Cerebellum (2010) 9:17–21
DOI 10.1007/s12311-010-0159-8

EDITORIAL

Cerebellar Nuclei: Key Roles for Strategically Located Structures

Mario Manto · Nordeyn Oulad Ben Taib

Keywords Cerebellar nuclei · Fastigial · Interpositus · Dentate · Neurons

With the exception of vestibular information, cerebellar nuclei represent the unique source of output of the cerebellar circuitry. The fastigial (FN), globose/emboliform (interpositus, IN), and dentate (DN) nuclei receive inhibitory GABAergic signals from Purkinje neurons and send back fibers to the cerebellar cortex. The numerous GABA-A inhibitory synapses between cerebellar cortex and cerebellar nuclei allow responses to high-frequency Purkinje cell firing [1]. Cerebellar nuclei receive excitatory collaterals of mossy fibers and climbing fibers, especially via AMPA and NMDA receptors [2]. A subset of small neurons in cerebellar nuclei project to the inferior olivary complex, providing a feedback to the inferior olive. Cerebellar nuclei thus integrate the converging excitatory and inhibitory signals to provide the final output of the cerebellar circuits. Each cerebellar nucleus has a separate somatotopic representation of the body [3]. The projections to different cerebral cortical areas originate from distinct areas of cerebellar nuclei. In particular, the DN is spatially divided into a motor and nonmotor zone, with a closed loop from the nucleus to the cerebral cortex and back to the nucleus.

Cerebellar nuclei control differentially the medial and lateral motor systems and their functions [4]. The vestibular and FN are concerned with the control of eye movements, control of head orientation, stance, and gait. FN can be functionally divided into rostral and caudal components [4, 5]. The rostral portion is involved in the control of somatic musculature, head orientation, and eye-gaze shifts [4]. The caudal FN plays key roles in saccade generation and smooth pursuit [6]. The IN is particularly active during the modulation of various reflexes and sensory feedback [7]. The eyeblink responses are typically associated with a modulation of activity in behaving animals [8]. The intermediate cortex and the IN fire in relation to the antagonist muscle group [9, 10], in agreement with a role in damping the limb oscillations and compensation of errors [11]. The IN participates in the excitability of the stretch reflexes [12]. The DN is especially concerned with voluntary movements of the extremities, including reaching and grasping. Dentate neurons preferentially fire at the onset of movement triggered by mental associations [4]. An influential theory is that cerebellar nuclei constitute temporal pattern generators that can contribute to the precise temporal control of motor or cognitive events [13, 14]. The plasticity of Purkinje neurons–cerebellar nuclei synapses is based upon synaptically driven changes in excitability and LTP/LTD [15–17]. In conjunction with the LTP/LTD in cerebellar cortex and the adaptations occurring in mossy/climbing fibers, such plasticity allows for reshaping of patterns of activities in cerebellar nuclei.

On the basis of GABA decarboxylase isoform 67 (GAD67) expression and electrophysiological properties, three types of cerebellar nuclei neurons have been described [18]: the large non-GABAergic neurons ("GADnL"; putatively corresponding to the glutamatergic projection neurons) and two classes of smaller neurons, one

M. Manto · N. Oulad Ben Taib
Service de Neurologie et Neurochirurgie, ULB Erasme,
Brussels, Belgium

M. Manto (✉)
Laboratoire de Neurologie Expérimentale, FNRS ULB,
808 Route de Lennik,
1070 Brussels, Belgium
e-mail: mmanto@ulb.ac.be

