by choline acetyltransferase activity and immunohistochemistry, J. Comp. Neurol. 317 (1992) 233–249.

[10] N.H. Barmack, R.W. Baughman, F.P. Eckenstein, H. Shojaku, Secondary vestibular cholinergic projection to the cerebellum of rabbit and rat as revealed by choline acetyltransferase immunohistochemistry, retrograde and orthograde tracers, J. Comp. Neurol. 317 (1992) 250–270.

[11] C. Batini, The cerebellar projections form the neurons of the raphe nuclei and the origin of the serotonergic innervation of the cerebellum, Serotonin, The Cerebellum, and Ataxia, Raven Press, New York, 1993, pp. 51–61.

[12] P. Bickford, Motor learning deficits in aged rats are correlated with loss of cerebellar noradrenergic function, Brain Res. 620 (1993) 133–138.

[13] P.C. Bickford, B.J. Hoffer, R. Freedman, Interaction of norepinephrine with Purkinje cell responses to cerebellar afferent inputs in aged rats, Neurobiol. Aging 6 (1985) 89–94.

[14] G.A. Bishop, Brainstem origin of corticotropin-releasing factor afferents to the nucleus interpositus anterior of the cat, J. Chem. Neuroanat. 15 (1998) 143–153.

[15] G.A. Bishop, R.H. Ho, The distribution and origin of serotonin immunoreactivity in the rat cerebellum, Brain Res. 331 (1985) 195–207.

[16] C. Bishop, C.W. Kerr, Y.F. Chen, J.S. King, The serotonergic system in the cerebellum: origin, ultrastructural relationships, and physiological effects, Serotonin, The Cerebellum, and Ataxia, Raven Press, New York, 1993, pp. 91–112.

[17] S.M. Carlton, G.R. Leichnetz, J.D. Mayer, Projections from the nucleus parafascicularis prerubralis to medullary raphe nuclei and inferior olive in the rat: a horseradish peroxidase and autoradiography study, Neurosci. Lett. 30 (1982) 191–197.

[18] R. Cespuglio, H. Faradji, M. Jouvet, Voltammetric detection of extracellular 5-hydroxyindole compounds at the level of cell bodies and the terminals of the raphe system: variations during the wake–sleep cycle in the rat in chronic experiments, C. R. Seances Acad. Sci. III 296 (1983) 611–616.

[19] W.Y. Chen, J.J. Wang, Q.X. Yu, Effects of dorsal raphe stimulation on activities of cerebellar nuclear neurons in the rat, Sheng Li Xue Bao 48 (1996) 132–140.

[20] J.E. Cheun, H.H. Yeh, Noradrenergic potentiation of cerebellar Purkinje cell responses to GABA: cyclic AMP as intracellular intermediary, Neuroscience 74 (1996) 835–844.

[21] R.M. Clavier, Afferent projections to the self-stimulation regions of the dorsal pons, including the locus coeruleus, in the rat as demonstrated by the horseradish peroxidase technique, Brain Res. Bull. 4 (1979) 497–504.

[22] V. Cornea-Hebert, M. Riad, C. Wu, S.K. Singh, L. Descarries, Cellular and subcellular distribution of the serotonin 5-HT2A receptor in the central nervous system of adult rat, J. Comp. Neurol. 409 (1999) 187–209.

[23] F. Crepel, D. Jalliard, Protein kinases, nitric oxide and long term depression of synapses in the cerebellum, NeuroReport 1 (1990) 133–136.

[24] P.A. Cumming-Hood, H.K. Strahlendorf, J.C. Strahlendorf, Effects of serotonin and the 5-HT2/1C receptor agonist DOI on neurons of the cerebellar dentate/interpositus nuclei: possible involvement of a GABAergic interneuron, Eur. J. Pharmacol. 236 (1993) 457–465.

[25] H. Daniel, C. Levenes, F. Crepel, Cellular mechanisms of cerebellar LTD, Trends Neurosci. 21 (1998) 401–407.

