The neural representation of time

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This review summarizes recent investigations of temporal processing. We focus on motor and perceptual tasks in which crucial events span hundreds of milliseconds. One key question concerns whether the representation of temporal information is dependent on a specialized system, distributed across a network of neural regions, or computed in a local task-dependent manner. Consistent with the specialized system framework, the cerebellum is associated with various tasks that require precise timing. Computational models of timing mechanisms within the cerebellar cortex are beginning to motivate physiological studies. Emphasis has also been placed on the basal ganglia as a specialized timing system, particularly for longer intervals. We outline an alternative hypothesis in which this structure is associated with decision processes.

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Abbreviations

CR	conditioned response
fMRI	functional magnetic resonance imaging
PD	Parkinson's disease
SMA	supplementary motor area

Introduction: scope of the review

The representation of temporal information remains one of the most elusive concepts for neurobiology. Unlike vision and audition, there are no dedicated sensors for time. Yet the passage of time is as perceptually salient as the color of an apple or the timbre of a tuba.

Fraisse [1] was the first to emphasize that a discontinuity in our sense of time was evident around 2–3 s. Lewis and Miall [2••,3] argue that timing in the shorter range is 'automatic', reflecting the engagement of processes associated with the production of skilled movements. Longer range timing is hypothesized to be 'cognitive', dependent on neural systems associated with attention and working memory.

In this review we focus on tasks in the shorter range. Even within this range, the phrase 'temporal processing' may refer to very different phenomena. Temporal order tasks require an ordinal judgment, indicating the order of successive stimulus events. These types of judgments are affected by the rate of temporal integration. Other tasks require a metrical judgment that involves the analysis of elapsed time. The assessment of duration might be either explicit, as in a duration discrimination task, or implicit, as in eyeblink conditioning, in which the response must be precisely timed to be adaptive. We restrict our review here to tasks in which timing would appear to be metrical.

Is there a specialized neural region for millisecond timing?

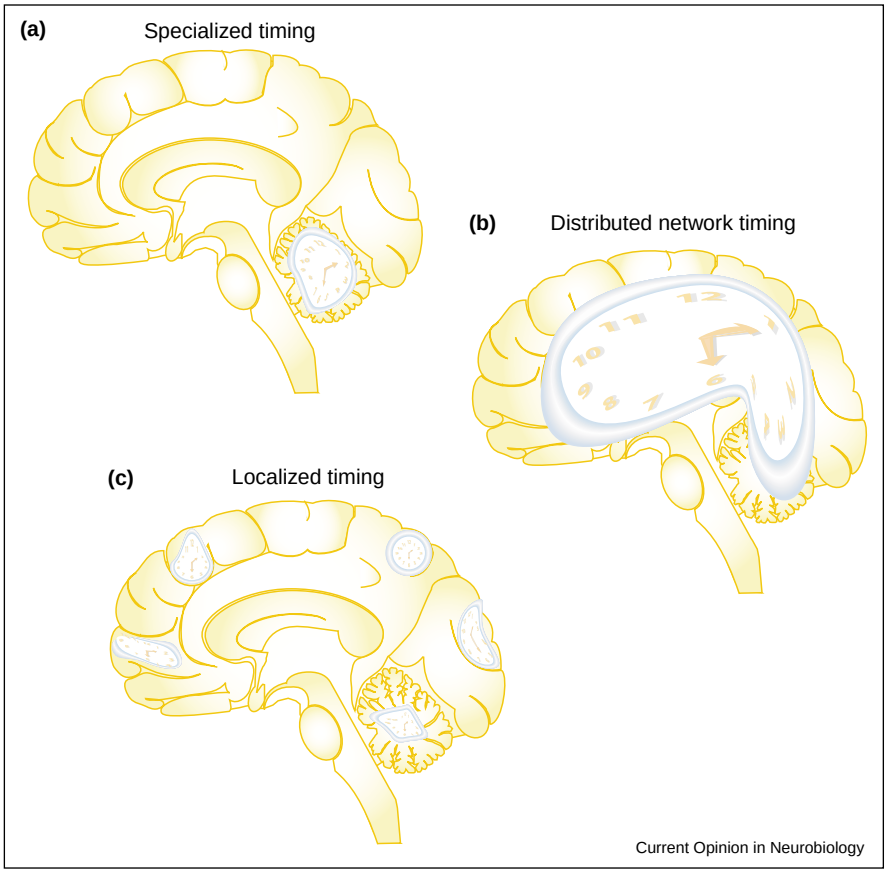
Does the existence of temporal regularities imply that some process is dedicated to representing time? Temporal regularities could be explicitly represented, reflecting a dedicated internal timing mechanism. Dedicated timing could be performed locally, or result from the operation of a specialized neural structure or distributed network (Figure 1). Alternatively, temporal regularities could be an emergent property, reflecting the fact that dynamic processes such as those involved in coordinating limbs for action [4,5] or selective attending in perception [6] occur in time.

