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Does the representation of time depend on the cerebellum?
Effect of cerebellar stroke

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Summary
Behaviours that appear to depend on processing temporal information are frequently disrupted after cerebellar damage. The present study examined the role of the cerebellum in explicit timing and its relationship to other psychological processes. We hypothesized that if the cerebellum regulates timekeeping operations then cerebellar damage should disrupt the perception and the reproduction of intervals, since both are thought to be supported by a common timekeeper mechanism. Twenty-one patients with cerebellar damage from stroke and 30 normal controls performed time perception and time reproduction tasks. In the time reproduction task, timing variability was decomposed into a central timing component (clock variability) and a motor component (motor implementation variability). We found impairments only in time reproduction (increased clock variability) in patients with medial and lateral damage involving the middle- to superior-cerebellar lobules. To explore potential reasons for the temporal processing deficits, time reproduction and perception performance were correlated with independent measures of attention, working memory, sensory discrimination and processing speed. Poorer working memory correlated with increased variability in the 'clock' component of time reproduction. In contrast, processing speed correlated best with time perception. The results did not support a role for the cerebellum in timekeeping operations. Rather, deficits in timing movements may be related to a disruption in acquiring sensory and cognitive information relevant to the task, coupled with an additional impairment in the motor-output system.

Keywords: cerebellum; temporal processing; sensorimotor function; cognition; attention; working memory

Abbreviations: DLPF = dorsolateral prefrontal; ITI = inter-tap interval; LC = left cerebellar; LI = left inferior; LN = left normal control; LS+ = left superior-plus; PEST = Parameter Estimation by Sequential Testing; PSE = point of subjective equality; RC = right cerebellar; RI = right inferior; RN = right normal control; RS+ = right superior-plus; RT = reaction time; SOA = stimulus onset-asynchrony; TMT = Trail Making Test; WAIS-R = Wechsler Adult Intelligence Scale–Revised

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Introduction
Our perception of time depends upon multiple processes that help structure actions and enable anticipation of events. Theories of timing (Gibbon *et al*., 1984; Killeen and Fetterman, 1988; Zakay and Block, 1996) use a clock metaphor to describe a timekeeping mechanism, which represents time through the accumulation of pulses. The

operation of the timekeeper depends upon attention, which controls the starting and stopping of pulses, thereby enabling anticipation of events. Once a representation of time is formulated, it is routed to working memory. Impaired temporal processing can therefore be due to a disruption in one or more of these processes. Though functional imaging methods have helped elucidate neural systems involved in temporal cognition, an understanding of the brain regions that are *essential* for regulating timing is limited due to the paucity of focal lesion studies.

The present study examined the role of the cerebellum in temporal processing. Cerebellar damage disrupts behaviours that depend upon accurate timing, such as conditioned learning (Raymond *et al*., 1996), force control (Hore *et al*., 2002) and regulation of agonist–antagonist muscle activity (e.g. dysmetria) (Hore and Flament, 1986). This work together with studies that implicated the cerebellum in explicit timing (Ivry *et al*., 1988; Ivry and Keele, 1989) rendered it a logical candidate for timekeeping functions. Direct support for this hypothesis remains limited, however, as most studies of timing have included patients with cerebellar atrophy (Ivry and Keele, 1989; Nichelli *et al*., 1996; Casini and Ivry, 1999), which is seldom focal. Although timing deficits have been reported in a few human studies of cerebellar tumors or strokes and in animals with lesions, deficits have been attributed to time-regulating properties of the cerebellum (Ivry *et al*., 1988; Clarke *et al*., 1996; Mangels *et al*., 1998) or other processes (Malapani *et al*., 1998; Breukelaar and Dalrymple-Alford, 1999).

Identifying the neural systems that regulate timekeeping operations is challenging because the relationship between timekeeping operations and performance (e.g. accuracy, variability) remains unclear (Wearden, 1999). Indeed, in neurological patients timing variability is increased after damage to the cerebral cortex (Harrington *et al*., 1998*b*), the basal ganglia (Artieda *et al*., 1992; Pastor *et al*., 1992; O'Boyle *et al*., 1996; Harrington *et al*., 1998*a*), or the cerebellum (Ivry *et al*., 1988; Ivry and Keele, 1989; Nichelli *et al*., 1996), making it difficult to identify the reasons for deficits. The problem is exacerbated by failures to demonstrate impairments across different measures of timing, which would strengthen the relationship between localized brain damage and deficient timekeeping operations. Altogether, this suggests a need for different analytical approaches, especially when studying the cerebellum because it modulates processes that might interact with timekeeping operations, including attention (Akshoomoff and Courchesne, 1994), working memory (Desmond *et al*., 1997) and sensory discrimination (Parsons *et al*., 1997).

To examine the role of the cerebellum in temporal cognition, we studied 21 patients with cerebellar damage from stroke. We investigated both time reproduction and perception to provide a stronger test of the cerebellar timing hypothesis, since the two are thought to involve a common central timekeeping mechanism (Treisman *et al*., 1992; Ivry and Hazeltine, 1995). We predicted that if cerebellar damage disrupts a central timekeeping operation, performance should be abnormal in the time reproduction *and* perception tasks. To better separate deficits specific to a timekeeper from those associated with other processes that influence timing, time reproduction and perception performance were correlated with independent measures of attention, working memory, sensory discrimination and processing speed.

We also investigated whether different regions within the cerebellum were more crucial for temporal processing than others. It has been suggested that the lateral, but not medial, cerebellum is involved in timekeeping (Ivry *et al*., 1988). Ivry and colleagues decomposed the variability in time reproduction (Wing and Kristofferson, 1973) into a clock component (which theoretically reflects the timekeeper) and a motor implementation component (which represents random movement implementation variability). They reported impaired clock variability in four lateral cerebellar damage patients, and impaired motor implementation variability in three medial cerebellar damage patients. The findings were intriguing because portions of the lateral cerebellum contain the dentate nuclei, which project to the premotor, dorsolateral prefrontal (DLPF) and parietal cortices (Middleton and Strick, 1994; Schmahmann and Pandya, 1997; Dum and Strick, 2003), areas that focal lesion research indicates are essential for time perception (Harrington *et al*., 1998*b*). However, different regions of the cerebellum may be more essential for perceiving time than timing movements given its topographical organization according to lobular and anterior–posterior boundaries (Brodal, 1979; Schmahmann and Pandya, 1997). Neuroimaging results are mixed, with studies ascribing time-regulating properties (for movement or perception) to the anterior (Jueptner *et al*., 1995; Rao *et al*., 1997; Kawashima *et al*., 2000; Lutz *et al*., 2000), the posterior (Sakai *et al*., 2000; Tracy *et al*., 2000), or both regions of the cerebellum (Penhune *et al*., 1998; Jancke *et al*., 2000). Some even implicate the vermis (Jueptner *et al*., 1996*a*; Jancke *et al*., 2000; Rao *et al*., 2001). In the present study, we explored this issue by separating patients into groups with or without significant damage to the middle to superior portions of the cerebellum, which included the dentate nuclei. Though few patients had lesions confined to the medial cerebellum, many had damage impinging onto this region, allowing us to test the hypothesis that medial damage disrupts motor implementation variability in time reproduction (Ivry *et al*., 1988).

