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Prefrontal cortical involvement in verbal encoding strategies

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Abstract

The lateral prefrontal cortex is critical for the control and organization of information in working memory. In certain situations, effective reorganization can attenuate task difficulty, suggesting a dissociation between lateral prefrontal activity and basic memory demand. In a verbal working memory task, we investigated the enhancement of performance that occurs when incoming information can be reorganized into higher-level groups or chunks. In the fMRI scanner, volunteers heard and repeated a sequence of digits. Mathematically structured sequences, encouraging 'chunking', were compared with unstructured, random sequences. Though structured sequences were easier to remember, fMRI showed increased lateral prefrontal activation for these sequences. Specifically, both the dorsolateral and ventrolateral prefrontal cortices were activated preferentially for the structured sequences during encoding. When visual stimuli that can be chunked using spatial structure are used, similar results are observed. These results demonstrate that cognitively less demanding tasks may elicit greater lateral prefrontal recruitment. Thus, the lateral prefrontal cortex appears to play a general role in strategically recoding information from memory, in order to optimize performance.

Introduction

Many studies have demonstrated that the prefrontal cortex (PFC) plays an important role in working memory (WM) (Owen, 1997; Fletcher & Henson, 2001). Early studies in monkeys indicated that this role was limited to WM storage (Funahashi *et al*., 1989; Wilson *et al*., 1993), although this view has been recently challenged (D'Esposito & Postle, 1999). More recent evidence, primarily from human neuroimaging studies, has suggested that the PFC – especially the dorsolateral prefrontal cortex (DLPFC) – also plays a role in the monitoring, control and organization of WM contents (Petrides, 1994; Owen, 1997; D'Esposito *et al*., 1998; Owen, 2000). Such terms, however, are difficult to define operationally and, in previous studies, a confounding factor has been task difficulty. The DLPFC is recruited, for example, when the items in a WM list must be rearranged in reverse (Owen *et al*., 2000) or alphabetical (Postle *et al*., 1999) order prior to making a response. Clearly in both of these cases the task is considerably more difficult when reorganization is required. This confound is important because increasing task difficulty is itself associated with DLPFC activation in many different cognitive domains (Duncan & Owen, 2000).

Neuropsychological data suggest that the PFC is also necessary for strategic control. Patients with prefrontal damage use poor strategies and exhibit behavioural incoherence when carrying out complex tasks (Petrides & Milner, 1982; Shallice & Burgess, 1991). In some circumstances, strategic processes are recruited in order to improve performance and thus lessen WM demand. In the WM literature, the best-studied strategy is performance improvement through 'chunking' (Miller, 1956). Chunking, as outlined by Miller (1956), is a key cognitive process that involves the recoding of a set of data into a more compressed, efficient form, thus extending WM capacity.

Chunking usually involves reorganizing material into familiar or regular structures and can sometimes improve WM performance very substantially (Ericcson *et al*., 1980). For instance, Ericcson *et al*. (1980) repeatedly gave digit span tests (memorising strings of digits) to a volunteer over a 20-month period. Due to the acquisition of increasingly sophisticated chunking strategies, the volunteer increased his digit span from 7 to 79 digits. In addition, in domains from sending and receiving Morse code (Bryan & Harter, 1899) to chess (Chase & Simon, 1973), chunking has been proposed as the major basis for increasing expertise through learning.

In a recent study using fMRI, strategic chunking was utilized by normal subjects to lessen WM demand, while increasing lateral prefrontal recruitment (Bor *et al*., 2003). Spatially structured sequences of locations, encouraging reorganization and chunking, were compared with unstructured sequences. Though structured sequences were easier to remember (as they tended to contain symmetries and regular patterns), event-related fMRI showed increased activation of lateral PFC (LPFC) for these sequences, in particular during memory encoding. Although further behavioural evidence supported the claim that the dissociation found between PFC activity and WM demand was due to chunking of the structured sequences, it remains unclear whether this result is specific to the visuo-spatial domain.

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Previous studies have clearly shown a multimodal role for LPFC in WM (Owen *et al*., 1999; Fuster *et al*., 2000; Henson *et al*., 2000; Martinkauppi *et al*., 2000). Therefore, it seems likely that the LPFC will be activated when chunking is involved, irrespective of stimulus domain. In this study, auditory–verbal stimuli that could be chunked mathematically were used to test this hypothesis. We predicted that, due to strategic reorganization, LPFC increases in activity would be observed, which would again be associated with a less demanding version of the task.

