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Interactive report

Mechanisms of motor learning in the cerebellum[1]

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Abstract

How the elaborate neuronal circuit in the cerebellum operates and is involved in motor learning is a question addressed in earnest in studies on the cerebellum. During the past four decades, experimental studies have revealed circuit and module structures of the cerebellum, established long-term depression (LTD) as a unique and characteristic type of synaptic plasticity in the cerebellum, and analysed signal contents of activates of cerebellar neurons related to motor learning. In the 1990s, these studies were developed to detailed analyses of the signal transduction underlying LTD, and to uncovering the involvement of the cerebellum in cognitive function. On the other hand, theoretical studies yielded epochal Marr–Albus network models of the cerebellum around 1970, and introduced control system principles explaining the essential roles of the cerebellum in motor learning as providing internal models, both forward and inverse. The author maintains the hypothesis that reorganisation of the neuronal circuit by error-driven induction of LTD constitutes the major memory and learning mechanisms of the cerebellum. In this article, we examine the validity of the hypothesis in light of currently available data in recent studies of the cerebellum.

Theme: Motor systems and sensorimotor integration

Topic: Cerebellum: reorganization and output

Keywords: Motor learning; Plasticity; Cerebellum; Long-term depression; Signal transduction; Error

1. Introduction

Motor learning is a function of the brain for acquiring new repertoires of movements and skills to perform them through practice, and it involves many areas of the brain. The prefrontal cerebral cortex is responsible for planning movements, and its premotor area for programming movements. The motor cortex, which forms commands sent to the lower motor centers in the brain stem and spinal cord, undergoes reorganization in motor learning [3]. Sensory and temporoparietal association areas may also be involved in learning to improve the perceptual capability required for movements. At subcortical levels, the basal ganglia and cerebellum are the two major structures involved in motor learning. Even the brain stem and spinal cord may contribute to motor learning to a certain extent based on their experience-dependent plasticity.

Results of classic lesion studies, as compiled by Dow and Moruzzi [14], suggest that the contribution of the cerebellum to motor learning is to enable us to learn to perform accurate and smooth movements, even at high speeds and without visual feedback. A central question addressed has been how this function originates from the elaborate neuronal circuit structure of the cerebellum as already described in detail early in the 20th century by Cajal [6]. Before 1960, while researchers with an experimental focus were engaged in anatomical [37] and lesion studies of the cerebellum [14], theorists formulated general neuronal network models as represented by Hebb's [25] neuron assembly and Rosenblatt's [72] Simple Perceptron. The two groups began to work closely with each other when an elaborate neuronal circuit in the cerebellum was revealed, as summarised in Eccles et al. [16] (Fig. 1). This experimental–theoretical interaction resulted in proposals of epochal network theories of the cerebellum by Marr [57], Albus [2] and others around 1970, which motivated subsequent experimental efforts to verify the theories. Much effort has since been devoted both theoretically and experimentally to produce a significant progress in our understanding of neural mechanisms of the cere-

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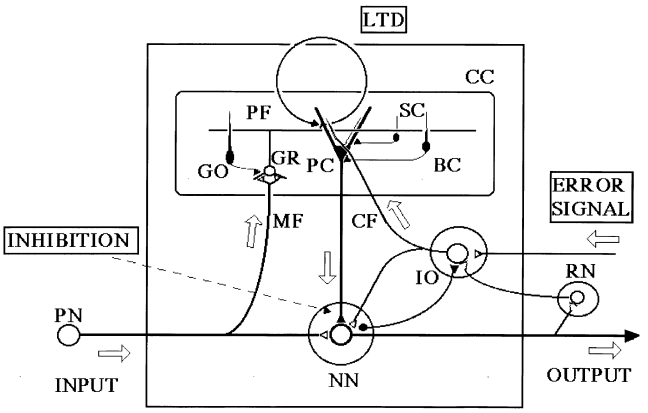

Fig. 1. Neuronal circuit structure in the cerebellum. CC, cerebellar cortex; NN, cerebellar and vestibular nuclei; IO, inferior olive; PN, precerebellar nucleus; RN, red nucleus (parvocellular part); MF, mossy fiber; CF, climbing fiber; PC, Purkinje cell; GR, granule cell; PF, parallel fiber; BC, basket cell; SC, stellate cell; GO, Golgi cell. Hollow triangle, excitatory synapse; Filled triangle, inhibitory synapse.

bellum. In this article, we focus on the hypothesis that error-driven LTD-based reorganization of the neuronal circuit in a microcomplex, functional module of the cerebellum is a major mechanism of motor learning.

