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Dissociation of the lateral and medial cerebellum in movement timing and movement execution

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Summary. In a previous study (Ivry and Keele, in press), cerebellar patients were found to be impaired on both a motor and a perceptual task which required accurate timing. This report presents case study analyses of seven patients with focal lesions in the cerebellum. The lesions were predominantly in the lateral, hemispheric regions for four of the patients. For the remaining three patients, the lesions were centered near the medial zone of the cerebellum. The clinical evaluation of the patients also was in agreement with the different lesion foci: lateral lesions primarily impaired fine motor coordination, especially apparent in movements with the distal extremities and medial lesions primarily disturbed balance and gait. All of the patients were found to have increased variability in performing rhythmic tapping when tapping with an effector (finger or foot) ipsilateral to the lesion in comparison to their performance with a contralateral effector. Separable estimates of a central timekeeper component and an implementation component were derived from the total variability scores following a model developed by Wing and Kristofferson (1973). This analysis indicated that the poor performance of patients with lateral lesions can be attributed to a deficit in the central timing process. In contrast, patients with medial lesions are able to accurately determine when to make a response, but are unable to implement the response at the desired time. A similar dissociation between the lateral and medial regions has been observed on a time perception task in patients with cerebellar atrophy. It is concluded that the lateral regions of the cerebellum are critical for the accurate functioning of an internal timing system.

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Introduction

In a preceding paper (Ivry and Keele, in press), we examined the performance of different neurological patient groups on a motor timing task and a perceptual timing task. The results strongly indicated that the integrity of the cerebellum was critical for accurate timing control. Only the cerebellar patients were impaired on both the motor and perceptual tasks. These patients were more variable on a rhythmic tapping task and were less accurate than the other groups in making perceptual judgments of time intervals bounded by acoustic signals. We interpret these results as demonstrating that one role of the cerebellum is to operate as a task-independent timing module. When a task requires some sort of explicit timing computation, the cerebellum is recruited for this operation.

Previous research and theory had suggested that timing control may be one function of the cerebellum. Classical clinical neurology has interpreted dysmetria and dysdiadochokinesia, cardinal signs of cerebellar dysfunction, as being the result of a breakdown in the patient's ability to time the onset and offset of antagonist pairs of muscles (Holmes 1939; Dichgans and Diener 1984). For example, the hypermetric movement overshoots the target because the muscular activity is not properly terminated (Eccles 1977; Hallett et al. 1975; Vilis and Hore 1980). Animal models have further demonstrated that lesions in the cerebellar nuclei can disrupt the temporal relations between antagonist muscles (Conrad and Brooks 1974; Vilis and Hore 1980).

While those studies suggest that the cerebellum is involved in timing control, the studies have only indirectly addressed the problem. Alternative explanations which do not involve a timing mechanism could be involed to account for these results. For instance, the onsets and offsets of the EMG bursts might be regulated by feedback from the periphery (Terzuolo et al. 1973) and cerebellar lesions could disrupt this closed loop process. Moreover, previous research had only considered the cerebellar role in motor timing. We have found (Keele et al. 1985b) significant correlations between healthy subjects' ability to accurately produce isochronous intervals and make perceptual judgments concerning the regularity of similar intervals. This finding led us to consider the hypothesize that the same timing system is used in both motor and perceptual tasks. We believe our patient study (Ivry and Keele, in press) provides the most direct evidence for the hypothesis that the cerebellum is part of an internal timing system used in motor control. In addition, the finding of a purely perceptual deficit in cerebellar patients was novel and demonstrated the general purpose nature of the cerebellar timing system.

In the present paper, we will report a detailed examination of the tapping performance of eight patients with focal cerebellar lesions. Whereas the group data presented in Ivry and Keele (in press) pointed out the importance of the cerebellum in timing, we will argue that the case studies demonstrate a dissociation between the respective contributions of the lateral and medial aspects of the cerebellum. The lateral regions of the cerebellum are required for accurate timing whereas the medial regions are primarily involved in the implementation and execution of motor responses.

The hypothesis that different functions are associated with the lateral and medial regions of the cerebellum is not novel. The most frequent division of cerebellar function has been to associate the lateral regions with movement planning and programming whereas the intermediate and medial regions are associated with the movement execution (e.g. Allen and Tsukahara 1974; Eccles 1977; see Brooks and Thach 1981 for a review). We will briefly review the evidence for this distinction drawing from anatomical, physiological, and clinical research. The cerebellum is typically segmented into three regions: the lateral, intermediate, and vermal regions which primarily project to the fastigial, interpositus (glubose/emboliform complex in humans), and dentate nuclei, respectively. The efferent projections from the nuclei remains segregated as they exit the cerebellum via the peduncles (Pansky and Allen 1980; Asanuma et al. 1983c) and show marked differences in terms of their target innervation sites at all levels of the central nervous system. Starting with the most descending fibers, only the fastigial and interpositus nuclei send projections directly to the spinal cord (Wilson et al. 1978; Asanuma et al. 1983c). At the next higher level, a contrast can be seen between the fastigial projections to the brainstem and the interpositus and dentate efferent pathways. The former include extensive terminations in the vestibular nuclei, reticular formation, and the pontine nuclei (Asanuma et al. 1983c) whereas the latter nuclei primarily project to the ventrolateral regions of the thalamus, the red nucleus, and the inferior olive (Kemp and Powell 1971; Pansky and Allen 1980; Asanuma et al. 1983a–c). Moreover, the dentate and interpositus terminations in the red nucleus, inferior olive, and ventrolateral thalamus are in non-overlapping regions (Flumerfelt et al. 1973; Asanuma et al. 1983a–c; Yammamoto et al. 1983). At the highest level, Sasaki (1984) has summarized electrophysiological evidence for cat and monkey showing marked differences in the cerebellocortical connections. According to Sasaki (1984), the medial and intermediate zones of the cerebellum are reciprocally connected with motor cortex (areas 4M and 4I, respectively). The reciprocal connections between the lateral cerebellum and cortex are much more extensive spanning prefrontal and premotor areas as well as motor cortex (area 4L). Schell and Strick (1984) have also argued that there are parallel pathways from the cerebellar nuclei to the cerebral cortex.

Single cell recordings have provided another line of evidence supportive of the functional distinction between the lateral and medial nuclei of the cerebellum. For example, Thach (1970, 1975, 1978) has examined discharge latencies in dentate and interpositus neurons under volitional and reactive movement conditions. When producing self-initiated movements, Thach observed that dentate latencies preceded EMG changes (Thach 1970) and tended to lead responses in motor cortex (Thach 1975). In contrast, the latencies of interpositus neurons were generally shorter than dentate latencies following the pertubation of a monkey's hand from a held position (Thach 1978). Similarly, Bava et al. (1983) reported that fastigial neurons were only recruited after movement onset. Taken together, these latency results match what would be expected if the lateral regions of the cerebellum contributed to movement planning and the more medial zones were involved in movement execution, regulation, and correction (see also Schwartz et al. 1987).

These anatomical and neurophysiological differences between the lateral and medial regions of the

cerebellum are mirrored in clinical findings. The most general distinction made by neurologists regarding cerebellar disorders is that medial lesions are associated with disturbances of gait and stance whereas lateral lesions produce deficits in fine motor coordination manifested in limb ataxia, intentional tremor, dysmetria, and dysdiadochokinesia (Holmes 1939; Ito 1984; Dichgans and Diener 1984). It seems reasonable to suppose that the deficits in hand and finger movements can be the result of planning deficits. The stance and gait deficits appear to be more posturally related and thus primarily associated with an implementation or feedback system. The correlation between site of lesion and this dochotomy, however, is not perfect. It is unlikely that the clinical differentiation between fine motor coordination and posture corresponds perfectly with the functional distinction between planning and implementation.