Materials and methods

Imaging study

Participants

In total, 14 right-handed participants (12 female, all aged 19–37) were scanned for ≈40 min of echo planar imaging (EPI) (20 min on an unrelated study) and 15 min for a structural scan. 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 Cambridgeshire Local Research Ethics Committee.

Stimuli

The digits one to nine, spoken by a native English speaking male, were recorded using a Digital Audio Tape (DAT) recorder at a 44.1 kHz sampling rate and 16-bits per sample. DAT recordings were made in a sound-proof room with recording equipment located outside the room. These were down-sampled to 22.05 kHz mono sound files, for playback using headphones in the scanner.

All sequences were eight digits in length. Two different types of sequence were presented. Structured sequences were made up of portions no longer than five digits in length of runs of either ascending or descending adjacent, even or odd numbers. An example of a structured sequence is: 8, 6, 4, 2, 3, 5, 7, 9. Unstructured sequences had no two contiguous numbers that followed any type of structured pattern (adjacent, even or odd runs). In addition, the unstructured sequences were designed to appear to be as random as possible, by avoiding any other type of obvious pattern (e.g. involving simple arithmetic patterns such as 3, 6, 9). Due to these constraints, the numerical distance between any two contiguous digits in a given sequence was generally greater if it was unstructured than if it was structured.

Task

For each trial, subjects were visually presented with a cross on a projector screen to indicate the start of the auditory presentation of a novel sequence of eight digits. Each digit was presented for 0.75 s. Following this, there was a variable delay of between 4 and 8 s, after which the word 'RECALL' was visually presented to indicate that the subjects were verbally to respond by repeating the sequence exactly as they had just heard it. Subject responses were recorded onto DAT tape in order to be able to analyse behavioural responses. However, unexpected technical difficulties meant that this behavioural data could not be analysed. From the commencement of the response to the start of the subsequent trial there was a variable delay of between 12.5 and 16.5 s. Subjects were not informed that there were different types of trials. The different trial types were pseudo-randomly interleaved during each run. Fourteen trials were presented for each run, and two runs were given to each subject, in addition to an initial practice session outside the scanner.

fMRI data acquisition and analyses

Subjects were scanned at the Wolfson Brain Imaging Centre (Cambridge, UK) on a 3T Bruker scanner using a head coil. Functional images were collected using 21 slices covering the whole brain (slice thickness 4 mm, interslice distance 1 mm, in-plane resolution 3.91×3.91 mm) with an EPI sequence (TR, 1.1 s; TE, 27.5 ms; flip angle, 65.5°). Five hundred and forty scans were acquired per run, including 18 dummy scans.

All fMRI data were processed and analysed using SPM99 software (Wellcome Department of Cognitive Neurology, London). Prior to analysis, all images were corrected for slice timing, with the middle slice in each scan used as a reference. Images were realigned with respect to the first image using trilinear interpolation, creating a mean realigned image. Using the mean realigned image, all images were normalized using affine and smoothly nonlinear transformations to an EPI template in Montreal Neurological Institute (MNI) space. Finally, all normalized images were spatially smoothed with a 10 mm full width, half maximum Gaussian kernel.

For the analysis, each trial was split into three events: encoding, delay and retrieval. Single subject statistical contrasts were set up by using the general linear model to fit each voxel with a combination of functions derived by convolving the standard haemodynamic response with the time series of the events and removing low-frequency noise with a high-pass filter. Group data were analysed with a random effects analysis. All reported peaks were from the group analysis, had to pass a whole-brain false detection rate (FDR) (Benjamini & Hochberg, 1995; Genovese *et al*., 2002) threshold of $P < 0.05$, and were required to be at least 20 voxels in volume. The FDR approach controls for the expected proportion of false positives among suprathreshold voxels. An FDR threshold is determined from the observed *P*-value distribution, and hence is adaptive to the amount of signal within a given contrast (Genovese *et al*., 2002).

All reported coordinates underwent a transformation from normalized MNI space to Talairach space (http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html), in order to ascertain more precisely the site of activation relative to the atlas of Talairach & Tournoux, (1988).