[26] E.J. Darrow, H.K. Strahlendorf, J.C. Strahlendorf, Response of cerebellar Purkinje cells to serotonin and the 5-HT1A agonists 8-

OH-DPAT and ipsapirone in vitro, Eur. J. Pharmacol. 175 (1990) 145–153.
[27] I. Dean, S.J. Robertson, F.A. Edwards, Serotonin drives a novel GABAergic synaptic current recorded in rat cerebellar Purkinje cells: a Lugaro cell to Purkinje cell synapse, J. Neurosci. 23 (2003) 4457–4469.
[28] H.C. Diener, J. Hore, R. Ivry, J. Dichgans, Cerebellar dysfunction of movement and perception, Can. J. Neurol. Sci. 20 (Suppl. 3) (1993) S62–S69.
[29] S. Dieudonne, A. Dumoulin, Serotonin-driven long-range inhibitory connections in the cerebellar cortex, J. Neurosci. 20 (2000) 1837–1848.
[30] O. Dillon-Carter, D.M. Chuang, Homologous desensitization of muscarinic cholinergic, histaminergic, adrenergic, and serotonergic receptors coupled to phospholipase C in cerebellar granule cells, J. Neurochem. 52 (1989) 598–603.
[31] K. Doya, Metalearning and neuromodulation, Math. Sci. 38 (2000) 19–24.
[32] K. Doya, K. Samejima, K. Katagiri, M. Kawato, Multiple model-based reinforcement learning, Neural Comput. 14 (2002) 1347–1369.
[33] M.S. Duxon, T.P. Flanigan, A.C. Reavley, G.S. Baxter, T.P. Blackburn, K.C. Fone, Evidence for expression of the 5-hydroxytryptamine-2B receptor protein in the rat central nervous system, Neuroscience 76 (1997) 323–329.
[34] M. Eldracher, A. Staller, R. Pompl, Adaptive encoding strongly improves function approximation with CMAC, Neural Comput. 9 (1997) 403–417.
[35] E.A. Fox, D.L. Gruol, Corticotropin-releasing factor suppresses the afterhyperpolarization in cerebellar Purkinje neurons, Neurosci. Lett. 149 (1993) 103–107.
[36] R. Freedman, B.J. Hoffer, D. Puro, D.J. Woodward, Noradrenaline modulation of the responses of the cerebellar Purkinje cell to afferent synaptic activity, Br. J. Pharmacol. 57 (1976) 603–605.
[37] J.H. Gao, L.M. Parsons, J.M. Bower, J. Xiong, J. Li, P.T. Fox, Cerebellum implicated in sensory acquisition and discrimination rather than motor control, Science 272 (1996) 545–547.
[38] F.J. Geurts, E. De Schutter, J.P. Timmermans, Localization of 5-HT2A, 5-HT3, 5-HT5A and 5-HT7 receptor-like immunoreactivity in the rat cerebellum, J. Chem. Neuroanat. 24 (2002) 65–74.
[39] T.J. Gould, C.E. Adams, P.C. Bickford, Beta-adrenergic modulation of GABAergic inhibition in the deep cerebellar nuclei of F344 rats, Neuropharmacology 36 (1997) 75–81.