Methods

Subjects

Participants included 21 patients with cerebellar damage from stroke and 30 healthy age- and education-matched control subjects. All control and 15 cerebellar subjects were recruited from the Albuquerque Veterans Affairs Medical Center and local private hospitals. Six cerebellar patients were recruited from the Tucson Veterans Affairs Medical Center. Most patients had unilateral cerebellar damage, but four had bilateral damage. For the data

Table 1 *Demographic characteristics*

	Control groups				Cerebellar groups			
	Right hand (n = 15)		Left hand (n = 15)		Right hemisphere (n = 10)		Left hemisphere (n = 11)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	67.2	5.8	55.5	11.1	65.9	8.2	51.9	11.6
Education (years)	13.9	2.7	15.8	2.4	12.0	3.3	16.5	2.8
Gender (% male)	60		87		70		64	
Years post-stroke					4.6	8.1	2.7	3.8
Symptom severity								
Total score*					16.4	13.9	9.0	10.6
Right upper limb†					6.0	5.3	3.7	6.29
Left upper limb†					3.2	3.1	0.9	1.5

Tabled values represent the group means and standard deviations (SD), except for the variable gender, which is the percentage of males. *Total scores (sum of all 26 symptom ratings) on the Cerebellar Symptom Rating Scale (unpublished) range from 0 to 104, with higher scores reflecting more prevalent and/or severe symptoms. Scores ranged between 4 and 42 in the right cerebellar group and 3 and 38 in the left cerebellar group. †Upper limb scores (sum of six symptom ratings) on the Cerebellar Symptom Rating Scale. Scores can range from 0 to 24 for each upper limb. In the right cerebellar group, scores ranged between 2 and 14 for the right upper limb and 0 and 9 for the left upper limb. In the left cerebellar group, scores ranged between 0 and 5 for the right upper limb and 1 and 20 for the left upper limb.

analyses, two bilateral patients were classified as having predominantly right cerebellar (RC) damage and the other two as having predominantly left cerebellar (LC) damage based on the hemisphere showing the largest lesion volume and the hand exhibiting the most severe motor symptoms. All control subjects were right-handed; one RC and two LC patients were left-handed. Informed consent was obtained according to the Declaration of Helsinki. Study procedures were approved by the Human Research and Review committees at the University of New Mexico Health Sciences Center and the University of Arizona.

Patients performed the experimental tasks using the hand ipsilateral to damage; patients with bilateral damage used their most impaired hand, which was ipsilateral to the most damaged hemisphere in all four patients. Table 1 shows that the RC group was older [$t(19) = 3.1$, $P < 0.01$] and less educated [$t(19) = 3.4$, $P < 0.01$] than the LC group. To control for these differences and the hand used to perform the tasks, two control groups were studied; one with subjects who performed with their right hand (right normal control; RN) and the other with subjects who performed with their left hand (left normal control; LN). Independent t-tests showed no significant differences between each cerebellar and respective control group in age or education. All patients were tested at least 6 months post-stroke. Disease severity was evaluated using a rating scale (unpublished) developed by the authors. The scale contained 26 items, scored on a five-point scale (0 = normal, 1 = mild, 2 = moderate, 3 = severe, 4 = marked). The scale assessed activities of daily life (clarity of speech, falls, walking, tremor); gait and balance (normal walking, heel to toe walking); intention tremor (upper and lower limbs); motor speed (finger tapping, open-closing of the hands); dysdiadochokinesia [rapid alternating movements of the hand (pronation–supination) and foot (heel to toe)]; dysmetria (finger to nose test); rebound (displacement of upper limbs with eyes closed); nystagmus (horizontal, vertical); and dysarthria. Table 1 shows that on average, patients exhibited mild symptoms, although some showed moderate to severe symptoms in specific areas. Table 1 also shows symptom severity for the right and left upper limb. Symptom severity in the upper limb ipsilateral to damage was worse than in the contralateral limb [$t(20) = 2.5$, $P < 0.025$] in both groups.

Table 2 shows the performance of each cerebellar group on neuropsychological tests, administered only to patients. This table shows the percentage of patients in each group whose performance exceeded –l SD of the published norms for each test. More than 90% of the patients performed within normal limits on the Digit Span subtest from the Wechsler Adult Intelligence Scale–Revised (WAIS-R) (Wechsler, 1981), which assesses short-term memory span. On the Trail Making Test (TMT) (Spreen and Strauss, 1991), >40% of the patients were impaired on Part A of the TMT, which measures visual-scanning and motor speed. Between 20 and 30% were impaired on Part B of the TMT, which assesses cognitive flexibility, an executive function of working memory.

To evaluate strength and speed in the hand ipsilateral and contralateral to damage, performance on the Hand Dynamometer Test (grip strength) (Reitan and Wolfson, 1993), Finger Tapping Test (Reitan and Wolfson, 1993) and the Grooved Pegboard Test (Heaton *et al*., 1991) were analysed. Grip strength did not differ between hands and was within normal limits in 80% or more of the patients (Table 2). Finger tapping (mean of five 10-s trials), a measure of cognitive-motor speed, was worse in the hand ipsilateral than contralateral to damage in both groups [$F(1,19) = 9.32$, $P < 0.01$]. Table 2 shows that contralateral tapping speed was impaired in over one-third of the patients, possibly reflecting generalized cognitive slowing (Prigatano and Wong, 1997) or motor deficits in the patients with bilateral cerebellar damage. There was a trend for grooved pegboard performance, a measure of fine motor coordination and speed, to be slightly worse in the hand ipsilateral than contralateral to damage in both groups [$F(1,19) = 3.6$, $P = 0.073$].

Procedures

Time perception task

Subjects completed two conditions of a time perception task, in which they judged the relative duration of two intervals, each defined by the time separating two 50-ms tones. On each trial, the standard interval was presented and followed 1 s later by a comparison interval. Subjects indicated whether the comparison interval was longer or shorter than the standard interval by making an index- or

Table 2 *Description of cerebellar lesion groups*

	Right cerebellar group			Left cerebellar group		
	Mean	SD	% Impaired*	Mean	SD	% Impaired*
WAIS digit span	48.7	8.9	10	53.3	6.8	0
Trial making test:						
Part A	37.4	14.6	40	39.5	10.9	55
Part B	38.3	14.0	20	39.6	11.7	27
Hand dynamometer						
Right hand	46.6	12.5	20	51.4	6.8	9
Left hand	48.9	13.3	20	49.9	6.1	0
Finger tapping						
Right hand	34.8	12.1	50	44.9	9.2	36
Left hand	41.1	9.1	40	40.0	14.8	46
Grooved pegboard						
Right hand	37.0	10.6	50	45.1	9.3	36
Left hand	41.5	8.3	30	40.4	9.4	18

*Values in this column reflect the percentage of subjects whose *t* scores exceeded –l SD of the published norms for each test. Tabled values represent the group means and SD.

middle-finger key-press. In one condition, the standard interval was 300 ms and, in the other condition, it was 600 ms. There were 30 possible longer and 30 possible shorter intervals, which varied in step sizes of 6 ms. The order of the standard interval conditions was counterbalanced across subjects.

The Parameter Estimation by Sequential Testing (PEST) procedure was used to derive a criterion threshold (Pentland, 1980). The PEST procedure produces a maximum-likelihood estimate about the position of the threshold on each trial, based on all previous responses. The procedure establishes a probability array based on a normal sigmoid-shaped psychophysical function, using this to determine the next best current estimate of a subject's longer or shorter duration threshold. In each standard interval condition, 10 practice trials were followed by 50 experimental trials consisting of 25 judgments each for the upper and lower thresholds. The test threshold was set to equal 1 SD from the *point of subjective equality* (PSE), which is the interval at which subjects are equally likely to respond shorter or longer. The PSE estimates bias towards over- or underestimating an interval and, thus, is a measure of accuracy. We computed the *difference threshold* by subtracting the upper and the lower duration thresholds and dividing this value by 2. The difference threshold is a measure of variability. The *coefficient of variation*, which is the difference threshold divided by the PSE, reflects processing efficiency.

