

Distributed circuit plasticity: new clues for the cerebellar mechanisms of learning

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Abstract

The cerebellum is involved in learning and memory of sensory motor skills. However, the way this process takes place in local microcircuits is still unclear. The initial proposal, that was casted into the Motor Learning Theory, suggested that learning had to occur at the parallel fiber – Purkinje cell synapse under supervision of climbing fibers. However, the uniqueness of this mechanism has been questioned and multiple forms of long-term plasticity have been revealed at various locations in the cerebellar circuit, including synapses and neurons in the granular layer, molecular layer and deep-cerebellar nuclei. At present, more than 15 forms of plasticity have been reported. There has been a long debate on which plasticity is more relevant to specific aspects of learning, but this question turned out to be hard to answer using physiological analysis alone. Recent experiments and models making use of closed-loop robotic simulations are revealing a radically new view: one single form of plasticity is insufficient while altogether the different forms of plasticity can explain the multiplicity of properties characterizing cerebellar learning. These include multi-rate acquisition and extinction, reversibility, self-scalability and generalization. Moreover, when the circuit embeds multiple forms of plasticity, it can easily cope with multiple behaviors endowing therefore the cerebellum with the properties needed to operate as an effective generalized forward controller.

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Introduction

The cerebellum is involved in the acquisition of procedural memory and several attempts have been done at linking cerebellar learning to the underlying neuronal circuit mechanisms. The first hypothesis was proposed within the Motor Learning Theory, which indicated that some form of LTD or LTP (Albus, 1971; Marr, 1969) had to occur at the parallel fiber - Purkinje cell (PF-PC) synapse under guidance of the CFs, which were assumed to convey an error signal. Following the demonstration that a form of PF-PC LTD compatible with theory actually exists (Ito & Kano, 1982), many other works have reported that several forms of synaptic and non-synaptic plasticity exist in the cerebellum. Now synaptic plasticity is known to be distributed in the granular layer, molecular layer and deep cerebellar nuclei (DCN) (D'Angelo, 2014; Gao *et al.*, 2012; Hansel *et al.*, 2001a) involving both excitatory and inhibitory synaptic transmission as well as neuronal intrinsic excitability. Most of these different forms of plasticity eventually impinge on three main neurons, namely granule cells (GrCs), PCs, and DCN cells, which act as nodes integrating excitatory and inhibitory plasticity.

These new findings have complicated rather than clarified the issue of how the cerebellum might learn and store information using its internal circuitry. At present, there is not yet agreement about the type of information conveyed by the climbing fibers into the cerebellum or about their potential role. The Marr-Albus theory maintains that climbing fibers carry either an error signal related to directional information (Kawato & Gomi, 1992) or a binary teaching signal (De Griijl *et al.*, 2012; Houk *et al.*, 1993). Conversely, considering the periodic nature of climbing fiber activity, others (Llinas *et al.*, 1997) maintain that IO activity is related with the timing of movement. However, investigations in which this periodicity was not observed (Keating & Thach, 1995) suggested that the climbing fiber activity was correlated with the onset of movements. The controversy extends to IO functional properties, which are not yet univocally defined (Bengtsson & Hesslow, 2006; De Zeeuw *et al.*, 1998; Van Der Giessen *et al.*, 2008). Finally, the different cerebellar plasticity mechanisms recently observed in the cerebellum and related nuclei suggest that motor learning may not be exclusively related to climbing fiber activity (D'Angelo, 2011; D'Angelo *et al.*, 2010; Hansel *et al.*, 2001c; Ohtsuki *et al.*, 2009). Alternative hypotheses have suggested an important role for plasticity in the DCN (Medina & Mauk, 1999) or in the vestibular nuclei (Yang & Lisberger, 2013). However, no clues were given to integrate the role of all the different plasticity mechanisms into a coherent view.

When trying to face this issue, a fundamental question emerges: how could the role of multiple plasticity mechanisms be determined within a complex system of circuit loops transporting feed-back signals related to ongoing behavior? Recently, the problem has been faced through two series of experiments, in which the cerebellar circuit was engaged in learning tasks during closed-loop signal processing.

In a first set of tests, eye-blink classical conditioning (EBCC) was elicited in humans and its effectiveness was impaired using TMS (Hoffland *et al.*, 2012; Monaco *et al.*, 2014), which proved able to alter specific learning components and cerebellar subcircuits. In the second set of tests, the cerebellar circuit was reconstructed using detailed models of neurons and synapses (Solinas *et al.*, 2010). Then, the models were adapted and inserted into robotic control systems capable of reproducing the same behaviors that are known to engage cerebellar learning in leaving beings (Casellato *et al.*, 2014; Casellato *et al.*, 2013; Casellato *et al.*, 2012; Garrido *et al.*, 2013a; Garrido *et al.*, 2013c; Luque *et al.*, 2014a). These robotic tests allowed a direct assessment of the way the

cerebellum might use distributed plasticity to process incoming information and generate an internal memory useful to drive sensori-motor adaptation.