[40] A. Graham, J.A. Court, C.M. Martin-Ruiz, E. Jaros, R. Perry, S.G. Volsen, S. Bose, N. Evans, P. Ince, A. Kuryatov, J. Lindstrom, C. Gotti, E.K. Perry, Immunohistochemical localisation of nicotinic acetylcholine receptor subunits in human cerebellum, Neuroscience 113 (2002) 493–507.
[41] M. Hamann, D.J. Rossi, D. Attwell, Tonic and spillover inhibition of granule cells control information flow through cerebellar cortex, Neuron 33 (2002) 625–633.
[42] M. Haruno, D.M. Wolpert, M. Kawato, Mosaic model for sensorimotor learning and control, Neural Comput. 13 (2001) 2201–2220.
[43] M.E. Hasselmo, C. Linster, Neuromodulation and memory functions, in: P.S. Katz (Ed.), Beyond Neurotransmission, Oxford Univ. Press, Oxford, 1999, pp. 319–348.
[44] J. Hertz, A. Krogh, R. Palmer, Introduction to the Theory of Neural Computation, Addison-Wesley Pub. Comp., Redwood City, CA, 1991.
[45] Y. Ikai, M. Takada, Y. Shinonaga, N. Mizuno, Dopaminergic and non-dopaminergic neurons in the ventral tegmental area of the rat project, respectively, to the cerebellar cortex and deep cerebellar nuclei, Neuroscience 51 (1992) 719–728.
[46] H. Imamizu, S. Miyauchi, T. Tamada, Y. Sasaki, R. Takino, B. Putz, T. Yoshioka, M. Kawato, Human cerebellar activity reflecting an acquired internal model of a new tool, Nature 403 (2000) 192–195.
[47] H. Imamizu, T. Kuroda, S. Miyauchi, T. Yoshioka, M. Kawato, Modular organization of internal models of tools in the human cerebellum, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 5461–5466.
[48] W.L. Inglis, P. Winn, The pedunculopontine tegmental nucleus: where the striatum meets the reticular formation, Prog. Neurobiol. 47 (1995) 1–29.
[49] K. Inoue, R. Kawashima, K. Satoh, S. Kinomura, R. Goto, M. Koyama, M. Sugiura, M. Ito, H. Fukuda, PET study of pointing with visual feedback of moving hands, J. Neurophysiol. 79 (1998) 117–125.
[50] M. Ito, The Cerebellum and Neuronal Control, Raven Press, New York, 1984.
[51] M. Ito, Long-term depression, Annu. Rev. Neurosci. 12 (1989) 85–102.
[52] M. Ito, M. Sakurai, P. Tongroach, Climbing fiber induced long term depression of both mossy fiber responsiveness and glutamate sensitivity of cerebellar Purkinje cells, J. Physiol. (1982) 113–134.
[53] D. Jaarsma, T.J. Ruigrok, R. Caffe, C. Cozzari, A.I. Levey, E. Mugnaini, J. Voogd, Cholinergic innervation and receptors in the cerebellum, Prog. Brain Res. 114 (1997) 67–96.
[54] M. Jueptner, S. Ottinger, S.J. Fellows, J. Adamschewski, L. Flerich, S.P. Muller, H.C. Diener, A.F. Thilmann, C. Weiller, The relevance of sensory input for the cerebellar control of movements, NeuroImage 5 (1997) 41–48.