Lesion studies

Various lines of evidence indicate that the cerebellar cortex provides a precise representation of the temporal relationship between successive events. Perhaps the most compelling evidence comes from studies of eyeblink conditioning in which the conditioned response (CR) must be timed to occur just before the unconditioned stimulus. Studies consistently demonstrate that the CR is disrupted following lesions of the cerebellum [7]. Whereas associative mechanisms operate at various levels within the cerebellum [8], accurate timing of the CR is dependent on the cerebellar cortex [9,10•]. Knockout species lacking the capability for long-term depression (LTD) at the parallel fiber–Purkinje cell synapses fail to exhibit adaptive timing [11••].

The movements of patients with cerebellar lesions are characterized by a breakdown of the timing between muscular events. For example, these patients are inaccurate in throwing, in part because of increased variability in timing the opening of the hand with respect to arm rotation [12,13]. However, such deficits do not necessarily imply the involvement of an explicit timing signal. Hand opening might be triggered by cerebellar computations of

Figure 1



General frameworks of the neural mechanisms for timing. **(a)** The specialized timing model is based on the idea that a particular neural region is uniquely capable of representing temporal information and that this system is recruited when this form of processing is required. This example illustrates the cerebellum as a specialized system. **(b)** In the distributed network timing model, the representation of temporal information results from the interactions within a set of neural structures. **(c)** The local timing model does not entail a dedicated timing system. Rather, temporal information is computed within the neural structures required for a particular task.

the dynamic transitions required between successive states, a form of forward modeling by the cerebellum [14].

The manner in which a task is conceptualized can influence how timing is achieved [15,16]. Patients with cerebellar lesions show increased variability on temporal production tasks, such as rhythmic tapping, or during the production of isolated movements with a specified target duration [17••]. However, these patients are unimpaired when the periodic movements are smooth and continuous. This dissociation is consistent with the hypothesis that tasks involving discontinuities or salient features embody an event structure. The cerebellum provides the signals specifying the timing of these events, similar to the way in which the conditioned and unconditioned stimuli in eyeblink conditioning define two salient events. By contrast, continuous movements lack this event structure and temporal regularities are an emergent property reflecting the operation of another control parameter (e.g. angular velocity) [15,16,17••].

Harrington *et al.* [18•] failed to observe consistent increased temporal variability on production or perception tasks in patients with unilateral cerebellar lesions. However, a subset of patients with lesions encompassing the superior cerebellum exhibited increased variability on the production task and a marginally significant increase on the perception task. Interestingly, disruption of eyeblink conditioning is also more pronounced in patients with superior cerebellar lesions when compared to those with inferior lesions [7].

Lesion studies have also implicated the basal ganglia in temporal processing. This work, conducted within the framework of the influential scalar timing model [19•], has generally involved intervals up to 40 s. Timing within this range is assumed to involve a set of separable components including a pacemaker, accumulator, gating mechanism, and decision processes, in which the output of the accumulator is compared to reference memory of stored intervals. The basal ganglia are hypothesized to be a

crucial component of the pacemaker/accumulator process. In contrast to normal animals, rats with striatal lesions fail to increase the rate of lever pressing at the time of an expected reward [20]. Additionally, dopaminergic agents lead to a systematic distortion of timed responses: agonists and antagonists lead to a shortening and lengthening, respectively, of perceived time. These results are consistent with the hypothesis that dopamine levels affect the speed of an internal pacemaker. However, dopamine deficiencies could disrupt memory functions [21] or, as will be discussed in the conclusions, alter decision processes.