Distributed plasticity in the cerebellar network

Recent reviews have been dealt with the multiple long-term forms of plasticity (at least 15 synaptic and 3 of intrinsic excitability) discovered in the cerebellar circuit (D'Angelo, 2014; Gao *et al.*, 2012; Hansel *et al.*, 2001a; Mapelli *et al.*, 2015). Here we report a brief summary of the major forms of plasticity experimentally observed in the cerebellum (Fig.1):

In the granular layer, synaptic plasticity has been described at the mossy fiber (MF) to granule cell (GrC) relay, as long-term potentiation (LTP) (D'Angelo *et al.*, 1999; D'Angelo *et al.*, 2005; Sola *et al.*, 2004) and long-term depression (LTD) (D'Errico *et al.*, 2009; Gall *et al.*, 2005). LTP and LTD have been also observed *in vivo* (Diwakar *et al.*, 2011; Roggeri *et al.*, 2008). MF-GrC LTP proved dependent on NMDAR (D'Angelo *et al.*, 1999) activation and showed a presynaptic expression probably mediated by NO release from GrCs (Maffei *et al.*, 2002; Maffei *et al.*, 2003). According to the Bienenstock-Cooper-Munro (BCM) plasticity rule (Bienenstock *et al.*, 1982), LTP and LTD induction correlated with stimulus duration and frequency through a postsynaptic calcium-dependent mechanism (D'Errico *et al.*, 2009; Gall *et al.*, 2005) with a sliding threshold controlled by neuromodulators (Prestori *et al.*, 2013). Forms of plasticity in the Golgi cell inhibitory loop remain hypothetical at the present (except for some evidence for LTD at the PF-GoC synapse; (Robberechts *et al.*, 2010)), although modeling predictions suggested they may provide a powerful regulatory mechanism (Garrido *et al.*, 2013c).

In the molecular layer, synaptic plasticity has been described in multiple forms at the parallel fiber to Purkinje cell (PF-PC) synapse, parallel fiber to molecular layer interneuron (PF-MLI) synapse and molecular interneuron - Purkinje cell (MLI-PC) synapse. At the PF-PC connection, several forms of plasticity have been observed: presynaptic LTP (Crepel & Jaillard, 1990; Shibuki & Okada, 1992), presynaptic LTD (Qiu & Knöpfel, 2007), postsynaptic LTP (Coemans *et al.*, 2004b; Lev-Ram *et al.*, 2002), postsynaptic LTD (Hartell, 2002; Wang & Linden, 2000; Xia *et al.*, 2000). The postsynaptic forms of LTP and LTD have been reported to be bidirectional according to an inverse BCM plasticity rule. Moreover, while postsynaptic PF-PC LTD is generally assumed to require paired climbing fiber (CF) activation, this may not be an absolute requirement in some cases (Ohtsuki *et al.*, 2009). Although PF-PC plasticity has been observed *in vivo* (Ito, 1972; Ito, 1989; Ramakrishnan & D'Angelo, 2012), it is not clear whether all these forms of plasticity are present *in vivo* and cooperate in regulating PC activity state.

A form of climbing fiber - Purkinje cell (CF-PC) plasticity has been reported and suggested to play a pivotal role in controlling the PF-PC state of activity. CF induced complex spikes in PCs are an important source of intracellular calcium that can determine the direction of plasticity at the PF-PC synapse. Indeed, CF-PC LTD (Shen *et al.*, 2002) was shown to affect the probability of postsynaptic LTP and LTD induction at the PF-PC synapses (Coemans *et al.*, 2004b). PF-MLI LTP (Bender *et al.*, 2009) and LTD (Soler-Llavina & Sabatini, 2006), respectively pre- and postsynaptically expressed, have been described. Interestingly, PF-MLI LTP may be induced by paired activation of PFs and CFs *in vivo* (Jörntell & Ekerot, 2002).

A form of MLI-PC LTP has been reported to depend on the CF-induced *rebound potentiation* of inhibitory currents in PCs (Kano *et al.*, 1992).

In the DCN, several forms of synaptic plasticity have been described, at MF-DCN and PC-DCN synapses. A MF burst that precedes a DCN post-inhibitory rebound depolarization (consequent to PC activation) induces a synapse-specific MF-DCN LTP (Pugh & Raman, 2006b). This induction protocol mimics the predicted time-course of excitation and inhibition during eye-blink conditioning. Interestingly, MF-DCN LTP has been shown to depend on the timing of the two different signals acting independently, rather than being a coincidence detector enabled by reaching a calcium threshold. This mechanism is likely to be adequate to allow adaptive plasticity during associative learning tasks (Medina & Mauk, 1999; Pugh & Raman, 2009). Moreover, a form of calcium-dependent MF-DCN LTD has been described (Zhang & Linden, 2006a).

At the PC-DCN connection both LTP (Ouardouz & Sastry, 2000) and LTD (Morishita & Sastry, 1996) have been observed. LTP and LTD appeared to depend on NMDARs activation and postsynaptic intracellular calcium increase. As a consequence, plasticity at this synapses strongly depends on excitatory (MF and CF) synapses activation level (Morishita & Sastry, 1996; Ouardouz & Sastry, 2000).

Plasticity mechanisms in the granular layer may serve to improve spatio-temporal recoding of MF inputs into specific GrC spike patterns [expansion recoding (D'Angelo & De Zeeuw, 2009)]. Overall, synaptic plasticity in the molecular layer may serve to store correlated granular layer spike patterns, through PFs activation, under the CFs teaching signal (D'Angelo *et al.*, 2011). Synaptic plasticity in the DCN may serve to store MF spike patterns (Bagnall & du Lac, 2006; Pugh & Raman, 2006b) depending on control signals generated through the cerebellar cortical loop. Recent works (Masuda & Amari, 2008b; Medina & Mauk, 1999; Medina & Mauk, 2000) have suggested the importance for MF-DCN and PC-DCN plasticity in controlling cerebellar learning in eye-blink conditioning and vestibulo-ocular reflex (VOR). Moreover, long-term changes in intrinsic excitability in GrCs (Armano *et al.*, 2000), PCs (Belmeguenai *et al.*, 2010; Schreurs *et al.*, 1998) and DCN (Aizenman & Linden, 2000; Zhang *et al.*, 2004) cells could further regulate the global activity level in these neurons contributing to homeostasis and plasticity in the circuit (e.g. see (Schweighofer *et al.*, 2001)).

