Neuroscience 162 (2009) 805–815

REVIEW

TIMING IN THE CEREBELLUM: OSCILLATIONS AND RESONANCE IN THE GRANULAR LAYER

**E. D'ANGELO,[a]* S. K. E. KOEKKOEK,[b,c]
P. LOMBARDO,[a] S. SOLINAS,[a] E. ROS,[d] J. GARRIDO,[d]
M. SCHONEWILLE[b] AND C. I. DE ZEEUW[b,c]**

[a]*Department of Physiology, University of Pavia, CNISM (Consorzio Nazionale Interuniversitario per le Scienze Fisiche della Materia), Via Forlanini 6, I-27100, Pavia, Italy*

[b]*Department of Neuroscience, Erasmus MC, 3000 DR Rotterdam, The Netherlands*

[c]*Netherlands Institute for Neuroscience, Royal Academy of Arts and Sciences (KNAW), Amsterdam, The Netherlands*

[d]*Department of Computer Architecture and Technology, University of Granada, E-18071 Granada, Spain*

Abstract—The brain generates many rhythmic activities, and the olivo-cerebellar system is not an exception. In recent years, the cerebellum has revealed activities ranging from low frequency to very high-frequency oscillations. These rhythms depend on the brain functional state and are typical of certain circuit sections or specific neurons. Interestingly, the granular layer, which gates sensorimotor and cognitive signals to the cerebellar cortex, can also sustain low frequency (7–25 Hz) and perhaps higher-frequency oscillations. In this review we have considered (i) how these oscillations are generated in the granular layer network depending on intrinsic electroresponsiveness and circuit connections, (ii) how these oscillations are correlated with those in other cerebellar circuit sections, and (iii) how the oscillating cerebellum communicates with extracerebellar structures. It is suggested that the granular layer can generate oscillations that integrate well with those generated in the inferior olive, in deep-cerebellar nuclei and in Purkinje cells. These rhythms, in turn, might play a role in cognition and memory consolidation by interacting with the mechanisms of long-term synaptic plasticity. © 2009 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: cerebellum, granular layer, oscillations, resonance, granule cells, Golgi cells.

Contents

The olivo-cerebellar system processes sensorimotor signals to rapidly control fine movement coordination and to store memories of past procedures (Eccles et al., 1967; Ito, 1984). Moreover, a role of the cerebellum in cognitive functions has been reported by several groups (Schmahmann, 2004; Leiner et al., 1993; Sacchetti et al., 2004; Ito, 1993; Schmahmann and Caplan, 2006; Allen et al., 2004). The cerebellum has a regular anatomical matrix structure (Fig. 1), which inspired the first comprehensive models of cerebellar functions such as the motor learning theory (Marr, 1969; Albus, 1971; Fujita, 1982). The concepts of these theories still provide classic references, but at the time they were based on relatively limited knowledge of the functional properties of neurons and synapses involved. It was not until the potential roles of the Golgi cells were considered in detail that the granular layer was proposed to process input temporal patterns (Fujita, 1982; Chapeau-Blondeau and Chauvet, 1991) and generate internal oscillatory dynamics (Maex and De Schutter, 1998; Medina and Mauk, 2000).

In recent years, important achievements were made on cellular and synaptic properties of the olivo-cerebellar circuit. The key elements that turned out to be relevant for models on cerebellar processing include the precise time patterns of spikes in the various neurons and the distribution of long-lasting synaptic plasticity inside the network (Hansel et al., 2001; De Zeeuw and Yeo, 2005). These elements are functionally related throughout the entire circuit and they influence one another without almost any exception (Casado et al., 2002; Coesmans et al., 2004; Nieus et al., 2006; Jörntell and Hansel, 2006; Steuber et al., 2007). More recent works attempt to address the issue as to how the network properties of the cerebellar system processes precisely the sequences of the timed signals and how it enforces the required internal dynamics (D'Angelo, 2008; Jacobson et al., 2008; De Zeeuw et al., 2008; D'Angelo and De Zeeuw, 2009). One of the intriguing properties in this respect is the capability of the olivo-

---

*Corresponding author. Tel: +39-0382-987606.
E-mail address: dangelo@unipv.it (E. D'Angelo).

Abbreviations: DCN, deep-cerebellar nuclei; IO, inferior olivary; LTD, long-term depression; LTP, long-term potentiation; UBC, unipolar brush cell; VN, vestibular nuclei.

0306-4522/09 $ - see front matter © 2009 IBRO. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuroscience.2009.01.048

