Chapter 37
Cerebellar Modules and Networks Involved in Locomotion Control

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Abstract Modern neuroscience is paving the way for new insight into cerebellar functions including the control of cognitive, autonomic and emotional processes. Yet, how the cerebellum coordinates basic motor behavior such as locomotion is still only partly understood. Here, we will review the role of the cerebellum in locomotion from the perspective of neuro-anatomical and clinical reports as well as cell-specific rodent studies. Evidence has been emerging that different modules and networks exert synergistic roles in the preparation, performance, adaptation and consolidation of locomotion, highlighting their contribution to interlimb coordination and the accuracy, efficiency and regularity of locomotion patterns.

Keywords Cerebellar modules networks • Locomotion • Interlimb coordination

37.1 Introduction

Whereas the cerebellum does not initiate movement, it does facilitate the acquisition and performance of well-timed, smooth and efficient movements aimed at a specific target in space and/or proper coordination with respect to other body parts.

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D.L. Gruol et al. (eds.), *Essentials of Cerebellum and Cerebellar Disorders*,
DOI 10.1007/978-3-319-24551-5_37

Accordingly, typical signs of cerebellar dysfunction include deficits in the acquisition and performance of such movements. In the initial stages of mild cerebellar disease, deficits are predominantly reflected in the inability to adapt the amplitude and timing of movements to new environmental challenges or to acquire new associative motor behaviors. However, when cerebellar degeneration progresses, performance deficits emerge, often leading to full-blown ataxia (De Zeeuw et al. 2011). The name *ataxia* literally means "without order" and highlights the robust coordination deficits of this disorder, while setting it apart from the inability to move (*paralysis*), a disorder occurring in non-cerebellar diseases such as amyotrophic lateral sclerosis or stroke of the cerebral motor cortex.

37.2 Modular Organization: Evidence from Neuro-Anatomical and Clinical Studies

The cerebellar cortex can be divided into distinct functional sagittal zones identified by their specific afferent and efferent connections (Voogd and Glickstein 1998). Each zone of cerebellar Purkinje-cells projects to a specific cerebellar or vestibular nucleus, which in turn inhibits the olivary subnucleus that provides the climbing fibers to the Purkinje-cells of the corresponding zone (De Zeeuw et al. 2011). These topographically organized triangular loops are referred to as olivocerebellar modules.

Lesion studies of the cerebellum or inferior olive in mammals suggest that most, if not all, modules are involved in locomotion, but probably each in a specific way. The medial zones of the cerebellum (A, B) regulate posture and balance by controlling extensor tone and modulate related rhythmic muscular activity by controlling spinal interneurons (Mori et al. 1999; Pijpers et al. 2008; Horn et al. 2010). By contrast, the intermediate zones (C1 to C3) are more relevant for controlling the trajectory, reflexes, timing and amplitude of limb movements (Chambers and Sprague 1955; Yu and Eidelberg 1983). Finally, the lateral zones (D1 and D2) are important in the adaptation of locomotion patterns to unusual and complex circumstances, especially when visual guidance is needed (Thach et al. 1992; Aoki et al. 2013). Indeed, retrograde transneuronal tracer studies show that multiple modules are involved in the control of individual hindlimb muscles (Fig. 37.1; Ruigrok et al. 2008).

Clinical studies of cerebellar patients suffering from focal lesions following stroke or resection of tumors also indicate that all olivocerebellar modules contribute to locomotion in specific ways. Here, too, lesions in the medial zones affect balance, posture and undisturbed gait, whereas those in the intermediate and lateral zones deregulate leg placement and interlimb coordination as well as planning and gait adaptation to demanding circumstances (Schoch et al. 2006; Morton and Bastian 2007; Ilg et al. 2008). Moreover, similar to animal studies, lesions affecting the cerebellar nuclei in humans are more difficult to compensate for than lesions

