Cerebellar Nuclei

42

Dieter Jaeger and Huo Lu

Abstract

Understanding the basic physiology of cerebellar nuclei (CN) is essential to the understanding of cerebellar function and disorders as they provide the only output from the cerebellum along with the vestibular nuclei. In addition to integrating the inhibitory input from cerebellar cortical Purkinje cells, CN neurons also receive direct excitation from mossy fibers and this direct excitatory input to the CN may in fact drive a number of behaviorally relevant activities. The complete picture is considerably more complex than that of a simple relay of incoming excitation and inhibition, however. Specifically, the functional significance of synaptic plasticity in the CN, high spontaneous spike rates, post-inhibitory rebound firing, and multiple output pathways including GABAergic inhibition feeding back to the inferior olive remain to be elucidated.

Keywords

Mossy fibers · Climbing fiber · Rebound spiking
Microzone · Gain control · Learning

42.1 Basic Physiology of CN Neurons

42.1.1 Cellular Physiology

CN neurons recorded in brain slices from any of the four nuclei present in rodents (lateral, anterior interposed, posterior interposed, and medial) are spontaneously regularly spiking (Jahnsen 1986), a property which is due to an intrinsic depolarizing plateau current (Raman et al. 2000). A robust property of CN neurons is their ability to fire rebound spike bursts following strong hyperpolarization induced by current injection (Llinas and Muhlethaler 1988; Jahnsen 1986; Aizenman and Linden 1999). The rebound activity has an initial fast burst component carried by T-type calcium currents (Molineux et al. 2006) and a longer-lasting 2–5 s increase of spike rate associated with persistent sodium currents (Sangrey and Jaeger 2010). The functional implications of CN rebound properties are hotly debated (Alvina et al. 2008; Hoebeek et al. 2010). While these basic properties are present in excitatory and inhibitory CN neurons, GABAergic cells can be distinguished physiologically by a broader spike width, a slower spike-afterhyperpolarization, and higher spike rate accommodation, and further differences are present between morphologically larger and smaller non-GABAergic neurons (Uusisaari et al. 2007).

42.1.2 Synaptic Physiology and Synaptic Plasticity

Early in vitro studies provided direct evidence that Purkinje cells' spiking causes monosynaptic inhibitory postsynaptic potentials (IPSPs) in the CN (Ito et al. 1964). These IPSPs are characterized by a large amplitude, a fast decay, and pronounced short-term depression (Person and Raman 2012). A single CN neuron receives large IPSPs from about 40 Purkinje cells, while smaller IPSPs may derive from many more Purkinje cells with fewer and/or more distal synaptic terminals (Person and Raman 2012). Robust excitatory postsynaptic potentials (EPSPs) can be elicited by stimulation of mossy fibers (Llinas and Muhlethaler 1988), which are collaterals of the same fibers projecting to cerebellar cortex (Shinoda et al. 1992). Climbing fibers also collateralize in the CN (Sugihara et al. 1999) and may induce a spike response in vivo (Blenkinsop and Lang 2011). Recent brain slice studies showed that excitatory responses to climbing

D. Jaeger (✉)
Department of Biology, Emory University, Atlanta, GA, USA
e-mail: djaeger@emory.edu

H. Lu
Biomedical Sciences, PCOM Georgia, Suwanee, GA, USA
e-mail: huo.lu@pcom.edu

D. L. Gruol et al. (eds.), *Essentials of Cerebellum and Cerebellar Disorders*, https://doi.org/10.1007/978-3-031-15070-8_42

fiber activation seen with intracellular recordings in CN neurons are small in adult mice, but more prominent in juveniles during development (Lu et al. 2016; Najac and Raman 2017).

