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Encoding Strategies Dissociate Prefrontal Activity from Working Memory Demand

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Summary

It is often proposed that prefrontal cortex is important in organization and control of working memory contents. In some cases, effective reorganization can decrease task difficulty, implying a dissociation between frontal activity and basic memory demand. In a spatial working memory task, we studied the improvement of performance that occurs when materials can be reorganized into higher level groups or chunks. Structured sequences, encouraging reorganization and chunking, were compared with unstructured sequences. Though structured sequences were easier to remember, event-related functional magnetic resonance imaging (fMRI) showed increased activation of lateral frontal cortex, in particular during memory encoding. The results show that, even when memory demand decreases, organization of working memory contents into higher level chunks is associated with increased prefrontal activity.

Introduction

Neuropsychological data suggest that the prefrontal cortex plays a key role in behavioral organization and control. In complex tasks, for example, patients with prefrontal damage use poor strategies and exhibit behavioral incoherence (Shallice and Burgess, 1991). Here we investigate the role of prefrontal cortex in organizational strategies used to decrease working memory demand.

Undoubtedly prefrontal cortex makes an important contribution to working memory. Though some studies emphasize simple working memory storage, neuroimaging data have also suggested that the prefrontal cortex—especially the dorsolateral prefrontal cortex (DLPFC)—plays a role in the monitoring, control, and organization of working memory contents (D'Esposito et al., 1998; Owen, 1997, 2000; Petrides, 1994). Such terms, however, can be hard to define operationally, and in previous studies, a complicating factor has been simple task difficulty. The DLPFC is recruited, for example, when the contents of a working memory list must be rearranged in reverse (Owen et al., 2000) or alphabetical (Postle et al., 1999) order prior to making a response. Evidently, in such cases the task is substantially harder when reorganization is required. This confound is important because increasing task difficulty is itself associated with DLPFC activation in many different cognitive domains (Duncan and Owen, 2000).

In the present study we sought direct evidence for a role of prefrontal cortex in a well-defined working memory strategy. In the working memory literature, the best-studied strategy is perhaps performance improvement through chunking. An opportunity to reorganize materials into familiar or regular structures can increase working memory capacity, sometimes very substantially (Ericcson et al., 1980). In domains from sending and receiving Morse code (Bryan and Harter, 1899) to chess (Chase and Simon, 1973), chunking has been proposed as the major basis for increasing expertise through learning. We investigated chunking in a standard spatial working memory task by manipulating the extent to which sequences of stimuli could be encoded into memory as simple configural representations. We predicted that trials that allowed such chunking would be less difficult to remember than trials that did not allow chunking. Despite this decrease in task difficulty, we predicted increased recruitment of the lateral prefrontal cortex.

In an initial, large-scale behavioral study, we acquired direct evidence that reorganization of structured sequences into higher level chunks is an effective strategy in spatial working memory. In a second study, we used event-related functional magnetic resonance imaging (fMRI) to compare brain activity during structured and unstructured sequences. A control fMRI study shows that the difference between structured and unstructured sequences is specifically associated with their role in the working memory task.

Results

Behavioral Study

Working memory for spatial sequences was tested using a modified spatial span task in which participants were required to remember sequences of locations on a 4 × 4 grid (Figure 1). Each participant's spatial span was calculated as the mean number of locations that could be recalled successfully following a single presentation. For any one participant, the sequences were either all structured, using an algorithm which tended to produce sequences containing familiar shapes, such as right angled triangles and parallelograms (Figure 1A), or all unstructured, using an alternative algorithm that produced sequences with less symmetry and fewer parallel sides (Figure 1B). The group that was presented with the structured sequences performed significantly better than the group that was presented with the unstructured sequences (mean span = 5.84 versus 5.05, $F[1, 210] = 56.79$, $p < 0.001$, see Figure 2).