Time reproduction task

Subjects completed two conditions of a time reproduction task, in which they tapped in synchrony to a series of 20 tones (induction phase), after which the tone stopped and they continued to tap at the same pace for 22 responses (continuation phase). The tones were 50 ms in duration. After the trial terminated, the mean inter-tap interval (ITI) during the continuation phase was displayed. In one condition, the tones were separated by 300 ms and in the other by 600 ms. Subjects completed six consecutive trials for each standard interval, the order of which was counterbalanced. Error trials were those in which a response interval fell outside ±50% of the standard interval. On error trials, the subject was reminded to listen carefully to the pacing of the tones, before they began to tap. Error trials were excluded and the trial was repeated, so that all subjects completed six trials at each target interval. This procedure reduces problems related to insufficient force or tremor (Ivry and Keele, 1989). In the present study, one control and five cerebellar subjects had one error trial; one control and two cerebellar subjects had two error trials. A Mann–Whitney test showed that there was not a significance difference between the control and cerebellar groups in the number of error trials for either standard interval condition.

Only the data from the continuation phase were analysed. The first two ITIs of the continuation phase were discarded and the analyses were performed on the remaining 20 ITIs, which were corrected for potential linear drift. On each trial, the following measures were computed and then averaged across the six trials for a standard interval. The *mean ITI* (accuracy) reflected the extent to which subjects achieved the standard interval. To examine the timing variability, unconstrained by model assumptions, we analysed the standard deviation of *total ITI variability* [var(T)] and the *coefficient of variation*, which was computed by dividing total ITI variability by the mean ITI.

The model of Wing and Kristofferson (1973) was then applied to obtain estimates of the clock and the motor implementation variability sources. In this model, var(T) is equal to the additive variability of the clock (C) and motor delay (MD) sources. This is expressed as var(T) = var(C) + 2var(MD). According to this model, the clock or internal timekeeper produces a pulse when the target interval passes and this activates the motor implementation processes. The motor delay component is doubled because each ITI includes two implementation processes, one for the first response and the other for the second response. The model assumes that subjects do not utilize feedback from a response to affect the timing of the next response, so that the two sources of variance are independent. This assumption predicts a negative covariance between successive ITIs (i.e. Lag-1).

In the data we will report that violations in negative Lag-1 covariance were found, but their magnitude was small (i.e. 0.07 or less) and always positive. The incidence of these violations was similar to previous studies (Ivry and Keele, 1989) and was comparable in the control (7% and 20% for the 300 and 600 ms intervals, respectively) and the cerebellar groups (14% and 10% for the 300 and 600 ms intervals, respectively). Presently, there is not an adequate approach to deal with these violations. At the same time,

existing adjustments for deviant Lag-1 covariance have negligible effects on estimates of clock and motor delay variability (O'Boyle *et al*., 1996; Harrington *et al*., 1998*a*), suggesting the model is robust with respect to this violation. Thus, we did not adjust for these violations.

Control tasks

Maximum tapping speed

A rapid tapping task was included to ensure that the base intervals in the time reproduction task did not exceed subjects' maximum tapping rate. Cerebellar patients tapped on a computer keyboard using their index finger ipsilateral to damage. The *mean ITI* across six trials (10 s each) measured their maximum tapping speed.

Frequency perception task

A frequency perception task controlled for the auditory processing and sensory discrimination requirements of the time perception task. Subjects judged the relative pitch of two tone-pairs that defined standard and comparison pitches. Tones were 50 ms in duration. The interval between the two tones in the standard and comparison pairs was 550 ms. On each trial, the standard pitch was presented and followed 1 s later by the comparison pitch. The standard tone-pair was 1000 Hz and the comparison tone-pairs consisted of higher or lower frequencies. Subjects pressed one of two keys to indicate whether the comparison pitch was higher or lower than the standard pitch. There were 30 possible higher and 30 possible lower frequencies, which varied in step sizes of 1 Hz. Ten practice trials were followed by 50 experimental trials, which consisted of 25 judgements each for the upper and lower thresholds. The PEST procedure was used to derive the PSE (accuracy) and difference threshold (variability).

Attention task

An attention task assessed subjects' ability to engage and disengage nonspatial attention. Subjects made an index or middle finger key press in response to an imperative stimulus (circle or triangle). The imperative stimulus was preceded by either a neutral (a cross), valid (circle or triangle matching the imperative stimulus) or invalid cue (circle or triangle mismatching the imperative stimulus). At the beginning of each trial, a 50 ms warning tone sounded, followed by the cue, which appeared at the centre of the monitor. After a random stimulus onset-asynchrony (SOA; 200, 350 or 500 ms), the response stimulus appeared at the centre of the monitor, just below the cue, and subjects immediately made a key-press response. Two blocks of experimental trials were given, each containing a random presentation of 63 neutral cue trials, 78 valid cue trials and 21 invalid cue trials. Eighteen practice trials preceded the experimental trials. The dependent measures were accuracy and reaction time (RT), which was the interval from the onset of the imperative stimulus to the key-press. RTs for valid cues are faster than for neutral cues, because the valid cue facilitates engagement of attention to the correct response. RTs for invalid cues are longer than for neutral cues, because attention must be disengaged from the invalidly cued response and re-engaged to the correct response. 'Automatic' attention mechanisms are engaged during shorter SOAs (200 ms), whereas 'controlled' attention mechanisms are engaged during longer SOAs (500 ms).

Lesion reconstruction

Lesion reconstructions were based on MRI scans in 20 patients and a CT scan in one patient. The slice thickness of scans was 5 mm with inter-slice gaps ranging from 0 to 2 mm. Scans were obtained at the time of stroke in one patient, within one week of the stroke in six patients, and more than 3 weeks post-stroke in 14 patients. Lesions were transcribed by a board-certified neuroradiologist onto axial templates derived from the atlas of Duvernoy (1995). Figures 1 and 2 show the eight modified axial sections used for reconstructing lesions of subjects (S) in the RC and LC groups. The three most superior sections (6, 7, 8) were separated by 4 mm and all others were separated by 6 mm. Sections 1–3 primarily represent the inferior cerebellum (i.e. inferior semilunar, gracile, biventer lobules, tonsil). Sections 4–8 represent the middle and superior portions (i.e. superior semilunar, posterior quadrangular, anterior quadrangular lobules, central lobule). Sections 4–6 contain the dentate nuclei.

A subset of analyses separated patients with dentate and/or lateral lesions on two or more sections (sections 4–8) and patients with principally inferior lateral (sections 1–3) or the medial cerebellum (all sections) damage. Figure 1 shows that four patients were classified into the right inferior (RI) cerebellar group (S1–S4) and Fig. 2 shows that six were classified into the left inferior (LI) cerebellar group (S11–S16). Three RI patients also had lateral (S2, S3) or tonsil (S4) damage on section 4, which did not impinge on the dentate. Two LI patients (S15, S16) also had medial cerebellar damage on sections 4 and/or 5. The remaining patients had lesions that, while typically involving the inferior portions of the cerebellum, also extended significantly into middle- and superior-lateral regions (sections 4–8). These patients were classified into the right superior-plus (RS+; S5–S10) or left superior-plus (LS+; S17–S21) cerebellar groups. All but one of the RS+ (S5) and one of the LS+ (S17) patients had damage to the dentate.

Three patients also had small lesions in areas outside the cerebellum. Two had lesions in the left (S7) and right (S18) occipital lobe, which is unlikely to affect temporal processing (Jueptner *et al*., 1995; Rao *et al*., 1997; Harrington *et al*., 1998*b*; Tracy *et al*., 2000; Rao *et al*., 2001). Another (S1) had a lesion in the medulla (Fig. 2, axial section 1), but was included because the patient's performance was within normal limits on all tasks.

