Chapter 38
Distributed Plasticity in the Cerebellar Circuit

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Abstract In contrast with the original Motor Learning Theory that included a single form of plasticity at the parallel fiber – Purkinje cell synapse, recent experimental work has revealed at least nine forms of long-term synaptic and non-synaptic plasticity (some of which bidirectional) distributed among the cerebellar cortex and deep cerebellar nuclei). Thus, understanding cerebellar plasticity requires now that the spatio-temporal interplay of these multiple mechanisms are analyzed during specific behaviors. A recent set of experimental and modeling investigations has opened a new view on how the multiple forms of long-term synaptic plasticity might cooperate to generate cerebellar learning and memory in sensori-motor control tasks.

Keywords Long-term synaptic plasticity • Cerebellum • Motor control

38.1 Introduction

Learning and *control* have been integrated into the *Motor Learning Theory* (Marr 1969; Albus 1971), in which the cerebellum has been proposed to learn sensori-motor contingencies and then to act as a *forward controller* predicting the consequences of motor acts and correcting intervening errors (Raymond et al. 1996; Ito 1984). Multiple processes may contribute to motor skill acquisition, which proceeds through a rapid convergence toward a stable state before being consolidated into persistent memory (Lee and Schweighofer 2009; Shadmehr et al. 2010). Although multi-rates models can indeed explain the cerebellar learning process (Smith et al. 2006), the specific role of plastic mechanisms remained unclear. These plastic mechanisms include long-term potentiation (LTP) and long-term depression (LTD)

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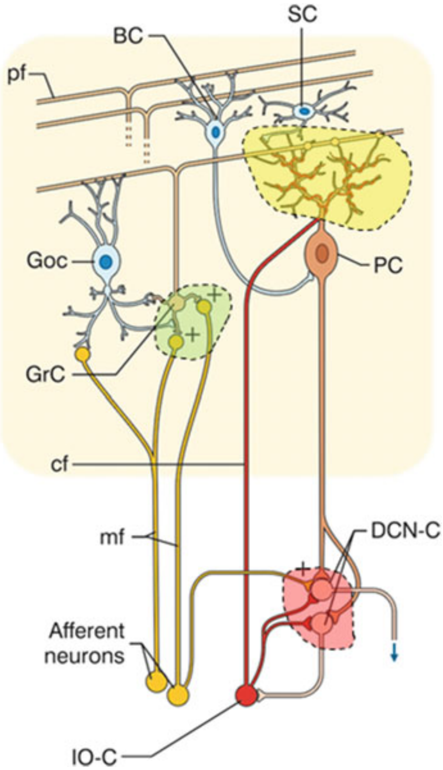

Fig. 38.1 Schematic drawing of the cerebellar circuit and its forms of plasticity. The principal elements of the cerebellar circuit and associate structures are indicated: mossy fiber (*mf*), parallel fiber (*pf*), climbing fiber (*cf*), granule cell (*GrC*), Golgi cell (*GoC*), Purkinje cell (*PC*), stellate cell (*SC*), basket cell (*BC*), deep cerebellar nuclei cell (*DCN-C*), inferior olive cell (*IO-C*). The cerebellar cortex is indicated by a shadowed area. The cerebellar circuit expresses at least nine recognized forms of plasticity, some of which bidirectional, included into three main subcircuits. (1) Granular layer (*green* area): mf – GrC LTP and LTD; GrC LTP of intrinsic excitability. (2) Molecular layer circuit (*yellow* area): presynaptic pf – PC LTP and LTD; postsynaptic pf – PC LTP and LTD; cf – PC LTD; SC/BC inhibitory LTP; PC LTP of intrinsic excitability. (3) Deep cerebellar nuclei (*red* area): mf – DCN-C LTP and LTD; PC – DCN-C inhibitory LTP and LTD; DCN cell LTP of intrinsic excitability (Taken with permission from D'Angelo 2014)

at the mossy fiber (mf) - granule cell (GrC) synapse, at the synapses formed by parallel fibers (pf), climbing fibers (cf) and molecular layer interneurons (MLI: stellate and basket cells) on Purkinje cells (PC), and at the synapses formed by mfs and PCs on deep-cerebellar nuclear cells (DCN-C), as well as LTP of intrinsic excitability in GrC, PC and DCN-C (Fig. 38.1) (for details see Hansel et al. 2001; DeZeeuw and Yeo 2005; D'Angelo and DeZeeuw 2009; Gao et al. 2012; D'Angelo 2014).

