Bareš, M., Apps, R., Avanzino, L., Breska, A., D'Angelo, E., Filip, P., Gerwig, M., Ivry, R. B., Lawrenson, C. L., Louis, E. D., Lusk, N. A., Manto, M., Meck, W. H., Mitoma, H., & Petter, E. A. (2019). Consensus paper: Decoding the Contributions of the Cerebellum as a Time Machine. From Neurons to Clinical Applications. *Cerebellum*, *18*(2), 266-286. https://doi.org/10.1007/s12311-018-0979-5

Consensus Paper: Decoding the Contributions of the Cerebellum as a Time Machine From Neurons to Clinical Applications

Martin Bareš[1,2], Richard Apps[3], Laura Avanzino[4,5], Assaf Breska[6], Egidio D'Angelo[7,8], Pavel Filip[1], Marcus Gerwig[9], Richard B. Ivry[6], Charlotte L. Lawrenson[3], Elan D. Louis[10,11], Nicholas A. Lusk[12], Mario Manto[13,14], Warren H. Meck[12], Hiroshi Mitoma[15], Elijah A. Petter[12]

1. First Department of Neurology, Faculty of Medicine, Masaryk University and St. Anne's Teaching Hospital, Brno, Czech Republic
2. Department of Neurology, School of Medicine, University of Minnesota, Minneapolis, USA
3. School of Physiology, Pharmacology and Neuroscience, University of Bristol, Bristol, UK
4. Department of Experimental Medicine, Section of Human Physiology and Centro Polifunzionale di Scienze Motorie, University of Genoa, Genoa, Italy
5. Centre for Parkinson's Disease and Movement Disorders, Ospedale Policlinico San Martino, Genoa, Italy
6. Department of Psychology and Helen Wills Neuroscience Institute, University of California, Berkeley, USA
7. Neurophysiology Unit, Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy
8. Brain Connectivity Center, Fondazione Istituto Neurologico Nazionale Casimiro Mondino (IRCCS), Pavia, Italy
9. Department of Neurology, University of Duisburg-Essen, Germany
10. Department of Neurology, Yale School of Medicine, Yale University, New Haven, Connecticut, USA
11. Department of Chronic Disease Epidemiology, Yale School of Public Health, Yale University, New Haven, Connecticut, USA
12. Department of Psychology and Neuroscience, Duke University, Durham, NC, USA
13. FNRS ULB-Erasme, Bruxelles, Belgium
14. Service des Neurosciences, UMons, Mons, Belgium
15. Tokyo Medical University, Medical Education Promotion Center, Tokyo, Japan

Corresponding author:

Martin Bareš MD PhD

1st Department of Neurology, St. Anne's Teaching Hospital, Brno, Czech Republic

e-mail: bares@muni.cz

Abstract

Time perception is an essential element of conscious and subconscious experience, coordinating our perception and interaction with the surrounding environment. In recent years, major technological advances in the field of neuroscience have helped foster new insights into the processing of temporal information, including extending our knowledge of the role of the cerebellum as one of the key nodes in the brain for this function. This consensus paper provides a state-of-the-art picture from the experts in the field of the cerebellar research on a variety of crucial issues related to temporal processing, drawing on recent anatomical, neurophysiological, behavioral, and clinical research.

The cerebellar granular layer appears especially well-suited for timing operations required to confer millisecond precision for cerebellar computations. This may be most evident in the manner the cerebellum controls the duration of the timing of agonist-antagonist EMG bursts associated with fast goal-directed voluntary movements. In concert with adaptive processes, interactions within the cerebellar cortex are sufficient to support sub-second timing. However, supra-second timing seems to require cortical and basal ganglia networks, perhaps operating in concert with Cerebellum. Additionally, sensory information such as an unexpected stimulus can be forwarded to the cerebellum via the climbing fiber system, providing a temporally constrained mechanism to adjust on-going behavior and modify future processing. Patients with cerebellar disorders exhibit impairments on a range of tasks that require precise timing, and recent evidence suggest that timing problems observed in other neurological conditions such as Parkinson's disease, essential tremor, and dystonia, may reflect disrupted interactions between the basal ganglia and cerebellum.

The complex concepts emerging from this consensus paper should provide a foundation for further discussion, helping identify basic research questions required to understand how the brain represents and utilizes time, as well as delineating ways in which this knowledge can help improve the lives of those with neurological conditions that disrupt this most elemental sense. The panel of experts agrees that timing control in the brain is a complex concept in whom cerebellar circuitry is deeply involved. The concept of a timing machine has now expanded to clinical disorders.

Introduction

Over the past generation, our thinking about the cerebellum has undergone a dramatic transition from an oversimplified functional view restricted to the motor system to one in which this subcortical structure is recognized as part of networks involved in virtually all aspects of cognition [1-4]. Although there had been conjectures about 'nonmotor' functions of the cerebellum over 50 years ago [5], the cerebellar cognitive revolution took off with the advent of technological advances in computational modeling, neuroimaging, and high-resolution neurophysiology. Prominent in this work has been the study of cerebellar contributions to the representation of temporal information, computations that are essential in both motor and cognitive domains. The very high number of neurons in the cerebellum with a specific anatomical arrangement and its dense connectivity with extra-cerebellar centers make of the cerebellum of unique structure which has often been compared to a computer involved in temporal aspects.

This consensus paper brings together the viewpoints of a group of established neuroscientists whose research programs cover a broad spectrum of methodological approaches to understand cerebellar function. The primary objective here is to summarize key concepts that may explain confirmed and potential roles of cerebellar circuits in timing. Breska and Ivry analyze the role of the cerebellum in the timing of isolated intervals; Lawrenson and Apps discuss the timing of climbing fiber inputs to the cerebellum and implications for their function. D'Angelo considers the regulation of spike timing and plasticity in the cerebellar network; Petter, Lusk and Meck emphasize the role of specific cerebellar structures in predictive timing and integrate this with basal ganglia function in their presentation of the Initiation, Continuation, Adjustment, and Termination (ICAT) model of temporal processing; Manto and Mitoma address cerebellar control of the timing of fast movements; Gerwig reviews the issue of timing and eyeblink conditioning with a focus on human studies. And, finally, the disruption of cerebellar processing in movement disorders with an emphasis on timing is outlined by Avanzino with respect to Parkinson's disease and dystonia, and by Filip and Louis with respect to essential tremor.

We are well aware that a final consensus cannot be made given our current understanding of this enigmatic structure. Nonetheless a broad agreement has been reached on the importance of the cerebellum in many aspects of timing. We hope that the ideas presented here will help stimulate studies of cerebellar function and its interaction with cortico-striatal timing circuits in the years to come.

The Cerebellum Represents Isolated Temporal Intervals Across Task Domains

Assaf Breska and Richard B. Ivry

It is widely accepted that the cerebellum contributes, in some manner, to temporal processing, but the functional domain and computational mechanisms remain the subject of considerable debate. An early hypothesis was that the cerebellum served as a centralized, dedicated timing system [6, 7]. Subsequent lines of research have associated timing with other brain structures, such as the basal ganglia (BG), supplementary motor area (SMA), and inferior parietal cortex [8-11], or with neural network dynamics that operate independent of specific neuroanatomical structures [12]. In order to understand cerebellar contributions to timing, and how this might differ from that of other brain structures, it is important to specify constraints on cerebellar timing, both in terms of how temporal information is represented within this system and the contexts in which this information is exploited.

Timing has been studied with a diverse set of tasks, such as eyeblink conditioning [13], duration estimation [6], and rhythmic circle drawing [14]. Given this diversity, taxonomic classifications can provide a roadmap to identify common computational principles [15]. Based on activation patterns in neuroimaging studies, Coull and Nobre [16] proposed an influential taxonomy in which timing tasks were mapped unto two dimensions. One dimension focused on whether timing was part of motor behavior or independent of movement (e.g. perceptual timing). The other, orthogonal dimension asked whether timing was explicit or implicit. Examples of explicit timing would be when the task requires an overt report of a temporal quantity or movement at a specific time; implicit timing is when temporal information facilitates performance on a non-temporal task such as is observed when making non-temporal judgments about sensory events that occur at predictable instead of random times.

