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THE ROLE OF CEREBELLAR STRUCTURES IN THE EXECUTION OF SERIAL MOVEMENTS

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SUMMARY

Thirteen patients with bilateral cerebellar disease and 12 patients with unilateral cerebellar disease were instructed to execute movement sequences in response to a simple reaction signal. Each to-be-executed sequence consisted either of a single, two, or three keypress components. Evidence for cerebellar involvement in the execution of programmed responses was sought in the pattern of response onset times and interkeypress times. Patients with mild bilateral cerebellar dysfunction or mild unilateral dysfunction, and neurologically unimpaired subjects showed increases in response onset time as sequence length increased from L = 1 to L = 3. In contrast to this, there were negligible or no effects of sequence length on response onset time in patients with moderate bilateral cerebellar dysfunction and in patients with moderate unilateral cerebellar dysfunction who responded with the hand ipsilateral to the lesion. Furthermore, cerebellar dysfunction was associated with significantly slower interkeypress reaction times. These results support the hypothesis that the translation of a programmed sequence of responses into action involves cerebellar structures which schedule a sequence of ordered responses before onset of movement.

INTRODUCTION

Acute damage or chronic atrophy of the cerebellum affects primarily complex motor action. Although cerebellar damage does affect simple movements, it is the execution of the more complex sequential movements which appears most vulnerable. The cardinal clinical sign of cerebellar damage is a 'decomposition of movement' (Holmes, 1917, 1939) in which serial muscle synergies of complex movements are decomposed into independent sequential constituents which are executed with errors or force, amplitude, and timing.

Decomposition of movement could occur during functionally distinct phases of action. It could occur during the *planning* (or conception) of movements, involve

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the *execution* of a complex response, or some intermediate phase. Noting that cerebellar dysfunction does not abolish complex movements and that cerebellar stimulation does not evoke a large number of complex responses, Brooks (e.g., 1984*a*, *b*) suggested that 'cerebellar contributions appear to lie in the less complex packaging of planned motor acts'. This view implies that the cerebellum is not critical for the generation of abstract motor plans; instead, it appears to control the parametric translation of a motor plan into action.

Some complex actions, which are composed of a number of constituent responses, can be executed at a rate too fast to be guided by sensory feedback. A neural representation of the entire action appears to be available before response onset which, when activated, triggers the automatic execution of the complex action as a single, fluid unit (Marsden, 1982). Since the hallmark of cerebellar damage is a decomposition of complex actions and an inability to execute movement sequences smoothly and swiftly, cerebellar damage could interfere either with the generation of a neural (motor plan) representation which comprises all components of a complex action, or with the parametric translation of a motor plan into action.

The current investigation tested the hypothesis that cerebellar damage disables the execution of a planned sequence of responses. An experimental paradigm developed by Sternberg *et al.* (1978) was used to measure simple reaction time (RT) to initiate movement *sequences* of varying complexity. Sternberg *et al.* found that the RT to initiate the first movement component of a sequence of responses (either spoken or typewritten) increased linearly with the length of the to-be-executed sequence. To account for the effect, it was proposed that an abstract representation of a response sequence (a motor program) is assembled before the initiation of the motor sequence and loaded into a 'motor buffer'. This programming phase is followed by the *execution phase* which is initiated when the reaction signal is perceived. During the execution phase, the motor program must be read out from the buffer to specify the spatiotemporal sequence of activation of peripheral muscles. As the number of component responses increases, so does the time required to read the motor buffer and to group the responses in their proper sequence, resulting in an increase in latency to initiate the first response component in the sequence (in the following this will be referred to as the 'sequence length effect'). Within this framework, the sequence length effect reflects real-time constraints on the translation of a programmed sequence of responses into action. The sequence length effect can be used to study this process in a way which is independent of slowness of peripheral responses, tremor, or other peripheral factors which can also affect RTs of cerebellar patients.

PATIENTS AND METHODS

In the present experiments, patients with bilateral lesions (Experiment 1) and unilateral lesion (Experiment 2) to the cerebellum executed a sequence of keypress responses consisting of either a

single, two, or three response components. If a cerebellar lesion impairs the translation of a programmed sequence of responses into action, then patients should execute a programmed movement sequence as if it consisted of independent response constituents and the sequence length effect in the T1 RTs should be reduced or absent. If, instead, cerebellar dysfunction does not affect the translation of a programmed sequence of responses into action but slows the rate of the translation process, then an abnormally large sequence length effect should be obtained. A comparison of T1 RTs with interkeypress RTs for noninitial responses can provide additional data to test the hypotheses. If cerebellar dysfunction disabled the translation of a programmed sequence of responses into peripheral response parameters prior to response onset, then noninitial responses should be executed as independent response units with relatively long interkeypress RTs. Consequently, a lack of a sequence length effect in the T1 data should be associated with long interkeypress RTs. If, however, cerebellar dysfunction simply slows the translation of a programmed sequence of responses into peripheral response parameters, then a cerebellar lesion should not affect interresponse times and noninitial responses should be executed with relatively short interkeypress RTs. Consequently, an abnormally large sequence length effect in the T1 data should be associated with relatively short interkeypress RTs. In the following, we will use the term 'negative position effect' when interresponse times are longer than T1 RTs and 'positive position effect' when interresponse times are shorter than T1 RTs.

