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Frontal lobe involvement in spatial span: Converging studies of normal and impaired function

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Abstract

Although monkey lesion studies involving the prefrontal cortex commonly report working memory deficits, and neuroimaging studies consistently show prefrontal involvement in such tasks, patients with damage to this region commonly fail to show any working memory impairment. Such a discrepancy may be due to insensitive testing measures for patients, as well as small, yet critical differences between working memory tasks in imaging and patient studies. The current study utilised a more sensitive measure of spatial working memory spans, based either on structured or unstructured spatial arrays. A PET study in normal subjects confirmed that both variants did indeed activate prefrontal cortex. The same tasks were given to frontal lobe patients and closely matched controls. Patients with large frontal lesions were significantly impaired on this task, with those patients with damage to the right dorsolateral prefrontal cortex appearing particularly impaired. This result demonstrates that prefrontal cortex is necessary for normal working memory, even in simple tasks, such as spatial span. It is suggested, however, that the patient deficit reflects strategic or goal-based dysfunction, rather than storage limitations.

Keywords: Prefrontal cortex; Positron emission tomography; Neuroimaging; Patient; Strategy

1. Introduction

There is considerable evidence from both human neuroimaging and animal studies that the lateral prefrontal cortex (PFC) is linked with working memory processes (Awh et al., 1996; Baddeley, 2000; Bor, Duncan, & Owen, 2001; Bor, Duncan, Wiseman, & Owen, 2003; Bor, Cumming, Scott, & Owen, 2004; Cabeza & Nyberg, 2000; Courtney, Ungerleider, Keil, & Haxby, 1997; D'Esposito et al., 1998; Jonides et al., 1997; Levy & Goldman-Rakic, 1999; Owen et al., 1998; Petrides, 1994; Petrides, 2000). Working memory can broadly be defined as the ability to maintain and manipulate data over a short time-period, commonly of the order of a few seconds (Baddeley, 1992). The spatial span test (also called the Corsi block test) is thought to be a paradigmatic index of spatial working memory, particularly for clinical populations (Milner, 1971).

In monkeys, frontal lobe lesions commonly elicit working memory impairments (Funahashi, Bruce, & Goldman-Rakic, 1989; Passingham, 1975; Wilson, Scalaidhe, & Goldman-Rakic, 1993). In simple span tasks like Corsi blocks, however, humans with frontal lobe lesions appear to be unimpaired (D'Esposito & Postle, 1999). Preserved performance in span tests is even more surprising given common frontal lobe activation in working memory neuroimaging studies. For instance, in both delayed matching to sample (Elliott & Dolan, 1999; Gold, Berman, Randolph, Goldberg, & Weinberger, 1996; Postle, Berger, & D'Esposito, 1999), and spatial span (Bor et al., 2001; Bor et al., 2003; Pochon et al., 2001; Owen, Evans, & Petrides, 1996; Owen et al., 1999), activation is consistently reported in lateral PFC.

One possible explanation for this apparent inconsistency is that previous patient testing in this area has not been sensitive enough to elicit a real, yet subtle deficit in low-level work-

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ing memory tasks. For instance, in spatial span, although no study known to us has reported a significant deficit in frontal lobe patients (Canavan et al., 1989; Greenlee, Koessler, Cornelissen, & Mergner, 1997; Miotto, Bullock, Polkey, & Morris, 1996; Owen, Downes, Sahakian, Polkey, & Robbins, 1990), most of these studies reported a numerical decrease in spatial span compared to healthy controls. It is also possible that subtle differences between the same type of tasks given to patients and those presented to healthy controls in the scanner are sufficient to involve a significantly different set of processes.

In this study, we attempted to develop a more sensitive paradigm for measurement of spatial span. First, a PET study was conducted on normal controls, in order to demonstrate that this precise version of spatial span was indeed associated with prefrontal activity. Based on previous evidence suggesting that the spatial layout of stimuli can differentially activate the dorsolateral and ventrolateral PFC (Bor et al., 2001; Bor et al., 2003; Owen, Evans et al., 1996; Owen et al., 1999), two different arrays were given in the PET scanner. Using exactly the same configurations of stimuli, a further behavioural study was then run on frontal lobe patients and closely matched controls. This study employed a technique that allowed for a continuum of span scores, unlike the method of spatial span testing commonly used, which produces integer results. It was predicted that, using our more sensitive paradigm, a span deficit would indeed be found in these patients.

