Disrupted Timing of Discontinuous But Not Continuous Movements by Cerebellar Lesions

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Disrupted Timing of Discontinuous But Not Continuous Movements by Cerebellar Lesions

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Patients with cerebellar damage are known to exhibit deficits in the temporal control of movements. We report that these deficits are restricted to discontinuous movements. Cerebellar patients exhibited no deficit in temporal variability when producing continuous, rhythmic movements. We hypothesize that the temporal properties of continuous movements are emergent and reflect the operation of other control parameters not associated with the cerebellum. In contrast, discontinuous movements require an explicit representation of the temporal goal, a function of the cerebellum. The requirement for explicit temporal representation provides a parsimonious account of cerebellar involvement in a range of tasks.

Lesions of the cerebellum disrupt the temporal properties of voluntary movements. Individuals with cerebellar lesions exhibit increased temporal variability on numerous motor tasks (*1–3*) and are impaired on nonmotor tasks that require a precise temporal representation (*4–9*). Neuroimaging has provided further evidence of a cerebellar role in motor and nonmotor timing (*10–12*). These results support the hypothesis that the cerebellum is part of an internal timing system in the millisecond-to-second range (*13*), which provides a representation of the interval to be timed.

Although there is substantial evidence for the role of the cerebellum in temporal processing across domains, it has been assumed that the temporal properties of many movements may be emergent, reflecting the operation of nontemporal control parameters (*14–16*). Evidence of such a distinction comes from studies in which participants made repetitive tapping or circle-drawing movements (*17*). Contrary to the prediction of a single timing process, temporal variability did not correlate across these tasks (*18*, *19*). However, when participants were required to pause between each cycle while circling, a manipulation designed to mimic pauses in tapping, temporal variability significantly correlated with variability in tapping (*20*). Importantly, intermittent circle drawing did not correlate with continuous circle drawing.

We hypothesized that the temporal control of continuous movements is emergent, whereas discontinuous movements require an explicit representation of the temporal goal, a function provided by the cerebellum (*21*). To test this hypothesis, we examined the performance of patients with cerebellar lesions on these two classes of movements.

In the first experiment, six patients with unilateral cerebellar lesions (fig. S1 and table S1) were tested on repetitive movement tasks with a target cycle duration of 800 ms (*22*). One task was finger tapping on a tabletop; the other two tasks involved circle drawing. For continuous circle drawing, participants were instructed to draw circles in a continuous, smooth manner; for intermittent circle drawing, participants were to pause before drawing each circle. Each task was performed with the right and left limbs in separate blocks, allowing for a within-subject comparison of performance with the impaired, ipsilesional limb to performance with the less impaired, contralesional limb.

Like healthy adults (*18–20*), the cerebellar patients paused briefly before the downstroke of the index finger in the tapping task (Fig. 1A). The duration of this pause is not as long as that observed during intermittent circle drawing; nonetheless, its presence verifies that performance in these two conditions consisted of a series of discontinuous movements. The mean interval produced in the table-tapping task was close to the goal of 800 ms (table S2). For the circle-drawing tasks, the means were considerably longer, similar to durations produced by healthy adults (*20*).

Because temporal variability increases with cycle duration (*23*), we used the coefficient of variation, defined as the standard deviation of the cycle durations divided by the mean cycle duration, as a normalized measure of temporal variability (*24*). Variability was significantly greater for the ipsilesional limb on the discontinuous tasks (Fig. 1B). In contrast, no difference was observed between limbs on the continuous drawing task (*25*). The coefficient of variation for continuous circling for both limbs was 4 to 5%, similar to that observed in healthy young adults (*18–20*).