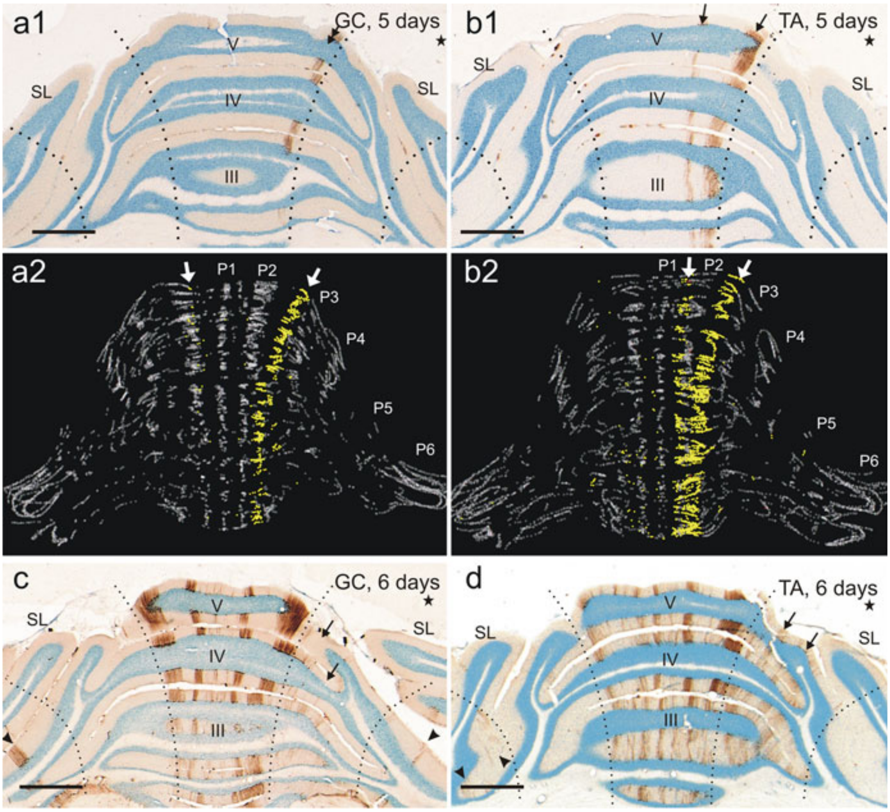

Fig. 37.1 Multiple cerebellar modules are involved in the control of single hindlimb muscles. (**a1**, **b1)** Injection of the retrogradely and transneuronally transported rabies virus into either the gastrocnemius (GC) or anterior tibial (TA) muscles of the rat resulted in zonal labeling of vermal Purkinje cells after 5 days survival time. (**a2**, **b2)** These zones adhered to the zebrin pattern as demonstrated in a plot of the anterior lobe based on ten superposed double labeled sections. This enabled identification of the labeled zones. Note that virtually all rabies-labeled cells are zebrin-negative. Minor differences exist between patterns resulting from GC and TA injections. *Yellow dots*, rabies-labeled Purkinje cells; *grey dots*, zebrin-positive cells; *red dots*, double labeled cells. (**c**, **d)** Lengthening the survival time to allow for a single more transsynaptic passage also labeled Purkinje cells in the paravermis (*arrows*) and hemispheres (*arrowheads*). *III*, *IV*, *V*, vermal lobules, *SL* simple lobule; *star*, injected side; *stippled lines* indicate approximate lateral border of vermis and paravermis; scale bar: 500 μm (Adapted from Ruigrok et al. 2008)

affecting solely the cerebellar cortex (Morton and Bastian 2004; Konczak et al. 2005; Schoch et al. 2006). Together, the cerebellar cortex and nuclei may act as an internal model of the motor apparatus, allowing sensorimotor predictions of body state in the future following particular motor commands (Wolpert et al. 1995; Bastian 2006).