To summarize, converging evidence points to the role of the lateral regions of the cerebellum in movement planning whereas the contribution of the medial regions appear to be evident during movement execution. Both regions might be expected to be required for successful performance in a rhythmic tapping task, but for different reasons. The task requires explicit timing control, at least as part of the abstract motor program. The timing mechanism will presumably determine when a response should occur. This function is clearly within the domain of the planning system. In line with the preceding review, we hypothesize that the timing functions previously associated with the cerebellum (Ivry and Keele, in press) arise from activity in the lateral regions. Focal lesions of the lateral regions would thus be expected to impair the operation of the timing mechanism. However, accurate timing does not ensure that the response is properly executed. The commands of the control system must be faithfully implemented. Since the medial regions of the cerebellum become prominent at this stage of motor control, it is hypothesized that lesions of this tissue may indirectly disrupt rhythmic tapping. In this situation, the timing mechanism may continue to operate properly, but the implementation system is impaired.

Method

Procedure. The subject was seated with the arm used for tapping resting on a table, palm down. The index finger of either the impaired or unimpaired hand was placed on a microswitch mounted on a wooden block. Pressing the microswitch provided a pulse to a computer which recorded all responses to the nearest millisecond.

Each trial began with a series of 50 ms tones (65 dBA) presented at regular intervals of 550 ms. This pace was sufficiently slower than the maximal tapping rate of all of the subjects, thus ensuring that no subject had a problem keeping up with the pace. A subject was instructed to begin tapping along with the tones once he or she had internally established the desired pace. After the subject's first response, 12 more tones were presented during which time the subject attempted to synchronize his or her responses. The subject was instructed to continue tapping at the same rate when the tones ended. After 31 self-paced taps had occurred, the computer signalled the end of the trial. Feedback was then provided to the subject indicating the mean interval produced with and without the tones and the standard deviation of the inter-response-intervals (IRI).

A block of trials was concluded once the subject had produced either six "error-free" trials of 12 paced and 31 self-paced responses each or six "unsuccessful" trials. A trial was considered unsuccessful if any IRI was less than or greater than 50% of the base duration (less than 275 ms or greater than 825 ms). The data from the unsuccessful trials were excluded from subsequent analysis. This is a criterion which we have adopted in our previous research since such deviant values could be due to either tremor or insufficient force to register a response.

Each subject alternated between blocks of tapping with the impaired and unimpaired index fingers. We have found that normal subjects are equally proficient at this task with either hand, regardless of hand dominance (Keely et al. 1985a). Thus, we are confident that any differences which emerge with the patients can be attributed to their neurological deficits. The first finger tested was randomly selected. Each testing session began with at least two practice trials, one with each finger. Some of the subjects were tested in a single session whereas others were tested over a number of sessions separated from one week to 18 months. The number of blocks and sessions varied and are given individually with each report.

Data analysis. Only the tapping data from the self-paced portion of the trials is included in the analyses. Our basic measure of performance consistency is the standard deviation of the 30 inter-response-intervals produced on each trial. The raw data (IRIs) were first fitted to a trend line and the deviation from this trend line was calculated. This procedure eliminates any variability that may arise from a constant drift in the timing process. In practice, however, the effect of the transformation is minimal. The six standard deviation scores from a block of trials were averaged to yield a single mean overall standard deviation score for each trial block.

More detailed analyses of the tapping data are based on a theoretical model of the timing of repetitive movements developed by Wing and Kristofferson (1973; also Wing 1980). This model assumes that there are two processes which are involved in periodic behavior: a timekeeper system that determines when a response should be emitted and an implementation system that executes that command. The Wing and Kristofferson model postulates that the variability of the IRIs will arise from the sum of variability from these two processes. Each process is assumed to behave as an independent random variable with normal variance. Furthermore, the two processes are assumed to operate independently of each other. Taken together, these assumptions mandate that the system operate in an open-loop (i.e. feedback-free) mode.

Figure 1a depicts these processes in a hypothetical series of responses in which the variability of the timekeeper is zero. Each IRI is the sum of a timekeeper interval plus the difference in motor delays associated with the initiation and termination of that response. Formally, the duration of interval j can be written as

$$I_j = C_j + MD_j - MD_{j-i} \quad (1)$$

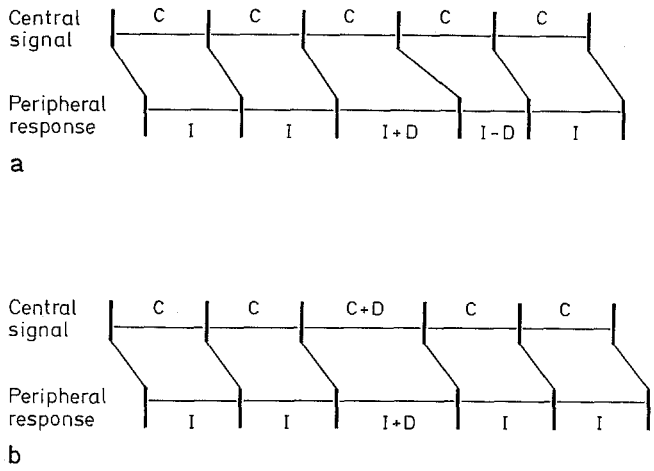

Fig. 1a, b. Hypothetical series of inter-response-intervals resulting from the two-process model of Wing and Kristofferson (1973). **a** Series of intervals in which the only variability is introduced on the fourth response resulting from added implementation (motor delay) time. **b** Series of intervals in which the only variability is introduced by the long clock time on the third interval

where I, C, and MD symbolize the interval, clock, and motor implementation (delay) durations, respectively. Since the two sources of variance are independent, it follows that

$$\sigma^2_I = \sigma^2_C + 2\sigma^2_{MD} \quad (2)$$

σ^2_I is directly obtained from the subject's data. It is the variance of the inter-response-intervals. The Wing and Kristofferson (1973) model decomposes this total variability into separable estimates of the timekeeper and the implementation variability from the covariance function of the series of responses. Briefly, a randomly large motor delay will produce both a long preceding response and a short following response. As depicted in Fig. 1a, Intervals 3 and 4 negatively covary due to the increased implementation time (longer diagonal line) on the fourth key press. The magnitude of that variance serves to estimate motor delay variance. Note that, although this may appear to be a corrective process, it is actually the result of the independence between the timekeeper and implementation system. Figure 1b, which depicts an analogous series of taps in which σ^2_{MD} equals zero, shows that there is no similar dependency between successive intervals as a function of imprecision in the timekeeper. Thus, an estimate of σ^2_{MD} is obtained from the lag one autocovariance, or more specifically:

$$\sigma^2_{MD} = -\text{autocov}(1) \quad (3)$$

σ^2_C can now be obtained by making the appropriate substitutions in Eq. 2. Note that the estimates of the two independent processes are not obtained independently. The estimate for clock variance is obtained by subtraction of motor variance from total variance.

This two-process model of periodic movement has received support from a number of different paradigms. First, of critical importance, is the finding that the model accounts well for the general autocovariance functions produced by normal subjects. The correlation between successive intervals is almost always negative (Wing and Kristofferson 1973). Moreover, as predicted by the model (see Wing and Kristofferson 1973), the covariance at lags greater than 1 is generally minimal and inconsistent. Second, Wing (1980) reported that only the estimate of the timekeeper variability was related to the duration of the base interval. This is predicted from the model since only the frequency of the timekeeper is adjusted following changes in the base duration, whereas the motor delay is assumed to be constant.

The model has also received support in neuropsychological testing. We (Ivry and Keele 1985; Ivry and Keele, in press; Keele and Ivry 1987) have proposed that patients with peripheral nerve damage provide a critical test for the model since they should only demonstrate an increase in the motor delay estimate. Indeed, this appears to be the case for all four patients tested to date who had incurred a variety of peripheral lesions. Furthermore, we have tested two patients who have clinically presented total sensory loss but intact motor function at the distal extremities. These functionally deafferented patients performed well within the normal range on the tapping task, providing support for the open-look assumption of the model (Ivry and Keele, in press).