[55] E.R. Kandel, J.H. Schwartz, T.M. Jessel, Principles of Neural Science, McGraw-Hill, New York, 2000.
[56] M. Kano, U. Rexhausen, J. Dreessen, A. Konnerth, Synaptic excitation produces a long-lasting rebound potentiation of inhibitory synaptic signals in cerebellar Purkinje cells, Nature 356 (1992) 601–604.
[57] P.S. Katz, Beyond Neurotransmission, Oxford Univ. Press, Oxford, 2000.
[58] S. Kawaguchi, T. Hirano, Suppression of inhibitory synaptic potentiation by presynaptic activity through postsynaptic GABA(B) receptors in a Purkinje neuron, Neuron 27 (2000) 339–347.
[59] S.Y. Kawaguchi, T. Hirano, Signaling cascade regulating long-term potentiation of GABA(A) receptor responsiveness in cerebellar Purkinje neurons, J. Neurosci. 22 (2002) 3969–3976.
[60] M. Kawato, H. Gomi, A computational model of four regions of the cerebellum based on feedback-error learning, Biol. Cybern. 68 (1992) 95–103.
[61] M. Kawato, D. Wolpert, Internal models for motor control, Novartis Found. Symp. 218 (1998) 291–304, (discussion 304-297).
[62] C.W. Kerr, G.A. Bishop, Topographical organization in the origin of serotoninergic projections to different regions of the cat cerebellar cortex, J. Comp. Neurol. 304 (1991) 502–515.
[63] C.W. Kerr, G.A. Bishop, The physiological effects of serotonin are mediated by the 5HT1A receptor in the cat's cerebellar cortex, Brain Res. 591 (1992) 253–260.
[64] Y. Kimoto, K. Satoh, T. Sakumoto, M. Tohyama, N. Shimizu, Afferent fiber connections from the lower brain stem to the rat cerebellum by the horseradish peroxidase method combined with MAO staining, with special reference to noradrenergic neurons, J. Hirnforsch. 19 (1978) 85–100.
[65] Y. Kimoto, M. Tohyama, K. Satoh, T. Sakumoto, Y. Takahashi, N. Shimizu, Fine structure of rat cerebellar noradrenaline terminals as visualized by potassium permanganate 'in situ perfusion' fixation method, Neuroscience 6 (1981) 47–58.
[66] J.S. King, P. Madtes Jr., G.A. Bishop, T.L. Overbeck, The distribution of corticotropin-releasing factor (CRF), CRF binding sites and CRF1 receptor mRNA in the mouse cerebellum, Prog. Brain Res. 114 (1997) 55–66.
[67] S. Kitazawa, T. Kimura, P.B. Yin, Cerebellar complex spikes encode both destinations and errors in arm movements, Nature 392 (1998) 494–497.
[68] P.H. Kitzman, G.A. Bishop, The origin of serotoninergic afferents to the cat's cerebellar nuclei, J. Comp. Neurol. 340 (1994) 541–550.

