Timing in the Cerebellum and Cerebellar Disorders

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1 Introduction

Over the past century, the function of the cerebellum was largely assumed to be that of movement coordination. This assumption, along with its geographic segregation from the cortex, led the cerebellum to be overlooked in many early neuroimaging studies. Yet the cerebellum contains roughly 10% of the brain's mass (Hutchinson et al., 2003; Swanson, 1995). Perhaps more striking, the cerebellum contains 65–75% of the total neurons of the brain (Herculano-Houzel, 2010). In other words, for every one cortical neuron there are three to four cerebellar neurons. Moreover, neurons of the cerebellum are uniquely arranged into arrays of neural loops. These loops repeat millions of times throughout the cerebellum, and are arranged into lobules. Those lobules are, in turn, composed of folia, structures reminiscent of the fractalian structure of a tree or cauliflower (Voogd and Glickstein, 1998). Thus, the cerebellum is architecturally unique and capable of performing a redundant computation. It has been proposed that the computation performed by the cerebellum is that of timing (Braitenberg, 1983; see review in Spencer and Ivry, 2013).

2 Timing in Cerebellar Ataxia

In humans, focal cerebellar damage is rare. While a hemorrhagic stroke to the cerebellum is particularly rare, ischemic stroke, the more common cerebellar stroke, nonetheless accounts for only 1–7% of all strokes (Bogousslavsky, Van Melle, and Regli, 1988; Macdonell, Kalnins, and Donnan, 1987; Vemmos et al., 2000). Other focal cerebellar lesions, due to tumors and tumor resection, are also uncommon particularly in adults.

Cerebellar atrophy that typically results in widespread cerebellar damage can arise in a number of ways. Genetic degenerative diseases, primarily spinocerebellar ataxia (SCA), that affect the cerebellum are heterogeneous. SCA is a

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group of autosomal dominant neurodegenerative disorders, many of which result in cerebellar degeneration. Prevalence estimates of SCA vary from .3 to 3 per 100,000 (van de Warrenburg et al., 2002). Moreover, of the approximately 30 different SCA subtypes (Schols et al., 2004), only a handful have a primarily cerebellar foci (e.g., SCA 6, 8, 15/16; Durr, 2010; Marelli et al., 2011). Of the degenerative cerebellar disorders, sporadic idiopathic cerebellar atrophy may have the greatest prevalence, estimated to have a prevalence rate of 8.4 per 100,000 (Muzaimi et al., 2004). Sporadic cases of cerebellar agenesis have also been reported (e.g., Glickstein, 1994; Macchi and Bentivoglio, 1977; Nowak, Timmann, and Hermsdorfer, 2007; Velioglu, Kuzeyli, and Ozmenoglu, 1998). Surprisingly, in many of these cases, motor performance is largely normal, suggesting possible compensatory mechanisms (for a review see: Glickstein, 1994; Macchi and Bentivoglio, 1977).

Seminal neurologists, Joseph Babinski and Gordon Holmes, are both credited for the earliest reports of the deficits associated with cerebellar damage in humans (Holmes, 1939, 1917; Trouillas et al., 1997). Babinski and Holmes described core symptoms associated with damage to the cerebellum – such as slurred speech, unsteady gait, and incoordination – and collectively referred to these as ‘cerebellar syndrome’. Holmes, studying survivors of gunshot wounds to the back of the head in World War I, came to use the term ‘ataxic’ to specifically describe the movements of individuals with cerebellar syndrome. Ataxia remains the commonly used term to describe the movements associated with cerebellar disorders. Ataxia is broadly characterized by postural deficits, impairments in upper and lower limb movements, speech impairments, and oculomotor dysfunction (Trouillas et al., 1997). However, the array of symptomatology varies according to localization and extent of damage (Dichgans and Diener, 1984).

There is evidence that the montage of symptoms associated with cerebellar ataxia is due to impaired timing. Most prominently, ataxic movements are uncoordinated. It has been suggested that the lack of coordination between muscles is due to increased time and temporal variability of muscle initiation for individual sub-movements (Day et al., 1998). Upper and lower limb ataxia is also marked by intention tremor, dysmetria, and dysdiadochokinesis on a clinical exam. Unlike the resting tremor that visibly marks Parkinson’s disease, intention tremor is not observed at rest; rather, it is most obvious at the end-points of visually-guided movements. Intention tremor contributes to dysmetria. Dysmetria is the tendency to overshoot or undershoot a target such as the physician’s finger. This, too, may be the result of impaired timing, in this case there is a breakdown in the timing between agonist and antagonist muscle contractions composing the movement (Flament and Hore, 1986). Impaired

production of rapid alternating movements, termed dysdiadochokinesis, has likewise been attributed to impaired timing of sub-movements (Conrad and Brooks, 1974).