An additional region of interest (ROI) analysis was carried out to directly test differential activation between the trial types in two specific frontal regions associated classically with WM tasks – mid-DLPFC and mid-ventrolateral PFC (VLPFC) (Duncan & Owen, 2000). The DLPFC ROI centres were −40, 28, 19 (left) and 35, 31, 22 (right), while the VLPFC ROI centres 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. These ROIs are identical to those used in our previous spatial span chunking study (Bor *et al*., 2003). In order to analyse the ROIs, an in-house software suite was used: (http://www.mrc-cbu.cam.ac.uk/Imaging/marsbar.html). For each ROI, a *t*-test was performed to compare the mean voxel value during the structured vs. the unstructured trials, as based on the whole brain group analysis.

Behavioural study

Subjects

In total, 30 right-handed subjects participated in the experiment (12 female; all aged 19–35). 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 Cambridgeshire Local Research Ethics Committee.

Stimuli and task

The task, stimulus set, and all timing parameters were identical to that of the imaging study, except that on seeing the word 'RECALL' subjects responded by typing in the sequence of digits on a keypad in front of them. This form of response was used in order to test

whether reaction times, in addition to accuracy scores, was different between the conditions.

Results

Behavioural study

Each trial was marked out of eight. A single response in a trial was marked correct if it matched the number and temporal position during presentation. The structured trials were performed significantly more accurately than the unstructured trials (87.6% vs. 81.3% for structured and unstructured trials, respectively; $t_{29} = 7.66$, $P < 0.01$). Although subjects weren't explicitly requested to make their responses as quickly as possible, structured trial responses were also significantly faster than unstructured trials (570 ms vs. 604 ms for structured and unstructured single responses, respectively; $t_{29} = -3.37$, $P < 0.01$). In addition, the majority of subjects when asked afterwards both recognized that some sequences involved structure, and found these trials easier to perform.

Imaging study

During encoding, structured trials yielded significantly greater activity than unstructured trials in a number of prefrontal regions (Fig. 1A and Table 1). Specifically, signal intensity increases were observed bilaterally in the inferior portion of the lateral surface, superiorly in premotor and supplementary motor regions, on the anterior surface, and within the posterior portion of the anterior cingulate. The caudate nucleus was the only subcortical structure to be active for this contrast. Outside the frontal lobes, there was significant activation in both inferior and superior parts of the parietal lobe, as well as posterior lateral temporal cortex regions.

During the delay between stimulus presentation and response, structured trials showed significantly greater activation than unstructured trials bilaterally in the hippocampus and parahippocampal gyrus, and in the left inferior parietal lobule (Table 2).

The reverse comparisons between unstructured and structured trials revealed no regions of significantly increased neural activity during either encoding or delay, even when the FDR threshold was lowered to $P < 0.50$.

The response events were not analysed due to subject movement related to verbal responses.

For the ROI analysis, during encoding, there was significantly greater activation for the structured, compared with the unstructured, sequences for the left DLPFC ROI ($t = 2.07$, $P = 0.029$) and VLPFC ROI ($t = 3.35$, $P = 0.002$), with the right DLPFC ROI approaching significance ($t = 1.71$, $P = 0.055$). However, no increases were found for the right VLPFC ROI. During the delay, no ROIs showed a significant increase for structured, compared with unstructured sequences, although the left VLPFC ROI alone was significant for the opposite contrast ($t = 2.21$, $P = 0.023$).

Discussion

Previous behavioural studies involving mathematically structured digit sequences have established that chunking does indeed occur with such stimuli (Koch & Hoffmann, 2000). In line with this, data from the current behavioural study indicated that a significant component of the verbal WM task was the reorganization of structured digit sequences into higher-level mathematical chunks. Performance on the structured sequences was enhanced relative to the unstructured sequences. In addition, both in the behavioural and fMRI studies, subjects tended to find the structured trials easier to perform.

The results of our fMRI study further demonstrated that the use of such chunking strategies during encoding relies largely on the recruitment of specific LPFC regions. Thus, for the mathematically structured sequences during encoding, significantly increased activity was observed bilaterally in the LPFC. A ROI analysis applied to the VLPFC and DLPFC confirmed that both these regions were more active for the structured sequences.

The extensive bilateral parietal activation observed for the structured trials during encoding may reflect the additional mathematical processes associated with these sequences. Previous studies with both humans and monkeys have demonstrated a critical role for the parietal lobe in mathematical tasks (Dehaene *et al*., 1998; Sawamura *et al*., 2002). On this basis, we suggest that in order to increase performance, the lateral PFC selectively relates the structured sequences to mathematically based information from memory, which increases activation in the parietal cortex. In this way, the lateral PFC plays an essential role in selecting appropriate high-level organizational chunks which then serve to facilitate memory by reducing overall cognitive load.