The literature indicates that the cerebellum may be involved to some extent in all four sub-domains of timing within the Coull and Nobre taxonomy. The cerebellum has a central role in motor timing, as is evident from symptoms of cerebellar ataxia, such as dysmetria, dysarthria and dysdiadochokinesia. Neuropsychological [7, 17, 18] and neuroimaging [19-21] evidence implicate the cerebellum in tasks that directly measure explicit motor timing, such as reproducing an interval from working memory or producing periodic taps after a metronome is turned off. A central role for the cerebellum is observed in tasks that rely on implicit motor timing in which a movement requires anticipating a forthcoming stimulus. Examples here include eyeblink conditioning, where an adaptive conditioned response must anticipate the precise time of the unconditioned stimulus [13, 22, 23], or interception tasks [24]. However, there are notable motor tasks involving temporal regularities that do

not rely on Cerebellum. The neuropsychological and neuroimaging literatures converge in indicating minimal involvement of the cerebellum when producing cyclic movements at a constant rate [14, 25].

While a role in motor timing fits with traditional perspectives in which the cerebellum is a critical part of a network for producing coordinated movements, the extension of the functional domain of cerebellar timing to perceptual tasks has proven more contentious. Perhaps the most basic perceptual tests of explicit timing are duration comparison and discrimination tasks in which participants indicate, for example, which of two temporal intervals is longer [6]. Again, there is some degree of convergence across the neuroimaging [26, 27] and neuropsychological literature [6, 28], with the latter showing that lesions of the cerebellum increase discrimination thresholds rather than produce a distortion of time (e.g., speed up or slow down). Interestingly, a different picture emerges if the task requires explicit judgment concerning the temporal structure of rhythmic perceptual events such as whether there is deviation from isochronism. Relative to explicit timing tasks conducted on isolated intervals, performance in these rhythmic tasks is less impaired in individuals with cerebellar degeneration and associated with less cerebellar activation [29, 30].

Implicit perceptual timing is mostly associated with tasks in which performance on a non-temporal task can benefit from a context that confers some sort of temporal predictability. One example is a scenario in which a target event can be anticipated to occur at a specific moment in time relative to some preparatory cue [31, 32]. Individuals with cerebellar degeneration show reduced ability to use this temporal regularity to facilitate preparation [33]. However, in scenarios in which the perceptual events occur rhythmically, typically allowing preparatory processes to fluctuate, or synchronize with a beat structure [34, 35], imaging studies failed to find cerebellar activation [36, 37], and even find reduced activity relative to a non-isochronous control condition [37].

The above suggests that the Coull and Nobre taxonomy [16] is not sufficient for specifying the functional domain of cerebellar timing. We suggest that another dimension is required, continuity, highlighting the distinction between “event” and continuous cyclic timing. By this view, the cerebellum is essential for event timing, where temporal information is defined by isolated intervals [14, 15, 38, 39]. This constraint seems to hold independent of whether the tasks are motoric or perceptual, explicit or implicit. In contrast, across domains, the cerebellum is not necessary when temporal information is defined by dynamic, cyclic events. Timing in such contexts may rely on controlling high-level movement parameters. For continuous, repetitive movements, timing might be emergent to the control of a constant angular velocity [38] (see [15] for discussion contrasting this form of timing with that required in repetitive tapping tasks]. In other contexts, especially those in which periodic events

shape temporal expectancies, timing may arise from neural oscillations entrained by the events [40-42] or dedicated rhythm processing circuits [37, 43].

Coull and Nobre had suggested a related conceptual distinction within their implicit perceptual timing category. In their view, a distinction can be made between contexts in which timing is driven by continuous stimulus dynamics or generated from a memory representation of an isolated interval, viewing this distinction as analogous to exogenous vs endogenous forms of attentional orienting. Consistent with this hypothesis, orienting in time based on rhythmic structure or from memorized isolated intervals are associated with distinct EEG signatures [44, 45]. Moreover, as outlined here, we propose that the event vs continuous distinction may pertain across task domains of timing, and that the former will require cerebellum.

In summary, the current state of research points toward a role for the cerebellum in timing of discrete, isolated intervals, but not when temporal information is contained within continuous task dynamics. This computational distinction appears to apply for both motor and perceptual timing, as well as for implicit and explicit timing tasks. Undoubtedly, this hypothesis requires direct evaluation; for example, comparisons should be made between tasks entailing isolated intervals or continuous temporal patterns that fall within the subdomains of the Coull and Nobre taxonomy.

The Timing of Signals Forwarded to the Cerebellum Provides Clues to Climbing Fiber Function.

Charlotte L Lawrenson and Richard Apps

The cerebellum plays an important role in the control of movement, and indeed a wide range of other functions, but how it does this is still a matter of considerable debate. It receives information mainly through an array of mossy fiber and climbing fiber (CF) pathways; and the prevailing view is that the latter holds the key to understanding cerebellar operation [46]. This is emphasized by the fact that damage to the inferior olive, which gives rise to the CF system, results in motor deficits that resemble those that occur after direct cerebellar damage [47-51].

In relation to the current consensus topic, various theories have implicated the cerebellum in timing, however ‘timing’ can be considered in different ways. For this discussion, we will focus on the times during behavior when information is forwarded to the cerebellum via the CF system. If the timing of transmission of signals is regulated (gated) then this restricts when CFs can influence cerebellar operation and thus places important constraints on their function.

To date, studies of this gating phenomenon have mainly investigated the timing of transmission in spino-olivocerebellar pathways (SOCPs) that arise from the limbs. These studies are based on the principle that the CF- Purkinje cell (PC) synapse is highly secure [52], and that each PC receives only one CF in the adult cerebellum [52-54]. As a result, any changes in the size of a CF field potential evoked by peripheral stimulation will reflect changes in excitability in the associated SOCPs because it is an indirect but reliable measure of the number of local PCs that are synchronously activated by their CF input.

The results from these studies have shown that the information SOCPs convey is not continuously available but is gated during active movements. For example, in a reach to grasp movement in cats the largest evoked responses (i.e. best transmission) in SOCPs that target the paravermal cerebellar cortical C1 and C3 zones occurs when the animal is sitting quietly at rest; the same responses are smallest (i.e. least transmission) when the SOCPs occur during the grasp phase of the movement [55, 56]. For the same SOCPs there is also a systematic variation in transmission during the step cycle in the ipsilateral forelimb: by comparison to rest, increased transmission occurs during the swing phase, while reduced transmission occurs during stance [57].

The swing phase is the time during the step cycle when a limb is most likely to encounter obstacles to progression, while the stance phase is when self-generated (reafferent) sensory information is most likely to occur (e.g. because of load bearing by the limb). These results have therefore been taken to suggest that the gating (at least in SOCPs that target the paravermal C1 and C3 zones) regulates the times when behaviorally predictable and unpredictable sensory events are forwarded to the cerebellum via the CF system during active movement. In particular, a reduction in transmission during active movements is hypothesized to reflect a gating out of self-generated (predictable) reafference [55, 57-59].

This possibility has recently been tested during exploratory behavior in rats [58]. Rearing is a natural behavior of rodents which allows them to survey their local environment. During such behavior transmission of sensory signals from the ipsilateral hindlimb to the cerebellar C1 zone was found to be reduced when rearing up or down compared to when the animal was fully upright. This finding is consistent with the notion that transmission via SOCPs of self-generated sensory inputs are gated out during movement but that the same pathways are open for transmission at a time during behavior when the animal is vulnerable to predatory attack and therefore needs to be able to respond to external sensory events. In other words, the gating of transmission in SOCPs that target the C1 and C3 zones may serve to gate out the predictable (internally generated) sensory consequences of a movement, while permitting transmission of unpredictable (externally generated) sensory signals.

If this is the case, then the pattern of gating in SOCPs should be modifiable if a sensory stimulus becomes predictable. Evidence for this was shown when the hindlimb stimulation was delivered repeatedly over many consecutive trials during the upright phase of rearing (when responses would normally be evoked when the stimulus was presented unpredictably). Over time the evoked field response became progressively smaller in size i.e. transmission was reduced when the occurrence of the peripheral stimulation became predictable [58].

