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Abstract

A functional characterization of the cerebellum centers on the hypothesis that this structure is essential for the representation of temporal relationships in the subsecond range. This hypothesis is supported by evidence involving a wide range of methods, including lesion studies, neuroimaging, and, to a limited extent, stimulation studies with transcranial magnetic stimulation. The extent of the cerebellar timing domain is not limited to tasks involving sensorimotor control but also extends to perceptual tasks that require the precise timing of salient events. Moreover, the timing hypothesis provides a parsimonious account of the cerebellar contribution to sensorimotor learning. This review presents a summary of this literature as well as highlights some of the limitations of cerebellar timing.

History/Background

David Marr, in his 1969 classic *A Theory of the Cerebellar Cortex*, proposed that the “happy combination” of simple and repeating fine structure in the cerebellum was ideal for motor learning (Marr 1969). While Marr’s model continues to inspire many lines of research, the regularity of cerebellar anatomy had already captivated the attention of anatomists, calling for a concise computational account of how the

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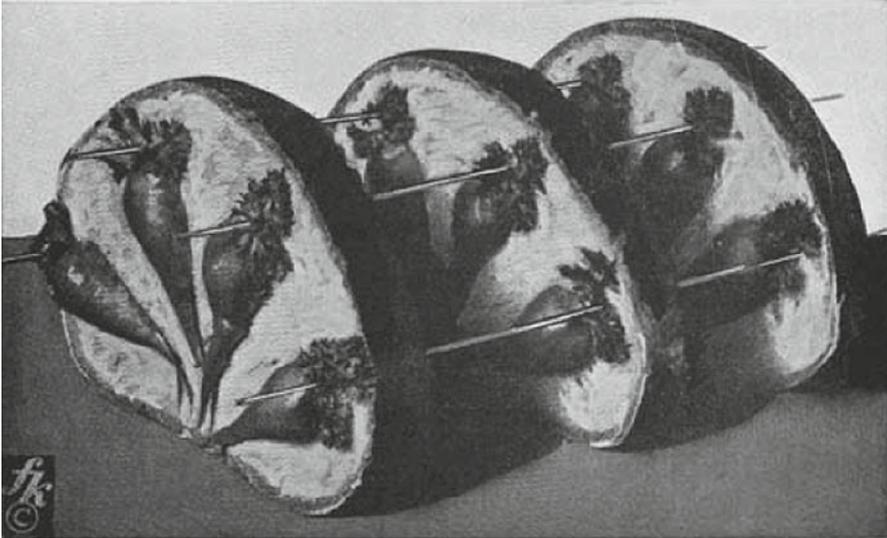


Fig. 52.1 Fritz Kahn's analogy of the cerebellar microstructure to radishes embedded in bread, preceded decades of more extensive research on the function of the cerebellum (used with permission from Kahn, 1943)

cerebellum might contribute to movement and learning. Twenty years prior to Marr's paper, the physician and artist Fritz Kahn was attracted to the macroscopic features of the cerebellar cortex, providing an analogy to radishes in bread slices (Kahn 1943). The bread slices referred to the prominent cerebellar folia; the radishes embedded in each slice were suggested by the repeating arrangement of the large Purkinje cells defining the circumference of the folia, with the leafy greens of the radishes representing the dendritic arbors of the Purkinje cells (Fig. 52.1). In his imaginative manner, Kahn suggested that knitting needles reflected how the parallel fibers provided a link across the folia. For Kahn, this redundant, interwoven architecture served the function of integrating sensory and motor information, the necessary ingredients for coordinated movement.

The anatomist Valentino Braitenberg was also drawn to the orderly manner in which parallel fibers synapse across a series of Purkinje cells. His observations led to a seminal attempt at a unified theory of cerebellar function, one that went beyond the realm of description and offered a specific computational account of how the cerebellum might contribute to the production of coordinated movement. Braitenberg (1967) hypothesized that parallel fibers serve as delay lines, providing a mechanism in which temporal information could be represented in a structural manner. In its simplest form, Braitenberg's proposal was that signals propagating along parallel fibers at a relatively constant rate could represent precise timing signals based on their distance from a fixed point of origin. By identifying the task-relevant parallel fiber-Purkinje cell synapse, a system could learn to impose the precise temporal patterns that define skilled movement. Braitenberg initially

conjectured that the length of parallel fibers might be sufficient to represent intervals spanning hundreds of milliseconds. However, he later came to realize that the range of delays was much more limited (Braitenberg 1983). Nonetheless, this important theoretical piece helped shift the focus to the question of how to characterize the specific contribution of the cerebellum within a distributed motor system and provided the novel conjecture that the cerebellum may be uniquely designed to provide some form of temporal representation.