2. Neuroimaging experiment

2.1. Materials and methods

2.1.1. Image acquisition and data analysis

PET scans were obtained with the General Electric Advance system, which produces 35 image slices at an intrinsic resolution of approximately 4.0 mm × 5.0 mm × 4.5 mm. Regional cerebral blood flow (rCBF) was measured during two separate scans for each of the three conditions. Six additional scans for each subject were taken during unrelated conditions which will not be discussed here. For each scan, subjects received a 20 s intravenous bolus of $H_2{}^{15}O$ through a forearm cannula at a concentration of 300 Mbq ml^{-1} and a flow rate of 10 ml min^{-1}. The scan length was 90 s from when the tracer first entered the cerebral circulation. Using SPM 99 (provided by the Wellcome Department of Cognitive Neurology, London, UK), the 12 PET scans for each subject were realigned by trilinear interpolation, using the first scan as a reference, to create a mean image. The mean PET images for each subject were normalised using bilinear interpolation, based on the SPM PET template. The normalised images were then smoothed using an isotropic Gaussian kernel with FWHM set at 16 mm.

For the condition analysis, a subject specific analysis of covariance (ANCOVA) model was fitted to the data at each voxel. All images were scaled to a grand mean value of 50. Proportional threshold masking was set at 0.8. Global calculation was set at mean voxel value.

Given recent evidence suggesting that head movement across scans is a confounding factor in many PET studies (Brett, Bloomfield, Brooks, Stein, & Grasby, 1999), *F*-value images were tested to determine whether scan order or any of the six head movement parameters were significantly associated with rCBF values. Those parameters with significant associations (scan order, translation in all directions, rotation in y and z) were set as covariates of no interest. This procedure is believed significantly to improve sensitivity and reduce noise in the data.

For the whole of the brain, an exploratory search involving all peaks within the grey matter (volume 600 cm^3) was conducted. The threshold for reporting a peak as significant was set at $p < 0.05$, corrected for multiple comparisons (Worsley, Evans, Marrett, & Neelin, 1992; Worsley et al., 1996). This equates to a threshold Z score of >4.41. In addition to this, when experimental conditions were compared to control, a small volume correction (Worsley et al., 1992) was applied to the activations in the frontal lobes (again, $p < 0.05$, with a Z threshold >3.90). This method implements a correction for multiple comparisons just within a specified region, in line with the a priori prediction that spatial span tasks would activate PFC (Bor et al., 2001; Owen, Evans et al., 1996; Owen et al., 1999).

A supplementary analysis examined mean activity in regions of interest (ROI) centred within dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC). DLPFC and VLPFC regions were specified by taking the mean of a range of published co-ordinates for these regions in various tasks, as listed in a recent review (Duncan & Owen, 2000). The DLPFC ROI centers were −40 28 19 (left) and 35 31 22 (right), while the VLPFC ROI centers were −41 20 0 (left) and 37 20 3 (right). The ROI in each case was defined as a 10 mm radius sphere surrounding the co-ordinates given above. In order to analyze the ROIs, an in-house software suite was used (http://www.mrc-cbu.cam.ac.uk/Imaging/marsbar.html). For each ROI, *t*-tests were carried out to compare the mean voxel in different conditions.

2.1.2. Subjects

Twelve normal right-handed volunteers, all males, participated in the study (age range = 21–38, mean age 25.6). Each subject underwent 12 PET scans (six of which are not reported here) within a single session. All subjects gave informed, written consent for participation in the study after its nature and possible consequences had been explained to them. The study was approved by the Local Research Ethics Committee.

2.1.3. Stimuli and testing conditions

Stimuli in all conditions were eight red squares (3.5 cm × 3.5 cm) presented on a black background, on a touch-sensitive monitor. Stimuli were presented in two types