Returning to the question of timing, these experiments therefore provide evidence that there is a powerful regulatory system in place that determines when CFs can transmit information to Cerebellum. This in turn may reflect the times when the CF system can modify cerebellar output. For example, an external skin tap to the forelimb of a cat could lead to a near synchronous activation of CFs in the relevant forelimb-receiving territory within the cerebellar paravermis via SOCPs. The fastest conducting of these SOCPs can transmit signals from the periphery to the cerebellar cortex in approximately 11ms, indicating that they are able to rapidly update the cerebellum concerning sensory events [57, 60, 61]. Subsequent modification of cerebellar output via cortico-nucleo-rubral-spinal circuits can occur within an additional 9ms, which means the overall loop time is ~19ms. This is sufficiently rapid that an external stimulus has the potential to modify an ongoing movement, such as the swing phase of the forelimb step cycle (which lasts ~200 ms – [which lasts ~200ms, 57], via supraspinal cerebellar circuits as illustrated in Figure 1.

In summary, the modulation of movements by the cerebellum is constrained by the timing of sensory information forwarded by SOCPs. An unexpected external stimulus can be forwarded to the cerebellum via the CF system at certain times during an on-going movement when a modification of the motor output would be behaviorally useful. Evidence has shown that repetitive patterns of sensory input during a behavior can modify such patterns of transmission and this mechanism might underlie how predictable sensory inputs from self-generated signals are gated out during movements

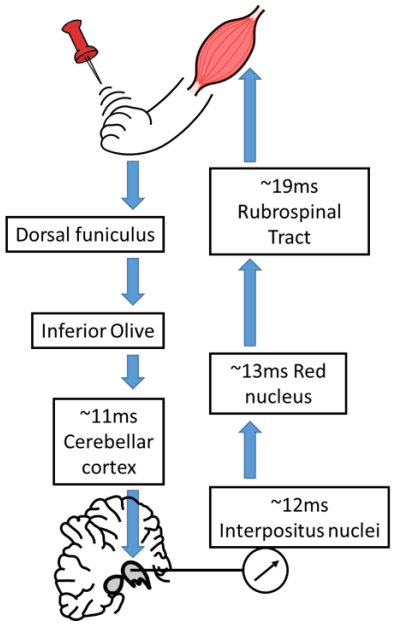

Figure 1. Following a forelimb perturbation and transmission through SOCPs, a response can be recorded in the cerebellar cortex with the fastest latency at ~11ms and nuclei beginning with a latency of ~12ms [55, 57, 61]. The interpositus-rubral projection is in the order of 1ms [62] and it takes approximately 5-6ms for the rubrospinal tract to modify an EMG response [63]. Therefore, the time it takes for the motor output from a sensory innervation to be modified is in the order of around 19ms.

Spike Timing and Synaptic Plasticity in the Cerebellum as the Basis of Temporal Processing

Egidio D'Angelo

Two seminal theories presented in the late 60s maintained that the cerebellum could operate either as a "timing machine" or a "learning machine" [64, 65]. While their formulation emphasized an apparent duality of function, a unifying interpretation is that the cerebellum is required to *learn* how to *predict* precise *timing* in a sequence of events, which can be either sensory stimuli, motor commands, or even logical elements in abstract reasoning [66]. Recently, the relationship between *timing and learning* has been brought down to the investigation of *spike timing and synaptic plasticity,* suggesting that these fundamental cerebellar functions are indeed tightly interconnected at the level of cellular and microcircuit mechanisms [67-69].

High-precision regulation of spike timing and plasticity in the cerebellar granular layer

Converging evidence suggests that, while well timed spike patterns eventually need to be emitted by neurons in the deep cerebellar nuclei, a privileged role in temporal processing is played by the cerebellar cortex, and in particular, by granule cells. These neurons are normally silent at rest and respond with short spike bursts when activated by mossy fiber inputs [70, 71]. Indeed, at least half of the information passing across the mossy fiber – granule cell relay is carried by the time to first spike, while the rest is carried by the number of spikes in the bursts [72, 73]. Experimental and modeling analysis has revealed that the emission time of granule cell spikes can be precisely tuned over a doubly fast and slow time-band through specific properties of ionic channels, synaptic receptors and neurotransmitter release, as well as of microcircuit wiring.

In granule cells, a K inward rectifier helps stabilizing resting membrane potential at a negative level, preventing generation of spurious spikes. This raises the signal to noise ratio and allows retransmission of salient spike sequences organized in bursts by exploiting synaptic integration and temporal summation [74-77].

The spike initiation mechanism of granule cells exploits specific properties of Na channels in order to allow rapid action potential generation in the axonal initial segment [78, 79]. The spikes invade the ascending granule cell axon in less than 0.1 ms and back-propagate into the dendrites in less than 0.3 ms [80]. This ensures almost instantaneous activation of the overlaying Purkinje cells [81] and sub-millisecond precise coincidence detection in granule cell dendrites. An A-current can delay the first spike by tens of milliseconds [82]. On a slower time scale, an M-like current tunes spike generation on the theta-band favoring the entrainment of granule cells in ensemble oscillations [74, 76]. In addition to regulating the number of emitted spikes, neurotransmitter release probability at the mossy fiber –

granule cell synapses can change the first spike delay by acting on EPSP temporal summation through changes in short-term facilitation and depression. Interestingly, release probability is specifically regulated by long-term synaptic plasticity, so that its increase during LTP minimizes first-spike delay, while its decrease during LTD protracts first-spike delay [75] see below).

Excitatory neurotransmission from mossy fibers is mediated by AMPA and NMDA glutamate receptors. Granule cell AMPA receptor-mediated currents are the fastest in the brain, ensuring sub-millisecond precision to spike initiation [83]. This mechanism integrates with that provided by the much slower NMDA receptor-mediated current, which operates on the 10-100 ms time window [70, 83] and is instrumental to the induction of synaptic plasticity through the regulation of calcium influx [84].

Inhibitory neurotransmission from Golgi cells is mediated by α1 and α 6 GABA-A receptors. Inhibitory neurotransmission, in addition to controlling first spike delay and burst duration, can increase their precision. The overall impact of α6 is larger than that of α1 subunit-containing receptors. However, α1-receptors-controlled granule cell responses in a narrow ±10 ms band while α6 receptors showed broader ±50 ms tuning [85, 86]. Therefore, like the excitatory system, also the inhibitory system is organized to operate on a double time band.

The granular layer is organized to feed well-timed Golgi cells inhibition onto granule cells [87] through the mechanisms reported above. Golgi cells show intrinsic pace-making in the theta band and, when an input comes, show phase-resetting. As such, these neurons may play a critical role for timing of discrete, isolated intervals as described above by Breska and Ivry. Moreover, specific delay lines can be generated by unipolar brush cells (UBCs) [88], which in rodents are almost exclusively present in the vestibulo-cerebellum [89]. UBCs can generate late-onset responses, in which the delay of spike emission is precisely regulated by H- and TRP-currents depending on the intensity and duration of mossy fiber activity.

These observations identify the granule cells as a pivotal point for spike-time control in the cerebellum, which is regulated on a double time-band. It can be anticipated that the mechanisms operating on the 1-ms band are critical for plasticity expression, while the mechanisms operating on the 100-ms (theta) band are critical for plasticity induction. Indeed, a recent form of spike-timing dependent plasticity (STDP) has been reported, whose induction exploits a dynamic range centered over the theta band and whose expression is sensitive to the relative phase of granule cell spikes and mossy fiber EPSCs with 1-ms precision [90]. A theoretical study actually predicts that STDP is the core mechanism for rapid memory acquisition in the cerebellum granular layer [91].

Spike timing and plasticity in the other regions of the cerebellar network.

While granule cells are silent at rest, all of the other cerebellar neurons act as pacemakers, including the principal neurons along the main retransmission line (Purkinje cells and deep cerebellar nuclei cells) and the inhibitory interneurons (Golgi cells and stellate cells) (for review see [92]). These neurons are likely to exploit different strategies for spike timing based on burst-pause responses [93]. Precise sequences of excitatory and inhibitory synaptic transmission have been suggested to govern plasticity in deep cerebellar nuclei and coincidence detection between complex spikes and simple spikes is required in Purkinje cells. However, both of these mechanism span over a 100 ms range. Therefore, precise timing may be first acquired in the granular layer and then be maintained and propagated through the rest of the network.

A summary view and Implications for neuropathology

In summary, the cerebellar granular layer appears especially suitable to carry out the timing operations required to confer millisecond precision to cerebellum computations. Oscillations and resonance in the theta band [94] may provide the clock that allows plasticity to be deposited through STDP rules during learning.

