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Inter-response interference contributes to the sequencing deficit in frontal lobe lesions

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Summary
In this study we investigated the contribution of inter-response interference to the sequencing deficit in frontal lobe lesions. We examined inter-response interference in choice sequences through the reduction in inter-response interval produced by stimulus preview when compared with sequences performed without preview. If frontal lobe lesions result in a stronger inter-response interference, the facilitative effect of preview on inter-response interval should be attenuated. We compared nine patients with a frontal excision with nine patients with a temporal excision and nine controls in a task requiring rapid keypress responses to each of five letters in a sequence. In the no-preview condition, the five letters were presented one at a time, immediately following the previous response. In the preview condition, the five letters were presented simultaneously before the response sequence. Patients with a frontal lesion showed slower response times than the other groups. In normal subjects and patients with a temporal lesion, stimulus preview produced the expected reduction of inter-response time and the slowing of sequence initiation. In frontal lesions, however, preview did not reduce inter-response time and exacerbated the slowing of sequence initiation. The results indicate that patients with a frontal lobe lesion show increased interference between adjacent responses as well as a sequence initiation problem.

Keywords: sequential responses; response time; interference; inertia; programming

Introduction
It has long been recognized that the contributions of frontal cortex to basic cognitive operations are difficult to circumscribe (Luria, 1966, 1969). Some of the reasons for the comparatively slow progress of this problem may be found in the complexity of the tasks used to assess frontal lobe damage. Complex tasks, such as problem solving tests, involve a wide variety of cognitive operations and do not help disentangle the deficient functions from the preserved ones. However, patients with a frontal lobe lesion have long been known to fail simple tasks such as response sequences. Indeed, while patients with a frontal lobe lesion can generally show good performance in simple discrete responses, their performance becomes suddenly faulty when required to produce multiple responses in a sequence (Luria, 1966; Stuss and Benson, 1986; Fuster, 1989). This contrast between individual and sequential performance indicates that some cognitive operations that come into play in sequential responses, either in the transition between responses or in the programming which precedes initiation, are deficient after frontal damage.

Sequence processing involves fundamental and widespread cognitive operations and it is not surprising that sequencing deficits have been observed in a wide variety of contexts. Patients with a frontal lobe lesion show deficient performance in copying consecutive hand movements (Luria, 1966; Kolb and Milner, 1981; Jason, 1985, 1986), facial movements (Kolb and Milner, 1981), and in self-ordered sequential pointing (Petrides and Milner, 1982), but also when asked to carry out multiple commands (Albert, 1972; Samuels and Benson, 1979), or solve multi-step problems such as maze tasks (Milner, 1964; Canavan, 1983), the Tower of London task (Shallice, 1982; Owen *et al.*, 1990), and multiple errands (Shallice and Burgess; 1991). These tasks contain a variety of features which may contribute to the poor performance of patients with frontal damage. However, they all have the planning and execution of multiple consecutive responses in common and there have been only few investigations into the contribution of fundamental operations shared by sequential response tasks in these deficits.

Response sequences share the characteristic of requiring significant programming. For example, they require planning the temporal order of multiple responses and anticipating the environmental consequences of these responses. Difficulties in the programming or planning of complex multi-step responses have been documented in patients with a frontal lesion (Shallice, 1982). Although the concept of planning is still poorly defined operationally (Goel and Grafman, 1995), the performance of patients with frontal lesions has often been described as characterized by a haphazard approach, observable in the initial responses and slow sequence initiation (Luria, 1966; Stuss and Benson, 1986). These behavioural phenomena have been interpreted as inefficient planning processes, a factor which could affect the performance of patients with frontal lesions on sequential tasks.