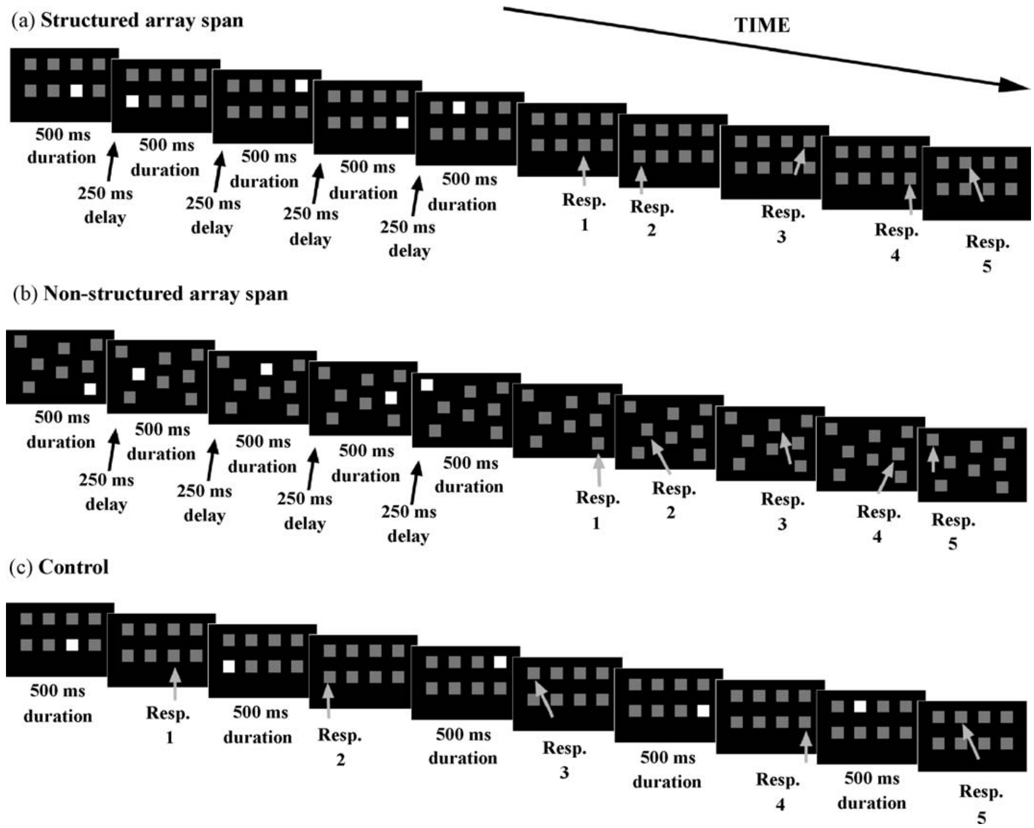

Fig. 1. Examples of trials from each of the three conditions in the PET experiment, as well as the two span conditions in the patient experiment. (a) For the structured array span task subjects were shown a sequence of spatial stimuli (each stimulus was indicated by a change from red to blue—from grey to white in figure), which they were required to copy by touching the same sequence of locations in the same order within a 3750 ms timeframe. (b) For the non-structured array span task, subjects performed exactly the same task as for the structured array span task. (c) For the control condition (PET only), subjects were required to touch each stimulus within a 1000 ms timeframe, after it had changed back from blue to red. Each stimulus and response cycle of the span tasks matched the duration of five stimulus and response cycles in the control task.

of array (see Fig. 1). For the "structured" array, there were four columns of two rows, with 3.5 cm between squares horizontally and 7 cm between squares vertically. For the "non-structured" array, the squares were arranged randomly on the screen. The monitor was approximately 50 cm away from the subject's head.

2.1.3.1. Structured array span condition. In this condition (see Fig. 1a), using the structured 4×2 array, one of the eight red squares would turn blue for 500 ms before turning red again. 250 ms after this, a second red square would turn blue for 500 ms and so on, until five of the eight red squares had turned blue. Once the last square had turned red again, the subjects were required to respond by touching the squares on the touch-sensitive monitor in the order that they had just changed colour. They were instructed to respond as fast as they could, but not so fast that they started making mistakes. Subjects were given a fixed interval of 3750 ms in which to respond, after which the next span would start.

2.1.3.2. Non-structured array span condition. The procedure was identical to that for the structured span condition, except that the non-structured array was used (see Fig. 1b). Although the array was the same throughout a single scan, the squares were presented in different non-structured locations in each of the 2 scans.

2.1.3.3. Visuomotor control condition. For this task (see Fig. 1c), one of the eight red squares, in a structured 4×2 array, would turn blue for 500 ms, and then turn red again. The subject was required to respond by touching the square that had just turned blue as fast as they could, but without making any mistakes. A fixed interval of 1000 ms followed each stimulus before onset of the next; subjects were required to complete their response within this time.

2.1.3.4. General condition parameters. The choice of stimulus locations was pseudo-randomly set in all conditions, so that particular span sequences in the span tasks, or particular squares in the control, did not immediately repeat. In addition, each span sequence involved no location repeats. Each of the three conditions was performed twice. The testing phase for each PET scan lasted 100 s, with an onset 10 s prior to the scan. In addition, a 100 s practice task for the upcoming condition was given to each subject approximately 4 min before each scanned task. This was carried out to ensure that the subject understood the task, and was performing proficiently. The scans were separated by 8 min. The three different tasks required an identical number of responses (60 per scanned condition). The scan order was designed in two blocks of three, with each block comprising the three different conditions, and the two blocks having a different condition order. Scan order was pseudo-randomly varied between subjects.

