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Dissociable roles of prefrontal subregions in self-ordered working memory performance

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ABSTRACT

The anatomical segregation of executive control processes within the prefrontal cortex remains poorly defined. The present study focused on strategy implementation on two working memory tasks: the CANTAB spatial working memory task and a visuospatial sequence generation task. These measures were administered to a group of frontal lesion patients and a comparison group of healthy subjects. Frontal patients with damage to the right inferior frontal gyrus were impaired on the CANTAB spatial working memory task, compared with healthy controls and patients without damage to this region. This deficit was most strongly related to the pars opercularis subregion (BA44) and was accompanied by poor strategy usage. On the sequence generation task, frontal lesion patients were impaired on a strategy-training phase when the working memory demands of the task were reduced, but had relatively intact performance on other phases of the task. Performance on the training phase was correlated with the amount of damage to the dorsolateral prefrontal cortex (DLPFC: BA46/9). These results support theoretical notions of prefrontal cortical function that emphasise its contribution to executive processes such as mnemonic strategies and monitoring over its role as a short-term memory store. Moreover, we provide evidence for the first time that such functions are dependent on dissociable brain regions within the prefrontal cortex.

1. Introduction

Working memory function is inextricably linked with the integrity of the prefrontal cortex (PFC), although the role of this region appears to be more sophisticated than the short-term maintenance of information, which may be handled by posterior cortical mechanisms (D'Esposito, Cooney, Gazzaley, Gibbs, & Postle, 2006; D'Esposito & Postle, 1999; Postle, Berger, & D'Esposito, 1999; Postle et al., 2006; Warrington & Shallice, 1969). The 'central executive', proposed by Baddeley and Hitch (1974), which controls ('monitors') and manipulates information held online, has been associated with the dorsolateral prefrontal cortex (DLPFC: D'Esposito, Postle, & Rypma, 2000; Petrides, 1996; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000). Recent functional magnetic resonance imaging (fMRI) evidence has suggested, of these operations, that the DLPFC is particularly critical for monitoring (Champod & Petrides, 2007), in line with studies using experimental animals. For example, Petrides (2000) showed that rhesus monkeys with lesions to the DLPFC were impaired when the number of items to be monitored in working memory was increased, contrasting with effects of inferotemporal cortical lesions which impaired delay period maintenance. Imaging data have also indicated that DLPFC may also be recruited during *easier* task conditions if strategy implementation is required. In a working memory task where strategic encoding was encouraged to improve performance (as a result of the structure of the information to be encoded), bilateral DLPFC activity was greater compared to a more difficult control task where information was encoded individually (Bor, Duncan, Wiseman, & Owen, 2003).

The present study aimed to extend these findings using neuropsychological evidence in patients with frontal lesions, to establish the causal role of the lateral PFC in mnemonic strategy use. We have studied two working memory tasks with strategic components. In the CANTAB self-ordered spatial working memory task (SWM: Owen, Downes, Sahakian, Polkey, & Robbins, 1990), subjects must find tokens hidden inside an array of boxes on a computer screen. Tokens only appear once at any given box location, and as such, the subject must avoid returning to boxes that have already yielded tokens. A common strategy to reduce the number

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of errors on this task is to search through the boxes in a systematic manner, starting each search from the same location and successively omitting locations where tokens have been found. Impaired implementation of this strategy has been selectively associated with frontal lobe damage, whereas elevated search errors have been reported following damage to frontal and temporal cortex (Owen, Morris, Sahakian, Polkey, & Robbins, 1996; Robbins, 1996). SWM impairments are predominantly associated with damage to the dorsal and lateral aspects of the PFC (Bechara, Damasio, Tranel, & Anderson, 1998; Manes et al., 2002), and may be right-lateralised (Clark et al., 2007; Miotto, Bullock, Polkey, & Morris, 1996; van Asselen et al., 2006). We recently reported a more focal association between SWM errors and the volume of damage to the right inferior frontal gyrus (RIFG: Clark et al., 2007).

Further evidence suggesting the RIFG contributes to spatial working memory performance has come from the study of the neglect syndrome. Lesions of the RIFG, particularly those affecting the pars opercularis (RIFGpo/BA44: Husain & Kennard, 1996; Vallar & Perani, 1986), can cause neglect syndrome, and impaired spatial working memory performance in patients with neglect has been demonstrated in several studies and on a variety of paradigms (Husain et al., 2001; Kennard et al., 2005; Malhotra et al., 2005; Mannan et al., 2005; Wojciulik, Husain, Clarke, & Driver, 2001), even when stimuli are presented at the midline (Malhotra et al., 2005). These findings are consistent with the idea that neglect reflects a general deficit of encoding or maintaining information about spatial locations. However, the deficits observed in neglect patients following frontal lesions may have a distinct cause from those following parietal lesions, and may result from perseveration or other failures of behavioural control (Kennard et al., 2005).

We also investigated performance of frontal lesion patients on a second strategy task ('Toucher': Chamberlain, Blackwell, Fineberg, Robbins, & Sahakian, 2006; Iddon, McKenna, Sahakian, & Robbins, 1998; Owen et al., 1995), which required the subject to generate 24 different sequences of button presses to four different locations. The task challenges working memory, to remember which sequences have been performed already, as well as the ability to generate new sequences. Working memory monitoring and sequence generation share similarities with the requirements of random number generation, and are therefore likely to require the central executive (Baddeley, Emslie, Kolodny, & Duncan, 1998). Performance can be improved by using an algorithmic strategy to organise responses and assist with generating new patterns (Iddon, 1997; Iddon et al., 1998). This strategy is taught to the subjects during a phase in which they are constrained to generate just six different sequences from the same starting button ('sub-goal strategy training'). This reduces the domain from which new sequences are generated, thus reducing working memory load, and making the search for new sequences easier. The subject generates 'sub-goals' of six sequences for each of the four starting positions in turn. After training, subjects are re-tested on the free generation phase, where healthy subjects show a benefit from their training. Iddon (1997) found that without this sub-goal strategy training, normal subjects did not derive the strategy spontaneously and performed the task at an equivalent level both times.

Frontal lesion patients were previously shown to have impaired sequence generation prior to training (Owen et al., 1995), and a reduced benefit of strategy training on the re-test phase (Iddon, 1997), which was also recently reported in patients with obsessive-compulsive disorder (OCD: Chamberlain et al., 2006). The earlier studies of Owen et al. and Iddon et al. did not examine task performance in relation to damage *within* the PFC. Following Bor and colleagues, we hypothesised that the DLPFC (Brodmann Areas 9 and 46), bilaterally, would play an important role in the performance of the task by mediating the implementation of an algorithmic strategy. We therefore predicted that DLPFC damage would reduce the improvement in sequence generation following strategy training. However, as a result of the complexity of Toucher, it should be noted that non-linear interactions between sequence size and monitoring demands are possible. Paradoxically, monitoring demands may be greater during the strategy-training phase when the size of the set of items to be monitored is smallest: if the set of items is too large, deliberative monitoring processes may not be used. Hence, we also anticipated the possibility that DLPFC damage might also influence performance on the strategy-training phase.

We tested a similar sample of frontal patients to those described by Clark et al. (2007) and were therefore also able to test an alternative hypothesis: that the self-ordered SWM impairment observed in patients with RIFG lesions generalised to other tasks of strategy use. Some of the data from the SWM task have previously been published (Clark et al., 2007) but are included here to enable a direct comparison with the Toucher task. Following Aron, Robbins, and Poldrack (2004), we also sought to examine RIFG subregions. These authors had suggested the pars opercularis subregion was more important for response inhibition performance on the stop signal task than the pars triangularis.

2. Methods

2.1. Participants

Forty-eight patients with lesions of the frontal lobe were recruited from the Cambridge Cognitive Neuroscience Research Panel at the MRC Cognition and Brain Sciences Unit. Forty control subjects were recruited from the local community. Controls had no history of psychiatric or neurological disease. The National Adult Reading Test (NART: Nelson & Willison, 1991) was administered to all subjects as a measure of (premorbid) intellectual functioning. All subjects provided informed consent in accordance with the Addenbrooke's NHS Trust Local Research Ethics Committee. Both controls and frontal patients were paid for their participation. There were some missing data-points due to time constraints, unavailability of patients for retesting and software failure such that in the frontal group, 34 completed Toucher and 43 completed SWM, and in the control group, 32 completed Toucher and 37 completed SWM. Twenty-nine patients and twenty-nine controls completed both SWM and Toucher. All patients completed at least one test. In several cases, the two tests were performed on different sessions, sometimes several years apart, hence the subjects have different lesion chronicity with respect to the two tests (see Table 1).