Whether or not the basal ganglia are involved in timing in the range of hundreds of milliseconds remains unclear. Some studies report time perception deficits in patients with Parkinson's disease (PD) ([22,23] but see [24]), and pharmacological manipulations in normal individuals can alter temporal acuity [25]. Graeber *et al.* [26] report that a subset of PD patients show a marked bias on a speech perception task in which the discrimination between two consonants is temporally cued. The patients' judgments suggested that the crucial interval was underestimated, consistent with the idea that dopamine depletion leads to the slowing of an internal pacemaker.

Time production studies in the milliseconds range, however, are inconsistent with this hypothesis. PD patients tend to speed up on finger tapping tasks [18•,27,28]. Moreover, the literature is inconsistent in terms of whether or not PD patients show increased temporal variability on production tasks [18•,27–29]. PD can be problematic for studying basal ganglia dysfunction given the widespread reduction in dopamine. A forthcoming study uses an alternative approach, testing patients with chronic focal lesions of the striatum [30]. Surprisingly, these patients exhibited no impairment on a finger tapping task.

Although lesion studies of timing in the milliseconds range have focused on the cerebellum and basal ganglia, a cortical locus cannot be dismissed. Various lines of evidence suggest that temporal processing could be differentially affected by lesions of the right and left hemispheres [31], or that the hemispheres integrate information at different speeds [32–34]. Surprisingly, few studies have tested patients with cortical lesions on time perception and production tasks. In one such study, patients with right hemisphere lesions were impaired on a duration discrimination task for intervals of 300 and 600 ms [35]. The impairment was attributed to attentional processes required for gating timing signals into working memory. Similarly, repetitive transcranial magnetic stimulation (TMS) over right prefrontal cortex in neurologically healthy individuals altered the perception of intervals spanning 5–15 s [36].

Neuroimaging studies

In contrast to the relatively sparse lesion literature, the number of neuroimaging studies of temporal processing has increased exponentially in recent years. Two recent reviews have summarized this work [3,37]. Given this, our review focuses on four new functional magnetic resonance imaging (fMRI) papers involving duration discrimination tasks with intervals in the millisecond range [2••,38–40].

Lewis and Miall [2••] asked participants to judge the duration of horizontal length of a visual stimulus. In the duration conditions, the stimuli could vary around 0.6 s or 3 s. Compared to the length conditions, duration judgments were associated with increased activation in prefrontal, insula, premotor (lateral and supplementary motor area [SMA]), and parietal cortices. Moreover, activation specific to the 0.6 s condition was observed in the right temporal lobe and left cerebellar hemisphere. Activation specific to the 3 s condition was observed in left parietal cortex and posterior cingulate. A similar pattern was found in a study using intervals around 1 s [39]. Compared to a temporal order judgment control task, duration discrimination led to increased activation in right prefrontal cortex, SMA, and left cerebellum. Basal ganglia activation during the duration tasks was not found in either study.

However, two fMRI studies have reported putamen activation during duration discrimination tasks. In one study [38], the stimulus duration was centered around 700 ms and participants judged either duration or brightness. Cortical foci in the duration task included bilateral prefrontal, temporal, and inferior parietal cortices, as well as the SMA, the left premotor area, and the right insula. Basal ganglia activation was restricted to the left putamen. Cerebellar activation in the vermis was similar in both tasks, suggesting that this region was not specifically recruited for temporal processing. A similar cortical network was observed active in a duration discrimination task with auditory stimuli when performance was compared to that during rest [40]. However, essentially the same areas were also recruited in the frequency discrimination control task. Right putamen activation was greater for the duration task, but only in a restricted analysis that used a liberal statistical threshold to evaluate activation within this region. Cerebellar coverage was limited in this study and thus a similar analysis could not be performed.

Studies of time production have focused on tasks in which rhythmic complexity is varied [41–43]. Identification of time-specific areas in such studies is difficult as baseline conditions also require the production of timed movements. An alternative approach is to look at changes in brain activation when participants learn movement patterns in which the sequence of finger responses is fixed, the sequence of inter-response intervals is fixed, or both

[44•]. The inferior temporal gyrus and the lateral cerebellum were the only activation foci specific to temporal learning.

