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Cerebellar Structures and the Programming of Movement Sequences

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Two patients with unilateral damage to the medial and lateral cerebellum were examined to determine whether local structures in the cerebellum are used to execute programmed movement sequences. Both patients performed a sequential tapping task which required the execution of either a single keystroke or of a sequence of three keystrokes. Movements executed with the contralateral hand showed increases in response onset times as the movement sequence increased from one to three response elements (sequence length effect). Furthermore, noninitial response elements were executed considerably faster than sequence initial responses (position effect). Movements executed with the ipsilateral hand showed a different pattern of results. Damage to medial cerebellar structure had no qualifying effect but damage to the lateral cerebellar structure eliminated effects of sequence length and of response position. The results suggest that the lateral cerebellum is implicated in the execution of programmed manual movement sequences.

Introduction

Several definitions of motor programming have been proposed most of which converge on the assumption that several components of a movement sequence can be represented prior to movement onset. Consider for instance, a recent study by Sternberg, Monsell, Knoll, and Wright (1978). In their experiment, neurologically intact subjects were required to execute a sequence of manual keystrokes (or utterances) in response to simple reaction signal. The complexity of the motoric task was varied and so that it comprised either a single movement element or several elements. The main result showed increased movement onset latencies as the complexity of the movement sequence increased. In the following, we will refer to this finding as the *sequence effect*. One way to account for the effect is to assume that all elements of a to-be-executed movement sequence are represented (programmed) prior to response onset. The retrieval time for the first element of a movement sequence may then increase with the complexity of the corresponding movement-sequence representation. Furthermore, Sternberg *et al.*'s results showed relatively short interkeypress times, i.e. the interval between two successive keypresses, was considerably shorter than response onset time, which is consistent with the notion that these responses had been

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represented (programmed) prior to response onset. In the following we will refer to this finding as the *position effect.* Within a sequential movement task, the sequence and position effects can thus be used to study real time constraints on the execution of programmed movement sequences.

Neurological Structures Supporting Motor Programming

A number of literature reviews suggested that several neurological structures, notably the basal ganglia and the cerebellum, are used to execute programmed movements (Brooks, 1984; Cheney, 1985). To examine this possibility, we (Rafal *et al.*, 1987) used a sequential tapping task to examine motor programming in patients with Parkinson's disease. Patients were required to execute either a single keystroke with the index finger, a sequence of two keystrokes with index and middle finger, or a sequence of three keystrokes involving index, ring, and middle fingers (in this sequence), in response to a simple reaction signal. In general, response onset times of these patients was relatively slow but, more important, there was a reliable increase in response onset time as sequence length increased. The magnitude of this sequence length effect matched the sequence length effect in neurologically unimpaired control subjects. This finding suggests that the execution of a programmed movement sequence is unaffected by impairment of the basal ganglia as occurs in Parkinson's disease.

Patients with moderate cerebellar impairment show a different pattern of results. Examination of thirteen bilaterally impaired cerebellar patients showed greatly reduced sequence length effects when compared to neurologically unimpaired controls. Analogously, unilateral damage to the cerebellum eliminated the sequence effect when movement sequences were executed with the (affected) ipsilateral hand but not when they were executed with the (unaffected) contralateral hand (Inhoff *et al.*, 1989). Furthermore, analysis of interkeypress times revealed no position effects for ipsilaterally executed movement sequences but revealed large position effects for contralaterally executed movement sequences. Taken together, these results indicate that cerebellar structures are implicated in the execution of programmed manual movement sequences.

The present study follows up on these earlier studies by addressing two specific questions: First, which anatomical region in the cerebellum supports the execution of programmed manual movement sequences? Second, what types of mental processes are implicated in the motor programming of these movement sequences?

Regions in the *lateral* cerebellum represent hand movements and may be of particular importance for the execution of programmed manual movements. To examine this possibility, we tested two patients with primarily unilateral cerebellar lesion. One patient suffered from unilateral cerebellar infarct in the right superior medial area (patient CG) and one patient suffered from unilateral cerebellar infarct in the left lateral area (patient ZS). As in the earlier studies (Rafal *et al.*, 1987; Inhoff *et al.*, 1989) subjects executed manual movement sequences requiring either one or three key-

strokes. If lateral cerebellar structures representing manual responses supported the execution of programmed movement sequences, then patient ZS should show an abnormal sequence and position effect for ipsilaterally executed movement sequences but normal effects for contralaterally executed movements. Patient CG, in contrast, should show relatively normal sequence and position effects during the execution of ipsi- and contralateral movement sequences.