[69] Y. Kobayashi, K. Kawano, A. Takemura, Y. Inoue, T. Kitama, H. Gomi, M. Kawato, Temporal firing patterns of Purkinje cells in the cerebellar ventral paraflocculus during ocular following responses in monkeys: II. Complex spikes, J. Neurophysiol. 80 (1998) 832–848.
[70] Y. Kobayashi, Y. Saito, T. Isa, Facilitation of saccade initiation by brainstem cholinergic system, Brain Dev. 23 (Suppl. 1) (2001) S24–S27.
[71] A.C. Kreitzer, A.G. Carter, W.G. Regehr, Inhibition of interneuron firing extends the spread of endocannabinoid signaling in the cerebellum, Neuron 34 (2002) 787–796.
[72] S. Kuroda, N. Schweighofer, M. Kawato, Exploration of signal transduction pathways in cerebellar long-term depression by kinetic simulation, J. Neurosci. 21 (2001) 5693–5702.
[73] M. Lee, J.C. Strahlendorf, H.K. Strahlendorf, Modulatory action of serotonin on glutamate-induced excitation of cerebellar Purkinje cells, Brain Res. 361 (1985) 107–113.
[74] W.C. Li, X.H. Tang, H.Z. Li, J.J. Wang, Histamine excites rat cerebellar granule cells in vitro through H1 and H2 receptors, J. Physiol. (Paris) 93 (1999) 239–244.
[75] R. Llinas, Y. Yarom, Oscillatory properties of guinea-pig inferior olivary neurones and their pharmacological modulation: an in vitro study, J. Physiol. 376 (1986) 163–182.
[76] T. Maeshima, F. Shutoh, S. Hamada, K. Senzaki, K. Hamaguchi-Hamada, R. Ito, N. Okado, Serotonin2A receptor-like immunoreactivity in rat cerebellar Purkinje cells, Neurosci. Lett. 252 (1998) 72–74.
[77] E. Marder, V. Thirumalai, Cellular, synaptic and network effects of neuromodulation, Neural Netw. 15 (2002) 479–493.
[78] D. Marr, A theory of cerebellar cortex, J. Physiol. 202 (1969) 437–470.
[79] G. Maura, M. Raiteri, Serotonin 5-HT1D and 5-HT1A receptors respectively mediate inhibition of glutamate release and inhibition of cyclic GMP production in rat cerebellum in vitro, J. Neurochem. 66 (1996) 203–209.
[80] G. Maura, A. Ricchetti, M. Raiteri, Serotonin inhibits the depolarization-evoked release of endogenous glutamate from rat cerebellar nerve endings, Neurosci. Lett. 67 (1986) 218–222.
[81] G. Maura, E. Roccatagliata, M. Ulivi, M. Raiteri, Serotonin-glutamate interaction in rat cerebellum: involvement of 5-HT1 and 5-HT2 receptors, Eur. J. Pharmacol. 145 (1988) 31–38.
[82] D.A. McCormick, Cholinergic and noradrenergic modulation of thalamocortical processing, Trends Neurosci. 12 (1989) 215–221.
[83] D.A. McCormick, R.F. Thompson, Locus coeruleus lesions and resistance to extinction of a classically conditioned response: involvement of the neocortex and hippocampus, Brain Res. 245 (1982) 239–249.
[84] A. Mendlin, F.J. Martin, L.E. Rueter, B.L. Jacobs, Neuronal release of serotonin in the cerebellum of behaving rats: an in vivo microdialysis study, J. Neurochem. 67 (1996) 617–622.
[85] R.C. Miall, D.J. Weir, D.M. Wolpert, J.F. Stein, Is the cerebellum a Smith Predictor?, J. Mot. Behav. 25 (1993) 203–216.
[86] G.A. Mihailoff, R.J. Kosinski, S.A. Azizi, B.G. Border, Survey of noncortical afferent projections to the basilar pontine nuclei: a retrograde tracing study in the rat, J. Comp. Neurol. 282 (1989) 617–643.
[87] H. Mitoma, S. Konishi, Long-lasting facilitation of inhibitory transmission by monoaminergic and cAMP-dependent mechanism in rat cerebellar GABAergic synapses, Neurosci. Lett. 217 (1996) 141–144.
[88] H. Mitoma, S. Konishi, Monoaminergic long-term facilitation of GABA-mediated inhibitory transmission at cerebellar synapses, Neuroscience 88 (1999) 871–883.
[89] M. Miyata, D. Okada, K. Hashimoto, M. Kano, M. Ito, Corticotropin-releasing factor plays a permissive role in cerebellar long-term depression, Neuron 22 (1999) 763–775.
[90] M. Mock, C. Schwarz, P. Thier, Serotonergic control of cerebellar mossy fiber activity by modulation of signal transfer by rat pontine nuclei neurons, J. Neurophysiol. 88 (2002) 549–564.