Results

It is difficult to definitively classify cerebellar patients as either lateral or medial patients. Lesions are usually not well circumscribed and the damage following stroke or tumor excision is generally much more extensive than that produced in the laboratory. Any lateral/medial distinctions can at best be viewed as approximations. Therefore, we have based our classification scheme on clinical evaluations as well as CT scans and surgical reports. The clinical focus was on whether the patient presented signs indicative of medial damage such as postural disturbances or whether the patients exhibited symptoms such as dysmetria, dysadiochokinesia, or intentional tremor when making voluntary movements with the upper extremities. In addition, the dentate nucleus is much larger in humans than either of the other nuclei and, correspondingly, is assumed to receive the bulk of the projections from the cerebellar cortex (e.g. Leiner et al. 1986). This led us to bias our classifications towards assigning patients to the lateral group for the largest lesions. Although some patients are clearly and consistently classified by all criteria, a few are more problematic and they will be noted.

All of the neuroradiological commentary was verified independently by a radiologist and a neurologist. One of these physicians was unaware of the purpose of the study and the other was not informed of the clinical and experimental performance of the subjects until after judging the CT scans. Due to the fact that some patients were tested in Germany and others in the United States, it was not possible to have all of the patients undergo identical clinical evaluations. Four of the patients (cases 1–3, 5) were evaluated by neurologists who were naive as to the nature of the study. For the other patients (cases 4, 6–7), the clinical reports are based on two sources. First, their hospital records provided a source of unbiased information. Second, one of the authors (RBI) conducted a brief clinical evaluation prior to

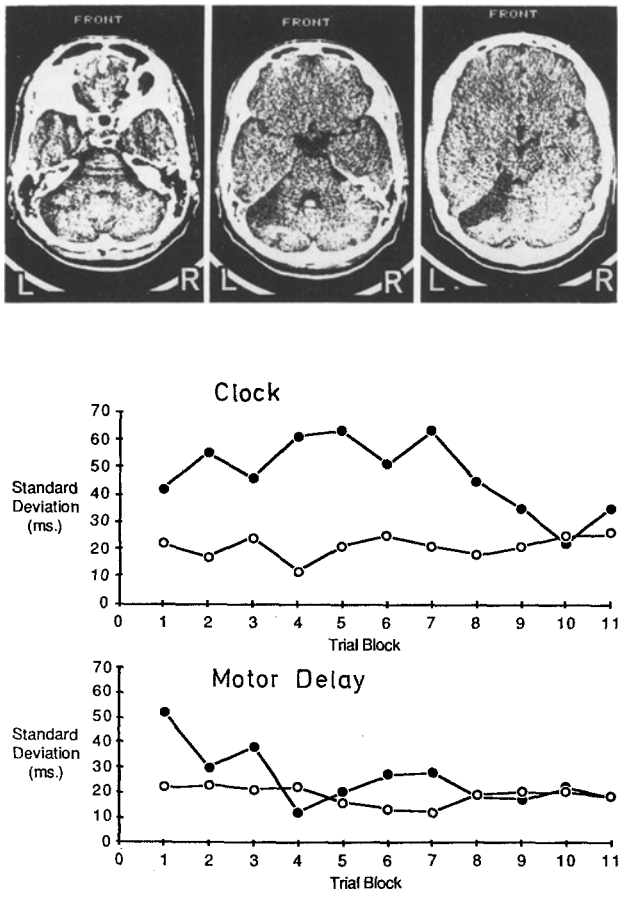

Fig. 2. CT scans and tapping estimates for Case 1, YOU. In the three CT slices shown in the top of the figure, the lesion can be seen in the lateral region of the left cerebellar hemisphere. Blocks 8–11 were completed eighteen months after Blocks 1–7. In Fig. 2 through 8, separate clock and motor delay estimates derived from the Wing and Kristofferson (1973) model are presented in the middle and bottom parts of the figure, respectively. Filled circles are for performance with the impaired effector and the open circles are for the unimpaired effector. Unless noted, impaired effector is the index finger ipsilateral to the lesion and unimpaired effector is the contralateral index finger. Each data point is the mean of six tapping trials

initial testing. Unfortunately, for cases 4 and 7 some specific tests, especially for locomotion (e.g. tandem walking) and balance (e.g. sway) were not conducted until follow-up sessions at which time the author was no longer naive regarding the patient's tapping performance.

T-tests were employed for all statistical comparisons. For each subject, a pair of t-tests for correlated samples: one on the clock estimates for each hand and a second for the motor delay estimates. Since the comparison was always between an a priori designated impaired and unimpaired effector, one-tailed criterion levels were used.

Case 1. YOU, a 25 year old female had suffered an infarction of the left cerebellar hemisphere. She was originally tested on four different occasions over a one-week period approximately one month after the accident. Follow-up testing was performed during a single session eighteen months later. At the time of the initial sessions, YOU demonstrated the general pattern of cerebellar signs on the left side: severe intentional tremor and dysmetria on finger pointing as well as ataxia. Finger-to-nose testing was poor and the patient was unable to perform rapid alternating movements with the left hand (dysadiochokinesia). Her upper left limb appeared to be more impaired than the left leg. Nonetheless, her gait was unstable and characterized by a wide stance to compensate for balance problems. Oculomotor function was also affected. She did not show any pyramidal or cerebellar signs on the right side.

YOU had shown a modest degree of improvement in terms of clinical evaluation during the eighteen month recovery period. Oculomotor function was still disturbed and YOU presented moderately severe intentional tremor and dysmetria when using the left arm and hand. Greater improvement could be observed in terms of left leg performance, stance, and gait.

The patient's CT scans taken at the time of initial testing are shown in the top half of Fig. 2. A large lesion can be seen along the left-most border of the cerebellum. The lesion is much more apparent in the slices showing the superior views of the cerebellum. The lesion is centered in the hemispheric regions of the left cerebellum rather than in the vicinity of the deep cerebellar nuclei. This patient can be unhesitantly assigned to the lateral group. Although vascular accidents involving the cerebellum frequently are accompanied by concomitant infarction of the brainstem, no evidence of brain stem involvement can be seen in the figure.

YOU participated in a total of 11 blocks of tapping with each hand, seven shortly after the stroke and four a year and a half later. Eack block in the follow-up session was composed of only five trials. She was unable to produce six error-free trials during three of the blocks with the left hand and thus the total number of error-free trials for the left hand is 59 in comparison to 62 for the right hand. Most of the errors were due to excessive intentional tremor which caused her to miss the microswitch.

The mean overall standard deviation for YOU was 61 ms for the left hand and 35 ms with the right. The bottom half of Fig. 2 displays the clock and motor delay estimates derived from the Wing and Kristofferson model for each block of trials. A few points stand out in this figure. First, the stability of the estimates for the unimpaired right hand over sessions spanning eighteen months is impressive. The mean of the first seven blocks is almost identical to that obtained in the last four blocks. In contrast, the left hand estimates show considerable improvement, presumably mirroring the patient's recovery process. Second, YOU demonstrated increased implementation variability with the left hand during the first seven blocks. However, during the last four blocks, the motor delay estimates were identical for each hand. This suggests that the increased implementation variability shortly after the stroke may reflect diffuse impairment of distant systems of the cerebellum, systems which recover with time. Indeed, as noted above, this type of lesion is frequently accompanied by infarction of the brain stem and any deficit in this region would be expected to produce increased variability in the motor delay estimate, only. Third, and of central interest, the clock estimate when tapping with the left hand is considerably higher than that obtained for the right hand ($t(10) = 5.36$, $p < 0.001$). Over the first seven blocks, the left hand clock estimate is 170% higher than the right hand estimate. Furthermore, this clock deficit, although reduced, is still present eighteen months post-trauma.