2.2. Lesion characteristics

Magnetic resonance imaging (MRI) data were acquired for all patients in a 1.5 T scanner with 3D set acquisition, using an SPGR (spoiled gradient recall) T1-weighted coronal sequence and a T2-weighted axial sequence. Lesions were traced onto each structural scan using MRIcro v1.40 (Rorden & Brett, 2000) to create a 3D lesion volume and normalised to the SPM 96 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK) average T1 structural scan from 152 healthy subjects, using cost function masking (Brett, Leff, Rorden, & Ashburner, 2001) to exclude the lesion from the calculation of normalisation parameters (Fig. 1).

On the basis of previous work with a similar patient group, we were particularly interested by the contribution of the RIFG to spatial working memory performance, so we grouped the subjects as to whether their lesion encroached on the RIFG, as determined by the template, thereby comparing three groups: RIFG lesion patients, non-RIFG lesion patients and controls. Three patients with damage to 1–4 voxels of RIFG were not included in RIFG group—the subject with the smallest amount of RIFG damage had suffered the equivalent of 19 voxels of damage to that region. Two patients had bilateral lesions (i.e. more than 100 voxels damage to each hemisphere of the PFC). One patient was in the RIFG group, the other was in the non-RIFG group. We were therefore not able to contrast unilateral and bilateral patients with separate subgroups.

Regions of interest were defined using the Brodmann Area template that accompanies the MRIcro software (http://www.sph.sc.edu/comd/rorden/mricro.html). Volumes of damage to different ROIs for each subject were calculated by determining the degree of overlap between each ROI and the subject's lesion. We combined the number of voxels of damage to the dorsolateral PFC (DLPFC: BA9 and 46), the inferior frontal gyrus (IFG: BA44, 45), the ventral aspect of the inferior frontal gyrus (VIFG: BA47), the superior frontal cortex (SFC: BA8), the orbitofrontal cortex (OFC: BA11), the rostral prefrontal cortex (RPFC: BA10) and the anterior cingulate cortex (ACC: BA 32, 24, 25) represented the total damage to the prefrontal cortex. As we used a slightly different together with the premotor cortex (BA6), we derived a measure of total damage to the frontal lobes. In order to rule out the possibility that effects of

Table 1
Patient details including age, NART, chronicity (months since trauma), missing data, medication details (carbamaz = carbamazepine) and the number of voxels of damage to the Frontal Lobes and subregions thereof

Patient	Aeitology	Age	NART	Chronicity	Completed SWM	Completed Toucher	Medication	Total frontal	Total PFC	Total DLPFC	Total RIFG	Central	Parietal	Temporal	Basal ganglia/ thalamus
Right inferior frontal gyrus patients															
1	Tumour	69/NT	121	71/NT	1	0	None	6802	6677	1163	1914	2930	0	2293	249
2	Aneurysm	53/58	124	26/84	1	1	Carbamaz	3951	3750	969	1695	664	0	46	0
3	Aneurysm	58/61	111	30/66	1	1	Phenytoin	7859	7746	635	1514	1747	0	149	97
4	Tumour	57/60	116	111/150	1	1	Carbamaz	11976	11975	2638	1439	2914	0	36	87
5	Tumour	55/NT	108	57/NT	1	0	None	11510	9954	3506	1418	1144	0	0	0
6	Infarct	NT/58	118	NT/52	0	1	Aspirin, simvastatin	3492	2743	29	1172	1909	0	784	825
7	Tumour	47/47	106	148/148	1	1	carbamaz, atorvastatin, ezetimibe, atenolol, ramipril, aspirin	1215	938	40	686	2197	0	25	541
8	Infarct	64/NT	119	67/NT	1	0	None	2071	807	153	653	1011	0	697	51
9	Tumour	27/30	113	29/44	1	1	Carbamaz, valproate	5891	3655	1146	540	1101	0	0	0
10	Tumour	47/51	104	46/84	1	1	Phenytoin	4907	4907	1202	429	568	0	0	0
11	Infarct	71/NT	121	42/NT	1	0	Warfarin	595	380	0	357	320	0	28	15
12	Tumour and Haemorrage	48/52	119	10/52	1	1	Carbamaz	9658	5121	1826	352	4283	201	0	62
13	Infarct	NT/69	123	NT/84	0	1	Aspirin, simvastatin, bendroflumethazide, amlodipine, perindopril	315	201	0	201	8	100	0	0
14	Tumour	40/44	111	27/72	1	1	Lamotrgine	8689	4262	1506	192	1819	0	0	0
15	Infarct or Haemorrage	44/49	120	84/144	1	1	Phenytoin, lamotrigine	3618	224	7	165	2432	101	10	0
16 BL	Tumour	67/67	114	180/180	1	1	Atenolol, simvastatin, lisinopril, bendroflumethazide	9736	9736	2916	164	485	0	0	0
17	Tumour	NT/62	126	NT/>26	0	1	Lamotrigine, carbamaz, atenolol	3283	1412	612	137	637	0	0	0
18	Haemorrhage	NT/51	104	NT/>54	0	1	Bisoprolol, lipitor, lisinopril, lansoprazole, sertraline	608	455	1	76	1791	2	13	953
19	Aneurysm	49/53	125	28/84	1	1	Phenytoin	6260	6260	724	19	1920	0	36	247
Non-right inferior frontal gyrus patients															
20 R	Tumour	56/NT	99	56/NT	1	0	None	1694	114	14	4	582	0	0	0
21 R	Tumour	65/65	123	NT/11	1	1	Benzoflurazide, lipitor	2886	1923	373	1	307	0	0	0
22 R	Tumour	69/73	120	240/278	1	1	Phenytoin	3468	452	70	1	620	0	0	0
23 R	Infarct	69/73	114	24/82	1	1	Warfarin	308	0	0	0	81	0	0	0
24 R	Tumour	54/58	111	30/68	1	1	Carbamaz, valproate	376	15	15	0	60	0	0	0
25 BL	Aneurysm	64/68	121	36/88	1	1	None	2329	2329	373	0	113	0	0	0
26 R	Haemorrhage	NT/48	112	NT/30	0	1	Epanutin, lamotrigine, citalopram	664	664	0	0	6	0	0	0
27	Tumour	54/56	123	54/84	1	1	Fluoxetine	65	65	61	0	156	0	0	0

28	Tumour	71/74	123	Jul-40	1	1	None	2270	332	4	0	405	0	0	0
29	Tumour	59/63	109	39/84	1	1	None	1880	961	86	0	368	0	0	0
30	Tumour	58/61	93	58/98	1	1	None	2065	2065	867	0	236	0	0	0
31	Haemorrhage	47/51	112	47/91	1	1	Carbemaz, atenolol, losartan	483	483	0	0	73	0	0	0
32	Infarct	58/62	91	58/106	1	1	Aspirin	820	444	27	0	18	0	0	0
33	Infarct	63/NT	124	63/NT	1	0	Aspirin	1882	1882	48	0	248	0	92	0
34	Tumour	41/43	121	61/92	1	1	Dothiepin	6888	6888	100	0	881	0	0	22
35	Aneurysm	58/62	118	23/60	1	1	None	141	141	62	0	0	0	1	3
36	Infarct	63/65	105	48/48	1	1	Aspirin	6019	5350	1415	0	1789	0	26	21
37	Tumour	51/NT	116	51/90	1	0	Valproate, phenytoin	6936	2188	579	0	3817	1669	0	0
38	Aneurysm	49/52	126	78/106	1	1	None	1321	1321	0	0	547	0	974	0
39	Aneurysm	56/60	111	56/100	1	1	Carbamaz, valproate	6866	2776	542	0	4172	47	0	50
40	Aneurysm and Infarct	42/42	121	96/96	1	1	None	3607	3607	235	0	657	0	1734	273
41	Tumour	41/41	123	NT/>37	1	1	Dexamethasone, carbamaz, ranitidine	4765	3768	663	0	2662	246	114	219
42	Haemorrhage	57/NT	108	56/NT	1	0	None	515	215	0	0	42	0	0	0
43	Tumour	47/NT	121	47/NT	1	0	Carbamaz	3635	3635	1238	0	372	0	0	0
44	Abscess	33/NT	126	33/NT	1	0	Carbamaz	2032	976	70	0	779	2	97	0
45	Aneurysm	65/NT	109	65/NT	1	0	None	1485	1485	4	0	160	0	0	0
46	Tumour	46/NT	125	46/NT	1	0	None	9128	9128	1645	0	1227	0	54	0
47	Tumour	46/NT	109	46/NT	1	0	Phenytoin	1584	742	0	0	672	0	0	0
48	Infarct	73/NT	123	73/NT	1	0	Aspirin	615	615	6	0	277	0	0	0
Mean			115.41					3733	2828	574	274	1067	49	150	77
Standard deviation			8.57					3275	3065	829	515	1142	244	445	199

Patients 1–19 were included in the RIFG group; patients 20–48 were included in the non-RIFG group. The 'Completed SWM' and 'Completed Toucher' columns show whether the subjects completed Choose or WPT. All of the RIFG patients had right-sided lesions except one patient with a bilateral lesion (BL, patient 16). All of the Non-RIFG patients had a left hemisphere lesion except the patients marked with R (=right) or BL (=bilateral) in the patient column.