The is compelling evidence that the ability of the cerebellum to learn the precise timing of actions can be altered in several instances. For example, patients with cerebellar ataxia are unable to predict the precise timing and gain of elementary motor acts in a sequence [95] generating symptoms such as dysmetria, dysarthria and dysdiadochokinesia. Experimentally, learning the precise gain and timing of actions can be altered by TMS in paradigmatic tests such as eyeblink classical conditioning (EBCC) [96, 97], vestibulo-ocular reflex (VOR) [98] and saccades [99]. In mice, timing can be altered by specific knock out of genes involved in granular layer mechanisms. It can therefore be envisaged that specific interventions to these mechanisms could reestablish timing and learning in Cerebellum.

An Integrated Role for the Cerebellum in Predictive Timing

Elijah A. Petter, Nicholas A. Lusk, and Warren H. Meck

Predictive timing requires a subject to learn the temporal relations among stimuli in order to perform anticipatory responses at correct times. A classic example of this is eyeblink conditioning, in which an auditory or visual conditioned stimulus (CS) predicts a future unconditioned stimulus (US) usually in the form of a periocular air puff. In order to avoid an aversive air puff, the subject must learn the temporal contingency between the two stimuli, closing their eyelid just prior to (US). While the cerebellum's contributions to timing and time perception have primarily been studied in relation to its role in timing in the milliseconds (ms) range [100-102], a number of experiments have provided evidence for a more

integrative role spanning multiple seconds [103]. This research traces the role of the cerebellum from projection neurons of the cerebellar cortex, through the dentate nucleus, and into thalamo-cortical-striatal circuits [104, 105]. As a consequence, the cerebellum may not be limited to timing sub-second durations but may in fact play an important role in the timing of discrete intervals in the millisecond-to-minutes range [15, 106].

Purkinje Cells

The principal cell type in the cerebellar cortex is the Purkinje cell (PC). PCs are thought to play a key role in predicting the US. Moreover, as early findings identified dissociable contributions of the medial and lateral cerebellar cortex to motor execution and motor timing respectively [107], studies on predictive timing have focused largely on PCs within the lateral cerebellar cortex. This temporal prediction comes in the form of adaptively timed pauses in simple spiking activity, which are learned from repeated pairings of the CS and US. Further, these responses are shown to be capable to elicit motor output through the use of optogenetics in head-fixed mice [108]. Recent work suggests that these cells do not just receive temporal information from an upstream circuit, but rather, the timed responses of the cerebellum may be intrinsic to PCs (e.g., [22, 109, 110]. This body of evidence demonstrates that after extensive training the responses of PCs can be elicited without a temporally coded input. Specifically, neither the length of the CS, nor circuit mechanisms are required for the pause in PC simple spiking. Taken together, this work suggests that there is an intrinsic memory component in the PCs that is capable of storing adaptive timing information important for associative learning [111, 112].

Deep Cerebellar Nuclei

The temporal information stored in PCs is sent downstream to the deep cerebellar nuclei. As PCs are GABAergic, these pauses in the PC activity cause disinhibition of downstream nuclei. Electrophysiological recordings within the dentate nucleus (DN), the most lateral portion of the deep cerebellar nuclei, have shown increased activity (i.e., ramping) to temporally regular stimuli presentations [113]. Additionally, when an expected stimulus is omitted or deviates temporally from the expectation, the increasing pattern of neural activity is disrupted.

Correlations between ramping in neural activity and saccade times have been demonstrated in neurons of the DN of non-human primates during a task involving self-timed saccades [114]. The ramping up of neuronal firing in the DN was observed to span both sub- and supra-second durations (400 – 2400 ms) though its contribution to timing behavior seems to differ between the two duration

ranges. Single-trial analysis found that ramping activity began shortly after cue onset and that saccade time correlated well with the slope of activity for delays of 400-1200 ms. In contrast, ramping activity for the 2400 ms delay started late in the interval with its onset time being correlated with self-timed saccade latency. This second finding suggests that the cerebellum may not be actively involved in tracking supra-second durations but may play an important role in the adjustment or tuning of predictive responses. Human patient studies have bolstered the specificity of the cerebellum in predictive timing, with deficits in anticipatory motor responses observed in spinocerebellar ataxia type 6 patients [115] as well as preferential activation of the cerebellum during predictive timing tasks compared to a reproduction task in healthy adults [116]. Similar timing deficits have also been displayed in cerebellar lesioned rodents [117].

The observation of the cerebellum's involvement in the timing of both sub- and supra-second durations aligns well with the recently proposed Initiation, Continuation, Adjustment, and Termination (ICAT) model of temporal processing [118]. As illustrated in Figure 2, the ICAT model accounts for interactions between the cerebellum and striatum during distinct phases of temporal processing across sub-second and supra-second durations. The neural architecture of the cerebellum makes it well-suited for mediating the *initiation* and *adjustment* phases of the timing model with its strongest influence occurring during the acquisition of timed response sequences. The ICAT model also proposes that the cerebellum is primarily responsible for automatic timing processes that underlie reflexive behaviors [119]. In contrast, cortico-thalamo-striatal (CTS) circuits provide controlled flexibility in support of the *continuation* mechanisms for interval timing. Moreover, this model fits quite well with the clinical observations of deficits in movement control and time estimation related to a variety of cerebellar disorders (e.g., [24, 120-124].

Adjustment of Downstream Circuits

Projections from the deep cerebellar nuclei have also been shown to play an important role in adjusting other timing circuits. These studies generally focus on the dentate nucleus, or the homologous lateral cerebellar nucleus (LCN) in rodents. In one study, efferents from the LCN were found to form disynaptic connections, via the thalamus, to other major timing loci such as the medial frontal cortex and basal ganglia [125]. Enhancement of LCN signaling to the medial frontal cortex by optogenetic stimulation of terminals within the thalamus increased precision on a supra-second predictive timing task in a rodent model of schizophrenia, as well as reinstated normal extracellular activity patterns [126].