being GABAergic and the other GAD67-negative. Small neurons include not only the local neurons, but also those projecting to the inferior olive [19]. A substantial number of glycinergic and glycine/GABA coexpressing neurons have also been observed. It has been considered that GABAergic and glycinergic neurons of the cerebellar nuclei are partially overlapping neuronal populations [20]. In this issue, Uusisaari and Knopfel report on two electrophysiologically and morphologically distinct sets of glycine transporter type 2 (GlyT2)-expressing neurons in the lateral cerebellar nucleus, using transgenic mouse line expressing enhanced green fluorescence protein under the control of the GlyT2 gene promoter [21]. GlyT2 is specific for glycinergic neurons [22]. The first set of neurons (Gly-A) shares electrophysiological properties with the previously characterized GABAergic cell group, corresponding to the histologically defined group of GABA/glycine coexpressing neurons. The second (Gly-I) projects in the direction of the cerebellar cortex and is characterized by an electrical silence in slices and neuronal discharges only upon depolarizing current injection, with an irregular firing. The projecting axons of Gly-I cells are directed towards the dorsolateral borders of the cerebellar nuclei and enter the granule cell layer in the lateral cerebellar cortex, findings indicative of a nucleocortical pathway [23]. Other recent studies have highlighted the presence of two populations of glycinergic neurons in the FN [24]. The observation of a population of electrophysiologically silent neurons in cerebellar nuclei is particularly interesting, given the fact that most neurons in lateral nuclei have a pacemaker activity (see below). The glycinergic nucleocortical pathway deserves special attention in future studies addressing the feedback loop from nuclei to cortical areas. One of main targets of Gly-I neurons is probably the population of Golgi cells.

Neurons of cerebellar nuclei receive an overwhelming amount of basal and driven inhibition from Purkinje neurons [25]. Spiking of nuclear cells is dependent upon the amount of corticonuclear inhibition. Moreover, the strength of inhibition is sensitive to the amount of spiking, through multiple forms of long-term plasticity. Zheng and Raman review the properties of synaptic excitation and inhibition, as well as the interactions among excitation, inhibition, and spiking that produce long-term changes in synaptic strength in cerebellar nuclei. The strength of inhibitory postsynaptic potentials (IPSPs) and excitatory postsynaptic potentials changes as the activity of cerebellar nuclear cells is changing. Homeostatic and nonhomeostatic mechanisms of self-regulation are discussed. Neurons of the cerebellar nuclei fire action potentials spontaneously, even in absence of synaptic input. These intrinsic firing rates generally lie between 10 and 50 Hz [26, 27], despite the fact that each nuclear cell is subject to a barrage of more than a thousand IPSPs per second caused by the inhibitory input from upstream Purkinje cells. Neurons can still fire despite a substantial inhibition. This results to intrinsic leak currents of cerebellar nuclear cells. Indeed, cerebellar nuclear cells express voltage-independent non selective cationic leak channels that reverse near −30 mV [28].

Pedroarena discusses the mechanisms supporting the transfer of inhibitory signals into the spike output of spontaneously firing cerebellar nuclear neuron in vitro [29]. Taken as a whole, two different intrinsic properties of cerebellar nuclei, rebound excitation and automatic firing, have been suggested. Whole-cell recordings of spontaneously firing cerebellar nuclei in cerebellar slices show that both mechanisms are effective in spontaneously firing cerebellar nuclei but operate at different ranges of membrane potential. There is a correlation between rebound and the duration/amplitude of the preceding hyperpolarization. Activation of Purkinje cell synapses with trains of stimuli few seconds long induce a rebound firing. The rebound frequency is significantly correlated to the synaptic stimulus strength. Rebound excitation is complementary to the decrement of firing rate strategy. Rebound frequency might encode the amplitude of inhibition and could transfer inhibitory signals in the cerebellar circuit. The fact that high sensitivity of cerebellar nuclei to hyperpolarizing inputs is preserved under spontaneous firing is particularly interesting. Understanding the mechanisms of encoding of inhibition remains an outstanding question for extraction of the roles of cerebellar circuitry.

