Cerebellar Nuclei and Cerebellar Learning 47

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Abstract

The cerebellar nuclei (CN) and the vestibular nucleus are the only recipients of output from the cerebellar cortex and provide the only final output pathway of cerebellar processing. This corticonuclear pathway is mediated entirely by GABA inhibition via Purkinje cell (PC) axons, yet conveys important information regarding the fine temporal control of behavior. Therefore, the interesting question arises of how one can control finely tuned CN output spike patterns with inhibition, challenging our understanding of neural coding. Using the technique of dynamic clamp, artificial inhibitory synaptic input patterns can be applied to CN neurons to explore this question. It was found that a population code in which a set of PCs pause at the same time creates an efficient code to precisely trigger individual CN spikes via disinhibition. Strong inhibition can paradoxically also evoke spiking, namely, by a mechanism of postinhibitory rebound, a pronounced property of CN neurons. Strong bursts of PC activity followed by pauses of firing create an ideal stimulus for rebound generation and are elicited by synchronous climbing fiber inputs to cerebellar cortex. Such a stimulus-evoked rebound could trigger specific behavioral responses, though direct evidence for this mechanism is currently lacking.

The conditioned eyeblink reflex in particular has been extensively studied with respect to learning mechanisms in the CN. Activity in the CN develops an increase just before the eyeblink during learning, and this CN activation depends on plasticity in the excitatory input to CN neurons by mossy fibers. Interestingly, this form of plasticity has been first predicted and then found to be controlled by the activity of inhibitory PC input. The cellular basis for this form of plasticity ultimately depends on a complex set of calcium signaling events during inputs in

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the required sequence of MF inputs followed by inhibition, followed by repolarization. A similar mechanism is proposed to also underlie the adaptation of vestibuloocular gain control coded by the vestibular nuclei. The involvement of similar or different learning mechanisms in the CN in more complex limb movement control remains to be determined, but behavioral and electrophysiological evidence points in the direction that the precise timing of predictive submovement activation in coordinated limb movements may be the predominant function of cerebellar output from the CN in this regard.

Introduction

The cerebellar nuclei (CN) provide the only output pathway from the cerebellum for most functions; only the vestibular cerebellum operates by a direct Purkinje cell projection to the vestibular nuclei (VN) (▶ Chap. 19 "Cerebellar Nuclei and the Inferior Olivary Nuclei: Organization and Connections"). Therefore, the CN and VN provide a bottleneck of cerebellar information transfer on the output side. Rather than just transmitting information from the cerebellar cortex as a relay station, these nuclei likely perform an important role in cerebellar information processing on their own. Notably, excitatory inputs from mossy and climbing fiber collaterals directly project to the CN, which allows for a fast loop of excitation through the cerebellum without cerebellar cortical involvement (Fig. 47.1). Details of the importance of this direct loop in cerebellar function and the mode of interaction with the massive inhibitory Purkinje cell projection to the CN (▶ Chap. 19, "Cerebellar Nuclei and the Inferior Olivary Nuclei: Organization and Connections") remain to be worked out, however. Two important subsystems need to be distinguished when considering CN function: Glutamatergic CN projection neurons form an excitatory output pathway to the spinal cord, brain stem motor nuclei, red nucleus, and motor thalamus (Jansen 1955; Chan-Palay 1977; Ito 1984). In contrast, a separate output pathway to the inferior olive (IO) is made by GABAergic projection neurons (Graybiel et al. 1973; Angaut and Sotelo 1989; Fredette and Mugnaini 1991) (▶ Chap. 19, "Cerebellar Nuclei and the Inferior Olivary Nuclei: Organization and Connections"). Both populations of output neurons are intermingled in all nuclei: the lateral (dentate in primates), anterior and posterior interpositus (globose and emboliform in primates), and the medial (fastigial in primates) nucleus (▶ Chap. 46, "Neurons of the Deep Cerebellar Nuclei"). The population of interneurons in the CN is small (Matsushita and Iwahori 1971a, b), consisting of cells colocalizing glycine and GABA (Chen and Hillman 1993) (▶ Chap. 46, "Neurons of the Deep Cerebellar Nuclei"). A lack of identified recordings from these interneurons and of observations of their effects on CN projection neurons leaves the important question of intrinsic network operations in the CN wide open to future research. In the following sections, first some important general functional considerations concerning the CN will be noted. Then the involvement of the CN in behavioral learning will be discussed with a focus on eyeblink conditioning, arguably the most studied learning paradigm in cerebellar
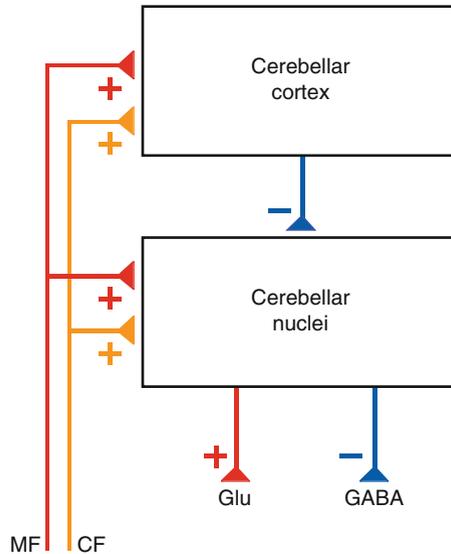
Fig. 47.1 Connections of CN – schematic. Basic connectivity of the cerebellar nuclei. Excitatory mossy fibers (MF) from spinal, brain stem, and pontine origin project to the cerebellar cortex and send collaterals to the CN. Excitatory input from the inferior olive ends as climbing fibers in the cerebellar cortex and also sends collaterals to the CN. The CN integrate this excitation with inhibition sent from the cerebellar cortex via inhibitory Purkinje cell projections. Thus, the net effect of any population of excitatory inputs to the cerebellum in the CN is expected to be a fast excitation, followed by inhibition. Two distinct output pathways emanate from the CN, a GABAergic one projects to the inferior olive, whereas glutamatergic excitatory output projects to diverse areas including spinal cord, brain stem nuclei, and the motor thalamus. Not shown is modulatory input to the CN; for instance, serotonergic input is clearly present