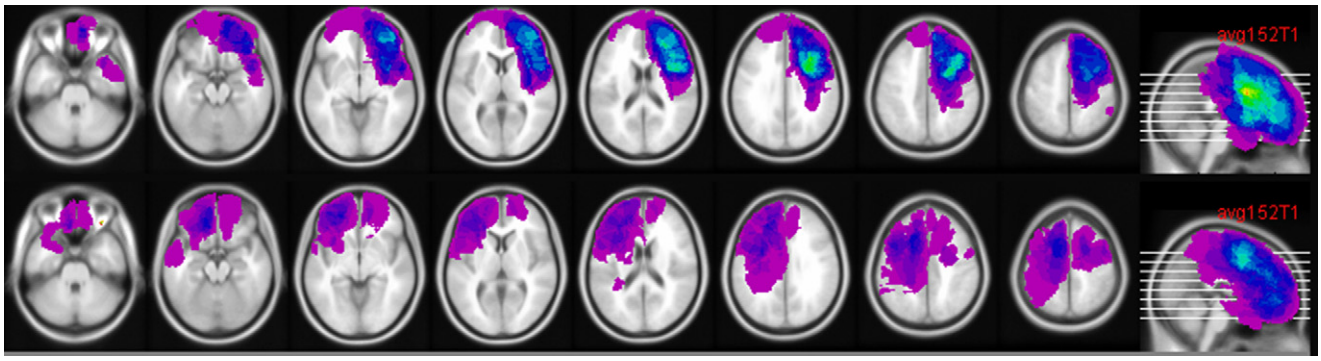

Fig. 1. Lesion location of RIFG lesion patients (top row); lesion location of non-RIFG lesion patients (bottom row). Different colours represent different degrees of lesion overlap, coded via colour spectrum (violet represents the least lesion overlap, i.e. one patient, red/orange represents the most lesion overlap). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

lesions on behaviour were driven by non-prefrontal regions into which the lesion had encroached rather than damage to the prefrontal region of interest itself, we also calculated damage totals for the parietal lobe (BA 5, 7, 39, 40), and the temporal lobe (BA 20–22, 28, 34–38, 41, 42), and a central ROI which also included BA 1–4, 6 and 43. We also estimated subcortical damage affecting the basal ganglia and thalamus using the Automatic Anatomical Labelling template of Tzourio-Mazoyer et al. (2002), as the Brodmann Area template does not define subcortical regions.

2.3. Neuropsychological tests

In many of the patients, the two tasks were given on separate occasions, though if the controls received both tasks, they would have received the tasks on the same occasion. Table 1 shows the chronicity of the lesion for each testing session.

2.3.1. Toucher (Figs. 2, 3, 4a and b)

The subject has to generate permutations of button presses. Four red boxes acting as buttons are organised in a square on a touch screen monitor. It is explained to the subject that the 'unit' of performance is a sequence where each of the four buttons is pressed once. The button briefly turns from red to blue if the button press is part of a legitimate sequence (i.e. the first time a button is pressed during an incomplete sequence). The version of the task used in this study had five phases:

Phase 1: A familiarisation/free performance phase, in which subjects are instructed to perform 24 sequences 'in any way they like'.
Phase 2: Pre-strategy permutation generation phase: the subject is asked to produce 24 different sequences. Subjects are given feedback about the total number of sequences they have performed, and the number of different sequences they have generated (Fig. 2).
Phase 3: Sub-goal strategy training: another permutation phase in which subjects are asked to produce six different sequences all starting from the same button; a sequence can only be initiated by starting from the current start button; the start button is changed after every six sequences, leading to a total of 24 sequences (Fig. 3).
Phase 4: Post-strategy permutation generation phase: procedurally identical to phase 2 (Fig. 2).
Phase 5: Transfer phase: in the final phase, the buttons are replaced with four differently coloured discs (red, blue, yellow, brown): the coloured discs drop down onto the lower part of the screen when pressed, and line up at the bottom of the screen in the sequence in which they have been pressed. Hence 24 different patterns of the discs can be produced (Fig. 4a and b).

Performance is represented by the number of repeated sequences: the number of times any sequence previously performed is repeated by a subject. The strategy score is a metric representing the extent to which the subjects organise the sequences they generate in terms of the box from which the sequence starts. Subjects are constrained to cluster their responses into four groups of 6 during phase 3 (strategy-training phase), but not during the other phases. Previous studies (e.g. Iddon, 1997) have suggested that using such a strategy improves performance on the task. We recorded the number of clusters of 5 or more sequences in a row starting from the same button, so the score is measured from 0 to 4. Only one cluster is allowed per start button.

2.3.2. CANTAB self-ordered spatial working memory (see Owen et al., 1990)

In this task, subjects must search for blue tokens hidden inside an array of boxes, whose number, position and colour remain constant during a given problem. On a given trial, a token can only appear in one box; once a box has yielded a token, the token will not appear there again. During a given problem, one token will appear in each box at some point. Thus, the subject can mentally mark successful locations and avoid returning to them. Returning to the box if it has yielded a token count as an error, which is the dependent variable representing performance on the task. The task is organised into 3, 4, 6 and 8 box problems, and task difficulty increases with

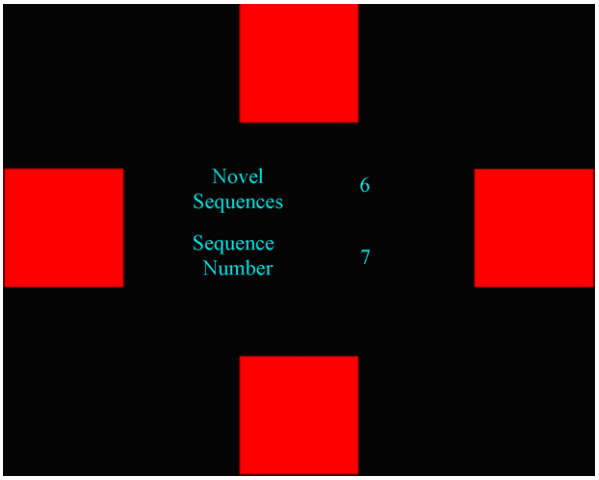

Fig. 2. Screenshot showing the Toucher screen on phases 2 or 4. The buttons turn blue when pressed the first time during an incomplete sequence. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

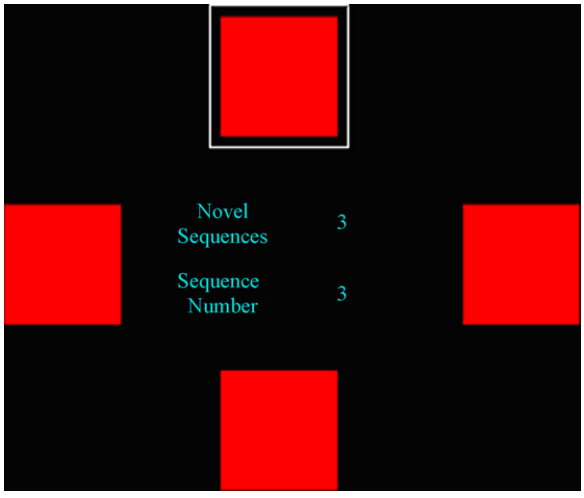

Fig. 3. Screenshot showing the Toucher screen during phase 3. The sequence must be started from the button with the white box around it.