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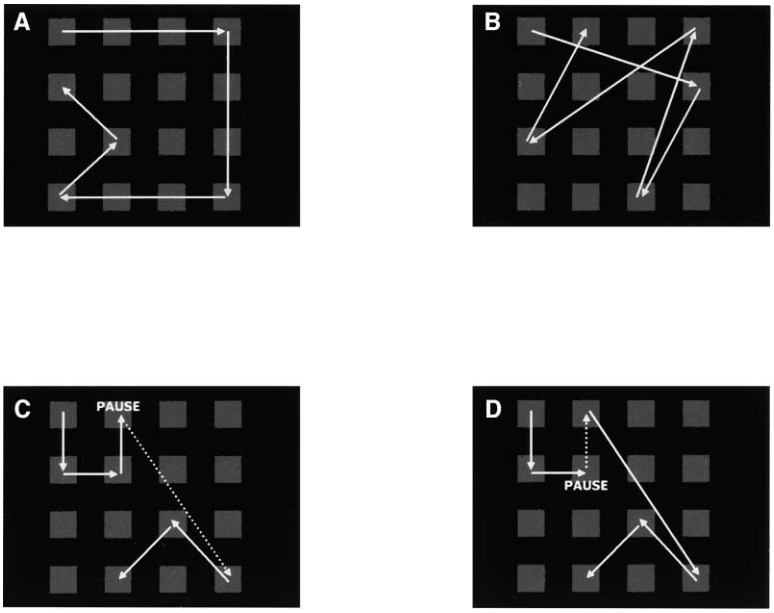

Figure 1. Example Trials from the Four Conditions of the Spatial Span Task

On each trial, participants memorized a sequence of locations. A set number of boxes in turn changed color from red to blue, followed by a test of recall (see Experimental Procedures). In structured trials (A), the sequence followed a predetermined rule which tended to produce orderly visuospatial configurations. In unstructured trials (B), such configurations were avoided. In temporally congruent trials (C), a brief interruption during the middle of the sequence effectively split it into two entirely structured sections, while in incongruent trials (D), a similar brief interruption effectively split the sequence into two semistructured sections.

Two further groups of participants were given sequence variants designed either to interfere with, or to facilitate, the organization of remembered material based on spatial encoding strategies. For one group of participants, sequences were interrupted briefly by a pause in presentation at a point that was congruent with the overall spatial configuration (i.e., divided the entire sequence into two spatially structured sequences; see Figure 1C). For a second group of participants, sequences were interrupted by a pause at a point that was not congruent with the overall spatial configuration (Figure 1D). The group who were presented with the temporally congruent sequences performed significantly better than the group who were presented with the temporally incongruent sequences (5.73 versus 5.46, $F[1, 200] = 4.45$, $p < 0.036$, see Figure 2).

In an additional behavioral study, participants rated the extent to which perceived spatial structure in each sequence would be helpful in memory. Four-location-structured and -unstructured sequences from the fMRI study (see below) were employed. On a scale of 1–10, mean ratings for structured and unstructured sequences were 7.47 versus 2.21 ($t = 21.47$, d.f. $= 56$, $p < 0.001$).

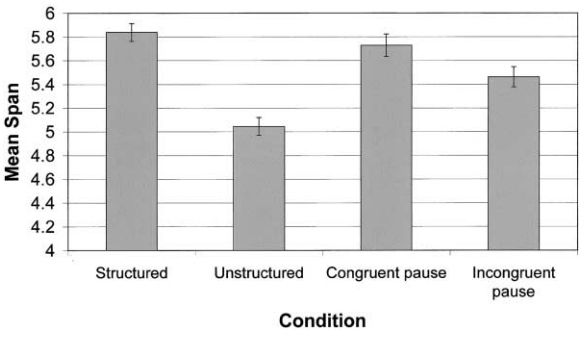

Figure 2. Mean Spans Achieved in the Four Conditions of the Spatial Span Working Memory Task

Bars represent standard error of the mean.

Together, these behavioral data suggest that, though subtle, our chunking manipulation was sufficient to alter the perceived structure and memorability of spatial sequences. As in other cases of chunking, memory was improved by an opportunity to reorganize materials into familiar structures or patterns.

