Exp Brain Res (2006) 175:667–675
DOI 10.1007/s00221-006-0584-6

RESEARCH ARTICLE

Learning hierarchically structured action sequences is unaffected by prefrontal-cortex lesion

Iring Koch · Carlo Reverberi · Raffaella I. Rumiati

Received: 15 February 2006 / Accepted: 1 June 2006 / Published online: 12 July 2006

Abstract This study tested the impact of prefrontal-cortex lesion on learning hierarchically structured action sequences. Using a visual-manual serial reaction time task, we had subjects first perform five blocks of trials with a hierarchically structured 14-element action sequence and then tested for sequence-specific learning by introducing a pseudo-random transfer sequence. Relative to control subjects ($N = 39$), we found that both lateral frontal ($N = 16$) and medial frontal ($N = 18$) patients showed reduced overall performance benefits across the training phase. In contrast, the negative transfer test showed significantly increased reaction times in all patient groups, indicating robust sequence-specific learning. This learning was not significantly different from that of the control group. Taken together, the data suggest that learning hierarchically structured action sequences is unimpaired in patients with prefrontal-cortex lesion.

Keywords Prefrontal cortex · Serial reaction time task · Hierarchies · Action sequences · Procedural learning

I. Koch (✉)
Institute of Psychology, RWTH Aachen University,
Jägerstr. 17-19, 52066 Aachen, Germany
e-mail: koch@psych.rwth-aachen.de

I. Koch
Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

C. Reverberi · R. I. Rumiati
Programme in Neuroscience,
Scuola Internazionale Superiore di Studi Avanzati,
Trieste, Italy

C. Reverberi
Università Milano-Bicocca, Milan, Italy

R. I. Rumiati
Institute of Medicine, Research Center Jülich,
Jülich, Germany

Introduction

Complex actions are composed of many subparts. For instance, to prepare a cup of tea, some actions typically belong to each other very closely, forming ordered subsequences (e.g. taking the kettle and filling it with water), whereas other actions are less closely related, such as searching for a tea bag in the drawer. However, together, they combine to form the higher order sequence of preparing a cup of tea. Obviously, the ability to learn such hierarchic sequences and form chunks (cf. Miller 1956) of actions plays an important role in human life.

The present study aimed to investigate learning of hierarchically structured sequences in frontal patients using a serial reaction time (SRT) task. In a typical version of this task, spatial stimuli were sequentially presented on the screen. Subjects were asked to respond to the stimuli as quickly as possible by pressing spatially corresponding keys (cf. Nissen and Bullemer 1987). With this task, sequence learning can be assessed by comparing performance in structured sequences with that in random sequences (see, e.g. Dienes and Berry 1997; Keele et al. 2003, for reviews).

It has been suggested that sequence learning is based on chunking processes (Curran et al. 2001; Kennerley et al. 2004; Koch and Hoffmann 2000b;

Sakai et al. 2003). The chunking account considers sequence learning as the process by which subjects decompose a longer, complex sequence of actions into subparts that can be efficiently stored in memory. This process should be most efficient when the sequence is relatively complex and hierarchically structured. From this theoretical perspective, one could hypothesize that this kind of learning of hierarchically structured action sequences might be impaired in patients with prefrontal-cortex lesions, who often experience severe difficulties with planning and scheduling of nested actions (Burgess et al. 2000; Shallice and Burgess 1991).

In the present study, we tested learning of hierarchically structured action sequences by using a sequence of 14 elements that contained structured relations among the elements (such as "reversals" of runs of two, e.g. 1221 or 3443). The systematicity of spatial relations can be manipulated while keeping the statistical structure (i.e. frequency information) constant (cf. Hoffmann and Koch 1998; Koch and Hoffmann 2000a). Such "relational" structures should help to form a hierarchical plan of the entire sequence (Restle 1970). This method has already been successfully applied to sequence learning in the SRT task with healthy young adults (Koch and Hoffmann 2000a, b). The important point in using a sequence that is structured by the systematicity of relations in the present study is that this type of sequence might be especially suitable to tap planning deficits expected in prefrontal patients.

There are already several studies on the role of prefrontal-cortex lesion in sequence learning. However, these studies have provided partially conflicting evidence. On the one hand, Gomez-Beldarrain et al. (1999, 2002) have shown that patients with lesions of the prefrontal cortex were impaired on a SRT task, and this impairment did not differ between left and right lateral patients. This role of prefrontal cortex in sequence learning is also supported by studies using transcranial magnetic stimulation (TMS) over the dorsolateral prefrontal cortex (DLPFC, see Pascual-Leone et al. 1996).