Physiological analysis of temporal processing

The literature is replete with sophisticated computational models for the representation of temporal information. Delay line mechanisms, operating in the microsecond range, have been proposed to underlie sound localization. Differences in the time required for neural signals to traverse fixed distances, coupled with coincidence detectors, can be exploited in simple networks to determine the horizontal position of a sound source [45]. Given the speed of neural conduction times, such mechanisms are unlikely to produce sufficient intervals for timing in the hundreds of milliseconds range [46], and would certainly fail for longer intervals. For temporal phenomena over longer ranges, physiological mechanisms fall into two broad classes [20,47]. One class is based on the idea that temporal codes are formed through the operation of oscillatory processes. As noted, the scalar timing model posits that the representation of duration entails a clock-counter mechanism [48]. Although this model was developed for tasks spanning many seconds, researchers have assumed that similar mechanisms operate at short intervals.

The other class can be defined by models in which the continuum of time can be represented without oscillatory events; these are termed 'spectral models'. Spectral models posit the translation of a temporal code into a spatial code. Different intervals are represented by the activation of non-overlapping neural elements, perhaps because of delays introduced by the stochastic properties of slow physiological processes [47,49••]. This does not mean that such delay properties are fixed; learning mechanisms could be used to shape input and output relationships. Alternatively, the dynamics of time-varying physiological events might be used to represent and produce temporal information [47,49••,50].

Physiological studies have just begun to test these models. Leon and Shadlen [51•] recorded from neurons in inferior parietal cortex of the monkey while the animals judged the duration of visual events centered around 300 ms or 800 ms. Psychometric functions derived from neural ensembles approximated the animals' behavior, suggesting that these cells provide a representation of time. Consistent with this idea, physiological mechanisms such as slow inhibitory post-synaptic potentials (IPSPs) are ubiquitous in the nervous system, and could serve as the building block for temporal processing [49••,52]. According to this view, timing information is locally computed in a task-dependent manner [51•,53,54]. Alternatively, the activity of these parietal neurons could reflect decision processes given that similar brain-behavior relationships are observed for a variety of psychophysical tasks [55,56]. According to this view, the stimulus duration might be computed upstream (e.g. in the cerebellum) then transmitted to neurons associated with specific response systems (e.g. eye movements as in the study by Leon and Shadlen [51•]). Evoked potential studies in humans are also consistent with the hypothesis that cortical signals indicate the evolution of decision processes [37,57–59].

Neurophysiological studies of eyeblink conditioning have provided the most detailed analysis of the emergence of time-dependent behavior [10•,11••]. As noted earlier, CRs persist after lesions of the cerebellar cortex, but the adaptive timing is abolished [9,11••]. Various models of the cerebellar cortex have been proposed, instantiating different forms of spectral coding [60•,61]. In one model, interactions between granule cells and Golgi cells produce a range of delays for the efficacy of parallel fiber input to Purkinje cells [62]. A representation of the unconditioned stimulus conveyed by climbing fibers is used to strengthen those inputs that are tuned to drive the CR at the optimal time.

Conclusions

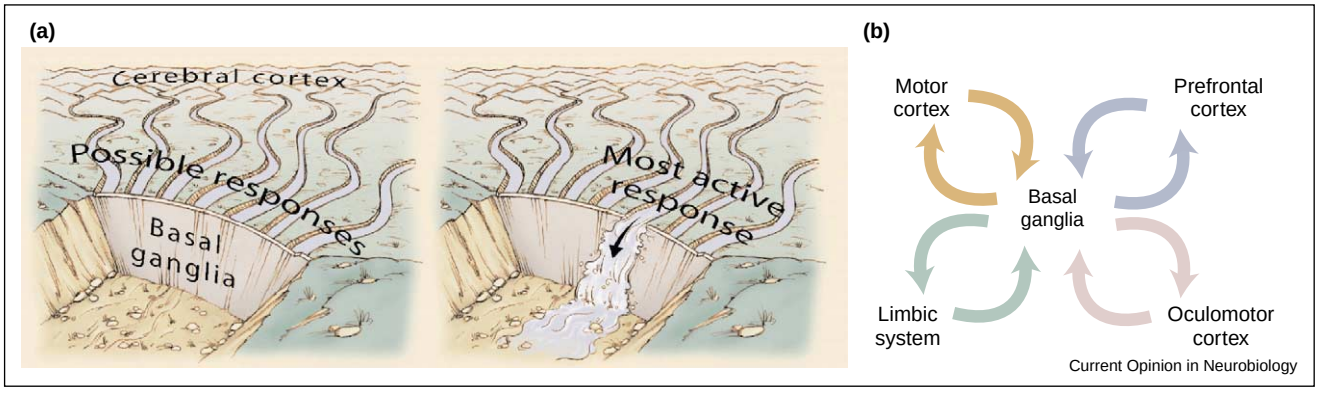
The recent neuroimaging literature is consistent with the hypothesis that the cerebellum is engaged during tasks requiring the precise representation of temporal information. This includes motor sequence learning [44•], rhythmic tapping [41–43], duration discrimination [2••,39], phoneme perception [63•], and attentional anticipation [64•]. Whereas imaging studies are best viewed in terms of a sufficiency argument, lesion studies provide a stronger test of necessity [65]. Again, the data from human and animal studies indicate that lesions of the cerebellum are associated with increased temporal variability.