[91] D.B. Morton, D.S. Bredt, Norepinephrine increases cyclic GMP levels in cerebellar cells from neuronal nitric oxide synthase knockout mice, J. Neurochem. 71 (1998) 440–443.
[92] F. Naka, T. Shiga, M. Yaguchi, N. Okado, An enriched environment increases noradrenaline concentration in the mouse brain, Brain Res. 924 (2002) 124–126.
[93] M. Nawrot, M. Rizzo, Chronic motion perception deficits from midline cerebellar lesions in human, Vision Res. 38 (1998) 2219–2224.
[94] O. Oscarsson, Functional organization of olivary projection to the cerebellar anterior lobe, in: J.C., et al (Ed.), The Inferior Olivary Nucleus: Anatomy and Physiology, Raven Press, New York, 1980, pp. 279–289.
[95] P. Panula, H. Takagi, N. Inagaki, A. Yamatodani, M. Tohyama, H. Wada, E. Kotilainen, Histamine-containing nerve fibers innervate human cerebellum, Neurosci. Lett. 160 (1993) 53–56.
[96] O. Pompeiano, Noradrenergic influences on the cerebellar cortex: effects on vestibular reflexes under basic and adaptive conditions, Otolaryngol. Head Neck Surg. 119 (1998) 93–105.
[97] R.E. Powers, D.T. O'Connor, D.L. Price, Noradrenergic innervation of human inferior olivary complex, Brain Res. 523 (1990) 151–155.
[98] H. Prast, A. Philippu, Nitric oxide as modulator of neuronal function, Prog. Neurobiol. 64 (2001) 51–68.
[99] J.R. Raymond, Y.V. Mukhin, A. Gelasco, J. Turner, G. Collinsworth, T.W. Gettys, J.S. Grewal, M.N. Garnovskaya, Multiplicity of mechanisms of serotonin receptor signal transduction, Pharmacol. Ther. 92 (2001) 179–212.
[100] J.N. Reynolds, B.I. Hyland, J.R. Wickens, A cellular mechanism of reward-related learning, Nature 413 (2001) 67–70.
[101] M. Roger, J. Cadusseau, Afferents to the zona incerta in the rat: a combined retrograde and anterograde study, J. Comp. Neurol. 241 (1985) 480–492.
[102] F. Saitow, S. Konishi, Excitability increase induced by beta-adrenergic receptor-mediated activation of hyperpolarization-activated cation channels in rat cerebellar basket cells, J. Neurophysiol. 84 (2000) 2026–2034.
[103] F. Saitow, S. Satake, J. Yamada, S. Konishi, Beta-adrenergic receptor-mediated presynaptic facilitation of inhibitory GABAergic transmission at cerebellar interneuron-Purkinje cell synapses, J. Neurophysiol. 84 (2000) 2016–2025.
[104] W. Schultz, Predictive reward signal of dopamine neurons, J. Neurophysiol. 80 (1998) 1–27.
[105] N. Schweighofer, M.A. Arbib, A model of cerebellar metaplasticity, Learn Mem. (1998) 421–428.
[106] N. Schweighofer, G. Ferriol, Diffusion of nitric oxide can facilitate cerebellar learning: a simulation study, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 10661–10665.
[107] N. Schweighofer, M.A. Arbib, P.F. Dominey, A model of the cerebellum in adaptive control of saccadic gain: I. The model and its biological substrate, Biol. Cybern. 75 (1996) 19–28.
[108] N. Schweighofer, M.A. Arbib, P.F. Dominey, A model of the cerebellum in adaptive control of saccadic gain: II. Simulation results, Biol. Cybern. 75 (1996) 29–36.
[109] N. Schweighofer, M.A. Arbib, M. Kawato, Role of the cerebellum in reaching movements in humans: I. Distributed inverse dynamics control, Eur. J. Neurosci. 10 (1998) 86–94.
[110] N. Schweighofer, J. Spoelstra, M.A. Arbib, M. Kawato, Role of the cerebellum in reaching movements in humans: II. A neural model of the intermediate cerebellum, Eur. J. Neurosci. 10 (1998) 95–105.
[111] N. Schweighofer, K. Doya, M. Kawato, Electrophysiological properties of inferior olive neurons: a compartmental model, J. Neurophysiol. 82 (1999) 804–817.
[112] N. Schweighofer, K. Doya, F. Lay, Unsupervised learning of granule cell sparse codes enhances cerebellar adaptive control, Neuroscience 103 (2001) 35–50.
[113] E. Senba, H. Takagi, S. Shiosaka, M. Sakanaka, S. Inagaki, K.