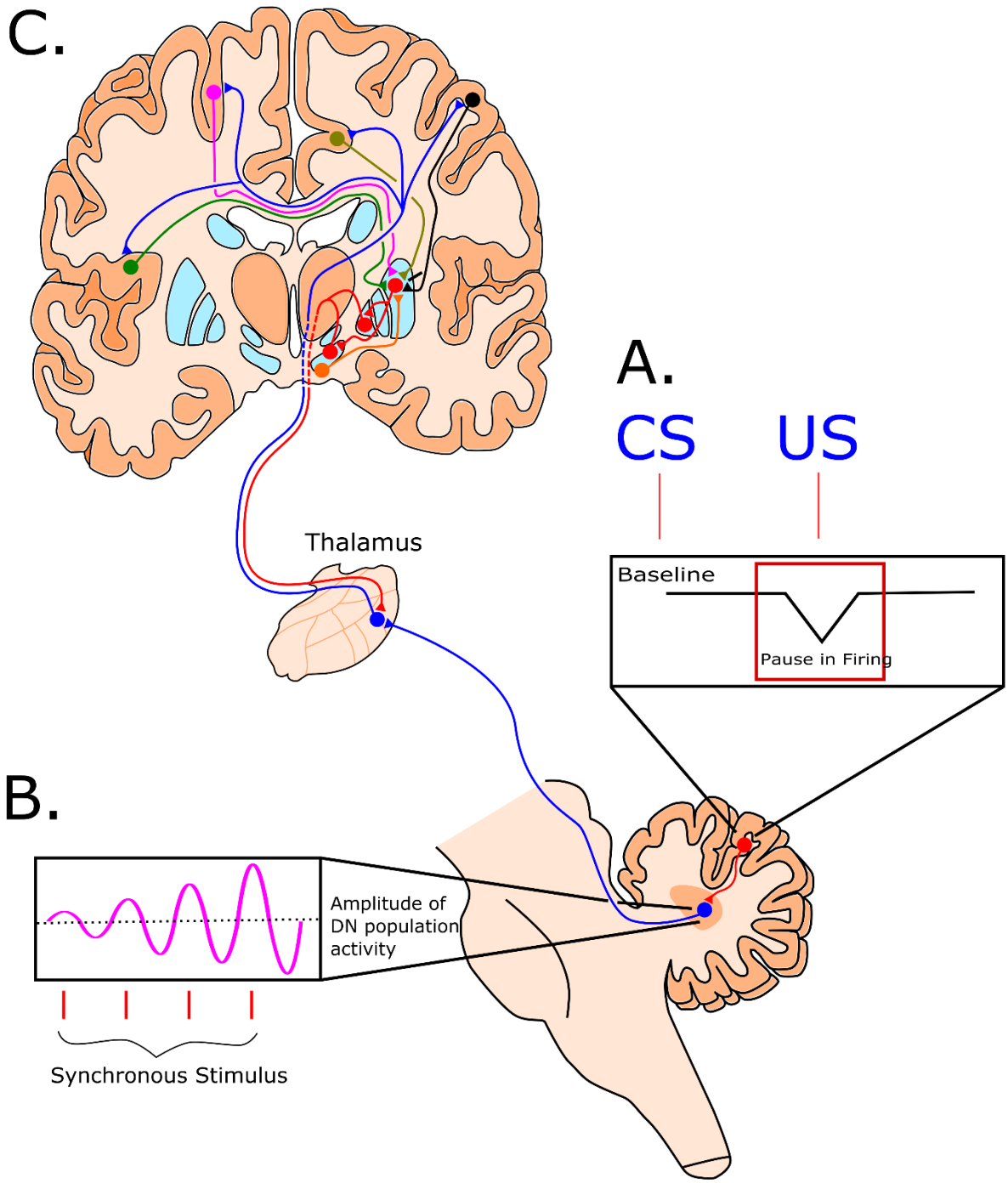

Figure 2. The cerebellum's contribution to temporal processing. The traditional role of the cerebellum in temporal processing has been studied through eye blink conditioning. This preparation involves a conditioned stimulus (CS) such as a tone, that predicts an unconditioned stimulus (US) such as an aversive air puff (A). Cerebellar Purkinje cells learn to pause their activity during the US in order to elicit an adaptively timed blink response. These pauses in Purkinje cell activity modulate the activity of neurons in the dentate nucleus of Cerebellum. This activity increases during timing tasks (B). This activity from the dentate nucleus then travels to the thalamus which can help initiate temporal processing in cortical-striatal circuits (C). Adapted from [120].

Computational Properties of the Cerebellum

The biology of the cerebellum, including cell types and circuit architecture, has been extensively studied and the resulting information has allowed researchers to model and investigate the computational nature of Cerebellum. This has led to the observation that there are numerous connections that can provide 'teaching signals' (e.g., climbing fibers – [127], as well as 'reciprocal connections' (e.g., PC to PC, or PC to interneuron – [128]) which are likely to play an important role in the dynamics of temporal processing within Cerebellum. Moreover, microzones have been identified in the cerebellum, which are regions that form the basic computational unit of the cerebellum [129], and it is these inputs and outputs that dictate the influence that these microzones have on timing and time perception (e.g., motor versus perceptual timing).

Computer simulations of the cerebellum suggest that this structure is ideal for the implementation of supervised, or even sequential supervised learning (SL), but performs poorly in reinforcement learning (RL – [130]. In these simulations, the difference between RL and SL is defined by the size of the delay between a required action and the error signal. RL is able to survive relatively long delays, whereas SL begins to fall apart with any delay. Moreover, the cerebellum does well when the required action overlaps with the error signal (i.e., from the climbing fiber), and the prediction of the response ranges from 100 ms to 1500 ms. The range of delays over which learning can occur seem to be contingent upon the timing between granule cell input to PCs and the 'teaching signal' coming from climbing fibers. Interestingly, while simulations of the cerebellum are capable of learning sequential patterns, the learning is agnostic to the order of the sequence [130]. Therefore, timing in the cerebellum may be more cumulative, rather than identifying unique temporal patterns.

Conclusions

While the cerebellum has traditionally been studied in isolation, such as in decerebrate preparations, it is gaining traction as a structure that adjusts processing in much of the brain. Accumulating evidence suggests that adaptive timing responses of PCs are sufficient for timing sub-second durations but rely on feedback from additional cortical and basal ganglia networks for timing supra-second durations. The temporal information supplied to the cerebellum for these longer durations is then sent back allowing for adjustments of cortical and subcortical circuits. Thus, the cerebellum should not be viewed as simply a sub-second motor timing network, but a component of a unified timing network spanning sub- as well as supra-second timing. Moving forward it is essential to study the cerebellum's role in both action timing and cognitive function, within the context of a larger integrated network (e.g., [100, 124, 131].

The role of the cerebellum in the control of timing of fast movements

Mario Manto, Hiroshi Mitoma

Fast, single-joint voluntary movements have been widely used to determine the physiological rules governing the velocity and accuracy of movements, both in monkeys and in humans [132, 133]. This is particularly relevant for the pathogenesis of cerebellar disorders because motor dysmetria is a cardinal feature of cerebellar ataxias [134]. Cerebellar dysmetria is particularly prominent for fast voluntary movements [135]. The most common form of dysmetria is hypermetria (overshoot of the target). Hypometria (undershoot) designates a premature arrest before the target [136] and is the prominent feature in some patients.

In humans, fast single-joint movements are characterized by a first agonist EMG burst (generating the acceleratory pulse), followed by a second burst in the antagonist muscle (providing the decelerator pulse), followed by a second burst in the agonist muscle (to reach the aimed target with accuracy) [137, 138]. The duration of first agonist burst is scaled according to the amplitude of the movement [139]. Learning of fast movements is associated with kinematic changes. During motor learning in healthy subjects, the first parameter which changes is reaction time, reaching quickly a steady baseline [140]. Time-related parameters (duration of acceleration, duration of deceleration, and movement duration) decrease at a slower rate.

A major defect in the timing of agonist-antagonist bursts has been unambiguously demonstrated in the monkey by cooling the dentate nucleus during the execution of a fast goal-directed movement [133, 141]. Physiologically, fast elbow flexions in monkeys show single-peaked velocities and a bi-/triphasic EMG pattern in the couple agonist/antagonist muscle. During the cooling of the dentate nucleus, movements become ataxic with a terminal tremor. The analysis of the kinematic profiles shows that the magnitude of the acceleration drops, whereas the magnitude of the deceleration increases. The agonist burst has a decreased rate of rise, is smaller in magnitude and shows a prolongation in the duration of the burst. Slowness of movements is one of the clinical features in human cerebellar ataxias and is presumed to be due to a defect in the recruitment of alpha-motoneurons as a consequence of an increased inhibition in the motor cortex [142, 143]. A major finding of cerebellar hypermetria observed in monkeys is the delayed onset latency of the antagonist EMG burst. Identical observations have been made in humans in various cerebellar ataxias [144, 145]. Calcium channels in the cerebellum are involved in the control of the timing of agonist/antagonist discharges as shown by the model of hyperventilation in spinocerebellar ataxia type 6 (SCA6) [146]. The defect in the rate of rise of the EMG burst is not restricted to the agonist EMG burst, but can affect also the antagonist EMG burst [147]. Human cerebellar hypometria is associated with two concomitant mechanisms contributing

to the undershoot: the prolongation of the duration of the antagonist EMG activity and a reduction in the intensity of the agonist EMG activity.

The antagonistic muscle discharges are centrally generated and not simply produced by stretch reflexes, since (1) they occur at or even before movement onset, and (2) they are preserved in deafferentiated patients [148]. Impairments in the second EMG burst might be the result of impaired predictive control. The predictive nature is observed clearly in a task using external loads. The impaired timing of the antagonist EMG burst is sensitive to the inertia of the moving limb in the case of cerebellar dysfunction from acute cerebellar intoxication: adding a mass increases the delay of the antagonist burst [149]. This inability to adapt to unexpected changes of the mechanical state of the limb fits with the current prevailing hypothesis of a key role for the cerebellum in sensorimotor prediction. The cerebellum would estimate and predict the movement dynamics of the body and inform the cerebral cortex in particular via the dentato-thalamo-cortical circuit [150]. The difficulties of cerebellar patients to adapt to changes in the damping of the joints also argue for such a predictive role [151].