This chapter provides an overview of the role of the cerebellum in temporal processing. The first sections address how the timing hypothesis provides a parsimonious account of the role of the cerebellum in motor control. The second sections focus on whether the timing hypothesis provides a useful heuristic for understanding the functional domain of the cerebellum more broadly. In particular, does a computational perspective, in which the cerebellum represents precise temporal relationships, offer a framework for understanding the role of this structure in perception and learning? This latter work has proven to be contentious, and this debate is reviewed in a final section, discussing constraints on cerebellar timing.

This review relies on evidence from neuropsychological, neuroimaging, and brain stimulation studies. Each of these approaches has provided converging evidence consistent with a role of the cerebellum in sensorimotor and perceptual timing. Neuropsychological studies have been fruitful in revealing the essential contribution of the cerebellum to timing functions. What these studies lack in spatial resolution has been addressed through a large neuroimaging literature, helping to point to the contributions of different cerebellar subregions. Although limited in number, more recent studies using transcranial magnetic stimulation (TMS) have provided a third tool in research with human participants.

Cerebellar Function in Sensorimotor Timing: Neuropsychological Studies

Individuals with cerebellar lesions, due to an injury or degeneration, are characterized as ataxic. Ataxia is a broad term literally meaning “without order,” in other words, lacking coordination. Characteristic features of cerebellar ataxia include movement decomposition, intention tremor, dysmetria (a tendency to overshoot or undershoot a target), and dysdiadochokinesis (difficulty in producing alternating movements) (Trouillas et al. 1997). At one level of analysis, these sensorimotor deficits can be viewed as a disruption of control in the temporal domain (Day et al. 1998; Flament and Hore 1986). Patients with parietal lesions may fail to retain knowledge of the functional intent of an action (e.g., ideational apraxia) or integrate spatial information between visual and proprioceptive space (e.g., optic ataxia). In contrast, the basic components of movements are present in patients with cerebellar ataxia: in reaching for an object, for example, the arm generally follows the appropriate spatial trajectory (but see Bastian et al. 1996), and the hand is appropriately configured to intersect the targeted object. However, the temporal features

are disrupted. Hypermetria arises when, during a rapid movement, the onset of the antagonist burst is delayed, resulting in the limb initially moving past the target (Flament and Hore 1986). Similarly, in dysdiadochokinesis, the patient is able to alternate between pronation and supination of the wrist but cannot maintain the precise temporal pattern required to do this in a rapid manner (Day et al. 1998).

These clinical observations inspired studies that sought to provide direct experimental tests of temporal control following cerebellar lesions. One favored task in this literature involves the production of repetitive, timed movements. In such tasks, a metronome is presented at the start of the trial and the participant is instructed to move in synchrony with the beat, usually by tapping a finger (synchronization). At some point, the metronome is terminated, thus requiring that the individual rely on intrinsic signals to maintain the target rate (continuation). People are generally quite good at matching their movement rate to a metronome across a range of movement speeds (e.g., intertap intervals ranging from 250 to 2,500 ms). The primary dependent variable in such studies is the temporal variability of the responses. This variance rises in a proportional manner to the target interval (Getty 1975), pointing to the operation of a signal-dependent underlying process or processes (Harris and Wolpert 1998). Notably, significant correlations are observed in healthy individuals when performing the task with different effectors [e.g., finger, jaw, arm, foot (Franz et al. 1992; Keele and Hawkins 1982; Keele et al. 1985)], suggesting that one source of variance is associated with an internal timing process.

The relative simplicity of the repetitive tapping task has made it ideal for neuropsychological investigations. Patients with lesions of the cerebellum, either arising from bilateral degenerative processes or unilateral focal lesions, exhibit a substantial increase in movement variability during repetitive tapping (Franz et al. 1996; Ivry and Keele 1989; Spencer et al. 2003). Such an increase in movement variability in patients with coordination problems does not come as a surprise. Critical to the neuropsychological approach is demonstration of specificity, either in terms of pathology or behavioral deficit. For instance, in working with cerebellar ataxia, it is important to rule out factors that may be general to movement disorders. Patients with Parkinson's disease do not exhibit a similar pattern of increased variability as those with cerebellar lesions, when tested either on or off dopaminergic medication (Ivry and Keele 1989), see also (Duchek et al. 1994; Spencer and Ivry 2005) but see (Harrington et al. 1998a).

Additional behavioral dissociations come from the employment of time series analytic methods decomposing the temporal variability. One such model decomposes timing variance into two theoretical constructs (Wing and Kristofferson 1973), one associated with central planning processes determining when to initiate the responses and the other associated with motor implementation of the responses. When applied to patient data, a dissociation is observed between patients with lateral and medial cerebellar lesions (Ivry et al. 1988). Lateral lesions are primarily associated with an increase in variability of the central planning process (Franz et al. 1996). In contrast, medial lesions produce a selective increase in timing variability associated with the motor response. This pattern is consistent with the

view that lateral cerebellar regions are linked with cortical regions involved in response preparation and planning, providing the temporal information that signals when each response should be initiated. More medial regions help ensure that these signals are properly implemented.