Long-term plasticity has also been observed for synaptic inputs to the CN. Excitatory mossy fiber undergoes long-term potentiation as a result of a distinct combination of inhibitory and excitatory inputs "that resemble the activity of Purkinje and mossy fiber afferents that is predicted to occur during cerebellar associative learning tasks" (Pugh and Raman 2009). Inhibitory Purkinje cell input can undergo either long-term potentiation or long-term depression, which is dependent on the amount of rebound depolarization produced by a burst of Purkinje cell inputs (Aizenman et al. 1998). The plasticity-inducing protocols in the CN generally require complex temporal conditions of excitation and inhibition, which may relate to the commonly hypothesized role of the cerebellum in motor timing. In addition, the effects of learning in the CN may also include changes in intrinsic excitability, as observed for the acquisition of eyeblink conditioning (Wang et al. 2018).

42.2 The Control of CN Spiking Output by Input Rates and Patterns

One might expect that CN neurons in vivo are silenced by strong inhibition from the inputs from 40 Purkinje cells with a strong conductance (Person and Raman 2012) and a fast spike rate that typically exceeds 50 Hz in awake animals. Contrary to this expectation, CN neurons in awake animals fire fast with a baseline rate between 10 and 100 Hz (Chabrol et al. 2019; Becker and Person 2019). While the spontaneous spiking activity of CN neurons likely contributes to their firing in vivo (Yarden-Rabinowitz and Yarom 2017), the intrinsic depolarizing current underlying it is overcome easily by current injection of only about −30 pA in brain slices (Raman et al. 2000). In contrast, the total Purkinje cell input current easily exceeds −1 nA at a membrane potential at −57 mV (Person and Raman 2012). Thus, a considerable excitatory input conductance is also needed in order to drive CN neurons to spiking in vivo, which can be confirmed by detailed biophysical modeling (Abbasi et al. 2017). Given the small relative size of climbing fiber inputs to CN neurons and their slow rate of firing, this task falls primarily to mossy fibers, and indeed a study in brain slices showed robust mossy fiber postsynaptic currents (Wu and Raman 2017). An intracellular study in vivo also confirmed a strong mossy fiber contribution to spiking activity (Yarden-Rabinowitz and Yarom 2017).

A number of studies are addressing the question of whether the CN produce spike output based on integrating smooth rates of incoming excitatory and inhibitory inputs, or whether there is a specific decoding mechanism for precisely timed synchronous inputs (Brown and Raman 2018; Najac and Raman 2015; Sarnaik and Raman 2018; Wu and Raman 2017; Abbasi et al. 2017; Sudhakar et al. 2015). In turn, the output of the CN may either convey an output rate code of input rates, or a precise spike time code where the millisecond timing stamp of outgoing spikes conveys important information. Of course, the answer could also be a combination of these possibilities. Indeed evidence is recently accumulating for both rate and temporal coding strategies (Brown and Raman 2018; Sarnaik and Raman 2018) at the level of the CN. Interestingly, some evidence suggests that distinct cell types in the CN show different coding strategies, namely slow synaptic integration and rate coding in nucleo-olivary cells and faster synaptic integration in larger premotor neurons resulting in a temporal code with precise spike timing following the offset of inhibition (Najac and Raman 2015).

Climbing fiber inputs to the cerebellum are well known for millisecond synchronization, and special coding of such synchronous events might be expected in the CN. Indeed, a recent study found that climbing fiber synchronicity is required for CN neurons to develop pronounced pauses of firing upon complex spike input from Purkinje cells (Tang et al. 2019). Notably, this study did not find any evidence for rebound bursts following such complex spike elicited pauses, which had been identified earlier with electrical Purkinje cell input stimulation in awake mice (Hoebeek et al. 2010). Finally, a recent study shows that rate and temporal coding principles combine in a cerebellar loop where the firing rate of nucleo-olivary cells controls the synchronicity of olivary input to Purkinje cells during a trained reaching movement (Wagner et al. 2021).