2.2. Results

2.2.1. Behavioural results

For the visuomotor control condition, a trial was marked as correct if the single square touched was the correct square for that trial. For the span conditions, in order to allow for a meaningful comparison, each trial had a maximum of five marks (since five responses were required) and a single correct mark was given for each square touched that was in the right spatial location and in the right temporal order. Accuracy in all three conditions was above 95%. There was no significant difference between the two span conditions in terms of mean time to produce each response (477 ms for structured array versus 490 ms for non-structured array) or mean accuracy (97.8% for structured array versus 96.9% for non-structured array). There was also no significant difference between conditions that were performed first and conditions that were performed second.

Subjects were asked after the experiment which of the span tasks they found the most difficult. Of the 10 subjects who expressed a preference, 9 subjects judged the non-structured array span task to be more difficult ($X^2 = 6.40$, d.f. = 1, $p = 0.011$).

2.2.2. Cerebral blood flow results

2.2.2.1. Non-structured array span versus control. When the control task was subtracted from the non-structured array span task (see Table 1a and Fig. 2a), significant increases in activation were observed bilaterally in the VLPFC (BA 45/47). The co-ordinates of this region were very close to those that have been reported previously in imaging studies using spatial span tasks with similar non-structured arrays (Owen, Evans et al., 1996; Owen et al., 1999). A significant increase in rCBF was also observed more posteriorly, in the right superior parietal cortex (BA 7).

When the non-structured array span task was subtracted from the control task (see Table 1b), significant increases in rCBF were observed in the left motor cortex (BA 4), sup-

Table 1
Peaks of significant task-related activity in standard subtractions

Regions of interest	Brodmann (area/s)	Stereotaxic co-ordinates			*Z*-statistic	*p*-Value (corrected)
		x	*y*	*z*		
(a) Non-structured array span minus control						
Left						
VLPFC/White matter		−22	26	10	4.10	0.024*
Right						
VLPFC	45/47	32	18	6	3.91	0.047*
Superior parietal cortex	7	20	−70	32	5.58	<0.001
Superior parietal cortex	7	36	−78	38	4.64	0.028
(b) Control minus non-structured array span						
Left						
Motor cortex	4	−22	−16	58	5.80	<0.001
Supplementary motor area	6	−12	−16	52	5.15	0.003
Right						
Striate cortex	17	18	−94	4	4.60	0.033
(c) Structured array span minus control						
Left (no significant activations)						
Right						
DLPFC	9/46	38	40	26	4.12	0.023*
VLPFC	45/47	34	18	0	4.71	0.002*
Superior parietal cortex	7	42	−64	52	4.74	0.019
Superior parietal cortex	7	20	−66	46	5.13	0.003
Extrastriate cortex	18	36	−84	30	4.52	0.046
(d) Control minus structured array span						
Left						
Motor cortex	4	−22	−16	58	7.30	<0.001
Right (No significant activations)						

Stereotaxic coordinates in Montreal Neurological Institute (MNI) space of SPM99. The x = medial-to-lateral distance relative to the midline (positive = right and negative = left); y = anterior-to-posterior distance relative to the anterior commissure (positive = anterior and negative = posterior); z = superior-to-inferior distance relative to the anterior commissure/posterior commissure line (positive = superior and negative = inferior). The p-values are corrected for multiple comparisons ($p < 0.05$), based either on whole brain volume (non-frontal activations) or frontal volume only (frontal volume corrections marked by an asterisk). Direct comparisons of structured array with non-structured array span were not included in the table as there were no significant activations for these contrasts.