It is important to note that in patients with unilateral cerebellar lesions, the impairment is generally limited to the ipsilesional side (Franz et al. 1996; Spencer et al. 2003; Ivry et al. 1988). This observation argues against the existence of a unitary internal “clock.” At a minimum, the lateralization of the deficit suggests that there must be some form of effector dependence within the cerebellum. Interestingly, performance with the impaired limb becomes less variable during bimanual tapping (Franz et al. 1996). While this could suggest that the patients become more reliant on the unaffected limb, an alternative model suggests that independent timing signals are generated for each limb, and the bimanual improvement reflects the integration of these two central signals. This integration model is consistent with the observation that the bimanual advantage is also observed in healthy individuals (Helmuth and Ivry 1996). A more nuanced view may be that temporal representation is a general feature of cerebellar processing, but the instantiation of this computation arises in an effector- or task-specific manner.

Experimental studies have also assessed whether variable timing may underlie ataxia-related deficits in more complex tasks such as throwing and speech production. Patients with cerebellar degeneration exhibit increased variability in the temporal relationship between the rotation of the arm and the release of the ball by the fingers (Timmann et al. 1999, 2000; Hore et al. 2002). Similarly, cerebellar dysarthria is marked by poor temporal control of speech. The duration of syllable repetitions is irregular, a result that stands in contrast to the slowing of speech associated with Parkinson’s disease. Dysarthric speech may also represent a temporal disruption. For example, cerebellar patients have difficulty producing the fine articulatory gestures required to temporally coordinate the onset of voicing and the release of airflow at the frontal articulators, whereas they are relatively unimpaired in coordinating the articulators to impose brief occlusions of the airflow (e.g., place of articulation) (Keele and Hawkins 1982, see also, Keele et al. 1985).

Cerebellar Function in Sensorimotor Timing: Neuroimaging and TMS Studies

Neuroimaging (PET and fMRI) studies provide further evidence of cerebellar involvement in sensorimotor timing and have been useful for evaluating the contributions of different cerebellar subregions. Functional MRI (Rao et al. 1997) and PET (Jueptner et al. 1995) studies of repetitive tapping reveal increased activation of the ipsilateral cerebellum during both synchronization and continuation compared to rest. Synchronization of movements to a timed metronome engages the cerebellum in a similar manner regardless of the modality of the pacing signal (Jancke et al. 2000; Jantzen et al. 2005). Notably, direct comparison of continuation and synchronization also reveals no differences in cerebellar

engagement, particularly in lateral cerebellum (Rao et al. 1997; Elsinger et al. 2003). Given that synchronized taps are anticipatory, meaning the response precedes the pacing signal by about 10 ms (Aschersleben and Prinz 1995; Miyake et al. 2004), this similarity lends further support to a single temporal computation being performed by the cerebellum across these tasks. Moreover, syncopated tapping, or tapping at the midpoint between pacing signals, yields greater activation of the cerebellum relative to synchronized tapping at the same rate (Mayville et al. 2002). Accurate estimation of the midpoint is a more challenging state estimation problem for predictive control.

Linking activation patterns to functional hypotheses has proven difficult in the timing literature. Generally, the cerebellar activation is centered around lobules V–VIII and is usually ipsilateral (see reviews in Lewis and Miall 2003a; Stoodley and Schmahmann 2009). When the temporal pattern must be held across a delay period prior to the response, the activation is more bilateral (Kawashima et al. 2000; Penhune et al. 1998; Bengtsson et al. 2005), similar to that seen during perceptual timing (described below). However, a number of imaging studies of sensorimotor timing have varied the demands on temporal processing, and here the picture is much more varied. For example, in one study (Penhune et al. 1998), people were presented with a temporal pattern and asked to reproduce an isochronous sequence (e.g., tap once every 250 ms), a repeating sequence of intervals (intervals of either 250 or 750 were presented in a repeating sequence and then reproduced), or a novel, nonrepeating sequence of intervals. For all three conditions, an auditory stimulus was used to present the interval sequence. Cerebellar activation was greatest in the nonrhythmic condition (see also Bengtsson et al. 2005). In a reactive motor timing task in which individual motor responses are made to cues that are either isochronous or irregular, the cerebellar signal was also greater for the irregular (nonisochronous) condition (Lutz et al. 2000). These results are problematic for a timing account of the cerebellar activation, given the assumption that the demands on internal timing would, a priori, seem to be greatest in the isochronous and rhythmic conditions. However, it is possible that the cerebellum was responding to the intervals defined by the nonrhythmic stimuli, and the larger activation here is due to the greater temporal variability for this condition.