Luria (1966) presented a different interpretation of the sequencing deficit of a patient with frontal lesions and hypothesized that some of the sequencing difficulties of patients with frontal lesions and especially their perseverative tendencies were due to a pathological inertia of motor responses, an excessive proactive interference between adjacent responses. This hypothesis is quite distinct from, although not incompatible with, a planning deficit. However, the interference hypothesis has never been systematically investigated. The response inertia of patients with frontal lesions could be an exacerbation of interference effects found on a smaller scale in normal subjects in contexts involving sequential responses. The interference between successive responses has been investigated for a long time in cognitive psychology (e.g. Telford, 1931; Welford, 1952; Pashler, 1994). Increased interference effects could account for the poor performance of patients with a frontal lesion in tasks involving multiple responses. Some findings with patients with frontal lesions in simple sequential tasks point to a sensitivity of these subjects to manipulations increasing the temporal proximity of successive responses, which increase inter-response interference. For example, Jason (1986) had patients with frontal lesions, patients with temporal lesions and normal subjects perform hand movement sequences while varying the inter-response interval from 0.3 to 2 s. The performance of patients with frontal lesions became deficient when the intervals between hand movements fell below 650 ms while intervals above 550 ms in patients with a temporal lesion and 440 ms in normal subjects had no adverse effect. These results suggest that patients with frontal lesions have problems processing multiple decisions rapidly.

One way to measure the size of the interference between successive responses is to look at the compressibility of successive responses with stimulus preview. Advance knowledge of upcoming stimuli has been shown to reduce inter-response time in response sequences (Leonard, 1953; Shaffer, 1976, 1991; Pashler, 1994). The effect of preview can be studied by having subjects perform a serial choice task where stimuli are either presented one at a time or all together at the beginning of the sequence. Compared with the no-preview condition, stimulus preview produces a reduction of inter-response time accompanied by a slowing of sequence initiation time (Leonard, 1953; Pashler, 1994). A preview of one, where only the next stimulus is shown in advance, yields a reduction of inter-response time similar to the total preview condition, indicating that preview facilitates the transitions between adjacent responses (Pashler, 1994). The facilitative effect of preview on inter-response time is generally interpreted as a gain in processing efficiency due to the overlap of some of the processes of adjacent responses (Leonard, 1953; Shaffer, 1976, 1991; Pashler, 1994). The slowing of sequence initiation by preview is a measure of the added preparatory processing needed to programme the sequential order of multiple decisions (Sternberg *et al.*, 1978; Semjen and Gottsdanker, 1992).

In the present study, we examined the preview effect in sequential choices in patients with frontal lesions, patients with temporal lesions and normal subjects in a task requiring rapid keypress responses to successive letters presented visually. If patients with frontal lesions suffer from an increased inter-response interference, stimulus preview should produce less facilitation or compression of serial choices. The programming problem of patients with frontal lesions may also show up in an increased sequence initiation time.

Methods

Subjects

Nine patients with a unilateral frontal excision (seven right, two left) were compared with nine patients with a unilateral temporal excision (four right, five left) and nine controls with no history of cerebral damage. Groups were matched in age (38 years, range 26–55 years) and education level (11 years, range 6–18 years). The excisions were performed in adulthood to alleviate epilepsy which had not responded to drugs and patients were tested at least 2 years following the surgical intervention. For all subjects, informed consent to participate in the study was obtained according to the rules of the institution and the local ethical committee approved the study.

Frontal excisions were variable in extent but always included dorsomedial structures (anterior cingulate gyrus, superior frontal gyrus, sometimes including the supplementary motor area) and a variable amount of dorsolateral cortex anterior to the precentral sulcus. Figure 1 shows the extent of the frontal resections. Eight of the patients with a frontal lesion showed a marked reduction in seizure frequency after surgery ($\geqslant$80%), two were seizure-free and all were on anticonvulsant medication. Anterior temporal lobectomies involved resection of the anterior portion of the temporal lobe (~5 cm from the anterior tip of the lobe), partial resection of the hippocampus, and sparing of Heschl's gyrus. All patients with a temporal lesion showed a marked reduction in seizure frequency (four were seizure-free) and five were still on anticonvulsant medication. All patients underwent post-surgery neurological and neuropsychological evaluation. None exhibited sensory or