On the other hand, some functional imaging studies have called for a critical role of the *right* prefrontal cortex in sequence learning (Doyon et al. 1996; Hazeltine et al. 1997; Honda et al. 1998; Jenkins et al. 1994). However, a recent fMRI study by Bischoff-Grethe et al. (2004) found both learning-related signal increases in bilateral medial and middle frontal gyri and in the *left* motor and premotor cortex. Finally, at variance with the findings of learning impairments in frontal patients, Doyon et al. (1997) reported that nine patients with lesions of the frontal lobes were not significantly impaired in sequence learning.

Taken together, the existing data on the role of prefrontal-cortex lesion in sequence learning appear to be ambiguous. It should be noted though that there is evidence suggesting that the role of prefrontal cortex in sequence learning may strongly depend on the nature of learning (i.e. implicit vs. explicit) and on the type of sequences. For example, Robertson et al. (2001) found that TMS applied over DLPFC interfered with implicit sequence learning only when learning was related to spatial cues and not when it was related to non-spatial colour cues. Also, the way the sequences are structured may also strongly influence the degree of learning impairment due to prefrontal-cortex lesion. In fact, all the above-mentioned studies were conducted to investigate implicit sequence learning using sequences that were not hierarchically structured.

The goal of the present study was to examine the role of prefrontal cortex in explicit learning of hierarchically structured action sequences to relate a learning impairment, if observed, to the deficit of higher order planning frequently observed in frontal patients (Burgess 2000, for a review). More specifically, we tested 34 frontal patients and 39 control subjects to pursue two aims.

The first aim concerned the possible differential contribution of the left and right prefrontal cortex to sequence learning in the SRT task. To this end, we compared performance of patients with unilateral left or right prefrontal-cortex lesion. Based on earlier studies it could be expected that right lateral patients perform worse than left lateral patients.

Second, we explored the possibly differential roles of lesions of lateral and medial prefrontal cortex in sequence learning. A role of the medial frontal cortex in sequence learning has been implicated by imaging studies (e.g. Bischoff-Grethe et al. 2004; Hazeltine et al. 1997). Also, particularly relevant for the present study, Kennerley et al. (2004) observed that TMS applied over the pre-SMA interfered with initiation of sequence chunks in well-learnt sequences. However, that study did not use highly structured sequences, unlike the present study, and the interference was apparent only when sequence performance was memory-guided. In contrast, the present study used visual guidance for each movement, so that it is only the learning-based anticipation of the next stimulus or response (cf. Koch and Hoffmann 2000b) that is guided by memory processes.

We assessed two aspects of learning. First, we measured the performance change as a function of practice with the task in order to obtain a general measure of procedural learning, comprising adaptation to the experimental setting, learning of the S-R assignment,

as well as the behavioural expression of learning of the hierarchic action sequence itself. Second, we assessed sequence-specific learning in isolation by using a negative transfer test. To this end, we compared performance in the structured sequence with that in a pseudo-random (random, hereafter) sequence (see, e.g. Dienes and Berry 1997, for a review). A random sequence violates sequence-specific anticipations, resulting in a disruption of performance. We tested whether the extent of this performance disruption was reduced in any or all prefrontal patient subgroups relative to controls.

Methods

Participants

The study has been approved by SISSA ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Thirty-four patients with a single focal brain lesion as determined by a CT or an MRI scan were recruited from the neurological and neurosurgical wards of Ospedale Civile in Udine (Italy). Patients with a clinical history of psychiatric disorders, substance abuse or previous neurological disease, neuroradiological evidence of diffuse brain damage, and age lower than 18 or higher than 70 were not included in the study. All patients gave their informed consent to participate in the study. The aetiology of the lesions was mixed (stroke and neoplasm). To classify the lesion location of each patient (see Fig. 1), a senior neuroradiologist blind to the experimental results was provided with the template of the study by Stuss et al. (1998). We used two different, partially overlapping lesion classifications (see Table 1). In the first classification, patients were assigned either to the lateral frontal ($N = 16$, corresponding to right and left dorsolateral groups in the Stuss et al.'s paper) or to the medial frontal group ($N = 18$, corresponding to inferior and superior medial groups). In a second classification, we distinguished frontal patients in unilateral right and unilateral left. For the second classification, we considered only patients with damage limited to one hemisphere. To this end, we excluded those patients with a bilateral medial lesion ($N = 8$). The onset of illness ranged between 7 days and 4.26 years (for the patients with neoplasm the onset refers to the day of surgery). This did not differ significantly between the lesion subgroups (medial vs. lateral: Mann–Whitney, $z = 0.274$, $P = 0.799$ two-tailed; unilateral left vs. unilateral right: Mann–Whitney, $z = 0.180$, $P = 0.866$). We also tested 39 control subjects matched for age and education. They were recruited from the slipped disc patients at the same hospital and from patients' relatives (see Table 2).