Response onset times and interresponse times may measure somewhat different processes. The reaction signal has to be encoded before response onset but no comparable visual coding needs to be done for noninitial responses. Furthermore, it appears that the translation of a motor program into action parameters occurs before response onset so that it affects T1 RTs but not interkeypress RTs. Nevertheless the comparison of T1 RTs (which include different types of start-up time) with interkeypress RTs (which do not include these start-up times) may be informative in that it may assess benefits associated with the execution of preplanned noninitial responses.

EXPERIMENT 1

Methods

Subjects. Thirteen patients with bilateral cerebellar dysfunction were tested. All patients suffered from chronic cerebellar disease and were outpatients of the Neurology Clinic at the University of Tübingen, West Germany. There were 8 men and 5 women, ranging in age from 20–74 yrs (mean 46 yrs). Two patients had Friedreich's ataxia and 4 had olivopontocerebellar atrophy (OPCA) with mainly cerebellar signs and minimal involvement of basal ganglia, pons, and spinal cord as revealed by clinical examination, CT scan, electro-oculography, evoked potentials (brainstem acoustic and sensory evoked potentials) and posturography. Six patients had diffuse cerebellar atrophy of unknown origin without clinical deficits outside the cerebellum. Patients with multiple sclerosis, chronic alcoholism, drug abuse, toxic cerebellar atrophy, or pathological CSF were excluded. A summary of these diagnoses, together with a scaling of the clinical signs of upper limb function is provided in Table 1. The scaling was performed by a neurologist who did not participate in the present study. A score of 0 indicates relatively normal function, a score of 5 severe dysfunction. Dysdiadochokinesia was evaluated by asking the patient to supinate and pronate the outstretched hand as fast as possible. Dysmetria was tested by asking the patient to point with the index finger to his/her nose and to follow and touch as fast as possible the suddenly moving finger of the examiner. Intention tremor was investigated with the same procedure but also during reaching for a target in front of the patient.

Eight neurologically unimpaired adults, tested by Rafal *et al.* (1987) in an identical task under comparable testing conditions were used as control subjects. These included 2 men and 6 women ranging in age from 45–78 yrs.

Apparatus and procedure. Reaction signals to begin movement execution were shown on a cathode ray tube (CRT) which was placed on top of a table approximately 60 cm in front of the patient's

TABLE 1. CLINICAL DATA FOR PATIENTS PARTICIPATING IN EXPERIMENT 1

Patient	Age (yrs)	Sex	Duration (yrs)	Diagnosis	Dysdia RH	Dysdia LH	FNT* RH	FNT* LH	Int. tremor* RH	Int. tremor* LH
Mild dysfunction										
A.D.	35	M	2	UO	1	1	1	1	0	0
H.O.	53	F	5	UO	2	2	1	1	1	1
R.A.	20	M	6	UO	2	2	2	3	0	0
R.O.	60	F	2	UO	2	2	1	1	0	0
B.U.	53	M	3	OPCA	3	3	1	1	2	2
H.E.	56	M	3	OPCA	2	2	2	2	1	1
M.A.	48	F	20	OPCA	3	3	2	2	1	1
Moderate dysfunction										
K.N.	51	M	10	UO	3	3	3	3	2	2
R.E.	74	F	9	UO	4	4	4	4	4	4
S.C.	60	M	5	UO	2	2	3	3	2	2
H.A.	24	F	10	Fried.	2	2	2	2	3	3
S.T.	25	M	12	Fried.	3	3	4	4	2	2
J.Z.	36	M	15	OPCA	3	3	3	3	3	3

* Disability ratings: 0 = minimal dysfunction, 5 = severe dysfunction. RH = right hand ratings; LH = left hand ratings. Dysdia = dysdiadochokinesia; FNT = finger-to-nose test, Int. tremor = intention tremor; OPCA = olivopontocerebellar atrophy; Fried. = Friedreich's ataxia; UO = lesion of unknown origin.

eyes. A response board with 4 spatially adjacent keys in its centre was placed in front of the CRT. Each patient sat in front of the table, rested his/her elbow on the table surface, and placed the 4 fingers of either the right or left hand on the 4 keys of the response board. Each key was 2.1 cm wide and 5 cm long which permitted a comfortable positioning of the fingers. Pressing a key with a finger resulted in a vertical displacement of 2 mm and triggered a microswitch which was mounted below each key. Each microswitch was connected to a microcomputer which controlled the experiment and measured reaction times to the nearest millisecond.