Empirical tests of timing in cerebellar patients also support the functional contribution of the cerebellum to movement timing. A repetitive tapping paradigm has been widely used to isolate motor timing in the laboratory setting. In such a task, participants are presented with a metronome that sets the goal pace, for instance a 500ms interval marked by brief metronome tones. At the beginning of a trial, the participant's goal is to tap at this goal pace (synchronization phase). After the metronome disengages (typically following 5–10 paced intervals), the participant's goal is to continue moving at that pace until the trial's end (continuation phase; e.g., after 15–20 unpaced taps). Importantly, individuals with cerebellar damage are impaired in repetitive tapping with a range of effectors (Ivry, Keele, and Diener, 1988). Specifically, temporal variability is greater for those with cerebellar damage relative to control groups (typically matched in age, education, handedness, and gender).

Moreover, a corpus of studies suggests that motor timing deficits in cerebellar patients may underlie movement inaccuracies. In a study of overarm ball throwing, inaccuracies of throws produced by individuals with cerebellar lesions were related to increased variability in the timing of the ball release within the rotation of the arm (Hore, Timmann, and Watts, 2002; Timmann, Richter, Bestmann, Kalveram, and Konczak, 2000; Timmann, Watts, and Hore, 1999). Likewise, ataxic speech may be greatly accounted for by a deficit in motor timing. The duration of syllable repetitions is slowed and irregular in ataxic speech. Speech slowing may be similar to that observed in individuals with Parkinson's disease (Ackermann et al., 1997b; Canter, 1963). However, cerebellar lesions also yield and increase the temporal variability of articulatory timing (Ackermann and Hertrich, 2000; Schalling, Hammarberg, and Hartelius, 2007).

These motor timing deficits are consistent with historical views of the cerebellum as being a motor structure, particularly for movement coordination. However, cerebellar patients are also impaired in non-motor, temporal perception tasks. A duration discrimination task provides an ideal probe of temporal perception with little motor demands. In a duration discrimination task, participants are presented with two intervals and asked to judge whether the second is shorter or longer than the first. By parametrically varying the difference between the intervals, a discrimination threshold and variability in discrimination performance can be obtained. While thresholds are generally similar between cerebellar patients and matched controls, variability in performance is greater for those with cerebellar lesions (Ivry and Keele, 1989) suggesting that the internal clock is 'noisy' (Ivry and Spencer, 2004a). Notably, differences

are only observed for temporal discriminations. When the task requires discrimination of the amplitude (or loudness) of the tones (Ivry and Keele, 1989) or frequency (Casini and Ivry, 1999), performance does not differ between individuals with cerebellar lesions and controls.

The impairment in temporal perception may also underlie the deficit in speech perception observed in individuals with cerebellar ataxia. Distinguishing temporal phonetic features is critical to discriminating speech successfully. In English, to distinguish between '*rabid*' and '*rapid*' relies on precise temporal coding. Using similar words from the German language, such as '*boden*' and '*boten*', Ackermann and colleagues (1997a) found impaired discrimination of speech sounds in individuals with bilateral cerebellar degeneration, and this deficit was specifically associated with the temporal cues innate in the speech stimuli.

A set of recent studies further illustrates that cerebellar lesions also lead to impaired perceptual timing of interception, a skill necessary to catch a ball or to catch a closing elevator. In one study, individuals with cerebellar ataxias and matched control participants played a computer game in which a moving target must be intercepted by a 'cannon ball'. As such, the task required integration of an estimate of the speed of the moving target as well as the speed of the cannon ball once it was released (through a finger press). Participants with cerebellar ataxia performed significantly worse at the task than healthy controls (Bares et al., 2007; Bares et al., 2010a,b) and participants with Parkinson's disease (Bares et al., 2010a) supporting a role of the cerebellum in this form of perceptual time estimation.

In addition to temporal production and perception tasks, the cerebellum contributes uniquely to temporal aspects of associative learning. While early studies focused on the contribution of hippocampal and cortical areas (Gormezano et al., 1962; Oakley and Russell, 1972), only cerebellar lesions eliminate learning of the conditioned response (McCormick and Thompson, 1984). This is often demonstrated with an eye blink classical conditioning paradigm. In a typical eye blink conditioning task, the individual experiences trials in which an air puff to the eye, which causes an unconditioned eye blink, is paired with a tone. Over time, the individual is conditioned to respond to the tone alone with an eye blink. When a delay is implemented between the tone and the air puff, precise timing of the eye blink in response to the tone is necessary in order for the response to be adaptive (i.e., eye closed at the time at which an air puff might arrive). In animal and human cerebellar lesion studies of eye blink conditioning, the subjects are able to learn the conditioned response following a cerebellar lesion. Importantly, however, the adaptive timing of the response is lacking (Gerwig et al., 2003; Perrett, Ruiz, and Mauk, 1993;

Woodruff-Pak, Papka, and Ivry, 1996). In other words, the cerebellar lesioned animal will appropriately learn the response (a blink), but this response is ill-timed relative to the conditioned stimulus and, thus, not adaptive.