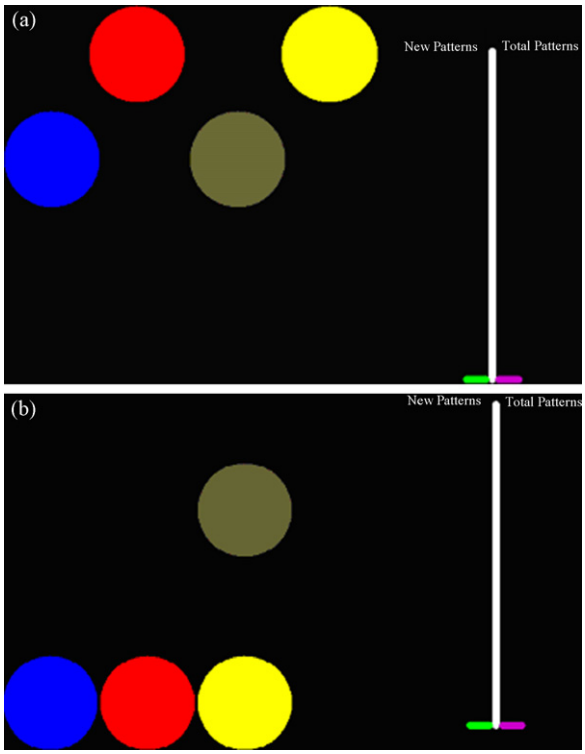

Fig. 4. Screenshots showing the screen during phase 5 of Toucher, both before a sequence has been started (a) and during the sequence (b). The brown disc will move to the right of the yellow disc for 1 s after being pressed, and then the discs will return to their original positions as shown on (a). The score is recorded visually on the bars to the right of the discs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

increasing box number. Between search error data from the 4, 6 and 8 box problems are analysed in a repeated-measures ANOVA. A strategy score is also extracted which represents how systematic the search for tokens is (to what extent searching for new tokens starts from the same box).

2.4. Statistical analysis

As some subjects failed to complete both tasks, one-way Analysis of Variance (ANOVA) for NART IQ and age were conducted separately for each task, ensuring adequate matching across groups. Behavioural performance was analysed using ANOVA with group as a two (controls, patients) or as a three-level between-subjects variable (controls, RIFG, non-RIFG). The Greenhouse-Geisser correction was applied when the homogeneity of variances was violated. An alpha level of 0.05 was used in all planned statistical comparisons.

Toucher performance was compared at two levels (controls and patients) using three separate planned comparisons of the within subject variables obtained on the different phases of the task: number of repeated sequences on phases 2–5 (four levels); number of repeated sequences on phase 2 versus phase 4 (two levels); number of repeated sequences on phase 2 versus phase 5 (two levels).

As Clark et al. (2007) had identified the RIFG as a critical region for SWM performance, we initially confirmed that this finding still held for our data (as our patient group and ROI techniques were slightly different from those used by Clark et al.) by dividing subjects on the basis of whether they had suffered damage to that region. SWM performance was compared at three levels: controls, RIFG ($n = 15$), and non-RIFG patients ($n = 28$). Within subjects variables included between search errors for the SWM task at three levels of difficulty (4, 6 and 8 box problems) and the strategy score.

To examine the effect of lesion size to different brain regions, Pearson correlation co-efficients were calculated for the associations between number of repeated sequences on phases 2–5 (Toucher), total between search errors and strategy score (SWM) and MRI volumes (total lesion size or region of interest damage). We also examined the correlation between task performance and RIFG subregions (pars opercularis (BA44) and pars triangularis (BA45)) via correlational analysis. In addition, on the basis of prior work, we were also interested by the contribution of the Dorsolateral PFC (DLPFC: BA9 and 46). We also investigated the role of this region via examining the correlational analysis.

In order to further delineate the specific contribution of different prefrontal regions to performance of these two tasks we used a partial correlation technique. Subjects with larger lesions are usually expected to perform worse. The null hypothesis was that the two regions contribute equally to each task: if this was the case, then even if the different tasks showed different numerical dependences on different brain regions, partialling out the effect of one brain region should render the effect of the other insignificant. However, if two brain regions had separate contributions to performance, the relationship between performance and damage to a region on which performance of the task depends should remain significant regardless of the amount of damage to the other region. Subgroup splitting would be a less efficient means of making the same inferences—for example, patients with RIFG lesions who had performed Toucher also had a greater volume of DLPFC damage ($t = 2.671$, d.f. = 17.562, $p = 0.016$). We therefore used partial correlations in order to control this possible confound. Because only 29 subjects had completed both tasks, we did not perform a task by region interaction using an analysis of covariance (ANCOVA), as there would have been a large reduction in power to detect such an effect.

Finally, further correlational analysis was performed to investigate the relationship in processing demands between the two tasks. In addition, the role of age and IQ in the performance of the two tasks was assessed.

3. Results

3.1. Toucher

3.1.1. Effect of frontal lesions: error scores

Number of repeats were analysed using a mixed-model ANOVA contrasting group (patients, controls) and phase (phases 2–5, i.e. phases in which subjects were instructed to produce different sequences). Raw scores are displayed in Table 2. Repeated measures ANOVA revealed a phase by group interaction ($F(2.484,158.999) = 3.151$, $p = 0.035$) and an effect of group ($F(1,64) = 4.614$, $p = 0.036$), as well as a powerful effect of phase ($F(2.484, 158.999) = 34.958$, $p < 0.001$). The groups could not be distinguished at phase 1 ('familiarisation/free performance': $t = -0.357$, d.f. = 64, $p = 0.722$). The groups were strikingly different at phase 3 ('sub-goal strategy training': $t = 2.942$, d.f. = 64, $p = 0.005$) however.

We examined our planned contrasts. Phase 2 ('pre-strategy permutation generation') and phase 4 ('post-strategy permutation generation') were entered into a repeated measures ANOVA. There was a significant main effect of phase ($F(1,64) = 4.815$, $p = 0.032$), no effect of group ($F(1,64) = 2.523$, $p = 0.117$) and a marginally significant phase by group interaction ($F(1,64) = 3.552$, $p = 0.064$). Follow up analysis of simple main effects showed that phase 4 ('post-strategy permutation generation': $t = 2.233$, d.f. = 64 $p = 0.029$) was more sensitive to the group difference than phase 2 ('pre-strategy permutation generation': $t = 0.069$, d.f. = 64, $p = 0.945$): this was in line with our *a priori* predictions. Paired *t*-tests showed that controls significantly improved on phase 4 compared to phase 2 ($t = 2.746$, d.f. = 31, $p = 0.010$) whereas patients did not ($t = 0.230$, d.f. = 33, $p = 0.819$).

Similarly, phases 2 and 5 ('transfer') were entered into a repeated measures ANOVA. There were no effects of phase or group (phase: $F(1,64) = 0.423$, $p = 0.518$; group: $F(1,64) = 0.103$, $p = 0.750$), or an interaction between the group and phase ($F(1,64) = 0.068$,

Table 2
Demographic information and Toucher performance of patients and controls

	Patient	Control
N	34	32
Age	56.74 (10.23)	54.50 (11.65)
NART	115.01 (8.77)	116.52 (5.36)
Phase 1 repeats	11.47 (4.34)	11.88 (4.86)
Phase 2 repeats	8.24 (2.90)	8.19 (2.71)
Phase 3 repeats	5.56 (2.88)	3.72 (2.11)
Phase 4 repeats	8.09 (3.65)	6.25 (2.98)
Phase 5 repeats	8.09 (1.48)	7.84 (2.29)

The patient and control groups could not be distinguished by age ($t = 0.830$, d.f. = 64, $p = 0.410$) or NART ($t = -0.851$, d.f. = 55.156, $p = 0.399$). The phases 1–5 repeats measure represent the number of sequences, out of the 24 sequences to be performed on each phase, which had been performed already and hence were errors.