Takatsuki, M. Tohyama, On the afferent projections from some meso-diencephalic nuclei to n. raphe magnus of the rat, Brain Res. 211 (1981) 387–392.
[114] M. Shidara, K. Kawano, H. Gomi, M. Kawato, Inverse-dynamics model eye movement control by Purkinje cells in the cerebellum, Nature 365 (1993) 50–52.
[115] J.C. Strahlendorf, G.D. Hubbard, Serotonergic interactions with rat cerebellar Purkinje cells, Brain Res. Bull. 11 (1983) 265–269.
[116] J.C. Strahlendorf, M. Lee, H.K. Strahlendorf, Effects of serotonin on cerebellar Purkinje cells are dependent on the baseline firing rate, Exp. Brain Res. 56 (1984) 50–58.
[117] I. Sugihara, E.J. Lang, R. Llinas, Serotonin modulation of inferior olivary oscillations and synchronicity: a multiple-electrode study in the rat cerebellum, Eur. J. Neurosci. 7 (1995) 521–534.
[118] R.S. Sutton, Adapting bias by gradient descent: an incremental version of the delta-bar-delta, The Tenth National Conference on Artificial Intelligence, MIT Press, Cambridge, MA, 1992, pp. 171–176.
[119] W.T. Thach, Discharge of Purkinje and cerebellar nuclear neurons during rapidly alternating arm movements in the monkey, J. Neurophysiol. 31 (1968) 785–797.
[120] S. Thellung, A. Barzizza, G. Maura, M. Raiteri, Serotonergic inhibition of the mossy fibre–granule cell glutamate transmission in rat cerebellar slices, Naunyn Schmiedeberg's Arch. Pharmacol. 348 (1993) 347–351.
[121] R.F. Thompson, The neurobiology of learning and memory, Science 233 (1986) 932–947.
[122] L. Tian, Y.Q. Wen, H.Z. Li, H.B. Xiong, J.J. Wang, The excitatory effects of histamine on cerebellar cortical Purkinje cells in the rat, Sheng Li Xue Bao 51 (1999) 219–223.
[123] P. Trouillas, The cerebellar serotoninergic system and its possible involvement in cerebellar ataxia, Can. J. Neurol. Sci. 20 (Suppl. 3) (1993) S78–S82.
[124] P.L. van Kan, A.R. Gibson, J.C. Houk, Movement-related inputs to intermediate cerebellum of the monkey [published erratum appears in J Neurophysiol 1993 Mar;69(3): following table of contents], J. Neurophysiol. 69 (1993) 74–94.
[125] S.C. Veasey, C.A. Fornal, C.W. Metzler, B.L. Jacobs, Response of serotonergic caudal raphe neurons in relation to specific motor activities in freely moving cats, J. Neurosci. 15 (1995) 5346–5359.
[126] S.C. Veasey, C.A. Fornal, C.W. Metzler, B.L. Jacobs, Single-unit responses of serotonergic dorsal raphe neurons to specific motor challenges in freely moving cats, Neuroscience 79 (1997) 161–169.
[127] Y. Wang, J.C. Strahlendorf, H.K. Strahlendorf, Serotonin reduces a voltage-dependent transient outward potassium current and enhances excitability of cerebellar Purkinje cells, Brain Res. 571 (1992) 345–349.
[128] M. Watson, J.G. McElligott, Cerebellar norepinephrine depletion and impaired acquisition of specific locomotor tasks in rats, Brain Res. 296 (1984) 129–138.
[129] M. Weiss, J. Pellet, Raphe–cerebellum interactions: I. Effects of cerebellar stimulation and harmaline administration on single unit activity of midbrain raphe neurons in the rat, Exp. Brain Res. 48 (1982) 163–170.
[130] M. Weiss, J. Pellet, Raphe–cerebellum interactions: II. Effects of midbrain raphe stimulation and harmaline administration on single unit activity of cerebellar cortical cells in the rat, Exp. Brain Res. 48 (1982) 171–176.
[131] L. Wiklund, A. Bjorklund, B. Sjolund, The indolaminergic innervation of the inferior olive: 1. Convergence with the direct spinal afferents in the areas projecting to the cerebellar anterior lobe, Brain Res. 131 (1977) 1–21.
[132] J. Xu, D.M. Chuang, Serotonergic, adrenergic and histaminergic receptors coupled to phospholipase C in cultured cerebellar granule cells of rats, Biochem. Pharmacol. 36 (1987) 2353–2358.
[133] T. Yoshida, K. Hashimoto, A. Zimmer, T. Maejima, K. Araishi, M. Kano, The cannabinoid CB1 receptor mediates retrograde signals for depolarization-induced suppression of inhibition in cerebellar Purkinje cells, J. Neurosci. 22 (2002) 1690–1697.