Collectively, these data demonstrate that temporal impairments may underlie ataxic movements. Perhaps more importantly, cerebellar lesions result in impaired timing in tasks explicitly measuring temporal perception and production (for reviews see Ivry and Spencer, 2004b; Ivry, 1996).

3 Timing: Localized or Distributed?

While cerebellar lesions result in timing impairment, this alone does not necessarily implicate the cerebellum in functioning as a single neural clock (i.e., a specialized dedicated timekeeper). Lesions in other subcortical or cortical regions may yield similar timing deficits that would support timing as a distributed function incorporating a network of brain areas (i.e., a distributed dedicated timekeeper). A third alternative is that multiple brain areas may have the ability to time depending on the relevant modality (i.e., intrinsic timing; for a review see Ivry and Schlerf, 2008).

A wealth of individual difference studies using repetitive tapping tasks, collectively favor a neural clock that functions across a range of durations. This individual difference work is carried out under the assumption that if there is a single neural clock, then a person with a “good clock” should perform well across a range of timing tasks and, likewise, a person with a rather “poor clock” should perform relatively poorly across tasks. In other words, one should see highly significant correlations in temporal performance across timed tasks. Indeed, temporal variability for a repetitive finger tapping task significantly correlates with variability for tapping with a range of other effectors. For instance, finger tapping (flexion/extension at the metacarpophalangeal joint) at a rate of 400ms per tap correlates with tapping with the arm (flexion/extension of the glenohumeral-shoulder-joint) and tapping the jaw (excursions of the temporomandibular joint) at the same rate (Franz, Zelaznik, and Smith, 1992). Likewise, temporal variability in the repetitive finger tapping task correlates with temporal variability for a repetitive foot tapping task (flexion/extension at the talocrural-ankle-joint; Keele et al., 1985).

Moreover, individual difference studies suggest that the capacity of the neural clock is not limited to motor tasks. Performance on repetitive tapping tasks is also predictive of performance on non-motor timing tasks (Keele et al., 1985). The duration discrimination task (described above) has been used to demonstrate this point. Importantly, performance on repetitive tapping tasks is

predictive of performance on the duration discrimination task, suggesting a shared timing process across motor and perceptual timing tasks.

Thus, there is certainly reason to believe that temporal performance draws on a single neural resource. Taken in conjunction with the evidence provided in Section 2, evidence points to the cerebellum as being this neural clock. While this proposed function of the cerebellum as a timekeeper has gained favor, recent work in our lab and others has focused on limitations of the cerebellar clock.

4 Limitations on Cerebellar Timing

4.1 *Event versus Emergent Timing*

Given the rather consistent pattern of correlations that our lab and others have observed amongst timing tasks (Franz, Zelaznik, and Smith, 1992; Keele and Hawkins, 1982; Keele et al., 1985), we were surprised to find a lack of correlation between temporal variability on a repetitive finger tapping task and a repetitive continuous circle drawing task. As an aside, continuous cycling (either circling or ‘wagging’ of an effector) was of interest given that research on motor coordination, another hypothesized function of the cerebellum, was largely based on continuous bimanual movements (e.g., Carson et al., 1997; Haken, Kelso, and Bunz, 1985; Kelso, 1984; Semjen, Summers, and Cattaert, 1995). Timing of continuous movements is also particularly unique as temporal variability is remarkably low for healthy young adults. While the coefficient of variation, a measure of variability normalized to movement time, is typically 5–8% of the mean movement time for finger tapping (Keele et al., 1985; Theoret, Haque, and Pascual-Leone, 2001), it is as low as 3–5% for circle drawing (Spencer et al., 2003; Spencer and Zelaznik, 2003; Zelaznik, Spencer, and Ivry, 2002). Most importantly, these measures of temporal variability do not correlate across these two tasks (Robertson et al., 1999; Zelaznik, Spencer, and Ivry, 2002).

In a continuous circle drawing task, participants are given a circle template to equate movement amplitude across participants. A visual target at the top of the circle template assists participants in aligning movements to the metronome; participants are to pass through this target coincident with the metronome beep during the paced portion of a trial, just as they are to touch the table coincident with the metronome for the repetitive tapping task (Robertson et al., 1999; Zelaznik, Spencer, and Ivry, 2002). Nonetheless, when one performs this task, it is quite obvious that this movement goal is much less salient for the continuous circle drawing task than it is for the repetitive finger tapping task.

This led us to propose the Event Timing Hypothesis: Movements or intervals that are marked by salient features would share a timing process, while movements lacking such a structure would not be amenable to such a process (Ivry et al., 2002). To test this hypothesis, we compared variability on the continuous circle drawing task to a discrete circle drawing task. In the discrete circle drawing task, participants traced the circle template for every other movement interval and paused at the top of the trajectory for the intervening intervals. Thus, these tasks were equated for movement speed, amplitude, and biomechanical demands. In spite of this, there were no correlations between continuous and discrete circle drawing. Consistent with the Event Timing Hypothesis, however, performance on the discrete circle drawing did predict performance on the repetitive tapping task (Zelaznik, Spencer, and Ivry, 2002).