There is hope that transcranial DC stimulation (tDCS) may enter in the therapeutic options (including for rehabilitative approaches) for cerebellar ataxias in the coming years. tDCS can modulate activity in the dentato-thalamo-cortical circuit. For example, activation of inhibitory Purkinje cells results in attenuation of cerebellar facilitation through the nuclear efferent pathways. This mechanism is called cerebellum-brain inhibition (CBI). Application of tDCS over the cerebellum is associated with an improvement of ataxia scores and CBI in cerebellar patients [152]. A favorable effect on the timing of agonist/antagonist bursts has been reported with transcranial cerebello-cerebral DC stimulation (tCCDCS) in SCA2 [153]. However, these results need to be confirmed in a large sample of patients and a consensus is missing on the parameters of stimulation that need to be used. Another option which remains to be explored is the use of electrical stimulation to assist the antagonist muscle and modify the relative timing of agonist/antagonist bursts [154].

The cerebellum is also a key-player for the precise timing of fast multi-joint movements. A typical demonstration comes from the study of finger opening in overarm throwing. Using this paradigm, it has been demonstrated that cerebellar patients throw slowly with inaccuracy, show enhanced variability in hand trajectories, and exhibit an increased variability in the timing, amplitude, and velocity of finger opening [155]. Finger opening times and ball release times are markedly impaired in ataxic patients. The lack of coordination between proximal joint rotations and timing of finger opening contributes to the dysmetria of throws [156]. Reduction in joint velocities and in joint accelerations/decelerations are associated with an inability to exploit interaction torques [157]. When the emphasis is put on both speed and accuracy, cerebellar patients produce inappropriate muscle torques relative to the dynamic interaction torques, a factor contributing to the incoordination of the elbow and shoulder resulting in curved trajectories and target overshoot [158].

Overall, the detailed kinematic and EMG analysis of fast single-joint movements has demonstrated that the cerebellum plays a major role in the control of the timing parameters underlying the triphasic pattern of muscle discharges. Hyper- and hypometria can be attributed partially to an impairment in the predictive timing of the agonist/antagonist muscle activities. Timing is also a critical factor under cerebellar control for fast goal directed multi-joint movements.

Timing and Eyeblink Conditioning: Evidence from Studies in Humans

Marcus Gerwig

As indicated above, animal models have elucidated in great detail the role of the cerebellum in eyeblink conditioning, an established model of associative learning. Findings in humans, mainly using delay eyeblink conditioning, are in very good agreement with those in animals [23, 159]. Patients with either cerebellar degeneration or focal cerebellar disorders are impaired in their ability to acquire classically conditioned eyeblink responses (CRs) [160-163]. By using high-resolution magnetic resonance imaging (MRI) in healthy subjects a significant correlation between cerebellar volume and the ability to acquire CRs was reported [164]. This was significantly related to the volume of the posterior lobe including lobule VI [165]. In patients with focal cerebellar lesions, eyeblink conditioning was significantly reduced in subjects with lesions including lobule Crus I and above [163]. Again, voxel-based lesion-symptom mapping (VLSM) analysis as well as functional MRI studies revealed a particular association between hemispheric lobule VI in the acquisition of CRs [166-169]. Animal experiments show that the interposed nuclei, but not the dentate or fastigial nuclei, are critically involved in the acquisition of CRs [170]. Human data are sparse because human lesion models with circumscribed affection of the cerebellar nuclei are lacking [171].

In eyeblink conditioning a basic aspect centers on the exact timing of CRs. Evidence that the human cerebellum may be involved in CR timing comes from dual-task studies [6] showing a selective interference between timed-interval tapping and delay eyeblink conditioning in healthy subjects [172, 173]. As already reported in early behavioral studies [174, 175] CR timing is important for the acquisition of CRs in healthy human subjects. After repeated presentation of the paired CS and US, subjects learn to lower the eyelid with a high temporal precision reaching the maximum amplitude close to the time of the US onset so that the eye is closed when the air puff arrives. The peak eyelid closure occurs independent of the CS-US interval. If the interval between conditioned and US is prolonged, the CR is delivered adaptively timed [176].

Disrupted CR timing has been found in patients with cerebellar disorders [166]. Compared to healthy controls, CRs occur significantly earlier in subjects with cerebellar cortical degeneration and with lesions of superior parts of the cerebellar hemisphere. In the rabbit, short fixed CR onset latencies

have been shown following large cortical lesions which involved the anterior lobe [13, 177]. Corresponding to these animal findings, VLSM analysis in focal cerebellar patients revealed that both CR onset and peak time was significantly earlier in subjects with cortical lesions including parts of the ipsilateral anterior lobe, in particular hemispheric lobule V [166]. However, findings need to be validated in larger groups of patients. Disordered timing with significantly earlier peak time CR latencies has also been reported in alcoholic patients and in abstinent chronic alcoholics in whom cortical degeneration of the anterior cerebellar lobe is to be expected [176]. Results suggest that cortical areas of the superior cerebellum may be involved in timing of conditioned eyeblink responses in humans. These areas appear to be separated from those that are most important for the CS-US association, in particular lobule HVI.

Animal studies have investigated the timing of conditioned eyeblink responses from the behavioral to the molecular level. It has been suggested that appropriate CR timing depends on the cerebellar cortex of the anterior lobe [178], whereas others argue that changes in CR timing may equally be explained by extracerebellar premotorneuronal disinhibition [179]. Recent data suggest that Purkinje cells appear to be equipped with an intrinsic cellular mechanism creating a memory of the time between the CS and US independent of external time codes showing that the cerebellar cortex itself learns to emit adaptively timed movements [101, 108].

In contrast to findings of shortened latencies, two previous human lesion studies reported a tendency of CRs to be delayed [161, 162]. However, while in animal studies lesions are applied to distinct structures in previously trained subjects, findings in humans are based on the remaining CRs in subjects with cerebellar diseases and primarily reduced CR acquisition. It has to be noted that the above human studies differed due to CR analysis in paired or unpaired trials, extent of lesions and additional damage of cerebellar nuclei.

Acquisition and timing of conditioned responses is impaired even after multiple sessions of conditioning [180, 181]. Neither degenerative nor focal cerebellar patients showed a significant increase of CRs across training sessions within three days. Disordered timing with shortened CR onset and peak time latencies was most marked in the degenerative group with no improvement across sessions. In patients with focal lesions CR timing deficits improved to normal values from the first to the third day as compared to healthy controls. A possible explanation is that the cortex of the anterior lobe was not affected in the majority of focal patients. Conclusions on CR timing, however, are limited because of the reduced number of CRs in particular in the degenerative patients.

The simple application and good agreement between animal and human studies suggest a direct comparison of cerebellar dysfunction in animal models of cerebellar disease and the corresponding human patient’s populations. For example, there are increasing numbers of mouse models of hereditary cerebellar disease. Furthermore, eyeblink conditioning was shown helpful to detect cerebellar

dysfunction even in a subclinical extent in various diseases. Impaired CR acquisition has been interpreted as evidence of a cerebellar contribution to essential tremor [182], dystonia [183], fragile X syndrome [184], migraine [185] and neuropsychiatric disorders including autism, schizophrenia, dyslexia, attention-deficit hyperactivity disorder (ADHD) [186, 187]. Corresponding to animal data the most robust marker of impaired eyeblink conditioning is reduced or abolished CR acquisition [188, 189]. Compared to controls, patients with schizophrenia showed fewer CR incidences and longer CR onset latencies while shifting of the interstimulus interval did not influence CR rates in both groups [190]. Reduced CR incidences are not always accompanied by disordered CR timing and patterns of impairment may differ. Also, in patients with essential tremor and in patients with migraine CR timing deficits were not reported [182, 185]. In children with ADHD, CRs occurred significantly earlier in a long interstimulus interval compared to controls [187]. Findings are in accordance with an animal model of ADHD [191] showing shortened latencies of CRs. As suggested in cerebellar lesion studies, the acquisition and timing of CRs depends on different areas within the cerebellar cortex which may be variably involved in the pathology of various diseases.