Case 2. CON, a 19 year old male, had undergone surgery one year prior to testing for removal of an astrocytoma of the left cerebellar

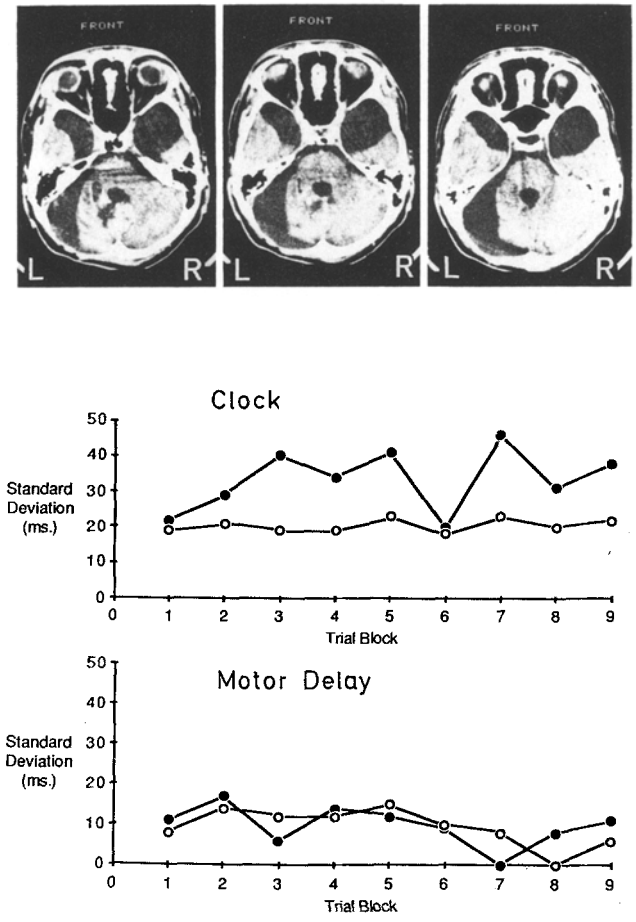

Fig. 3. CT scans and tapping estimates for Case 2, CON. The postoperative scans show a large tumor situated in the lateral region of the left cerebellar hemisphere. Blocks 6–9 were completed eighteen months after Blocks 1–5

hemisphere. Before surgery, the patient had been mildly ataxic on the left side. However, immediately after surgery, CON showed pronounced cerebellar symptoms. These included an inability to stand, very severe ataxia and hypotonia of the left hand, and some mild sensory deficits on the left side. Recovery was rapid, especially on measures of posture control and locomotion. By six weeks, CON could walk unassisted and had regained all sensory functions. At the time of the first test session, reflexes tested normal at all four extremities. The only persistent cerebellar signs involved the left hand, which was moderately affected in testing for dysdiadochokinesia and dysmetria, and oculomotor function. CON had a moderate amount of difficulty in finger-to-nose testing, showing some intentional tremor.

CT scans taken 2 months after surgery are shown in Fig. 3. As can be seen in the figure, nearly the entire left cerebellar hemisphere was removed. The deep cerebellar nuclei were spared. The lesion does not appear to extend into the vermis, although a small medial hypodense region is visible. It is unclear whether this represents artifact or unexcised tumor. A potential drawback in interpreting this patient's results is that the CT also revealed large arachnoidal cysts in both temporal regions, especially on the right side. The patient has been included in a number of previous cerebellar studies since he has never shown any neurological symptoms associated with temporal lobe lesions and the cysts appear to have existed for a long time. Furthermore, the anterior pole of the temporal lobe is not generally associated with motor function and cysts of this region generally remain asymptomatic.

For the first session, CON produced five blocks of tapping with each hand. A second session was conducted one month later at which time four more blocks were completed. These latter blocks were composed of five trials. This created a data set of 50 tapping trials with each hand.

As was expected from the clinical report, CON had more difficulty on this task when tapping with the left hand. The overall IRI standard deviations were 37 ms and 25 ms for the left and right hands, respectively. As shown in Fig. 3, applying the Wing and Kristofferson model to the data indicates that the increased variability can be entirely attributed to the timekeeper process ($t(8) = 5.19$, $p < 0.001$). The motor delay estimates are approximately equal while the clock estimate is always higher for the left hand. Note that the motor delay estimates were consistently lower during the second session. We have consistently observed that while mean values may fluctuate across sessions, the general differences between hands remains constant.

The results, unfortunately, cannot be so simply interpreted because the subject demonstrated a consistent negative correlation between non-adjacent intervals. The basic Wing and Kristofferson (1973) model predicts that there should be no reliable correlation between any intervals other than adjacent pairs. This finding indicates that at least one of the basic assumptions of the Wing and Kristofferson model was violated.

Wing (1977) has considered the effects on the covariance function of certain violations of the assumptions underlying the basic model. Inspection of the data from individual trials indicated that none of the alternative models proposed in Wing (1977) could account for CON's performance. The data revealed that CON was generally quite regular in tapping. In fact many left-handed trials were indistinguishable from right-handed performance. However, on certain trials, CON produced exceptionally long intervals on one or two occasions out of a series of 30 intervals.

Additional analysis suggests that these long intervals should be attributed to a deficit in the timekeeper rather than the implementation system. If the long intervals were due to the implementation system, then each long interval should be followed (or preceded) by a short interval since the clock is assumed to be ignorant of the added delay. This was not the case. The long intervals were neither followed nor preceded by shorter than average intervals. Detailed data on this point, extracted from the individual trials are shown in Ivry (1986). There it is also shown that the negative covariance at higher lags can be attributed to the fact that the deviant intervals were not randomly distributed, but rather, were always long.

It seems plausible to account for the performance of CON when tapping with the left hand by assuming that the cerebellar timing system is impaired. The patient shows little residual effect of having undergone left cerebellectomy, indicating that new pathways have been established to compensate for lost function. It would not be surprising, however, if these new pathways were still somewhat unstable. Thus when a timing command is needed, activation of the appropriate pathway may occasionally be delayed. This post-hoc model would account for the aberrant pulses always being long.

Case 3. The third lateral patient, BRO, was presented in an earlier technical report (Keele et al. 1985a). In 1979, this woman underwent a craniotomy to remove a hemangioblastoma limited soley to the left cerebellar hemisphere. Due to swelling, subsequent surgery was required for placement of a ventricular shunt. Testing was conducted five years post surgery at which time BRO was 44 years old. At this time, the patient was still unable to

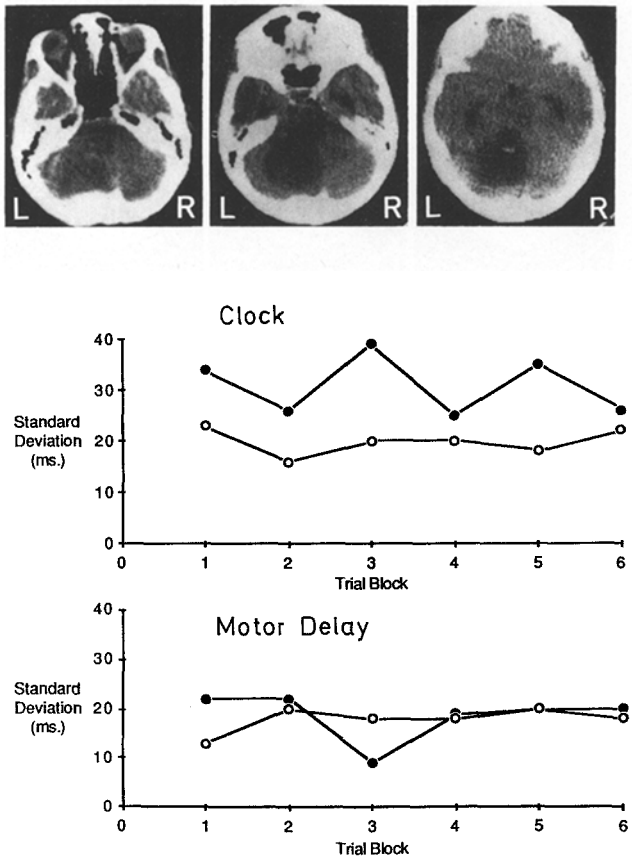

Fig. 4. CT scans and tapping estimates for Case 3, BRO. The preoperative scans show a large lesion extending from the midline through the left cerebellar hemisphere. Each block of data was obtained at a separate test session, spanning a total period of six months