At this point, we know little about how continuous movements are timed. It has been suggested that timing for such tasks may be emergent. The idea of emergent timing is derived from Dynamical Systems Theory applied to studies of motor control (Turvey, 1977). Accordingly, timing for continuous tasks may emerge from the dynamics of the limbs. Alternatively, other properties of the movement, rather than timing being under the direct control of a neural clock, may be under direct neural control and result in well-timed movements. For instance, in a continuous circle drawing task, neural processes controlling movement velocity or jerk (Hogan and Flash, 1987) may result in precise temporal consistency without the direct control of time. Supporting the concept of an array of unique emergent processes, we found that temporal processes underlying continuous circling and continuous line drawing are distinct, and these processes are also independent of that used for discrete movements such as finger tapping (Spencer and Zelaznik, 2003). In other words, there seems to be no single 'continuous movement timer'. To illustrate this, we applied a slope analysis to the variability of timing across these tasks. The slope analysis, the examination of the relation between the timed interval and timing variance, assumes two independent sources of variability to movement timing: A duration-independent source associated with variability in implementing a timed movement command and a duration-dependent source associated with the central clock-like process (Wing and Kristofferson, 1973). When movement time is plotted against temporal variability for a given task a linear relationship is observed, particularly for millisecond to second range tasks (Gibbon, 1977; Gibbon and Church, 1990). Importantly, if two tasks share a neural timing process, they should have the same variability-interval relationship, or shared slope (Ivry and Corcos, 1993; Ivry and Hazeltine, 1995). Consistent with this, we observed the same

variability-interval slopes for two line drawing tasks. Likewise, the slope was the same for two continuous circle drawing tasks. However the slopes were unique for continuous circle drawing relative to continuous line drawing. Thus, these results suggest a degree of independence for timing processes underlying continuous movement timing, but within any given task (e.g., variants of a continuous circling task), a shared timing source is used (Spencer and Zelaznik, 2003).

Even under indirect control, however, it is speculated that continuous movements may rely on a neural 'clock' to align early movement cycles to the metronome-instructed temporal goal. According to this Transformation Hypothesis, early cycles of a repetitive movement may utilize an explicit timing process to set the pace of the movement before a non-clock process (e.g., velocity-based control) may take over. Supporting this, Zelaznik and colleagues (2005) again compared temporal performance for repetitive finger tapping and repetitive continuous circle drawing but focused analyses on the initial, early cycles of the trials. Variability in the first cycle of these tasks was significantly correlated. Yet, consistent with work reviewed above, temporal variability for subsequent cycles did not correlate. This suggests that tasks with a precise temporal goal may initially require the event-based temporal representation, or internal clock, even though other non-clock timing processes may take over once the appropriate rate is adopted consistent with the Transformation Hypothesis (Zelaznik et al., 2005).

Individual difference studies into event timing in healthy individuals have provided insight as to how the cerebellar 'clock' measures time for movements and percepts. That is, the cerebellum may serve as a timer when salient features are available by which to start and stop the neural clock (Ivry et al., 2002). If such were the case, cerebellar lesions would yield impaired timing on repetitive movement tasks and duration perception tasks that require the timing between discrete events (e.g., metronome beeps, table touches when finger tapping), deficits that have been consistently reported. However, if the cerebellum provides only discrete/eventful timing measures, this yields a rather counterintuitive prediction, that is that individuals with cerebellar lesions may be unimpaired in the timing of continuous movements. We tested this in a series of studies of individuals with cerebellar ataxia.

In one such study, we compared temporal performance on repetitive finger tapping (on a table top; i.e., 'eventful'), continuous circle drawing, and discrete circle drawing (Spencer et al., 2003). The goal movement time for all tasks was 800ms per cycle. Participants were individuals with focal, unilateral lesions of the cerebellum due to stroke or tumor resection. With focal

unilateral cerebellar lesions, impairments are observed unilaterally, in the ipsilesional limb (the cerebellum receives crossed projections from the cortex, and therefore, control is ipsi- rather than contra-lateral; Franz, Ivry, and Helmuth, 1996; Ivry, Keele, and Diener, 1988). Thus, this group allows for within-subject comparisons of the limb under control of the lesioned cerebellum to the unimpaired limb. Similar to previous studies (e.g., Ivry, Keele, and Diener, 1988), we found that temporal variability was greater with the ipsilesional, impaired limb relative to the contralesional, unimpaired limb for the table tapping task. Likewise, variability was greater for the ipsilesional limb relative to the contralesional limb for the discrete circle drawing task. Importantly, consistent with the predicted role of the cerebellum for timing of events, there was no difference in performance across limbs for the continuous movement task. Strikingly, the coefficient of variation was remarkably low, only about 3% for both the unimpaired and impaired limb in the cerebellar lesion group for the continuous circle drawing task (Figure 9.1; Spencer et al., 2003).