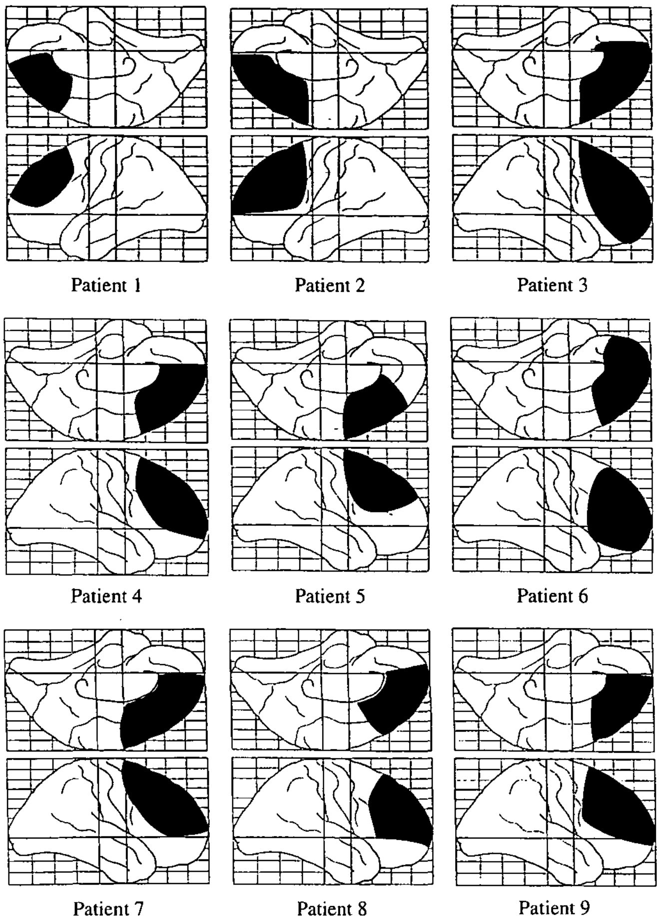

Fig. 1 Extent of medial and lateral resection of the frontal excisions.

motor impairment nor any hemispatial neglect on standard clinical measures. All patients had a WAIS IQ above 80, and all could demonstrate comprehension and retention of the instructions of the task. Neuropsychological evaluation revealed no significant deficits in language, episodic memory or praxis. Patients with frontal lesions and those with temporal lesions showed normal response times in simple reaction time and in two-choice decisions, although patients with frontal lesions made significantly more errors in two-choice decisions.

Tasks and procedure

The experiment was controlled by a 486 computer running Neuroscan software. Each trial consisted of a sequence of five letters and five corresponding responses. All letter sequences consisted of As, Bs and Cs. The three letters were mapped to adjacent buttons on a keypad. Sequences were pseudo-randomly generated with the constraints that at least one exemplar of each letter was present and there was no immediate repetition of a letter. Letters measured 1 cm wide by 1.5 cm high (subtending a visual angle of 1° wide and 1.4° high at a viewing distance of 60 cm) and were presented in white against a black background. The letter sequences were presented in a horizontal fashion at the centre of the screen and the total display of five letters measured 6 cm. In the no-preview condition, the first letter appeared at the leftmost position and the second letter was presented next to it, immediately following the response to the first one and so on. The letters remained on the screen until the end of the trial. In the preview condition, all five letters appeared simultaneously at the beginning of the trial and remained there until the completion of the trial.

Subjects were instructed to respond as quickly and accurately as possible to each character and a figure showing the associative rules between letters and keys was presented. Subjects responded to the letters (A, B and C) by pressing three keys with the first three fingers of the dominant hand (index finger for A, middle finger for B, and ring finger for C). Comprehension of the instructions was verified before each condition through appropriate questioning.

The task included 12 experimental blocks consisting of 10 trials each. Subjects were tested through a fixed sequence consisting of three blocks with no-preview, followed by three blocks with full-preview, repeated twice. The first block of each condition was preceded by a practice block of 10 trials. An error tone was delivered whenever an error was made. Responses with latencies below 150 ms or above 2500 ms were excluded. Five-second pauses separated successive trials while a 1-min pause separated successive blocks.

Table 1 *Mean percentage of errors of each group in the two conditions*

Condition	Normal subjects	Patients with temporal excision	Patients with frontal excision
No-preview	3.4 (1.7)	4.3 (4.6)	8.4 (4.3)
Preview	7.8 (3.0)	8.1 (4.5)	13.9 (6.3)

SDs are in parentheses.