Task and apparatus

The stimuli were circles presented sequentially in black on white at one of four horizontally aligned locations on the screen of a 15-in. LCD monitor. The locations were marked by horizontal lines throughout the experiment. Four response keys on an E-Prime response box were assigned in a spatially compatible manner to the four stimulus locations. Subjects either used the index, middle, ring, and little fingers of the right or left hand.

Procedure

Participants were asked to respond to the stimuli as quickly and accurately as possible. Participants were then asked to put their fingers of either the left or the right hand on the appropriate response keys. The experiment consisted of seven blocks of 84 trials each. The sequence was constant for a given participants, but for more generality we used two different sequences (see Sect. "Design"), counterbalanced across subjects in each group. However, in block 6, a (pseudo-) random sequence was presented. Each stimulus remained on the screen until a response was made. The response–stimulus interval (RSI) was set to 500 ms. If participants pressed the wrong key, the word *error* appeared on the centre of the screen during the RSI. The transitions between each block were not visible to participants. The experiment took about 15 min.

Design

The experiment tested whether different groups of patients with prefrontal lesion display an impairment of sequence learning relative to age-matched healthy control subjects. Sequence learning was assessed by comparing reaction times (RTs) in sequenced blocks 1–5 and 7 with RTs in block 6, in which the sequence was random. The structured sequence of 14 locations was cycled six times in blocks 1–5 and 7, resulting in 84 trials per block. Two sequences were used, counterbalanced across subjects: 1,2,2,1,3,4,4,3,1,2,2,3,3,4 and 3,4,4,3,1,2,2,1,4,3,3,2,2,1. Both sequences were highly structured by relational patterns, such as simple transpositions (e.g. 1,2) and (higher-order) inversions (e.g. [1,2][2,1]). The random sequence was devised to have, across the entire block, the same frequency of each of the four stimuli and the same first-order transition