2. Circuit and module structures of the cerebellum

In the cerebellar cortex, Purkinje cells (PCs) in the cerebellar cortex receive input from axons of granule cells (GAs) that relay mossy fibers (MFs) arising from diverse precerebellar nuclei (Fig. 1). GAs ascend from the granular layer to the molecular layer and bifurcate to parallel fibers (PFs), which extend by 2–3 mm on each side. Each PC receives as many as 60 000 to 175 000 PFs on their dendritic spines [65,69]. The ascending segments also contribute about 20% of the total GA input, preferentially on the smallest-diameter, distal regions of the PC dendrites [23].

PCs also receive input from climbing fibers (CFs) which originate from the inferior olive in the medulla oblongata. In contrast to the convergence of numerous GAs to a PC, only one CF normally comes into contact with each PC and forms numerous discrete synaptic junctions on stubby dendritic spines of the PC. The number of junctions formed between a CF and a PC in the rat could be as large as 26 000 because a 100-μm length of PC dendrite is in contact with 11.45 GAs and 1.7 CFs on average [66].

MFs, GAs and CFs are excitatory in their synaptic actions. MFs supply excitatory synapses to the nuclear neurons via collaterals, as do CFs. The cortical circuit also includes Golgi cells, basket cells and stellate cells, which are all inhibitory in nature. PCs providing the sole output pathway of the cerebellar cortex were defined as exclusively inhibitory for their target neurons in the vestibular and cerebellar nuclei. In addition, the nucleo-olivary inhibitory neurons and parvocellular red-nucleus neurons form accessory circuits.

While the basic structure of the neuronal circuit is virtually identical throughout the cerebellum, the modular structure of the cerebellum was revealed in the 1970s [21,22]. The least functional unit of the cerebellar cortex has been determined to be a microzone that has a specific CF connection with a small area of the inferior olive [68]. The corticonuclear microcomplex (hereafter referred to as the microcomplex) constitutes a functional module of the cerebellum, and has a skeleton structure such that a cortical microzone is paired with a small distinct group of neurons in a cerebellar or vestibular nucleus and also with a small group of inferior olive neurons [31]. A microzone is 0.3 to 1 mm wide and about 10 mm long. Since the entire surface area of the human cerebellum is 50 000 mm^2, it could contain 5000–15 000 microcomplexes.

3. Long-term depression (LTD)

As any computer requires memory elements, the neuronal circuit in the cerebellum was suggested to have a type of synaptic plasticity as memory element [2,57]. In the 1980s, heterosynaptic LTD (referred to as LTD hereafter) was discovered and established as a unique, characteristic synaptic plasticity in the cerebellum [32,35,36,17]. LTD occurs when impulses of a set of GAs and one CF reach the same PC synchronously and repeatedly; synaptic transmission from the GAs to the PC is then persistently depressed. LTD occurs optimally by conjunctive CF and PF stimulation at 4 Hz with 100 pulses in vivo or at 1 Hz with 300 pulses in cerebellar slices in the presence of a $GABA_A$ antagonist. LTD is indicated by the persistent reduction in the firing index of a PC in response to MF or GA stimulation in extracellular recording [36,9], the amplitude of GA-evoked extracellular field potentials [35,9], the initial slope of GA-evoked excitatory postsynaptic potentials (EPSPs) [73,43], and the size of GA-evoked excitatory postsynaptic currents (EPSCs) [24] or spontaneously arising miniature EPSCs (mEPSCs) [62].

LTD as a memory mechanism of the cerebellar circuit has been questioned for various reasons as listed below together with answers now available.