investigations. After reviewing the cellular physiological properties of CN neurons with respect to their properties of synaptic integration, the evidence for specific cellular mechanisms of plasticity in the CN will be linked to involvement of the CN in behavioral learning. As we will see, many details have emerged in the past 50 years of cerebellar research, yet the computational function of CN in motor control remains an area of active research as well as speculation.

Functional Considerations

The general layout of the CN preserves the mediolateral divisions of function domains in the cerebellar cortex (Goodman et al. 1963). Based on anatomical tracing experiments and physiological recordings, the concept of cerebellar corticonuclear complexes or modules has emerged, in which each sagittally elongated strip of cerebellar cortex or microzone is connected to a matching nuclear area (Garwicz and Ekerot 1994; Ekerot et al. 1995). Each of these modules may

form a functional unit in that the same population of mossy and climbing fiber inputs can both directly excite and via a cerebellar cortical pathway indirectly inhibit the CN. Nevertheless, at multiple stations in these modules, there is also considerable potential for cross talk, notably by transmission through parallel fibers in the cerebellar cortex, but also through ramifying axonal terminals of Purkinje cells in the CN (De Zeeuw et al. 1994; Teune et al. 1998). As we will see in more detail below, multiple mechanisms of synaptic plasticity exist in the CN as well as the cerebellar cortex. These forms of plasticity likely underlie the motor learning for which the cerebellum is known for since the Marr-Albus theory started dominating our thinking about the cerebellum (Marr 1969; Albus 1971), but they may also relate to mechanisms of homeostatic balancing of activity (De Schutter 1995). Providing direct evidence for the involvement of specific plasticity mechanisms expressed by CN neurons in specific forms of motor learning presents yet one of the great challenges for future work.

With regard to spike activity in the CN, generally a fast tonic spike rate is observed in vivo (Harvey et al. 1979; Armstrong and Edgley 1984). This activity constantly fluctuates in relation to behavioral events, both sensory and motor. In anesthetized animals, strong widespread sensory responses to peripheral tactile input to the perioral areas and whiskers but also the paws are expressed (Armstrong et al. 1975; Rowland and Jaeger 2005). Similar responses are present in awake animals with sensory nerve shock stimuli (Armstrong and Rawson 1979). These sensory responses, even when a touch stimulus is only a few ms long, show multiple excitatory and inhibitory components extending over several 100 ms (Fig. 47.2). Late response components show a strong correlation with activity in the inferior olive (IO) and cerebral cortex (Rowland and Jaeger 2008). This finding indicates that even a simple sensory input during anesthesia evokes complex reentrant loop activation of the CN, a feature likely to get even more complex during sensory-motor integration in awake animals.