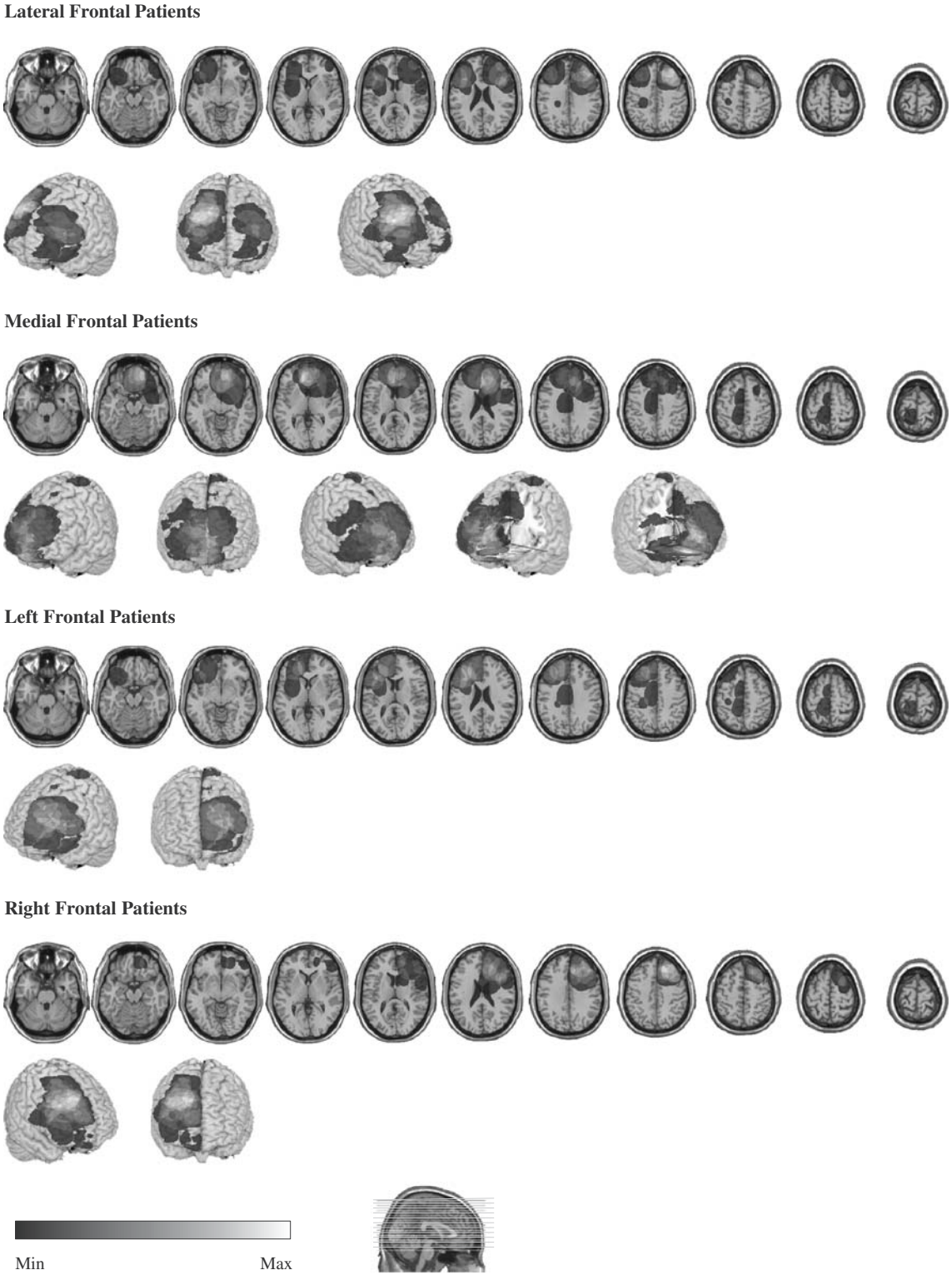

Fig. 1 Overlay lesion plots for the four lesion subgroups. The number of overlapping lesions in each voxel is illustrated on a *grey scale*—the lighter a voxel, the higher the number of patients with damage to that voxel. The *grey scale* is devised so that voxels that were damaged with *maximal* frequency within a patient subgroup are shown in *white*. Thus, *white areas* were damaged in 7 out of 16 lateral frontal patients, in 8 out of 18 medial frontal patients, in 6 out of 12 left frontal patients, and in 8 out of 14 right frontal patients. Talairach *z*-coordinates (adapted from Talairach and Tournoux 1988) of each transverse in all plots section are 45, 55, 65, 75, 85, 95, 105, 115, 125, 135, 145 (see schema on the median sagittal slice, *bottom row*)

Table 1 Patients' aetiology (a) according to the medial vs. lateral classification (left columns) and (b) according to the side of lesion (left vs. right) for unilateral lesion patients (right columns)

	Medial	Lateral	Side of lesion	
			Left	Right
Meningioma	11	9	7	6
Glioma	4	5	3	5
Metastases	1	–	–	1
Lymphoma	–	1	–	1
Stroke	2	1	2	1
N	18	16	12	14

Note that patients classified in (a) as medial frontal could be reclassified in (b) as left or right lateral provided that the lesion was not bilateral. In the latter classification, eight patients with a (medial) bilateral lesion were excluded

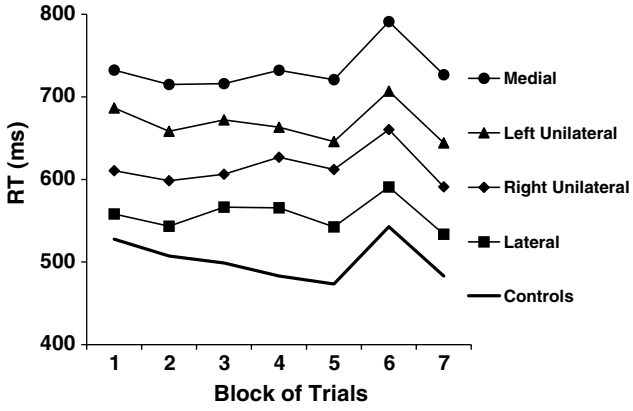

Fig. 2 RTs as a function of block of trials and group. The sequence in block 6 was pseudo-random

probabilities as the structured sequences, so that the difference between the structured sequence and the random sequence refers to sequential transitions beyond the level of stimulus pairs (cf. Hoffmann and Koch 1998; Reed and Johnson 1994).

The dependent variables were, first, the general practice benefit, measured as performance improvement over blocks 1–5, and second, the sequence-specific learning score, which we determined as the difference between the RT of the random block and the average of RTs in blocks 5 and 7. Block 7 was included in the calculation of the learning score to control for unspecific practice or fatigue effects. The effects on the dependent variables were evaluated covarying for age and education.