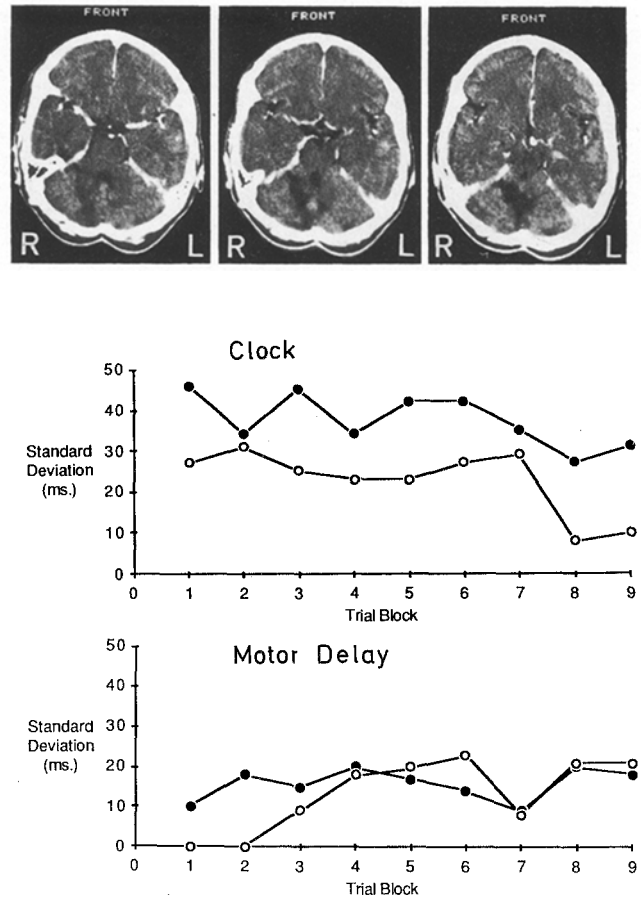

Fig. 5. CT scans and tapping estimates for Case 4, PRI. The postoperative scans show a lesion extending in the anterior/posterior direction on the right side of the cerebellum. The lesion appears to include both vermal and hemispheric regions. Data for Blocks 1–3, 4–6, and 7–9 were collected at separate sessions over a two month period

resume work as a typist, reflecting her persistent deficit in left-handed coordination. Sequential tasks were performed slowly and in a clumsy manner on the left and she presented some dysmetria in pointing tasks. Saccadic eye movements were also hypermetric, especially on gaze to the left. Lower extremity testing revealed only minor deficits: Although there appeared to be some general clumsiness in left-footed movements, there was no dysmetria and heel-to-shin testing was performed normally with both legs. The patient's gait was normal except for a slight widening of the base. Her pace and stride were normal and she could stand on either foot, although she was unable to hop on her left foot.

The patient's pre-operative CT scan is presented in Fig. 4. The films show a large cystic tumor situated in the left cerebellar hemisphere which clearly extends to the midline. The surgeon's report indicates that the tumor was located about 1 cm under the cortex, although upon excision, the cyst was found to have penetrated a small section of the left cerebellar cortex. It is difficult to classify this patient solely on the basis of the CT scans. Indeed, her post-operative scans, although of poor quality, do not reveal any sign of the lesion. Nonetheless, given the clinical picture, the size of the lesion and the fact that the tumor clearly extended into the hemisphere, we believe the patient can be considered to have a lateral cerebellar syndrome. Caution, of course, is well warranted in interpreting this patient's classification as lateral.

BRO was tested on six sessions spanning a six-month period. Each session consisted of a single tapping block with each hand. Her overall standard deviation was 42 ms when tapping with the left hand and 33 ms when tapping with the right. These overall scores were decomposed into separable estimates of the clock and implementation components according to the Wing and Kristoffer-son model (Fig. 4). For each session, the clock estimate is higher for the left hand ($t(5) = 2.73, p < 0.02$). No consistent differences emerge in comparing the implementation estimates. In fact, the mean estimates of the motor delay component are approximately equal for the two hands. As with the preceding two patients, a clock deficit is still present despite the fact that a substantial period of time had elapsed since the cerebellar surgery.

Case 4. PRI, a 46 year old female had undergone surgery four years prior to testing for the evacuation of a right cerebellar hematoma. At the time of testing PRI demonstrated persistent dysfunction in the use of her right arm and hand. Finger-to-nose testing presented a moderate degree of difficulty, pointing movements were hypermetric, and dysadiochokinesia was clearly evident when the patient was asked to rapidly rotate her wrist. Intentional tremor was present, although not excessive. While PRI

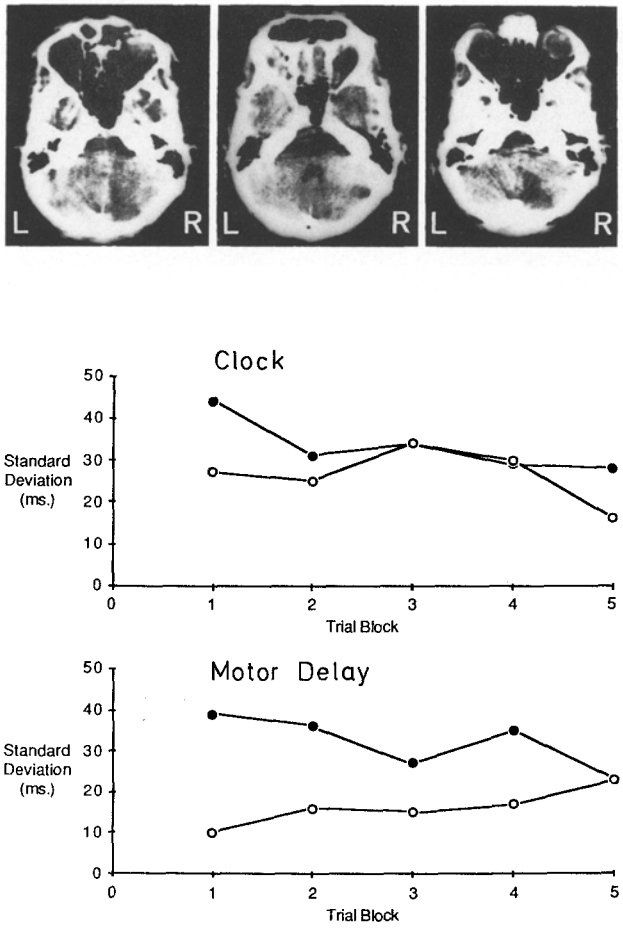

Fig. 6. CT scans and tapping estimates for Case 5, BOC. The lesion is located in the right vermis. The clearest portion can be seen in the more posterior region. The data were all collected in a single session