Results

Timing tasks

The first set of analyses examined the *effect of cerebellar damage* on task performance, irrespective of lesion location. Mixed-model repeated-measures analyses of variance (ANOVA) tested the effects of group (control, cerebellar), performing hand (right, left), standard interval condition (300 and 600 ms). A second set of analyses examined the *effect of lesion location* on task performance by testing the effect of group (control versus inferior cerebellar group; control versus superior-plus cerebellar group), performing hand (right, left), and standard interval condition (300 and 600 ms). In all analyses, the alpha level was 0.05. Preliminary analyses showed that the testing order of the standard interval conditions in both timing tasks did not affect performance or interact with other factors, so we omitted this factor from the model.

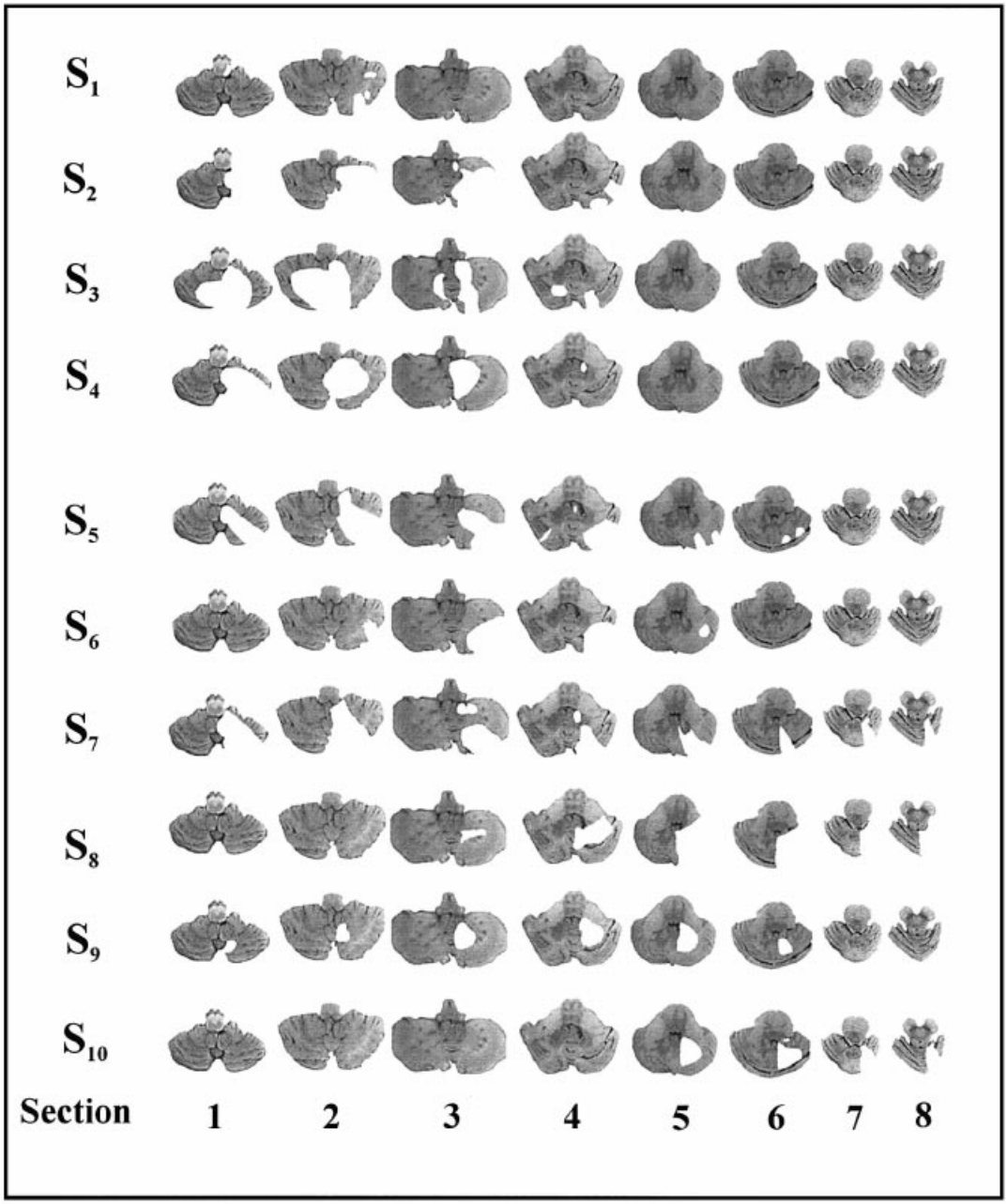

Fig. 1 Axial reconstructions for 10 subjects (S) in the right cerebellar group. Two patients (S3, S5) had bilateral lesions, with more extensive right cerebellar damage. Patients were classified as having inferior damage if their lesions were principally in the inferior lateral (sections 1–3) or medial cerebellum (all sections). Patients were classified as having middle to superior lateral damage if they had lateral lesions on two or more sections involving the superior lateral cerebellar hemispheres (sections 4–6). These patients typically had damage on section 1 to 3 as well. There were four patients in the right inferior (RI) group (S1–S4). Three RI patients also had lateral (S2, S3) or tonsil (S4) lesions on section 4, which did not impinge on the dentate nucleus. The remaining patients were in the right superior-plus (RS+) group (S5–S10) and all but one (S5) had dentate damage.

Time perception

Effect of cerebellar damage.

Figure 3A, C and E displays the PSE, difference threshold and coefficient of variation for the control and the cerebellar groups. We found no group or hand effects related to PSE (timing accuracy). As expected, PSE varied as a function of standard interval [$F(1,47) = 2090.2$, $P < 0.0001$]. There were no group or hand effects related to the difference threshold (timing variability). The difference threshold was lower for the 300 than the 600 ms standard interval [$F(1,47) = 40.1$, $P < 0.0001$]. There were also no effects related to the coefficient of variation (processing efficiency). Timing was nonscalar in all groups [Standard Interval Effect: $F(1,47) = 5.6$, $P < 0.025$; mean = 0.13, SD = 0.07 for 300 ms standard; mean = 0.10, SD = 0.05 for 600 ms standard]. This finding may be related to

