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Modeling the generation of output by the cerebellar nuclei

Volker Steuber [a,*], Dieter Jaeger [b]

[a] Science and Technology Research Institute, University of Hertfordshire, College Lane, Hatfield, AL10 9AB, UK
[b] Department of Biology, Emory University, Atlanta, GA 30030, USA

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ABSTRACT

Functional aspects of network integration in the cerebellar cortex have been studied experimentally and modeled in much detail ever since the early work by theoreticians such as Marr, Albus and Braitenberg more than 40 years ago. In contrast, much less is known about cerebellar processing at the output stage, namely in the cerebellar nuclei (CN). Here, input from Purkinje cells converges to control CN neuron spiking via GABAergic inhibition, before the output from the CN reaches cerebellar targets such as the brainstem and the motor thalamus. In this article we review modeling studies that address how the CN may integrate cerebellar cortical inputs, and what kind of signals may be transmitted. Specific hypotheses in the literature contrast rate coding and temporal coding of information in the spiking output from the CN. One popular hypothesis states that post-inhibitory rebound spiking may be an important mechanism by which Purkinje cell inhibition is turned into CN output spiking, but this hypothesis remains controversial. Rate coding clearly does take place, but in what way it may be augmented by temporal codes remains to be more clearly established. Several candidate mechanisms distinct from rebound spiking are discussed, such as the significance of spike time correlations between Purkinje cell pools to determine CN spike timing, irregularity of Purkinje cell spiking as a determinant of CN firing rate, and shared brief pauses between Purkinje cell pools that may trigger individual CN spikes precisely.

1. Introduction

Many experimental and theoretical studies have addressed the question how neuronal activity is processed in cerebellar cortex, but there is still no unified view about the computational role of the cerebellum as a whole. One of the main reasons for this lack of understanding of cerebellar function is that we still know very little about the processing of incoming signals and the generation of output by the cerebellar nuclei (CN). This is an important topic, as almost the entire output from the cerebellar cortex through Purkinje cell (PC) axons ends as GABAergic inhibition in the CN (Fig. 1), with an additional small specialized component going to the vestibular nuclei. Thus, cerebellar function cannot be determined without considering processing at the level of CN, where inputs from PCs are integrated with signals from the excitatory mossy fibers and climbing fibers that also drive cerebellar cortical processing (Fig. 1).

Neural coding can be broadly categorized as rate based, where the number or rate of spikes in a particular time window is the carrier of information, or as temporal coding, where information is represented by the timing of individual spikes or bursts of spikes. Both temporal and rate coding have been observed to take place in the cerebellum and are likely to serve important functions (De Zeeuw et al., 2011; Walter & Khodakhah, 2009). With respect to rate coding, linear response mechanisms of CN neurons can sum the combination of input rates from PCs, which themselves can exhibit a linear spike rate code of external events such as smooth eye movements (Medina & Lisberger, 2009). Potentially important mechanisms serving temporal coding are given by synchronized PC complex spiking, and by the ability of CN neurons to fire rebound spike bursts following strong inhibition (De Zeeuw et al., 2011). In this review, we summarize the existing field of modeling studies by others and by ourselves that have tried to elucidate how CN neurons could use different forms of neural coding to transmit signals from the cerebellar cortex to the rest of the brain. Moreover, we relate these results to the involvement of the CN in simple computational tasks, and we discuss computer simulations of pathological responses in CN neurons that are associated with motor dysfunction.

2. Simple models of CN neurons and temporal coding

A central question of simulation studies that have included computational models of CN neurons has been how the cerebellum could use temporal coding to generate appropriately timed output signals. A simple behavioral paradigm that requires the generation

* Corresponding author. Tel.: +44 1707 284350; fax: +44 1707 284303.
E-mail address: v.steuber@herts.ac.uk (V. Steuber).

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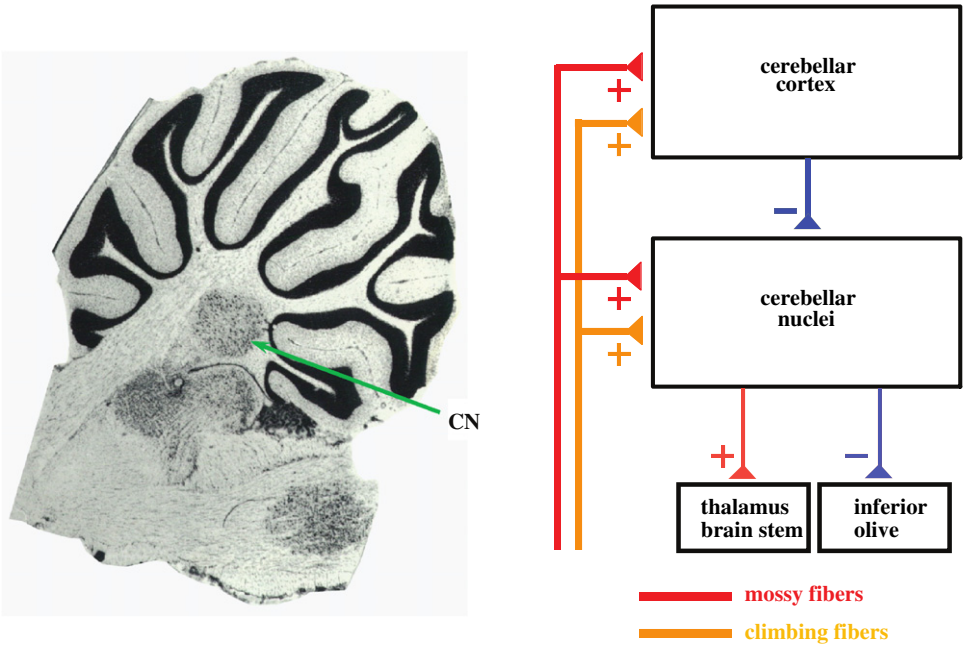