Relations to movement execution are present in the activity of CN neurons for any type of movement that has been studied. A particular frequently studied simple behavior is given by the conditioned eyeblink reflex, about which much more will be said below in relation to motor learning, as it has been used extensively to study representation of classical conditioning in the CN. A different well-studied motor behavior with respect to cerebellar representation is given by saccadic and smooth pursuit eye movements. Though mostly studied in the cerebellar cortex, recordings in the CN also indicate a strong modulation with both saccadic (Hepp et al. 1982; Ohtsuka and Noda 1991) and reflexive smooth eye movements (Gardner and Fuchs 1975; Heinen and Keller 1996; Shaikh et al. 2005). The vestibuloocular reflex (VOR) in particular has also been used as a model system to studying learning in the cerebellum with its output flowing through the VN (Miles and Lisberger 1981; Ramachandran and Lisberger 2008). Limb movement activity in the CN has also been extensively studied, with activation seen both before the onset and during movement (Grimm and Rushmer 1974; Harvey et al. 1979). The specific relations to kinematic or position parameters of limb movement are less clear, with different studies pointing to different relations. CN activity in one study involving reaching
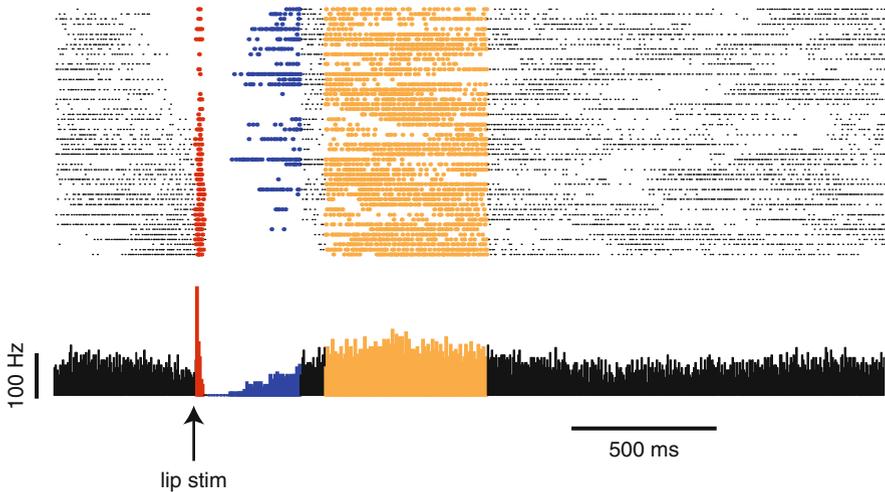
Fig. 47.2 Strong sensory modulation. Response of CN neuron to brief tactile stimulation to the face in an anesthetized rat. A fast excitatory response (*red*) is likely due to mossy fiber input from the trigeminal nucleus and occurs within 15 ms following stimulus onset. This excitation is followed by a pronounced inhibition (*blue*), likely due to Purkinje cell activation by mossy fibers. A long-latency excitation (*yellow*) frequently follows the inhibition. The source of this response component is unclear, but likely involves long-loop pathways involving the inferior olive and cerebral cortex (Rowland and Jaeger 2008). Note that a touch of just 10-ms duration leads to a response pattern of over 300 ms. Different CN neurons may express the different response components to a different degree, given the potential of a complex set of temporal output patterns to this input. See Rowland and Jaeger (2005) for details

movements in monkeys was not found to be clearly related to movement direction, but rather code for the coordination of reaching and grasping (van Kan et al. 1994). Others have reported a more well-defined relation to movement direction when an external force is applied to disturb movement (Strick 1983).

An important functional question is which synaptic input pathways drive behavioral spike modulations in the CN. While the dominant pathway is often assumed to come from the cerebellar cortex via Purkinje cell inhibition, many recorded behavioral spike modulations in the CN consist of increases in spiking. Paradoxically, such excitation may occur during the same time in which Purkinje cells in the same functional module also show increased firing. CN activation in these circumstances persists after Purkinje cell inactivation (Holdefer et al. 2005), i.e., is not due to disinhibition. Therefore, the direct mossy fiber (and possibly climbing fiber) activation of CN neurons may often have overriding influence over CN activity. In fact, this direct loop of excitation through the CN may provide a primary pathway controlling cerebellar output, which is only modulated by PC inhibition in specific circumstances. One of these circumstances may be the adjustment of precise timing of cerebellar output, since precise timing of behavior in motor coordination and motor error correction are likely major functions of the cerebellum (Braitenberg 1967; Ivry 1996; Ivry and Spencer 2004) – see ▶ Chap. 52, "Cerebellum and Timing."