Mf-GrC LTP and LTD are expressed through mechanisms altering the synaptic strength and dynamics of repetitive signal transmission in the granular layer. Multiple forms of pf-PC LTP and LTD, along with plasticity at molecular interneuron synapses, control the state of PC activation. PC-DCN and mf-DCN LTP and LTD are regulated by mfs and PCs. In addition, plastic changes affect intrinsic excitability in granule cells, PCs and DCN cells. In front of this complexity, how does cerebellar learning occur? Are all these forms of plasticity required to learn and control complex behaviors? How are these forms of plasticity engaged during a learning task (Mauk 1997; Llinas et al. 1997)?

38.2 Evidence for Distributed Cerebellar Plasticity During Behavior

The properties of cerebellar learning can be investigated through adaptation of the eye-blink classical conditioning (EBCC) reflex (Garcia and Mauk 1998; Medina et al. 2001), which combines the three major aspects of cerebellar activity: *learning*, *prediction and timing*. In EBCC, the cerebellum allows learning of appropriate timing between conditioned (CS) and unconditioned stimuli (US), such that of US can be precisely predicted based on the occurrence of CS. The functions of cerebellar cortex and nuclei in EBCC have been dissected using micro-injection of the $GABA_A$ receptor agonist muscimol (Attwell et al. 2002; Cooke et al. 2004) and computational modeling has shown that the cerebellar cortex can account for the faster component and the deep cerebellar nuclei for slower components of EBCC learning (Medina and Mauk 2000). Moreover, dynamic transfer of plasticity among multiple sites has been suggested to rebalance synaptic weights moving associative learning from cortical to nuclear sites (Medina et al. 2001; Garrido et al. 2013a). We have recently faced the issue of EBCC learning in humans by using cerebellum transcranial magnetic stimulation (TMS) (Monaco et al. 2014). Interestingly, TMS pulses delivered over the oculo-motor cerebellum just after EBCC training, were able to disrupt the fast mechanism but not the slow mechanism of learning or even consolidation, suggesting that memory was acquired in superficial structures and dynamically transferred to deeper structures, according to the multi-rate model (Shadmehr et al. 2010).

38.3 Distributed Plasticity in Computational Models

In order to investigate the interplay of multiple plasticities in the cerebellum under realistic operating conditions, we have integrated cerebellar network models into the feed-back and feed-forward circuits of a robot (Garrido et al. 2013a; Casellato et al. 2014) generating both the motor commands (simulating cerebral cortex activity) and sensory signals (derived from various sensors measuring the consequences of movement). In robotic simulations, multiple plasticities played different roles on different timescales (Garrido et al. 2013a). Plasticity at the pf-PC synapse rapidly acquired sensori-motor correlations but was labile and was overwritten by new signals. As soon as pf-PC plasticity was formed, PC firing changed and modified the synapses in the DCN. By transferring plasticity into the DCN, the whole system became more stable. Moreover, error feed-back through sensory reafferences and the entire control system allowed plasticity self-rescaling preventing pf-PC synapse saturation. A remarkable acceleration of learning was achieved through plasticity in the internal feed-forward loop passing from the inferior olive (IO) to DCN (Luque et al. 2014), which allowed system errors to be learnt in the DCN without the need of complex signal processing through the cortical loop (granular and molecular layers). These robotic simulations thus suggest that the multiple forms of plasticity observed in the cerebellar network are needed to obtain flexible, fast and stable learning as observed in biological systems.

It should be noted that these cerebellar models did not include granular layer plasticity. Plasticity at the mf-GrC synapse is critical to regulate the number and precision of spikes generated by granule cells (D'Angelo and DeZeeuw 2009) and may be assisted by plastic changes at the mf-Golgi cell (GoC) synapse and at the GoC-GrC synapses (Garrido et al. 2013b). Moreover, changes in synaptic strength at the mf-GrC synapse are critical to determine the variety of granular layer response patterns generated by the granular layer (Rossert et al. 2014). Thus, since granular layer plasticity is critical to process time-dependent multi-dimensional inputs, three problems need to be solved before including it into adaptive sensori-motor controllers: (i) the coding scheme should be based on timing rather than firing rates, (ii) the input dimensionality should be increased, (iii) the learning rules should be determined experimentally. The development of large-scale spiking networks coupled to extended sensory and command systems, as well as the inclusion of local oscillations coupled with STDP learning rules, may help solving the issue.