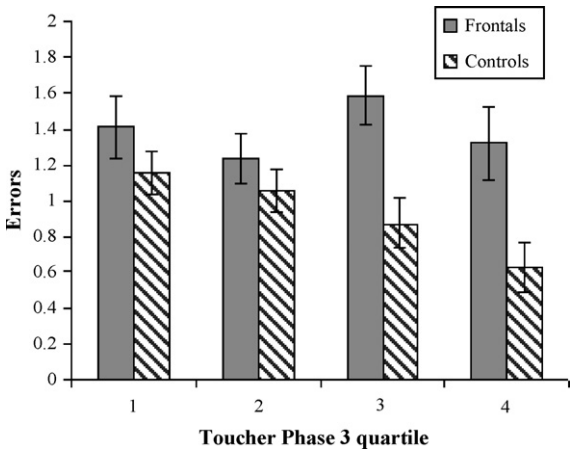

Fig. 5. Toucher phase 3 performance of patients (filled) and controls (diagonal stripes), split by quartile.

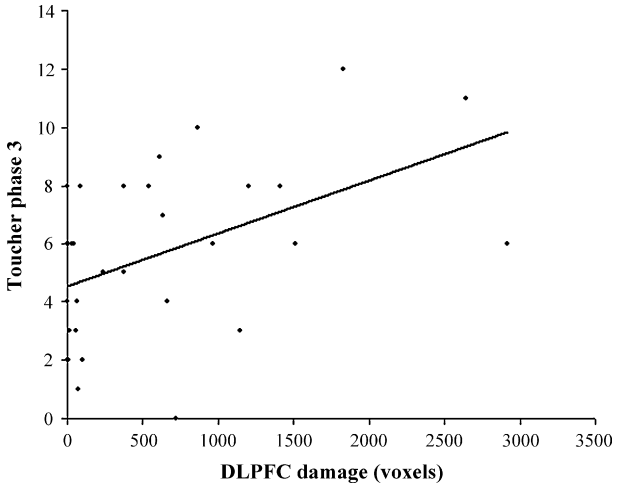

Fig. 6. Graph showing relationship between DLPFC damage and Toucher phase 3 performance in lesion patients ($r = 0.482$, $n = 34$, $p = 0.004$).

$p = 0.795$). This is evidence that neither patients nor controls were able to transfer the beneficial effect of the strategy to perform phase 5. This was also evident in the comparison of strategy scores, in which there were no effects of phase or group (phase: $F(1,64) = 1.165$, $p = 0.284$; group: $F(1,64) = 0.179$, $p = 0.673$), or an interaction between the group and phase ($F(1,64) = 1.773$, $p = 0.188$).

In order to gain further insight into the nature of the deficit during the sub-goal strategy-training phase (phase 3), we separated phase 3 errors accrued from the four starting boxes ('box location'), and analysed this as a repeated-measures factor (see Fig. 5). The effect of group remained similarly significant ($F(1,64) = 8.653$, $p = 0.005$). There was a marginally significant effect of box location ($F(2.89,184.929) = 2.477$, $p = 0.065$), and a group by box location interaction ($F(2.890,184.929) = 2.756$, $p = 0.046$). Paired t-tests showed that controls improved over the four locations (making fewer errors on the fourth location than the first: $t = 3.056$, d.f. = 31, $p = 0.005$), whereas patients did not ($t = 0.442$, d.f. = 33, $p = 0.661$).

3.1.2. Effect of frontal lesions: strategy scores

Strategy scores followed a very similar pattern to raw scores. Entering phase 2 and 4 strategy scores into a repeated-measures ANOVA yielded a main effect of phase ($F(1,64) = 29.152$, $p < 0.001$), a marginally significant group by phase interaction ($F(1,64) = 3.560$, $p = 0.064$), and no main effect of group ($F(1,64) = 0.256$, $p = 0.615$). Paired t-tests showed that both controls and patients significantly improved strategy scores on phase 4 compared to phase 2 (controls: $t = -4.676$, d.f. = 31, $p < 0.001$; patients: $t = -2.764$, d.f. = 33, $p = 0.009$). Within group correlations between each subject's phase 4 strategy score and phase 4 performance were similar for each group (controls: $r = -0.581$, $n = 32$, $p < 0.001$; patients: $r = -0.460$, $n = 34$, $p = 0.006$).

In contrast, entering phases 2 and 5 strategy scores into a repeated-measures ANOVA yielded no main effect of phase ($F(1,64) = 1.165$, $p = 0.284$), no group by phase interaction ($F(1,64) = 1.773$, $p = 0.188$), and no main effect of group ($F(1,64) = 0.179$, $p = 0.673$). This is evidence that phase 4 ('post-strategy permutation generation') performance is dependent on the strategy, but that the strategy cannot be transferred onto a similar permutation task ('transfer'/phase 5).

3.1.3. Toucher: neural substrates

We examined the effect of damage to cortical and subcortical subregions, in order to identify more specifically the critical regions involved in the performance of Toucher. Phase 3 performance correlated strongly with damage to the DLPFC ($r = 0.482$, $n = 34$, $p = 0.004$; Fig. 6). No other significant correlations were observed between performance on any stage or with other regions of interest (SFG, OFC, VIFG, RPFC), aside from a weak correlation with the IFG ($r = 0.369$, $n = 34$, $p = 0.032$) and phase 3 errors. This correlation is likely to be a result by the correlation between DLPFC and IFG damage and partialling out the volume of IFG did not affect the significance of the DLPFC/phase 3 correlation ($p = 0.393$, d.f. = 31, $p = 0.024$).

We examined the contribution of the ACC and non-prefrontal regions, on to which the lesion had encroached in some subjects. There was weak evidence that two non-PFC regions appeared to contribute to performance on other phases (Table 3). Importantly however, it was confirmed via partial correlations that damage to neither of these areas could account for the correlation between DLPFC and phase 3 performance (partialling out basal ganglia/thalamus: $r = 0.510$, d.f. = 31, $p = 0.002$; partialling out parietal: $r = 0.472$, d.f. = 31, $p = 0.006$; partialling out central: $r = 0.381$, d.f. = 31, $p = 0.029$). Moreover, this correlation was still significant despite partialling out total lesion volume of the frontal lobes ($r = 0.350$, d.f. = 31, $p = 0.046$), or total PFC lesion volume ($r = 0.428$, d.f. = 31, $p = 0.013$).

3.2. Self-ordered spatial working memory

3.2.1. Contrasting patients with and without lesions to the right inferior frontal gyrus and controls

In order to confirm our predictions about the role of the right inferior frontal gyrus in spatial working memory, we divided the groups into patients with damage to the right inferior frontal gyrus (BA44 and 45: $n = 15$) and those without damage to that region ($n = 28$: see Fig. 7). A repeated-measures ANOVA was performed comparing these two groups with controls. There was a significant main effect of level of difficulty ($F(1.726, 132.894) = 210.739$, $p < 0.001$), a marginally significant group by difficulty interaction ($F(3.452, 123.969) = 2.528$, $p = 0.052$) and a significant main effect of group ($F(2,77) = 3.543$, $p = 0.034$). Tukey HSD corrected post hoc tests revealed that the RIFG group was marginally impaired compared to the non-RIFG patients ($p = 0.051$) and significantly impaired compared to controls ($p = 0.039$), whereas the non-RIFG patients and controls could not be distinguished ($p = 1.000$). Details of the whole patient and control groups on this task are present in Table 4.

Table 3
Effects of non-PFC regions on behaviour (*r* in main text, *p* in parentheses, *N* = 34 for Toucher data, *N* = 43 for SWM data)

Region	TPhase 2	TPhase 3	TPhase 4	TPhase 5	Total SWM	Strategy
BG/T R (*p*)	0.211 (0.230)	0.099 (0.578)	0.171 (0.335)	0.381* (0.026)	0.050 (0.752)	0.029 (0.852)
BG/T t (*p*)	1.477 (0.149)	1.071 (0.292)	−0.014 (0.989)	2.227* (0.033)	1.534 (0.133)	1.510 (0.139)
Parietal R (*p*)	0.133 (0.455)	0.204 (0.243)	0.014 (0.936)	0.072 (0.687)	−0.098 (0.530)	0.088 (0.574)
Parietal t (*p*)	1.320 (0.196)	1.398 (0.172)	1.142 (0.262)	0.180 (0.859)	−0.084 (0.933)	−0.325 (0.747)
Temp R (*p*)	−0.031 (0.864)	−0.059 (0.886)	−0.025 (0.886)	0.266 (0.128)	0.050 (0.749)	0.043 (0.784)
Temp t (*p*)	0.840 (0.407)	0.330 (0.344)	1.358 (0.184)	1.673 (0.104)	2.007 (0.051)	1.378 (0.176)
Central R (*p*)	0.384* (0.025)	0.331 (0.056)	0.149 (0.402)	0.141 (0.426)	0.083 (0.595)	0.037 (0.815)
ACC R (*p*)	0.261 (0.136)	0.330 (0.057)	−0.003 (0.986)	−0.033 (0.854)	0.289 (0.060)	0.151 (0.335)
ACC t (*p*)	1.090 (0.284)	0.809 (0.425)	0.505 (0.617)	1.267 (0.214)	0.018 (0.986)	−0.327 (0.746)

T-tests were not performed for central regions as almost all subjects had some damage to these regions. $^{*}p \leq 0.05$; $^{**}p \leq 0.005$.