Cellular Properties and Synaptic Integration in the CN

Modulation of Spike Rate

A general overview of cellular properties of CN neurons is given in ▶ Chap. 10, "Development of Cerebellar Nuclei" and ▶ Chap. 46, "Neurons of the Deep Cerebellar Nuclei". With respect to properties that are likely important with respect to how the CN are involved in learning, a few points should be highlighted. First, CN neurons are autonomously active due to intrinsic depolarizing currents (Jahnsen 1986a, b; Raman et al. 2000). This intrinsic spike cycle is easily overcome by inhibition, however, and for sustained spiking seen in the presence of any appreciable Purkinje cell input, a counteracting balance of excitatory input is needed (Gauck and Jaeger 2000). Precise relations between controlled input patterns and CN spike output can be examined with the technique of dynamic clamping, in which artificial synaptic conductances can be computed in real time with a fast feedback loop and applied via a whole-cell recording electrode (Robinson and Kawai 1993; Sharp et al. 1993). Using this technique, it was found that the spike rate of CN neurons is generally dictated by the balance of excitation and inhibition present, but that the temporal pattern of inputs is equally important in controlling the output spike rate as is the input rate (Gauck and Jaeger 2000, 2003). Notably, when populations of Purkinje cells are synchronized, a much higher spike rate in CN neurons will result than with asynchronous PC inputs (Gauck and Jaeger 2000). This is due to the fact that synchronous PC activity patterns lead to a much higher degree of fluctuations in the total PC input conductance to a single CN neuron. The convergent input to single CN neuron may actually arise from over 800 individual PCs of which 400 may terminate on the soma or proximal dendrites (Palkovits et al. 1977). When the instantaneous spike frequency between an appreciable proportion of these 400–800 PCs is correlated, then distinct patterns of increases and decreases in the total inhibitory input conductance to individual CN neurons occur (Fig. 47.3). Because PC input to CN neurons is inhibitory, individual CN spikes may follow precisely timed common pauses of the received Purkinje cell inputs (Fig. 47.3) (Gauck and Jaeger 2000). Such joint pauses in PC activity have been detected in vivo (Shin and De Schutter 2006; Steuber et al. 2007; De Schutter and Steuber 2009) and may present a code for precise CN output spike coding. Using pauses of PC activity as a code for cerebellar output is an idea originally proposed by Albus in 1971 when he updated Marr's ideas based on the insight that PC output is inhibitory. In the Albus hypothesis, pauses in PC input are originally caused by climbing fiber inputs as an unconditioned stimulus, and indeed, climbing fiber responses often include a short pause after the initial complex spike (Granit and Phillips 1956; Sato et al. 1992). Cerebellar long-term depression (LTD) of parallel fiber (PF) input to PCs would be simultaneously triggered by the same climbing fiber inputs, ultimately leading to common pauses in PC activity due to a reduction in PF input at particular times. In fact, it is still this idea that movements are triggered by reduced PC output at times of increased CN activity that is used in modern models of eyeblink delay conditioning (Medina et al. 2000).
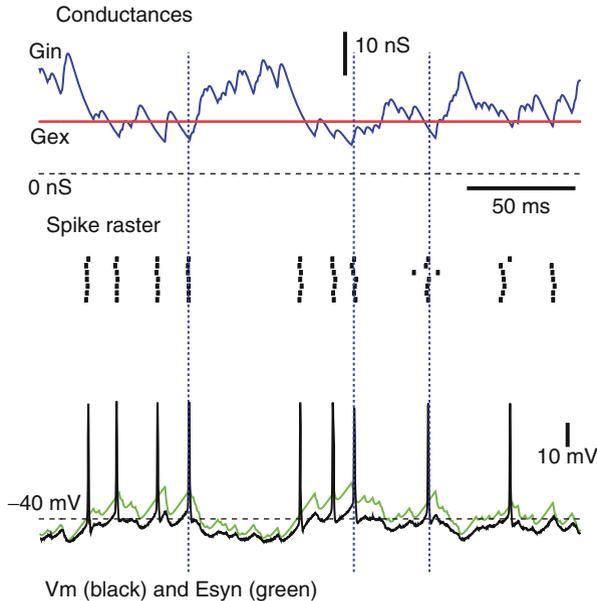
Fig. 47.3 Dynamic clamp integration of Purkinje cell input. Application of inhibitory input pattern to CN neuron in rat brain slice recording. The inhibitory synaptic conductance (Gin, *blue*) is given by the activation of synchronous activations of small populations of Purkinje cells. Excitation is given as a constant baseline (Gex, *red*) to study the effect of temporal information in inhibitory input in isolation. Each time this input pattern is applied via dynamic clamping through a whole-cell recording, the CN neuron responds with a highly precise temporal spike pattern (spike raster shows repeated trials of the same stimulus; *black trace* below shows a single trace of membrane-voltage recording). The *green trace* indicates the combined synaptic reversal potential of excitation and inhibition given by the applied inputs. The larger the distance between the *green* and *black trace*, the larger the synaptic driving force, and the larger the current applied through the dynamic clamp circuit. Note that decreases in inhibitory synaptic conductance lead to a depolarization of the combined reversal potential and the neuron. Spikes are triggered at distinct reductions in inhibitory input given by pauses in PC input (*blue dotted lines* indicate three examples). See Gauck and Jaeger (2000) for details

Activation of Rebound Firing

A very robust property of CN neurons recorded in brain slices is their ability to fire rebound spike bursts following strong hyperpolarization induced by current injection (Jahnsen 1986b; Aizenman and Linden 1999). These rebounds are both seen in GABAergic and glutamatergic CN neurons (Uusisaari et al. 2007). The rebound activity has an initial fast burst component and a longer-lasting 2–5 s increase of spike rate associated with it (Fig. 47.4) (Sangrey and Jaeger 2010). The fast spike burst is carried by T-type calcium channels, which is strong in some cells, but much weaker in others (Molineux et al. 2006, 2008). The longer-lasting spike rate increase is associated likely with a slowly inactivating persistent sodium current (Sangrey and Jaeger 2010). Strong high-frequency bursts of inhibitory input can
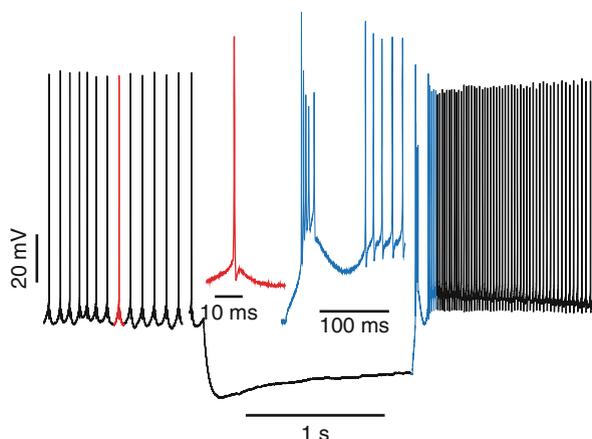
Fig. 47.4 Rebound. Rebound response of CN neuron to hyperpolarizing current injection. A CN neuron during whole-cell recording in rat brain slice is subjected to 1.5-s-duration hyperpolarization by injection of −150-pA current. During the hyperpolarization, inward rebound currents are deinactivated and lead to a combination of a fast rebound burst carried by a T-type calcium current and a prolonged speedup in spiking following the offset of hyperpolarization. See Sangrey and Jaeger (2010) for details