Beyond cerebellar lesion and imaging studies, transcranial direct current stimulation (tDCS) has been used in healthy subjects to assess whether acquisition and timing of conditioned eyeblink responses is modulated by this form of noninvasive stimulation. The main findings of a first study on CR acquisition showed a polarity specific effect, with significant enhancement following anodal tDCS and significant attenuation following cathodal stimulation compared to sham [192]. Moreover, during anodal tDCS, CR onset occurred increasingly earlier, with the mean onset of responses shifted closer to CS onset. In the cathodal stimulated subjects, CR onset appeared to be delayed but CRs were markedly less; thus, clear conclusions on timing data during cathodal stimulation could not be drawn. However, the shifting of the initiation of the CR closer to CS onset during anodal stimulation does not mean that the timing is less adaptive. Earlier studies report that the first CRs were initiated just before the US, but then CR initiation rapidly shifted to progressively earlier portions of the CS-US interval [175, 193]. However, a follow-up study did not reveal clear polarity dependent effects of cerebellar tDCS on CR acquisition and timing as previously described [194]. It is poorly understood why cerebellar tDCS effects on eyeblink conditioning are largely variable. Thresholds and current flow based on individual anatomy may play a role. Furthermore, individual variation in transmitter levels or genetic polymorphisms may also be relevant as recently shown for brain derived neurotrophic factor (BDNF) [195, 196].

In conclusion, disturbed timing of conditioned eyeblink responses has been reported in various studies investigating patients with cerebellar disorders and other neurological diseases. Future studies using eyeblink conditioning models in humans may help to better understand the role of timing in associative motor learning.

Timing in movement disorders (Parkinson's disease and Dystonia)

Laura Avanzino

Since some years ago, the basal ganglia and cerebellum were viewed as non-interacting neural structures, both involved in motor control, but the former more at a level of ideation and planning whereas the second more in coordination. Nowadays this view is recognized as too simplistic. Recent evidence showed anatomical bilateral connections between the two structures in animal models [197-199] and in humans by means of MRI [200, 201]. Thus, a functional connectivity in a variety of tasks, from sensory processing to motor control to cognitive functions has been hypothesized. In particular, this concept has been expanded to physiology of the processing of timing information and indeed evidence suggests that both basal ganglia and cerebellum are involved in this process [202-204].

Translating to the clinic, movement disorders that were previously ascribed to basal ganglia are now recognized as system-level or network disorders [205-207]. I will first discuss Parkinson's disease (PD), a neurodegenerative disorder characterized by motor dysfunctions including, among others, tremor, bradykinesia, rigidity as well as non-motor functions. PD dysfunctions were thought to result primarily from degeneration of dopamine-producing cells in the substantia nigra pars compacta, an area in the midbrain mainly targeting the striatum, the input nucleus of the basal ganglia. However, evidence collected in the last years showed that the cerebellum has structural and functional modulations in PD patients [208] that may contribute to clinical symptoms of PD like tremor [209] or impairment in dual task performance [210]. A similar picture is emerging in studies of dystonia, a movement disorder that is characterized by involuntary muscle contraction, abnormal movements and posture. Traditionally, dystonia has been considered a disorder of the basal ganglia. However, recent evidence points to a pathophysiological role of the cerebellum [211, 212].

Here we will summarize the most striking evidence related to timing abnormalities in PD and dystonia and we will discuss a possible pathophysiological role of cerebellum in these abnormalities. An important question remains concerning whether the cerebellar links to these disorders is (i) primary, arising from neurodegenerative/dysfunction process; (ii) secondary, reflecting an abnormal drive from the malfunctioning basal ganglia or (iii) compensatory due to basal ganglia dysfunction.

Parkinson's disease

In PD, abnormal timing performance is already evidenced in one of the main clinical characteristics, the impaired sequencing of motor action. Bradykinesia (slowness of movement initiation and execution) is particularly evident for internally generated sequential movements [213, 214] and commonly occurs in gait [215, 216]. Furthermore, a large amount of experimental evidence demonstrates that PD patients

are impaired in a variety of timing tasks, ranging from perceptual to production timing abnormalities and from implicit to explicit timing tasks (for a review see [217].

Starting from explicit timing tasks, by means of the synchronization or the synchronization-continuation paradigms, several studies have shown abnormalities in finger tapping in PD even during the planning phase of movement [218], that become even more striking during execution [219-222]. Altogether, the continuation phase highlighted major differences between PD patients and controls likely reflecting the difficulties of PD subjects with internally generated movements.

Neuroimaging studies supported a possible role of the cerebellum in timing abnormalities in PD. Elsinger and co-workers reported decreased activation within the sensorimotor cortex, cerebellum, and medial premotor system in PD patients off-levodopa compared to controls during paced finger tapping that was partially “normalized” by dopaminergic therapy [223]. Differently, in a group of PD patients off-levodopa, enhanced activation of the cerebellum and of the supplementary motor area was shown with fMRI [224] and PET [225] during a synchronization-continuation finger-tapping task. Further, Jahanshahi and coworkers [225] showed that cortical activation was significantly more predominant when patients where in the on-medication state, whereas cerebellar activations were higher in the off-medication state. All these findings are highly heterogeneous and currently do not help in discerning the role of cerebellum in timing abnormalities in PD.

However, interesting hints come from predictive timing studies. Predictive timing refers to those tasks when temporal information is processed to predict the outcome of self-executed or externally driven movements in an implicit fashion [16]. Cerebellar pathways seem to be largely involved in predictive timing. Indeed, when temporal information inherent to the spatial-temporal trajectory of a dynamic visual stimulus was used to predict its final position, fMRI studies revealed activation in different cortical areas [226, 227], and in the cerebellum [228, 229].

In a set of important studies, Bares and co-workers showed that, unlike patients with cerebellar ataxia and essential tremor, patients with PD do not exhibit impaired motor timing during a task requiring the interception of a moving target [24, 120, 121]. However, the same authors showed subtle differences between PD patients in an early-stage disease and in an off-medication state and healthy controls [230]. Indeed, PD patients had trouble postponing their actions until the right moment and adapting from one trial to the next after these failures. Task performance was accompanied by fMRI activations in both the basal ganglia and cerebellum in controls, with cerebellum associated exclusively with postponement of action until the right moment, and both basal ganglia and cerebellum needed for performance adaptation. PD patients showed a “hypoactivation” in cerebellum and striatum relative to controls [230]. Further, by using dynamic casual modelling to investigate effective connectivity between

supplementary motor area, basal ganglia and cerebellum during the same interceptive task, different connectivity patterns were observed between the PD patients and controls [231].

Dystonia

Timing has been assessed in task-specific forms of dystonia, generated by movements like musical playing or writing and in non-task-specific forms of dystonia [204]. Kinematic analyses of scales or finger tapping performed on a digital piano by pianists with dystonia showed inaccuracies in tone and interval duration and rhythmic inconsistency [232, 233]. However, some measures improved with botulinum toxin therapy, supporting the idea that abnormal performance may represent a consequence of the motor overflow during musical performance [233, 234]. Furthermore, explicit timing performance in these patients appeared similar to controls [235], suggesting that processing of temporal properties while performing timed movements may be preserved in dystonia.

Related to predictive motor timing, Avanzino and co-workers [236] showed that the cerebellum is engaged when temporal information is used to predict the temporal outcome of a motor act. The authors developed an *ad hoc* task in which participants were required to observe a movement in a video and predict the end of the same movement. Crucially, a few seconds after its onset, the video was darkened for a given time interval; thus the task could only be performed by extrapolating time-related features of observed motion sequence. When lateral cerebellar activity was inhibited with 1Hz-repetitive transcranial magnetic stimulation, a deterioration of timing performance selectively for the estimation of a movement involving a body segment (handwriting) and not an inanimate object was observed [206]. The same task was applied in patients with focal dystonia [237, 238]. Patients with either task-specific (writer's cramp) [237] or non-task-specific (cervical) dystonia [238] were less accurate in predicting the temporal outcome of a visually perceived movement, and this was observed for human body, but not inanimate object motion.

In another paradigm, it has been shown that cervical dystonia patients were impaired in predictive motor timing when they were asked to mediate the interception of a moving target [123]. Interestingly, through functional MRI imaging techniques, the same authors showed cerebellar hypo-activity and connectivity with the basal ganglia and the motor cortex during this task performance in cervical dystonia patients [239]. Taken together, such deficits may be linked to an abnormal internal model of motor commands reflecting dysfunction of cerebellar outflow pathways. Consistent with this hypothesis, Avanzino and co-workers have recently demonstrated deficits in anticipatory movement control in patients with cervical dystonia [240]. The term 'anticipatory' indicates the feed-forward portion of a movement that is planned in advance and relies on the internal model of motor act. Interestingly, the results showed that abnormal anticipatory control was observed only in a subgroup of patients with

cervical dystonia who presented with tremor in the dystonic or not dystonic body parts, thus suggesting that the cerebellum might play a specific role in the occurrence of dystonic tremor. This hypothesis requires further study.