To verify that the patients' deficit was related to movement discontinuity, we modified the discontinuous tasks in a second experiment in which each action was produced discretely, in an attempt to produce one tap interval or one circle cycle in 550 ms. The continuous drawing task was identical to that of Experiment 1, except that the target interval was 550 ms (table S3). Patients with unilateral cerebellar damage again exhibited a selective increase in temporal variability on the discrete tasks when performing with the impaired limb relative to the unimpaired limb (Fig. 2). There was no between-limb difference on the continuous drawing task. A similar pattern was observed in a comparison between patients with bilateral cerebellar degeneration ($n = 7$) and healthy control par-

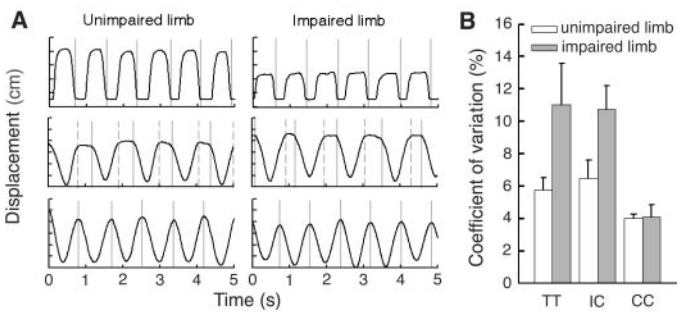

Fig. 1. Disrupted timing of discontinuous but not continuous movements by cerebellar lesions. (**A**) Representative kinematic trajectories produced by a cerebellar patient in Experiment 1. The onset of each cycle is marked by the gray vertical lines. Top row: Cycle duration for tapping was defined by the interval between successive contact points with the table. Middle row: For intermittent circling, the onset of the movement phase was marked when velocity exceeded 5 cm/s; the onset of the pause was marked when velocity fell below 5 cm/s (dashed vertical lines). Bottom row: For continuous circling, cycle onset was defined as the point of maximum displacement in the *y* dimension. (**B**) Coefficient of variation scores for the tapping (TT), intermittent circle drawing (IC), and continuous circle drawing (CC) tasks. The patients were more variable (paired *t* tests) when performing with their ipsilesional, impaired hand on tapping ($P = 0.02$) and intermittent drawing ($P < 0.001$) tasks. No impairment was evident on the continuous circle drawing task ($P > 0.4$). Error bars refer to the standard error of the mean, a measure of between-subject variability.

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ticipants ($n = 7$). These patients were more variable than controls on the discrete tasks, yet there was no significant difference in performance between these groups on the continuous drawing task.

The lack of impairment in the patients' performance on the continuous drawing task in these two experiments is striking, given that these movements involve multiple joints, whereas finger tapping involves a single joint. As noted in the classic writings of Holmes (*26*), the effects of cerebellar lesions are most evident in complex movements. If difficulty were based on the number of joints and resulting interactional torques (*27*), or on the spatial demands of the tasks, tapping should be easier than continuous drawing. However, temporal performance on tapping was impaired, whereas continuous drawing was unimpaired.

Given that ballistic movements are most affected by cerebellar lesions (*28*) and that patients had difficulty in matching the target intervals in Experiment 2, we designed a third experiment to assess whether the variable that mediated performance was velocity rather than the distinction between continuous and discontinuous movements. All of the tasks were restricted to flexion/extension movements of the index finger. One condition required table tapping similar to Experiment 1. For the other conditions, the participants were instructed to "tap" in the air, moving the index finger in either a smooth, continuous manner or by pausing briefly before each downstroke (Fig. 3A). A 1000-ms target duration was used for all movements (table tapping, intermittent movement, and continuous movement). In addition, the continuous task was performed with a 500-ms target duration. We used the synchronization-continuation procedure from Experiment 1; for conditions other than table tapping, participants were instructed to synchronize flexion with each tone (*22*). We tested patients with unilateral cerebellar lesions ($n = 5$) or bilateral cerebellar degeneration ($n = 5$) and control participants ($n = 5$).