37.3 Network Organization: Evidence from Cell-Specific Rodent Studies

The cerebellar cortex is a continuous sheet of repeated networks of neurons folded into folia. Its most remarkable structural feature is the orthogonal arrangement of many of its cells and afferents. The dendrites and axons of Purkinje-cells, axons of molecular layer interneurons, ascending axons of granule-cells, dendritic domains of Golgi-cells as well as the climbing-fibers and Bergmann glia-sheaths are all predominantly oriented in sagittal planes, whereas the parallel-fibers originating from the ascending granule cell axons are orthogonally oriented in a medio-lateral direction (De Zeeuw et al. 2011). In this respect, the mossy-fibers exhibit a somewhat ambiguous distribution in that they can show sagittally oriented input patterning as occurs in large parts of the anterior lobe, whereas in other parts they traverse multiple modules (Gao et al. 2012). Interestingly, the sagittally oriented mossy-fiber inputs also entail some of the areas involved in locomotion, such as those receiving input from the spinal cord and dorsal column nuclei (Gerrits et al. 1985).

Purkinje-cells are most critical for operations at the network level of the cerebellar cortex; deleting these cells in rodents leads to irregular and smaller movements of the limbs just like those of other body parts such as the eyes (De Zeeuw et al. 2011; Vinueza Veloz et al. 2014). Their climbing-fiber input has been suggested to carry an error signal affecting the strength of their parallel-fiber inputs (Marr 1969; Albus 1971). With regard to adaptation of locomotion patterns, intrinsic plasticity of Purkinje-cells and long-term potentiation (LTP), but not long-term depression (LTD), of the parallel fiber-Purkinje-cell synapse appear to be essential (Schonewille et al. 2011; Vinueza Veloz et al. 2014). Moreover, processing at the level of the interneurons in both the granular layer and molecular layer also appears to contribute to gait patterns, albeit less prominently and predominantly during demanding tasks (Galliano et al. 2013; Vinueza Veloz et al. 2014). Likewise, electrotonic coupling of neurons in the inferior olive is also critical for fast modification of locomotion reflexes (Van Der Giessen et al. 2008). Thus, although Purkinje-cells and their potentiation are most critical for generating accurate, efficient, and consistent walking patterns, their input structures also all play a relevant role; and this role is most prominent during interlimb coordination and obstacle crossings (Stroobants et al. 2013; Vinueza Veloz et al. 2014). Indeed, the cerebellar networks operate in a distributed synergistic fashion allowing for ample possibilities of compensation (Gao et al. 2012).

Acknowledgements This work was supported by the Dutch Organization for Medical Sciences (ZonMw), Life Sciences (ALW), Senter (Neuro-Bsik) and ERC-adv of the European Community.