Patients were tested individually. At the beginning of the experiment, each patient was familiarized with the equipment and instructed which sequences of manual responses were to be executed. Three different blocks of sequences were used, each of which contained either a single keystroke with the index [I] finger (L = 1), a sequence of two keystrokes with the index finger as first and the ring finger as second response component [I-R] (L = 2), or a sequence of three keystrokes (L = 3) with the index finger as first, the ring finger as second, and the middle finger as third response component [I-R-M]. Each hand was tested separately. Sequence length was blocked so that the response to be made was the same for every trial in a block. Thus subjects had information of the movement to be made which allowed them to prepare the sequence fully before the reaction signal appeared. Subjects were instructed to execute the sequences as 'quickly and accurately' as possible and try to execute the sequences smoothly 'like a single movement'. Because our goal was to study the programming and execution of learned movement sequences, subjects practised each of the response sequences until they reported that they could no longer improve (approximately 30 practice trials per condition). After this, experimental trials were initiated.

Each trial began with the display of the outlines of a bright square with a side length of 10 cm in the centre of the screen. Half a second later, a 50 ms tone was sounded to alert the patient; 250 ms after the tone, the reaction signal, consisting of a large bright 'X' sign was shown in the centre of the square. Patients were instructed to tap the prespecified sequence of responses (L = 1, L = 2, or

L = 3) as swiftly as possible after the occurrence of the reaction signal. After the required number of component responses were executed, the screen went blank for 3 s after which the central square was lit and another trial began. Feedback was given after each trial. A high pitched tone for a correct response, a low pitched tone if the sequence was incorrect or if, for any reason, the correct response was not executed within 3000 ms of the reaction signal. No catch trials were included and the regular and predictable sequence of each trial was designed to encourage motor programming. To minimize the degree to which premature responses could affect the outcome, subjects were carefully monitored for responses which occurred before the reaction signal appeared; when these occurred, subjects were cautioned not to initiate the action before the reaction signal occurred. Moreover, RTs of less than 150 ms were excluded from analysis. Each patient was tested on 12 blocks of 30 trials each. Sequence length L = 1 to L = 3 was tested in separate blocks of trials so that each hand was used in 2 blocks of trials of a particular sequence length. The order of the blocks of trials of a given sequence length was randomized. Seven randomly selected subjects started a doublette of blocks of a particular sequence length with the right hand and then switched to the left hand, the reversed order of hands was used for the remaining patients. The computer kept a record of the intervals between the onset of the reaction signal and the sequence initial keypress responses (T1), between the onset of the initial and the second keypress responses (T2), and between the onset of the second and third keypress responses (T3).

RESULTS AND DISCUSSION

Responses were considered correct when they were initiated within 3 s following the onset of the reaction signal and when component responses were executed in their correct order. Responses with reaction times for the initial response (T1) of less than 150 ms were excluded from analysis because these extremely short responses were assumed to be due to anticipations. Approximately 11% of the trials were classified as errors. An inspection of errors suggested that they were primarily caused by unintended keypress responses; no other systematic error pattern was evident. RTs of correctly executed trials were subjected to statistical analyses. Following the earlier study (Rafal *et al.*, 1987), response onset T1 latencies for initial index finger movements were analysed as a function of sequence length to determine sequence length effects; furthermore, T1 latencies were compared with interkeypress latencies for noninitial responses (T2 and T3) to determine position effects.

Median T1 RTs of bilateral cerebellar patients are shown in fig. 1, which also shows the corresponding T1 data of 8 neurologically unimpaired subjects who were tested in an earlier study (Rafal *et al.*, 1987). The data were subjected to an analysis of variance (ANOVA) with the between subjects factor groups (cerebellar damage vs control) and the within subjects factor sequence length (L = 1, L = 2, and L = 3). T1 RTs of control subjects were somewhat shorter than T1 RTs of cerebellar patients; this difference was not significant $F < 1$. Overall, T1 increased with sequence length, $F(2,38) = 17.33$, $P < 0.001$. More importantly, this main effect of sequence length was qualified by a significant interaction of sequence length and groups, $F(2,38) = 3.93$, $P < 0.05$. As shown in fig. 1, for control subjects, response onset time to execute the identical index finger movement increased by 93 ms as sequence length increased from L = 1 to L = 2 and

increased by an additional 72 ms as sequence length increased from L = 2 to L = 3. The corresponding increases of bilateral cerebellar patients were significantly smaller and amounted to 35 ms and 26 ms, respectively. These results agree with the hypothesis that cerebellar disease impairs the translation of a programmed sequence of responses into action.

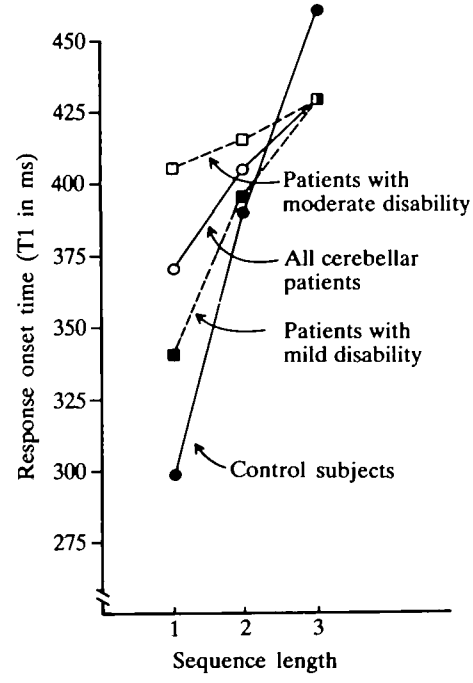

FIG. 1. Sequence length effect in Experiment 1. Reaction time to initiate the first response (T1) in the sequence as a function of sequence length: L = 1 for index finger responses, L = 2 for index and ring finger response sequences, and L = 3 for index, ring, middle finger response sequences. All cerebellar patients (solid line, open circles) are compared with normal control subjects (solid line, closed circles). In addition, a subgroup of patients with moderate disability (dashed line, open squares) is compared with a subgroup of patients with mild disability (dashed line, closed squares).