Transcranial magnetic stimulation (TMS) studies have been used to perturb cerebellar activity, asking how this affects sensorimotor performance. In an initial study with this method, Theoret and colleagues (Theoret et al. 2001) observed an increase in temporal variability following low-frequency stimulation over medial cerebellum. A similar increase was also found when the TMS was targeted at lateral cerebellum (but see Jancke et al. 2004). TMS of this region using theta burst stimulation also disrupted temporal error correction in a sensorimotor task. Specifically, participants tapped with a regular auditory stimulus (600 ms metronome) and continued to tap with the stimuli following a perturbation of the pace. Participants were less able to correct for errors in synchronous tapping following TMS over lateral cerebellum (Bijsterbosch et al. 2010). Error corrections for larger perturbations (90 ms) were more impaired than corrections to small perturbation of the pacing stimulus. While cerebellar subregions cannot be clearly delineated with

TMS techniques, the fact that lateral and not medial stimulation influenced the temporal error correction would be consistent with evidence pointing to a role of hemispheric lobules V–VIII in motor timing.

Cerebellar Contributions to Perceptual Timing: Neuropsychological Studies

There appears to be a strong association between processes involved in motor and perceptual timing in the range relevant for sensorimotor control. Experimental support for this comes from individual difference studies in healthy young adults: assays of temporal variability on time production and time discrimination tasks show reasonably high correlations (Keele et al. 1985; Zelaznik et al. 2002). This observation motivated studies of perceptual timing in patients with cerebellar pathology. As predicted, the patients were impaired on a duration discrimination task (Rao et al. 1997) (Fig. 52.2a). Importantly, the deficit was not reflective of a generalized impairment on challenging psychophysical tasks: if the discrimination involved judging the loudness of the stimuli, the patients performed at a comparable level as control participants. Recently, Grube and colleagues (2010) created a hierarchical set of perceptual timing tasks. The most basic level required duration discrimination. At higher levels, this information was used to develop more complex temporal representations defining the underlying beat of a rhythmic pattern or the relative durations of a series of intervals. Consistent with earlier studies, the patients had elevated thresholds on the basic duration discrimination task. However, the patients were unimpaired on the assays of more complex temporal representations. This result suggests that the cerebellum may be essential for representing temporal information in a metrical manner – for example, specifying the exact interval being presented on a trial – but not for using this information to form more abstract temporal representations such as those that underlie rhythms (e.g., ratio-based information).

Problems with perceptual timing have also been observed in studies using electrophysiological methods. EEG research has identified a potent marker of violations of sensory expectations, the mismatch negativity response (MMN). This response is delayed in patients with cerebellar degeneration when the sensory violation is in the temporal domain (Moberget et al. 2008). The results appear to be somewhat specific to timing given that the patients' MMN to pitch and location deviants was unaffected. However, the patients also showed an abnormal response to deviations in loudness. Violations of temporal expectancies in the somatosensory domain also produce a physiologic signal localized to the cerebellum (Tesche and Karhu 2000).

Tasks such as driving or stepping onto an escalator require using temporal information not only to gauge the dynamics of the perceived event but also to guide movement. Experimental tasks designed to capture this problem show that individuals with cerebellar lesions have difficulty formulating temporal predictions required to execute accurate responses (Bares et al. 2007, 2010a). Perceptual

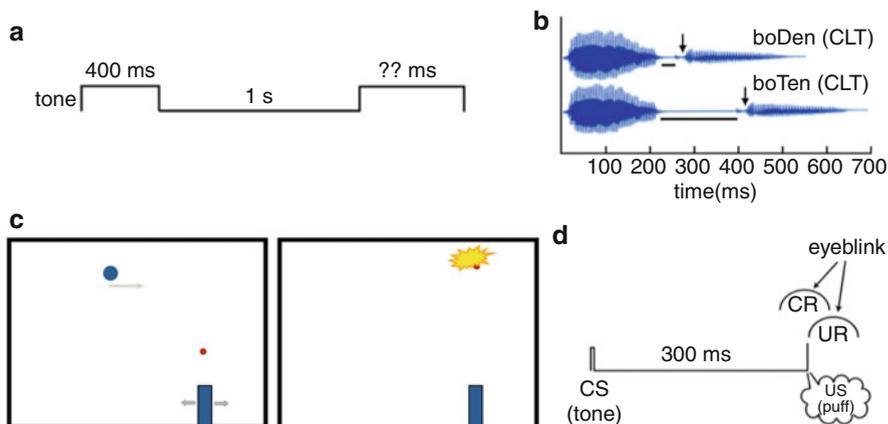


Fig. 52.2 Representative tasks associated with sensory timing deficits in patients with cerebellar pathology. **(a)** Duration discrimination task in which participant judges if second interval is shorter or longer than first interval; **(b)** speech discrimination of two words where the phonetic contrast is based on the duration of a silent period; **(c)** sensorimotor prediction task in which participant must time a button press to release a “missile” that will intercept a moving target; **(d)** importance of precise timing in eyeblink conditioning; the animal must learn to blink just prior to the onset of the US (Adapted from Manto et al. in press)