In a second experiment, we compared temporal variability for the repetitive finger tapping task under four conditions: (1) tapping on a table top, a variant of the task most commonly used in previous studies, at a rate of 1000ms per cycle; (2) a discrete air tapping task, also at a rate of 1000ms per cycle, in which taps were made with the finger held away from any table surface and movements were instructed to be 'discrete and staccato-like'; (3) a continuous air tapping task, at a rate of 1000ms per cycle, in which taps were, again, made without surface contact and participants were instructed to "move smooth and

FIGURE 9.1 Coefficient of variation (standard deviation divided by mean movement time) for repetitive finger tapping, discrete circle drawing and continuous circle drawing. Movements were performed by individuals with unilateral cerebellar lesions with both their impaired and unimpaired limbs. Error bars represent standard error.

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continuously”; and (4) a continuous air tapping task at a rate of 500ms per cycle (Spencer et al., 2003). Note that the last task, the fast continuous task, was included to equate for the faster velocity of the movement component of each cycle in the discrete tasks relative to the continuous tasks. That is, when tapping discretely, the velocity of the finger must be faster than in the continuous task in order to include a brief pause within the trajectory, thereby making the movement discrete. As such, one might argue that impairments associated with cerebellar lesions in timing of discrete movements, such as table tapping, are simply due to the speed of the movement, a deficit that may not be surprising to observe in conjunction with any movement disorder. Importantly, results were consistent with the Event Timing Theory and the hypothesized role of the cerebellum in timing movements with salient events. That is, for individuals with focal cerebellar lesions, variability was greater with the ipsilesional, impaired limb relative to the contralesional, unimpaired limb for the discrete tasks, table tapping, and discrete air tapping. There was no difference in performance across limbs for either the fast (500ms/cycle) or slow (1000ms/cycle) continuous air tapping tasks.

We found a similar pattern of results when comparing a group of individuals with bilateral cerebellar lesions (degeneration due to SCA or sporadic cerebellar ataxia) to healthy matched controls. Here, performance with the dominant hand was compared for individuals with bilateral cerebellar ataxia (SCA3, SCA6, or sporadic cerebellar ataxia) and a group of healthy age- and education-matched control participants. Individuals with bilateral cerebellar lesions exhibited greater variability than the control group for the discrete tasks. There was no difference in performance across groups for the continuous movement tasks (Spencer et al., 2003).

Finally, neuroimaging evidence supports the Event Timing Theory of cerebellar function. We examined the Blood-oxygen-level dependent (BOLD) response (i.e., neural activation) using functional magnetic resonance imaging (fMRI) when healthy young adults performed the continuous and discrete air tapping tasks described above. While activation in lobule VI of the cerebellum was observed for both conditions, additional activity (located in the superior vermis) was selectively activated for the discrete movement. This is consistent with the hypothesis that the cerebellum plays a unique role in discrete movement timing (Spencer et al., 2007).

Together, this work demonstrates that the cerebellar clock function is restricted. Specifically, the manner in which the cerebellum computes time, by representing intervals demarcated by salient events, by nature restricts this role to a subset of movement and perceptual tasks that are amenable to such a timekeeper.

4.2 *Interval Range of the Cerebellar Timing: Long versus Short Interval Timing*

Importantly, tasks discussed to this point involved intervals in the millisecond range, mostly less than 2000ms. For intervals greater than this, the contribution of the cerebellum to timing may decrease, with increasing weight of the non-temporal processes contributing greatest to performance variability. For instance, Mangels, Ivry, and Shimizu (1998) compared performance on a short, 400ms, interval task with performance on a long, 4 s, interval task in individuals with cerebellar lesions and age- and education- matched healthy control participants. The task was a duration perception task, ruling out the contribution of motor deficits to short versus fast movements. They found that individuals with cerebellar lesions were impaired, relative to healthy control participants, in perception of both the short and long intervals. To examine whether the neocortex further supports this timing function, via attention or working memory mechanisms, a group of individuals with focal lesions to the prefrontal cortex were also included. Individuals with lesions of the prefrontal cortex were impaired, relative to healthy controls, on the long interval perception tasks. There was no difference in performance for these two groups on the short, 400ms, perception task. The authors suggest that, for longer intervals, cortical contributions are necessary to maintain the standard in working memory and to attend to the task over the long interval. However, it may be somewhat surprising that the deficit in performance was not reduced for the longer, 4 s, interval for those with cerebellar lesions. One explanation for this finding is that, for longer interval timing, a sub-interval timing strategy may be used. That is, when faced with the task of timing a 4-s interval, one may internally time four 1-s intervals. As such, the cerebellar contribution to millisecond timing would be evident in this way.