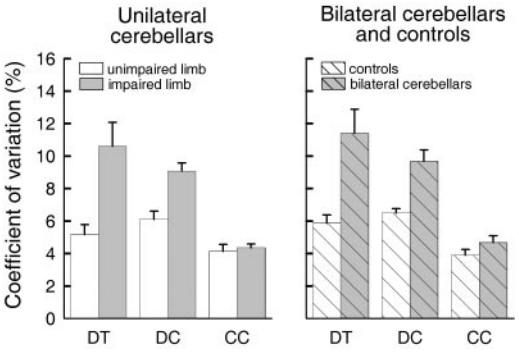

Fig. 2. Patients with cerebellar lesions exhibited increased temporal variability only on tasks that involved discontinuous movements, discrete tapping (DT), or discrete circle drawing (DC). Unilateral cerebellar patients, between-limbs variability in DT: $P = 0.01$; in DC: $P < 0.001$. Bilateral cerebellar patients compared to the controls (unpaired t tests), in DT: $P = 0.001$; in DC: $P < 0.001$. The bilateral patients and controls performed the task with both limbs; no effect of hand was obtained for either group, so the data were averaged across limbs.

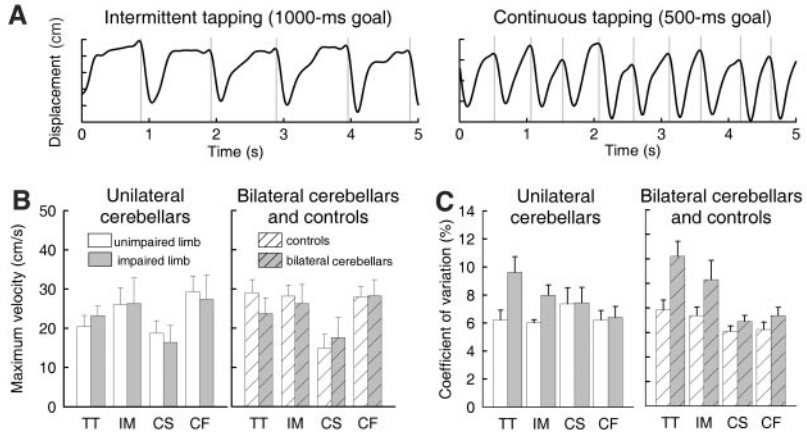

Fig. 3. Normal timing on continuous tasks held across a range of movement velocities. (**A**) Kinematic trajectories from one control participant on the 1000-ms intermittent and the 500-ms continuous movement tasks. The movement phase was similar for the two conditions. Cycle onset for the "air-tapping" conditions was determined as the point when movement velocity exceeded 5 cm/s (vertical lines). (**B**) Maximum velocity was calculated for each downstroke and averaged across cycles. IM, intermittent movement; CS, slow continuous movement (1000-ms target); CF, fast continuous movement (500-ms target). (**C**) Coefficient of variation scores. Within-subject comparisons (paired t tests) for the unilateral patients were only significant on the discontinuous tasks (TT: $P = 0.02$; IM: $P = 0.008$). A similar pattern was obtained in the between-subject comparison (unpaired t tests) of bilateral patients and controls (TT: $P = 0.04$; IM: $P = 0.005$).

Mean durations approximated the target for all conditions (table S4). The maximum velocity increased by at least 67% in the fast (500 ms) continuous condition compared to the slow (1000 ms) continuous condition (Fig. 3B). Moreover, maximum velocity was similar for the intermittent and fast continuous conditions. Nonetheless, patients with unilateral cerebellar damage exhibited a temporal impairment on the intermittent and table-tapping tasks but were unimpaired on the continuous tasks (Fig. 3C). Providing additional evidence against a velocity-based account, the unilateral patients were more consistent when moving at the faster rate on the continuous task and there was no interaction between the response hand and velocity.

Results for the patients with bilateral degeneration also favor movement continuity as the critical variable. Although the group means for bilateral cerebellar patients indicate greater variability on all tasks relative to controls, statistically this group was only more variable than the controls on the discontinuous tasks. These patients also failed to exhibit an increased impairment in the fast continuous task compared to the slow continuous task.

These results provide neuropsychological evidence of dissociable neural systems for the temporal control of discontinuous and continuous movements, with the cerebellum selectively involved in the former. Converging evidence for the distinct neural control of discontinuous and continuous movements is provided by a study of bimanual coordination after callosotomy (*29*). These patients' hands were temporally coupled on a bimanual version of the intermittent tapping task in Experiment 3. In contrast, the two hands became uncoupled when the movements were continuous.