1. Since each granule cell discharges spontaneously, there will be a frequent chance of conjunctive activation of GAs with spontaneous CF impulses so that all GA synapses in a PC could be depressed in a relatively short time [56]. However, LTD induction has a prominent frequency-dependence, so that it would not happen with the slow, irregular background discharges of CFs.
2. If CF signals continuously depress GA input to PCs, behavior of PCs should be shaped to a mirror image of

CF signals. This is often the case [19,78,81], but not always [79]. This is not surprising because behavior of PCs reflects a summed effect of excitation mediated by GAs and inhibition mediated by basket and stellate cells. Even if LTD depresses GA–PC synapses, the inhibition-dependent component of PC behavior will remain unchanged because LTD does not influence the MF-induced inhibition in PCs [36].

3. LTD has not been demonstrated to occur in behaving animals [5] except for the experiment of Gilbert and Thach [20]. However, conditions required for LTD induction in terms of frequency and number of conjunctions are not usually fulfilled in the reported experiments on behaving animals.
4. TD may be incomplete as a mechanism for learning because of the lack of a known opposing process which would prevent all GA–PC synapses from being depressed [56]. Theoretically, it has been assumed that those GA–PC synapses escaping conjunctive activation with CFs are potentiated or that the total effect of GA-derived synapses in each PC is kept constant by nonspecific occurrence of long-term potentiation (LTP). In reality, LTP occurs in GA–PC synapses presynaptically when GAs are activated without conjunction with CFs. Even though LTD occurs entirely postsynaptically (see below), LTP counteracts it in terms of synaptic efficacy, so that their combination provides a complete learning mechanism from computational viewpoints.

4. Signal transduction for LTD

Various reduced forms of LTD have been generated by replacing stimulation by either GAs or CFs, or both, with chemical stimulation or application of electrical currents to PCs. In cerebellar slices, the CF stimulation can be replaced by the application of depolarizing pulses, which bring about the entry of Ca^{2+} ions into PCs through voltage-gated channels. In cultured PCs devoid of both GAs and CFs, a reduced form of LTD is induced by a combination of glutamate (or quisqualate) pulses and membrane depolarization [54]. Use of these reduced forms of LTD facilitated studies of signal transduction underlying LTD.

Diverse chemical reactions have been found to underlie LTD induction [34,52] (Fig. 2). They can roughly be classified into the following seven major pathways. (1) Glutamate released from GAs reacts with AMPA receptors in PCs, which open associated cation channels for Na^+ and K^+ ions to generate EPSPs. These EPSPs function to open voltage-dependent Ca^{2+} channels. (2) GA-derived glutamate also reacts with type-1 metabotropic glutamate receptors (mGluR1s), which in turn activate phospholipase C (PLC) through the Gαq protein. PLC produces diacylglycerol (DAG) which activates protein kinase C

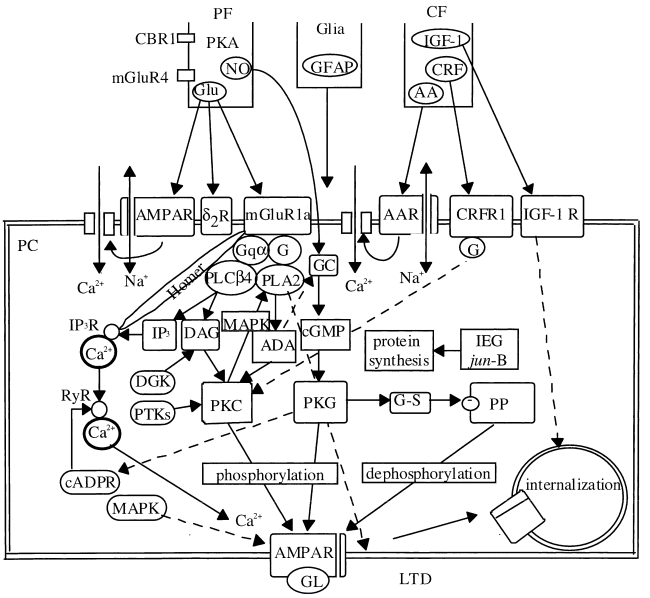

Fig. 2. Signal transduction underlying LTD. AMPAR, AMPA receptor; AAR, yet-unidentified amino acid receptor; ADA, arachidonic acid; δ2R, δ2 receptor; G-S, G-substrate; IEG, immediate early gene; RyR, ryanodine receptor. Other abbreviations are defined in the text. Broken lines indicate suggested, but not proven relationships.