During the delay, increases were observed for the structured trials bilaterally in the hippocampus. This is broadly consistent with a recent WM study that reported hippocampal activation during delay, but not during encoding or recognition of face stimuli (Ranganath & D'Esposito, 2001). In this study, increased hippocampus activity relating specifically to the structured trials may reflect more effective rehearsal strategies that are likely to be associated with these stimuli. Alternatively, such activity might be due to an additional long-term memory component of the structured trials as it is well known that chunking greatly increases chances of accurate long-term retrieval of working memory items (Ericcson *et al*., 1980).

No activation was observed during delay in the whole brain analysis for the random compared with the maths trials, even at reduced thresholds. However, there was significantly greater activity for the random trials in the predefined left VLPFC region for the ROI analysis. Various studies have suggested that inferior portions of the left LPFC, including Broca's area, are centrally involved in rehearsal of verbal material (Chein & Fiez, 2001). Therefore, this reduction in activation for the maths trials during rehearsal might reflect the fact that these sequences were encoded in a more efficient form.

The results of this study relate closely to those of a previous investigation involving spatial stimuli (Bor *et al*., 2003) (Fig. 1B). In that study, healthy volunteers were required to remember structured and unstructured spatial stimuli in the fMRI scanner. In both studies, when compared with the unstructured trials, the structured trials yielded considerable lateral PFC activation, including the DLPFC (Fig. 1). Therefore, the current results indicate that the LPFC recruitment in strategically using chunking is modality independent.

Previous studies have reported additional PFC activity when a task involving manipulation of WM items is compared to a more basic, though performance-matched, WM task (Postle *et al*., 1999). Although such studies indicate that PFC activation need not correlate with difficulty, the absence of a behavioural difference could reflect insensitivity in the design. However, the current study and that of a related previous investigation (Bor *et al*., 2003) demonstrate that it is possible to dissociate PFC activity from task demand.

It is of course conceivable that there are functional subdivisions based on modality within the large areas of PFC activated by the structured sequences, but that these were undetected, given the spatial resolution parameters available. Recent single-unit recording evidence in monkeys, however, indicates that there is no such differentiation in the LPFC (Rao *et al*., 1997; Rainer *et al*., 1998a,b; Asaad *et al*., 2000;