Results

Error analysis

The mean percentage of errors of each group in the two conditions is shown in Table 1. An ANOVA on the number of errors revealed a significant group effect [$F(2,24) = 5.87$, $P < 0.01$], a significant effect of preview [$F(1,24) = 27.52$, $P < 0.001$] but no significant interaction between group and preview condition [$F(2,24) = 0.39$, n.s.]. Stimulus preview resulted in an increased error rate for all groups. Patients with a frontal lesion made significantly more errors than normal subjects and patients with a temporal lesion in both preview conditions (Tukey's *honestly* significant difference: 6.1, $P < 0.02$ between normals and frontals; 5.7, $P < 0.05$ between temporals and frontals; 0.3, n.s. between normals and temporals).

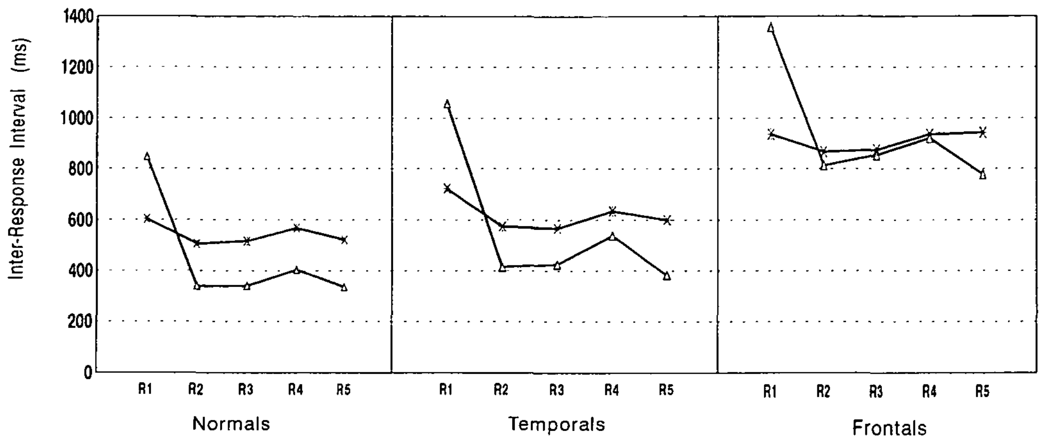

Fig. 2 Mean response latencies in each group for the five responses in choice sequences executed with and without stimulus preview. R1 represents sequence initiation time, while R2–R5 represent the inter-response time. Stars represent the no-preview condition; open triangles represent the preview condition.

Response time analysis

Figure 2 presents the mean response latencies of correct responses in each group for both preview conditions. In the no-preview condition, all latencies represent the time between stimulus onset and the following response (reaction time). In the preview condition, the first latency (R1) represents the sequence initiation time, while the remaining latencies are inter-response intervals (R2–R5).

In the no-preview condition, the first response appeared to be slower than the next four responses and response latencies were increased in patients with a frontal lobe lesion compared with the other groups. An ANOVA on reaction time revealed a significant group effect [$F(2,24) = 22.4$, $P < 0.001$], a significant response position effect [$F(4,96) = 17.5$, $P < 0.0001$] and a significant interaction between group and response position [$F(8,96) = 2.2$, $P < 0.05$]. The removal of R1 from the previous analysis made the interaction disappear [$F(6,72) = 1.1$, n.s.], indicating an absence of interaction between group and response position effects for R2'R5.

Figure 2 shows that preview increased the latency of the first response in all groups. An ANOVA on the latency of R1 revealed a significant group effect [$F(2,24) = 17.6$, $P < 0.0001$], a significant preview effect [$F(1,24) = 178.7$, $P < 0.0001$], and a significant interaction between preview and group effects [$F(2,24) = 4.2$, $P < 0.03$]. Simple effects revealed that, for the first response, patients with frontal lesions were more affected by preview [$F(1,24) = 96.8$, $P < 0.0001$] than normals [$F(1,24) = 33.7$, $P < 0.001$] and patients with temporal lesions [$F(1,24) = 56.36$, $P < 0.0001$].

