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EDITORIAL

The Cerebellar Nuclei Take Center Stage

Laurens Witter · Chris I. De Zeeuw · Tom J. H. Ruigrok · Freek E. Hoebeek

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Despite the central location of the cerebellar nuclei neurons (CN) and those in the vestibular nuclei (VN) that receive Purkinje cell input, the neuroscience community has addressed surprisingly little attention to neurons in these central structures compared to various other down- and upstream components of olivo-cerebellar network. One such example is the cerebellar Purkinje cell, which forms the sole output of the cerebellar cortex: many detailed publications on their inner workings such as intracellular signal transduction (synaptic), integration, and plasticity are published every month. Ultimately, all these influences on Purkinje cell firing can only have an effect on behavior by means of the CN and VN. In these downstream nuclei, tens to hundreds of Purkinje cells converge on a single neuron [1–3]. Together with the synaptic inputs from mossy to climbing fiber collaterals, the Purkinje cell inputs control the timing of the intrinsically generated action potentials of CN and VN neurons and thereby control the true output of the cerebellum [4, 5]. The spiking activity of both the CN and VN are projected to a wide variety of downstream targets, like premotor nuclei in the brainstem, thalamic nuclei, and the spinal cord [6]. This large variability in projection areas indicates that the information content of the CN activity is extremely diverse and cannot be captured in few words. It was the goal of the recent FENS satellite meeting "Cerebellar Nuclei – Ins and Outs" held in Amsterdam to clarify how CN activity comes about and what information is encoded at the various stages of the network. The current issue of the journal cerebellum contains the proceedings of this meeting.

L. Witter · C. I. De Zeeuw
Netherlands Institute for Neuroscience,
Royal Academy for Arts and Sciences,
Meibergdreef 47,
1105 BA, Amsterdam, The Netherlands

C. I. De Zeeuw (✉) · T. J. H. Ruigrok · F. E. Hoebeek (✉)
Department of Neuroscience, Ee 1202, Erasmus MC,
P.O. Box 2040, 3000 CA, Rotterdam, The Netherlands
e-mail: c.dezeeuw@erasmusmc.nl
e-mail: f.hoebeek@erasmusmc.nl

Starting to Understand What CN Activity Encodes

Before the question "What do CN neurons encode in their spike output?" can be answered, the information encoded by their main afferent, the Purkinje cells, must be deciphered. Two important aspects need to be elucidated: what information is transmitted by Purkinje cells and how do Purkinje cells encode this information. Several speakers at the satellite meeting addressed these important questions.

The correlation between several forms of motor behavior and Purkinje cell firing is well documented in the literature. Especially Purkinje cell activity during the optokinetic reflex and vestibulo-ocular reflex in rabbit [7] and mouse [8], as well as during foveal eye movements [9–11] and reaching movements in monkey [12, 13] have been described in detail. For smooth pursuit eye movements, it has been recently proposed that on a single trial level, Purkinje cell activity shows a high correlation with movement initiation [11]. An in depth review concerning internal models represented by Purkinje cell output is provided by Ebner in this issue [14].

Purkinje cells have at least two modes of information encoding: by their synchrony of an ensemble of Purkinje cells and by their individual firing frequency. The correlation between a single Purkinje cell and motor output [11]

suggests that ensembles of Purkinje cells may encode information at an ever higher resolution. This possibility is further supported by the correlation of complex spike activity and simple spike activity found between individual Purkinje cells [11, 15–17]. The relevance of this ensemble patterning becomes evident at the level of the CN, where synchronized pauses enable the generation of action potentials [4, 18]. The rate of firing of individual Purkinje cells seems also important, since short-term synaptic plasticity operates as a function of firing rate to set the synaptic efficacy [19, 20]. In the present issue of *Cerebellum* both Jaeger and Luthman et al. provide new insights on how CN neurons might interpret Purkinje cell synchronicity and firing frequency [21, 22].

Is Rebound Activity a Physiologically and Behaviorally Relevant Phenomenon?

The fact that neurons in the CN and VN show rebound activity after strong hyperpolarizations has been shown by several research groups. In response to such hyperpolarizations, low-voltage-activated T-type calcium channels deinactivate, I_H-currents activate, and voltage-dependent sodium and calcium channels become more available. The contribution of each of these currents to rebound depolarization and rebound firing has been debated: some results advocate a major involvement of T-type calcium channels [23–26], whereas others reveal a substantial role for high-voltage activated calcium channels [27]. Similarly, a substantial role for I_H channels [28–31] and voltage-dependent sodium channels [25, 26, 32, 33] have been both advocated and disputed [30, 34]. Critical to these arguments are the exact conditions during the recordings, such as recording configuration, contents of the recording electrode, and temperature. Moreover, current reports on the functional implications of rebound activity in CN neurons are not in line with each other in that some studies showed prominent rebound activity following sensory stimulation, electrical stimulation, or during ongoing activity [26, 35, 36], whereas others did not [37–39]. The review by Jaeger in this current issue sheds more light on these and other controversies considering rebound activity [21].