deficits have also been observed on tasks that do not directly assess duration. Velocity perception requires integrating a change in position over time. While the literature has focused on the role of cortical areas such as area MT for velocity representation, the cerebellum also must have access to this information to calibrate the metrics of smooth pursuit and saccadic eye movements, as well as partition motion signals from those generated by the environment and those generated by the body (e.g., Suzuki and Keller 1988). Indeed, patients with cerebellar pathology are impaired on velocity discrimination tasks (Ivry and Diener 1991).

Speech is another domain in which the precise representation of temporal information is essential. For example, a prominent cue to distinguish “rabid” and “rapid” is the duration of the closure period for the stop consonant at the start of the second syllable (Fig. 52.2b). Ackermann and colleagues (Ackermann et al. 1997) showed that patients with cerebellar degeneration performed very poorly on this type of discrimination.

One study involving a large group of cerebellar patients failed to observe impaired performance on a duration discrimination task (Harrington et al. 2004). This study involved 21 individuals with focal cerebellar lesions. Even when the analysis was restricted to those with lesions of superior cerebellum (above Crus II), perceptual performance fell within the normal range. It is possible that this null result reflects the fact that these lesions were unilateral. As noted above, the motor literatures points to a distributed, task-specific involvement of cerebellar circuits for timing. By this hypothesis, one would expect that the sensory events would trigger bilateral temporal representations (e.g., from left and right auditory input pathways), the outputs of which are combined to support the perceptual judgments.

Models of optimal sensory integration predict that, even if the signal was much more variable in one hemisphere due to pathology, the integrated signal would only show a slight increase in variability (Ernst and Banks 2002). Indeed, the patients with unilateral lesions showed a marginally reliable deficit on the perceptual task.

Cerebellar Contributions to Perceptual Timing: Neuroimaging Studies

A relatively large number of neuroimaging studies have been conducted to explore the neural systems involved in temporal processing (for a review, see Lewis and Miall 2003a). In the auditory domain, PET and fMRI studies consistently report greater cerebellar activation during temporal discrimination tasks compared to conditions in which the participants judge the pitch (Rao et al. 2001) or intensity (Belin et al. 2002) of the stimuli. Similarly, in the visual domain, duration judgments are associated with greater cerebellar activation compared to judgments of size (Lewis and Miall 2003a) or brightness (Maquet et al. 1996). However, there are also numerous reports failing to show cerebellar-related activation during time perception tasks (Harrington et al. 1998b) or reporting similar activation during temporal and nontemporal tasks (Ferrandez et al. 2003). Moreover, temporal-specific activation is never limited to the cerebellum; similar patterns of activation are frequently observed in cortical and basal ganglia regions (for a review, see Meck et al. 2008).

Even more problematic have been efforts to identify regions within the cerebellum that are associated with perceptual timing. The results here are quite inconsistent. For example, one study of visual timing pointed to a critical region around the border of left Crus I/II, activation (Lewis and Miall 2003b). Other studies have pointed to a region within lobule VI (Aso et al. 2010) or superior vermis (Tesche and Karhu 2000; Xu et al. 2006). The lack of consistency, of course, may reflect the task and effector specificity of cerebellar subregions in timing. By this view, one would not expect common regions of activation when the temporal information is conveyed by auditory or visual inputs, nor would these regions necessarily overlap with those involved in motor timing.

Tasks requiring the formation of temporal predictions or expectancies also elicit cerebellar activation. Lateral cerebellum (lobule VI) is activated when healthy participants produce a simple button press to launch a “missile” to intercept a moving target (Bares et al. 2007, 2010b) (Fig. 52.2c). While this task requires an accurate temporal prediction regarding the visual information as well as the upcoming motor response, O’Reilly and colleagues (O’Reilly et al. 2008) have employed a task that focused on purely perceptual predictions. In this study, an object moved across the screen at a constant velocity before being briefly occluded. In separate conditions, the participants were asked to judge whether the object, after reappearing, had been altered in terms of its spatial trajectory or velocity. Only the latter produced an increase in activation in the cerebellum. Moreover, through connectivity analysis, activation was shown to be correlated with changes in frontal

and parietal regions (Aso et al. 2010). The specificity of the cerebellar activation to the velocity condition is especially interesting given models linking the cerebellum to forward modeling (e.g., Wolpert et al. 1998). If the cerebellum is part of a general network for internal simulation, one would expect that this structure to be similarly engaged for both the spatial and temporal-spatial judgments. However, the results suggest that the predictive functions may be limited to those that involve the representation of temporal information.