Imaging Study

Event-related fMRI was used to examine the neural correlates of the observed improvement in performance in the structured sequence condition (condition 1; Figure 3A) relative to the unstructured sequence condition (condition 2; Figure 3B). Structured and unstructured trials were presented in a pseudo-random order, with participants given no indication that trials differed in this way. For this experiment, the sequence length was fixed at 4. Again, recall was significantly more accurate (95.8% versus 89.6% sequences correct, $t = 6.54$, d.f. $= 15$, $p < 0.001$), as well as being faster (time to make complete response 2.54 s versus 2.78 s, $t = 6.27$, d.f. $= 15$, $p < 0.001$) for the structured sequences.

Analysis of the fMRI data identified statistically significant differences in cortical activity between the two types of trials. For this purpose, each "event" was considered to be the entire trial, from the presentation of the first stimulus to the execution of the fourth and final response. We report results of analyses including all trials, though essentially identical results were obtained following exclusion of trials with erroneous responses. To correct for multiple comparisons, we set a whole-brain false detection rate (Benjamini and Hochberg, 1995; Genovese et al., 2002) threshold of $p < 0.01$.

Structured trials yielded significantly greater activity than unstructured trials in the lateral prefrontal cortex, the inferior parietal lobe, and the fusiform gyrus of both hemispheres (Figure 4; Table 1). There were additional small clusters of activation in medial frontal and right sensorimotor cortex (Table 1). The reverse comparison between unstructured trials and structured trials re-

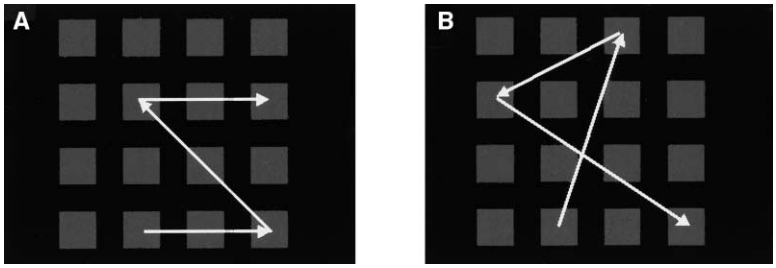

Figure 3. Example Trials from the Two Types Presented to Participants in the fMRI Study

Structured trials (A) and unstructured trials (B) were generated from the same rules as in the behavioral study (see Figure 1 and Experimental Procedures).

vealed no regions of significantly increased neural activity, even when the false detection rate threshold was lowered to $p < 0.50$.

A supplementary analysis was conducted to examine separately the encoding (sequence presentation), maintenance/rehearsal (delay period), and retrieval (response generation) stages of structured and unstructured trials. Results from the encoding analysis closely mirrored those of the whole-trial analysis; thus, comparison of structured and unstructured trials again showed significantly increased activity bilaterally in the lateral frontal cortex, the inferior parietal lobule, and the fusiform gyrus. During the delay phase, no significant activations were found for the structured minus unstructured comparison. However, the opposite contrast yielded significant activation largely in parietal cortex, particularly on the right (coordinates 30 −50 53 for right, −30 −46 48 and −12 −54 50 for left), with additional activation in occipital and premotor cortices. There were no significant differences between the trial types during the response phase. Separate estimates of activation for each task stage showed greatest lateral prefrontal increases at encoding, along with the greatest difference between structured and unstructured trials (Figure 5).

A second supplementary analysis was conducted to examine the relationship between neural activity and the ease with which the structure aided recall of each sequence as directly rated in the behavioral study described above. Entering the mean rating for each sequence as a covariate of interest into the imaging analysis revealed that activity within the right lateral frontal cortex (coordinates 60 20 10), the left fusiform gyrus (coordinates −50 −60 −18), and the right inferior parietal lobule (56 −56 40) correlated significantly with independent ratings of sequence structure.