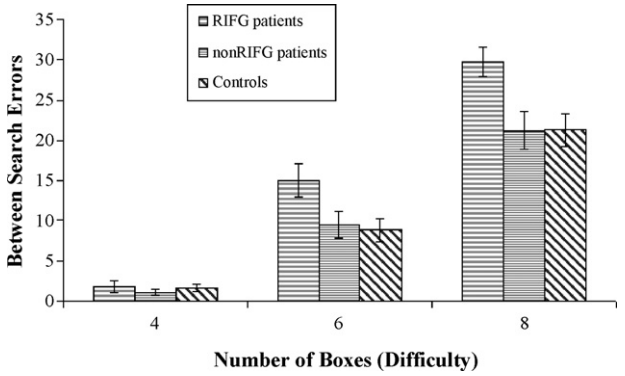

Fig. 7. Performance of RIFG patients (horizontal stripes), non-RIFG patients (filled) and controls (diagonal stripes) on the self-ordered spatial working memory task.

Student's *T*-tests suggested that the trend interaction was caused because the sensitivity of the test to RIFG damage increased with increasing difficulty: RIFG patients were not significantly impaired compared to non-RIFG patients or controls on the 4-box problem (versus non-RIFG: $t(41) < 1$; versus control: $t(50) < 1$), but were impaired on the 6-box problem (versus non-RIFG: $t(41) = 2.075$, $p = 0.044$; versus control: $t(50) = 2.412$, $p = 0.020$) and 8-box problem (versus non-RIFG: $t(40.458) = 2.871$, $p = 0.006$; versus control: $t(42.963) = 3.068$, $p = 0.004$). Non-RIFG patients and controls were not significantly different at any level of difficulty ($t(63) < 1$ in all cases).

3.2.2. Strategy scores

Likewise, when strategy scores were compared in a univariate ANOVA, there was a main effect of group ($F(2,77) = 3.455$, $p = 0.037$). Post hoc tests showed that the RIFG group were impaired on this measure compared to non-RIFG patients ($p = 0.014$) and controls ($p = 0.026$), whereas the non-RIFG patients and controls were not significantly different from one another ($p = 0.653$).

We performed the same repeated-measures ANOVA described above using between search errors at the three different difficulty levels, but also included the strategy score as a covariate. There were a highly significant main effect of strategy ($F(1,76) = 49.863$, $p < 0.001$), and strategy by difficulty interaction ($F(1.736,131.898) = 25.272$, $p < 0.001$). Inclusion of strategy score as a covariate rendered the group by difficulty interaction ($F(3.471,131.898) = 0.735$, $p = 0.552$) and main effect of group ($F(2,76) = 0.876$, $p = 0.421$) as non-significant, suggesting that the spatial working memory impairment in the RIFG patients may be mediated by poor strategy usage.

Table 4
Demographic information and SWM performance of patients and controls

	Patient	Control
N	43	37
Age	54.67 (10.75)	54.54 (11.01)
NART	115.27 (8.62)	116.66 (5.21)
4 Box Between Errors	1.35 (2.43)	1.65 (2.76)
6 Box Between Errors	11.40 (8.66)	8.81 (8.50)
8 Box Between Errors	24.19 (11.40)	21.30 (12.27)
Strategy	34.77 (6.16)	33.84 (5.13)

The patient and control groups could not be distinguished by age ($t = 0.055$, d.f. = 78, $p = 0.956$) or NART ($t = -0.885$, d.f. = 70.438, $p = 0.379$).

3.2.3. Spatial working memory: neural substrates

Patients with RIFG damage had a significantly larger mean lesion size (mean lesion volume of prefrontal cortex = 5092.80 voxels, s.d. = 3680.15) than non-RIFG patients (1925.00 voxels, s.d. = 2219.92: $t(41) = 3.050$, $p = 0.006$). Covarying for total PFC lesion volume reduced the significance differences in performance between the two lesion groups (effect of group: $F(1,40) = 3.722$, $p = 0.061$).

Within the RIFG, there was evidence that the pars opercularis (BA44) was critically involved, as total error score and the strategy score both correlated significantly with damage to that region (total errors: $r = 0.389$, $p = 0.010$; strategy: $r = 0.419$, $p = 0.005$; $n = 43$ for each), whereas damage to the pars triangularis (BA45) correlated significantly only with the strategy score (total errors: $r = 0.266$, $p = 0.085$; strategy $r = 0.319$, $p = 0.037$, $n = 43$). The correlations between RIFGpo and total errors and strategy SWM score (total errors: $r = 0.323$, $p = 0.037$; strategy: $r = 0.377$, $p = 0.014$; d.f. = 40) remained significant if total lesion volume of the PFC was partialled out. The correlation between total errors or strategy and pars triangularis was not significant if PFC lesion volume was partialled out (total errors: $r = 0.107$, $p = 0.500$; strategy: $r = 0.237$, $p = 0.130$; d.f. = 40). No other significant correlations were observed between performance on any stage or with other regions of interest (SFG, OFC, IFG, RPFC), aside from a weak correlation between the volume of damage to the VIFG and between search errors ($r = 0.300$, $n = 43$, $p = 0.050$). Partialling out the volume of VIFG damage did not affect the significance of the correlations between RIFGpo and between search errors or strategy scores ($p = 0.323$, d.f. = 40, $p = 0.037$; $p = 0.366$, d.f. = 40, $p = 0.017$, respectively).

We examined the contribution of non-prefrontal regions and the ACC, on to which the lesions had encroached in some subjects (Table 3). None of the effects reached significance, although the contribution of the temporal lobe and ACC to total errors approached significance. We inserted these variables as covariates into the repeated-measures ANOVA contrasting RIFG patients, non-RIFG patients and controls at three levels of difficulty (reported above). The magnitude of temporal lobe damage had no detectable effect on performance (main effect of lesion: $F(1,40) < 1$; lesion by difficulty interaction: ($F(1.688,67.523) < 1$), and did not affect the significance of the group by difficulty interaction ($F(1.688,67.523) = 3.189$, $p = 0.056$) or the main effect of group ($F(1,40) = 6.789$, $p = 0.013$).

Table 5
Correlation matrix describing effects of RIFGpo and DLPFC damage on Toucher and SWM performance (r in main text, p in paentheses, $N = 34$ for Toucher data, $N = 43$ for SWM data)

Region	TPhase 2	TPhase 3	TPhase 4	TPhase 5	Total SWM	Strategy
RIFGpo	0.336 (0.052)	0.238 (0.175)	0.114 (0.520)	0.200 (0.163)	0.389* (0.010)	0.419** (0.005)
DLPFC	0.245 (0.162)	0.482** (0.004)	−0.023 (0.895)	0.112 (0.527)	0.232 (0.135)	0.114 (0.467)
Total PFC	0.137 (0.441)	0.304 (0.080)	−0.066 (0.709)	0.187 (0.291)	0.313* (0.041)	0.225 (0.147)

*$p \leq 0.05$; **$p \leq 0.005$.

Likewise, the magnitude of ACC damage had no detectible effect as a covariate (main effect of lesion: $F(1,40) = 2.277$, $p = 0.139$; lesion by difficulty interaction: ($F(1.606,64.251) = 0.144$); it did reduce the significance of the group by difficulty interaction ($F(1.606,64.251) = 2.416$, $p = 0.108$) but did not affect the main effect of group ($F(1,40) = 5.434$, $p = 0.025$).