Results

For RT analysis, we excluded errors, the trials following an error, the first 12 trials in the first block, and RTs above 2,500 ms (outliers: 0.6% for controls and 1.5% for patients). We then determined the median RT for each subject as a function of block of trials. Figure 2 shows RT as a function of group. To examine general practice benefits, we analysed performance in the training phase by running a 2 (group: patients vs. control) × 5 (blocks 1–5) ANCOVA with age and education as covariates. Following the anatomical–functional questions specified in the Introduction we report several separate contrasts.

First, when comparing performance of lateral frontal patients and controls, we obtained significant main effects for the covariate of age [$F(1, 51) = 8.446$, $P < 0.01$] and of block [$F(4, 204) = 6.215$, $P < 0.001$], but not for education, $F < 1$. These main effects indicate that RT level was higher with increasing age, and that RT level decreased with practice. We also found a significant effect of group [$F(1, 51) = 4.301$, $P < 0.05$], indicating that RTs of patients were higher than those of controls (554 ms vs. 498 ms). Importantly, this analysis also yielded a significant interaction between block and group [$F(4, 204) = 4.393$, $P < 0.01$], showing that the decrease of RTs as a function of practice was pronounced in controls but basically absent for the patient group. When tested separately, the general practice

Table 2 Demographic variables of the control group and prefrontal lesion patients (classification like in Table 1)

	Control	Medial	Lateral	Side of lesion	
				Left	Right
N	39	18	16	12	14
Age [mean (SD)]	43 (10)	55 (10)	44 (15)	49 (15)	48 (9)
Education [mean (SD)]	10.7 (3.3)	9.6 (3.6)	10.9 (3.7)	10.8 (2.6)	9.5 (3.4)
Female	19	9	8	7	7
Male	20	9	8	5	7
Days since lesion [median (range)]	–	194 (7–1,555)	140 (8–1,356)	189 (8–1,507)	62 (7–1,356)
Lesion size [median (cc)]		35	26	32	24

For age and education the mean and the (SD) is given in years; for the time of testing since onset, the mean and the (range) are given in days

benefit was significant for controls [i.e. RT decreased from 527 to 473 ms, $F(4, 152) = 17.734$, $P < 0.001$] but not for the patients [i.e. RT decreased non-significantly from 558 to 543 ms, $F(4, 132) = 0.799$, $P > 0.1$]. This data pattern suggests that there is a relative impairment in general aspects of performance in lateral frontal patients.

Second, when comparing performance of medial frontal patients and controls, the analysis yielded significant main effects for the age covariate [$F(1, 53) = 11.598$, $P < 0.001$], group [$F(1, 53) = 9.354$, $P < 0.01$], and block [$F(4, 212) = 3.344$, $P < 0.01$]. Again, the education covariate did not affect RT significantly ($F < 1$). These main effects indicate that the medial frontal patients were slower than controls, and that RT decreased with practice. This practice benefit was numerically clearly weaker in the medial frontal patients than in controls (12 ms benefit vs. 54 ms benefit), but the interaction of group and block was not yet significant [$F(4, 212) = 2.345$, $P = 0.056$]. When tested separately, the general practice benefit was non-significant for the medial frontal patients (i.e. RT decreased from 732 to 720 ms, $F < 1$).

Third, when comparing the performance of lateral and medial frontal patients, the age covariate was significant [$F(1, 30) = 11.073$, $P < 0.01$], but neither the main effects of education ($F < 1$), group [$F(1, 30) = 1.483$, $P > 0.1$], and block ($F < 1$), nor the interaction of group and block were significant ($F < 1$).

Finally, when we compared the two lateral frontal subgroups, the interaction of block and group was clearly non-significant ($F < 1$), indicating that right lateral frontal lesions did not produce more severe performance deficits than left lateral lesions. However, when compared to controls, we found that only right lateral frontal lesions showed clear and significant performance deficits [block × group: $F(4, 196) = 6.919$, $P < 0.01$], whereas left lateral patients did not significantly differ from the controls ($F < 1$). Given the absence of a significant performance difference between right and left lateral patients, the present data are not fully conclusive, even though they appear to suggest that only right lateral frontal patients display a clear performance deficit relative to controls.

In the next step, we analysed sequence-specific learning by computing the average of RT in blocks 5 and 7 and subtracted it from RT in block 6. We report the same pair-wise group contrasts as above. The mean sequence-specific learning scores for each of the frontal patient groups were similar to that of the control group. The scores were similar also among the different patient subgroups (see Table 3). In particular, relative to the control group the learning score was not significantly different for lateral frontal patients [$F(1, 51) = 1.006$, $P > 0.1$] and medial frontal patients ($F < 1$). Moreover, the direct contrast between the two subgroups (i.e. lateral and medial) was not significant [$F(1, 30) = 1.483$, $P > 0.1$]. Finally, the learning score did not differ for right and left lateral frontal lesion ($F < 1$). This pattern of results indicates that there was no significant sequence-specific learning impairment in frontal patients in our study.