also elicit these rebounds (Aizenman and Linden 1999; Hoebeek et al. 2010; Tadayonnejad et al. 2010), although in a less pronounced form. The strength of rebound is reduced because the chloride reversal potential limits the amount of hyperpolarization that can be achieved with inhibitory input to about −75 mV in CN neurons (Llinas and Muhlethaler 1988), which is barely sufficient to deinactivate the inward rebound conductances (Steuber et al. 2011). In fact, there is some debate on whether inhibitory inputs occurring naturally might even be sufficient to trigger appreciable rebound activity (Alvina et al. 2008). Nevertheless, the idea of using rebound activity for behaviorally relevant events, notably eyeblink conditioning, has been proposed and does produce functional rebounds in a compartmental model of CN neurons when Purkinje cell activity is first up- and then downregulated with proper CS-US timing (Wetmore et al. 2008). Specifically, in this model, the intrinsic rebound properties in the CN are proposed to form a temporal filter or "lock," that when activated with the matching "key" of biphasic modulation of PC activity to first deinactivate rebound mechanisms with increased PC input and then support a rebound with reduced PC input. Note that this mechanism is not dependent on synaptic plasticity in the CN.

The Eyeblink Conditioning Paradigm as a Blueprint for Learning Mechanisms in the CN

When animals are given an unconditioned stimulus (US) such as an air puff to the eye, they will close their eyelids as a protective reflex. This response can be paired

with a conditioned stimulus (CS) such as a tone or light that initially does not evoke eyelid closure, but after pairing with the US will. Delayed eyeblink conditioning occurs when the CS precedes the US by some constant amount of time, and results in an eyeblink reflex that will follow the CS onset by the training interval even after the US is no longer given. Finally, in trace conditioning, the CS is also delayed from the US, but the CS stops some time before the US is delivered, thus requiring a memory of the CS "trace" in order to allow conditioning. Each of these forms of eyeblink conditioning has been extensively used in cerebellar research, starting with the work by Richard Thompson and David McCormick in the early 1980s (McCormick et al. 1981, 1982) that established a critical role for the cerebellum in the learning of this simple motor behavior. When neural activity of cerebellar cortical Purkinje cells and neurons in the interpositus and medial dentate nuclei was recorded during eyeblink conditioning, responses developed in parallel with learning (McCormick and Thompson 1984). In particular, in the CN, the activity showed an excitatory response just before the eyelid response. Subsequent work delineated the site of learning with lesioning and inactivation experiments in different parts of the cerebellar pathway. While early on some controversial findings were obtained, the final outcome of these studies reveals that the dorsolateral portion of the anterior interpositus nucleus is the essential site of learning in which the memory trace for eyelid closure is stored (Christian and Thompson 2003; Thompson and Steinmetz 2009). However, this is only the case for immediate eyelid closure upon CS onset. When delay conditioning is used, coding of the correct temporal delay requires cerebellar cortical input to the interpositus (Perrett et al. 1993). After delay conditioning, lesion of the anterior lobe of rabbit cerebellar cortex leads to a loss of the proper delayed timing of the conditioned reflex, and instead an early short-latency response (SLR) is expressed (Perrett et al. 1993). Interestingly, the same group also found that extinction of the conditioned reflex with multiple unpaired exposures of the CS is also impaired by lesioning the same part of cerebellar cortex (Perrett and Mauk 1995). This is taken as evidence that the learning in the interpositus nucleus depends on intact input from Purkinje cells in the cerebellar cortex. This interpretation is corroborated by results finding that learning of new conditioned eyelid responses is impaired after cerebellar cortical lesions (Garcia et al. 1999). The eyeblink conditioned responses triggered by CN excitation were further shown to be specific to the original training stimulus, and after cerebellar cortical lesioning, no generalization to other stimuli is possible (Ohyama et al. 2003). These findings suggest a synapse-specific form of plasticity in the CN that enhances the response to very specific inputs but not others.

It should not be thought, however, that eyeblink conditioning is solely a function of the cerebellum. More recent studies probing more complex aspects of eyeblink conditioning do indeed find critical involvement of other brain structures. Cross-modal transfer is a mechanism, by which training a second CS of a different modality (e.g., a light) occurs faster than training with a first CS (e.g., a tone). Such cross-modal transfer critically depends on feedback interactions between the CN and the pontine nuclei (Campolattaro et al. 2011). An important interaction with the hippocampus is observed in trace conditioning, when a memory

of the CS needs to be established before the response can be elicited (Hoffmann and Berry 2009; Berry and Hoffmann 2011). Trace conditioning depends on both structures, and during the conditioning, a phase-locked theta rhythm (6–7 Hz) is observed between cerebellar and hippocampal activity.