Under what conditions does motor programming occur? Subjects may program a to-be-executed movement sequence whenever there is sufficient time to program a movement sequence prior to the onset of the reaction signal. This is usually the case in simple reaction conditions as used in prior experiments (Rafal *et al.*, 1987; Inhoff *et al.*, 1989). No motor programming may occur, however, when there is no preparatory time between the onset of the reaction signal and movement execution.

To determine the conditions under which manual motor programming can occur, we varied the degree to which each movement sequence could be prepared prior to the onset of the reaction signal. A modified choice reaction task was used in which the patient was required to execute one of two possible movement sequences in response to a two-choice reaction signal. The choice reaction signal comprised either the letter *X* or *O*, *X* indicating, for instance, that the sequence index-middle-ring finger was to be executed and the *O* indicating that the sequence middle-ring-index finger was to be executed. A precue was given on each trial which informed the subject about the identity of the subsequently presented choice signal. On 80% of the trials, the precue correctly informed the subject about the subsequent choice signal (called *valid* trials), on the remaining 20% of the trials, the cue misinformed the subject about the identity of the subsequently presented choice signal (called *invalid* trials). Movement preparation could thus be performed prior to the onset of the reaction signal on valid trials but not on invalid trials. If the sequence effect reflected a process which occurs when sufficient time is allotted to prepare a sequence of responses prior to response onset, then it should occur on valid trials but not on invalid trials. If, however, the sequence effect reflected an obligatory process, comprising the access of a movement-sequence representation, then a sequence length effect may be observed irrespective of any effect of cue validity.

Methods

Case histories

Subject CG A 75-year-old hypertensive woman without a past history of stroke, alcohol abuse or any other neurological problem. Hospitalized on 17 December 1988, because of a sudden onset of vertigo, ataxic gait and clumsiness of the right arm and leg. Neurological examination revealed no nystagmus or severe gait ataxia. By 22 December 1988, she was able to walk with a slight unsteadiness and evidenced only minimal dysmetria of the arm

and leg. At no time did she have any mental impairment, weakness, sensory loss, or abnormal reflexes. CT scan, revealed a relatively small infarct in the right anterior, superior cerebellar hemisphere.

Subject ZS A 58-year-old woman who suffered a stroke 8 years before testing in December 1988. The stroke was due to cardiac embolus from heart valve prosthesis. No other history of stroke or alcohol abuse was evident. Neurological examination revealed a larger nystagmus to the right than to the left. There were no signs of dysarthria, but there was a mild left arm dysmetria with normal strength, sensation, and reflexes. She displayed a steady gait, with a slight wide base. Her CT scan showed a large infarct in the left to lateral medial cerebellar area.

Apparatus Each subject sat viewing a cathode ray tube (CRT) which was placed on a table approximately 80 cm in front of each patient. A response panel with four spatially adjacent keys was placed in front of the CRT. The response panel was similar to a four-key segment of a piano keyboard. Each