Complex spatiotemporal dynamics of cerebellar learning

The nature of cerebellar learning is complex and different components and properties have been revealed in experiments in animals and humans. A useful test that can be used to explore cerebellar learning is the EBCC reflex. An unconditioned stimulus (US, like a corneal touch or an electrical stimulus on the supraorbital nerve) elicits an eye-blink. This can be associated with a conditioned stimulus (CS, like a tone) to elicit a blink with precise time relationship to US. The EBCC is useful as it involves *prediction* of an event with precise *timing* through associative *learning*, thereby summarizing in an elementary form the essential elements of cerebellar functioning (D'Angelo & Casali, 2013). A leading hypothesis in EBCC is that the fast reversible learning phase of the reflex occurs in the cerebellar cortex, while persistent memory is stored into deeper structures, for example the DCN.

The involvement of the cerebellar cortex in EBCC was previously suggested by experiments in which the GABAA receptor agonist muscimol was infused to transiently inactivate local circuit functions in rats. Infusion of muscimol in the posterior cerebellar cortex (lobule HVI) was effective

after short (5–45 min) (Attwell *et al.*, 2002) but not after longer delays (90 min) (Cooke *et al.*, 2004). Conversely, muscimol infusion in the anterior interpositus nucleus just after training was poorly effective. These experiments suggested that learning was transferred quite early from a cortical into a nuclear neuronal site.

In recent experiments (Fig. 2), EBCC has been elicited and then its components have been disrupted using TMS in humans (Hoffland *et al.*, 2012; Monaco *et al.*, 2014). Consistent with animal experiments, TMS applied just after training (5–10 min) affected the transient phase of learning. The cellular mechanisms of EBCC learning are thought to depend on long-term synaptic plasticity at cortical and deep cerebellar nuclei (DCN) synapses (Attwell *et al.*, 2002; Attwell *et al.*, 2001; Cooke *et al.*, 2004). The parallel fiber–Purkinje cells synapse is strategically located at the convergence between the mossy fiber–parallel fiber pathway (carrying the CS) and the climbing fiber pathway (carrying the US). Another site of convergence is the DCN, which collects both mossy fiber and climbing fiber signals, in addition to being modulated by Purkinje cells (D'Angelo, 2014).

At both sites, long-term synaptic plasticity has been suggested to play important roles in EBCC (De Zeeuw & Yeo, 2005). In particular, cortical plasticity has been associated with the fast learning process, and DCN plasticity with the slow learning process (Garrido *et al.*, 2013a; Medina & Mauk, 2000). Thus, the effect of TMS is compatible with disruption of cortical rather than DCN plasticity. Given the distributed nature of cerebellar cortical plasticity, a working hypothesis is that TMS operated at multiple cortical sites (D'Angelo, 2014): (i) in the granular layer, on N-methyl-D-aspartate (NMDA) receptor-dependent LTP and LTD at the MF-GrC synapses as well as on long-lasting changes in granule cell intrinsic excitability; (ii) in the molecular layer, on various forms of NMDA receptor-independent LTP and LTD at PF-PC, at climbing fiber–Purkinje cell synapses, at molecular interneuron synapses as well as on long-lasting changes in Purkinje cells intrinsic excitability.

Models of cerebellar synaptic plasticity

In order to conceptualise the different forms of cerebellar plasticity, a set of 4 simplified rules has recently been proposed following the main biological properties reported above (cf. Fig. 1). All these plasticity rules were conceived to be bidirectional and have been based on simplified formalisms. These rules have been rescaled and assigned to specific synapses and cerebellar microcomplexes (i.e. the morpho-functional units in which the cerebellar model has been subdivided) in order to deal with the complexity that neurorobotic tasks imposed (see below).

1) *PF-PC synaptic plasticity* is, by far, the most investigated cerebellar plasticity mechanism, as evidenced by the large amount of studies supporting the existence of multiple forms of LTD (Boyden *et al.*, 2004; Coesmans *et al.*, 2004a; Ito & Kano, 1982) and LTP (Boyden *et al.*, 2004; Coesmans *et al.*, 2004a; Hansel *et al.*, 2001b). Proof of this PF-PC plasticity trace was recently encountered in both anaesthetised (Ramakrishnan and D'Angelo, unpublished observations) and alert animals (Márquez-Ruiz & Cheron, 2012). The most renowned form of LTD is heterosynaptically driven by CF activity and therefore to the complex spikes (CSs) elicited in PCs, whereas the main form of LTP does not require CF activity and, therefore it is related to the simple spikes generated by PF activity. The specific formalism developed to describe the PF-PC plasticity rule depended on the model adopted to describe the cerebellar granular layer. Assuming that PFs were active

following a certain time sequence during movement (Yamazaki & Tanaka, 2005; Yamazaki & Tanaka, 2007b; Yamazaki & Tanaka, 2009), PF-PC synaptic plasticity could be implemented as follows (Garrido *et al.*, 2013b; Luque *et al.*, 2014b):

$$\Delta W_{PF_j-PC_i}(t) = \begin{cases} \frac{LTP_{Max}}{(IO_i(t)+1)^\alpha} - LTD_{Max} \cdot IO_i(t), & \text{if } PF_j \text{ is active at } t \\ 0 & \text{otherwise} \end{cases}$$

where $i \in \{1, 2, \dots, \text{Number of microcomplexes}\}$

where $\Delta W_{PF_j-PC_i}(t)$ represents the weight change between the j^{th} PF and the target PC associated with the i^{th} microcomplex. $IO_i(t)$ stands for the current activity coming from the associated climbing fibre, LTP_{Max} and LTD_{Max} are the maximum long term potentiation/ long terms depression (LTP/LTD) values, and α is the LTP decaying factor. This rule assumes that LTP and LTD coexist at the same PF-PC synapse. Since LTP and LTD, by definition, induce opposite effects in relation to CF activity, providing the mathematical expression with appropriate parameters makes the synaptic weight variation to be positive (LTP) when CF activity is approaching 0 (low error levels in the movement), and makes the weight variation to be negative (LTD) and linearly proportional to CF activity otherwise. In previous approaches, a linear function was used (Masuda & Amari, 2008a) when the synaptic weight were modified according to a teaching signal, but this implied the inability of the synaptic learning rule to fully remove the manipulation error since LTD was always counterbalanced by “unsupervised” LTP. The present rule overcomes the linearity problem by inserting the α decaying factor.