42.3 A View at CN Function

42.3.1 Behavioral Correlates of CN Activity Changes

A substantial number of studies has been undertaken to study the spiking activity of CN neurons in behaving animals, often revealing complex relationships between CN spike rate increases or decreases and sensory stimuli as well as movements. One of the most studied behaviors with respect to CN activity is the delayed eye blink reflex, where CN activity is clearly related to the learnt timing of the motor command (Thompson and Steinmetz 2009). In a more general sense, CN output activity is congruent with representing an internal or forward model of movement execution (Lisberger 2009; Miall and Reckess 2002) that is important in the predictive control of behavior. Recent experiments in which mice are trained in a reaching task show a close relation of anterior interposed nucleus activity with the deceleration of the reach to grasp movement (Becker and Person 2019). Supporting a

causal role of anterior interposed neuron firing in reach deceleration, these authors found that optogenetic activation of the anterior interposed nucleus led to a shortened reach, while optogenetic inhibition resulted in reaches overshoot their target. The activity of the lateral nucleus neurons was probed with similar methods in a locomotor task where head-fixed mice were trained to run through a virtual visual environment (Chabrol et al. 2019). A specific visual target pattern denoted the impending delivery of reward. Many lateral nucleus neurons robustly increased firing in preparation of the reward delivery, closely resembling preparatory firing properties recorded in anterolateral motor cortex (ALM). Optogenetic silencing lateral nucleus neurons resulted in decreased preparatory activity in ALM, supporting a role of lateral nucleus neurons in cortical motor preparatory processing. A similar preparatory activity was also observed in the medial nucleus in a cued licking task with a delay (Gao et al. 2018). In this study, optogenetic stimulation experiments also revealed that preparatory activity in ALM depended on medial nucleus neural activity. In addition, the authors show that this loop is closed and preparatory activity in the medial nucleus is also dependent on ALM preparatory activity, presumably via mossy fibers from the pontine nuclei relaying ALM activity (Gao et al. 2018).

42.3.2 Multiple Functional Areas in the CN and Microzonal Organization

Each CN nucleus and to some degree different areas in each nucleus will be engaged in controlling behaviors related to the anatomical inputs of the respective nucleus, such as the vestibulo-ocular reflex and balance in the vestibular nuclei (Lisberger and Miles 1980), limb movements in the interposed and dentate nuclei (Strick 1983; Becker and Person 2019), and the control of timing in tasks such as finger tapping in humans (Stefanescu et al. 2013) in the dentate nucleus. The concept of time estimation as a cerebellar function was also confirmed in monkeys through observing a close relationship between single cell activity in the dentate nucleus and the interval duration in a self-timed saccade task (Ohmae et al. 2017). This activity may be specifically used for the fine adjustment of self-timed intervals (Kunimatsu et al. 2018). Increasingly, we also understand that the CN output may be involved in multiple cognitive functions including working memory and language processing (Wagner and Luo 2020).

The microzonal organization of the cerebellar cortex is preserved in the CN (Apps and Garwicz 2000). This allows for functionally relevant climbing fiber synchrony evoking complex spikes in cerebellar cortical microzones to converge in the CN and elicit behaviorally relevant responses that may depend on this synchrony (De Gruijl et al. 2014; Person and Raman 2012; Wagner et al. 2021).

42.3.3 Output of the CN Is Split into Distinctive Pathways

GABAergic neurons in CN are traditionally thought to solely project to the inferior olive where they often terminate near gap junctions in olivary glomeruli (De Zeeuw et al. 1998). This arrangement allows CN output to influence both the occurrence and the synchrony of olivary spikes (Lefler et al. 2014; Wagner et al. 2021), which may be important in controlling olivary motor error signals (Simpson et al. 1996).

Excitatory CN neurons project to a variety of targets, notably including the motor thalamus, red nucleus, and brainstem motor nuclei. The functional impact of CN activity on these targets is often not clearly understood, but given the high tonic rates of CN firing in vivo and behaviorally related phasic and tonic changes in CN firing a temporally highly precise effect on motor performance is expected (Heck et al. 2013).