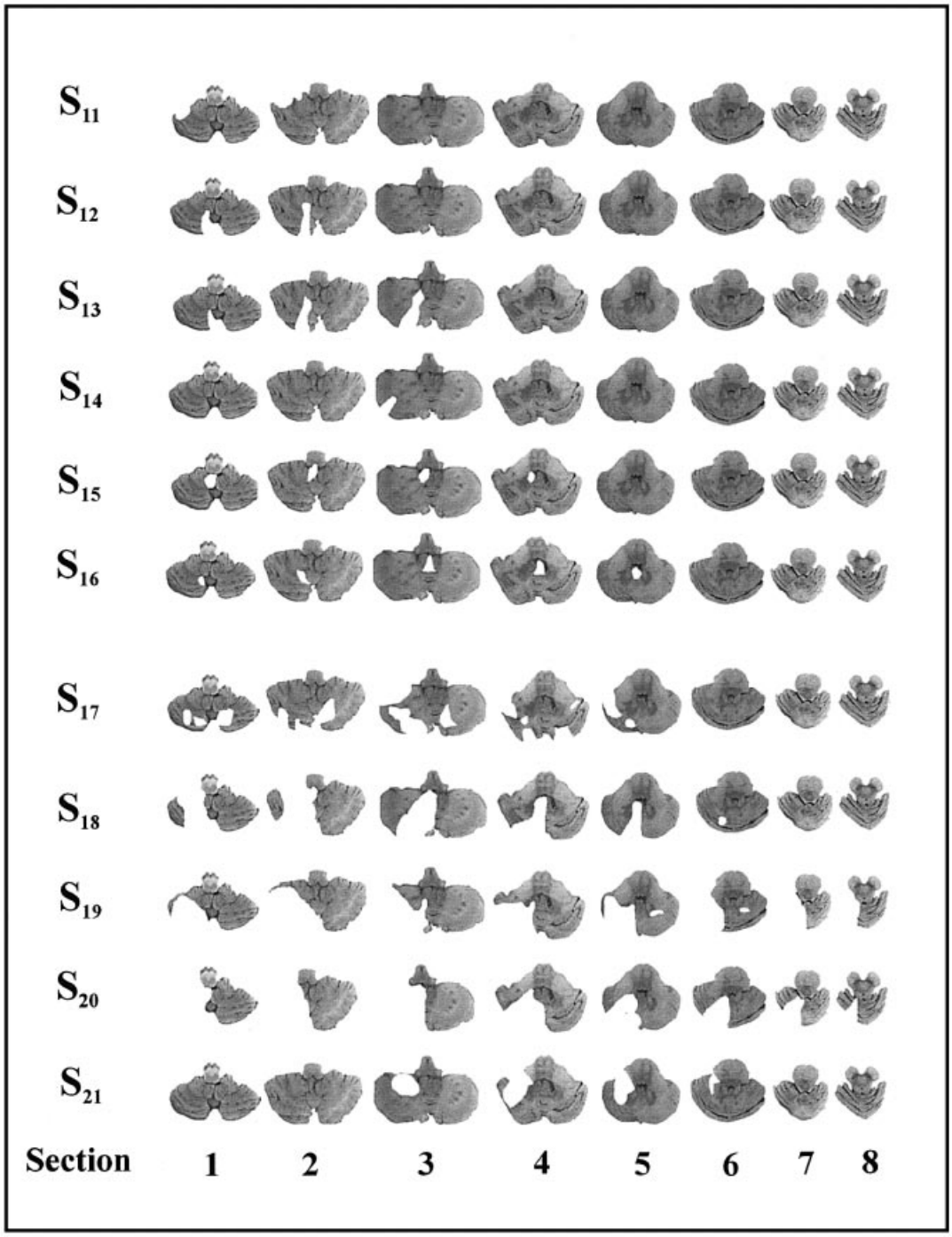

Fig. 2 Axial reconstructions for 11 subjects (S) in the left cerebellar group. Two patients (S17, S19) had bilateral lesions, with more extensive left cerebellar damage. Patients were classified into inferior and superior-plus groups using the same criteria specified in the caption for Fig. 1. There were six patients in the left inferior (LI) group (S11–16); two (S15, S16) also had damage on sections 4 and/or 5 involving the medial cerebellum. The remaining patients were in the left superior-plus (LS+) group (S17–S21), and all but one (S17) had dentate lesions.

more automatic processing of intervals lasting 400 ms or less compared with longer ones, in which a more controlled-processing strategy can be exerted (Gibbon *et al*., 1997).

Effect of lesion location.

Figure 3B, D and F displays the same data for patients with inferior and superior-plus damage. There was no difference in

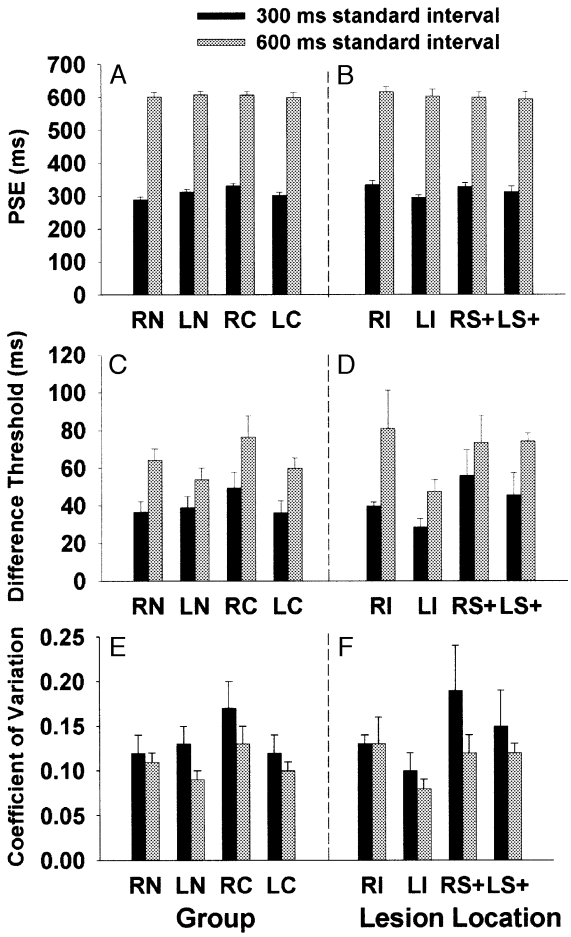

Fig. 3 Mean (SEM) point of subjective equality (PSE; top), difference threshold (middle), and coefficient of variation (bottom) for the 300 and 600 ms standard interval conditions in the time perception task. The 300 and 600 ms interval conditions are depicted by the black and the grey bars, respectively. (**A**), (**C**) and (**E**) display the results for the right normal control (RN), left normal control (LN), right cerebellar (RC) and left cerebellar (LC) groups. The same patient data are presented in (**B**), (**D**) and (**F**) for people showing predominantly right inferior (RI), right superior-plus (RS+), left inferior (LI), and left superior-plus (LS+) cerebellar damage.

PSE (Fig. 3B) between the control and either cerebellar subgroup, irrespective of performing hand. Difference thresholds (Fig. 3D) did not differ between the control and inferior cerebellar damage groups ($F < 1.0$, $P < 0.90$), but there was a trend for elevated difference thresholds in the superior-plus cerebellar groups [$F(1,37) = 3.4$, $P = 0.07$]. Three patients with superior-plus damage (S6, S10, S21) who showed elevated difference thresholds (i.e. >1 SD of the control group) had relatively small lesions. This contrasted with the normal difference thresholds in several patients with much larger lesions extending across the inferior–superior boundaries (S2, S3, S5, S7, S17, S19, S20). These observations suggest that lesion volume does not explain the trend for impaired difference thresholds. Finally, there were no differences in the coefficient of variation (Fig. 3F) between the control and either lesion subgroup, irrespective of performing hand. A trend for an increased coefficient of variation was seen in the superior cerebellar groups relative to the control groups [$F(1,37) = 3.18$, $P < 0.09$]; however, Fig. 3F suggests this was largely related to the 300 ms standard interval condition.

Time reproduction

Inter-tap interval

Effect of cerebellar damage.

Figure 4A displays the results for the mean ITI (timing accuracy) in the control and the cerebellar groups. We found a main effect of target interval [$F(1,47) = 9455.6$, $P < 0.0001$]. The ITI did not differ between groups or performing hand.

Effect of lesion location.

We found no difference in mean ITI between the control and either cerebellar subgroup (Fig. 4B), irrespective of performing hand or target interval.

Total variability and coefficient of variation

Effect of cerebellar damage.