(PKC), as well as inositol trisphosphate (IP_3) which induces IP_3 receptors to release Ca^{2+} ions from intracellular stores. (3) mGluR1s activated by GA-derived glutamate also stimulate phospholipase A2 via G proteins, eventually producing unsaturated free fatty acids including arachidonic acid and oleic acid. (4) GA-released NO diffuses into PCs and activates guanylyl cyclase (GC) which produces cyclic GMP (cGMP). cGMP in turn activates protein kinase G (PKG), which, following phosphorylation, converts a protein, G-substrate, into a potent inhibitor of protein phosphatase (PP). (5) A CF-derived amino acid transmitter (most likely glutamate, as yet unidentified) reacts with receptors and opens associated channels for Na^+ and K^+ ions to induce production of a large EPSP, which in turn causes Ca^{2+} influx through voltage-dependent Ca^{2+} channels. (6) A CF-derived corticotropin-releasing factor (CRF) reacts with type-1 CRF receptors and associated G proteins, and then yields an as yet unidentified second messenger, which interacts with PKC. (7) A CF-derived type-1 insulin-like growth factor (IGF-1) may facilitate internalization of receptors by endocytosis [82].

Crosstalk may occur between these pathways. Protein tyrosine kinases (PTKs), mitogen-associated protein kinases (MAPKs), glial fibrillary acid proteins (GFAP), an as yet unidentified rapidly turned-over protein(s) and an immediate early gene, *Jun*-B, are also implicated in LTD induction. These complex chemical reactions eventually lead to removal of AMPA receptors by internalisation [59,82].

Some important properties such as integration of signals

across multiple time scales, generation of distinct output depending on input strength and duration, and self-sustained regeneration, may emerge from the complex chemical networks of signal transduction [4]. Integration of signals across a multiple time scales may explain how delayed CF signals that arrive after GA signals still induce LTD [26]. Nonlinear accumulation of signals may occur in the network, which would also explain the frequency dependence and requirement for a certain number of repetition of LTD-inducing stimuli. These properties that emerged from the network may provide a safety device that prevents an incidental occurrence of LTD and that enables LTD to occur robustly whenever its occurrence is required.

5. Error representation by CFs

Since the 1970s, various experimental paradigms for testing cerebellar function such as vestibulo-ocular reflex adaptation [15,19,30], hand/arm movement [20], eyeblink conditioning [58] and locomotion [27,85] have been developed, and the contents of signals generated by cerebellar neurons in these paradigms were analysed.

Arrival of CF signals at a PC is indicated by the generation of complex spikes from the PC [80]. In simple situations such as reflexes, CFs convey sensory signals such as those evoked by a sudden loud sound [61] or pain [38]. These sensory signals suggest a harmful consequence of an inadequately executed movement. In various types of ocular movements, CF signals represent retinal slips caused by a deviation of a realized eye movement from a desired one, that is, an error in controlling eye movement [18,19]. These observations support the view that during the repeated exercise of a movement, error signals arising as a result of movements drive LTD and that the LTD reshapes the neuronal circuit of the cerebellum in the direction that minimizes errors [31,32]. The so-called credit assignment problem has been presented that the delay time for CF signals representing consequence errors to reach PCs prevents conjunction between CF and GA signals. This problem can be solved when one considers that chemical reactions underlying LTD (Fig. 2) often last long. In fact, CF impulses applied after a train of GA stimuli effectively produced LTD [74].

In more complex situations such as voluntary movements of hand and arms, CF signals arise in three phases of movement: at the beginning, before the end and after [48]. CF signals therefore encode not only the consequence errors detected through sensory systems by discharges in the third phase, but also other types of errors arising from the internal mechanisms of the motor systems by discharges in the first and second phases.