38.4 Conclusions

A new picture is emerging beyond the original intuition that learning had to occur at the pf-PC synapse of the cerebellum under guidance of CF signals in order to allow motor control. Cerebellar plasticity is distributed and dynamically transferred through the different synaptic sites and can perform various operations: it is probably needed for expansion recoding in the granular layer, then it allows fast signal association in the Purkinje cell layer, finally it allows slow memory stabilization in the DCN. The plasticity transfer into deep structures requires internal and external feedback, and it is possible that memory traces are also transferred outside the cerebellum, e.g. in the cerebral cortex and brainstem (Koch et al. 2008). Cerebellar plasticity seems therefore unavoidably bound to local circuit dynamics (D'Angelo and DeZeeuw 2009) and to the extended recurrent networks formed by the cerebellum with extracerebellar areas.

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References

Albus JS (1971) A theory of cerebellar function. Math Biosci 10:25–61
Attwell PJE, Cooke SF, Yeo CH (2002) Cerebellar function in consolidation of a motor memory. Neuron 34:1011–1020
Casellato C, Antonietti A, Garrido JA et al (2014) Adaptive robotic control driven by a versatile spiking cerebellar network. PLoS One 9(11):e112265
Cooke SF, Attwell PJ, Yeo CH (2004) Temporal properties of cerebellar-dependent memory consolidation. J Neurosci 24:2934–2941
D'Angelo E (2014) The organization of plasticity in the cerebellar cortex: from synapses to control. Prog Brain Res 210:31–58
D'Angelo E, De Zeeuw CI (2009) Timing and plasticity in the cerebellum: focus on the granular layer. Trends Neurosci 32:30–40
De Zeeuw CI, Yeo CH (2005) Time and tide in cerebellar memory formation. Curr Opin Neurobiol 15:667–674
Gao Z, van Beugen BJ, De Zeeuw CI (2012) Distributed synergistic plasticity and cerebellar learning. Nat Rev Neurosci 13:619–635
Garcia KS, Mauk MD (1998) Pharmacological analysis of cerebellar contributions to the timing and expression of conditioned eyelid responses. Neuropharmacology 37:471–480
Garrido JA, Luque NR, D'Angelo E, Ros E (2013a) Distributed cerebellar plasticity implements adaptable gain control in a manipulation task: a closed-loop robotic simulation. Front Neuroci Circ 7:159
Garrido JA, Ros E, D'Angelo E (2013b) Spike timing regulation on the millisecond scale by distributed synaptic plasticity at the cerebellum input stage: a simulation study. Front Comput Neurosci 7:64
Hansel C, Linden DJ, D'Angelo E (2001) Beyond parallel fiber LTD: the diversity of synaptic and non-synaptic plasticity in the cerebellum. Nat Neurosci 4:467–476
Ito M (1984) The cerebellum and neural control. Raven Press, New York
Koch G, Mori F, Marconi B et al (2008) Changes in intracortical circuits of the human motor cortex following theta burst stimulation of the lateral cerebellum. J Clin Neurophysiol 119:2559–2569
Lee JY, Schweighofer N (2009) Dual adaptation supports a parallel architecture of motor memory. J Neurosci 29:10396–10404
Llinas R, Lang EJ, Welsh JP (1997) The cerebellum, LTD, and memory: alternative views. Learn Mem 3:445–455
Luque NR, Garrido JA, Carrillo RR et al (2014) Fast convergence of learning requires plasticity between inferior olive and deep cerebellar nuclei in a manipulation task: a closed-loop robotic simulation. Front Comput Neurosci 8:97
Marr D (1969) A theory of cerebellar cortex. J Physiol 202:437–470
Mauk MD (1997) Roles of cerebellar cortex and nuclei in motor learning: contradictions or clues? Neuron 18:343–346
Medina JF, Mauk MD (2000) Computer simulation of cerebellar information processing. Nat Neurosci 3(Suppl):1205–1211
Medina JF, Garcia KS, Mauk MD (2001) A mechanism for savings in the cerebellum. J Neurosci 21:4081–4089

Monaco J, Casellato C, Koch G et al (2014) Cerebellar theta burst stimulation dissociates memory components in eyeblink classical conditioning. Eur J Neurosci 40(9):3363–3370

Raymond JL, Lisberger SG, Mauk MD (1996) The cerebellum: a neuronal learning machine? Science 272:1126–1131

Rössert C, Solinas S, D'Angelo E et al (2014) Model cerebellar granule cells can faithfully transmit modulated firing rate signals. Front Cell Neurosci 8:304

Shadmehr R, Smith MA, Krakauer JW (2010) Error correction, sensory prediction, and adaptation in motor control. Annu Rev Neurosci 33:89–108

Smith MA, Ghazizadeh A, Shadmehr R (2006) Interacting adaptive processes with different timescales underlie short-term motor learning. PLoS Biol 4(6):e179