Additional support for this hypothesis was obtained in a separate post hoc analysis. An inspection of the individual patient data revealed a sequence length effect for some patients but not for other patients. Furthermore, the inspection suggested a correlation between the severity of cerebellar disability and the magnitude of the sequence length effect. Such a correlation could be theoretically important in that it would provide additional evidence for cerebellar involvement in the translation of a programmed sequence of responses into action. To test this, we separated the patient data into two approximately equal-size groups: one group of 7 patients with mild clinical disability and another group of 6 patients with moderate clinical disability. The grouping was based on disability ratings for upper limb function (dysdiadochokinesia, finger-to-nose test, and intention tremor). Patients with an average disability rating of less than 2.3 (*see* Table 1) were classified as mildly disabled, and those with a rating of more than 2.3 as moderately disabled. This procedure separated patients into 2 groups: a mildly

impaired group with patients without or with only minimal disability in using their hands for daily activities and a moderately impaired group with some disability. Patients with severe signs could not perform the task and were therefore not represented in the study. An ANOVA with the factors severity of disability (mild vs moderate) and sequence length was applied to this new set of T1 data. There was no main effect of disability, $F < 1$, and T1 RTs increased with sequence length, $F(2,22) = 14.59$, $P < 0.001$. More critically, the analysis showed that the sequence length effect was larger for mildly disabled patients than for moderately disabled patients (*see* fig. 1). This interaction was significant, $F(2,22) = 5.25$, $P < 0.025$, providing further support for the hypothesis that cerebellar structures control the translation of motor programs into action, presumably by specifying the spatiotemporal parameters of the complete sequence of responses prior to response onset.

To assess *position effects*, RTs for the sequence initial response (T1) were compared with interkeypress RTs (T2 and T3). T1 and T2 RTs for 2 component movements of $L = 2$ sequences were 407 ms and 360 ms for patients, and 392 ms and 352 ms for control subjects. The corresponding T1, T2, and T3 RTs for 3 component movements of $L = 3$ sequences were 430 ms, 373 ms, and 415 ms, respectively, when patients were tested, and 463 ms, 392 ms, and 369 ms when control subjects were tested. One ANOVA was applied to the 2 component sequence index/ring finger and another ANOVA was applied to the 3 component sequence index/ring/middle finger. Each of the two analyses contained one between subjects factor (patients vs controls) and one within subjects factor (response position: first, second, (third)). Both ANOVAs failed to reveal significant main effects or significant interactions even though there was an expected tendency towards larger position effects in control subjects.

An inspection of individual patient data was, again, informative. It showed positive position effects for patients with mild cerebellar disability and negative position effects for patients with moderate cerebellar disability. To evaluate this tendency, separate post hoc ANOVAs with the factors severity of disability and response position were applied to $L = 2$ and $L = 3$ sequences. The results, as shown in fig. 2, revealed a large positive position effect in patients with mild disability and a negative position effect, with shorter response onset RTs than interkeypress RTs, in patients with moderate disability. This interaction approached statistical significance in $L = 2$ sequences, $F(1,11) = 3.42$, $P < 0.09$, and was significant in $L = 3$ sequences, $F(2,22) = 5.87$, $P < 0.01$.

To summarize, the results of Experiment 1 revealed two major findings. Cerebellar patients showed a smaller sequence length effect and a tendency towards smaller position effects than control subjects. Additional post hoc analyses revealed that the magnitude of sequence length and position effects was qualified by patients' disability. Mild clinical disability was associated with relatively normal sequence length and position effects; moderate clinical disability, in contrast, virtually eliminated position and sequence length effects.

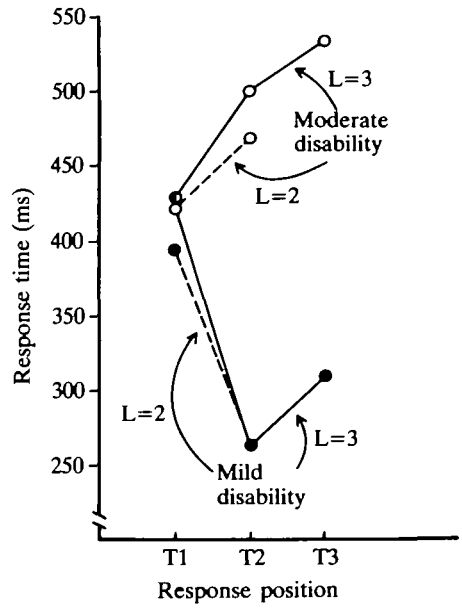

FIG. 2. Position effect in Experiment 1. Response times as a function of the position of response components in the sequence are shown for patient groups with moderate and mild disability. L = 2 sequences comprise the interval between the reaction signal and the first keypress response (T1) and the interval between the first and second keypress response (T2). L = 3 sequences comprise the interval between the reaction signal and the first keypress response (T1), the interval between the first and second keypress response (T2), and the interval between second and third keypress response (T3). Moderate impairment is indicated by open circles, mild impairment is indicated by closed circles. Data from L = 2 sequences are shown in dashed lines, data from L = 3 sequences are shown in solid lines.