The participation of the cerebellum in neocortical rhythms is discussed by Schwarz [30]. The cerebrocerebellar projection consists of massive fiber systems connecting neocortex and the cerebellum via the pontine nuclei. In human, pontine nuclei make up about 35% of the volume of the brain stem. Signals on mossy fibers originating in the pontine nuclei are under a direct reciprocal feedback control from the cerebellar nuclei. There is evidence that pontine nuclei are more than a pure relay station. The “fractured topography” [31, 32] is a major feature of the afferent loop. The peculiar spatial arrangement of pontine nuclei might be a prerequisite for the adaptation of the neuronal firing in neocortex into spatiotemporal patterns of firing rates which can be processed by the cerebellar modules. Simultaneous multineuron recordings show that slow burst firing is readily conveyed within the pontonuclear feedback loop. Slow wave activity is known to be correlated over large parts of the neocortex [33]. Slow wave activity appears to be transmitted via the entire cerebrocerebellar loop, despite distinct intrinsic membrane properties. Although many single units in cerebellar nuclei oscillate in the gamma range, they fail to synchronize with other units in either cerebellar nuclei or pontine nuclei. Fast gamma oscillations might be incompatible with cerebellar processing. Signals in this frequency band might be converted into another exploitable code using the feedback control loop.

The extensive reciprocal connections of the IN with the cerebral cortex, brain stem, and spinal cord put this structure in a unique position to process both motor commands and the volley of sensory information. Casabona et al. discuss the role for the IN in the representation of limb kinematics [34]. Overall, the contribution of this nucleus is greater with goal-directed movements of the hand [35, 36]. Inactivation of the nucleus impairs limb movement kinematics, with instability in movement direction, velocity, and final position. Studies on forelimb movements show a significant relationship between nuclear neurons and limb kinematic parameters such as position and movement velocity [37]. The anterior and posterior parts of the IN appear to play distinct roles. Manipulation of objects is preferentially located in the anterior portion, whereas reaching movements are more represented in the posterior part [34]. The hypometria in case of lesion of the anterior portion contrasts with the hypermetria observed in posterior lesions [38]. Encoding of movement speed is preferentially represented in the posterior part of the IN. Indeed, the activity of a large fraction of posterior neurons shows a clear modulation with the speed component of the movement velocity vector [34]. Purkinje cells activity have the capacity to combine direction and speed to encode the velocity vector [39]. Limb movement-related representations might thus be parceled [40] and the IN could be a key structure to extract information related to movement speed and to send processed information to the spinal cord, brain stem, and thalamic nuclei. Both red nucleus and motor cortex also show specific neuronal patterns of activity related to the movement kinematics. The IN could build an internal spatial reference frame required to tune motor commands [34]. This is compatible with the leading theory of internal models related to motor predictions [41], since internal models require updating for accurate feedforward control. This fits also with the large spatial information coding capacity of the cerebellar cortex [42].

Garcia-Martinez and colleagues discuss the roles of the cerebellum during copulation [43]. Rat sexual behavior can be considered as a natural model to study the mechanisms related to the acquisition of motor skills. Given the key roles of the cerebellum in acquisition of new skills, control of movement, and sensorimotor integration, the number of studies in this field is growing. Sensory sexual stimulation of male rats produces the highest significant activation of granule cells at lobules 6 to 9 of the vermis region [44]. Cerebellar cortex exhibits a subsequent phase of reduction of activity in granule layer. Initially, naive male show the highest multiunit amplitude for mount and intromission patterns at lobules 6a and 7 and at the inferior olive, followed by a gradual decrease as learning progresses. FN shows mirror-like responses. Execution of more complex movements is required for skilled copulation. Emotional and cognitive aspects during sexual behavior do influence also cerebellar responses. The role of the cerebellum in reproduction deserves further studies.

The function of the cerebellar circuitry is under the influence of numerous neuropeptides, but little is known about their roles in motor control. Yu and colleagues have investigated the effects of orexins (also called hypocretins) on neuronal activity in slices [45]. The orexinergic fibers emerging from the lateral hypothalamus/perifornical region project to various areas in the brain, including the cerebellum [46]. Cerebellar circuitry is directly connected with the hypothalamic nuclei [47]. Orexins were initially considered as neurotransmitters stimulating food intake, but it is now established that they are involved in many physiological processes, including energy homeostasis, sleep–awake cycle, pain, drug addiction, or emotion. This is also the case for the cerebellar circuitry [48]. Both orexin A and B induced a concentration-dependent excitatory response in the rat cerebellar interpositus nucleus. Orexins stimulate cerebellar neurons through OX2R receptors. Injection of orexin A into cerebral ventricles or specific areas in the midbrain or medulla facilitate muscle tone and maintain a higher level of locomotor activity in animals. Impairment of the orexinergic system functions elicit hypotonia [49], a deficit which is classically observed in acute cerebellar lesions. The possibility of an orexinergic modulation of the activity of the interpositus nucleus opens a new door for a tuning of nuclear activity by neuropeptides. Since orexinergic neurons in the hypothalamus also exert an excitatory effect on Purkinje cells in flocculus of the cerebellum, Yu et al. speculate that the orexinergic afferents from the hypothalamus may actively tune the cerebellar outputs through their innervations of the flocculus Purkinje cells as well as the cerebellar neurons of the IN. Overall, the excitatory orexinergic drive for the cerebellum might contribute to the control of muscle tone and contribute to a somatic–visceral integration of responses [50].