An additional region of interest (ROI) analysis was carried out to directly test differential activation between the trial types in two specific frontal regions classically associated with working memory tasks (Duncan and Owen, 2000; Owen, 1997), mid-DLPFC, and midventrolateral prefrontal cortex (VLPFC) (see Experimental Procedures). There was significantly greater activation for the structured, compared with the unstructured, sequences for the left DLPFC ($t = 3.30$, $p = 0.002$), with the right DLPFC approaching significance ($t = 1.55$, $p = 0.071$). However, no significant increases were found for the VLPFC.

Control Study

In the control study, a second group of participants viewed the same structured and unstructured sequences as before, but this time with no working memory requirement (see Experimental Procedures). This time a comparison of structured and unstructured trials revealed no significant peaks of activation at corrected levels. When the working memory and control studies were compared directly, the interaction of experiment by sequence type yielded a single, significant peak in the right lateral prefrontal cortex (coordinates 44 11 18, $t = 7.87$). This activation is within 5 mm of the greatest peak of activation for structured minus unstructured contrast of the previous study (see Table 1).

Discussion

The performance data from both behavioral and fMRI studies confirm that a significant component of the spatial working memory task used in this study is the reorganization of structured sequences into higher level spatial chunks. Thus, in both cases, performance on the structured sequence trials was enhanced relative to performance on the unstructured sequence trials, and independent ratings confirmed that structured sequences were perceived to be more easily encoded. In addition, performance was superior when a brief interruption in

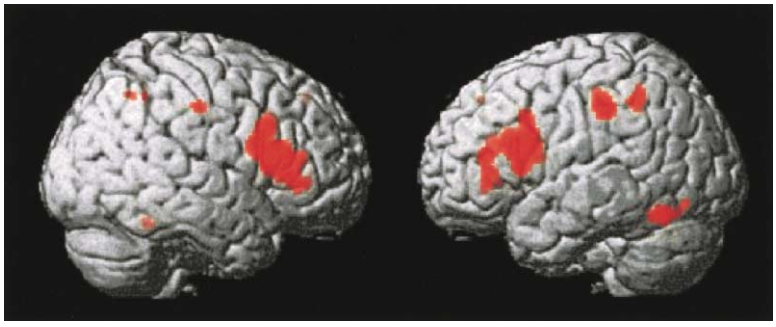

Figure 4. Regions of Increased Activation during Structured Trials as Compared to Unstructured Trials

Activations are those exceeding a whole-brain false detection rate threshold of $p < 0.01$, rendered onto the canonical T1-weighted brain image of SPM99.

Table 1. Peak Increases in Activation for Structured Compared to Unstructured Sequences

Brain Regions and Brodmann Areas	Coordinates			t Score
	x	*y*	*z*	
R lateral prefrontal cortex				
47/45	53	29	0	7.09
45	55	20	16	9.21
9/44	46	13	20	9.50
L lateral prefrontal cortex				
45	−48	20	16	7.06
45	−53	16	7	6.24
9/44	−46	13	21	7.17
Medial frontal cortex				
8	0	39	40	4.92
R sensorimotor cortex				
1/4	61	−18	38	6.00
R inferior parietal lobule				
40	53	−46	47	5.07
40	38	−54	47	5.53
L inferior parietal lobule				
40	−57	−27	38	8.94
40	−48	−43	43	5.66
R fusiform gyrus				
37	36	−48	−16	5.20
L fusiform gyrus				
37	−48	−59	−12	8.47
L occipital cortex				
19	−44	−70	−7	5.18

All regions presented pass the threshold of $p < 0.01$ false detection rate (Benjamini and Hochberg, 1995). Coordinates have been transformed (www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html) from MNI space to that of Talairach and Tournoux (1988).

stimulus presentation was congruent with spatial structure in the sequence, compared with a different interruption in the same sequence that was incongruent with spatial structure.

The results of our fMRI study confirmed that the implementation of such chunking strategies at encoding relies on the corecruitment of specific lateral frontal and posterior systems. Thus, during the structured sequences, significantly increased activity was observed bilaterally in the lateral frontal cortex, the inferior parietal lobule, and the fusiform gyrus, all effects being most pronounced at encoding. Moreover, the signal change in these areas correlated significantly with independent ratings of sequence structure.