For R2–R5, Fig. 2 shows that preview produced the expected reduction in inter-response interval in normals and patients with a temporal lobe lesion but not in patients with a frontal lobe lesion. ANOVAs at each position revealed a significant group effect [all $Fs(2,24) > 25.39$, $P < 0.001$], a significant preview effect [all $Fs(1,24) > 35.4$, $P < 0.0001$] and a significant interaction [all $Fs(2,24) > 4.2$, $P < 0.02$] for R2–R4. Simple effects revealed that patients with frontal lesions did not benefit from stimulus preview [all $Fs(1,24) < 0.39$, ns] in contrast to normal subjects [all $Fs(1,24) > 20.1$, $P < 0.0001$] and patients with temporal lesions [all $Fs(1,24) = 6.6$, $P < 0.01$]. For R5, the ANOVA revealed a significant group effect [$F(2,24) = 31.5$, $P < 0.0001$], a significant preview effect [$F(1,24) = 81.3$, P 0.0001] but no significant interaction [$F(2,24) = 0.5$, n.s.].

In separate analyses, we examined the time taken to execute the complete sequence of five responses in each condition, so as to try to clarify the relation between preview effects on R1 and on later responses. In the no-preview condition, sequence execution required an average of 2.7 s (SD = 0.5) for normals, 3.1 s (SD = 0.4) for patients with a temporal lesion, and 4.6 s (SD = 0.9) for patients with a frontal lesion, while in the preview condition, normals took 2.3 s (SD = 0.6), patients with a temporal lesion 2.8 s (SD = 0.5), and patients with a frontal lesion 4.7 s (SD = 1.1). An analysis of variance on the total sequence execution time revealed a significant group effect [$F(2,24) = 25.7$, $P < 0.001$], a significant effect of preview [$F(1,24) = 7.4$, $P < 0.01$], and a significant group × preview interaction [$F(2,24) = 6.6$, $P < 0.005$]. Simple effects indicated that preview decreased sequence execution time in normals [$F(1,24) = 13$, $P < 0.001$] and patients with temporal lesions [$F(1,24) = 5.9$, $P < 0 .02$] but not in patients with frontal lesions [$F(1,24) = 1.72$, n.s.]. Figure 2 suggests that the absence of preview effect in patients with a frontal lobe lesion may be due to the facilitation of the fifth response in this group.

Inspection of the individual subject data revealed that three patients with frontal lesions (Patients 1, 6 and 7 in Fig. 1) did benefit from stimulus preview as observed by the reduction of inter-response interval. Patients 1 and 6 had lesions more anterior of either the left (Patient 1) or right (Patient 6) dorsolateral and medial cortex, sparing the supplementary motor area, while Patient 7 had a larger right lesion of the dorsolateral and medial cortex, that included the supplementary motor area. However, Patients 4, 8 and 9 had similar lesions that spared the supplementary motor area but failed to benefit from stimulus preview. Individual differences were also observed on other measures; Patients 1 and 3 were faster than others in sequence initiation time and in average response time in the no-preview condition. Patients who performed better than the average of the frontal group on the various measures could not be distinguished from others in terms of duration of epilepsy before surgery, nor on the type of anticonvulsant medication.

We found no laterality effects on response time nor on the magnitude of inter-response interference. Our small sample size (two left lesions, seven right lesions), however, precludes any firm conclusions about this absence of laterality effect.

Discussion

The results obtained in the present task indicate that preview produces very different effects on patients with a frontal lobe lesion compared with other groups. With advance knowledge of the stimuli in a choice sequence, patients with frontal lesions did not show the normal reduction in inter-response interval and showed an exacerbated slowing of sequence initiation time. The former result suggests a problem in inter-response interference, while the latter suggests a sequence programming problem.

The main result of this study is that while preview reduced the inter-response interval in normal subjects and patients with temporal lesions, no such effect was observed in patients with frontal lesions. Preview of even a single stimulus reduced inter-response intervals in normals (Pashler, 1994). Patients with frontal lesions appear not to be able to benefit from this advance information, making each choice as if stimuli had been presented one at a time. This may have occurred because the mechanisms using this information are deficient or because a processing limit external to these mechanisms prevents preview from having a facilitative effect. Whatever the mechanism, the absence of facilitative effect of preview in patients with frontal lesions is compatible with an increased inertia of responses affecting the transitions between successive responses as suggested by Luria (1966). This inertia may not be completely independent of a sequence programming difficulty, but it is clearly present.