Our knowledge of cerebellar anatomy is still expanding, and recent genetic and intersectional labeling techniques allow the identification of new connections. Important recent additions to our anatomical CN connectivity diagram include a GABAergic output to the brain stem (Judd et al. 2021), excitatory feedback to the cerebellar cortex (Houck and Person 2014), and output to the ventrolateral periaqueductal grey involved in the control of fear memories (Frontera et al. 2020). Our understanding of cerebellar-thalamic pathways is also increasing, showing not only connections to the primary cerebellar motor thalamus, but also to ventromedial and centrolateral thalamic areas (Gornati et al. 2018). The rapid pace of new findings suggests that we have yet to learn a lot about the detailed functional contribution of CN output to the processing of sensory-motor tasks in cortical and brainstem areas.

References

Abbasi S, Hudson AE, Maran SK, Cao Y, Abbasi A, Heck DH, Jaeger D (2017) Robust transmission of rate coding in the inhibitory Purkinje cell to cerebellar nuclei pathway in awake mice. PLoS Comp Biol 13(6):e1005578. https://doi.org/10.1371/journal.pcbi.1005578

Aizenman CD, Linden DJ (1999) Regulation of the rebound depolarization and spontaneous firing patterns of deep nuclear neurons in slices of rat cerebellum. J Neurophysiol 82(4):1697–1709

Aizenman CD, Manis PB, Linden DJ (1998) Polarity of long-term synaptic gain change is related to postsynaptic spike firing at a cerebellar inhibitory synapse. Neuron 21(4):827–835

Alvina K, Walter JT, Kohn A, Ellis-Davies G, Khodakhah K (2008) Questioning the role of rebound firing in the cerebellum. Nat Neurosci 11(11):1256–1258. https://doi.org/10.1038/nn.2195

Apps R, Garwicz M (2000) Precise matching of olivo-cortical divergence and cortico-nuclear convergence between somatotopically corresponding areas in the medial C1 and medial C3 zones of the paravermal cerebellum. Eur J Neurosci 12(1):205–214

Becker MI, Person AL (2019) Cerebellar control of reach kinematics for endpoint precision. Neuron 103(2):335–348. https://doi.org/10.1016/j.neuron.2019.05.007

Blenkinsop TA, Lang EJ (2011) Synaptic action of the olivocerebellar system on cerebellar nuclear spike activity. J Neurosci 31(41):14708–14720. https://doi.org/10.1523/jneurosci.3323-11.2011

Brown ST, Raman IM (2018) Sensorimotor integration and amplification of reflexive whisking by well-timed spiking in the cerebellar corticonuclear circuit. Neuron 99(3):564–575.e562. https://doi.org/10.1016/j.neuron.2018.06.028

Chabrol FP, Blot A, Mrsic-Flogel TD (2019) Cerebellar contribution to preparatory activity in motor neocortex. Neuron 103(3):506–519.e504. https://doi.org/10.1016/j.neuron.2019.05.022

De Gruijl JR, Hoogland TM, De Zeeuw CI (2014) Behavioral correlates of complex spike synchrony in cerebellar microzones. J Neurosci 34(27):8937–8947. https://doi.org/10.1523/jneurosci.5064-13.2014

De Zeeuw CI, Hoogenraad CC, Koekkoek SKE, Ruigrok TJH, Galjart N, Simpson JI (1998) Microcircuitry and function of the inferior olive. TINS 21(9):391–400

Frontera JL, Baba Aissa H, Sala RW, Mailhes-Hamon C, Georgescu IA, Léna C, Popa D (2020) Bidirectional control of fear memories by cerebellar neurons projecting to the ventrolateral periaqueductal grey. Nat Commun 11(1):5207. https://doi.org/10.1038/s41467-020-18953-0

Gao Z, Davis C, Thomas AM, Economo MN, Abrego AM, Svoboda K, De Zeeuw CI, Li N (2018) A cortico-cerebellar loop for motor planning. Nature 563(7729):113–116. https://doi.org/10.1038/s41586-018-0633-x

Gornati SV, Schäfer CB, Eelkman Rooda OHJ, Nigg AL, De Zeeuw CI, Hoebeek FE (2018) Differentiating cerebellar impact on thalamic nuclei. Cell Rep 23(9):2690–2704. https://doi.org/10.1016/j.celrep.2018.04.098