During the delay, increases were observed for the unstructured trials in bilateral parietal and premotor cortices. Various neuroimaging studies have associated the parietal cortex with working memory storage, particularly in the spatial domain (Coull et al., 1996; Paulesu et al., 1993; Pochon et al., 2001). In addition, many studies have found activation in premotor cortex for working memory tasks generally (Cabeza and Nyberg, 2000). Therefore, this activation might reflect a decrease in storage and general working memory demands for the structured trials, as a result of more efficient encoding.

Some prior neuropsychological data support the strategic role of prefrontal cortex in working memory. Patients with frontal lobe damage are impaired on some, but not all, working memory tests, and in some cases, deficits have been shown to relate to the inefficient use of organizational strategies which improve performance in healthy controls (Owen et al., 1996; Petrides and Milner, 1982). 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).

A possible confound in our study is that activity in lateral PFC could simply reflect the recognition of familiar shapes in structured sequences. This issue is addressed in our control fMRI study, where participants again viewed structured and unstructured sequences but this time without a working memory demand. In this task, participants simply decided whether they had perceived a regular shape within the sequence or not. Comparison of structured and unstructured sequences, defined exactly as in the working memory experiment, showed no significant differences. Furthermore, a direct comparison between the control and the main fMRI study revealed a significant structure by task interaction in the lateral prefrontal cortex only. This result confirms that the search for, and recognition of, familiar shapes within the structured sequences is not itself sufficient to induce an increase in lateral prefrontal activity. Rather, greater activity in this region is observed when the structured information is used to facilitate memory encoding.

Our results might also relate to a recent paper addressing integrated information coding in working memory (Prabhakaran et al., 2000). Letters and locations to be remembered were either presented together, as properties of the same object, or separately. In the integrated case, prefrontal activity was increased. Chunking is certainly another form of working memory integration, suggesting a possible overlap between the two studies. However, in the Prabhakaran et al. (2000) study, frontal activity was anterior to ours, largely in the frontal pole.

In addition to increased lateral frontal activity during structured trials, strong bilateral activity was observed in the fusiform gyrus. The fusiform gyrus has been repeatedly associated with object perception, and object recognition is impaired following damage to this region in patients (Arguin et al., 1996; Gerlach et al., 1999). On this basis, we suggest that in order to increase performance, the lateral frontal cortex selectively relates the structured sequences to object-based information from memory, which increases activation in the fusiform gyrus. In this way, the lateral frontal cortex plays an essential role in selecting appropriate high-level organizational chunks which then serve to facilitate memory by reducing overall cognitive load.

The structuring of information in working memory is to some extent analogous to semantic clustering in verbal episodic memory paradigms. Our results are reminiscent, therefore, of left frontal recruitment when participants are explicitly instructed to reorganize encoded word sequences into semantic categories (Fletcher et al., 1998; Savage et al., 2001), though in this case, a complicating factor is association of left inferior frontal cortex with semantic processing itself (Buckner et al., 1999; Cabeza and Nyberg, 2000).

Many human (Bor et al., 2001; Cabeza and Nyberg, 2000; Fletcher and Henson, 2001; Jonides et al., 1997; Owen, 1997; Owen et al., 1998) and animal (Goldman-Rakic, 1998; Miller and Cohen, 2001; Petrides, 1995, 1998; Rainer et al., 1998; Rao et al., 1997) studies have