These findings indicate that cerebellar structures are implicated in the translation of a programmed sequence of responses into action. Elements of a practised sequence of ordered movements, which are grouped into response ensembles prior to movement onset in control subjects and in patients with mild cerebellar disability, were executed as functionally independent units in patients with moderate cerebellar disability.

EXPERIMENT 2

The results of Experiment 1 revealed a relationship between bilateral cerebellar disease and the magnitude of sequence and position effects. However, since cerebellar disease was a between-subjects factor, alternative interpretations are possible. For example, patients with moderate disability may have been less alert than patients with mild disability or control subjects. A deficit in alerting, rather than a deficit in motor planning, might thus account for some of the results. It is also possible that patients with moderate disability suffered from larger memory deficits than other subjects which may have interfered with their execution of noninitial responses. A further possibility is that patients with moderate disability were more likely to suffer from extracerebellar damage. Consequently, extracerebellar damage, rather than damage to the cerebellum itself, could account for the results of Experiment 1.

Experiment 2 controlled these possibilities. Twelve patients with unilateral damage to the cerebellum were tested in identical conditions to Experiment 1. In all 12 patients, one hand was unimpaired and one hand was mildly to moderately impaired due to cerebellar damage. Experiment 2 was designed so that each patient served as his/her own control by comparing the intact (contralateral) hand with the impaired (ipsilateral) hand. If the findings of Experiment 1 were specific to cerebellar damage, then a larger sequence length effect should be obtained for patients' contralateral responses than for their ipsilateral responses; furthermore, interkeypress RTs should

be shorter for contralateral responses than for ipsilateral responses. In contrast, no systematic differences between hands should emerge in these patients if general performance factors, e.g., attention, alerting, memory, or global CNS damage, underlie sequence and position effects.

Methods

Subjects. Twelve patients (5 male, 7 female) with unilateral cerebellar lesion confirmed by CT scan were tested. They were aged between 20 and 69 yrs (mean 43 yrs). Seven chronic patients were tested at the Neurology Clinic at the University of Tübingen; these patients were subjected to the same clinical examinations as the 13 bilateral patients who participated in Experiment 1. One acute patient was tested at Roger Williams Hospital in Providence, Rhode Island, and 4 chronic patients at the Good Samaritan Hospital and Medical Center, Portland, Oregon. A descriptive summary of the 12 participating patients is given in Table 2.

Apparatus and procedure. The identical apparatus and procedure were used as in Experiment 1.

TABLE 2. CLINICAL DATA FOR PATIENTS PARTICIPATING IN EXPERIMENT 2

					Dysdia		*FNT**		*Int. tremor**	
Patient	*Age (yrs)*	*Sex*	*Duration (yrs)*	*Diagnosis*	*RH*	*LH*	*RH*	*LH*	*RH*	*LH*
Mild dysfunction										
A.C.	50	F	14	Vasc., L	0	2	0	1	0	0
O.E.	53	F	2 mo.	Vasc., L	0	1	0	1	0	0
B.O.	49	M	5	Vasc., R	1	0	1	0	0	0
R.U.	20	M	5	Tumour, R	1	0	1	0	0	0
P.R.	47	F	5	Vasc., R	2	0	2	0	1	0
K.A.	69	M	1	Tumour, L	1	1	0	2	0	2
Moderate dysfunction										
B.R.	45	F	4	Vasc., L	0	2	0	2	0	2
J.A.	26	F	1	Vasc., L	0	4	0	3	0	3
R.B.	54	M	1 w	Vasc., L	0	3	0	3	0	2
S.C.	46	F	4	Vasc., L	0	4	0	3	0	3
B.I.	55	M	4	Vasc., R	3	1	3	1	3	0
F.E.	53	F	1	Tumour, R	5	1	4	0	4	0

Vasc. = ischaemia or haemorrhage; L = left, R = right. Other abbreviations as in Table 1.

RESULTS AND DISCUSSION

As in Experiment 1, responses were considered correct when the prespecified keys were depressed and the sequence was tapped in the correct order. Responses shorter than 150 ms and longer than 3000 ms were excluded from analyses. Approximately 11% of the trials were classified as errors. An inspection of errors revealed no systematic tendencies. As in Experiment 1, RTs of correct responses were subjected to ANOVAs to assess sequence and position effects.