Table 3 General practice benefit, and sequence-specific learning scores for RT (SD) of patients (classification as in Table 1) and of control subjects

	Control	Medial	Lateral	Side of lesion	
				Left	Right
General practice benefit	54 (58)	12 (106)	15 (63)	40 (93)	−2 (52)
Learning score	64 (41)	67 (36)	53 (29)	62 (33)	59 (32)

The number of errors averaged across all blocks was low both in the control group (3.65%, SD = 2.93%) and in the frontal patients (4.91%, SD = 4.35%). Moreover, when we compared the error rates in the patient subgroups to that of the control group, the patients did not produce a significantly higher amount of errors across all blocks [lateral frontal: $F < 1$; medial frontal: $F(1, 53) = 1.535$, $P > 0.1$]. Importantly, confirming the pattern of the RT learning score, there were no significant differences between the sequence-specific error score (i.e. calculated like the RT score) of any of the frontal groups and that of the control group (Fs < 1).

In further analyses, we explored whether baseline speed (measured as RT in block 6), the length of the interval between lesion onset and testing session, type of aetiology, and lesion size had an effect on general practice benefits or sequence-specific learning. Each of these factors was introduced as independent variable in a regression analysis with either sequence-specific learning or general practice benefits as dependent variable, and with age and education as covariate. The analysis was computed for each lesion group under examination. We found that neither general practice benefits nor sequence-specific learning were significantly affected by any of the mentioned factors in any of the frontal subgroups (all Ps > 0.1).

To check further whether the lack of significant differences between control and lesion groups on the sequence-specific learning score could have been caused by the differences in the baseline speed across groups, we re-ran the analyses on sequence-specific learning introducing the average RTs in block 6 (baseline speed) as covariate. All the relevant comparisons remained non-significant [lateral vs. controls: $F(1, 50)$

= 2.238, $P > 0.1$; medial vs. controls: $F(1, 52) = 0.118$, $P > 0.1$; left vs. controls: $F(1, 46) = 1.058$, $P > 0.1$; right vs. controls: $F(1, 48) = 2.406$, $P > 0.1$].

In a final step, we looked at the performance of the patient groups and of the control group at a more detailed level to examine the pattern of chunking within the 14-element sequence. To do this, we determined RT as a function of position within the 14-trial sequence for the two groups. We averaged across the two configurations because these were structurally completely comparable. To have enough data for this specific analysis, we also averaged across all patient groups. To make the RT-profiles more comparable to each other, we partialled out differences in baseline speed (see Fig. 3).

As it could be seen in Fig. 3, patients produced a chunking pattern very similar to the controls: specifically, RT in positions 3, 7, 11, and 13 is very short. These positions are characterized by stimulus repetitions, leading to response repetitions. Strong increases in the RT-profile can be interpreted as indicating the beginning of a next chunk (e.g. Kennerley et al. 2004; Koch and Hoffmann 2000a; Sakai et al. 2003). However, because of the obvious similarity of the serial RT-profiles, we refrain from running statistical between-group comparisons. Clearly, the most important conclusion to be drawn is that there were apparently no meaningful differences in the pattern of within-sequence chunking between frontal lesion patients and controls.

Discussion

In the present study, we tested the effect of prefrontal-cortex lesion on learning a hierarchically structured action sequence. We measured learning in two different ways. First, we assessed general performance benefits as a function of practice. Here, we found that patients with a lateral frontal lesion (primarily a right lateral lesion) were overall slower and did not show as much improvement over practice as did the control group. The same pattern, although statistically less reliable, was found for the medial frontal patients. These data appear to suggest that there is an impairment in general aspects of performance in frontal patients. However, our measure of *sequence-specific* learning showed clear learning in all patient subgroups, and this learning did not differ from that found in the control group.