Habas reviews the functional imaging of cerebellar nuclei, focusing on DN [51]. Activation of FN and IN is difficult to distinguish from activation of the DN because of the size and location of FN/IN, partial volume effects, and issues related to statistical thresholding. FN and IN are involved in controlling voluntary and automatic movements. DN is involved in a myriad of functional networks including thalamic nuclei, sensorimotor and associative cortices, striatum, and hypothalamus. Functional imaging data suggest that the DN is primarily involved in executive and affective networks devoted to attention, working memory, procedural reasoning, and salience detection. A functional coherence between DN and (1) prefrontal, cingulate, insular, precentral, inferior parietal, and occipital cortices, (2) thalamus, (3) striatum, (4) hypothalamus, and (5) anterior and posterior cerebellum has been found [52]. The activation of DN increases with the complexity of the tasks, in polymodal cue-guided and cue-timed tasks and when the attention load is higher. It is assumed that the DN is involved in a circuit (a) comparing intended/expected and actual consequences of a mental act and (b) assessing their degree of discrepancy in various domains, such as perception, action, language, or cognition [51]. DN is involved in implicit and explicit skill learning, in conjunction with the cerebellar cortex. DN is also clearly implicated in planning tasks.

Cerebellar nuclei are thus a masterpiece within the cerebellar circuitry. They occupy a strategic position. The papers gathered in this issue highlight recent advances in our understanding of cerebellar nuclei. The myriad of functions of cerebellar nuclei are to be considered, keeping in mind their structure and the recent discoveries in terms of connectivity. Attempts to modulate the activity of the dentatothalamocortical pathway in order to improve motor recovery are an example of the potential translational applications [53].