Adaptation of the Vestibuloocular Reflex (VOR) Gain Shares Many Features with Eyeblink Conditioning

Adapting the VOR gain provides another learning paradigm with extensive studies of cerebellar involvement conducted since the early 1980s (Miles and Lisberger 1981; Lisberger 1988). Basically, the VOR gain is naturally adaptive in order to match eye movement amplitudes to exactly compensate head movement in the opposite direction. Gain changes in the VOR can be easily elicited by artificially manipulating the excursion of image motion on the retina during eye movement. As the task of the VOR is to stabilize the image, a lack of image stability with eye movement leads to adaptation of the VOR. Similar to the results described for eyeblink conditioning above, VOR adaptation studies find that it is cerebellar dependent, and that an important site of learning is in the structure that receives Purkinje cell inhibition, namely, the VN in this case. Further, plasticity in the VN depends on intact cerebellar cortical output (Raymond et al. 1996). Several reviews note these close parallels between eyeblink conditioning and VOR gain control adaptation (Raymond et al. 1996; Mauk 1997; Boyden et al. 2004). While there has been a long-standing controversy regarding the involvement of cerebellar cortical LTD in VOR adaptation (Ito 1993; Lisberger 1994a; Lisberger et al. 1994a, b), a possible resolution of this question is again in parallel to eyeblink conditioning, namely, that the precise timing of muscle activation may require LTD of Purkinje cell activity (Raymond et al. 1996 #7631).

Learning Limb Movements Does Not Take Place in the CN

Is the cerebellum then in general, and the CN in particular, a general site for all forms of motor learning? Many would consider acquisition of new limb movements in response to external stimuli the prototype of complex motor learning. In fact, during learning of conditioned forelimb movements in cats, behaviorally linked responses in the CN are established in parallel with learning (Milak et al. 1995). However, these responses diminish with subsequent overtraining. These trained movements do also not disappear upon transient inactivation of the CN with muscimol (Milak et al. 1997; Wang et al. 1998), indicating that the primary learning of motor sequences is taking place elsewhere. However, the timing of joint angel velocities between different components of the movements is disturbed upon CN inactivation, again suggesting an involvement of cerebellar output in the control of precise behavioral timing (Milak et al. 1997) and the anticipatory coordination of shoulder, elbow, and wrist movement (Cooper et al. 2000).

Cellular Plasticity in the CN

As mentioned above, inactivation experiments during eyeblink conditioning lead to the prediction that a conditioned response can be stored in the CN, though not with a delay following the CS. Because activation of the CN is required to elicit the CR, the hypothesis is that the MF to CN synapse is plastic to allow strengthening the input from specific MF populations activated by the CS (Raymond et al. 1996; Mauk 1997; Ohyama et al. 2006). Further, modeling experiments predict that only MF plasticity that is gated by the level of PC activity could lead to stable learning, while MF plasticity that is Hebbian, i.e., gated by high-frequency MF activity resulting in postsynaptic spiking, or gated by CF activity, would lead to unstable motor memories (Medina and Mauk 1999). Notably, these modeling predictions were made without any experimental evidence at the time supporting them.

Plasticity in the Mossy Fiber Inputs to CN Neurons

An early investigation of plasticity in the CN of the rat showed that indeed LTP can be evoked by high-amplitude, high-frequency burst stimulation of the inferior peduncle when field potential and population spike responses to single electrical stimuli in the peduncle were measured (Racine et al. 1986). These experiments, however, were somewhat unspecific by strongly activating multiple pathways and circuits. Direct testing of specific mechanisms of LTP in the CN only occurred relatively recently in the lab of Indira Raman. Interestingly, most of the modeling predictions were upheld by these experiments and led to the discovery of a novel and unusual plasticity mechanism. Essentially, it was found to be true that a Hebbian mechanism does not evoke LTP in the MF input to CN of mouse slices, as tetanic stimulation of excitatory input while inhibition was blocked did not lead to plasticity (Pugh and Raman 2006). Instead, in this study, LTP of the MF input pathway to the CN was found when MF burst stimulation was paired with hyperpolarization and a resulting rebound response. In subsequent experiments, it was verified that indeed PC activation could also control the hyperpolarization necessary to elicit this MF LTP in agreement with the prediction by Medina and Mauk (Pugh and Raman 2008). Interestingly, the timing of the MF activity had to precede the hyperpolarization, and the hyperpolarization elicited rebound by about 400 ms for this mechanism to work. In their most recent studies, the authors track down the molecular mechanisms underlying this complex form of LTP to a sequence of calcium signals that starts with an activation of calcineurin during MF burst stimulation, then requires a dip in intracellular calcium that leads to activation of CaMKII after resumption of calcium inflow (Zheng and Raman 2009; Person and Raman 2010). This form of plasticity is synapse specific (Pugh and Raman 2008), i.e., only synapses that are activated during MF burst stimulation are potentiated, and overall provides a good fit with the modeling predictions set out by Medina and Mauk in 1999. Essentially, the requirement for hyperpolarization agrees with the finding that learning in the CN cannot take place when the cerebellar cortex is

inactivated (Garcia et al. 1999). Because strong hyperpolarization of the CN and rebound depolarization most likely occur when PCs are synchronously activated by CFs (Hoebeek et al. 2010; Bengtsson et al. 2011), plasticity in the CN during eyeblink conditioning may be linked to the same CF US that also leads to the PF LTD in the cerebellar cortex (Mauk 1997). A synchronous CF signal may also be shared with more complex forms of motor learning, in which climbing fiber activity has also been implicated to present a "teacher" signal (Ito and Kano 1982; Ito 2001).