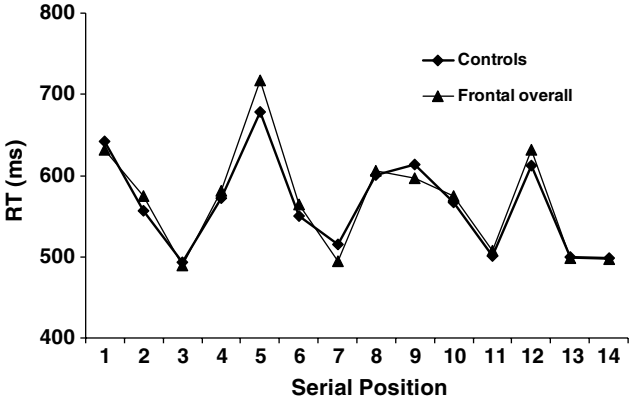

Fig. 3 RTs for the control group and the patient group (collapsed across all patient groups) as a function of serial position in the 14-trial sequence. To make the RT-profiles more comparable to each other, we partialled out differences in baseline speed

One possibility to account for the reduced general practice benefits in frontal patients relative to the control group is to attribute it to a problem in automatizing manual responding to a visuo-spatial stimulus, whereas this practice-related automatization may have led to the benefit of extended practice in the control group. An alternative account, however, is that the reduced practice benefit in frontal-cortex lesion patients reflects a fatigue effect (even though the serial RT task lasted only about 15 min). Most likely, the present data pattern in patients reflects an undifferentiated blend of both factors. However, if we assume that both factors led to generally slower motor responses in patients relative to controls, then this could explain the observed pattern of an impaired practice benefit in patients but fully spared sequence-specific learning effects. The latter effect was measured in our study as a benefit *relative* to random sequences rather than in terms of absolute RTs, so that this difference measure of learning should not be affected by general slowing.

The finding of completely unimpaired sequence-specific learning in frontal patients appears to be at variance with other studies reporting learning deficits in such patients (e.g. Gomez-Beldarrain et al. 1999, 2002). We speculate that this difference between the present study and other studies might be based primarily on differences in the way the sequences were structured. These other studies focussed on implicit learning, so they typically used sequences that were chosen so as to avoid any particular patterns. In contrast, the present study used sequences that were systematically structured by highly orderly spatial patterns (cf. Hoffmann and Koch 1998; Koch and Hoffmann 2000a). This kind of hierarchically structured sequence typically leads to "explicit" learning (see, e.g. Dienes and Berry 1997). We did not test formally whether patients and control subjects were able to completely remember the sequence, but previous work (e.g. Koch and Hoffmann 2000b) showed that such sequences, when tested post-

experimentally with direct memory measures (e.g. free recall), were easily noted by almost all subjects and thus led to a high degree of sequence awareness.

However, because performance can be based on a mixture of implicit and explicit learning (Keele et al. 2003), it is possible that implicit learning contributed to performance more strongly in our present sample of frontal-cortex lesion patients and age-matched controls than it did in previous studies using young and healthy subjects. Therefore, it will be important in future studies on the role of frontal cortex in sequence learning to test more formally for explicit knowledge and to compare learning of relational structures (as in the present study) with learning of structures that were defined based on differences in frequency information relative to random transfer sequences (Koch and Hoffmann 2000a, b). Also, we are cautious in attributing the present finding of spared sequence-specific learning *uniquely* to frontal-cortex lesion because we do not have an appropriate lesion control group. At this point in time, we can thus conclude that the present finding of unimpaired sequence-specific explicit learning of hierarchic action sequences does not necessarily contradict reports of impaired *implicit* learning in frontal patients (e.g. Gomez-Beldarrain et al. 2002).

The finding of unimpaired sequence-specific learning in frontal patients was not anticipated when we devised the present task. In fact, we argued in the introduction that using long but highly structured action sequences might be a good tool to investigate planning deficits often observed in frontal patients (e.g. the "strategy application disorder," cf. Burgess et al. 2000; Shallice and Burgess 1991). It might have been that the complexity of the present task was still too low to reveal specific impairments in frontal patients. Also, a relevant aspect of the present task was that sequential action planning was not done off-line and memory-guided but rather on-line, with the current stimulus as cue to retrieve the chunks. It might have been that we would have found a clear sequence-specific impairment in frontal patients if we had asked them to perform the sequence completely from memory, without the aid of presenting the stimuli as visual action cue (cf. Kennerley et al. 2004).

In summary, we found that frontal-cortex lesion patients did not have difficulties in learning of a relatively long sequence of 14 elements when this sequence was hierarchically structured, stimulus-guided, and easy to chunk. Thus, it appears that frontal patients show unimpaired sequence performance as long as they have clearly structured action sequences that follow simple rules. We believe that this finding can be useful for designing training tasks in cognitive rehabilitation of frontal patients.