In a meticulous analysis of temporal perception and production across a range of suprasecond intervals (2–12 s), a recent study found further evidence that the cerebellar contribution is greatest for short intervals although the deficit is still present for longer intervals (Gooch et al., 2010). In the duration production task under consideration, participants were required to reproduce the duration of a 2, 4, 6, 8, 10 or 12 s stimulus (a red square on a computer screen). The authors report a significant group (cerebellar patients versus controls) by interval interaction, reflecting highly variable temporal performance for the cerebellar patients relative to controls at the shortest intervals (2 s and, less so, 4 s) with little group differences observed at the longer intervals. Likewise, a temporal estimation task, requiring participants to produce intervals of 2, 4, 5, 6, 10 or 12 s from memory, revealed consistently worse performance for individuals with cerebellar lesions compared to controls across all intervals,

although the deficit was again greatest at the shorter durations. Notably, when the patient group was divided into those with middle-to-superior cerebellar lesions and those with damage outside of middle-to-superior cerebellum, only those with middle-to-superior damage differed from controls. This suggests that the cerebellar clock may be localized to superior cerebellum, an issue we will return to below.

Individuals with Parkinson's disease are also reported to be impaired in temporal perception and production tasks. Movements of individuals with Parkinson's disease are visibly slow, a deficit termed bradykinesia. As such, one might predict that individuals with Parkinson's disease would be slow on a repetitive tapping task. Counter-intuitively, however, these individuals actually tend to speed up movements (Harrington et al., 2004; Ivry and Keele, 1989; O'Boyle, Freeman, and Cody, 1996). Whether temporal variability is increased in individuals with Parkinson's disease, as would be expected for an impaired neural clock, is unclear. Considering intervals in the millisecond range (less than 2 s), some studies report increased temporal variability in Parkinson's disease (Harrington, Haaland, and Hermanowicz, 1998) relative to matched controls, while others find no difference (Ivry and Keele, 1989; Spencer and Ivry, 2005). While Parkinson's disease patients are often examined as a model of basal ganglia dysfunction, isolation of the disease to basal ganglia is not pure. Importantly, Aparicio and colleagues (2005) found that individuals with focal lesions of the basal ganglia, most in the putamen, some extending to the caudate, internal capsule or globus pallidus, due to stroke, were unimpaired on a repetitive tapping task. Variability of taps, with a goal pace of 400ms, did not differ for basal ganglia lesion patients relative to healthy controls nor was there a difference in variability between the contralesional, impaired limb and the ipsilesional, unimpaired limb. While this work remains to be replicated, it calls into question the conclusion of some that the basal ganglia is an internal clock for millisecond range intervals.

It is worth considering that the basal ganglia may contribute to timing of suprasecond intervals, those intervals greater than the 200–2000ms that seems to be the expertise of the cerebellum. Supporting this, Matell and colleagues (2003) illustrated the ability of the striatum to time intervals of 10 and 40 s. By recording striatal neurons in rats trained to time press a lever 10 or 40 s after a stimulus onset, it was clear that these neurons distinguished between the two intervals just as response rates were distinct for the two trial types. More importantly, a relationship between the time of peak firing and performance was observed (Matell, Meck, and Nicolelis, 2003).

The selective role of basal ganglia for suprasecond intervals and not subsecond intervals was distinguished in a recent study in humans using deep brain

stimulation (DBS) to the subthalamic nucleus (STN; Wojtecki et al., 2011). DBS is used to treat symptoms of Parkinson's disease. When the stimulation was off, these participants were impaired relative to matched controls; specifically, 15-s intervals were underestimated in length. Low frequency (10 Hz) stimulation resulted in further underestimation when reproducing the 15-s interval. Conversely, high frequency (130 Hz) stimulation reduced the amount of underestimation, resulting in performance similar to that of controls. However, neither high nor low frequency DBS to the same region influenced duration discrimination in the millisecond range (800–1600ms), supporting a distinction in the temporal range that the basal ganglia may expertly time.

The corollary to the consideration of a separate, perhaps basal ganglia-based, timing process for longer intervals, is to consider whether there is a lower limit to the cerebellar timing function. Can the cerebellum time intervals on the range of 50 or 100ms? Mounting evidence suggests that timing for such ultra-short intervals is also distinct. In fact, ultra-short intervals may be unique from other intervals in that timing for ultra-short intervals might not draw on the function of a single neural clock but rather the timing process may be modality dependent, drawing on cortical areas associated with that modality. Termed the State-Dependent Network model, Karmarkar and Bounomano (2007) proposed that networks of neurons within a given cortical region can accurately detect time. The basis for the State-Dependent Network model is that time is implicitly represented in the synaptic properties or state of a neural network (Buonomano and Mauk, 1994; Karmarkar and Buonomano, 2007; Yamazaki and Tanaka, 2005). By simulating a series of state-dependent networks, Karmarkar and Buonomano (2007) showed that, when presented with a brief (e.g., 100ms) interval marked by two tones, the first tone of the pair will generate activity in the network. This activity then changes predictably over time and includes fast and slow inhibitory post-synaptic potentials and short-term synaptic plasticity in the connections between nodes in the network. When the second tone of the interval arrives, the dynamical state of the network has been changed as a result of the first tone, so there is a different pattern of activity in the network in response to the second tone even if the second tone is identical to the first tone in duration, pitch, and frequency. The temporal interval defined by the two tones can be interpreted from the final state of the network. Importantly, if the stimulus (100ms interval marked by two tones) is preceded by any event, the state of the network is changed. As such, if standard and test intervals are presented in two different contexts, the dynamics of the state-dependent network would differ and the ability to encode duration would fail. This creates a 'reset problem', which has been used to demonstrate support for the State-Dependent Network (SDN) hypothesis. In the Reset Task