References

Albus JS (1971) A theory of cerebellar function. Math Biosci 10:25–61
Aoki S, Sato Y, Yanagihara D (2013) Lesion in the lateral cerebellum specifically produces overshooting of the toe trajectory in leading forelimb during obstacle avoidance in the rat. J Neurophysiol 110:1511–1524
Bastian AJ (2006) Learning to predict the future: the cerebellum adapts feedforward movement control. Curr Opin Neurobiol 16:645–649
Chambers WW, Sprague JM (1955) Functional localization in the cerebellum. II. Somatotopic organization in cortex and nuclei. AMA Arch Neurol Psychiatry 74:653–680
De Zeeuw CI, Hoebeek FE, Bosman LW, Schonewille M, Witter L, Koekkoek SK (2011) Spatiotemporal firing patterns in the cerebellum. Nat Rev Neurosci 12:327–344
Galliano E, Gao Z, Schonewille M, Todorov B, Simons E, Pop AS, D'Angelo E, van den Maagdenberg AM, Hoebeek FE, De Zeeuw CI (2013) Silencing the majority of cerebellar granule cells uncovers their essential role in motor learning and consolidation. Cell Rep 3:1239–1251
Gao Z, van Beugen BJ, De Zeeuw CI (2012) Distributed synergistic plasticity and cerebellar learning. Nat Rev Neurosci 13:619–635
Gerrits NM, Voogd J, Nas WS (1985) Cerebellar and olivary projections of the external and rostral internal cuneate nuclei in the cat. Exp Brain Res 57:239–255
Horn KM, Pong M, Gibson AR (2010) Functional relations of cerebellar modules of the cat. J Neurosci 30:9411–9423
Ilg W, Giese MA, Gizewski ER, Schoch B, Timmann D (2008) The influence of focal cerebellar lesions on the control and adaptation of gait. Brain 131:2913–2927
Konczak J, Schoch B, Dimitrova A, Gizewski E, Timmann D (2005) Functional recovery of children and adolescents after cerebellar tumour resection. Brain 128:1428–1441
Marr D (1969) A theory of cerebellar cortex. J Physiol 202:437–470
Mori S, Matsui T, Kuze B, Asanome M, Nakajima K, Matsuyama K (1999) Stimulation of a restricted region in the midline cerebellar white matter evokes coordinated quadrupedal locomotion in the decerebrate cat. J Neurophysiol 82:290–300
Morton SM, Bastian AJ (2004) Cerebellar control of balance and locomotion. Neuroscientist 10:247–259
Morton SM, Bastian AJ (2007) Mechanisms of cerebellar gait ataxia. Cerebellum 6:79–86
Pijpers A, Winkelman BH, Bronsing R, Ruigrok TJ (2008) Selective impairment of the cerebellar C1 module involved in rat hind limb control reduces step-dependent modulation of cutaneous reflexes. J Neurosci 28:2179–2189
Ruigrok TJ, Pijpers A, Goedknegt-Sabel E, Coulon P (2008) Multiple cerebellar zones are involved in the control of individual muscles: a retrograde transneuronal tracing study with rabies virus in the rat. Eur J Neurosci 28:181–200
Schoch B, Dimitrova A, Gizewski ER, Timmann D (2006) Functional localization in the human cerebellum based on voxelwise statistical analysis: a study of 90 patients. Neuroimage 30:36–51
Schonewille M, Gao Z, Boele HJ, Veloz MF, Amerika WE, Simek AA, De Jeu MT, Steinberg JP, Takamiya K, Hoebeek FE, Linden DJ, Huganir RL, De Zeeuw CI (2011) Reevaluating the role of LTD in cerebellar motor learning. Neuron 70:43–50
Stroobants S, Gantois I, Pooters T, D'Hooge R (2013) Increased gait variability in mice with small cerebellar cortex lesions and normal rotarod performance. Behav Brain Res 241:32–37
Thach WT, Goodkin HP, Keating JG (1992) The cerebellum and the adaptive coordination of movement. Annu Rev Neurosci 15:403–442
Van Der Giessen RS, Koekkoek SK, van Dorp S, De Gruijl JR, Cupido A, Khosrovani S, Dortland B, Wellershaus K, Degen J, Deuchars J, Fuchs EC, Monyer H, Willecke K, De Jeu MT, De Zeeuw CI (2008) Role of olivary electrical coupling in cerebellar motor learning. Neuron 58:599–612

Vinueza Veloz MF, Zhou K, Bosman LW, Potters JW, Negrello M, Seepers RM, Strydis C, Koekkoek SK, De Zeeuw CI (2014) Cerebellar control of gait and interlimb coordination. Brain Struct Funct 220:3513–3536

Voogd J, Glickstein M (1998) The anatomy of the cerebellum. Trends Neurosci 21:370–375

Wolpert DM, Ghahramani Z, Jordan MI (1995) An internal model for sensorimotor integration. Science 269:1880–1882

Yu J, Eidelberg E (1983) Recovery of locomotor function in cats after localized cerebellar lesions. Brain Res 273:121–131