References

1. Telgkamp P, Padgett DE, Ledoux VA, Woolley CS, Raman IM (2004) Maintenance of high-frequency transmission at Purkinje to cerebellar nuclear synapses by spillover from boutons with multiple release sites. Neuron 41:113–126
2. Anchisi D, Scelfo B, Tempia F (2001) Postsynaptic currents in deep cerebellar nuclei. J Neurophysiol 85:323–331
3. Orioli PJ, Strick PL (1989) Cerebellar connections with the motor cortex and the arcuate premotor area: an analysis employing retrograde transneuronal transport of WGA-HRP. J Comp Neurol 288:612–626
4. Bastian A, Thach WT (2002) Structure and function of the cerebellum. In: Manto M, Pandolfo M (eds) The cerebellum and its disorders. Cambridge University Press, Cambridge
5. Büttner U, Fuchs AF, Markert-Schwab G, Buckmaster P (1991) Fastigial nucleus activity in the alert monkey during slow eye and head movements. J Neurophysiol 65:1360–1371
6. Fuchs AF, Robinson FR, Straube A (1994) Participation of the caudal fastigial nucleus in smooth-pursuit eye movements. I. Neuronal activity. J Neurophysiol 72:2714–2728
7. Oulad Ben Taib N, Manto M (2008) Effects of trains of high-frequency stimulation of the premotor/supplementary motor area on conditioned corticomotor responses in hemicerebellectomized rats. Exp Neurol 212:157–165
8. Gruart A, Delgado-García JM (1994) Discharge of identified deep cerebellar nuclei neurons related to eye blinks in the alert cat. Neuroscience 61:665–681
9. Vilis T, Hore J (1977) Effects of changes in mechanical state of limb on cerebellar intention tremor. J Neurophysiol 40:1214–1224
10. Smith AM, Bourbonnais D (1981) Neuronal activity in cerebellar cortex related to control of prehensile force. J Neurophysiol 45:286–303
11. Elble RJ, Schieber MH, Thach WT Jr (1984) Activity of muscle spindles, motor cortex and cerebellar nuclei during action tremor. Brain Res 323(2):330–334
12. Gilman S (1969) The mechanism of cerebellar hypotonia. An experimental study in the monkey. Brain 92:621–638
13. Medina JF, Mauk MD (2000) Computer simulation of cerebellar information processing. Nat Neurosci 3:1205–1211
14. Rowland NC, Jaeger D (2005) Coding of tactile response properties in the rat deep cerebellar nuclei. J Neurophysiol 94:1236–1251
15. Aizenman CD, Linden DJ (2000) Rapid, synaptically driven increases in the intrinsic excitability of cerebellar deep nuclear neurons. Nat Neurosci 3:109–111
16. Ouardouz M, Sastry BR (2000) Mechanisms underlying LTP of inhibitory synaptic transmission in the deep cerebellar nuclei. J Neurophysiol 84(3):1414–1421
17. Hong S, Optican LM (2008) Interaction between Purkinje cells and inhibitory interneurons may create adjustable output waveforms to generate timed cerebellar output. PLoS ONE 3(7):e2770
18. Uusisaari M, Obata K, Knöpfel T (2007) Morphological and electrophysiological properties of GABAergic and non-GABAergic cells in the deep cerebellar nuclei. J Neurophysiol 97:901–911
19. Bengtsson F, Hesslow G (2006) Cerebellar control of the inferior olive. Cerebellum 5(1):7–14
20. Bäurle J, Grüsser-Cornehls U (1997) Differential number of glycine- and GABA-immunopositive neurons and terminals in the deep cerebellar nuclei of normal and Purkinje cell degeneration mutant mice. J Comp Neurol 382:443–458
21. Uusisaari M, Knöpfel T (2010) GlyT2+ Neurons in the lateral cerebellar nucleus. Cerebellum (this issue)
22. Zafra F, Aragón C, Giménez C (1997) Molecular biology of glycinergic neurotransmission. Mol Neurobiol 14:117–142
23. Chan-Palay V (1977) Cerebellar dentate nucleus: organization, cytology and transmitters. Springer, New York
24. Bagnall MW, Zingg B, Sakatos A, Moghadam SH, Zeilhofer HU, Lac SD (2009) Glycinergic projection neurons of the cerebellum. J Neurosci 29:10104–10110
25. Zheng N, Raman IM (2010) Synaptic inhibition, excitation, and plasticity in neurons of the cerebellar nuclei. Cerebellum (this issue)
26. Jahnsen H (1986) Electrophysiological characteristics of neurones in the guinea-pig deep cerebellar nuclei in vitro. J Physiol 372:129–147
27. Llinás R, Mühlethaler M (1988) Electrophysiology of guinea-pig cerebellar nuclear cells in the in vitro brain stem-cerebellar preparation. J Physiol 404:241–258
28. Raman IM, Gustafson AE, Padgett DE (2000) Ionic currents and spontaneous firing in neurons isolated from the cerebellar nuclei. J Neurosci 20(24):9004–9016
29. Pedroarena CM (2010) Mechanisms supporting transfer of inhibitory signals into the spike output of spontaneously firing cerebellar nuclear neuron in vitro. Cerebellum (this issue)
30. Schwarz C (2010) The fate of spontaneous synchronous rhythms on the cerebrocerebellar loop. Cerebellum (this issue)
31. Shambes GM, Gibson JM, Welker WI (1978) Fractured somatotopy in granule cell tactile areas of rat cerebellar hemispheres revealed by micromapping. Brain Behav Evol 15:94–140
32. Brodal P (1968) The corticopontine projection in the cat. I. Demonstration of a somatotopically organized projection from the primary sensorimotor cortex. Exp Brain Res 5:210–234
33. Amzica F, Steriade M (1995) Short- and long-range neuronal synchronization of the slow (<1 Hz) cortical oscillation. J Neurophysiol 73:20–38
34. Casabona A, Bosco G, Perciavalle P, Valle M (2010) Processing of limb kinematics in the interpositus nucleus. Cerebellum (this issue)
35. van Kan PL, Houk JC, Gibson AR (1993) Output organization of intermediate cerebellum of the monkey. J Neurophysiol 69:57–73