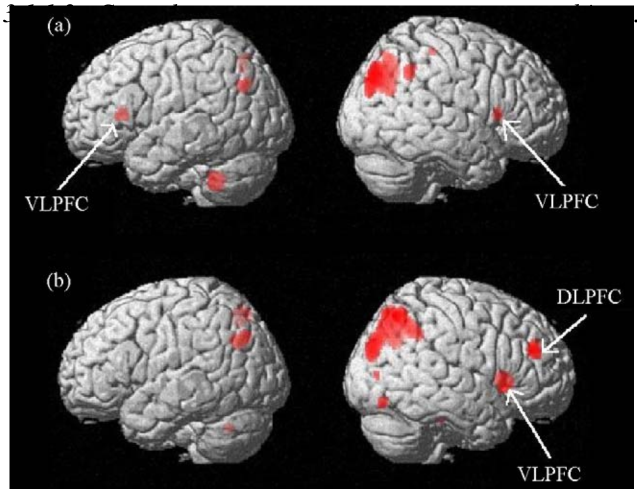

Fig. 2. PET subtraction images rendered onto the surface of a standard MNI 3D MRI from SPM99: (a) non-structured array span task minus control task and (b) structured array span task minus control task. In each case, all activations above the small volume correction calculated just for the frontal lobes ($Z = 3.91$) are shown. Posterior activations appearing in the figure but not listed in Table 1 should be taken as non-significant, as these would not pass the whole brain corrected threshold. (DLPFC = dorsolateral prefrontal cortex; VLPFC = ventrolateral prefrontal cortex.)

plementary motor area (BA 6) and the right striate cortex (BA 17).

The ROI analysis revealed a significant increase in activation for the non-structured array, compared to the control in the right VLPFC ($t = 2.34$, $p = 0.008$). There were no observed increases in right DLPFC, or in either left hemisphere ROI.

2.2.2.2. Structured array span task versus control. When the control task was subtracted from the structured array span task (see Table 1c and Fig. 2b), a significant increase in activity was observed in the right DLPFC region (Brodmann's area (BA) 9/46), as well as in the right VLPFC region (BA 45/47). Significant increases in activity were also observed more posteriorly in the right superior parietal cortex (BA 7), and right extrastriate cortex (BA 18).

In contrast, when the structured array span task was subtracted from the control task (see Table 1d), significantly increased activation was only observed in the left motor cortex (BA 4).

The ROI analysis revealed a significant increase in activation in the right DLPFC ($t = 1.80$, $p = 0.038$) and VLPFC ($t = 3.75$, $p < 0.001$) for the structured array span, compared to the control. There were no significant differences on the left for the same contrast.

2.2.2.3. Structured array span task versus non-structured array span task. The standard SPM99 voxel-based analysis showed no significant differences in a direct comparison of the two span conditions. The ROI analysis indicated a trend towards more activation in the right VLPFC for the structured array, compared with the non-structured array ($t = 1.36$, $p = 0.089$). However, no significant differences were observed in the other regions, or in any region for the opposite contrast.

3. Patient experiment

3.1. Materials and methods

3.1.1. Subjects

3.1.1.1. Frontal lesion patients. The 19 unilateral frontal lobe lesion patients from the Cambridge Cognitive Neuroscience Research Panel were included in this study (see Table 2). Only those with lesions limited to the frontal lobes were included. Eight left hemisphere patients included two aneurysms of the anterior communicating artery, two infarcts, one drained abscess, one haemangioma, one encephalemalacia due to a haemorrhage, and one meningioma resection. The average period between referral time and time of testing was 32 months (range: 8–71 months). The 11 right hemisphere patients included three infarcts, three meningioma resections, two oligodendroglioma resections, one astrocytoma resection, one aneurysm of the middle cerebral artery, and one aneurysm of the anterior communicating artery. The average period between onset and time of testing was 41 months (range: 12–111 months). All patients had English as their first language. All but one (right hemisphere lesion) patient was right hand dominant.

Structural MRI scans of all patients' brains were acquired on a 1.5 T scanner (T1-weighted SPGR, 3D, resolution of 0.98 mm × 2 mm × 0.98 mm, whole brain coverage). Lesions were traced on contiguous slices by a neurologist using MRIcro (Rorden & Brett, 2000). Brains were normalized to MNI space using SPM99 (http://www.fil.ion.ucl.ac.uk/spm), with affine plus nonlinear transforms and cost function masking (Brett, Leff, Rorden, & Ashburner, 2001). Fig. 3 illustrates the location and size of the lesions for the 19 patients.

Table 2
Summary of characteristics of the unilateral left frontal patients, the unilateral right frontal patients and the controls

Group	*N*	M/F	Age (years)	Average lesion volume (cubic mm)	NART verbal IQ
Left frontal	8	5/3	51 (10.0)	34590 (34690)	117 (6.2)
Right frontal	11	4/7	56 (8.9)	58270 (46490)	114 (6.8)
Control	20	8/12	56 (8.7)	–	117 (3.8)

M/F = male/female numbers; NART = National Adult Reading Test. Figures in brackets (where given) are standard deviations.