Figure 4C displays the findings for the total ITI variability in the control and the cerebellar groups. We found an effect of standard interval [$F(1,47) = 94.7$, $P < 0.0001$], but no effect of group or performing hand. Similarly, there were no effects of group or performing hand for the coefficient of variation (Fig. 4E and F). Total variability was slightly nonscalar in all groups [Standard Interval Effect: $F(1,47) = 10.1$, $P < 0.01$; mean = 0.065, SD = 0.02 for 300 ms standard; mean = 0.056, SD = 0.02 for 600 ms standard]. Although the magnitude of the coefficient of variation was lower for time reproduction than time perception, values <10 are common, perhaps due to repeatedly timing the same interval (Gibbon *et al.*, 1997).

Effect of lesion location.

Total variability (Fig. 4D) did not differ between the control and either cerebellar subgroup, irrespective of the performing hand or target interval. Similarly, the coefficient of variation (Fig. 4F) was not related to any of these factors.

Clock variability

Effect of cerebellar damage.

Figure 4G displays the findings for clock variability in the cerebellar and control groups. There was an effect of target interval [$F(1,46) = 87.9$, $P < 0.0001$], but clock variability did not differ between the control or the cerebellar groups, irrespective of performing hand.

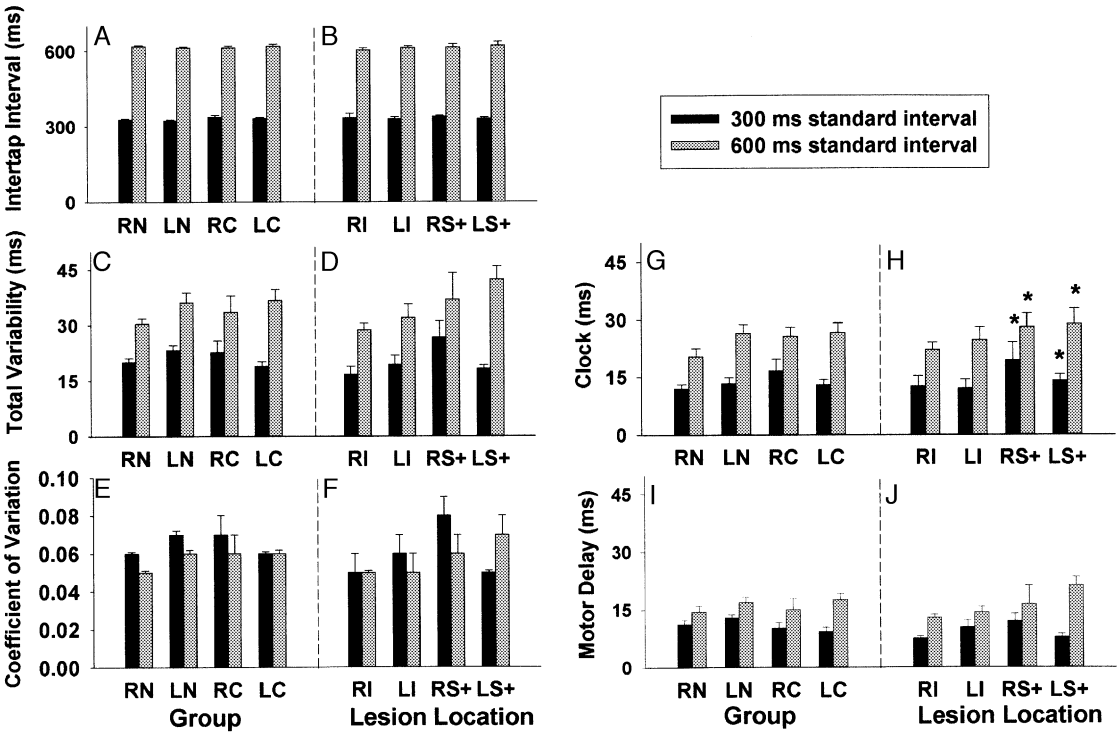

Fig. 4 Mean performance (SEM) for the 300 and 600 ms standard interval conditions in the time reproduction task. The 300 and 600 ms interval conditions are depicted by the black and the grey bars, respectively. The top row (**A**, **B**) displays the mean ITI results. The remaining graphs plot the total variability (**C**, **D**), coefficient of variation (**E**, **F**), clock variability (**G**, **H**), and motor delay variability (**I**, **J**). Variability is the SD of the ITIs. The data in the left column of each graph display the results for the right normal control (RN), left normal control (LN), right cerebellar (RC), and left cerebellar (LC) groups. The same patient data are displayed in the right column of each graph for people showing predominantly right inferior (RI), right superior-plus (RS+), left inferior (LI), and left superior-plus (LS+) cerebellar damage. In (**H**) asterisks above the bars designate the standard interval conditions in which clock variability was significantly elevated in the RS+ and the LS+ groups relative to the control groups.

Effect of lesion location.

In the lesion subgroup analyses, there was no effect of performing hand on clock variability. However, clock variability for both standard intervals was greater in the superior-plus cerebellar groups relative to the control groups [$F(1,37) = 4.4$, $P < 0.05$], irrespective of performing hand. Clock variability did not differ between the control and inferior cerebellar groups (Fig. 4H). Three patients (S8, S10 and S21) with impaired clock variability (i.e. >1 SD of the control group) had relatively small lesions distributed primarily on sections 4–8. By comparison, clock variability fell within normal limits in several patients with larger lesions extending across the inferior–superior boundaries (S2, S3, S5, S7, S17, S19, S20). Thus, lesion volume did not appear to relate to deficits in clock variability.

Motor delay variability

Effect of cerebellar damage.

Motor delay variability did not differ between the control and cerebellar groups (Fig. 4I), irrespective of performing hand. There was a significant effect of target interval [$F(1,47) = 26.2$, $P < 0.001$], which has been reported in other studies (Harrington *et al.*, 1998*a*).

Effect of lesion location.

There were no differences between the control and either cerebellar subgroup motor delay variability (Fig. 4J), irrespective of performing hand or target interval.

Control tasks

Maximum tapping speed

Mean maximum tapping speed in the limb ipsilateral to damage was significantly slower [$F(1,47) = 4.9$, $P < 0.05$] in both cerebellar groups (RC: mean = 189.7 ms, SD = 166.6; LC: mean = 232.2, SD = 108.8) relative to the control groups (RN: mean = 189.7 ms, SD = 16.0; LN: mean = 183.4, SD = 42.5), irrespective of performing hand. In the analysis of lesion subgroups, maximum tapping speed was significantly slowed relative to the controls only in patients with superior-plus damage (mean = 231.7 ms, SD = 95.1) [$F(1,37) = 6.9$, $P < 0.025$], but not inferior cerebellar damage (mean = 186 ms, SD = 31.7).

Frequency perception

There were no differences in PSE between the control and cerebellar groups, irrespective of performing hand. Similarly, there were no significant effects related to PSE in the analyses of lesion location. In the difference threshold analysis, we found no significant differences between the cerebellar (RC: mean = 12.5 Hz, SD = 10.1; LC: mean = 4.5 Hz, SD = 3.3) and control groups (RN: mean = 8.6 Hz, SD = 6.6; LN: mean = 10.0 Hz, SD = 8.8). The group × hand interaction [$F(1,47) = 4.77$, $P < 0.05$] showed a trend for better pitch acuity in the LC than the LN group ($P < 0.06$). In the analyses of lesion subgroups, the superior-plus and inferior cerebellar damage groups showed normal perceptual acuity for pitch (superior-plus: mean = 8.9 Hz, SD = 7.8; inferior: mean = 9.2 Hz, SD = 7.0).