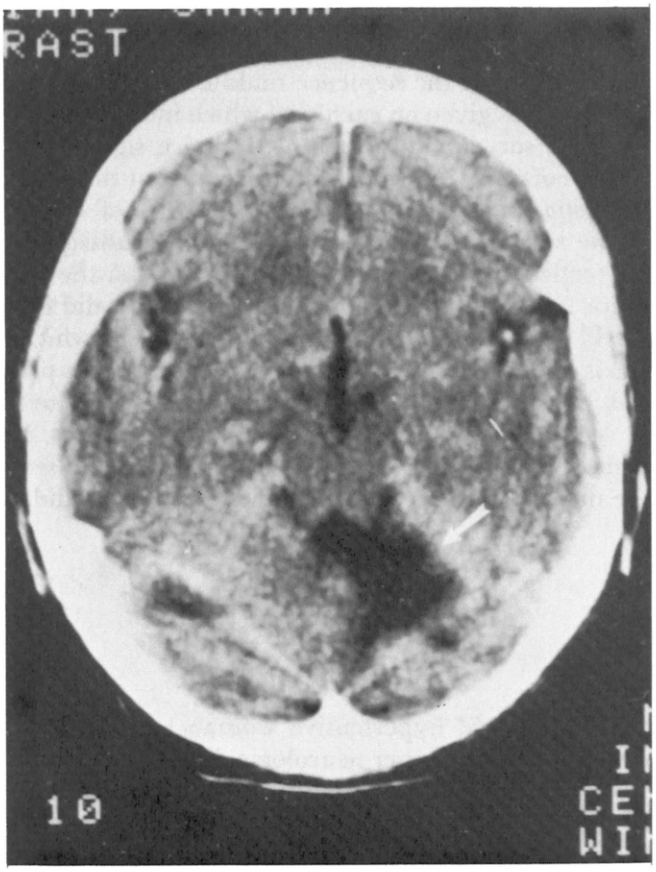

FIG. 1. CT scan of patient CG. Note the infarcted medial cerebellar structure.

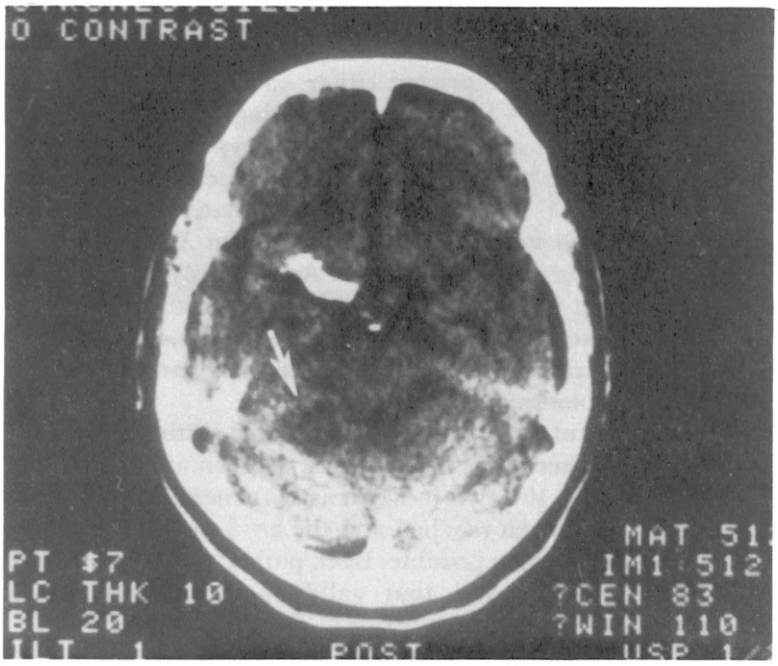

FIG. 2. CT scan of patient ZS. Note the infarcted lateral cerebellar structure.

patient rested the four fingers of one hand on the four consecutive keys of the response panel. Each key was 2·1 cm wide and triggered a microswitch when its vertical displacement exceeded 2 mm. A microcomputer, equipped to perform real time measurements to the nearest millisecond (ms) controlled the visual display as it appeared on the CRT and sampled response onset time, comprising the interval between the onset of the choice reaction signal and the first keypress, and interkeypress times, comprising the interval between two successive keypresses.

Procedure Each patient was instructed to monitor the CRT for the outlines of a bright square with a line length of 10 cm; 500 ms after the onset of the square, a visual cue was shown in the center of the square comprising either the letter *X* or the letter *O*. Each cue was ·5 cm high and ·75 cm wide and remained on the screen for 250 ms. One second after cue onset, the reaction signal was shown in the center of the square again comprising the symbols *X* and *O*. Each reaction signal was 2·5 cm high and 1·5 cm wide. On 80% of the trials, cue and target stimulus were identical (except for size); i.e. the cue correctly predicted the identity of the subsequently presented target. As indicated before, these trials will be referred to as *valid* trials. On the remaining 20% of the trials, cue and target were of different identities, i.e. the cue comprised the symbol *X* and the target comprised the symbol *O* or vice versa. In these instances, the cue incorrectly predicted the identity of the subsequently presented target. These trials will be referred to as *invalid* trials.