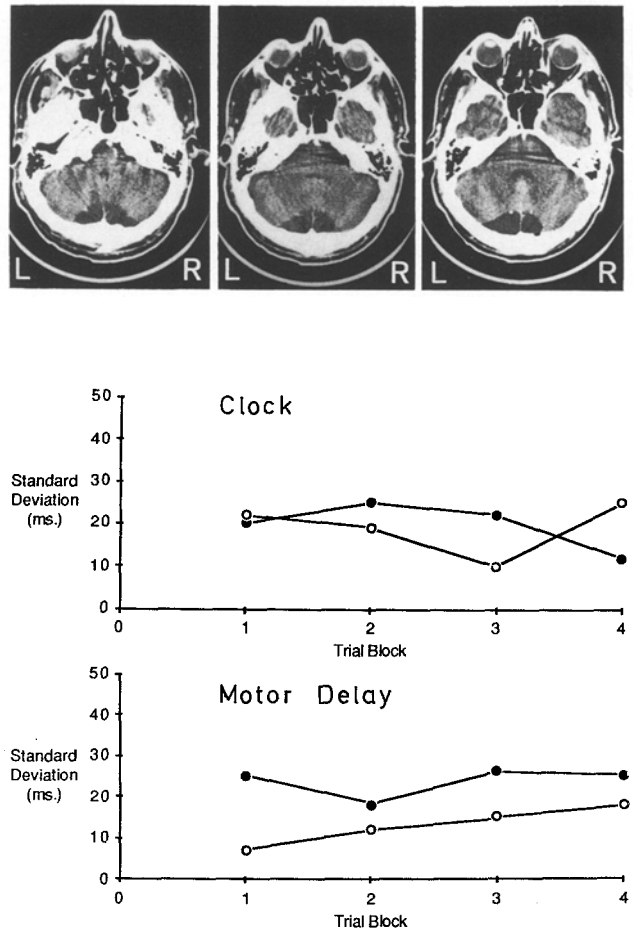

Fig. 7. CT scans and tapping estimates for Case 6, FIN. The postoperative scans show a bilateral lesion in the posterior vermis. Blocks 3 and 4 were completed two months after Blocks 1 and 2. Impaired effector refers to performance with the left foot and unimpaired effector was the left index finger

reported using a cane when walking on irregular surfaces, only minimal postural or ambulatory disturbances could be observed in the laboratory. She was able to tandem walk for a few steps as well as stand and hop on either foot singly.

The postoperative CT scans (Fig. 5) for PRI show a lesion extending across the right side of the cerebellum. It is not possible to unambiguously assign PRI to either a lateral or medial group on the basis of the scans: the lesion appears to extend into both the right cerebellar hemisphere and vermis. Even more so than with BRO, the classification of PRI as a lateral patient is primarily dependent on the clinical examination rather than the neuroimaging results since there appears to be residual structural damage in the vermis.

PRI was tested on three sessions. Each session consisted of three blocks of tapping with both hands. The overall standard deviations were 44 ms for the impaired, right hand and 32 ms for the unaffected, left hand. The clock and motor delay estimates from the Wing and Kristofferson model are given in the bottom half of Fig. 5. Note that on the first session, the motor delay estimate averaged –1 for the left hand. However, no clear violation of the assumptions underlying the model (Wing 1977) were evident, and thus, this may reflect sampling error. Furthermore, the difference in the clock estimate was similar in all three sessions. The clock estimate is much higher for the right hand than for the left ($t(8) = 6.71$, $p < 0.001$). The motor delay estimates show no laterality effect.

Case 5. BOC, a 48 year old male, had suffered an ischemic lesion focused on the right, posterior part of the cerebellum in 1981. Shortly after the accident, the patient presented the typical array of cerebellar symptoms. One notable exception was that BOC showed only a mild intentional tremor whereas this tends to be the most dominant sign following lesions of the lateral regions of the cerebellum and dentate nucleus. At the time of testing, BOC presented no persisting clinical signs related to his accident. Recovery appeared to be complete.

The CT scans shown in Fig. 6 are of poor contrast. Nonetheless, a hypodense region can be seen in the medial portion of the cerebellum. A clearer posterior focus, displaced slightly to the right side of midline, is apparent in the more superior views of the cerebellum. This is the region where the vermis is most extensive. It is unclear whether the damage extends into the right cerebellar hemisphere. The CT report, together with the fact that the patient showed only mild tremor suggests that the lesion affected midline structures more than the lateral portions of the cerebellum.

BOC was tested in a single session in which he completed five blocks of tapping with each hand. As usual, testing alternated

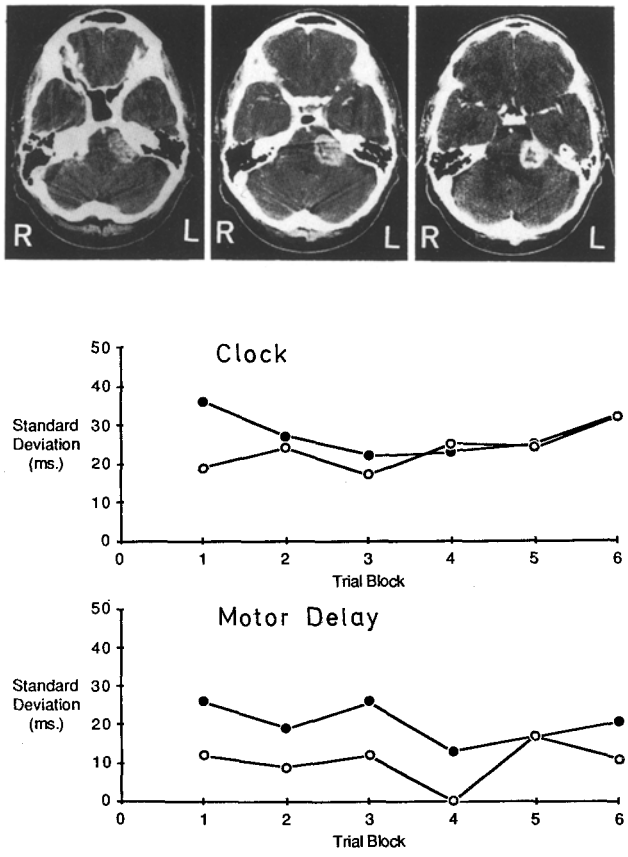

Fig. 8. CT scans and tapping estimates for Case 7, DUV. The preoperative scans show a tumor in the vicinity of the anterior, medial region of the left cerebellum. Blocks 1–3 were completed one month prior to Blocks 4–6

between hands. Despite the absence of any clinical signs, BOC was much more variable when tapping with the right hand. The mean standard deviation with the affected hand was 56 ms whereas the mean for the unimpaired hand was 36 ms. Following the Wing and Kristofferson analysis, the mean clock estimate for the right hand of 33 ms was found to be 7 ms higher than that for the left. As can be seen in the bottom half of Fig. 6, this difference was only observed in three of the five blocks with the estimate being equal for the two hands in Block 3. Therefore, it can not be confidently stated that BOC shows a clock deficit.

The picture is less ambiguous in terms of the implementation estimates. The motor delay estimate is considerably higher for the right hand on four of the five blocks and equal for the two hands on the remaining block. The mean implementation estimate for the right hand is twice as large as the comparable score for the left hand ($t(4) = 3.29$, $p < 0.02$). Unlike the first four patients, BOC has difficulty in implementing a response.

Case 6. FIN, a 59 year old male began to experience dizziness in the early part of 1985. In the next few days, he was noted to have difficulty in walking, with his gait characterized by a side to side sway. In addition, he would occasionally lose his balance entirely and fall down. The patient reported no loss of coordination in the upper limbs. CT scans revealed a bilateral hematoma in the posterior vermis of the cerebellum. A craniectomy was performed for the evacuation of the hematoma (post-operative scans in Fig. 7). The lesion was completely restricted to the posterior region and was consistent throughout the superior-inferior views. The lesion does appear to be slightly more pronounced on the right side, but no lateralized differences were ever observed during neurological testing before or after surgery. FIN was tested seven months after surgery. At this time he was able to walk with the assistance of a cane. Postural and balance control were still greatly disturbed. His gait was wide-based and unsteady. He was unable to perform tandem walking or stand on either foot individually. He presented no cerebellar signs in hand movements.