Discontinuous movements are characterized by salient events such as onsets and offsets or contact with the table while tapping. We hypothesize that temporal control of these tasks is achieved by the setting of explicit temporal goals for successive events and that the cerebellum is essential for this representation. In contrast, the goal for the continuous task is to move smoothly while achieving the directed pace. We hypothesize that for these movements, the temporal properties are emergent (*30*). The cerebellum may be involved in the initial establishment of the temporal goal, but once initiated, performance is controlled by other parameters that satisfy constraints such as minimizing jerk (*31*) or spatial noise (*32*), through a control parameter such as joint stiffness (*33*). In this manner, what was an explicit goal becomes an emergent property.

Conceptualizing cerebellar function as representing the timing of salient events provides a parsimonious account of the involvement of this structure in both motor and

nonmotor tasks. Eyeblink conditioning requires that an animal not only learn the association between a neutral and an aversive stimulus; it is only adaptive if the animal also learns when to expect the aversive stimulus. More generally, the consolidation of motor skills centers on learning to specify the precise timing between successive movements. Cerebellar ataxia is characterized as a disruption in the timing of these events (*3*, *26*, *28*), rather than as a loss of the conceptual knowledge for actions observed in apraxia. Similarly, comparing the duration of two successive events requires a judgment of whether the second event occurred earlier or later than expected. Our results extend previous theories concerning the role of the cerebellum in temporal processing, indicating that this function is limited to tasks that require an explicit specification of the timing of behaviorally meaningful events.

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22. Materials and methods are available as supporting material on *Science* Online.
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Supporting Online Material

www.sciencemag.org/cgi/content/full/300/5624/1437/DC1
Materials and Methods
Fig. S1
Tables S1 to S4

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Characterization of Mammalian Selenoproteomes

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In the genetic code, UGA serves as a stop signal and a selenocysteine codon, but no computational methods for identifying its coding function are available. Consequently, most selenoprotein genes are misannotated. We identified selenoprotein genes in sequenced mammalian genomes by methods that rely on identification of selenocysteine insertion RNA structures, the coding potential of UGA codons, and the presence of cysteine-containing homologs. The human selenoproteome consists of 25 selenoproteins.

In the universal genetic code, 61 codons encode 20 amino acids, and 3 codons are terminators. However, the UGA codon has a dual function in that it signals both the termination of protein synthesis and incorporation of the amino acid selenocysteine (Sec) (*1*–*3*). Available computational tools lack the ability to correctly assign UGA function. Consequently, there are numerous examples of misinterpretations of UGA codons as both Sec codons (*4*) and terminators (*5*, *6*), including annotations of the human genome (*7*, *8*), where no selenoproteins have been correctly predicted. With 18 human selenoprotein genes previously discovered (*3*), the estimates of the actual number of such genes vary greatly (*9*). All previously characterized selenoproteins except selenoprotein P (*10*) contain single Sec residues that are located in enzyme-active sites and are essential for their activity. Thus, misidentification of UGA codons leads to a loss of crucial biological and functional information. Sec is cotranslationally incorporated into nascent polypeptides in response to UGA codons when a specific stem-loop structure, designated the Sec insertion sequence (SECIS) element, is present in the 3′ untranslated regions (UTRs) in eukaryotes and in archaea, or immediately downstream of UGA in bacteria (*1*, *11*–*13*). Trans-acting factors, including Sec tRNA, Sec-specific elongation factor, selenophosphate synthetase (SPS), Sec synthase, and a SECIS-binding protein, are also required for Sec biosynthesis and insertion (*1*, *3*, *13*–*15*). Most known selenoprotein genes have homologs, in which Sec is replaced with cysteine (Cys). However, these proteins are poor catalysts as compared with selenoproteins (*3*).

We hypothesized that the UGA dual-function problem could be solved by identifying selenoprotein genes in sequenced genomes and assigning terminator functions to the remaining in-frame UGAs. The requirement of SECIS elements for Sec insertion and the presence of Cys-containing homologs of selenoproteins suggested two independent bioinformatics methods for selenoprotein identification. In addition, we used an ob-

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