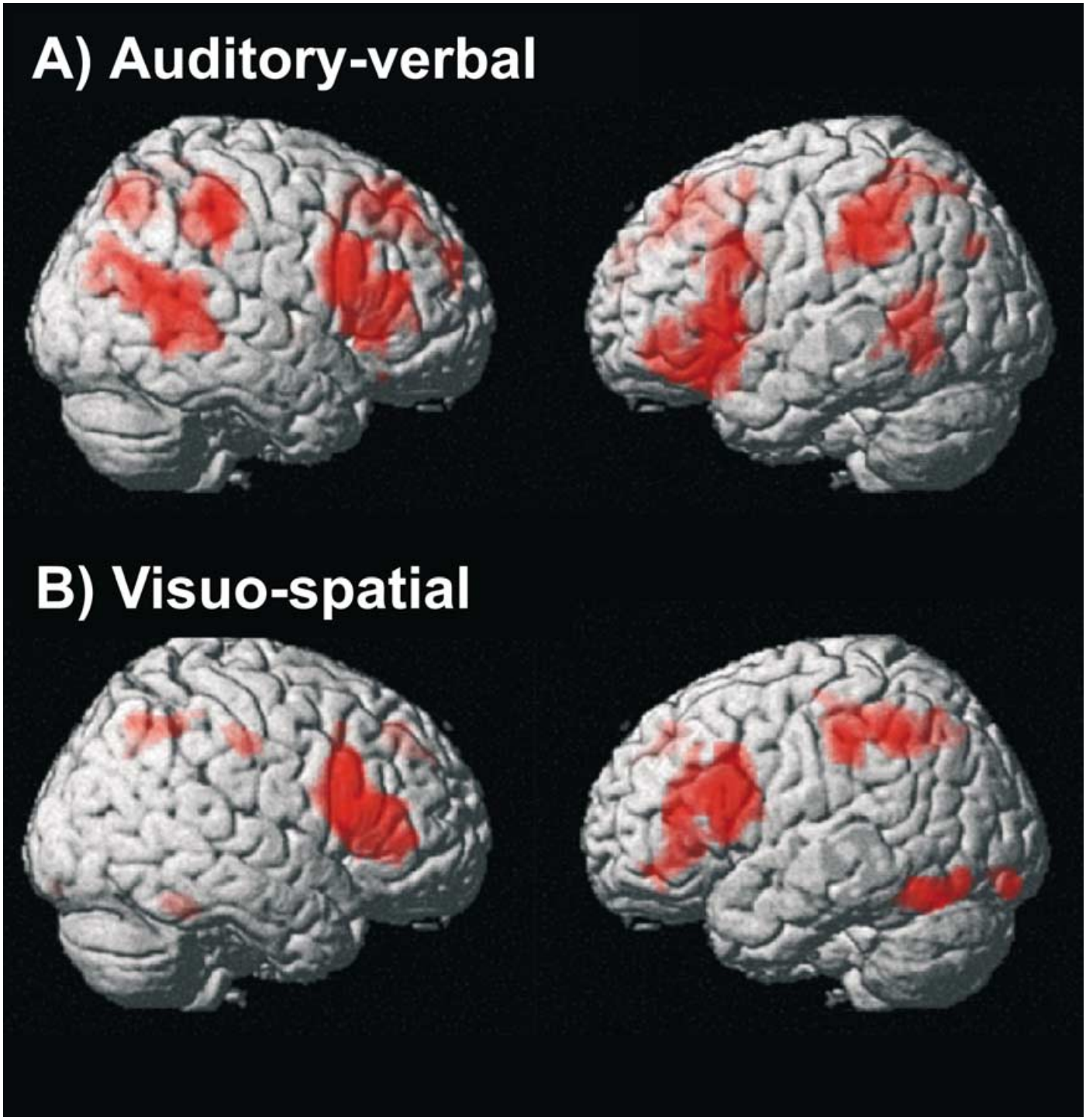

FIG. 1. Regions of increased activation during encoding for structured trials as compared to unstructured trials. (A) The auditory-verbal task of the current study. (B) The spatio-temporal task of a previously published study (Bor *et al*., 2003). Activations are those exceeding a whole-brain false detection rate threshold of $P < 0.05$, and a cluster size of 20, rendered onto the canonical T1-weighted brain image of SPM99.

Fuster *et al*., 2000). Instead, neurons distributed throughout the lateral prefrontal surface exhibit activity that is independent of stimulus modality, but reflects the subgoals of the task currently being performed. For example, Rao *et al*. (1997) showed that same prefrontal neurons can code for either location or object, depending on the task context. One alternative possibility is that various subprocesses within chunking are mediated by different areas within LPFC. For instance, discrete prefrontal regions may be involved in the search for suitable data to be chunked, the recoding of that information into useful memory chunks, and the production of feedback as to the efficiency gained by the specific form of chunking used.

Another cognitive domain regularly associated with the PFC is fluid intelligence. Several neuroimaging studies have demonstrated a positive correlation between PFC activity and IQ (Duncan *et al*., 2000; Gray *et al*., 2003). In addition, neuropsychological data demonstrates that patients with frontal lobe damage are impaired at fluid intelligence

TABLE 1. Peak increases in activation for structured compared to unstructured sequences during encoding

Brain region and Brodmann area	Coordinates			*t*-Score
	x	*y*	*z*	
Anterior PFC				
BA 10	12	59	22	4.36
R. lateral PFC				
BA 45	50	33	9	4.91
BA 47	50	20	−1	4.30
BA 44	48	9	13	6.03
L. lateral PFC				
BA 47	−42	28	−22	5.97
BA 45	−56	21	4	6.81
BA 47	−50	17	−3	6.79
Superior PFC/premotor cortex				
BA 8	15	40	39	5.11
BA 8	−9	40	37	5.36
BA 8	−6	28	43	6.55
BA 6	−27	14	49	3.78
Anterior cingulate				
BA 24	0	13	19	4.29
BA 24	0	7	27	3.66
BA 24	0	−2	28	4.02
R. inferior parietal lobule				
BA 40	48	−30	48	5.60
BA 40	59	−30	43	5.58
BA 40	42	−39	38	5.72
L. inferior parietal lobule				
BA 40	−62	−22	29	4.89
BA 40	−56	−33	35	6.05
R. superior parietal cortex				
BA 7	21	−62	50	5.03
L. precuneus				
BA 7	−15	−47	60	5.25
R. lateral temporal cortex				
BA 22	56	−43	16	5.29
BA 22	50	−49	11	5.10
BA 21	59	−52	0	5.46
L. lateral temporal cortex				
BA 21/22	−48	−55	11	4.29
BA 22	−42	−57	17	4.29
BA 37	−59	−58	−2	4.71
Subcortical				
Caudate nucleus	−12	12	−1	5.00

All reported peaks passed a whole-brain false detection rate (Benjamini & Hochberg, 1995; Genovese *et al*., 2002) threshold of $P < 0.05$, and were required to be at least 20 voxels in volume. Coordinates underwent a transformation from normalized MNI space to Talairach (Talairach & Tournoux, 1988). BA, Brodmann area; R., right; L. left.