Average median T1 RTs, as a function of sequence length (L = 1 to L = 3) and hand (ipsilateral vs contralateral) are shown in Table 3. T1 RTs were subjected to an ANOVA with the within subjects factors hand and sequence length. Response

TABLE 3. SEQUENCE AND POSITION EFFECTS OF CEREBELLAR PATIENTS WITH UNILATERAL DISABILITY*

	Executing hand					
	Ipsilateral			*Contralateral*		
	T1	*T2*	*T3*	*T1*	*T2*	*T3*
Sequence length L = 1						
Mild disability	342			335		
Moderate disability	475			378		
Means	408			356		
Sequence length L = 2						
Mild disability	358	260		384	206	
Moderate disability	483	500		435	298	
Means	420	380		409	253	
Sequence length L = 3						
Mild disability	403	287	276	396	238	237
Moderate disability	467	557	498	460	377	338
Means	435	422	387	428	307	288

Patients with mild and moderate disability are listed separately. T1 = reaction time for the sequence initial response in ms; T2 and T3 = interval (in ms) between first and second responses and second and third responses, respectively.

onset time increased with sequence length and amounted to 383 ms, 415 ms, and 432 ms for sequences of L = 1, L = 2, and L = 3, respectively, $F(2,22) = 9.542$, $P < 0.001$. There was also a tendency towards shorter response onsets for contralateral responses (398 ms) than for ipsilateral responses (422 ms); this difference, however, failed to reach statistical significance, $F(1,11) = 2.096$, $P < 0.2$. More importantly, there was the predicted tendency towards a smaller sequence length effect for ipsilateral responses than for contralateral responses. The interaction of the factors hand and sequence length also failed to reach statistical significance, $F(2,22) = 2.194$, $P < 0.14$. The T1 data thus suggest cerebellar involvement in the execution of serial action, but the outcome of statistical tests does not warrant a firm conclusion.

A post hoc inspection of individual patient's T1 data was also consistent with the view that cerebellar structures are implicated in the control of serial movement execution. As in Experiment 1, the inspection showed that severity of cerebellar disease affected the magnitude of sequence length effects. Patients with mild unilateral cerebellar dysfunction showed sequence length effects for responses executed with contralateral and ipsilateral hands; patients with moderate unilateral cerebellar dysfunction, in contrast, showed a sequence length effect for responses executed with the intact contralateral hand but not for responses executed with the impaired ipsilateral hand. Following this inspection, we partitioned patients into 2 equal-size groups. One group of 6 patients suffering from relatively mild

unilateral cerebellar disease and one group of 6 patients suffering from moderate unilateral cerebellar disease. Patients with average disability ratings of less than 2.0 (*see* Table 2) were classified as 'mildly' disabled and those with a disability rating of 2 or more as 'moderately' impaired. An ANOVA with the within-subjects factors hand and sequence length was applied to T1 RTs of each group.

The statistical comparison of T1 RTs in patients with mild and moderate disability shows a qualitatively different pattern of T1 RTs in the 2 patient groups (*see* Table 3). Patients with moderate cerebellar disability revealed shorter T1 RTs for responses executed with the unaffected contralateral hand than for responses executed with the affected ipsilateral hand, $F(1,5) = 4.144$, $P < 0.09$. Patients with mild cerebellar disability did not show significant T1 RT differences between affected and unaffected hands, $F < 1$. Furthermore, T1 RTs of patients with moderate cerebellar disability revealed a substantial sequence length effect for responses executed with the intact hand contralateral to the lesion but not for responses executed with the impaired hand ipsilateral to the lesion; the interaction of sequence length and executing hand was significant in this patient group, $F(2,10) = 5.504$, $P < 0.025$. T1 RTs of patients with mild cerebellar disability showed sequence length effects for ipsilateral and contralateral responses and the interaction of sequence length and executing hand was not significant, $F < 1$. The results of these post hoc analyses thus suggest that cerebellar structures are implicated in the execution of planned serial responses.

As in Experiment 1, position effects were assessed separately. RTs for sequence initial and noninitial responses, as a function of hand (ipsilateral vs contralateral) and response position (first, second (third, $L = 3$ sequences only)), are shown in Table 3. Separate analyses of variance with the 2 within subjects factors hand and response position were applied to $L = 2$ and $L = 3$ data of all 12 cerebellar patients. The results showed shorter $L = 2$ and $L = 3$ execution times when the intact contralateral hand was used than when the impaired ipsilateral hand was used, $F(1,11) = 4.466$, $P < 0.05$, and $F(1,11) = 11.455$, $P < 0.01$, respectively. $L = 2$ and $L = 3$ sequences also showed positive position effects with shorter interresponse times than response onset (T1) times, $F(1,11) = 18.697$, $P < 0.001$, and $F(2,22) = 7.219$, $P < 0.005$, respectively. As expected, the position effect was qualified by the laterality of the executing hand. Specifically, the positive position effect was larger for sequences executed with the contralateral hand than for responses executed with the ipsilateral hand; the interaction of the factors hand and response position was statistically significant in the $L = 2$ data, $F(1,11) = 9.230$, $P < 0.01$, and approached significance in the $L = 3$ data, $F(2,22) = 2.471$, $P < 0.1$.