Plasticity in the Purkinje Cell CN Pathway

Although LTP of the MF input to the CN best explains conditioned eyeblink responses in the absence of cerebellar cortex, the majority of synapses on CN neurons are inhibitory PC inputs (Palkovits et al. 1977). Plasticity in this pathway would modify the signals from cerebellar cortex, and LTP, for instance, would strengthen inhibitory responses. Such modification of inhibition might be particularly useful during the control of more complex limb movements requiring agonist/antagonist muscle sequences of activation. The traditional mechanism of changed levels of inhibition in the CN is given by up- and downregulating PC spike rates via cerebellar cortical LTD and LTP of excitatory and inhibitory inputs to PCs. However, if inhibitory synapses onto CN were also plastic, additional strengthening or weakening of CN responses to PC inputs may occur. Indeed, experiments in slices indicate that this connection does undergo plastic changes. A low-frequency stimulation of PC input to CN neurons at 10 Hz leads to LTD of this pathway (Morishita and Sastry 1996). Later work found that LTD is elicited when PC input is too weak to elicit rebound depolarization, but that in the presence of rebound depolarization following strong PC burst input, the PC pathway is potentiated (Aizenman et al. 1998). This form of plasticity, therefore, would support a mode of learning, in which strong PC signals that elicit rebounds are selectively reinforced. Nevertheless, a demonstration for involvement of this plasticity rule in the control of behavior is still lacking.

Other Forms of Plasticity in the CN

While LTP and LTD form the staple of cellular mechanisms expected to underlie behavioral learning mechanisms, other forms of plasticity also provide important mechanisms to shape the pattern of neural activity. Short-term plasticity allows shaping of responses to high-frequency inputs, where facilitation enhances and depression weakens the response to bursts of input. Interestingly, the PC inputs to CN neurons show marked short-term depression (STD) (Telgkamp and Raman 2002; Pedroarena and Schwarz 2003), which reduces the impact of the fast PC complex spike burst in response to climbing fiber input in the CN. In addition, STD will reduce the effect of fast tonic PC inputs, which in the face of several hundred

fast firing PC inputs to an individual CN neuron helps explain the ability of CN neurons to maintain tonic spiking activity themselves. Following a decrease or pause of PC inhibition, the subsequent resumption of PC firing then would have a disproportionally large effect, which might help strengthen biphasic response patterns consisting of disinhibition followed by inhibition. Again, such a mechanism has not been demonstrated to play a functional role in behaving animals to date, and deserves future investigations.

Another form of plasticity that has come to the forefront of attention more recently is excitability plasticity, in which intrinsic neural properties such as inward or outward voltage-gated currents are altered such that neurons become more or less excitable (Desai et al. 1999; Daoudal and Debanne 2003; Beck and Yaari 2008; Sjostrom et al. 2008). Such plasticity has also been found in the CN and in the VN, in which Purkinje cell inhibition mediates important aspects of VOR adaptation (Miles and Lisberger 1981; Broussard and Lisberger 1992; Lisberger 1994b). In the VN, strong inhibition leads to an increased excitability mediated by a reduction in calcium-activated potassium current (Nelson et al. 2003). This mechanism leads to the phenomenon of firing rate potentiation after inhibition, which the authors speculate may be functionally involved in VOR gain adaptation processes. Excitatory input can also lead to excitability plasticity in cerebellar output pathways, as the CN show an increase in excitability following strong excitatory synaptic input or direct depolarization with current injection (Aizenman and Linden 2000).

Perhaps the ultimate form of plasticity that solidifies memories is structural plasticity, in which new connections are formed, and unused ones degenerate. In fact, in the CN, this is the form of plasticity noted earliest (Chanpala 1973). This study looked for degenerating axons in normal brains and found strong evidence in the CN, but not in the cerebellar cortex, suggesting the former as a predominant site for long-lasting memory reorganization in the cerebellum.

Conclusion and Future Directions

The CN have proved to be a lot more than a relay station on the output side of the cerebellum. It appears that specific populations of Purkinje cells that converge onto individual CN neurons are evaluated for correlations in their activity through synaptic integration in the CN. Populations of PCs that pause together form a particularly strong signal for triggering CN spiking. These spikes can be precisely timed within 1 ms through the mechanism of disinhibition. Strong bursts of PC inhibition converging onto a CN neuron may trigger a postinhibitory rebound, though the presence and function of such a rebound mechanism during the control of behavior in vivo have yet to be determined.