Attention task

Percentage correct trials and RT were first analysed using a mixed-model repeated-measures ANOVA that tested the effects of SOA (200, 350, 500 ms), cue type (neutral, valid, invalid), group (control, cerebellar) and hand. The accuracy analyses showed that valid cues were the most accurate (mean = 98%, SD = 4%), followed by neutral (mean = 97%, SD = 4%) and invalid cues (mean = 96%, SD = 5%) [$F(1.6,94) = 7.1$, $P < 0.01$]. The cue type by SOA interaction [$F(3.5\ 188) = 3.3$, $P < 0.025$] showed improved accuracy with longer SOAs, but only for neutral and invalid cues. Performance in both groups was highly accurate (control: mean = 97%, SD = 3%; cerebellar: mean = 97%, SD = 5%) and did not differ as a function of cue type or SOA. Likewise, in the analyses of lesion subgroups, accuracy did not differ between the control and superior-plus (mean = 98%, SD = 2%) groups or the control and inferior (mean = 95%, SD = 7%) groups, irrespective of hand, SOA, or cue type.

Similar analyses examining the effect of cerebellar damage on RT showed expected RT reductions as SOA increased [$F(1.9,94) = 91.2$, $P < 0.0001$]. Figure 5A shows that RTs also depended on cue type [$F(1.8,94) = 230.8$, $P < 0.0001$]; valid cues facilitated and invalid cues prolonged RT relative to neutral cues. The group effect [$F(1,47) = 10.0$, $P < 0.01$] showed that RTs were longer in the cerebellar than control groups, irrespective of hand, SOA or cue type. Thus, cerebellar damage slowed response times, but had no effect on engaging or switching attention, or on automatic and controlled attention process. In the analyses comparing lesion subgroups (Fig. 5B), there was a group × hand interaction when the control and inferior cerebellar groups were compared [$F(1,36) = 10.4$, $P < 0.01$]. This interaction indicated slowed RTs in the RI [$F(1,17) = 12.3$, $P < 0.01$], but not the LI group, irrespective of SOA or cue type. Comparisons between the control and superior-plus damage groups showed longer RTs in patients than in controls [$F(1,37) = 8.4$, $P < 0.01$], irrespective of performing hand, SOA or cue type (Fig. 5B).

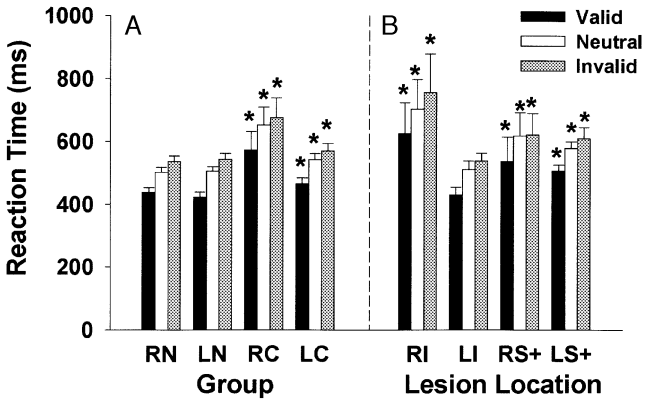

Fig. 5 Mean reaction times (SEM) for valid (black), neutral (unfilled) and invalid (grey) cues in the attention task. The left graph displays the results for the right normal control (RN), left normal control (LN), right cerebellar (RC) and left cerebellar (LC) groups. The right graph displays the same patient data for individuals showing predominantly right inferior (RI), right superior-plus (RS+), left inferior (LI), and left superior-plus (LS+) cerebellar damage. Asterisks above the bars designate the cue type conditions (valid, neutral, invalid) in which RT was significantly longer in a cerebellar group relative to the control subjects.

Relationship of cognitive functioning to timing

To explore the basis for impaired clock variability and the trend for elevated difference thresholds, we computed composite measures of variability, first by averaging across the standard intervals, since timing deficits were found for both. In patients, clock variability correlated positively with difference thresholds ($r = 0.47$, $P < 0.025$), suggesting that time perception and reproduction shared some common underlying processes. There was no relationship between motor delay variability and difference thresholds. Total symptom severity correlated positively with difference thresholds ($r = 0.50$, $P < 0.025$), but was not related to clock or motor delay variability ($P > 0.25$). Contralateral and ipsilateral upper limb symptom severity did not correlate with any measures of timing performance. Timing accuracy (i.e. mean ITI, PSE) did not correlate with performance on control tasks, neuropsychological tests or symptom severity (total score, upper limb scores).

Next, stepwise-regression analyses explored relationships between cognition and timing performance in patients with cerebellar damage. Difference thresholds and clock variability were separately regressed on (i) finger-tapping *t* scores (Reitan and Wolfson, 1993) from the hand contralateral to damage (processing speed), (ii) *t*-scores on Parts A and B of the TMT (visual-motor speed and executive functions of working memory, respectively), (iii) mean RT from the attention task (speed and focused attention) and (iv) difference thresholds for pitch perception (sensory discrimination). Contralateral tapping speed [$F(1,19) = 8.5$, $P < 0.01$, $r^2 = 0.31$] and performance on the TMT Part A [$F(1,18) = 7.4$, $P < 0.025$, $r^2 = 0.20$] accounted for 51% of the variance in difference thresholds. In contrast, performance on the TMT

Part B [$F(1,19) = 9.0$, $P < 0.01$, $r^2 = 0.32$] accounted for 32% of the variance in clock variability. Slower performance on each of these measures was associated with higher difference thresholds or greater clock variability.

Discussion

Our results showed that cerebellar damage did not consistently impair performance on both timing tasks. When deficits were found, they correlated with damage to the middle- to superior-cerebellar lobules, and only disrupted time reproduction performance. When we examined the relationship between neuropsychological measures of cognition and timing performance, processing speed correlated with clock variability, whereas working memory related to difference thresholds. This suggested that the emphasis on some processes differed between the two timing tasks, which might help explain why cerebellar damage can sometimes disrupt performance on timing tasks. We now turn to a discussion of these results.

Temporal information processing in the cerebellum

Though others have reported that cerebellar damage due to a variety of etiologies disrupts the reproduction of intervals lasting 1 s or less (Ivry *et al*., 1988; Ivry and Keele, 1989; Spencer *et al*., 2003), few studies have related these deficits to cerebellar anatomy. Our results indicated that disturbances in clock estimates of time-reproduction variability were associated with medial and/or lateral damage to the middle- to superior-cerebellar lobules, rather than simply the lateral cerebellar hemispheres (Ivry *et al*., 1988). These findings are in keeping with most functional imaging studies in healthy adults, which show that more superior cerebellar lobules, including the anterior lobe (IV and V), are activated during motor timing tasks (Jueptner *et al*., 1995; Rao *et al*., 1997; Penhune *et al*., 1998; Kawashima *et al*., 2000). In contrast to other work (Ivry *et al*., 1988), motor delay estimates of time-reproduction variability were not associated with medial cerebellar damage or, for that matter, cerebellar damage. We also did not find reliable impairments in time perception, contrary to studies that have included patients with cerebellar degenerative disorders (Ivry and Keele, 1989; Mangels *et al*., 1998; Casini and Ivry, 1999). Though we observed trends for deficient time perception in patients with more superior cerebellar damage, they were not robust. These results are not likely due to insufficient statistical power since our sample sizes were as large or larger than samples previously studied. The discrepant findings in other studies may be due in part to the inclusion of patients with cerebellar atrophy, who show marked deficits in time perception relative to patients with cerebellar lesions (Casini and Ivry, 1999). Altogether, our results cast doubt on the proposal that the cerebellum regulates a common timekeeping mechanism.