An additional qualitative evaluation of position effects was informative in showing somewhat different position effects in mildly and moderately disabled patients. As shown in Table 3, mildly disabled patients revealed positive position effects for sequences executed with ipsilateral and contralateral hands. Moderately disabled patients also revealed positive position effects for sequences executed

with the intact contralateral hand, but revealed negative position effects for sequences executed with the impaired ipsilateral hand.

To summarize, the results of Experiment 2 are consistent with the results of Experiment 1. As in Experiment 1, mild cerebellar dysfunction had negligible effects on sequence length and position effects. Moderate cerebellar dysfunction, in contrast, appeared to influence the two effects. Specifically, moderately impaired cerebellar patients with unilateral cerebellar disease revealed relatively normal sequence length and positive position effects for responses executed with the intact contralateral hand and a lack of a sequence length effect and negative position effects for responses executed with the impaired ipsilateral hand. This pattern of results cannot be attributed to global impairments which may affect the encoding of the reaction signal, to attention or alerting deficits, to memory impairments, or to extracerebellar damage, since each subject served as his/her own control. Consequently, the results of Experiment 2 are consistent with the hypothesis that cerebellar structures are used to translate motor programs into actions, possibly by setting response parameters for peripheral effectors which are involved in the execution of a sequence of responses.

GENERAL DISCUSSION

The speed, smoothness, and precision which characterizes the execution of practised sequential movements appears to follow the motor programming of all sequence constituents prior to response onset (Keele, 1968; Sternberg *et al.*, 1978; Rosenbaum *et al.*, 1984). Decomposition of complex movements, which is the hallmark of cerebellar disease (Holmes, 1917, 1939), suggests a cerebellar involvement in the execution of such programmed movements. Reviewing a number of studies, Brooks (1984*a*, *b*, *c*) concluded that the cerebellum controls the 'packaging of planned motor acts'. According to this view, the cerebellum acts like a 'clutch' between response planning and response execution, that is, before response onset, the cerebellum translates the intent of the individual into response parameters which control peripheral muscles. When cerebellar damage occurs, the temporal composition of an orderly timed sequence of a motor program with multiple functional subunits becomes deranged (Dichgans and Diener, 1984).

Evidence for this hypothesis has been derived primarily from the detailed study of agonist-antagonist interactions during individual movements. The current investigation tested whether cerebellar lesions also affect the execution of practised (and programmable) *sequences* of movements. Two groups of patients were studied. One group of 13 subjects had bilateral cerebellar disease and another group of 12 subjects had unilateral cerebellar disease. Using a paradigm developed by Sternberg *et al.* (1978), two separate indices of the efficiency of patients in translating programmed movement into action were obtained, consisting of the sequence length effect and the position effect. If cerebellar dysfunction prevented

subjects from effectively translating a programmed sequence of responses into peripheral response parameters prior to response onset and obliged them instead to execute each element of a sequence of responses as a separate unit, then the time to initiate the execution of the sequence of responses should be unaffected by subsequent responses; i.e., no sequence length effect should occur. Furthermore, if cerebellar dysfunction prevented setting of response parameters for a group of responses before response onset then the normal facilitation of noninitial responses (relative to initial RTs) should be lost and each component should be a functionally independent unit, i.e., no positive position effect should be present or the positive position effect should be greatly reduced.

Three major comparisons were performed in the present sudy. First, patients with generalized cerebellar dysfunction were compared with neurologically unimpaired controls who had participated in an earlier study (Rafal *et al.*, 1987). Secondly, patients with mild bilateral cerebellar disability were compared with patients with moderate bilateral disability and, thirdly, patients with mild and moderate unilateral cerebellar lesions were studied comparing the performance of their clinically affected hand ipsilateral to the lesion with the performance of their clinically unaffected hand contralateral to the lesion. The pattern of results was highly consistent across all comparisons. Specifically, the results suggest that sequence length and positive position effects which characterize the performance of neurologically unimpaired subjects were absent when movements were executed with hands moderately affected by clinical disability from cerebellar dysfunction. These results could indicate that moderate cerebellar dysfunction prevents the translation of a programmed (or programmable) sequence of responses into action prior to response onset.

The current observations contrast strikingly with the performance of patients with Parkinson's disease who performed the identical sequential tapping task with movement sequences of L = 1 to L = 3 (Rafal *et al.*, 1987). In contrast to cerebellar patients, Parkinson's disease patients had slower response onset times than neurologically unimpaired control subjects, regardless of sequence length. Dysfunction of the basal ganglia thus affected some component of motor function. However, sequence length and position effects were nearly identical in patients with Parkinson's disease and control subjects. Consequently, disruption of the translation process that is used to transfer a motor program to the effector system, as it was found in the present study, is not the result of any CNS lesion affecting motor function. Other explanations of the present results, which attribute the absence of sequence length and position effects to general cognitive impairments of encoding operations, short-term memory capacity, readiness, or attention can also be excluded. In Experiment 2, each moderately impaired subject served as his/her own control so that any global impairment which affected ipsilateral responses would have equally affected contralateral responses. Nevertheless, laterality affected the execution of a sequence of planned manual responses. Sequence length and positive position effects were obtained when patients used

their intact contralateral hand to execute response sequences, but both effects were absent when moderately impaired subjects used their impaired ipsilateral hand to execute the sequences.