Heck DH, De Zeeuw CI, Jaeger D, Khodakhah K, Person AL (2013) The neuronal code(s) of the cerebellum. J Neurosci 33(45):17603–17609. https://doi.org/10.1523/jneurosci.2759-13.2013

Hoebeek FE, Witter L, Ruigrok TJ, De Zeeuw CI (2010) Differential olivo-cerebellar cortical control of rebound activity in the cerebellar nuclei. Proc Natl Acad Sci U S A 107(18):8410–8415. https://doi.org/10.1073/pnas.0907118107

Houck BD, Person AL (2014) Cerebellar loops: a review of the nucleocortical pathway. Cerebellum 13(3):378–385

Ito M, Yoshida M, Obata K (1964) Monosynaptic inhibition of the intracerebellar nuclei induced from the cerebellar cortex. Experientia 20:575–576

Jahnsen H (1986) Electrophysiological characteristics of neurones in the Guinea-pig deep cerebellar nuclei in vitro. J Physiol 372:129–147

Judd EN, Lewis SM, Person AL (2021) Diverse inhibitory projections from the cerebellar interposed nucleus. eLife 10:e66231. https://doi.org/10.7554/eLife.66231

Kunimatsu J, Suzuki TW, Ohmae S, Tanaka M (2018) Different contributions of preparatory activity in the basal ganglia and cerebellum for self-timing. eLife 7:e35676. https://doi.org/10.7554/eLife.35676

Lefler Y, Yarom Y, Uusisaari MY (2014) Cerebellar inhibitory input to the inferior olive decreases electrical coupling and blocks subthreshold oscillations. Neuron 81(6):1389–1400. https://doi.org/10.1016/j.neuron.2014.02.032

Lisberger SG (2009) Internal models of eye movement in the floccular complex of the monkey cerebellum. Neuroscience 162(3):763–776. https://doi.org/10.1016/j.neuroscience.2009.03.059

Lisberger SG, Miles FA (1980) Role of primate medial vestibular nucleus in long-term adaptive plasticity of vestibuloocular reflex. J Neurophysiol 43(6):1725–1745

Llinas R, Muhlethaler M (1988) Electrophysiology of Guinea-pig cerebellar nuclear cells in the in vitro brain stem-cerebellar preparation. J Physiol 404:241–258

Lu H, Yang B, Jaeger D (2016) Cerebellar nuclei neurons show only small excitatory responses to optogenetic olivary stimulation in transgenic mice: in vivo and in vitro studies. Front Neural Circuits 10:21. https://doi.org/10.3389/fncir.2016.00021

Miall RC, Reckess GZ (2002) The cerebellum and the timing of coordinated eye and hand tracking. Brain Cogn 48(1):212–226

Molineux ML, McRory JE, McKay BE, Hamid J, Mehaffey WH, Rehak R, Snutch TP, Zamponi GW, Turner RW (2006) Specific T-type calcium channel isoforms are associated with distinct burst phenotypes in deep cerebellar nuclear neurons. PNAS 103(14):5555–5560

Najac M, Raman IM (2015) Integration of Purkinje cell inhibition by cerebellar nucleo-olivary neurons. J Neurosci 35(2):544–549. https://doi.org/10.1523/jneurosci.3583-14.2015

Najac M, Raman IM (2017) Synaptic excitation by climbing fibre collaterals in the cerebellar nuclei of juvenile and adult mice. J Physiol 595(21):6703–6718. https://doi.org/10.1113/jp274598

Ohmae S, Kunimatsu J, Tanaka M (2017) Cerebellar roles in self-timing for sub- and supra-second intervals. J Neurosci 37(13):3511–3522. https://doi.org/10.1523/jneurosci.2221-16.2017

Person AL, Raman IM (2012) Purkinje neuron synchrony elicits time-locked spiking in the cerebellar nuclei. Nature 481(7382):502–506. https://doi.org/10.1038/nature10732

Pugh JR, Raman IM (2009) Nothing can be coincidence: synaptic inhibition and plasticity in the cerebellar nuclei. TINS 32(3):170–177. https://doi.org/10.1016/j.tins.2008.12.001