TABLE 2. Peak increases in activation for structured compared to unstructured sequences during delay

Brain region	Coordinates			*t*-Score
	x	*y*	*z*	
R inferior parietal lobule				
BA 40	42	−69	45	7.22
L subcortical				
Hippocampus	−27	−9	−27	6.49
Hippocampus	−33	−18	−18	10.62
Parahippocampal gyrus	−30	−27	−24	6.48
R subcortical				
Hippocampus	36	−15	−21	5.64
Parahippocampal gyrus	39	−24	−24	5.92

For table description, see Table 1. BA, Brodmann area.

tests (Duncan *et al*., 1995). In order to examine the psychological components of fluid intelligence, Carpenter *et al*., (1990) analysed the performance of volunteers on the Raven Progressive Matrices Test (Raven, 1962). The core component for successful performance on the test was a 'strategy for encoding and inducing the regularities in each problem.' The discovery and encoding of regularities within each sequence of digits in the current study is similar in many respects to this fundamental aspect of fluid intelligence tests. Therefore, cognitive components underpinning chunking in the current study might also significantly contribute to the association between the PFC and fluid intelligence.

One possible confound in the current study is the lower error rate for the structured trials, as indicated by the behavioural study. Consequently, the greater LPFC activation for these trials might reflect more consistent WM processes, rather than the preferential involvement of recoding strategies. This possibility is unlikely, however, because in the previous study, which was methodologically identical except for the modality of the stimuli used, the analysis was performed both with and without error trials excluded, and almost identical results were found (Bor *et al*., 2003). Unfortunately, technical difficulties with recording the volunteers' voices during scanning precluded such an analysis in the current study.

A further potential confound in the current study is the possibility that subjects were merely recognizing regular mathematical patterns during the structured trials, rather than using these to assist them with the task. This is again unlikely, however, because in the previous study (Bor *et al*., 2003), a control fMRI experiment was performed where subjects merely observed the same structured and unstructured sequences, and after a delay had to report whether they had perceived a structured pattern or not. There was no increased prefrontal activation during the recognition of a structured trial, relative to an unstructured trial. In fact, there was a significant study by trial interaction, such that the LPFC was only significantly more active for the structured trial when it was within the context of the WM task (Bor *et al*., 2003).

Prior neuropsychological data support the role of PFC in applying strategies to obtain greater proficiency in WM tasks. Patients with frontal-lobe damage are impaired on some WM tests due to the inefficient use of organizational strategies, which improve performance in healthy controls (Petrides & Milner, 1982; Owen *et al*., 1996). Importantly, if such tasks are modified such that no obvious strategy exists to facilitate performance, frontal-lobe patients can perform normally despite the fact that task difficulty may be substantially increased (Owen *et al*., 1996).

Many human (Jonides *et al*., 1997; Owen, 1997; Owen *et al*., 1998; Cabeza & Nyberg, 2000; Bor *et al*., 2001; Fletcher & Henson, 2001) and animal (Petrides, 1995; Rao *et al*., 1997; Goldman-Rakic, 1998; Petrides, 1998; Rainer *et al*., 1998a; Miller & Cohen, 2001) studies have examined the role of the PFC in WM and have suggested contributions to encoding, storage and retrieval (Goldman-Rakic, 1998; Postle *et al*., 1999). A frequent result, however, in neuroimaging has been simple increase of recruitment with increasing task difficulty or demand (Duncan & Owen, 2000). Our results provide further evidence that, for a large region of prefrontal cortex including DLPFC, this common effect of task difficulty can be reversed. Regardless of the modality or type of information to be recoded, prefrontal cortex plays a specific role in the recognition and use of suitable information chunks to facilitate memory performance.

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Abbreviations

DLPFC, dorsolateral prefrontal cortex; EPI, echo planar imaging; FDR, false detection rate; PFC, prefrontal cortex; ROI, region of interest; VLPFC, mid-ventrolateral PFC; WM, working memory.

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