Sequence length was blocked and manipulated orthogonal to cue validity. On half of all blocks of trials, the patients were required to execute either a single keystroke comprising either an index finger keypress or a middle finger keypress ($n=1$); on the remaining blocks of trials, patients were required to execute a sequence of three keypresses comprising either the sequence index, ring, middle finger or the sequence middle, ring, index finger ($n=3$). On $n=1$ blocks of trials, each patient was instructed to execute an index finger keypress in response to the *X* signal and a middle finger keypress in response to the *O* signal. Analogously, on $n=3$ trials, each patient was instructed to execute the index, ring, middle finger sequence in response to the *X* choice reaction signal and the middle, ring, index sequence in response to the *O* reaction signal. Right and left hand performance was assessed in separate blocks of trials.

At the beginning of each block of trials, each patient was familiarized with the two choice alternatives which were used on a given block of trials. Each patient practiced the two movement sequences until it was felt that peak performance had been reached and the $n=3$ movement sequence was executed as a fluid unit when possible. Each patient was also informed about the usefulness of precues and that valid cues preceded the target in approximately four of five trials.

Design The factor Cue Validity was varied within each block of 35 trials, the factors Executing Hand and Sequence Length were varied between blocks. Blocks were ordered according to a modified ABBA design, such that each patient first used one hand to execute two blocks of trials comprising sequence lengths 1 and 3, then executed four blocks of trials (two of sequence length $n=1$ and two of sequence length $n=3$) with the other hand, and then shift hands again to execute the remaining two blocks of trials. Sequences of length $n=1$ and $n=3$ were executed in alternating order.

Results

Three types of measurements were obtained comprising error rate, response onset time (to determine the sequence effect), and interkeypress times for $n=3$ sequences (to determine the position effect). Statistical analyses were applied to reaction time measures obtained on correctly executed trials. Given the small number of invalid trials, statistical analyses were applied to valid trials only. However, examination of the pattern of invalid trial data shows that the results mimic the pattern of data obtained on valid trials. Each patient's reaction time data was analyzed separately. Given the single subject design, we used movement variability (RT) for all responses within a specific condition as an estimate of error variability and the variability between conditions as an estimate of experimentally induced variability (generated by the different experimental conditions).

Error rate

Error rate amounted to 2% for patient ZS (lateral cerebellar infarct) and to 13% during the testing of patient CG (medial cerebellar infarct). An inspection of the errors revealed no differences between ipsi- and contralateral hands in both patients. Approximately four out of five errors occurred in the valid condition which is appropriate given the distribution of valid and invalid trials. Similar to earlier studies, error rates were thus of little diagnostic value.

Response onset time (position effect)

Response onset times as a function of Sequence Length and Executing Hand for valid and invalid trials are shown in Table 1. As can be seen in the Table, patient CG showed sizable sequence effects, with longer response onset times for the $n=3$ sequences than for the $n=1$ sequences, $F(1, 38)=15{\cdot}987$, $p<001$. This effect occurred even though the identical movement was executed in response to the choice reaction signal; i.e. the patient performed either an index finger keypress or a middle finger keypress in response to the choice reaction signal. More important, the sequence effect was not qualified by the factor Executing Hand and the interaction of Sequence Length and Executing Hand was not significant, $F<1$. This finding indicates that unilateral damage to the medial structure of the cerebellum has little effect on the sequence length effect of ipsilaterally executed movement sequences.

As can also be seen in Table 1, patient ZS showed a different pattern of results. The overall effect of Sequence Length was relatively small and did not reach statistical significance, $F(1, 40)=1{\cdot}113$, $p<{\cdot}3$. There was also a small effect of Executing Hand, with slower response onset times for movements executed with the ipsilateral hand, but this effect failed to reach significance, $F(1, 40)=2{\cdot}959$, $p<{\cdot}1$. More important, examination of the

TABLE 1. *Response onset times of patients CG and ZS on valid and invalid trials as a function of Sequence Length and Executing Hand (Standard Errors are shown in parentheses—valid trials only).*

	Executing Hand			
	Ipsilateral		*Contralateral*	
	Sequence Length			
	$n=1$	$n=3$	$n=1$	$n=3$
Patient CG				
Ipsilateral	687	875	681	833
	(38)	(47)	(36)	(38)
Contralateral	801	810	745	910
Patient ZS				
Ipsilateral	1042	996	874	1010
	(43)	(44)	(42)	(40)
Contralateral	941	935	1031	1020

data revealed that the sequence effect was qualified by the factor Executing Hand. There was a large sequence effect for movements executed with the contralateral hand but no sequence effect (or a negative sequence effect) for movement sequences executed with the ipsilateral hand. The interaction of Sequence Length and Executing Hand was statistically significant, $F(1, 41) = 5{\cdot}880$, $p < {\cdot}025$.