We do not wish to suggest that the instantiation of temporal processing within the cerebellum is generic; rather we assume that subregions within the cerebellar cortex will be recruited for timing in a task-dependent manner [66]. Thus, we emphasize a general computational principle of the cerebellum. Neuroanatomical considerations make it unlikely that internal timing would be task independent; such a hypothesis would be exceedingly complex in terms of the mapping between inputs and outputs across diverse tasks.

The current evidence does not preclude distributed models or hypotheses that assign a central role for timing to another specialized system, such as the basal ganglia. As reviewed here, the results of imaging and lesion studies are ambiguous with respect to the role of the basal ganglia in timing short intervals.

A clear dissociation between the cerebellar and the basal ganglia contributions on temporal processing tasks

Figure 2



Hypothesized gating operation of the basal ganglia as part of a decision making process. **(a)** Potentiated cortical representations provide input to the basal ganglia. The output from the basal ganglia reflects selected representations that have reached threshold. (From Gazzaniga *et al.* [71], art work by F Forney.) **(b)** The functional consequences of this gating process will depend on input–output circuitry [72]. For example, the motor loop will trigger overt movements, whereas the prefrontal loop involves the updating of working memory.

remains elusive, primarily because similar deficits have been observed in patients with lesions of either structure ([22,28,67,68] but see [68]). The cerebellar hypothesis offers a parsimonious account over a broad set of tasks, and neurobiologically feasible models have been developed. Nonetheless, a specialized system hypothesis must be able to account for similar patterns of performance following damage to distinct systems.

As a starting point, we propose that the basal ganglia are an integral part of decision processes, operating as a threshold mechanism (Figure 2). Activations into the basal ganglia are gated such that only those reaching threshold are implemented [69]. The activation functions for different decisions can reflect multiple factors, such as goals, sensory inputs, and contextual information. These representations engage in a competitive process for control. According to this view, the basal ganglia ensure that response implementation or working memory updating does not occur until a criterion level of activation is reached. Dopamine inputs to the striatum modulate threshold settings, providing one mechanism by which the competition can be biased. Thresholds for reinforced actions are lowered, increasing the likelihood of implementation, even if the input patterns are unchanged.

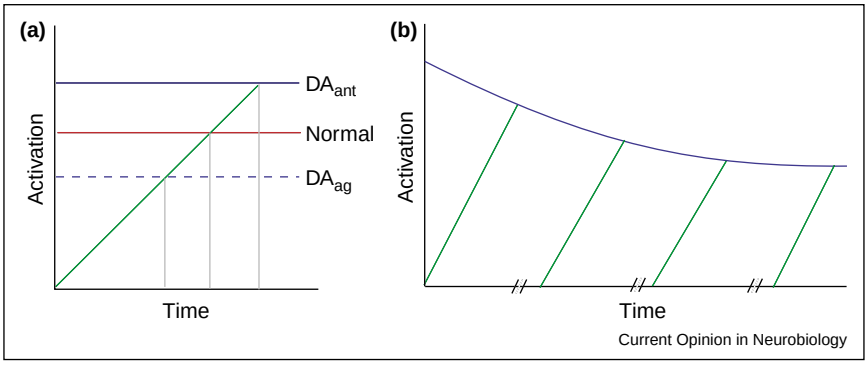
Although this hypothesis is intended to describe the role of the basal ganglia in response or set selection, it provides a novel perspective of impairments on temporal processing tasks associated with basal ganglia dysfunction. Consider the perception of intervals on the order of multiple seconds. Judging the amount of elapsed time for such intervals is attention mediated [70], or what has been called cognitive timing [2••,3]. One way such timing could be achieved is by monitoring the number of updates of working memory, a form of an accumulator model. Dopamine levels distort the perception of time (Figure 3a). In the threshold model, dopamine agonists would lower thresholds, leading to more frequent updates and a criterion number of updates would be reached earlier. Likewise, time perception would be lengthened when thresholds are raised by dopamine antagonists.