2) *MF-DCN synaptic plasticity* has been shown to depend on the intensity of DCN cell excitation (Medina & Mauk, 1999; Pugh & Raman, 2006a; Racine *et al.*, 1986; Zhang & Linden, 2006b) and could be implemented as follows (Garrido *et al.*, 2013b; Luque *et al.*, 2014b)

$$\Delta W_{MF-DCN_i}(t) = \frac{LTP_{Max}}{(PC_i(t)+1)^\alpha} - LTD_{Max} \cdot PC_i(t),$$

where $i \in \{1, 2, \dots, \text{Number of microcomplexes}\}$

where $\Delta W_{MF-DCN_i}(t)$ represents the weight change between the active MF and the target DCN associated with the i^{th} microcomplex, $PC_i(t)$ is the current activity coming from the associated PCs, LTP_{Max} and LTD_{Max} are the maximum LTP/LTD values, and α is the LTP decaying factor. The MF-DCN learning rule, despite its resemblance to the PF-PC learning rule, bores two significant differences. The first difference is a consequence of the limited capability of MFs, compared with PFs, to generate sequences of non-recurrent states (Yamazaki & Nagao, 2012; Yamazaki & Tanaka, 2007a; Yamazaki & Tanaka, 2009). The second difference involves the connection driving LTD

and LTP. Whilst PF-PC plasticity is driven by CF activity, MF-DCN plasticity is driven by PC activity. This mechanism is capable of optimising the activity range in the whole inhibitory pathway comprising MF-PF-PC-DCN connections: high PC activity causes MF-DCN LTD, whereas low PC activity causes MF-DCN LTP. This mechanism implements an effective cerebellar gain controller able to adapt its output activity range in order to minimise the amount of inhibition generated in the MF-PF-PC-DCN inhibitory loop.

3) *PC-DCN synaptic plasticity* was reported to depend on the intensity of DCN cells and PC excitation (Aizenman *et al.*, 1998; Masuda & Amari, 2008a; Morishita & Sastry, 1996; Ouardouz & Sastry, 2000) and could be implemented as follows (Garrido *et al.*, 2013b; Luque *et al.*, 2014b):

$$\Delta W_{PC_i-DCN_i}(t) = LTP_{Max} \cdot PC_i(t)^\alpha \cdot \left(1 - \frac{I}{(DCN_i(t)+I)^\alpha} \right) - LTD_{Max} \cdot (1 - PC_i(t)),$$

where $i \in \{1, 2, \dots, \text{Number of microcomplexes}\}$

where $\Delta W_{PC_i-DCN_i}(t)$ is the synaptic weight adjustment at the PC-DCN connection reaching the DCN cell associated with the i^{th} microcomplex, $PC_i(t)$ is the current activity coming from the associated PCs and finally DCN is the current activity regarding DCN cells. LTP_{Max} and LTD_{Max} are the maximum LTP and LTD values, and α is the LTP decaying factor. This learning rule leads the PC-DCN synapses into a synaptic weight appropriate to match the activity from the cortex (MF-PF-PC-DCN) and the activity from the excitatory pathway (MF-DCN). According to this learning rule LTP occurs only when both the PCs and their target DCN cell are simultaneously active.

4) Finally, it has recently been proposed that *IO-DCN synaptic plasticity* may provide an efficient way to embed the feedback controller predicted by Ito (Ito, 2008) within the cerebellar circuitry. This controller was able to generate a proper command in motor cortex capable of tuning the viscoelastic properties of the musculo-skeletal system. This was conceived as a fast mid-term adaptation mechanism to cope with the initial control phase when plasticity has not yet progressed in the rest of the cerebellar circuit. Within this hypothesis, IO-DCN plasticity was implemented to regulate the initial synaptic strength of DCN cells driven by the IO as follows (Luque *et al.*, 2014b):

$$\Delta W_{IO-DCN,i}(t) = MTP_{Max} \cdot IO_i(t) - \frac{MTD_{Max}}{(IO_i(t)+I)^\alpha}$$

, where $i \in \{1, 2, \dots, \text{Number of microcomplexes}\}$

where $\Delta W_{IO-DCN,i}(t)$ represents the differential synaptic weight factor related to the active connection at time t (whose associated activity state corresponds to $IO_i(t)$). The connection corresponds to the DCN cell associated to the i^{th} microcomplex. $IO_i(t)$ stands for the current activity coming from the associated climbing fibre. MTP_{Max} and MTD_{Max} are the maximum mid-term potentiation and depression, and α is the MTD decaying factor. MTP_{Max} and MTD_{Max} are large in comparison to LTP and LTD at the other synapses ensuring a fast response and a negligible contribution to the learning process in the long term.

Whilst these equations appropriately address the learning process of the cerebellar network, some issues remain to be clarified experimentally, including assumptions regarding the LTP decaying rate and the biologically plausible mechanism through which LTP and LTD relative scaling factor parameters actually find correspondence in real synapses. Moreover, the variety of biological mechanisms is not fully represented by these equations. In fact, there are many more plasticity rules located at the PF-PC synapses than considered here, as well as there are plasticity mechanisms within the granular layer that were sidestepped. Conversely, plasticity at the IO-DCN connection was predicted but its existence remains to be proved.