Other investigators have examined the effects of advance information in patients with frontal lesions. For example, Alivisatos and Milner (1989) reported that in a spatial task, patients with frontal lesions did not benefit to the same extent as patients with temporal lesions and normal subjects, from a directional cue presented 1500 ms before the test stimulus onset. Although this task is clearly different from the present one, both involve speeded processing of a cue to direct behaviour.

The absence of preview effect on inter-response interval points to a temporal limit in the sequencing ability of patients with frontal lesions. This suggestion agrees with the observations of Jason (1986) with sequences of manual gestures. Jason found that patients with frontal lesions were impaired when the interval between responses was significantly decreased. Studies in normal subjects have shown that decreasing the interval between two adjacent choices decreased the speed of the second response due to the sequential interference between responses (Rabitt, 1969, 1980; Krueger and Shapiro, 1981; Wilkinson, 1990). Recent results from our laboratory suggest that patients with frontal lesions show an increased sensitivity to inter-response delay in rapid choices (Chouinard *et al.*, 1995), bringing further support to the notion that patients with frontal lesions show increased response inertia.

Luria's concept of response inertia was proposed to account for errors in motor sequences. However, response inertia or increased interference could be a common denominator of a variety of sequencing deficits in patients with frontal lesions. Tasks which involve adjacent responses may induce proactive interference between responses which slows down performance and/or increases the probability of errors. We have previously found increased sequential interference in rapid visual streams in patients with frontal lobe excisions (Richer and Lepage, 1996). It would be interesting to test whether complex sequential tasks which pose problems to patients with frontal lesions such as the execution of multiple commands (Samuels and Benson, 1979) and multistep problems (Shallice, 1982) also induce increased inter-response interference in these patients.

Two patients with more anterior frontal lesions and a third patient with a more posterior frontal lesion did benefit from stimulus preview. However, patients with anterior frontal lesions similar to the first two patients (Patients 4, 8 and 9), were unable to benefit from stimulus preview which precludes any conclusions about the type of lesion that specifically interferes with the preview effect.

Patients with frontal lesions showed a reduction in inter-response interval before the last response in the preview condition. This effect could simply be an artifact produced by the length of the sequence or other parameters of the task used here. Another possibility resides in the fact that the last response is the only one where there can be no overlapping preparatory processing since it is not followed by a response. This situation may produce a decreased interference before the last response which accelerates the performance of patients with frontal lesions. It is also possible that decisional mechanisms increase in efficiency as the sequence comes to an end. These possibilities will have to be examined in future studies.

Patients with frontal lesions also showed problems in the initiation of the response sequence in our task. Although every group showed a marked slowing of sequence initiation time in the preview condition, the slowing found in patients with frontal lesions was much greater than that observed in normals and patients with temporal lesions. This slowing of sequence initiation in patients with frontal lesions may be attributed to inefficient programming operations as suggested by studies with normal subjects (Sternberg *et al.*, 1978; Semjen and Gottsdanker, 1992). This result is compatible with previous observations reporting difficulties in patients with frontal damage in the initiation of a sequence of actions (Luria, 1966). Recently, Viallet *et al.* (1995) found that patients with frontal lesions were slower than normal subjects in initiating a sequence of two actions; releasing a metal platform then pointing to a visual target. Similarly, Halsband *et al.* (1993) reported increased sequence initiation time in two patients with a unilateral lesion to the supplementary motor area in a sequential digit task under delayed conditions. Compared with other tasks, however, timed response sequences have the advantages of being quite simple, as exemplified by the low error levels found in all groups, and of allowing the quantification of preparatory and interference processes.

The results of the no-preview condition indicate that patients with frontal lesions are slower in the execution of choice sequences compared with patients with temporal lesions and normal subjects. The slowing of patients with frontal lesions is attributable to the context of sequential responses, since the same patients can respond as fast as normals and patients with temporal lesions in tasks involving speeded simple responses and two-choice responses (Décary and Richer, 1995). Future studies will be needed to determine whether this general slowing is related to other dimensions of the sequential response deficits such as the inter-response interference or the programming difficulty.

In conclusion, the performance of patients with frontal lesions in sequential choices with and without preview indicates the presence of an exacerbated inter-response interference as well as difficulties in sequence initiation and general slowing. Further research will have to examine the relationships between these components of the frontal sequencing deficit.

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