This hypothesis can also be applied to short intervals without postulating a direct role for the basal ganglia in the representation of time. Dopamine agents would again be expected to distort perceived time [25]. Moreover, an appealing feature of this hypothesis is that the same mechanism can account for PD akinesia, the difficulty to initiate movement. In the absence of dopamine, thresholds are elevated. The gating operation would thus be delayed, requiring extended accrual for a particular activation pattern.

This simple model would not account for PD patients' impairments in judging the duration of a short stimulus, given our assumption that the representation of stimulus duration is derived in the cerebellum. However, it is reasonable to assume that the depletion of dopamine not only changes the threshold setting but also introduces additional noise into these settings. In this manner, perceptual judgments would be more variable, reflecting threshold fluctuations or response biases. However, such deficits should not be specific to duration discrimination, a prediction not supported by one study [22].

With one additional modification, the threshold model can account for the tendency of PD patients to speed up during repetitive movements [22,27,28], a result that seems at odds with pacemaker models. We assume that dopamine primarily acts as a long-term modulator of thresholds; over the short term, thresholds will be sensitive to recent

Figure 3



Gating of activated representations through threshold adjustment. The green line represents the activation signal that serves as an input to the basal ganglia. Drop-lines indicate time of gating for a particular threshold setting. **(a)** Dopamine agonists lower the threshold, leading to the gating operation being invoked with less activation. Dopamine antagonists raise the threshold. This mechanism can be applied to understand the effects of dopamine depletion in Parkinson's disease (PD) or the effects of dopamine-based reinforcement. For the latter, reinforcement signals serve to lower thresholds, leading to increased probability of an input reaching threshold in the future. **(b)** Tendency of PD patients to speed up during unpaced finger tapping could result from short-term modulation of elevated thresholds. After each output, the system resets and a new activation signal accrues for the next response. The gaps indicate that the input to the gating mechanism might not be immediate, but builds up near the target time, reflecting activation in upstream systems that determine onset time (e.g. cerebellum). Assuming that variation in the activation function is random, gating will tend to occur earlier as the threshold is reduced over cycles.

context effects (Figure 3b). Thus, a threshold recently triggered will be lowered, especially when the initial state is inflated. As a result, successive cycles through a circuit will gradually decrease in cycle rate, even if the input remains constant.

We recognize that one could reinterpret cerebellar timing deficits within a non-timing hypothesis, similar to what we have attempted with respect to the basal ganglia. Our intent here is to offer functional hypotheses that can motivate new empirical and computational endeavors. Such efforts will be necessary as part of the continuing efforts to disentangle the contributions of different neural systems to temporal processing.

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The authors made single unit recordings in the cerebellar lobule HVI of decerebrate guinea pigs during eyeblink conditioning with the initial interval between the conditioned and unconditioned stimuli set to 250 ms, followed by transfer to an interval of 400 ms. The majority of cells showed time-dependent response to the conditioned stimulus, although the pattern could be excitatory, inhibitory, or complex. However, the profile of individual cells was uncorrelated for the two inter-response intervals (ISIs). Their results stand against the hypothesis that the new timing is learned by simple shift of output properties of learning-related cells; rather, learning of new timing required recruitment of different neural populations within the cerebellum.

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Previous studies (Zelaznik *et al.* [73]) had shown that individual differences in timing acuity were not correlated between rhythmic production tasks in which the movements involved discontinuities between successive cycles (slight pause or contact with response surface) and rhythmic production tasks in which the movements were produced in a smooth, continuous manner. As predicted, patients with cerebellar lesions were selectively impaired on the tasks involving discontinuities. The lack of impairment on the continuous tasks is especially striking given that these movements required coordination across multiple joints and involved significant interaction torques.

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