To interpret this rather complex situation of CF discharges in hand/arm movements, control system structures for voluntary movements have to be taken into consideration. In the 1970s, control system theories were introduced to studies of motor learning, and the cerebellum was essentially considered an organ that enables us to perform motor control without feedback [29]. An initial hypothesis was that a cerebellar microcomplex provides an internal model that simulates properties of a controlled object (later defined as a forward model) [28,31]. Provided that the forward model in the cerebellum learns to have signal transfer properties equivalent to those of the hand/arm system, the cerebral cortex can perform a control of the hand/arm system by referring to the internal feedback through the cerebellum even without referring to the external feedback about the actual hand/arm movement (Fig. 3). In the 1980s, another hypothesis was presented, in which a cerebellar microcomplex learns to acquire signal transfer properties inversely equivalent to the hand/arm system [46] (Fig. 4). Instruction signals applied to an inverse model are converted to command signals to the hand/arm system to generate movement exactly as instructed. Kawato et al. [46] proposed a unique two-degrees-of-freedom control system; while the cerebral cortex performs feedback control, an inverse model is formed in the cerebellum, which in turn performs feedforward control (Fig. 4). The forward model matches the cerebrocerebellar loop formed between the motor cortex and the intermediate part of the cerebellar hemisphere, while the inverse model matches the parallel connections of the cerebellar hemisphere to the cerebral association cortex [31]. Recent theoretical study suggests that a combination of these two forms of control with forward and inverse models generates a system with high learning capabilities [84].

As the most plausible choice for the two-degrees-of-freedom control system, Kawato et al. [46] adopted the

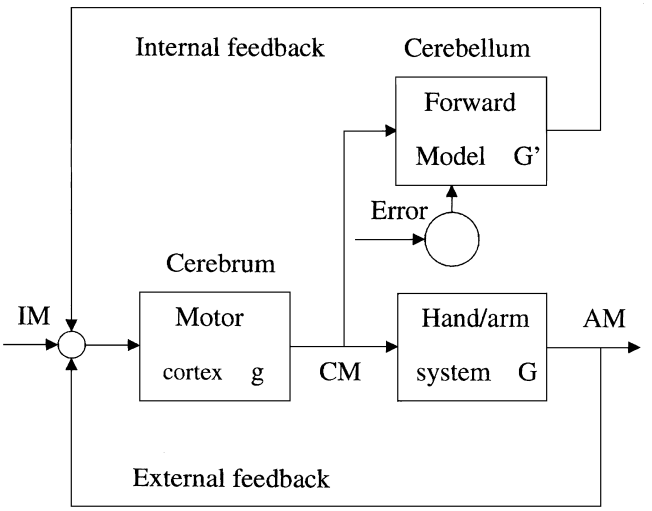

Fig. 3. Seemingly feedforward control system with an internal feedback through a forward model. AM becomes equivalent to IM if the signal transfer characteristics of the forward model G′ is equal to that of the hand/arm system G (modified from Fig. 156 of [25]).

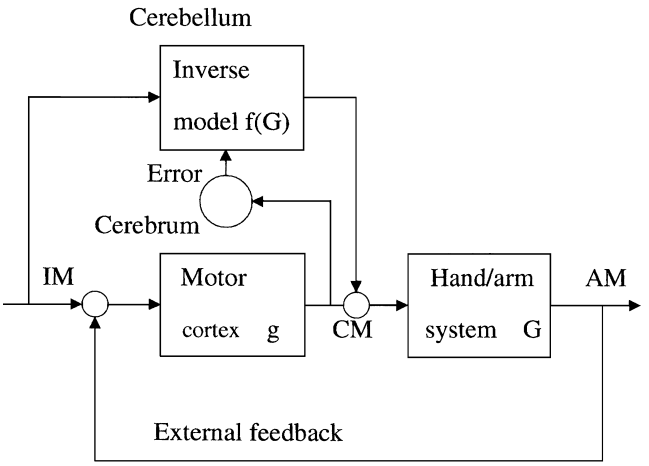

Fig. 4. Two-degrees-of-freedom control system [35]. A feedback control system involving the cerebral cortex is connected in parallel with a feedforward control system involving the cerebellum. AM becomes equivalent to IM if the signal transfer characteristics of the inverse model *f*(G) is inversely equal to that of the hand/arm system G.

feedback error learning rule that errors are derived from the output of the cerebral cortex that also generates the motor commands to the hand/arm system. In this design, the hand position predicted by internal feedback through the cerebellum is fed to the inferior olive via the cerebral cortex (see Fig. 3). This may explain the second CF response in the reaching movement. The earliest component of CF responses can also be explained by assuming that the instruction of movement toward the target position is fed to the inferior olive via the cerebral cortex. If the instruction represents the discrepancy between the initial set position of the hand and the visually instructed target position, or between the target position actually viewed and that which a monkey anticipates from preceding experiences, this implies an error.