Repetitive TMS (rTMS) over right lateral cerebellum and medial cerebellum have been shown to affect performance on time perception tasks. Interestingly, this effect has not been manifest as an increase in variability, the focus of the patient literature. Rather, rTMS led participants to perceive the stimulus as longer compared to conditions in which no stimulation was given or stimulation was targeted at a cortical region (Koch et al. 2003, 2007). Moreover, the distortion of perceived duration was limited to conditions in which the stimuli were less than 1 s. Perception of suprasecond durations (1,000–2,400 ms) was not altered by rTMS over any cerebellar site, an issue requiring future investigation.

Cerebellar Timing Function in Sensorimotor Learning

A wealth of literature points to the importance of the cerebellum in motor learning (Purves et al. 1997; Kandel et al. 1995). People with cerebellar pathology show a striking impairment on a range of sensorimotor learning tasks that require learning novel dynamics such as force field learning (Smith and Shadmehr 2005), visuomotor adaptation (Tseng et al. 2007; Morton and Bastian 2004), and anticipatory postural adjustments (Diedrichsen et al. 2005). Cerebellar learning is reviewed extensively in other entries of this volume; as such, this review will focus on the importance of timing in certain forms of sensorimotor learning. Consider a complex task such as learning to play tennis or play an intricate piece of music. For both tasks, skill requires not only learning the proper sequence of events but also the precise timing that allows the dynamics to unfold in a coordinated, rapid manner.

Classical conditioning of the eyeblink response (or nictitating membrane conditioning in the rabbit) has served as an important mammalian model for studying the neural mechanisms of learning (Fig. 52.2d). The classic work of Richard Thompson (McCormick and Thompson 1984) first identified the critical role of the cerebellum in eyeblink conditioning. Lesions of the cerebellum in trained animals abolished the conditioned response without affecting the unconditioned response; lesions prior to training prevented the acquisition of the conditioned response. These results stand in contrast to the effects resulting from cortical or hippocampal lesions (Moyer et al. 1990), at least under conditions in which memory demands of the conditioned stimulus are minimal.

It is important to ask why the cerebellum is essential for eyeblink conditioning. A critical feature of this form of learning is that the animal must not only learn to associate the CS and US but must also learn the precise temporal relationship between these two events. That is, the animal must learn to protect the eye in

anticipation of the arrival of the US. It has been proposed that the cerebellum has the requisite machinery to take the error signal associated with the US and use this to associate and shape the CR in a near-optimal manner (Ivry and Keele 1989). Thus, following selective lesions of the cerebellar cortex, the CR may persist, but the adaptive timing is abolished. Now the animal tends to blink immediately after the onset of the CS (Woodruff-Pak et al. 1985; Woodruff-Pak and Thompson 1985). Various mechanisms have been suggested to account for how the cerebellum supports the dynamics for eyeblink conditioning (Bracha et al. 2009; Gerwig et al. 2007; Christian and Thompson 2003). All of these provide a mechanism that can operate as an interval timer.

The requirements for precise timing, and presumably the cerebellum's capability for providing a temporally extended representation of the CS, likely underlie the fact that there is an optimal range of intervals for eyeblink conditioning (e.g., 100–400 ms). When this interval is lengthened, or when there is a gap between the CS and US, lesions of other structures such as the hippocampus can also disrupt learning (Moyer et al. 1990). It appears that these structures provide memory capabilities that extend the effective range of cerebellar timing. Functional MRI studies in humans have identified neural correlates of eyeblink conditioning for both delay (CS/US overlap) and trace (CS/US are separated) conditioning. When delay and trace conditioning are acquired in parallel, there is no difference in cerebellar engagement for learning while the hippocampus is uniquely active for trace conditioning (Cheng et al. 2008).

It is also informative to consider “motor learning” tasks that do not appear to be dependent on the cerebellum. One example here is motor sequence learning in which participants are presented with a series of stimulus events that follow a fixed pattern or are selected at random. With practice, reaction times become shorter when the elements are predictive. While this learning effect is typically absent in patients with cerebellar degeneration (e.g., Gomez-Beldarrain et al. 1998; Shin and Ivry 2003), it has recently been shown that the deficit is not related to sequence learning per se, but rather to the demands associated with maintaining the stimulus–response associations (Spencer and Ivry 2009). When the S-R associations were highly constrained, the patients showed normal sequence learning. This result suggests important constraints on the cerebellum and sensorimotor learning. Sequence learning is different from tasks such as sensorimotor adaptation in two ways. First, learning is minimally dependent on errors since people make relatively few errors during sequence learning. Second, learning does not involve, at least in the early stages of practice, a change in task dynamics, or what would involve precise timing. The relative importance of error sensitivity or timing, or the conjunction of the two, may prove to be essential for defining the domain of cerebellar learning.