Closed-loop robotic simulations embedding multiple plasticity rules

In a recent series of papers, we have explored the impact of distributed cerebellar plasticity using a reverse engineering approach, i.e. making a biologically plausible reconstruction of the system to explore its internal mechanisms of function (Fig. 3). Since the classical long-term synaptic plasticity between parallel fibers (PFs) and Purkinje cells (PCs), which is driven by the inferior olive (IO), can only account for limited aspects of learning, we have used distributed forms of plasticity in the molecular layer and deep cerebellar nuclei (DCN) (Casellato *et al.*, 2014; Casellato *et al.*, 2015; Garrido *et al.*, 2013a; Luque *et al.*, 2014a). In the model, the climbing fibers provide a teaching signal driving long-term synaptic plasticity both at the IO-PC and IO-DCN connections.

The robotic simulations revealed that PF-PC plasticity was fundamental to relate cerebellar plasticity to motor errors, but also revealed that PF-PC plasticity proved insufficient *per se* to make the cerebellum an effective forward controller. LTD and LTP had to co-evolve dynamically in order to control PF-PC transmission making it reversible for resetting and reuse. The memory stored in the PF-PC synapse was then transferred into the DCN allowing consolidation. This memory transfer was controlled by feedback signals arriving through extracerebellar loops and proved critical to allow self-rescaling and automatic gain adjustment, preventing PF-PC saturation. This operation required double adjustment of MF-DCN and PC-DCN synapses in order to balance memory deposition in DCN neurons. Moreover, in order to accelerate and stabilize learning, the closed-loop robotic simulations suggested that cerebellar gain control could be adjusted through MF-DCN and PC-DCN synaptic plasticity working in equilibrium with IO-DCN plasticity. IO-DCN connections ensure stable outputs in the early learning stages, when the strength of MF-DCN and PC-DCN connections is not set yet through the learning process. When the strength of the synaptic weights of MF-DCN and PC-DCN connections begins to stabilize, the synaptic strength of the IO-DCN connection diminishes. Therefore, at the end of the learning process, the effect of the IO-DCN connection in determining the cerebellar output is negligible. Nonetheless, the IO-DCN connection remains ready to act when new unexpected patterns have to be learnt. In addition, a proper synaptic weight adjustment at DCN synapses allows the PFs to operate over their complete frequency range, enhancing the precision of the cerebellar output. To sum up, the IO-DCN pathway could allow a global feedback error reduction facilitating early and fast error corrections. The MF-PF-PC-DCN system would operate by achieving more accurate corrections in the long term but it required slow learning (Luque *et al.*, 2014a).

An interesting aspect of the robotic simulations was that they could be successfully applied to different behaviors known to involve the cerebellum, including VOR, EBCC, force field correction, arm trajectory control (Casellato *et al.*, 2014; Casellato *et al.*, 2015), indicating that the

implicit algorithm of the cerebellar network was of general applicability. With reference to the EBCC case illustrated above, EBCC simulations supported the concept that memory transfer between PF-PC and DCN synapses has to occur rapidly after the beginning of learning, helping to define the possible patterns of alterations leading to EBCC impairment caused by cTBS (Casellato et al. unpublished).

Distributed plasticity: new perspectives for cerebellar learning

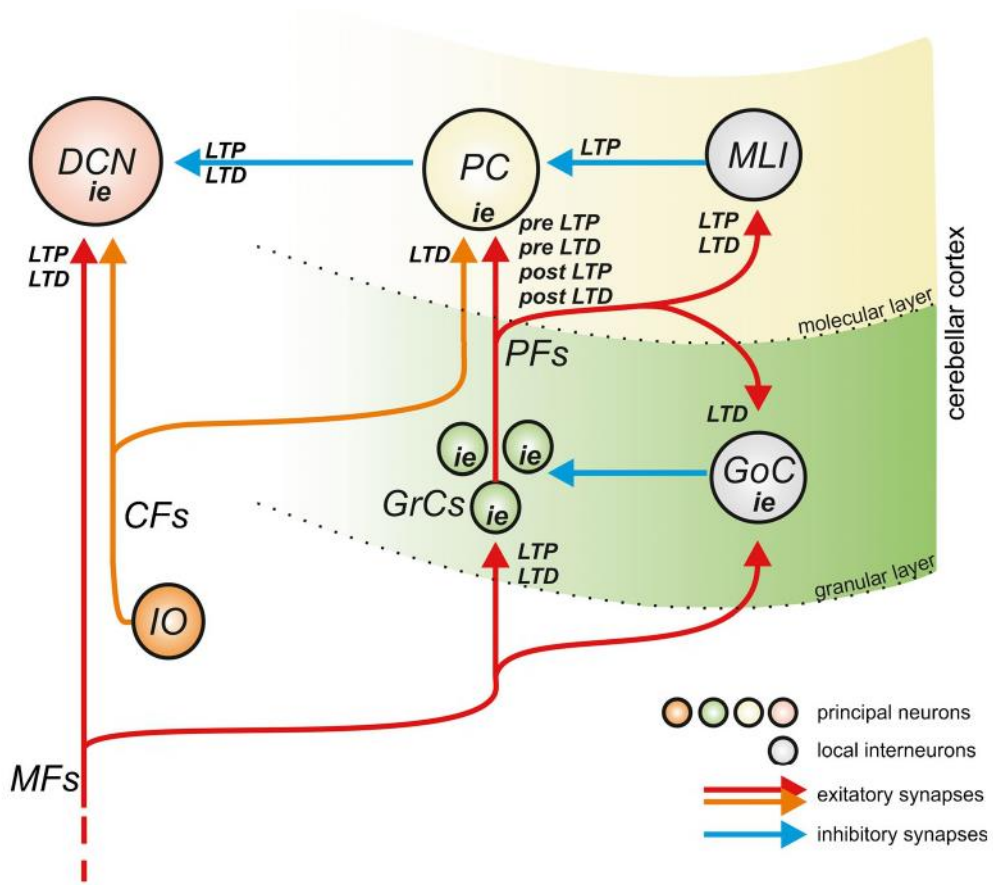
TMS – EBCC experiments in humans *in vivo* and closed-loop robotic simulations have provided new insight on how the sensori-motor control system could exploit distributed plasticity in the cerebellar network to generate biologically plausible learning. TMS – EBCC experiments have indicated that memory has to be transferred from the cerebellar cortex to DCN in order to stabilize learning, although the exact time constant of memory transfer is still unknown. Robotic simulations have implemented this memory transfer by allowing the cerebellar circuit to dynamically adjust synaptic weights between the PF-PC synapse and the DCN by exploiting the sensory-feedback deriving from ongoing activity in closed-loop.