Given this clinical picture, the standard test procedure was modified with FIN. Rather than compare his tapping performance across the two hands, a comparison was made between his left hand and left foot. The foot is therefore considered the impaired effector and FIN's performance with the hand can serve as the control. A previous study in our laboratory (Keele et al. 1985b) had found no difference in tapping ability between the hand and foot with normal subject, a finding we have replicated in unpublished data.

FIN completed four error-free blocks with both the left hand and left foot over two test sessions. On the first day the two blocks with the hand were run before any testing with the foot. On the second session, testing alternated between the left hand and left foot. The two sessions were separated by 10 weeks.

The overall mean standard deviations for the left finger and foot were 27 and 40, respectively. The bottom half of Fig. 7 displays the clock and motor delay estimates for each block. The most outstanding feature of this figure is the large increase in the motor delay estimate for the left foot ($t(3) = 3.86$, $p < 0.02$). The inflated implementation estimates were observed in all four blocks. There appears to be little difference between the clock estimates for the hand and foot. Note, however, the low clock estimates observed during two blocks of the second session. It is assumed that these low estimates are the result of sampling error rather than transient improvement in a timing process since these scores are lower than observed in normal subjects.

Case 7. DUV, a 66 year old male, had undergone surgery five years prior to testing for removal of an acoustic neuroma. The VII and VIII nerves were not preserved, thus creating a facial paralysis and left ear deafness. The patient has experienced persistent diplopia which is corrected by prism glasses.

Postoperative neurological reports have been lost. The patient reports that his balance problems were so severe as to prevent him from walking for three months. Many of these problems remain. DUV requires a cane, displays a wide-based gait, is unable to tandem walk, and shows a moderate degree of sway when standing still. He is unable to stand on his left foot and can only retain his balance for a couple of seconds on the right foot. There are slight indications of dysmetria and intentional tremor when pointing with the left hand. Finger-to-nose testing was minimally impaired on the left. In addition, DUV presented moderate coordination problems on heel-to-knee testing.

The preoperative CT scans are presented in Fig. 8. The tumor, situated in the pontine angle, is in the vicinity of the anterior, medial region of the left cerebellum. At this level, the portions of the anterior lobe wrap around the brain stem, projecting forward of the fourth ventricle. Indeed, the surgeon's report indicates that the tumor was found to be densely adherent to the cerebellum. It is also evident in the scan that the tumor was compressed against the pons and, in fact, the surgeon noted that small amounts of tumor were not removed because of the risks involved in brain stem operations. The clinical picture for DUV is very consistent with a postoperative cerebellar syndrome. The cerebellar signs may be due to damage in either the anterior lobe of the inferior cerebellar peduncle. The more superior views of the

Table 1. Summary of case studies. Top figure in each pair refers to performance with impaired effector, bottom figure is for unimpaired effector. [a] indicates significant difference

Patient	Lesion focus	Clinical evaluation		Tapping performance	
	Vermal/ hemisphere	Medial syndrome	Lateral syndrome	Clock estimate	Implementation estimate
1. YOU	H	−	+	47[a]	26
				21	17
2. CON	H	−	+	33[a]	10
				20	9
3. BRO	H	−	+	31[a]	19
				20	18
4. PRI	H, V	−	+	37[a]	16
				23	13
5. BOC	V	+	−	33	32[a]
				26	16
6. FIN	V	+	−	20	24[a]
				19	13
7. DUV	V	+	−	28	20[a]
				24	10

tumor appear to extend to the level of this output pathway from the fastigial nucleus.

DUV completed three blocks of tapping with each hand on each of two sessions. The overall standard deviation with the left hand was 40 ms whereas the comparable score for the unimpaired, right hand was 20 ms. The clock and motor delay estimates (Fig. 8) are consistent with a deficit in the implementation system. The clock estimate is only slightly higher for the left hand. In contrast, the motor delay score is twice as large for the left hand as the right ($t(5) = 4.66$, $p < 0.01$).

Discussion

The results for the case studies are summarized in Table 1. The neuroimaging findings have been categorized on the basis of whether the lesion focus was hemispheric or vermal. The summary of the clinical evaluations was more problematic, principally because the dimensions typically used such as postural/volitional or lower limbs/upper limbs are not orthogonal to each other and the endpoints within either dimension do not define distinct syndromes. The last two columns present the individuals' clock and motor delay estimates derived from the Wing and Kristofferson (1973) model. The upper number in each pair is the estimate from when the subject was performing with his or her impaired effector and the lower number is the control score obtained from performance with the unimpaired effector.

Poor tapping performance for four of the patients was attributed to increased variability in the clock component. According to the logic underlying the Wing and Kristofferson model, these patients have difficulty determining when a response should be initiated. For each of these patients, the lesion included the hemispheric region of the cerebellum. Indeed, in a couple of the cases (Cases 1 and 2), the lesion was restricted to this part of the cerebellum. All four of these patients presented clinical signs consistent with this type of lesion: dysmetria during pointing tasks, intentional tremor, and dysadiochokinesia. Note, though, that any trials disrupted by tremorous responses (a significant problem only for YOU, Case 1) were not included in the analysis.

The remaining three patients were found to have a deficit in the tapping task due to increased variability in the motor delay component. These patients can thus be assumed to have difficulty in implementing a planned response. That is, although they are able to accurately time when a periodic movement should occur, they are unable to execute the response precisely at the indicated time. The lesion was found to include the vermal zone of the cerebellum in all three cases. The clinical picture, however, was unambiguous. All of the patients demonstrated disturbances of gait and stance which were clearly more pronounced than deficits elicited in upper limb volitional tasks.

In summary, the results are consistent and convincing. The data reveal an important dissociation of separable neural systems within the cerebellum in the production of voluntary, rhythmic movements. The lateral region of the cerebellum is critically involved in the operation of a timing process. In contrast, the role of the medial region is associated with the implementation of the response. We believe the reliability of these results is quite impressive. Across the seven patients, a total data set of 50 blocks of six trials each was collected. The Wing and Kristofferson estimates deviated from the general pattern in only three blocks: Block 10 for the lateral patient YOU (Case 1) produced a higher clock estimate for the unimpaired effector and Blocks 5 for medial patients BOC and DUV (Cases 5 and 7) produced equal motor delay estimates for the two effectors. In the remaining 47 tapping blocks the estimates were in accord with the hypothesis that the clock estimate would be affected by lateral lesions and the motor delay estimate would increase following damage to the medial region.

It is of interest that some of the focal patients reported in this paper have relatively large implementation estimates even when tapping with their "unimpaired" hand. In our earlier study (Ivry and Keele, in press), the mean motor delay estimates were 9.6 and 11.0 ms for the college aged and elderly control subjects, respectively. Only 7.9% of all the tapping blocks for the control subjects produced

motor delay estimates greater than 16. In contrast, 47.3% of the tapping blocks for the eight patients reported in this paper yielded estimates greater than 16 when tapping with the hand contralateral to the lesion. Moreover, relatively high motor delay estimates were frequently observed with either hand for three of the four patients with lateral lesions. Thus, YOU, BRO, and PRI (Cases 1, 3, and 4, respectively) may not only have lateralized clock deficits, but more generalized implementation problems. This could be explained by the fact that much of the cerebellar cortex (Braitenberg 1967) is continuous across the midline and lesions may affect fibers which descend to either medial nuclei. In addition, whereas lesions in the lateral nuclei produce purely ipsilateral effects, the situation is less clear for the medial nuclei. Asanuma et al. (1983c) report that axons from the fastigial nuclei exit the cerebellum bilaterally. Given these findings, it would be of interest to examine the motor performance of the contralateral limbs in hemicerebellar patients in comparison to normal subjects.

The cerebellar case studies clarify a critical issue raised by our previous study in which we employed a group methodology (Ivry and Keele, in press). In that paper, we reported that cerebellar lesions can affect either the timekeeper or the implementation process in the production of rhythmic responses. It was unclear from the group results whether the two forms of tapping deficits could be dissociated. Within subject control was not possible with most of the patients since their lesions were the result of advanced atrophy and thus the deficits were symmetric. These problems were avoided in the present study by selecting only patients with focal lesions who could serve as their own controls.