The findings of impaired clock variability, but not accuracy (ITI), are consistent with the cerebellum's role in modulating processes other than timekeeping, since changes in the rate of the timekeeper are thought to affect timing accuracy (Gibbon *et al*., 1984). For example, the administration of dopamine agonists and antagonists in animals immediately produces overestimations and underestimations of learned intervals, ostensibly because they change the rate of the internal clock (Maricq and Church, 1983). By comparison, increases in variability alone have been attributed largely to other processes that support timing (Meck and Church, 1987; Gibbon *et al*., 1997). For example, increasing working memory demands during temporal processing results in robust increases in clock variability and difference thresholds (Sergent *et al*., 1993; Casini and Ivry, 1999), but does not necessarily alter timing accuracy (Casini and Ivry, 1999). Likewise, impaired temporal processing variability, but not accuracy, after damage to cortical systems known to modulate working memory and attention (Nichelli *et al*., 1995; Harrington *et al*., 1998*b*; Casini and Ivry, 1999) further suggests that variations in processes other than timekeeping account for much of the increased variability in performance. Still, an understanding of the mechanisms that influence accuracy and variability is incomplete (Wearden, 1999). In theory, a disruption in the clock process could influence variability to some extent (Gibbon and Church, 1990). However, if this were the case, both time perception and reproduction variability should have been impaired in cerebellar patients, since a common timekeeping mechanism supports both (Keele *et al*., 1985; Treisman *et al*., 1992). This was not found, thus our results suggest that abnormalities in other processes contributed to deficient clock variability.

Insight into why cerebellar damage reliably increases clock variability in time reproduction, but does not consistently produce time perception deficits, can be gained by considering clock variability in the impaired and the unimpaired hand after unilateral cerebellar damage. In these patients, both hands are able to achieve the target interval (i.e. normal accuracy), but clock variability is increased only in the impaired hand (i.e. ipsilateral to damage) (Ivry *et al*., 1988; Franz *et al*., 1996; Spencer *et al*., 2003). Notably, deficient clock variability in the impaired hand can be remedied by simultaneously tapping with both hands (Franz *et al*., 1996). These findings were interpreted as evidence for separate timing mechanisms in the right and left hands. A common gating mechanism was proposed that integrated the timing signals from the two hands, by averaging the two signals. Although this model accounts for reduced clock variability in the impaired limb of cerebellar patients, it has difficulty explaining the absence of a concomitant *increase* in clock variability in the unimpaired limb (Franz *et al*., 1996). This explanation also does not easily accommodate the view that a common timekeeping mechanism supports both perception and movement (Treisman *et al*., 1992; Ivry and Hazeltine, 1995).

Alternative explanations do not necessitate separate timing mechanisms for different hands. Rather, cognitive processes such as explicit timing are thought to generalize across effectors. Indeed, learning a timing pattern with one effector (e.g. arms) transfers to others (e.g. legs) (Kelso and Zanone, 2002). Moreover, to make a compelling case for a deficient central process, it is important to demonstrate that temporal processing impairments are independent of sensorimotor deficits. Otherwise, a more parsimonious explanation for increased clock variability in the impaired, but not the unimpaired limb is that it is more related to slow, inaccurate, jerky and reduced amplitude movements caused by cerebellar damage. At the same time, improvements in clock variability in the impaired limb during bimanual movements may reflect an emergent property of the strong coupling of the two hands, which enhances stability and reduces variability in the motor system (Kelso *et al*., 1979). This explanation was challenged recently by findings showing that unilateral cerebellar damage does not disrupt the timing of continuous movements in the impaired hand (i.e. circle drawing), in which it was speculated that the temporal properties were emergent (Spencer *et al*., 2003). It appears, however, that these results may be due to strategic factors, as continuous movements in both limbs were considerably slower in cerebellar patients than in the control subjects, suggesting a strategy of slowing down to increase performance consistency.

The suggestion that the cerebellum does not specifically regulate timekeeping processes has received support from several functional imaging studies. We reported that cerebellar activation was not unique to timing movements in healthy adults who underwent functional MRI (fMRI) as they performed a similar time reproduction task (Rao *et al*., 1997). In an event-related fMRI study of time perception, we separated brain activation related to encoding the standard interval, which should involve timekeeping processes, from activity associated with comparing intervals and decision-making (Rao *et al*., 2001). Activation in the vermis (VIIB), but not the lateral cerebellum, was associated only with the decision-making phase. Altogether, these studies did not implicate the cerebellum in timekeeping.

Cognition and the cerebellum

The present results suggest that temporal processing deficits in cerebellar patients might relate more to other psychological processes involved in the timing tasks. In our time reproduction task, the standard interval was reproduced repeatedly for 6 s or longer, whereas in the time perception task the standard and comparison intervals were presented once, within seconds of one another. One might speculate that time reproduction placed greater demands on working memory than time perception, consistent with the correlation between clock variability and the TMT Part B. This prospect is supported by fMRI research showing that the continuation phase of time reproduction activates a covert auditory-rehearsal network in prefrontal cortex (Rao *et al*., 1997). Additionally, lobules VI and VIIA are sensitive to verbal working-memory load, suggesting the cerebellum processes input from prefrontal working-memory systems (Desmond *et al*., 1997). Collectively, this suggests that cerebellar damage may disrupt the maintenance of intervals in working memory during time reproduction. These results contrast with our finding that difference thresholds correlated with processing speed (contralateral tapping speed, TMT Part A). In the time perception task, successive trial events quickly follow one another, such that the speed of processing rapid sensory inputs might be more important than during time reproduction. Though time perception was not reliably impaired after cerebellar damage, the trend for deficits in some patient groups may be due to a generalized slowing in processing speed. This was evident in patients' longer response times in the attention task, slowed contralateral tapping speed, and impaired TMT Part A performance. This is consistent with the proposal that the cerebellum is principally involved in temporal processing when intervals are short (1 s or less) (Ivry, 1996; Breukelaar and Dalrymple-Alford, 1999). More generally, temporal processing may be particularly vulnerable in neurological disorders that impair processing speed.

Conclusions

Collectively, our findings are not consistent with a role for the cerebellum in timekeeping operations. It is not known whether the cerebellum provides a unique contribution to cognition. Part of the difficulty in specifying the function of the cerebellum stems from its broad role in sensorimotor and cognitive processes (Schmahmann, 1997) including eyelid conditioning (Mauk and Donegan, 1997), tactile perception (Gao *et al*., 1996; Parsons *et al*., 1997), working memory (Desmond *et al*., 1997), attention (Akshoomoff and Courchesne, 1994), learning (Leggio *et al*., 2000; Penhune and Doyon, 2002) and speech production (Paulesu *et al*., 1993). Though some of these behaviours may require explicit timing, our results indicate that it is not necessary to adopt a timing explanation to account for the cerebellum's role. One model suggests that the cerebellum monitors and adjusts input from the cerebral cortex (Bower, 1997; Parsons *et al*., 1997), perhaps to signal discrepancies between an intended action and the actual sensory consequences (Blakemore *et al*., 2001). Cerebellar activity has been linked to event-expectancy (Mauk *et al*., 2000) and may act on sensory information by scaling output to optimize sensorimotor or cognitive operations of the cerebral cortex. By this account, cerebellar damage should slow sensory acquisition, disrupting a wide range of behaviours, especially those that unfold quickly. According to this view, clock variability increases in the limb ipsilateral to cerebellar damage because there is a disruption in acquiring auditory or cognitive input relevant to an intended temporal goal and coordinating it with an impaired motor-output system. Indeed, greater cerebellar activation has been reported in healthy adults when sensory cues guide

movements than when the same movements are self-generated (Jueptner *et al*., 1996*b*). It is also likely that computations in different cerebellar lobules mirror the functions of interconnecting cortical areas (Dum and Strick, 2003), providing a neuroanatomical means to affect higher-order cognitive functions (Schmahmann, 1997).

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