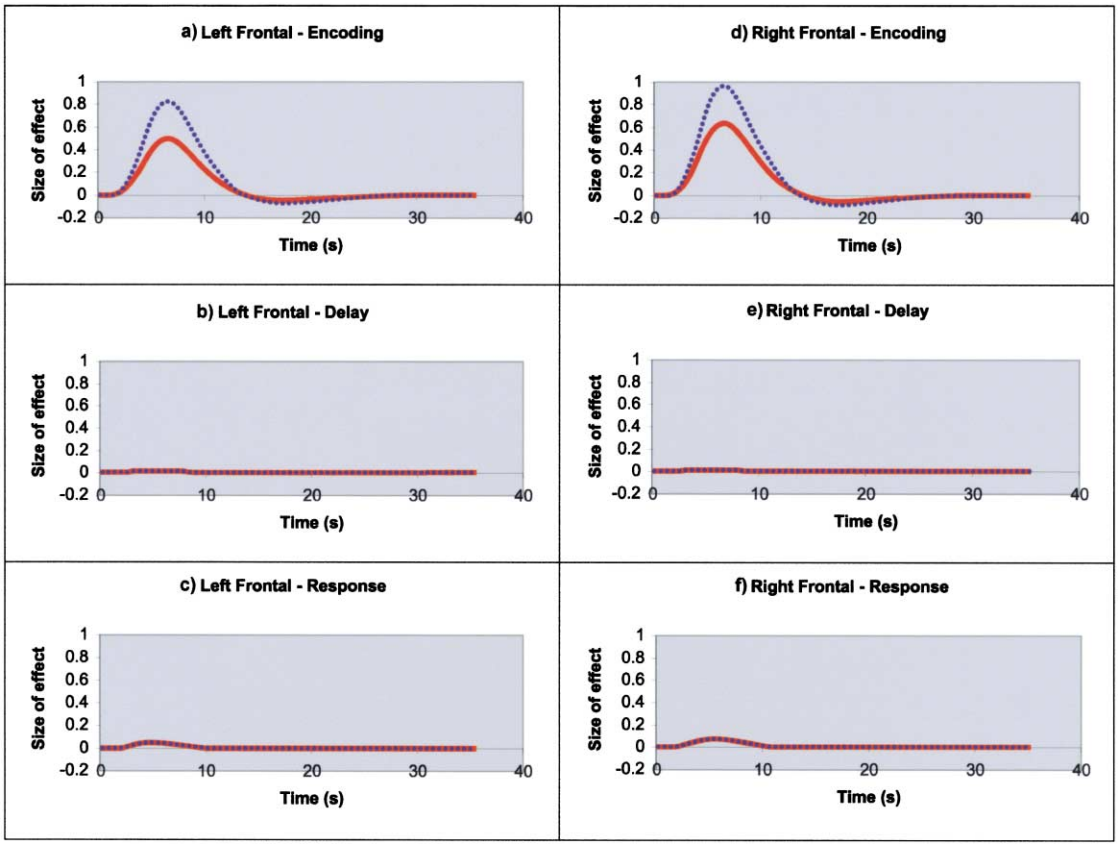

Figure 5. Time Course of Regional Activity Relating to Encoding, Delay, and Response Events

Dotted blue lines refer to the structured trials, while continuous red lines refer to the unstructured trials. (A)–(C) show neural responses at the maximal activation peak in left lateral prefrontal cortex (coordinates −46 13 21), while (D)–(F) show neural responses at the maximal activation peak in the right lateral prefrontal cortex (coordinates 46 13 20). (A) and (D) relate to the encoding stage, (B) and (E) relate to the delay stage, and (C) and (F) relate to the response stage. Functions show magnitude (arbitrary units) of fitted response to each task event, following deconvolution of event durations.

examined the role of prefrontal cortex in working memory 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 and Owen, 2000). Our results show that, for a large region of prefrontal cortex including DLPFC, this common effect of task difficulty can be reversed. When working memory is improved by chunking, prefrontal cortex plays a specific role in recognition and use of suitable information chunks.

Experimental Procedures

Behavioral Studies

414 volunteers (262 males, 152 females; mean age 26.6) participated in a large-scale behavioral study which formed part of the 2001 Creating Sparks Exhibition at the London Science Museum. Each participant was randomly assigned to one of four simple variations on the classic spatial span task of Corsi (Milner, 1971) (Figure 1). In all four conditions, the participants were required to memorize sequences of locations which were illuminated on a 4 × 4 grid presented on a touch-sensitive screen. Specifically, on each trial, a sequence of red squares flashed blue, each square changing color for 500 ms with a 250 ms interval between squares. At the end of the sequence, a short tone prompted the participants to respond by touching the same series of locations with the index finger of the dominant hand. Accuracy and reaction time data were collected, although the participants were only instructed to reproduce the sequences as accurately as possible. Ten trials were given in total, beginning with a three location sequence and then increasing by one square following each successful trial and decreasing by one square following each unsuccessful trial. In this way, the participant's performance tended to asymptote within a few trials and then oscillate around maximum span capacity. Participants scoring less than 3.0 were excluded from the analysis, since previous studies have demonstrated that this is greater than two standard deviations from the mean performance for a neurologically normal sample (Owen et al., 1990). In each case, average span capacity was calculated as the mean length of sequences presented in all ten trials.