Raman IM, Gustafson AE, Padgett D (2000) Ionic currents and spontaneous firing in neurons isolated from the cerebellar nuclei. J Neurosci 20(24):9004–9016

Sangrey T, Jaeger D (2010) Analysis of distinct short and prolonged components in rebound spiking of deep cerebellar nucleus neurons. Eur J Neurosci 32(10):1646–1657. https://doi.org/10.1111/j.1460--9568.2010.07408.x

Sarnaik R, Raman IM (2018) Control of voluntary and optogenetically perturbed locomotion by spike rate and timing of neurons of the mouse cerebellar nuclei. eLife 7:e29546. https://doi.org/10.7554/eLife.29546

Shinoda Y, Sugiuchi Y, Futami T, Izawa R (1992) Axon collaterals of mossy fibers from the pontine nucleus in the cerebellar dentate nucleus. J Neurophysiol 67(3):547–560

Simpson JI, Wylie DR, DeZeeuw CI (1996) On climbing fiber signals and their consequence(s). Behav Brain Sci 19(3):384

Stefanescu MR, Thürling M, Maderwald S, Wiestler T, Ladd ME, Diedrichsen J, Timmann D (2013) A 7T fMRI study of cerebellar activation in sequential finger movement tasks. Exp Brain Res 228(2):243–254

Strick PL (1983) The influence of motor preparation on the response of cerebellar neurons to limb displacements. J Neurosci 3(10):2007–2020

Sudhakar SK, Torben-Nielsen B, De Schutter E (2015) Cerebellar nuclear neurons use time and rate coding to transmit Purkinje neuron pauses. PLoS Comput Biol 11(12):e1004641. https://doi.org/10.1371/journal.pcbi.1004641

Sugihara I, Wu HS, Shinoda Y (1999) Morphology of single olivocerebellar axons labeled with biotinylated dextran amine in the rat. J Comp Neurol 414(2):131–148

Tang T, Blenkinsop TA, Lang EJ (2019) Complex spike synchrony dependent modulation of rat deep cerebellar nuclear activity. eLife 8:e40101. https://doi.org/10.7554/eLife.40101

Thompson RF, Steinmetz JE (2009) The role of the cerebellum in classical conditioning of discrete behavioral responses. Neuroscience 162(3):732–755. https://doi.org/10.1016/j.neuroscience.2009.01.041

Uusisaari M, Obata K, Knopfel T (2007) Morphological and electrophysiological properties of GABAergic and non-GABAergic cells in the deep cerebellar nuclei. J Neurophysiol 97(1):901–911

Wagner MJ, Luo L (2020) Neocortex–cerebellum circuits for cognitive processing. Trends Neurosci 43(1):42–54. https://doi.org/10.1016/j.tins.2019.11.002

Wagner MJ, Savall J, Hernandez O, Mel G, Inan H, Rumyantsev O, Lecoq J, Kim TH, Li JZ, Ramakrishnan C, Deisseroth K, Luo L, Ganguli S, Schnitzer MJ (2021) A neural circuit state change underlying skilled movements. Cell 184(14):3731–3747.e3721. https://doi.org/10.1016/j.cell.2021.06.001

Wang D, Smith-Bell CA, Burhans LB, O'Dell DE, Bell RW, Schreurs BG (2018) Changes in membrane properties of rat deep cerebellar nuclear projection neurons during acquisition of eyeblink conditioning. Proc Natl Acad Sci 115(40):E9419–E9428. https://doi.org/10.1073/pnas.1808539115

Wu Y, Raman IM (2017) Facilitation of mossy fibre-driven spiking in the cerebellar nuclei by the synchrony of inhibition. J Physiol 595(15):5245–5264. https://doi.org/10.1113/jp274321

Yarden-Rabinowitz Y, Yarom Y (2017) In vivo analysis of synaptic activity in cerebellar nuclei neurons unravels the efficacy of excitatory inputs. J Physiol 595(17):5945–5963. https://doi.org/10.1113/jp274115