Sternberg *et al.* (1978) proposed a specific model to account for the sequence length effect in the sequential tapping task. In their model, the parameters of each element of a sequence of responses are specified before response onset and all specified (and programmed) elements are loaded into a motor buffer. When the reaction signal is perceived, a serial and self-terminating search is made for the sequence initial response which, when accessed, is passed on to the effector system. As the length of the sequence increases, buffer search time increases, resulting in a linear sequence length effect. Position effects could accrue because fewer searches are performed for noninitial responses. An alternative model to account for the sequence length effect has been proposed by Rosenbaum (1985). According to Rosenbaum, a sequence of to-be-executed responses can be ordered along a time dimension. Once the delay between successive responses has been specified, the order of these responses is also determined. A motor program then consists of a *schedule* of successive motor events and motor programming is the process of determining which motor commands are to be employed and with which clock pulse they are to be associated. Executing a motor program is the process of allowing responses to be triggered when their associated clock pulses occur. Within this perspective, the magnitude of the sequence length effect reflects real time demands for the set-up of response schedules for peripheral muscle effector systems and the position effect reflects, at least in part, benefits due to the advance scheduling of noninitial responses. According to this model, the lack of sequence length and position effects in cerebellar patients with moderate dysfunction indicates an inability to schedule a sequence of successive motor events before movement onset.

The hypothesis that cerebellar disease disrupts the scheduling of a sequence of movements before movement onset agrees with recent studies which reveal specific timing deficits in cerebellar patients (Ivry, 1986). In this study, a quantitative analysis of the variability of successive finger tapping intervals (Wing and Kristofferson, 1973) was used to identify two components of response variability. One component which reflects peripheral variability, due to changes in force, finger position, limb or body movements and a second component which reflects variability of a central time keeper. Ivry's results indicate that the increased response variability of cerebellar patients is due to damage to the central time keeping mechanism. This timing mechanism may also control the scheduling of successive movement elements in the present study.

Our observations in human patients also agree with physiological studies in experimental animals. Unit recordings from dentate neurons revealed increased firing rates after a reaction signal occurred and before response onset; the intensity of the discharge correlated with RTs, suggesting that the neurons encode timing for movement onset (Lamarre *et al.*, 1983). A more direct demonstration of

cerebellar involvement in the timing of programmed responses was provided by Hore and Vilis (1984). In their experiments, animals held a handle that loaded triceps. During the holding task, predictable and unpredictable perturbations were applied. An early antagonist response, which appeared to be synchronized to a torque pulse onset, occurred only for predictable perturbations. More critically, no early antagonist responses occurred for predictable perturbation during dentate cooling. Functional disconnection of the cerebellum thus resulted in the elimination of a time-locked predictive response component. Dentate recordings also support the notion that the cerebellum is involved in the planning of a sequence of movements. Robertson and Grimm (1975) trained 3 squirrel monkeys to execute a sequential button pressing task while 87 dentate neurons were recorded. The results showed some elevation in the discharge pattern of most dentate neurons for each button press response; in addition, the activation pattern of all dentate neurons increased somewhat on movement onset and increased for some neurons just before the sequence initial response.

The present results also raise a number of questions. First, patients with a mild cerebellar lesion showed relatively normal sequence length and position effects, even though they suffered from noticeable behavioural deficits during clinical examination. It is possible that mild cerebellar disease is more likely to be observed when response execution requires the use of a large number of muscle systems (e.g., grasping or pointing towards a target), as generally required in neurological examinations. When relatively few muscle systems are implicated in a response, as required in the present study, effects of mild cerebellar lesion might be negligible. Secondly, the present experiments cannot uniquely determine the mechanism which underlies the lack of a sequence length effect and the negative position effect in patients with a moderate cerebellar lesion. It could be possible, for example, that moderately impaired cerebellar patients are able to specify the temporal coordinates of a whole sequence of responses before response onset but may refrain from doing so, possibly because impaired peripheral feedback no longer signals that a previous response element has been executed. Thirdly, it could be argued that the results of Experiments 1 and 2 primarily reflect a disability in the execution of sequence initial responses. Impairment of the sequence initial response could eliminate sequence length effects and influence the execution of noninitial responses resulting in a negative position effect. Again, this view implies that patients with moderate cerebellar damage could translate a programmed sequence of responses into action parameters before response onset, but refrain from doing so because other disabilities render this strategy futile. Future research will be needed to assess the validity of these hypotheses.

In summary, converging evidence from human and animal studies indicates that a practised movement sequence is programmed before movement onset so that the sequence will be executed as a single fluid unit. The translation of a programmed sequence of responses into peripheral effector commands appears to occur only when a relatively intact cerebellar structure can be contacted. When the cerebellum

is moderately disabled, the movement sequence becomes 'decomposed' and patients execute each element of the sequence as a functionally separate unit.

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