Comparison of response onset times across patients showed that the magnitude of the contralateral sequence effect in patient ZS corresponded to the magnitude of the sequence effect for ipsi- and contralateral movement sequences in patient CG, indicating that patients ZS's contralateral movements remained unaffected by cerebellar lesion. The elimination of the sequence effect in patient ZS during the execution of ipsilateral movement sequences thus suggests that structures in the lateral cerebellum are implicated in the execution of programmed movement sequences.

Quite surprisingly, response onset times on invalid trials (see Table 1) were no longer than response onset times on valid trials. The pattern of response onset times on invalid trials mimicked response onset times on valid trials in both patients, except for the lack of a sequence length effect in patient ZS's contralateral responses. However, given the small set of trials, the absence of a sequence effect could be due to sampling error. Two accounts of the similarity of responses on valid and invalid trials seem plausible: First, impaired cerebellar structures may disable preparatory processes, thereby eliminating effects of cue validity; second, both patients may have simply ignored pre-cues, given that these cues were incorrect on some of the trials.

Interkeypress times (position effect)

Response onset time and interkeypress times of valid $n = 3$ sequences were analyzed to determine effect of medial and lateral cerebellar lesion on the execution of movement sequences. As occurred in the response onset times, interkeypress times showed nearly identical results and valid and invalid trials. Statistical analyses were applied to valid trials using the factors Position (first, second, third keypress) and Executing Hand.

As can be seen in Table 2, patient CG showed large position effects with long movement onset times and relatively short interkeypress times. The main effect of Position was significant, $F(1, 38) = 98{\cdot}305$, $p < {\cdot}001$. There was a slight tendency towards shorter ipsilateral movement times, but this effect failed to reach statistical significance, $F(1, 38) = 2{\cdot}085$, $p < {\cdot}15$. More important, the magnitude of the position effect was nearly identical for ipsi- and contralateral movement sequences and the interaction of Position and Executing Hand was not significant, $F < 1$.

As can be seen in Table 2, patient ZS showed, again, a different pattern of results than patient CG. Although noninitial keypresses of patient ZS were again considerably shorter than the initial keypress, which manifested itself in a highly significant sequence effect, $F(2, 80) = 129{\cdot}463$, $p < {\cdot}001$, there was a considerably smaller position effect for movements executed

TABLE 2. *Response onset time and interkeypress times of patients CG and ZS on valid–invalid trials as function of Response Position and Executing Hand (Standard errors are shown in parentheses for valid trials)*

	Executing Hand					
	Ipsilateral			*Contralateral*		
	Response Position					
	First	*Second*	*Third*	*First*	*Second*	*Third*
Patient CG						
Valid trials	874	468	558	833	443	517
	(47)	(31)	(29)	(38)	(19)	(36)
Invalid trials	810	466	559	910	494	655
Patient ZS						
Valid trials	995	795	746	1010	499	512
	(44)	(20)	(37)	(40)	(14)	(18)
Invalid trials	935	801	761	1020	515	540

with the ipsilateral hand. The interaction of Executing Hand and Position was significant, $F(2, 80) = 18{\cdot}641$, $p < {\cdot}001$. In addition, the data revealed a main effect of Executing Hand, $F(1, 40) = 35{\cdot}200$, $p < {\cdot}001$, with longer movement times for ipsilateral movements.

Comparisons across patients show that patient ZS contralateral position effect closely corresponds to the ipsi- and contralateral position effect of patient CG, indicating that these movement sequences were executed in a relatively normal manner. Again, abnormal effects occurred when movement sequences were executed with the hand ipsilateral to lateral cerebellar lesion, indicating that damage to this structure may have affected the execution of programmed movement sequences.