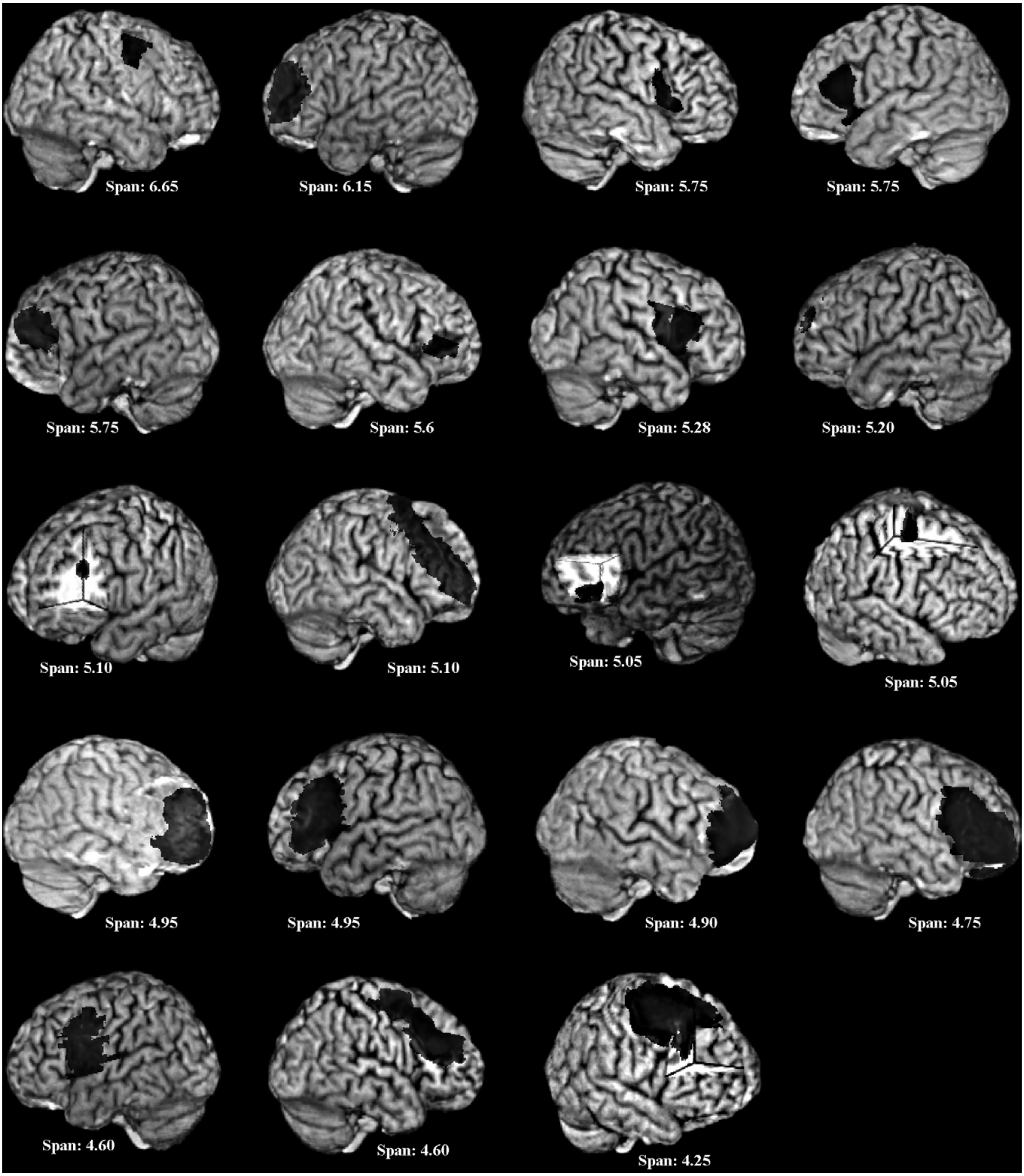

Fig. 3. Normalised structural MRI scans of patients, presented in descending order of span score. Black shading indicates lesion area. Scans were rendered in 3D using MRICRO (http://www.psychology.nottingham.ac.uk/staff/cr1/mricro.html). Lesions appearing largely on the lateral surface include any lesion area within 20 mm of the surface. Lesions that are largely or completely medial have been illustrated by a "cutaway" into medial areas.

Controls were 20 right-handed healthy volunteers from the MRC Cognition and Brain Sciences Unit volunteer panel. All had English as their first language and were matched to patients for sex, age and premorbid IQ, measured with the National Adult Reading Test (Nelson, 1982).

All control subjects and patients gave informed, written consent for participation in the study after its nature and possible consequences had been explained to them. The study was approved by the Local Research Ethics Committee.