The dissociation between the effects of lateral and medial lesions on tapping performance are in accord with the anatomical, clinical, and experimental research reviewed in the Introduction. The general picture that has emerged from these diverse paradigms is that the lateral and medial regions of the cerebellum contribute differently to motor control. The lateral regions have been associated with the planning and preparation of movements. Setting up the temporal parameters of a motor program would certainly be one aspect of motor planning. This process might take a number of different forms. For instance, the cerebellar timing mechanism might operate in an abstract, effector-independent mode, performing real-time computations to determine when each of a series of responses can be initiated. In this modular view, other neural systems might be expected to compute non-temporal parameters of the movement such as selecting the appropriate effector or setting the desired force level. The effect of these independent computations could then be integrated in the motor cortex. On the other hand, the computations could be in terms of the duration of specific responses such as setting the timing for the reciprocal activation of antagonist muscles. These alternative computational modes are not mutually exclusive.

While the lateral regions are part of the planning processes, the medial zone of the cerebellum is associated with the implementation or on-going regulation of a motor response. The Wing and Kristofferson model assumes that rhythmic tapping is performed in an open-loop mode and thus a deficit in a feedback mechanism would not be expected to disrupt performance of the clock. However, it is clear that disruption in either a feedforward or postural control mechanism could adversely affect the implementation of a planned movement. For example, if a limb was not correctly stabilized due to a medial lesion, a given command signal might not produce the desired goal since the initial conditions were not correctly established. Note that whatever the specific roles of the medial cerebellum, the Wing and Kristofferson model lumps together into the implementation system all processes which influence a motor response after the command signal is issued. Thus, a variety of deficits could increase the variability of the implementation component. Of greatest interest in the present study is the fact that, unlike lateral lesions, damage to the medial region of the cerebellum does not appear to impair the timing component of the command signal.

Performance on a perception test of timing are also supportive of the hypothesis that the integrity of the lateral regions of the cerebellum is critical for accurate timing control. We found (Ivry and Keele, in press) that, as a group, cerebellar patients were impaired in their ability to make perceptual discriminations based on temporal differences in comparison to healthy control and other patient groups. The convergent deficit in both a production and perception task led to our argument that the cerebellum played a central role in timing control. However, the acoustic inputs to the cerebellum do not appear to be strongly lateralized (Moyer 1980; Musiek and Baran 1986; Aitkin and Boyd 1975). This prevents making a perceptual within-subject comparison similar to the tapping data presented above. Nonetheless, we have observed two types of cerebellar patients who have difficulty in the perception of time task.

The first group is composed of sporadic and hereditary atrophy patients. As reported in Ivry and Keele (in press), these patients were significantly impaired in judging the relative duration of a variable interval in comparison to a 400 ms standard interval.

This group included subjects in whom the atrophy is diagnosed as extending upstream from the cerebellum into the pons and olive as well as patients in which the latter two systems were clinically judged to be intact. While it is evident that all cerebellar systems can be involved in advanced atrophy, these forms of cerebellar atrophy have a predominant focus in the hemispheres and lateral nuclei (Greenfield 1958; Konigsmark and Weiner 1970). Cerebellar atrophy of the lateral regions can be contrasted with cerebellar atrophy secondary to long-term alcohol abuse. The focus of this disorder has been found to be almost exclusively restricted to the vermal region of the anterior lobe (Adams and Victor 1985; Allsop and Turner 1966). We have recently tested five patients (unpublished data) who were diagnosed as suffering from cerebellar atrophy due to chronic alcoholism. All presented symptoms consistent with the diagnosis: ataxia of gait and incoordination of the lower limbs. According to the hypothesis and data presented in this paper, damage to the anterior vermis should not impair the timing process. As predicted, their performance on the time perception task was equal to that observed for elderly control subjects and non-cerebellar neurological patients. Note that on a control task in which the loudness of tone pairs was compared, the two atrophy groups showed no difference from each other or from the control subjects. In summary, the perceptual data from patients suffering bilateral cerebellar atrophy is consistent with the motor timing data in suggesting that the essential timing circuitry is in the hemispheric regions.

The second group of patients ($n = 7$) who show a perceptual deficit is composed of patients tested shortly after suffering a cerebellar stroke or after surgery for the removal of a cerebellar tumor. The poor performance of these patients on the time perception task can be compared with seven patients who also have focal lesions, but have had at least eleven months of recovery since incurring their lesion. This latter group demonstrated no deficit on the perception task, even though some demonstrated increased clock estimates on the tapping task (e.g. Cases 2 and 4).

Reviewing the case study analyses jointly with the perception results begins to provide some additional answers concerning the organization of the timing system. One question concerns whether the cerebellar timing process is part of a single clock. The simplest answer must be no given that we have observed unilateral timing deficits. At a minimum, the circuitry appears to be duplicated in each hemisphere. Perhaps in the intact brain, the two (or more?) circuits are coupled. Certainly people have great difficulty in following independent time courses in rhythmic behavior with two hands (Klapp 1979; Yamanishi et al. 1980; Kelso and Scholz 1985). However, as shown in the present study, a certain degree of independence must be possible since the circuitry that subserves timing for one hand can be damaged without effecting the performance of the other hand.

Early after cerebellar damage, however, temporal perception may be impaired even though the damage is unilateral. This could be due to spreading effects from the lesion which diminish with recovery. Alternatively, the perceptual timing system may normally involve a linkage between different timing circuits. For example, the perceptual judgments may be based on the dual output of the two halves of the cerebellum working in concert. Part of the recovery process could involve establishing the dominance of the intact side. As noted above, unlike the production task, the perception task can be performed with the circuitry available on the nonlesioned side after sufficient recovery. Thus, the results of the perception task also seem to require the conclusion of duplicate timing circuitry in the two cerebellar hemispheres.

Though we conclude that the cerebellar timing system involves duplicate circuitry in the two hemispheres, there are additional issues regarding the finer structure of the clock which can not be presently answered. Is there a single circuit within each hemisphere which is used in any task requiring timing be it hand tapping, foot tapping, or perception? Or, does the timing for these disparate tasks depend on different regions of the lateral cerebellum. Our correlational work (Keele et al. 1985b) suggests that the functioning of the timing system is correlated between different effectors and with perception. Such correlations could be due, however, either to identical circuitry or to distinctly different circuits which are functionally similar because of some shared parameters such as a general rate setting or a common tonic level of activation. Moreover, a hybrid model is possible in which some computational elements are activated across tasks whereas others are task specific.

The final point we wish to make is more speculative. It is quite striking that the regions involved in timing of motor and perceptual functions are similar to the regions implicated in classical conditioning (McCormick and Thompson 1984; Yeo et al. 1985). While the similarity may be fortuitous, classical conditioning may involve the lateral cerebellum because of the necessity of precise timing. Thompson and his colleagues (Thompson et al. 1984) have used a 250 ms interval between the conditioned (CS) and

unconditioned (US) stimuli. Yeo et al. (1985) using a different CS but the same US have employed an interval of 500 ms. In both cases, the conditioned response, an eye-blink, occurs just before the US, a puff of air to the eye. This makes the CR adaptive in that the animal is able to avoid the aversive stimulus. Thus the conditioned responses in these learning paradigms do not occur at a fixed interval after the CS, but at a fixed interval before the US. If the interval between the CS and US is consistently lengthened or shortened, the interval between the CS and CR will be adjusted (reviewed in Hal 1976). This form of learning may involve the lateral cerebellum because of the requisite timing computations. It is worth noting that forms of classical conditioning (e.g. emotional conditioning) which do not demonstrate such precise temporal linkages do not require the cerebellum (Thompson et al. 1984).

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