It is clear that the CN are involved in several forms of motor learning, of which eyeblink conditioning and the vestibuloocular reflex gain adaptation are the best studied. In both behaviors, plasticity in the excitatory mossy fiber input to CN neurons is required and is under the control of Purkinje cell inhibition. However, plasticity in the cerebellar cortex, likely via parallel fiber LTD, is also needed to

shift responses in the CN to the correct time. This has most notably been explored in delay conditioning of the eyeblink reflex. The outcome of the overall plasticity is firing rate increases in the CN that grow with learning and directly precede the behavior to be triggered. For more complex limb movements, however, the primary site of learning appears to be outside of the cerebellum, while cerebellar output is likely needed in the control of precisely timing submovement sequences. The need for and specific forms of plasticity in the CN during such optimization of limb movement control need yet to be explored, however.

Although much knowledge has been gained in the past 50 years about the control and function of CN activity, maybe the most important aspects of the computation taking place in this structure remain yet to be determined. Several key features of missing knowledge are readily identified. (1) Although there are axon collaterals of CN output neurons within the CN as well as a small number of local inhibitory interneurons, we know nothing about network interactions within the CN. Such network interactions could be crucial in the coordination of activity between populations of CN neurons. (2) In fact, there are very few experimental data regarding population coding in the CN. What is the degree of correlation between CN neurons on a trial-by-trial basis, and is such correlation related to specific aspects of behavioral control, such as submovement coordination? Presumably, different populations of CN neurons would need to be activated in a precise pattern that is different in each trial in order to correct for variability in motor execution and potentially engage in error correction driven by on-line sensory feedback. (3) There are two major output populations in the CN, a GABAergic one projecting to the inferior olive and a glutamatergic one projecting to the motor thalamus, red nucleus, brain stem, and spinal cord. The cellular properties of these two populations are surprisingly similar – but are their activity patterns during behavior distinct? What is the specific function of the feedback loop to the inferior olive?

It is clear that new and improved methods besides the traditional ones of behavioral training, lesioning, inactivation, single-unit recording, slice recordings, etc., are needed to address these and other questions regarding the function of the CN and in fact the cerebellum. Fortunately, we are at a point in time where key new methods are being rapidly developed and deployed. In particular, genetic techniques in rodents are coming to the forefront and allow the examination of specific cellular mechanisms and cell types in the control of behavior. These techniques have already resulted in several key insights in the cerebellar cortex, where specific proteins can be inactivated or modified in Purkinje cells in an inducible manner that, for instance, leads to the inactivation of inhibitory input or LTD (Wulff et al. 2009; Boele et al. 2010; Burguiere et al. 2010). Similarly targeted gene manipulations in GABAergic or glutamatergic CN neurons will undoubtedly provide important details regarding their function. The recent addition of optogenetics to the experimental repertoire (Boyden et al. 2005) will also allow genetic expression of light-gated excitatory channelrhodopsin or inhibitory halorhodopsin ion channels into specific classes of CN neurons, which then can be activated with precise timing during behavior via an implanted glass fiber conducting laser light to the CN. Such experiments will lead to future groundbreaking insights for sure.

Experimental approaches generally address detailed questions regarding biological function. To ultimately understand information processing in a system as complex as the cerebellum, computer simulations provide the ideal tool to regenerate and analyze the dynamical interactions between the many biological components determined experimentally. Cerebellar research in fact has been on the forefront of using such computer simulations for many years, which range from biologically single cell level (Pellionisz and Llinás 1977; De Schutter and Bower 1994; Gabbiani et al. 1994; Solinas et al. 2007) to biological cerebellar cortical network models (Pellionisz and Szentagothai 1974; Maex and De Schutter 2005; Solinas et al. 2010) to more abstract models of cerebellar function (Pellionisz and Llinás 1979; Medina and Mauk 1999; Medina et al. 2001). Each of these models synthesizes a number of biological functions and tests whether specific interactions between model components confirm or predict aspects of cerebellar function. Modeling of the CN has clearly lagged behind cerebellar cortical modeling, but a detailed model of CN neurons with realistic dynamics is now available (Steuber et al. 2011) and can be integrated in future cerebellar network models with a more realistic representation of the cerebellar nuclei. New developments in the field of computer modeling such as simulator-independent model specification standards of neural morphology and dynamic properties (Crook et al. 2007, 2009; Gleeson et al. 2010) and tools that can parse these model definition scripts into different simulators (Gleeson et al. 2007) will greatly aid in the development of collaborative network model development and model sharing. This will allow the formation of a common model basis that can be studied and verified independently by multiple labs, which provides an important step in testing of our understanding cerebellar computational algorithms taking place in the cerebellar cortex and the cerebellar nuclei.

Cross-References

▶ Cerebellar Nuclei and the Inferior Olivary Nuclei: Organization and Connections
▶ Cerebellum and Eyeblink Conditioning
▶ Cerebellum and Sensory Processing
▶ Cerebellum and Timing
▶ Development of Cerebellar Nuclei
▶ Neurons of the Deep Cerebellar Nuclei

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