3.3. Dissociable neural substrates: distinct effects of damage to the DLPFC and RIFG

The first step was to examine the correlation matrix (Table 5). Our previous analyses had identified Toucher phase 3 as particularly sensitive to frontal lobe injury, and we identified the DLPFC as a region likely to be particularly critical for performance of this phase. This region was not so important for the performance of the spatial working memory task, however (total errors $r = 0.232$, $p = 0.135$; strategy score $r = 0.114$, $p = 0.467$, $n = 40$ for each: see Table 5). In contrast, our previous analyses identified the RIFGpo as important for the performance of the spatial working memory task, but damage to this region had little effect on Toucher performance, except perhaps the pre-strategy permutation generation phase (phase 2).

To confirm that damage to the RIFGpo and the DLPFC made independent contributions to variance in the performance of SWM and Toucher phase 3 respectively, we performed two partial correlations. The RIFGpo/SWM correlation remained significant for total between search errors and strategy score despite partialling out DLPFC lesion volume (total errors: $r = 0.343$, $p = 0.026$; strategy: $r = 0.406$, $p = 0.008$; d.f. = 40 for both). The group effect, demonstrating that RIFG patients are impaired compared to controls and non-RIFG patients, remained significant even when correcting for DLPFC lesion volume ($F(1,40) = 4.463$, $p = 0.041$). Likewise, the DLPFC/Toucher phase 3 correlation remained significant despite partialling out the effect of RIFGpo lesion volume ($r = 0.461$, $p = 0.007$, d.f. = 31).

3.4. Effect of demographic variables

In addition, the effects of NART score and age on Toucher phase 3 and spatial working memory respectively showed a similar pattern to the neural substrates (DLPFC and RIFGpo, respectively). NART correlated with Toucher phase 3 ($r = -0.372$, $p = 0.002$, $n = 66$) but not with SWM (total errors: $r = 0.097$, $p = 0.392$, $n = 80$; strategy: $r = 0.077$, $p = 0.498$, $n = 80$). Age, however, was negatively correlated with SWM errors (total errors: $r = 0.336$, $p = 0.002$, $n = 80$) but less strongly with Toucher phase 3 ($r = 0.162$, $p = 0.194$, $n = 66$). The effect of age on SWM strategy was not significant ($r = 0.148$, $p = 0.190$, $n = 80$), while the correlation between age and SWM error scores was significant even when strategy was partialled out ($r = 0.321$, $p = 0.004$, d.f. = 77).

Nonetheless, across all patients and controls, as would be expected, performance of Toucher and self-ordered spatial working memory showed a substantial shared variance: in particular, Toucher phase 4 (post-strategy performance) correlated strongly with SWM strategy score ($r = 0.502$, $p < 0.001$: see Table 6).

3.5. Summary

Frontal lesion patients were particularly impaired on the sub-goal strategy-training phase of Toucher (phase 3), an effect that was largely dependent on the integrity of the DLPFC within subjects. By contrast, self-ordered spatial working memory performance was dependent on the integrity of the RIFG, in particular, to the pars opercularis (BA 44). Further, we were able to show that damage to the RIFGpo and DLPFC regions predicted performance on the self-ordered spatial working memory task and Toucher training phase performance (phase 3), respectively, independent of damage to the other region.

4. Discussion

In this study, we examined performance of a large group of patients with frontal lobe damage and healthy matched controls on two tests of working memory with a strategic component: 'Toucher', a visuospatial sequence generation task, and the CANTAB self-ordered spatial working memory task (SWM). On Toucher, frontal lesion patients did not show impairments on spontaneous generation of visuospatial sequences (phase 2) compared with matched controls, and were only subtly impaired on retest after strategy training (phase 4). However, we demonstrated that patients were robustly impaired on the sub-goal strategy-training phase, phase 3, where working memory requirements were reduced by *externally* imposing a simple strategy on subjects' performance. Such a pattern of effects has not been observed in previous studies of Toucher on different patient groups, and rules out the possibility that there was a general impairment on the task as a whole, as seen, for example, by Lawrence (1997) in symptomatic Huntington's Disease patients. Moreover, we observed that the number of errors at this stage correlated significantly with damage to the DLPFC, bilaterally. In an overlapping group of patients, performance on the CANTAB self-ordered working memory task (SWM) depended instead on the integrity of the RIFG, particularly the pars opercularis (RIFGpo). The former correlation remained sig-

Table 6
Correlation matrix describing relationships between performance on SWM and Toucher (r in main text, p in parentheses, $N = 58$ for all)

	Phase 2	Phase 3	Phase 4	Phase 5
Total SWM	0.384 (0.003)**	0.264 (0.046)*	0.453 (<0.001)**	0.182 (0.171)
Strategy	0.230 (0.082)	0.414 (0.001)**	0.502 (<0.001)**	−0.002 (0.989)

*$p \leq 0.05$; **$p \leq 0.005$.

nificant even when RIFGpo damage, or total PFC lesion volume, was partialled out. Likewise, the correlation between RIFGpo and SWM performance was significant even when total PFC lesion volume was partialled out.

Our results resist general explanations relating to difficulty, symptom severity or lesion volume. Although patients with RIFG damage had large lesions and were impaired on SWM compared to controls and non-RIFG patients, who had smaller lesions, this impairment was particularly related to the amount of damage to the RIFGpo. If the reason for this was simply that patients with RIFGpo damage suffered a general, non-specific impairment, perhaps as a result of the size of their lesion, we would expect RIFGpo to lead to a general, non-specific deficit on Toucher. We did not observe this for two reasons. Firstly, when considered as a single group, patients did not show a general, non-specific deficit on Toucher: their deficit was relatively selective to phase 3 or the strategy-training phase of the task. Moreover, performance on this phase was correlated with bilateral DLPFC damage but not RIFGpo damage. The former correlation remained significant even when RIFGpo damage was partialled out. In addition, although DLPFC lesion volume was closely associated with total lesion volume to the frontal lobe, the correlation between DLPFC lesion volume and phase 3 remained significant even when total PFC lesion volume was partialled out. Likewise, the correlation between RIFGpo and SWM performance was significant even when total PFC lesion volume was partialled out.

Although some patients had lesions that extended beyond the frontal lobe, we demonstrated that damage to non-frontal regions did not account for these impairments, as patients with damage to these non-frontal regions were no more impaired than patients without non-frontal damage. This is not to say that posterior cortical areas do not contribute to working memory performance—indeed there is good evidence that they do (e.g. Owen et al., 1996). We argue, however, that the degree of encroachment of these lesions into non-frontal regions in a minority of patients is unlikely to account for our findings. We argue, however, that the degree of encroachment of these lesions into non-frontal regions in a minority of patients is unlikely to account for our findings. Nonetheless, the lack of selectivity of these regions does temper the conclusions we can draw on the basis of our data. Specifically, we have evidence that the regions we discuss (RIFG, DLPFC) are *necessary* for normal working memory performance, but not that, among PFC subregions, these regions are *sufficient* for normal working memory performance. It could be that it is the combination of lesions to these regions and adjacent regions that precipitates the impairments we observe.

In addition, there are a number of other reasons for cautious interpretation of the degree of precision of the anatomical localization of the regions identified: it is possible that the SWM impairment, in particular, could have arisen if a critical region (other than the RIFGpo) was highly correlated with the region. In particular, there are reasons for thinking that the ventral aspect of the middle frontal gyrus (BA6/8) might be important as damage to this region results in a form of neglect in rhesus monkeys (Rizzolatti, Matelli, & Pavesi, 1983). Alternatively, white matter tracts connecting the frontal and parietal lobes might be disrupted by lesions proximal to BA44, causing a frontal/parietal disconnection. Fibers linking the caudal part of area 9/46 run to the parietal cortex underneath BA44 and also fibers linking BA6/8 with the inferior parietal lobule run under the upper part of BA44 (Petrides & Pandya, 2006). Moreover, factors such as cortical distortion as a result of the lesion, cortical plasticity and functional compensation following the lesion, or error in transforming the lesion location into standard space may have added noise to our estimate of lesion–behaviour association. Further research with larger samples will be required to distinguish these possible confounds or control for sources of unwanted variance.

In the SWM task, strategy usage and performance are confounded by the nature of the task: it is impossible to get independent estimates of strategy usage and working memory storage capacity. Although the SWM deficit observed in RIFG patients could be explained if the RIFG is acting as a visuospatial working memory store, we demonstrated using analysis of covariance (ANCOVA) that the impairment was accompanied by poorer strategy usage, and that elevated error rates were no longer significant after covarying for strategy score. We conclude that the poor SWM performance in the RIFG patients is associated primarily with impaired strategy implementation. SWM deficits have been observed in the absence of strategy impairment in certain patient groups (Owen et al., 1992, 1996), but strategy impairments are generally not observed in the absence of performance deficits. We argue that an increase in errors combined with a strategy deficit represents a qualitatively different syndrome from increases in errors without strategy deficits, and that frontal lobe damage is associated with the former syndrome.