designed to test this problem, similar to the duration perception task described above, human participants were presented with an interval of approximately 100ms marked by two tones and were to respond as to whether the interval was short or long relative to a 100ms standard interval (Figure 9.2A; Spencer, Karmarkar and Ivry, 2009). Performance was similar if the test interval was preceded by a distractor interval also of 100ms. This result is consistent with the SDN hypothesis given that a fixed distractor interval would allow for building a stable representation of this fixed state based on trial-by-trial feedback. More importantly, when the distractor interval was of varying length (50–150ms), discrimination thresholds were greatly increased relative to the no-distractor condition. This is consistent with the prediction of the SDN hypothesis. That is, that the variable length distractor results in the network being in a different state each time the target interval is presented and a stable representation cannot be extracted (Karmarkar and Buonomano, 2007).

Recently, we revisited this effect, considering attentional issues that may also produce the context effects observed in the Reset Task (Spencer, Karmarkar, and Ivry, 2009). We predicted that using very brief intervals (i.e., 100ms and 100ms $\pm$ 50ms), which may trigger automatic attentional capture (Posner, 1978), imposed unique sources of variability. In other words, attention would be drawn to the distractor interval by attentional capture thereby impairing attention when presented with the target interval. To test this, we replicated the Reset Task using both conditions from the original Karmarkar and Buonomano study (2007; approximately 100ms for both the distractor and target intervals; 100–100 task) and a novel condition with a 300ms distractor and 100ms target interval (300–100 task). First, with respect to the 100–100 task, our results replicated those of Karmarkar and Buonomano (2007) in that thresholds were elevated in both the fixed and variable distractor conditions, relative to the no-distractor conditions, and thresholds were greatly increased in the presence of a variable distractor interval (Figure 9.2B; Spencer, Karmarkar and Ivry, 2009). This was not the case in the 300–100 task. While there was a small but significant main effect of a distractor, performance with a variable distractor was not worse than a fixed distractor in this condition. This result limits the range of the SDN model. That is, the original model assumes that any distractor interval (100- or 300-ms) should alter the state of the network when presented with the target interval. Rather, these results are consistent with our hypothesis that unpredictable ultra-short intervals (<150ms) may disrupt timing of the target interval. Importantly for the purposes of the present discussion, this work supports a distinction in timing for ultra-short (50–150ms) and longer millisecond range (200–2000ms) timing. Furthermore, we report that variants of the Reset Task with a 300ms target interval and either a 100ms (100–300 task) or 300ms

(300–300 task) distractor interval also failed to find the increased threshold in the variable distractor condition relative to the fixed condition or no-distractor conditions. These results indicate how attentional processes can influence the perception of brief intervals, as well as point to important constraints of SDN models. As such, we posit that the SDN model, which proposes that timing may be computed in cortical regions supporting the task modality, may support ultra-short interval timing (<200ms) but not millisecond range timing (200–2000ms; Spencer, Karmarkar, and Ivry, 2009).

5 Localization of Timing within the Cerebellum

Given the evidence supporting the function of the cerebellum in millisecond range timing, we turn to consideration of where such a function might be located within the cerebellum. Architecturally, the cerebellum is composed

FIGURE 9.2 A) The Reset Task described by Karmarkar and Buonomano (2007). Participants judged the length of the target (T) relative to a previously presented standard interval when the target was presented without a distractor (top), with a fixed interval distractor (D ; middle), or a variable length distractor (bottom). B) Consistent with Karmarkar and Buonomano (2007), we found an increased threshold with a variable distractor condition for the 100–100 condition. This was not the case in the 100–300, 300–300, or 300–100 conditions.

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of repeating loops. These loops underlie three longitudinal divisions – the vermis, the paravermis, and the hemispheres. Each of these divisions is, in turn, composed of multiple lobules. This elaborate arrangement may either suggest a highly specialized single map (Apps and Hawkes, 2009) or multiple functional units (Grodd et al., 2001). Mounting evidence suggests a specialized role of superior cerebellum in timing. As described above, timing impairments are exaggerated in individuals with superior cerebellar lesions relative to those with inferior lesions (Gooch et al., 2010). Like Gooch and colleagues (2010), Harrington and colleagues (2004) studied timing in individuals with superior versus inferior cerebellar lesions and found that timing impairments were associated with superior lesions. In this study, Harrington and colleagues compared two groups of cerebellar lesion patients: those with lesions to inferior cerebellum (approximately lobules VII–X) and those with superior cerebellar lesions (approximately lobules I–VI). Those individuals with superior, but not inferior cerebellar lesions, were more variable relative to healthy controls on the duration perception task with standards of 300 and 600ms, although this reached only trend-level for significance ($p = .07$; see Ivry and Spencer, 2004a). Moreover, those with superior cerebellar lesions were more variable than the control group on a repetitive finger tapping task at both 300 and 600ms. Specifically, total variability was modeled to dissociate the variability due to the central timekeeping process (i.e., ‘clock’ variability) from variability due to noisy motor implementation (i.e., motor variability; Wing and Kristofferson, 1973). The deficit observed in individuals with superior cerebellar damage was associated with the former, supporting an impaired clock process in superior cerebellum.