3.1.2. Stimuli and testing conditions

3.1.2.1. Structured array span condition. This condition was identical to the structured array span condition described for the PET study, except that the length of each stimulus sequence was not fixed at five items. The initial length of the sequence was three. After each correct trial, the sequence length of the next trial was increased by one. After each incorrect trial, the sequence length of the next trial was decreased by one. Maximum and minimum sequence lengths were eight and one.

3.1.2.2. Non-structured array span condition. The procedure was identical to that used for the structured span condition, except that the non-structured array was used.

3.1.2.3. General condition parameters. After a brief familiarisation with the task, subjects performed two blocks of each condition, with each block lasting 15 trials. Only the last 10 trials were analysed, since in the first 5 trials subjects would invariably be climbing or descending towards their optimum span. Blocks were administered in ABBA order, with the starting condition counterbalanced across subjects. For each condition, span was defined as the mean sequence length in the last 10 trials of each block, collapsing across blocks.

3.2. Results

Initial analyses examined mean span scores across structured and non-structured conditions. The mean span for the patient group (5.23) was worse than for the control group (5.52), but this failed to reach significance ($t = 1.35$, d.f. = 37, $p = 0.09$, 1-tailed). There was no difference in overall span between left (5.32) and right (5.17) patients ($t = 0.53$, d.f. = 17, $p = 0.60$).

A secondary analysis was carried out following a median split of the patient group by lesion volume. There was no difference in mean span score between patients with small lesions ($n = 9$, span = 5.59) and controls ($t = 0.25$, d.f. = 27, $p = 0.80$). However, patients with large lesions (span = 4.91) were significantly worse than both small lesion patients ($t = 3.04$, d.f. = 17, $p = 0.004$, 1-tailed) and controls ($t = 2.42$, d.f. = 28, $p = 0.01$, 1-tailed). In addition, there was a significant correlation between lesion volume and span score ($r = 0.50$, d.f. = 17, $p = 0.015$, 1-tailed) (see Fig. 4).

Further analyses investigated relations between lesion position and span, again collapsed across structured and non-structured conditions. Using the DLPFC and VLPFC ROIs as defined above for the PET study, those patients with damage that included the DLPFC ($n = 12$, span = 5.09) exhibited a trend towards a lower span score than those with damage that entirely spared the DLPFC ($n = 7$, span = 5.49) ($t = 1.49$, d.f. = 17, $p = 0.08$, 1-tailed). However, extent of DLPFC damage significantly correlated with lesion volume ($r = 0.61$, d.f. = 17, $p = 0.005$). When the effect of lesion volume was factored out using an ANCOVA, there was no longer a trend towards lower span score for those patients with damage that included the DLPFC ($F(1, 16) = 0.19$, $p = 0.67$). In contrast, the correlation between lesion volume and span score was still significant when the effect of DLPFC damage was factored out using a partial correlation analysis ($r = 0.40$, d.f. = 16, $p = 0.048$, 1-tailed).

Patients with damage to the right DLPFC ($n = 7$, span = 4.83) had a significantly lower span score than those with left DLPFC damage ($n = 5$, span = 5.44) ($t = 2.15$, d.f. = 10, $p = 0.03$, 1-tailed) or with controls ($t = 2.36$, d.f. = 25, $p = 0.01$, 1-tailed). However, the difference between left and right DLPFC patient span scores no longer reached significance when lesion volume was factored out using an ANCOVA ($F(1, 11) = 1.66$, $p = 0.115$, 1-tailed). There was no difference in span score between those patients with damage to the VLPFC ($n = 8$, span = 5.22), and those with no damage ($n = 11$, span = 5.24) ($t = 0.07$, d.f. = 17, $p = 0.95$). In addition, no hemispheric differences in patients with VLPFC damage were found.

Separating out the structured and non-structured conditions revealed no significant group by span condition interactions, either when comparing patients with controls, or when splitting patients according to lesion hemisphere, lesion volume, VLPFC damage, or DLPFC damage.