Robotic simulations revealed that a supervised mechanism relating cerebellar learning to motor errors at the PF-PC synapse remains a critical constraint. However, PF-PC plasticity also proved insufficient *per se* to make the cerebellum an effective forward controller and other forms of plasticity distributed throughout the network appeared to be critical. These include plasticity in the DCN but also probably in the granular layer and molecular, although plasticity in these two latter subcircuits has not been tested in robotic simulations yet. Plasticity in the granular layer is indeed expected to determine and store the large variety of spatio-temporal patterns required to implement the expansion recoding of MF signals to be presented to PCs and could become critical when multiple forms of input signals from extended sensori-motor structures will be considered.

There are some predictions descending from these investigations about the nature of plasticity mechanisms in the cerebellar circuit. First, all plasticities should be reversible, so they could have both LTP and LTD. Secondly, since the memory transferred into downstream structures (e.g. from PF-PC into DCN) is controlled by feedback signals arriving through extracerebellar loops, understanding distributed plasticity requires the whole system working in closed-loop. Thirdly, there are forms of plasticity that may not last for long in the freely behaving animal (e.g. PF-PC LTD itself) and this should be taken into account when searching for such plasticities experimentally. Fourthly, there could be forms of plasticity that have not yet been identified experimentally but could have remarkable impact on cerebellar learning (e.g. the IO-DCN plasticity). Finally, DCN neurons could process not just two but even three forms of plasticity coming from MF-DCN, PC-DCN and potentially also IO-DCN synapses. Therefore, further experimental investigation on plasticity of synapses impinging on DCN neurons is needed.

The robotic cerebellar models need themselves to be improved by implementing more realistic spiking networks and learning rules. For example, the variety of plasticities impinging on PC and DC synapses is not yet represented in the models. Moreover, the granular layer needs still to be fully implemented. Finally, robotic simulations will have to be counterchecked by performing biological experiments in which critical plasticities can be selectively switched off to see whether comparable alterations emerge in animal behavior. Genetic mutant mice with inducible cell-specific alterations may be used to selectively block one or more plastic mechanisms. Alternatively, optogenetics may be used to switch on-off plasticity at certain synapses.

In conclusion, distributed plasticity is opening a new perspective for interpreting the complex processes underlying cerebellar learning and its understanding needs to make use of the new tools provided by neural circuit modeling and neurorobotics in combination with advanced biological techniques for selective brain circuit control and monitoring. It is also envisaged that new robotic controllers and robots embedding distributed plasticity rules will demonstrate improved versatility and self-adapting properties allowing in turn to better understand how the forward controller operations of the cerebellum take place in nature.