Functional imaging studies, by and large, find anterior cerebellum is active in conjunction with timed movement and perception tasks. For instance, using positron emission tomography (PET), Penhune and colleagues (1998) found that performance on the repetitive finger tapping task produces activation in lobule V beyond that seen in a control condition in which participants simply listened to the metronome. Likewise, neuroimaging of perceptual timing tasks also yields cerebellar activation. However, the localization within the cerebellum for these tasks is less clear. For example, one study of visual timing pointed to a critical region around the border of left Crus I/II, activation (Lewis and Miall, 2003). Other studies have pointed to a region within lobule VI (Aso et al., 2010) or superior vermis (Teschke and Karhu, 2000; Xu et al., 2006).

The anterior cerebellum has a known somatotopic arrangement, akin to the homunculus of the motor cortex. Using functional neuroimaging, mapping of the activation in this region suggests an inverted body map with the foot superior to the hand and the hand superior to the lips and facial representations

(Grodd et al., 2001; Habas, Axelrad, and Cabanis, 2004; Nitschke et al., 1996; Rijntjes et al., 1999). It has been proposed that underlying this body map is a series of interval representations (Ivry, 1996). In other words, the cerebellum may have an effector by interval arrangement akin to the ocular dominance columns in visual cortex. This model would be consistent with the observed unilateral impairment associated with lateralized cerebellar lesions.

In addition to the somatotopic organization of the anterior lobe, somatotopy has been observed in the inferior aspect of the posterior lobe of the cerebellum (lobules VIIIB and VIII; Habas, Axelrad, and Cabanis, 2004; Rijntjes et al., 1999) and, most recently, we have reported evidence of a somatotopic arrangement in lateral cerebellum, lobules VI and VII (Schlerf, Verstynen, Ivry, and Spencer, 2010). In that study, we used fMRI to map movements of the fingers and toes that were either simple (i.e., flex/extend all fingers/toes simultaneously) or complex (i.e., flex/extend individual digits sequentially). Movements were repetitive at a rate of approximately 500ms. For all movements, ipsilateral activation was observed in anterior cerebellum and this activation was somatotopically organized, that is, foot movement responses were distinct from, and inferior to, hand movement responses. Interestingly, when movements were complex, activation was also observed in lobules VI and VII. This lateral cerebellar activation was particularly noteworthy for two reasons. First, unlike the unilateral activity observed in the anterior cerebellum, activation in lateral cerebellum in conjunction with complex movements was bilateral. Second, the activation was somatotopically arranged here as well. This is particularly interesting in lateral cerebellum given that this region has previously been associated with the non-motor functions of the cerebellum (Akshoomoff and Courchesne, 1992; Desmond, Chen, and Shieh, 2005). Such a role is supported by connectivity studies, which illustrate that lateral cerebellum is functionally connected to prefrontal cortex (Kelly and Strick, 2003; Krienen and Buckner, 2009; Middleton and Strick, 2001). Thus, finding somatotopic organization here would be akin to finding somatotopic organization in the frontal cortex. To make sense of this arrangement, from these observations, we propose that the lateral cerebellum may support the anterior cerebellar function under conditions with high cognitive demands – such as movements with high complexity (Schlerf, Verstynen, Ivry, and Spencer, 2010) or working memory when a task requires response mapping (Spencer and Ivry, 2009).

6 Conclusions

It should be clear from this Chapter that the cerebellum plays a critical role in timing and, for this reason, timing deficits are central to the impairments

associated with cerebellar lesions and disorders. However, this chapter also emphasizes a critical distinction in temporal processing for ultra-short intervals, millisecond, and supra-second intervals. Timing of ultra-short intervals (approximately those less than 200ms) may utilize SDN in relevant cortical regions. Supra-second intervals (approximately those greater than 2 s) may utilize basal ganglia processes with an increase in weight from cortical areas, such as the frontal cortex, for cognitive demands such as working memory. Central to our review is the cerebellum's role for millisecond range intervals (approximately 200–2000ms). While such a distinction may seemingly diminish the functional capacity of the cerebellum, we posit that a deficit in millisecond range timing has substantial ramifications as evidenced by the ataxic movements and impaired perceptions of individuals with cerebellar lesions and disorders.

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