Fig. 1. Cerebellar circuit diagram. The left panel shows a sagittal section of the rat cerebellum at the level of the lateral nucleus. The right panel shows a simplified circuit diagram of the cerebellum, highlighting the central position of the cerebellar nuclei (CN) in processing cerebellar cortical Purkinje cell inhibition before the final output leaves the cerebellum.
Source: Diagram adapted from Paxinos and Watson, The Rat Brain in Stereotaxic Coordinates, Academic Press, 2006.

of such a well-timed output signal by the cerebellar circuitry is delay eye-blink conditioning. When an animal is trained during eye-blink conditioning, a conditioned stimulus (CS, such as a tone) is paired repeatedly with an unconditioned stimulus (US, for example periorbital electrical stimulation). In delay conditioning, the CS and US co-terminate, and the onset of the US follows the CS onset by an inter-stimulus interval (ISI), which is typically between 100 ms and 1 s. The animal then learns to respond to presentations of the CS alone with eye-blink conditioned responses (CRs) that are timed adaptively so that the peak of the CR occurs at the time of the US presentations during training.

Several lines of evidence indicate an involvement of the CN in the execution of these timed responses. Electrical stimulation of the interpositus nucleus can elicit eye-blinks, and interpositus neurons show an increase in activity that precedes and resembles eye-blink CRs (McCormick & Thompson, 1984). Based on these experimental results, computational studies of cerebellum-dependent eye-blink conditioning have assumed that the output of CN neurons predicts the amplitude and timing of conditioned eye-blink responses (Medina, Garcia, Nores, Taylor, & Mauk, 2000; Wetmore, Mukamel, & Schnitzer, 2008). An example of such a computational study is the cerebellar network model by Medina et al. (2000). In the model by Medina and collaborators, the neural network model of cerebellar cortex by Buonomano and Mauk (1994) has been extended to include six CN neurons that provide the output from the model, generating spike responses with temporal profiles that replicate experimentally measured eye-blink responses. Each of these CN neuron models receives inhibitory input from 15 PCs and excitatory input from 100 mossy fibers; the CN neurons are implemented as leaky integrate-and-fire models and provide a simple readout mechanism for the combined excitatory and inhibitory input. The Medina model generates appropriately timed responses based on long-term depression (LTD) at parallel fiber–PC synapses that are active at the same time as the US, and it suppresses responses at incorrect times based on long-term potentiation (LTP) at these synapses when they are activated without a coincident US. Moreover, LTP at mossy fiber–CN neuron synapses is included to be able to replicate the short-latency responses that are observed after lesions to the cerebellar cortex.

Apart from adjusting synaptic parameters based on available electrophysiological data, the Medina model does not make any specific assumptions about the physiological characteristics of the different cerebellar neurons. A hallmark behavior of CN neurons is the generation of rebound spike responses at the offset of inhibitory synaptic inputs and hyperpolarizing current injections (Fig. 2). The rebound responses that follow hyperpolarizing current injections are well characterized, and they are formed by varying combinations of fast rebound spike bursts, and prolonged periods of accelerated spiking (Llinas & Muhlethaler, 1988; Sangrey & Jaeger, 2010) (Fig. 2). Rebound responses can also follow strong bursts of inhibitory synaptic inputs, but these have been studied to a lesser extent and their relevance for cerebellum dependent behaviors and their contribution to cerebellar computation and neural coding are unresolved questions (Alvina, Walter, Kohn, Ellis-Davies, & Khodakhah, 2008; Bengtsson, Ekerot, & Jorntell, 2011; Tadayonnejad et al., 2010; Tadayonnejad, Mehaffey, Anderson, & Turner, 2009).

Rebound bursts are a prime candidate mechanism for temporal coding in that they create a well-timed spike burst following a specific input event. In their computational study of cerebellar learning, Wetmore et al. (2008) suggest that the rebound spike responses that can follow inhibitory input to CN neurons are crucial for the recall of memories and the generation of appropriately timed output from the cerebellar circuitry. According to their "lock-and-key" hypothesis, the induction of LTD and LTP at parallel fiber–PC synapses is necessary, but not sufficient, to generate a desired cerebellar output. In addition, cerebellar cortical synaptic plasticity has to result in temporal patterns of PC activity that can elicit rebound responses in CN neurons (Fig. 2). Rebounds will only be triggered by temporal input spike patterns that comprise an increase followed by a decrease in the PC spike rate. Thus, Wetmore et al. consider these temporal spike patterns a "key", and the temporal filtering properties of CN neurons that determine whether or not a rebound response occurs a "lock". They demonstrate the potential contribution of rebound responses