3.3. Discussion

In accord with the PET study, the results from the patient study confirm frontal lobe involvement in spatial working memory. Patients with large lesions of the frontal lobe, or with specific damage to the right DLPFC, were significantly

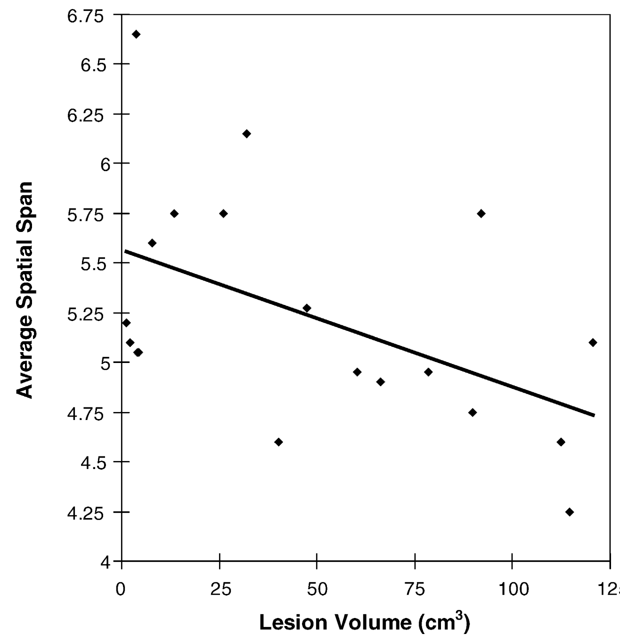

Fig. 4. Scatter plot of relationship of average span score to lesion volume, with best fitting regression line.

impaired on the spatial span task. To our knowledge, no previous studies show a significant spatial span impairment in frontal lobe patients (Canavan et al., 1989; Greenlee et al., 1997; Miotto et al., 1996; Owen et al., 1990). Quite possibly, trends toward impairment in previous studies were non-significant because of low task sensitivity or low statistical power. The present findings confirm that, with more sensitive testing methods, a significant difference can be observed.

The evidence that those patients with DLPFC damage, especially in the right hemisphere, were particularly impaired compared with non-DLPFC patients, is closely in line with neuroimaging studies of spatial span, where right DLPFC activations are the most consistent area reported (Bor et al., 2001; Bor et al., 2003; Bor et al., 2004; Kondo et al., 2004; Pochon et al., 2001). However, it should be noted that this result might be confounded by lesion volume, since larger frontal lesions were more likely to include DLPFC damage.

In the PET study, a non-structured array span task yielded significant activation in the VLPFC. Similar results have been reported previously in two PET studies using comparable stimuli (Owen, Evans et al., 1996; Owen et al., 1999). In addition, the structured array span task yielded significant increases in both VLPFC and DLPFC. In the right VLPFC ROI, there was a non-significant trend towards greater activity for the structured, compared with the non-structured array span condition, while no other ROIs approached significance. These results are broadly similar to other studies examining differences in lateral prefrontal activity when comparing structured and non-structured information (Bor et al., 2003; Bor et al., 2004). However, in this case no additional DLPFC activations were observed for the structured versus the non-structured conditions. While other studies have used fMRI (Bor et al., 2003; Bor et al., 2004), this study involved the less powerful imaging method of PET, which might explain why fewer prefrontal differences were observed. It is also possible that manipulating the array only, rather than maximising the level of structure of individual spatial sequences themselves (Bor et al., 2003), is an inefficient paradigm to induce a strategic difference in the way the subjects approach the span conditions.

Almost all significant activations occurred in the right hemisphere. This was broadly consistent with the results of the patient study, which showed that right DLPFC patients were significantly worse than both left DLPFC patients and controls. In addition, the right frontal lobe patients overall performed non-significantly worse than the left frontal lobe patients. These results also concur with the suggestion that the right frontal lobe is preferentially involved in spatial tasks (Smith, Jonides, & Koeppe, 1996). Though the present results clearly show prefrontal involvement in a simple span task, it remains uncertain precisely what role this region plays. Recent fMRI evidence has suggested that superior parietal cortex might be at least as important a region for the storage of visual working memory items (Todd & Marois, 2004). Simple though they are, spatial span tasks have a number of components, including temporal sequencing as well as spatial memory. In addition, evidence from frontal lobe patients has implicated the frontal lobes in strategy formation and maintenance (Morris et al., 1999; Owen, Morris, Sahakian, Polkey, & Robbins, 1996; Shallice & Burgess, 1991), including application of a searching strategy in a spatial working memory task (Owen, Morris et al., 1996). To some extent, such processes are likely to contribute to any task, even one as simple as spatial span. It therefore seems likely that the observed working memory impairment in the current patient study should not be simply attributed to impaired storage. At least as important may be broader deficits in strategy production, goal maintenance (Duncan, Emslie, Williams, Johnson, & Freer, 1996), or other aspects of task organisation. Meanwhile, our data resolve some of the apparent discrepancy in the previous literature. As previously suggested by imaging data, and now confirmed by our lesion evidence, frontal cortex does play some significant role in spatial span performance.

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