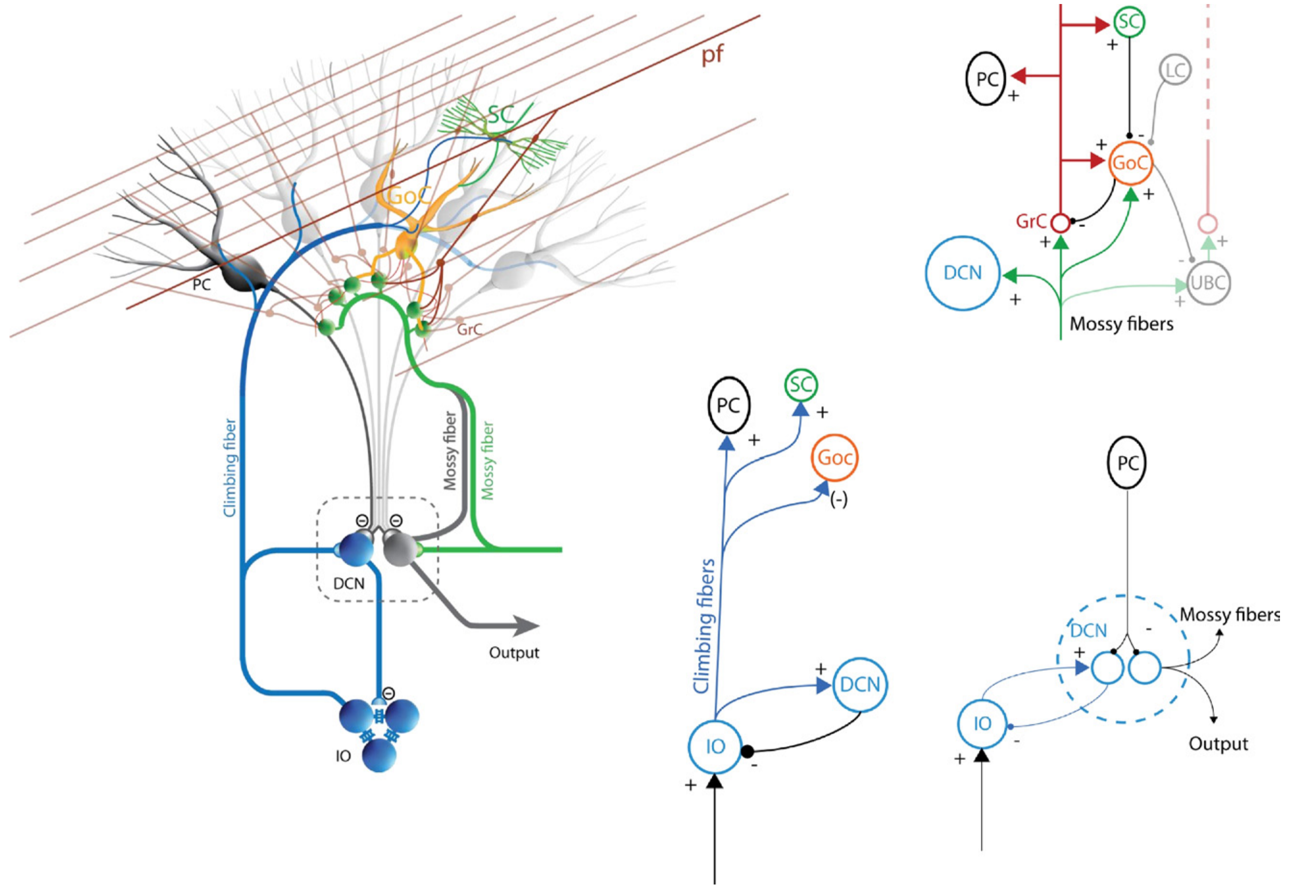

Fig. 1. The organization of a cerebellar module. This schematic drawing shows the most relevant connections within a cerebellar module. The cerebellar module is made of a series of connections, in which different circuit elements communicate in closed loops and are contacted by the same afferent fiber set. The mossy fibers contact granule cells (GrC) and DCN cells which, in turn, receive inhibition from the same common set of Purkinje cells (PC). Moreover, the IO cells emit climbing fibers that contact DCN and PC, which also project to the same DCN cells. For convenience, the circuit can be divided in three sections illustrated schematically in the insets. The top-right inset also shows a Lugaro cell (LC) and a UBC, this latter typical of the vestibulocerebellum. Note that connections exist between the climbing fiber and mossy fiber sections, although these have often been considered as separated.

cerebellar network to show oscillatory activities. Question remains which network factors cause the cerebellum to generate particular internal rhythms and to operate at preferential frequency bands, and what the functions of these oscillations might be (Buzsáki, 2006; De Zeeuw et al., 2008).

Although the EEG of the cerebellum is not used in daily clinical practice, experimental analysis has revealed that the cerebellum, in humans, can express all series of rhythms encompassing the theta, alpha, beta, gamma and very high frequency (VHF) bands (Dalal et al., 2008; Gross et al., 2002). These rhythms are likely to arise to a large extent from electric fields generated in the molecular layer (Isope et al., 2002; Cheron et al., 2008; de Solages et al., 2008; Middleton et al., 2008), but the granular layer is likely to contribute as well to at least some of these rhythms (for review see De Zeeuw et al., 2008). Extracellular field recordings in freely behaving animals have shown that large granular layer areas can oscillate in synchrony demonstrating remarkable coherence in the 7–25 Hz frequency range (Pellerin and Lamarre, 1997; Hartmann and Bower, 1998; Courtemanche et al., 2002; Courtemanche and Lamarre, 2005; Schnitzler, 2005; Schnitzler and Gross, 2006). In keeping with this, granular layer neurons are well equipped with appropriate membrane channels favoring activity in this band (D'Angelo et al., 2001; Solinas et al., 2007a,b). Moreover, computational modeling has predicted that the granular layer can generate theta-frequency oscillations (Kistler and De Zeeuw, 2003) and may also undergo cycles of activity at relatively higher frequencies (up to 40 Hz; Maex and De Schutter, 1998).

Interestingly, all these frequencies have been observed in muscular responses either as tremor or through EMG spectral analysis and are somehow species-specific. For example, eyelid oscillates at ~10 Hz in humans, ~20 Hz in cats and 25–30 Hz in rats, guinea pigs (Gruart et al., 2000) and mice (Koekkoek et al., 2002). Therefore, the cerebellum may be able to sustain oscillations at different frequencies to synchronize with other areas of the brain involved in sensorimotor control (Domingo et al., 1997; Gruart et al., 1997; Sanchez-Campusano et al., 2007).

While we recently focused on the interplay between timing and plasticity in shaping the granular layer response to external inputs (D'Angelo and Dezeeuw, 2009), here we