The Range of Cerebellar Timing

The representation of temporal information is important not just for producing well-coordinated movements but also in many perceptual tasks, spanning a wide range of

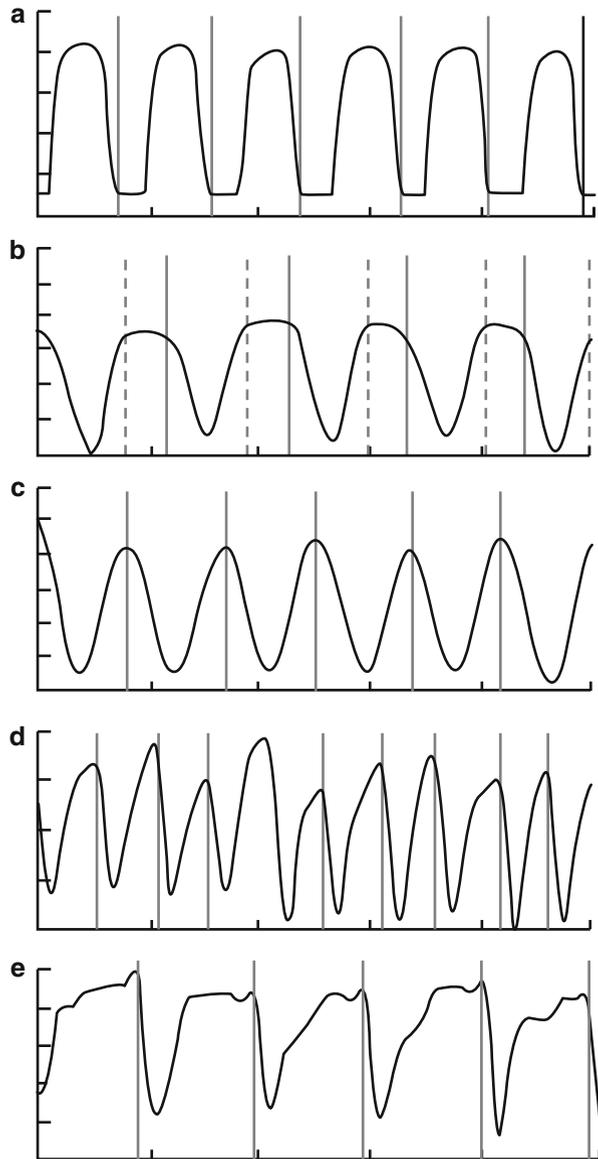
intervals. At the microsecond level, the auditory system uses miniscule differences in arrival time to localize sounds. At the millisecond level, temporal cues provide important phonological information. Moving to seconds and beyond, temporal representation can be important for anticipating predictive events or evaluating the relative payoff for continued foraging in an area with limited resources (Collyer and Church 1998). It is unlikely that a single neural system is capable of representing time across intervals spanning several orders of magnitude.

Individuals with cerebellar lesions are impaired in discrimination of both short (400 ms) and long intervals (4 s) (Mangels et al. 1998), and more recent evidence suggests that individuals with cerebellar lesions are impaired in the production (but not perception) of intervals as long as 10 s (Gooch et al. 2010). Nonetheless, as suggested above, the range of cerebellar timing is generally considered to be limited to the subsecond range, with an integration of this system and memory processes for longer intervals. Separable neural substrates for sub- and suprasedond interval timing is an idea consistent with the psychophysical work of Fraisse in the 1960s (Fraisse 1963). In a meta-analysis of neuroimaging studies of perceptual and motor timing, Lewis and Miall (2003a) suggested distinct neural correlates associated with subsecond and suprasedond timing. Subsecond timing processes, in their view, are “automatic,” relying on motor circuits in the absence of attention. Suprasedond processes are “cognitively controlled,” relying on executive processes such as attention and working memory. This meta-analysis, comparing studies using <1 s intervals with those using >1 s intervals, failed to distinguish distinct cerebellar roles for long and shorter interval. However, some studies have supported the view of a limited range for cerebellar timing (Lewis and Miall 2003b). It is possible that subdividing long interval into short subintervals provides a strategy that allows processing to fall within the temporal extent of cerebellar timing capabilities (Koch et al. 2009).