Although the strategy is thought to improve performance in both Toucher and SWM, Toucher represents a purer measure of strategy usage as the nature of the paradigm allows performance to be assessed with and without the strategy. However, due to the pattern of our results, our inferences about the nature of the algorithmic strategy are somewhat limited. Patients were impaired at a more basic level than the strategy, as evidenced by performance on the strategy-training phase (phase 3), so we can make no strong inferences about sub-goal strategic processing *per se*. Among the possible accounts of these data, one parsimonious account is that the DLPFC contributes to monitoring of the sequences that have been performed, to prevent repeating them. The monitoring requirement of the task is most evident on phase 3, because the set size is sufficiently small for a monitoring strategy to be possible. This account finds support in animal lesion (Petrides, 2000) and human fMRI data (Champod & Petrides, 2007). Given this account, the failure to observe a relationship between DLPFC damage and SWM performance is surprising, as monitoring should be essential for performance of this task. This perhaps reflects the importance of strategy for SWM performance and the extent to which working memory demands can be reduced by employing one.

A study of Koechlin and Jubault (2006) implicates the inferior frontal gyrus in the performance of action sequences that are divided into sub-goals at different hierarchical levels. The authors examined neural activity associated with transitions between motor sequences and simple motor actions. The premotor cortex (BA6) was activated during the latter transitions, whereas the inferior frontal gyrus was activated between transitions between motor sequences. The authors distinguished between simple motor sequences ('simple chunks') and sequences of simple chunks ('superordinate chunks'): BA44 (posterior IFG) was activated by transitions between simple chunks, while BA45 (anterior IFG) was activated by transitions between superordinate chunks. In the SWM paradigm, the strategic performance requires repetition of similar action sequences while searching for tokens. The deficit in strategic performance of patients with BA44 lesions could arise because BA44 is necessary to guide behaviour at the end of an action sequence, perhaps by engaging a new sequence. In the absence of such a mechanism, searching performance becomes disorganised, as we observed. Koechlin and Jubault found bilateral IFG activation, whereas our effects on SWM are right lateralised: this may be caused by the requirement for spatial processing in the SWM task, which the paradigm of Koechlin and Jubault lacks. The data of Koechlin and Jubault may also suggest a role for the IFG in the normal performance of Toucher. For instance, BA45 might be a good

candidate for mediating Toucher strategy (which would be present at phase 4), while BA44 or BA6 might be critical at a more basic level of organising each sequence. Unfortunately, due to the powerful effect of the DLPFC on Toucher phase 3, which we argue results from a sequence generation failure, it is difficult to dissociate out pure strategy impairments that might be observed in patients with RIFG lesions.

Consistent with the notion that the RIFG is important for strategic performance on both tasks, there was a particularly large correlation between the strategy score and performance on the post-strategy permutation generation phase of Toucher (phase 4, see Table 6) across subjects. This is somewhat surprising as there are reasons for thinking that different types of mnemonic strategy might be useful for each task: Toucher phase 4 requires the use of a formal algorithmic strategy, whereas the strategy used in SWM is derived spontaneously, perhaps as a convenient heuristic for searching the boxes. Although this result is consistent with the idea that similar psychological or neurobiological underpinnings mediate performance on both tasks, this shared variance might suggest that both tasks suffer from the task impurity problem discussed by Miyake and colleagues (Miyake et al., 2000): as yet unspecified cognitive resources that differ between subjects may facilitate performance on both tasks.

Our finding that the RIFG is critical for SWM consistent with a growing literature of neuropsychological studies examining lesion-behaviour associations, ascribing spatial working memory function to the right hemisphere (Bor, Duncan, Lee, Parr, & Owen, 2006; Miotto et al., 1996; van Asselen et al., 2006), in contrast to a more traditional position that the DLPFC, regardless of hemisphere, is critical (Bechara et al., 1998; Manes et al., 2002). Our recent paper isolated SWM errors to the IFG region of the right hemisphere, based on a strong and selective correlation with the volume of damage affecting this region in a group of 21 right frontal patients. The present study confirms this analysis by contrasting patients with and without RIFG damage. In addition, further evidence has come from studies with left visual field neglect patients, who have damage to the right hemisphere, usually right parietal, inferior frontal or basal ganglia regions (Husain et al., 2001; Kennard et al., 2005; Malhotra et al., 2005; Mannan et al., 2005; Wojciulik et al., 2001). We did not specifically examine the performance of these patients on tasks of spatial attention, though an earlier study in similar patients recruited from the same panel (Peers et al., 2005) observed a subtle spatial bias, but one that was relatively mild in comparison with spatial biases observed in neglect. In our study, patients were tested at least 1 year post-lesion, to render it unlikely that they were suffering from acute neglect. However, more subtle spatial biases may remain. Likewise, the spatial working memory deficits we observe in this study may be relatively subtle compared to those observed with neglect patients on similar tasks. This remains to be investigated.

Clark et al. (2007) suggest that a failure of inhibitory processing may be responsible for this deficit, due to the high correlation between performance on the SWM task and the ability to inhibit a pre-potent response on the stop-signal reaction time task. Given the framework of Miyake, Friedmann and others (Friedman et al., 2006; Miyake et al., 2000), it seems intuitive that the concept of strategic working memory might be better reflected by the latent variable representing 'Updating', as loading on this latent variable predicted performance on a number of working memory tasks, and less with the latent variable reflecting 'Inhibition'. Age was associated with SWM performance, as has been previously observed. Consistent with the suggestion that failure of inhibitory processes may lead to SWM deficits (Clark et al., 2007), aging has been associated with deficits on inhibitory tasks (Kramer, Humphrey, Larish, Logan, & Strayer, 1994). Moreover, consistent with Clark and colleagues' (2007) evidence that right PFC regions might implement these processes, there is some evidence that these regions are preferentially affected by healthy aging compared to left PFC regions (Rajah & D'Esposito, 2005). However, it is important to note that there was no evidence that aging was accompanied by strategy deficits, and partialling out the strategy score of the age/between search errors correlation had no effect on the significance of the test. There therefore seem to be qualitative differences between the effects of RIFG lesions and aging on SWM performance.

The data from Toucher suggest that a second orthogonal factor is required to account for performance on different tasks of strategic working memory, perhaps one which accords with the 'Updating' factor of Friedman and colleagues (Friedman et al., 2006). Recently Friedman, Miyake and colleagues group found that performance on 'Updating' tasks correlated with intelligence, both fluid and crystallised forms (Friedman et al., 2006), which may reflect processes related to working memory monitoring. Consistent with this, our measure of premorbid IQ (albeit a measure of crystallised intelligence rather than fluid intelligence), NART, correlated with Toucher phase 3 (strategy training) across all subjects. Given this association, our observation of a role for the DLPFC in this phase 3 of the Toucher is compatible with data implicating the DLPFC in fluid intelligence (Duncan et al., 2000).

We have some evidence that the performance enhancement afforded by the strategy training is relatively domain specific, in that the performance improvement following training (on phase 4) did not generalise to phase 5 (transfer). This phase was structurally identical to the pre- and post-training phases (2 and 4) but its surface features were different. It is possible that phase 5 is inherently more difficult for some reason, but there is no obvious reason relating to difficulty to explain why subjects did not transfer the strategy from the training phase. The most straightforward account at this stage is that the context shift between the two tasks or the difference in surface features prevented the subjects retrieving or utilising the strategy. Hence performance on this stage returned to an equivalent level as phase 2 (pre-training phase).

4.1. Summary

We have shown that different brain regions are required for intact self-ordered spatial working memory performance using two tests: Toucher, a visuospatial sequence generation task, and the CANTAB self-ordered spatial working memory task. We show that the bilateral DLPFC (BA46/9) is required for generating visuospatial sequences when memory demands are reduced on the Toucher task, whereas lesions of the right inferior frontal gyrus, pars opercularis (BA44), lead to increases in errors and poorer strategy usage while searching for hidden boxes in a spatial array on SWM. Both tasks require the executive control of working memory: thus our data are consistent with the theory that the central executive itself may consist of dissociable subsystems, compatible with the theory of Shallice and Burgess (1998).

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