olivo-cerebellar system

Fig.1

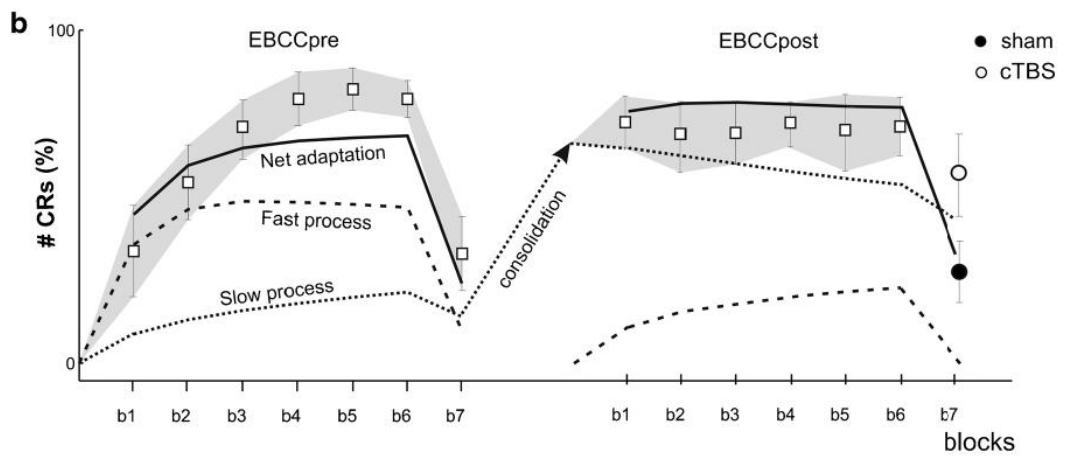
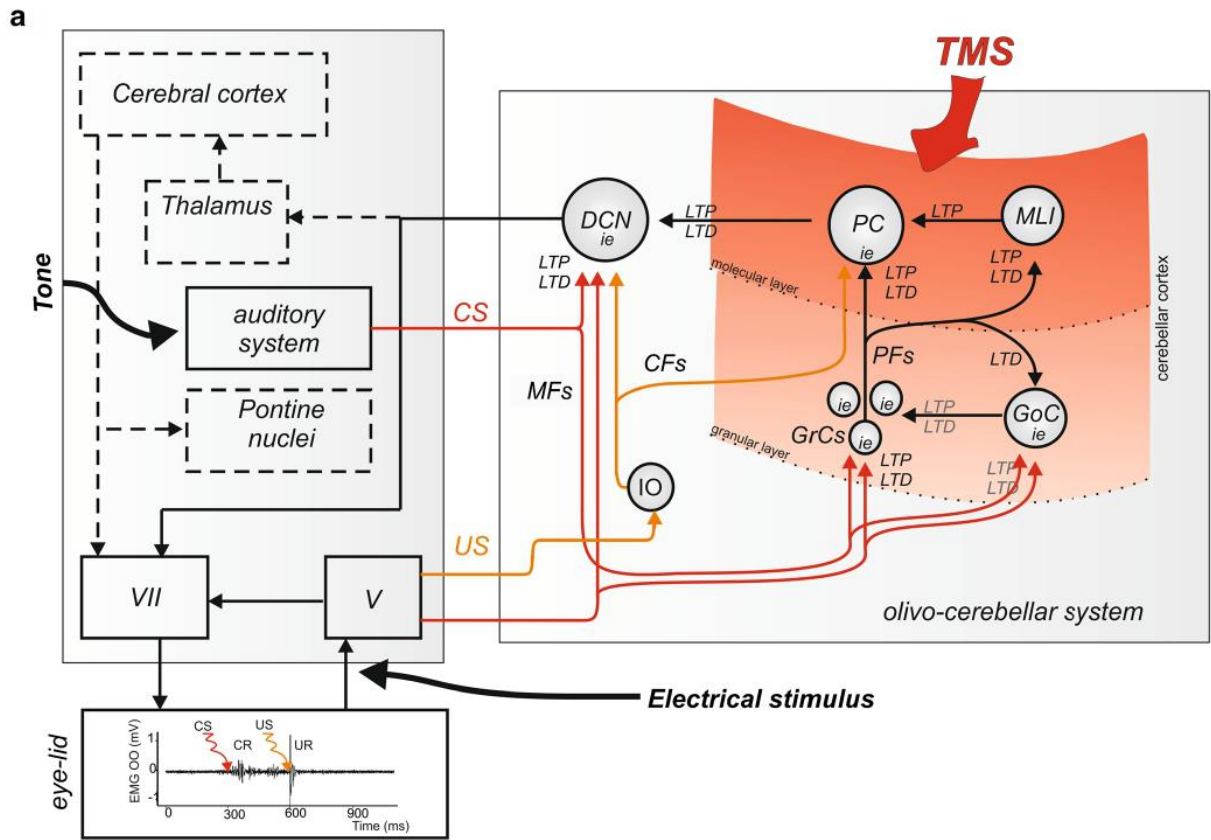


Fig.2

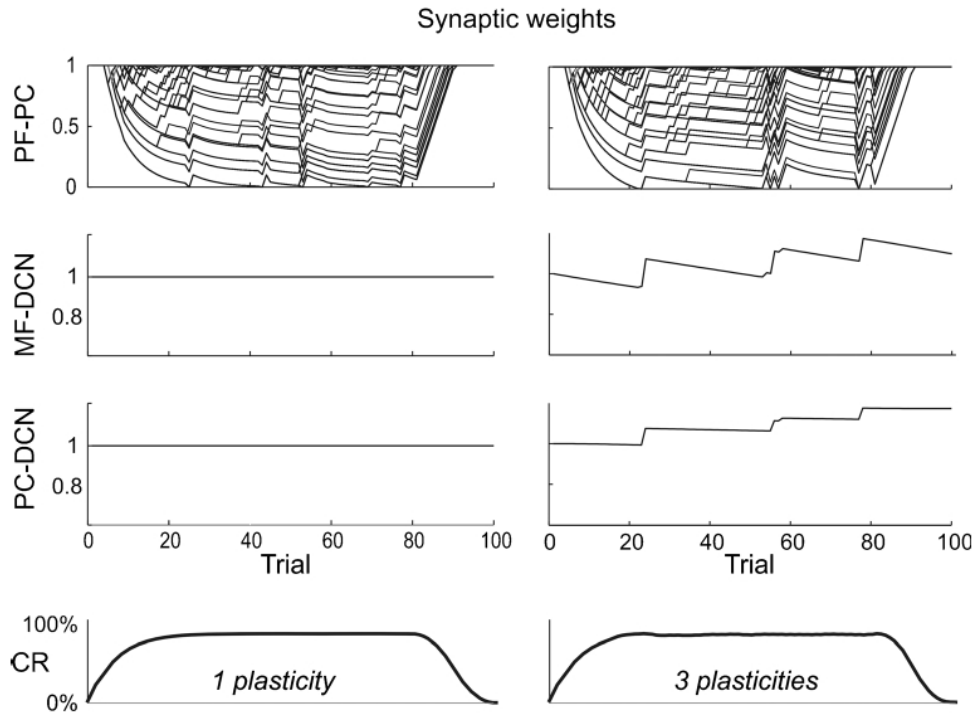


Fig.4

Figure legends

Figure 1. Distributed plasticity in the olivo-cerebellar circuit.