In summary, there is broad evidence that timing properties are impaired in patients with PD and dystonia, and that cerebellum may be involved in these abnormalities. To date, these findings do not help in discerning between the “primary”, “secondary”, or “compensatory” hypothesis related to the role of cerebellum. Future studies are needed to better define the contribution of cerebellum with the aim of improving the therapeutic approaches for these conditions.

Timing in Movement Disorders: Essential Tremor

Pavel Filip, Elan D. Louis

Essential tremor (ET) is one of the most common movement disorders. Its hallmark feature is slowly progressive kinetic tremor [241], predominantly in the forearms and hands, which often spread to other body regions [242, 243]. The pathophysiological mechanisms of ET are not completely understood. While simple models of single centers or individual loops do not provide feasible explanations consistent with the clinical expression of the disease, including its non-motor aspects [244], converging evidence from imaging [245], animal model [246], clinical [247], physiological [248] and neuropathological studies [249] implicates defects in a complex network encompassing a significant part of the motor system, mainly the oscillatory system involving cerebello-thalamo-cortical loops. This network, with varying engagement of the individual components, repeatedly appears in modern theories about internal time representation, which envisage the processing of temporal information as mediated by distributed timing models, which derive data from the coincidental activation of various neural populations [250, 251]. This vast spectrum of models postulates the representation of time as ubiquitous, encoded in the entire activity pattern in more networks, which also process other stimulus properties, with relative dominance of several nodes, including the cerebellum, for sub-second timing tasks [252].

Hence, the presence of a dynamic oscillatory disturbance in ET in this network may lead to an impairment in tasks requiring exact timing. Nonetheless, studies analyzing reaction time produce discrepant results on measures using either mean reaction time and movement time and an impaired performance in a visual reaction time-based task [253-256] in ET patients and control subjects. The same inconsistency may be found in repetitive movements spanning a larger scale with significant deterioration reported in one study [257], but no difference found in the speed of alternating pronation-supination movements [256]. On the other hand, the confirmed impairment in the performance of tasks based on rhythmic repetitive finger movements, with longer touch duration,

shorter tapping interval and increased temporal variability of movement [256, 258], may be interpreted as a sign of cerebellar dysfunction and defective temporal processing, including the disrupted synchronization with extrinsic timing signals. These conclusions are corroborated by a severe impairment in event-based rhythm generation in ET [259], providing firm ground to support the hypothesized defect in intrinsic temporal processes. In addition to the retrospective timing domain captured by the above stated studies, a predictive motor timing task based on the interception of a moving object, a seemingly simple, quotidian activity ensuring synchrony and reliable interaction with our surrounding environment, revealed a markedly disrupted performance in ET patients [121, 122].

Unfortunately, kinematic studies of arm and hand movements in ET are inherently contaminated by tremor, the main clinical feature of the disease. However, eye motion analyses are able to provide information devoid of tremor artefacts. A deficit in smooth pursuit initiation [260], eye-hand coordination [261] and abnormally prolonged latencies with lower velocity profiles [262] all provide further evidence of timing disruptions in ET, even in these seemingly simple movements.

Furthermore, a temporal deficit may lead to one of the hallmarks of ET, the terminal accentuation of tremor at the end of precise movements. The triphasic pattern of electromyogram (EMG) activity (the first agonist burst to initiate the movement, followed by the antagonist burst to decelerate, and the second agonist burst to attenuate oscillations induced by the deceleration [263]) has been repeatedly shown to be abnormal in ET patients, with disruptions of timing of burst discharges. In particular, delays are seen in the onset of the phasic activity of the second agonist muscle, leaving the antagonist unopposed for a longer period, thus resulting in a series of dampened oscillations at the target point [264, 265]. Moreover, the latency of the second agonist burst in EMG correlates with the tremor period [264].

Interestingly, the impairment of temporal processing may be partially reversible. Repetitive transcranial magnetic stimulation over the cerebellum was able to significantly improve finger tapping performance in ET [258] and both thalamotomy and deep brain stimulation of the ventral intermediate nucleus of thalamus virtually restored perturbations in internal timing mechanisms, in the range of hundreds of milliseconds, to normal [266].

We are far from a clear understanding of the underlying mechanisms triggering the oscillations and changes in time processing networks in ET. The current evidence suggests that these networks share certain nodes. There is even a distinct improvement of the performance of ET patients in the temporal realm when utilizing complex therapeutic methods. However, both a definite model completely explaining the processing of temporal inputs in our brain and a cure for the primary cause of ET, are still out of reach.

Summary of Concepts

The current Consensus paper highlights the importance of the cerebellum in the control of elementary mechanisms of timing, not only at a cellular level but also for brain networks. Both the anatomy of the cerebellum with a geometric repetition of microcircuits and its dense connectivity with cerebral cortex, basal ganglia, brainstem and spinal cord make of the “small brain” an ideal candidate to coordinate elemental events required for optimal motor control and beyond. The theoretical concept of the cerebellum as a timing device raised by Braitenberg in 1961 has now expanded to clinical disorders [267].

However, the exact nature of more complex operations and processes running in the cerebellum remains elusive. Even though the cerebellum, with its myriads of neurons, definitely possesses the crude computing power to delineate expected future states of both the external environment and the body itself, it is not completely clear whether these processes are really intrinsic to the cerebellar cortex or emerge from a network, where cerebellum is but a mere node. Indeed, its vast interaction with basal ganglia, cortex, thalamus and other parts of the brain and feedforward character of data processing may imply the later. Nonetheless, the character of the cerebellar granular layer might point to the first option, as it is more than suitable for timing operations with millisecond precision and its oscillations and resonance in the theta band may be the basis for plasticity necessary in the learning of precise timing actions. At the intersection of this ostensible discrepancy and possibly providing its solution, the ICAT (Initiation, Continuation, Adjustment, and Termination) model of temporal processing poses the Initiation and Adjustment phase to the cerebellum, with Continuation and Termination phases being governed mainly by supratentorial structures as described above by Petter et al. [118] and illustrated in Figure 2. This position of cerebellum may be one of the reasons why a broad spectrum of timing disturbances has been implied in not only essential tremor, but also in Parkinson’s disease and dystonia, even though its role in these pathologies, be it primary, secondary or compensatory, still remains unclear.

Nonetheless, this overview of the position of the cerebellum in the complex timing processes is far from complete. There has been an undisputable progress in the spread of the general idea that the cerebellum is a structure critical not only for the precision of movement, but virtually for every cerebral process requiring feedback and fine-tuning. Hence, we are slowly shifting from simplistic views of neocortex as the primary driver in more complicated domains to a new paradigm conceptualizing an integrated network of distinct brain regions, including some maybe counter-intuitive areas, as the notional “mirror” of human psyche.

Table 1 **Consensus to the Position of Cerebellum in Timing Processes: Agreement and Warranted Research**

Agreement	The cerebellum is an important node in multiple domains of temporal analysis, including motor and non-motor timing, implicit and explicit timing, but mostly in discrete, isolated intervals. The cerebellum should not be viewed as a mere sub-second processing node, it provides important contribution in the supra-second spectrum, allowing for adjustments of cortical and subcortical circuits. The cerebellum plays a major role in the control of the tri-phasic patter of muscle discharges. Crucial role of the cerebellum in the predictive timing in multiple domains – eyeblink, interception tasks, locomotion phases, sequential movements.
Warranted research	Precise identification of cerebellar pathways and Contribution of cerebellum in various neurodegenerative disorders – primary, secondary or compensatory role? New perspectives in both neurological and psychiatric disorders traditionally viewed as not linked to cerebellum Studies with non-invasive brain stimulation, both in research and clinical treatment

Acknowledgments:

This work was supported by a grant from the EU H2020 Marie Skłodowska RISE project #691110 (MICROBRADAM); National Institute of Health (NS092079); European Union grant Human Brain Project (HBP-604102)

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