Quite another role of the CFs has been proposed that they provide a clock for movement control [55], based on the following two lines of evidence. (1) Under the influences of harmaline, complex spikes discharge rhythmically at a rate around 10 Hz, and (2) in slice conditions, inferior olive neurons exhibit a marked oscillation in membrane potentials. However, PCs in awake behaving monkeys did not reveal clock-like discharge patterns of complex spikes [47]. The discrepancy may be explained based on the results of a computer simulation study that electrical coupling between inferior olive neurons through gap junction acts to either synchronize or desynchronize coupled inferior olive cells, depending on the coupling strength [76].

Another hypothesis for a role of CFs has been proposed based on the observations in a certain area of rat cerebellar cortex, where CFs discharged rhythmically and time-locked to licking movement when the tongue was fully extended, some PCs firing in synchrony with each other [83]. This CF discharge was not affected by deafferentation of the oral or perioral structures. Welsh et al. [83] suggest that the CF activities are transferred to cerebellar nuclear neurons via PC axons to eventually aid tongue motoneurons that execute movement. However, another possibility would be that the licking-driven CF discharge reflects the internal errors derived from internal mechanisms of the voluntary movement control such as proposed for hand/arm movements (Figs. 3 and 4).

6. Involvement of LTD in motor learning

Roles of LTD in motor learning have been tested by two methods of observation: (1) Whether PC activities are modified in motor learning in a manner consistent with the occurrence of LTD [20,30,78], and (2) whether blockade of LTD impairs motor learning. The second method is effective in demonstrating the involvement of LTD in motor learning, when other types of synaptic plasticity exist in the cerebellar circuit and other roles of LTD such as prevention of overexcitation of PCs [12] or Ca^{2+} mediated excitotoxicity [56] have been proposed. Advances in our knowledge of signal transduction for LTD enable us effectively apply the second method by manipulating LTD in behaving animals, either pharmacologically or genetically.

NO is required for LTD induction in cerebellar slices, and NO scavengers and NOS inhibitors block LTD. Adaptation of the vestibuloocular reflex is blocked by superfusing the cerebellum in rabbits and monkeys with a NO scavenger, hemoglobin [63], or by injecting an inhibitor of NO synthase (NOS) into the goldfish cerebellum [53]. Transgenic mice that selectively express the pseudosubstrate PKC inhibitor in Purkinje cells lacked the vestibuloocular reflex adaptation consistent with the loss of LTD induction in cerebellar slices obtained from these mice [13]. Neural NOS (nNOS)-deficient mice lacked adaptation of the optokinetic eye movement response, which normally occurs under continued rotation of the visual field around a stationary animal [44]. Subdural applications of a scavenger or NOS inhibitor to the paraflocculus–flocculus depressed the adaptation of smooth pursuit in monkeys [64].

Rabbits administered a NO synthase inhibitor exhibited learning deficits in the conditioned eyeblink response [8]. GFAP-deficient mutant mice exhibited a loss of LTD and also showed impaired eyeblink conditioning [77]. Injection of an IGF-1 antisense oligonucleotide in the inferior olive, which reduces the IGF-1 level in the cerebellum, probably below that required for LTD induction, blocked conditioned eyeblink learning in rats [7].

When a decerebrate cat walking on a treadmill experienced a sudden increase in the speed of the running belt under only the left forelimb, regular stable walk was restored in 51–100 steps [85]. Injection of a NOS inhibitor into the cerebellum blocked this adaptation. mGluR1-de-

ficient mice walking on a treadmill exhibited abnormally dispersed locomotor cycles of two limbs and did not adapt to an increase in the belt velocity [27]. The occurrence of impaired interlimb coordination in locomotion diminished when the mGluR1 deficiency was rescued in the cerebellum.