This schematic view shows the main architecture of cerebellar microcircuits. Inputs from mossy fibers (MFs, in red), parallel fibers (PFs, in red) and inferior olive (IO) projections (climbing fibers, CFs, in orange) provide the excitatory drive, while the inhibitory connections are shown in blue. In particular, the granular layer and the molecular layer are endowed with an inhibitory loop mediated by local interneurons (Golgi cell, GoC, and molecular layer interneuron, MLI, respectively), while the whole cerebellar cortex acts as the inhibitory loop to the deep cerebellar nuclei (DCN) neurons, through the Purkinje cell (PC) connection. MFs and CFs project both to the cerebellar cortex and to the DCN neurons. MFs contact granule cells (GrCs) and send collaterals to inhibitory GoCs. GrCs originate the PFs that make synaptic contact with PCs, MLI and GoCs (originating a granular layer feedback loop).

The major forms of plasticity reported in the cerebellar network are indicated: synaptic long-term potentiation (LTP), synaptic long-term depression (LTD), and plasticity of intrinsic excitability (ie). At the PF-PC connection the forms of presynaptic LTP or LTD (pre LTP, pre LTD) and postsynaptic LTP or LTD (post LTP, post LTD) are specified.

Figure 2. EBCC in two-session protocols reveals multiple learning mechanisms.

EBCC was induced in human subjects in a two-session protocol.

(A) The EBCC is a reflex in which the olivo-cerebellar system operates in closed-loop. The Conditioned Stimulus (CS) is an electrical stimulus to the supraorbital nerve and is conveyed to the sensory trigeminal nucleus (V). The Unconditioned Stimulus (US) corresponds to a tone. CS and US coterminate ("delay" EBCC). The olivo-cerebellar circuit learns to produce a Conditioned Responses (CRs), i.e. an eyelid blink anticipating the US onset. In this system the movement is triggered by stimulus and can be subsequently corrected in the nuclei of the facial nerve (VII) by the cerebellar intervention. The US is conveyed to the IO and generates CF signals, the CS is conveyed through the auditory system and generates MF signals. No loop between cerebellum and cerebral cortex is required. The eyelid muscles and skin also convey proprioceptive and esteroceptive signals to MFs.

(B) Number of CRs (%) along trials progressively learnt to generate CRs anticipating the US, to rapidly extinguish them and to consolidate the learnt association to be exploited in the re-test session.

Figure 3. Closed-loop simulations using an olivo-cerebellar model single plasticity

An olivo-cerebellar spiking-neural network (OC-SNN) model was coupled to a robotic control system through a radial basis function (RBF) interface to simulate an *obstacle collision avoidance task*, an associative Pavlovian-like behavior emulating EBCC (cf. Fig.2). IN this task, the IO-SNN operated as a forward controller operated by regulating the firing pattern in DCN neurons under PC control.

(A) The OC-SNN was operated in closed-loop. The Conditioned Stimulus (CS) represents a *Warning* signal, detected by the optical tracker, activating at a give distance distance threshold between the moving robot end-effector and the fixed obstacle placed along its trajectory. The Unconditioned Stimulus (US) corresponds to the collision event (crash). CS and US coterminate (as

in the “delay” EBCC). The olivo-cerebellar model learns to produce Conditioned Responses (CRs), i.e. an arm elevation (avoidance) anticipating the US onset. In this system, the trajectory planner generates a movement that is subsequently corrected in the motor controller by the cerebellar intervention. No loop is active between cerebellum and trajectory planner. The US is generated by collision during the task and conveyed by the sensory controller to the IO. The CS is generated by the optical tracker. The sensory controller also conveys proprioceptive signal from the robotic arm sensors to MFs of the OC-SNN.

(B) Number of CRs (%) along trials (80 acquisition trials and 20 extinction trials for two sessions in a row; CR% is computed as percentage number of CR occurrence within blocks of 10 trials each). The black curve is the median on 15 tests, and the grey area is the inter-quartile interval. Despite uncertainty and variability introduced by the direct interaction with a real environment, the OC-SNN progressively learnt to generate CRs anticipating the US, to rapidly extinguish them and to consolidate the learnt association to be exploited in the re-test session. Note the similarity with EBCC acquisition in Fig.2.

(C) PCs and DCNs spike distribution along trial time (500 ms from CS onset, t_0) for all trials. Each pixel represents one time-bin of 10ms, within which the number of spikes of the correspondent group is computed (first column PC cell population, second column DCN cell population). After learning, the response of PCs to MF inputs decreased and this increased the discharge in DCN neurons. The process was better exemplified in the adaptation of the EBCC, in which a precise time relationship between the events can be established. Since the DCN spike pattern changes occurred before the US arrival, the DCN discharge accurately predicted the US and therefore could facilitate the release of an anticipatory behavioral response. At the same time, the IO signal carrying US decreased. The prediction of a noxious stimulus triggers an anticipatory motor command. The inhibition mechanism of the IOs by the DCNs translates the motor command into a sensory prediction signal, allowing a single cerebellar area to simultaneously tackle both motor execution and sensory prediction.

Figure 4. Dynamic plasticity processing in closed-loop robotic simulations using an olivo-cerebellar model with distributed plasticity

An olivo-cerebellar neural network (OC-NN) model embedded with distributed plasticity was coupled to a robotic control system as in Fig.3 to simulate an *obstacle collision avoidance task*, an associative Pavlovian-like behavior emulating EBCC (cf. Fig.2). In this task, the IO-NN operated as a forward controller operated by regulating the firing pattern in DCN neurons under PC control. Plasticity was implemented at the PF-PC, MF-DCN and PC-DCN synapses.

(A) EBCC learning with 1 or 3 plasticity rules ...

(B) Dynamic development of plasticity ... fast acquisition in PF-PC ... slow transfer to MF-DCN and PC-DCN ... fast extinction in PF-PC ... maintenance in MF-DCN and PC-DCN ...

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