The Cerebellum as an Event Timer

In addition to temporal range, a second constraint related to cerebellar timing relates to task dynamics. In particular, a distinction has been made between event and emergent timing. Event timing refers to tasks in which the representation of temporal information is an explicit part of the task goal. For example, in finger tapping, the participant is trying to align movements with specific salient events such as an external metronome beat, or during the unpaced phase, an internalization of this beat. Similarly, in duration discrimination tasks, the system must represent the duration of an event, one that need not be linked with the presence of a physical stimulus (i.e., an empty interval marked by two events). Emergent timing refers to tasks in which temporal regularities may arise from the dynamics of a continuous event. An example here is repetitive circle drawing: periodic intervals can be produced by maintaining a constant velocity, even if the control system does not entail a representation of the cycle duration (Fig. 52.3). The distinction between event and emergent timing was based on individual difference studies in healthy

Fig. 52.3 Sample trajectories for event-based and emergently timed movements. **(a)** Finger tapping on a surface; **(b)** discrete circle drawing requires the insertion of a pause between movement cycles similar to the finger tap. **(c)** Continuous circle drawing at the rate equated to the velocity of the movement portion of the intermittent drawing task; **(d)** continuous air tapping is kinematically similar to **c**. **(e)** Discrete air tapping is kinematically similar to **a** (Adapted from Spencer et al. 2003)



young adults. Timing variability is correlated between repetitive movement tasks involving discontinuities, but not between these tasks and ones in which the movements are continuous. Moreover, perceptual timing is only correlated with the event-based motor tasks (Zelaznik et al. 2002). Event and emergent timing reveal distinct profiles in time series analyses of covariance (Spencer and Zelaznik 2003; Huys et al. 2008; Studenka and Zelaznik 2011).

Converging evidence for a dissociation between event and emergent timing has been observed in neuropsychological studies. Individuals with cerebellar pathology show a disproportionate increase in temporal variability on event-based tasks such as finger tapping or intermittent circle drawing (Spencer et al. 2003; Spencer and Ivry 2005). In contrast, the deficit is reduced when the rhythmic movements are produced in a continuous manner (Spencer et al. 2003; Spencer and Ivry 2005; Schlerf et al. 2007). The event-emergent difference has been observed in comparisons of patients with bilateral degeneration and matched controls, as well as in within-patient comparisons involving patients with unilateral lesions (Spencer et al. 2003).

Perhaps the most striking contrast is between discrete and continuous tapping. In both conditions, participants produce finger tapping movements in the air (i.e., no contact with any surface). However, instructions indicate that participants should either move in an abrupt and staccato-like fashion (discrete air tapping) or in a smooth, continuous manner. Individuals with cerebellar lesions are selectively impaired in the discrete condition. In an fMRI study, both types of movements engaged motor regions of ipsilateral cerebellum (Spencer et al. 2007), but an additional region of activation during the discrete movements was observed in superior vermis.

It is possible that the cerebellar contribution to event-based tasks may not be related to the demands on timing per se, but more related to the control of movement onsets and offsets (Bo et al. 2008). This question was addressed in a study in which participants were required to make a single keypress in response to movement cues. The cue indicated if the key should be held down for a short amount of time (550 ms), a long amount of time (950 ms), or released immediately. While all three conditions were relatively taxing in terms of the control of movement initiation and termination, patients with cerebellar degeneration were only impaired when the responses required the insertion of a delay (Spencer et al. 2005).

Conclusions

This article has reviewed the broad range of evidence that points to a critical role for the cerebellum in temporal processing. Collectively, the cerebellar timing hypothesis provides a parsimonious account of cerebellar contributions across a diverse set of task domains, ranging from the timing of EMG patterns during simple movements to computations required for sensory predictions or speech comprehension. The linkage across these domains is the demands on the representation of precise temporal information.

It is important to emphasize that other neural regions have also been associated with temporal processing. Although the range of task domains is generally narrower, the supplementary motor area, basal ganglia (Grahn and Brett 2007), and lateral prefrontal cortex (Jones et al. 2004) have also been linked to timing in neuroimaging studies (reviewed in Lewis and Miall 2003a). Moreover, individuals with Parkinson's disease (Pastor et al. 1992; O'Boyle et al. 1996) or prefrontal or parietal lesions (Harrington et al. 1998b) have been shown to exhibit timing

impairments, similar to those observed in patients with cerebellar pathology. The functional contribution of these regions, and more importantly, how they interact, remains an important focus of study (Ivry and Spencer 2004). Timing is not something that occurs in isolation, but is frequently associated with tasks that involve working memory, selective attention, and decision making (Wiener et al. 2010). It may well be that the cerebellum is uniquely capable of providing a precise, metrical representation of defined temporal intervals. Alternatively, timing may either be a distributed process, arising through the interaction of different neural systems, or be represented in a local, yet distributed manner, arising from the intrinsic dynamics of neural processing (Karmarkar and Buonomano 2007). The question of whether timing is dependent on a specialized system such as the cerebellum, or distributed across many neural regions, recruited in a task-dependent manner, is likely to shape research on temporal processing over the coming years (Ivry and Schlerf 2008).

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