Cell Identity and Function

Even though current textbooks show an oversimplified CN that contains only one type of neuron, the original anatomical descriptions of the CN (and VN) reveal several types of neurons [1]. Likewise, electrophysiological examinations have grossly neglected neuronal subtypes for a long time, in that most studies merely included a single subpopulation and thereby generalized the results. Only recently, a few electrophysiological studies have systematically described the different neuronal subtypes in CN and VN [30, 40–43]. From these studies, an interesting wiring diagram for the CN and VN is emerging. Large glutamatergic neurons provide an excitatory drive for extracerebellar non-olivary nuclei [42]. Inhibition to the inferior olive seems to be provided by the smallest GABAergic neurons [42]. Interestingly, both larger GABAergic neurons and glycinergic neurons might operate to provide local inhibition [41, 42]. In contrast, other populations of glycinergic neurons might provide direct inhibitory feedback to the cerebellar cortex [43] or feed forward inhibition to the ipsilateral brainstem nuclei [40].

Apart from the individual roles of CN and VN neurons, they also differ significantly in their electrophysiological parameters [30, 42]. The cause of these differences remains largely unknown [44]. In the current issue, Pedroarena reveals how two potassium currents may influence the generation of the action potential waveform of large CN neurons and thereby their overall output [45]. Uusisaari and Knöpfel provide an overview about neuronal classes in the CN [46].

The Interplay of Excitation and Inhibition

CN are not only bombarded by Purkinje cell inhibitory input, but also receive considerable excitatory input [32, 47, 48] and each of these components influences the firing pattern of CN neurons. For neocortical neurons, it has been proposed that the firing rate is determined by the interplay between the excitatory drive and the synchrony of several inhibitory inputs [49, 50], where a more precise coherence of inhibitory inputs evokes a higher firing rate in target neurons. A similar mechanism has been proposed to play a role in the generation of CN neuron firing where short $GABA_A$R-mediated IPSPs [20, 47] are intermixed with short AMPAR and long NMDAR-mediated EPSPs [47, 51]. Although the precise contribution of the NMDA current to the total excitatory synaptic input to CN neurons is unclear, it seems that during sustained synaptic activity ~50% of the synaptic current is carried by NMDA receptors [32, 47]. This large NMDA component spreads excitation over a longer time and gives inhibitory inputs preference in determining spike times in CN neurons [5]. On longer timescales inhibition and excitation are subject to synaptic plasticity. For instance, long-term potentiation (LTP) of excitatory mossy fiber input in CN neurons can be induced when NMDA receptor activation is followed by inhibition [32, 52]. Although the calcium influx via NMDA receptors is limited, it could provide a priming or selection signal for

synapses to initiate LTP [52]. The subsequent activation of CaMKII, which is most likely mediated by synaptic inhibition and rebound depolarization, seems critical for the induction of mossy fiber LTP [52]. Similar mechanisms for potentiation have been seen in VN neurons that are innervated by Purkinje cells [53]. Interestingly, both plasticity of inhibitory inputs and plasticity of the intrinsic excitability seems to be regulated via postsynaptic calcium concentrations as well [28, 29, 54, 55]. Together these findings indicate that the modulation of CN firing rates is multifaceted and that the plastic adaptations of synaptic inputs and intrinsic spiking activity further shape the information coding by the CN.

The CN and VN in Relation to the Rest of the CNS

The central location of the CN and VN raises the expectation of strong correlations between their activity and other parts of the brain. Indeed, recent investigations have shown that the output of the cerebellar cortex correlates with the output of the cerebral cortex and that the main direction of information may be from the cerebral cortex to the cerebellum via the mossy fiber system [56, 57]. However, in this issue, Lang and Blenkinsop show that in their preparation the neocortex does not drive the output of the cerebellar nuclei via modulation of simple spike activity, but via controlling both the synchrony of climbing fiber activation and the strength of the mossy fiber input to the CN [58].

The high level of complexity of inputs to and connections between neurons in the CN and VN trouble the dissection of individual contributions to the output of the olivo-cerebellar system and ultimately to motor coordination [39, 59, 60]. Similarly, at the Purkinje cell level, it is challenging to characterize the coding mechanism that is needed to drive CN neurons and control their effects on motor behavior and procedural memory. In the current issue Sánchez-Campusano and colleagues [61] present a meta-analysis revealing how CN neurons can change their activity during delayed eye-blink conditioning.

Conclusion

The five issues above suggest that the CN and VN have a large arsenal of mechanisms to encode information. It seems that the CN and VN can integrate multimodal information presented by precerebellar structures and the cerebellar cortex and thereby have an active role in controlling movements. Future work should focus on elucidating the role of the CN and VN in controlling behavior by deciphering the coding mechanisms employed by individual types of neurons.

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