References

Bischoff-Grethe A, Goedert KM, Willingham DT, Grafton ST (2004) Neural substrates of response-based sequence learning using fMRI. J Cogn Neurosci 16(1):127–138

Burgess PW (2000) Strategy application disorder: the role of the frontal lobes in human multitasking. Psychol Res 63(3–4):279–288

Burgess PW, Veitch E, de Lacy Costello A, Shallice T (2000) The cognitive and neuroanatomical correlates of multitasking. Neuropsychologia 38(6):848–863

Curran T, Smith MD, DiFranco JM, Daggy AT (2001) Structural influences on implicit and explicit sequence learning. In: Medin DL (ed) The psychology of learning and motivation, vol. 40. Academic, San Diego, pp 147–182

Dienes Z, Berry D (1997) Implicit learning: below the subjective threshold. Psychon Bull Rev 4(1):3–23

Doyon J, Owen AM, Petrides M, Sziklas V, Evans AC (1996) Functional anatomy of visuomotor skill learning in human subjects examined with positron emission tomography. Eur J Neurosci 8(4):637–648

Doyon J, Gaudreau D, Laforce R Jr, Castonguay M, Bedard PJ, Bedard F, et al (1997) Role of the striatum, cerebellum, and frontal lobes in the learning of a visuomotor sequence. Brain Cogn 34(2):218–245

Gomez-Beldarrain M, Grafman J, Pascual-Leone A, Garcia-Monco JC (1999) Procedural learning is impaired in patients with prefrontal lesions. Neurology 52(9):1853–1860

Gomez-Beldarrain M, Grafman J, Ruiz de Velasco I, Pascual-Leone A, Garcia-Monco C (2002) Prefrontal lesions impair the implicit and explicit learning of sequences on visuomotor tasks. Exp Brain Res 142(4):529–538

Hazeltine E, Grafton ST, Ivry R (1997) Attention and stimulus characteristics determine the locus of motor-sequence encoding. A pet study. Brain 120(Pt 1):123–140

Hoffmann J, Koch I (1998) Implicit learning of loosely defined structures. In: Stadler MA, Frensch PA (eds) Handbook of implicit learning. Sage Publications Inc., Thousand Oaks, pp 161–199

Honda M, Deiber MP, Ibanez V, Pascual-Leone A, Zhuang P, Hallett M (1998) Dynamic cortical involvement in implicit and explicit motor sequence learning. A pet study. Brain 121(Pt 11):2159–2173

Jenkins IH, Brooks DJ, Nixon PD, Frackowiak RS, Passingham RE (1994) Motor sequence learning: a study with positron emission tomography. J Neurosci 14(6):3775–3790

Keele SW, Ivry R, Mayr U, Hazeltine E, Heuer H (2003) The cognitive and neural architecture of sequence representation. Psychol Rev 110(2):316–339

Kennerley SW, Sakai K, Rushworth MF (2004) Organization of action sequences and the role of the pre-sma. J Neurophysiol 91(2):978–993

Koch I, Hoffmann J (2000a) Patterns, chunks, and hierarchies in serial reaction-time tasks. Psychol Res 63(1):22–35

Koch I, Hoffmann J (2000b) The role of stimulus-based and response-based spatial information in sequence learning. J Exp Psychol Learn Mem Cogn 26(4):863–882

Miller GA (1956) The magical number seven, plus or minus two: some limits on our capacity for processing information. Psychol Rev 63:81–97

Nissen MJ, Bullemer P (1987) Attentional requirements of learning: evidence from performance measures. Cogn Psychol 19(1):1–32

Pascual-Leone A, Wassermann EM, Grafman J, Hallett M (1996) The role of the dorsolateral prefrontal cortex in implicit procedural learning. Exp Brain Res 107(3):479–485

Reed J, Johnson P (1994) Assessing implicit learning with indirect tests: determining what is learned about sequence structure. J Exp Psychol Learn Mem Cogn 20:585–594

Restle F (1970) Theory of serial pattern learning: structural trees. Psychol Rev 77(6):481–495

Robertson EM, Tormos JM, Maeda F, Pascual-Leone A (2001) The role of the dorsolateral prefrontal cortex during sequence learning is specific for spatial information. Cereb Cortex 11(7):628–635

Sakai K, Kitaguchi K, Hikosaka O (2003) Chunking during human visuomotor sequence learning. Exp Brain Res 152(2):229–242

Shallice T, Burgess PW (1991) Deficits in strategy application following frontal lobe damage in man. Brain 114(Pt 2):727–741

Stuss DT, Alexander MP, Hamer L, Palumbo C, Dempster R, Binns M, et al (1998) The effects of focal anterior and posterior brain lesions on verbal fluency. J Int Neuropsychol Soc 4(3):265–278

Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. Thieme, Stuttgart