36. Ekerot CF, Garwicz M, Jörntell H (1997) The control of forelimb movements by intermediate cerebellum. Prog Brain Res 114:423–429
37. Casabona A, Valle MS, Bosco G, Garifoli A, Lombardo SA, Perciavalle V (2003) Anisotropic representation of forelimb position in the cerebellar cortex and nucleus interpositus of the rat. Brain Res 972:127–136
38. Martin JH, Cooper SE, Hacking A, Ghez C (2000) Differential effects of deep cerebellar nuclei inactivation on reaching and adaptive control. J Neurophysiol 83:1886–1899
39. Johnson MT, Ebner TJ (2000) Processing of multiple kinematic signals in the cerebellum and motor cortices. Brain Res Brain Res Rev 33:155–168
40. Mason CR, Miller LE, Baker JF, Houk JC (1998) Organization of reaching and grasping movements in the primate cerebellar nuclei as revealed by focal muscimol inactivations. J Neurophysiol 79:537–554
41. Wolpert DM, Ghahramani Z, Flanagan JR (2001) Perspectives and problems in motor learning. Trends Cogn Sci 5:487–494
42. Huang C (2008) Implications on cerebellar function from information coding. Cerebellum 7:314–331
43. Garcia-Martinez R, Miquel M, Garcia LI, Coria-Avila GA, Perez CA, Aranda-Abreu GA, Toledo R, Hernandez ME, Manzo J (2010) Multiunit recording of the cerebellar cortex, inferior olive, and fastigial nucleus during copulation in naive and sexually experienced male rats. Cerebellum (this issue)
44. Manzo J, Miquel M, Toledo R et al (2008) Fos expression at the cerebellum following non-contact arousal and mating behavior in male rats. Physiol Behav 93:357–363
45. Yu L, Zhang XY, Zhang J, Zhu JN, Wang JJ (2010) Orexins excite neurons of the rat cerebellar nucleus interpositus via orexin 2 receptors in vitro. Cerebellum (this issue)
46. Sakurai T (2007) The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. Nat Rev Neurosci 8:171–181
47. Haines DE, Dietrichs E, Mihailoff GA, McDonald EF (1997) The cerebellar-hypothalamic axis: basic circuits and clinical observations. Int Rev Neurobiol 41:83–107
48. Borsook D, Moulton EA, Tully S, Schmahmann JD, Becerra L (2008) Human cerebellar responses to brush and heat stimuli in healthy and neuropathic pain subjects. Cerebellum 7:252–272
49. Takakusaki K, Takahashi K, Saitoh K, Harada H, Okumura T, Kayama Y, Koyama Y (2005) Orexinergic projections to the cat midbrain mediate alternation of emotional behavioural states from locomotion to cataplexy. J Physiol 568:1003–1020
50. Ito M (2009) Functional roles of neuropeptides in cerebellar circuits. Neuroscience 162:666–672
51. Habas C (2010) Functional imaging of the deep cerebellar nuclei: a review. Cerebellum (this issue)
52. Allen GA, McComm R, Barnard H, Ringe WK, Fleckenstein J, Cullum CM (2005) Magnetic resonance imaging of cerebellar-prefrontal and cerebellar-parietal functional connectivity. Neuroimage 28:39–48
53. Machado AG, Baker KB, Schuster D, Butler RS, Rezai A (2009) Chronic electrical stimulation of the contralesional lateral cerebellar nucleus enhances recovery of motor function after cerebral ischemia in rats. Brain Res 1280:107–116