The duration that an animal can remain on a horizontally placed rotating rod has been measured as a convenient index for evaluating motor coordination in mice as representing a cerebellar function. Among eight types of gene-manipulated mice showing motor discoordination to a more or less extent, 4 types (mGluR1- [1,11,51], GluRδ2- [45], Gαq- [60,67] or nNOS-deficient [44]) lacked LTD (Table 1). However, two types (PKCγ- [10] or mGluR4-deficient [70]) retained LTD (no report about the remaining two types, namely, PCLβ4- [42] or NR2A/NR2C-deficient [39] mice). Nevertheless, motor discoordination in these 8 types of mutants can be explained by the occurence of the persistent multiple innervations of PCs by CFs or abnormal GA–PC or MF–GA transmission (Table 1).

GFAP-deficient mice and PKC-inhibitor-transfected mice [10,77] were reported to exhibit motor coordination indistinguishable from wild-type mice in spite of the lack of LTD (Table 1). The reasons underlying this discrepancy need to be investigated. It is necessary to identify neuronal circuits responsible for motor coordination and to introduce sensitive methods for evaluating their disturbances, particularly in learning situations. nNOS-deficient mice show no obvious motor discoordination during day time, but they exhibit peculiar motor discoordination during night [49]. It is also recalled that even with cerebellar lesions, the vestibuloocular reflex appears normal unless visuovestibular conflicting conditions are imposed on the animal.

7. Towards 2010

Toward the final goal of understanding learning mechanisms of the cerebellum, the following two questions are to be addressed.

First, how is LTD eventually converted to permanent memory? The observation time for LTD is usually limited to 0.5 to 1 h, and occasionally for 2 to 3 h. LTD induced in mEPSCs in cultured PCs by conjunctive application of 50 mM K^+ and 100 μM glutamate was observed to last for 36 h and return to the original level after 48 h [62]. This observation, however, would not exclude the possibility that LTD lasts more persistently in adult PCs, because the recovery of mEPSPs could be due to synaptogenesis occurring in cultured PCs. When the rabbit cerebellum was sliced 24 h after the rabbit had been trained for conditioning, sequentially-applied GA and CF stimuli failed to induce LTD, which occurred in slices dissected from control rabbits [75]. This suggests that LTD underlying the eyeblink conditioning persists for at least 24 h and precludes eliciting another LTD. The possibility is maintained that LTD as functional depression is consolidated as a structural change in synaptic contacts and spines. There is yet no evidence showing morphological changes correlated to LTD.

Second, can the microcomplex concept be expanded to apply beyond motor learning to implicit learning in general? It has been applied to various physical functions including reflexes, compound movements (such as locomotion and saccade), animal behavior and even voluntary movement, and an obvious next target of cerebellar research is to determine the cerebellar contribution to certain mental functions such as cognition, language and thought [33]. Involvement of the cerebellum not only in

Table 1
Cerebellar dysfunction in mutant mice[a]

Genetic abnormality	Cellular abnormality			Behavioral abnormality		
	LTD	CF	MF/GA/PC	VOR/OKR adaptation	Eyeblink conditioning	Motor coordination
mGluR1	X	X				X
GluRδ2	X	X				X
Gαq	X	X				X
nNOS	X			X	X	X
PKCγ	○	X				X
mGluR4	○		X			X
PCLβ4		X				X
NR2A/NR2C		(X)	X			X
GFAP	X	○			X	?
PKC inhibitor	X	X		X		?

[a] X: under LTD, lack of LTD; under CF, multiple CF innervation of PCs; under MF/GA/PC, abnormal MF-granule cell or GA–PC transmission; under VOR/OKR, lack of adaptation in VOR or OKR; under eyeblink, impaired eyeblink conditioning; under motor coordination, motor discoordination at various degrees; ○, normal; (x), possible occurrence of multiple innervation; ?, seemingly normal [1,9,11,39–42,44,49,52,60,67,70,71].

motor control but also in cognitive functions has originally been proposed based on the parallel evolutionary development of the cerebellar hemisphere and cerebral association cortex [50], and is supported by results of noninvasive measurements as well as clinical observations. On the theoretical ground, the multiple paired control system equipped with both forward and inverse models has been proposed to entirely explain the conjoint operation of the cerebral cortex and the cerebellum [84].

The two research directions, one to extend LTD studies to reveal memory mechanisms of the cerebellum and the other to extend from motor learning to implicit learning in general, should be promoted together to lead us to understanding of the entire mechanisms and functional roles of the cerebellum in implicit learning that governs a major part of our life.

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