Discussion

The two major findings of the present study were, first, the ipsilesional loss of the sequence length effect in patient ZS and the presence of a normal sequence length effect in both hands in patient CG in the response onset times; second, the ipsilesionally decreased position effect in patient ZS and the presence of similar sequence length effects for ipsi- and contralateral position effects in patient CG. There are several differences which could account for these findings. In patient ZS, the lesion is in the left cerebellar hemisphere, while in patient CG, it is in the right cerebellar hemisphere. It is possible that there is a functional asymmetry of the cerebellum with the left being dominant for programming sequential movements. In our previous study which measured the sequence length effect under similar RT conditions, no such difference was found between left and right hemisphere lesions, and it seems unlikely that this is the explanation for the current results. Another obvious difference is that the lesion is larger in patient ZS.

Certainly a mass action principle may be at work here: the deficit in patient ZS may affect response onset and interkeypress times because enough cerebellar cortex was destroyed to prevent functional compensation. This explanation seems unlikely, however, because the lesion in patient ZS was approximately eight years old whereas the lesion in patient CG was acute. It seems plausible to assume that the difference in the vintage of the lesion should have compensated for the difference in size.

The explanation we favor to account for the response onset times and interkeypress times relates the deficit to the distribution of the lesions within the cerebellar hemispheres. In both patients the lesion involved the medial superior hemisphere and vermis—a region representing the leg and trunk. Only in patient ZS does the lesion extend far enough caudal and lateral to involve the representation for the hand. Since the task specifically required the programming of manual movement sequences, we propose that the programming deficit found in patient ZS was the result of this localized lateral lesion.

The results of patient ZS is in close empirical agreement with prior group study results which showed that moderate damage to cerebellar structures decreased the magnitude of position and sequence effects in a simple reaction task (Inhoff *et al.*, 1989). It extends these group data in two significant ways: First, the present data suggest that damage to a *specific* area of the cerebellum eliminates or reduces these effects. Second, the data show that simple reaction tasks and choice reaction tasks yield similar results; i.e. both types of paradigms can be used to study the execution of programmed responses in this patient population.

Why does damage to the lateral cerebellum disable the execution of programmed movement sequences? As indicated earlier (Inhoff *et al.*, 1989), several possibilities seem plausible. First, damage to this structure may affect the use of feedback from the peripheral motor system, i.e. structures in the lateral cerebellum may be used to trigger the release of one response element given that some feedback is received indicating that the prior movement element has been executed. If this peripheral feedback is no longer available, the patient's best strategy would be to execute each movement element as a functionally separate unit. As a result, sequence and position effects should be eliminated. However, no data have been reported which would indicate that lateral cerebellar structures differ from other cerebellar structures in that they are dedicated to the recording of peripheral feedback.

Second, the lateral cerebellum could be implicated in the retrieval of programmed movement elements. This account follows Sternberg *et al.*'s (1978) view which maintained that sequence effects are due to real time demands during the retrieval of movement elements; i.e. retrieval time is assumed to increase, as the number of to-be-executed responses increases. Again, no data have been reported which would show that lateral cerebellar structure differs from other cerebellar structures in that they are dedicated to the retrieval of movement sequences.

Third, the lateral-cerebellum could be used to support specific functions which are used during the programming and execution of movement

sequences. Consider, for instance, Rosenbaum's (1985) scheduling theory of motor programming. According to this view, elements of a sequence of to-be-executed responses are ordered along a time dimension and each element of the movement sequence is associated with a specific trigger-time value. During movement execution, a response element is triggered (and executed) whenever its clock pulse occurs. According to this view, the sequence effect indicates real-time demands for the setup of movements schedules, with increases in set-up time as sequence length increases from $n=1$ to $n=3$; position effects may indicate benefits during movement execution which result from the automatic triggering of movement elements.

Recent results suggest that the lateral cerebellum may serve as a specialized internal timing mechanism. Specifically, Ivry, Diener, and Keele (1988) showed that damage to lateral structures of the cerebellum disrupts an internal motor timing mechanism, whereas damage to medial cerebellar structure leaves motor timing virtually intact. Within the framework of a scheduling theory of motor programming, structures in the lateral cerebellum could provide clock pulses which may be used to trigger the execution of programmed movement elements.

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