In one of the conditions, all of the sequences followed a structured rule such that every location was either in the same column, the same row, or on the same diagonal as the location preceding it (Figure 1A). In a second condition, an alternative "unstructured" rule was applied such that two successive locations were never in the same column, in the same row, or on the same diagonal (Figure 1B). The result of this manipulation was subtle, such that the structured sequences tended to contain more familiar shape components, involving symmetry and parallel sides, and were thus more easily organized into higher level patterns (Bor et al., 2001). In the third and fourth conditions, all of the sequences involved two sections that were structured according to the rule used for condition 1. The two sections were connected by an unstructured link, according to the rule used to generate sequences for condition 2. One interstimulus interval between two of the stimuli in each sequence was increased from 250 to 750 ms. This temporal segregation between two

sections of the sequence was manipulated so as to be congruent (condition 3; see Figure 1C) or incongruent with (condition 4; see Figure 1D) the two structured sub-sequences. Aside from the difference in temporal location of the extended interstimulus interval, everything—including the exact stimulus set used—was identical between conditions 3 and 4. There was always a difference of one location between the temporal segregation position on any sequence for conditions 3 and 4. The position was always as close to the middle of the sequence as possible, with conditions 3 and 4 balanced for closeness of the segregation to the center.

In a supplementary behavioral study, five neurologically normal volunteers (two males, three females; mean age 28.6) were given the exact same sequences of structured and unstructured trials as in the fMRI study and were explicitly asked to rate on a scale of 1–10 the extent to which the structure of each sequence made it easy to remember (1 = most difficult, 10 = easiest).

Imaging Study

Sixteen neurologically normal participants (six males, ten females; ages 21–34) were scanned while remembering structured and unstructured sequences (Figures 3A and 3B). Sequence length was fixed at four, with the structured and unstructured sequences generated from the same rules applied to the trials of conditions 1 and 2 respectively of the prior behavioral study. Due to the constraints imposed by the rules to generate the trial types, the average distance between adjacent squares in the unstructured sequences was 1.65 times longer than that for the structured sequences. Stimuli were back projected onto a translucent screen positioned within the bore of the magnet and behind the head of the participant, visible via an angled mirror placed above the participant's head. Sixteen red squares, arranged as an equidistant 4×4 matrix, were presented on the screen against a black background. There was no central fixation point, and subjects were not given any instructions concerning eye movements. On each trial, four of the red squares flashed blue, changing color for 500 ms with a 250 ms interval between each. The participant was required to remember the sequence and to maintain that information across a delay randomly varying between 6 and 10 s. At the end of this period, the participants were required to make a series of responses, prompted by the simultaneous appearance of sixteen yellow dots, one dot placed randomly on the left or right side of each of the sixteen squares. Touching screen locations was impossible in the fMRI environment; instead, by pressing a button under the first or second finger of the dominant hand, corresponding to a dot on the left or a dot on the right, participants were asked to indicate dot positions for each of the four locations in memory, in the order originally presented. Trials were judged incorrect if any of the four responses was wrong. Though some such trials might be correct by chance, high performance overall (see Results) shows that participants complied well with memory instructions. Trials were presented in blocks of 20, pseudo-randomly structured such that ten structured and ten unstructured sequences were presented in each block. For each participant there were three blocks, each comprising one separate scanning run.

Participants were scanned 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 echo planar imaging sequence (TR = 3.02 s, TE = 115 ms, flip angle = 90°). The beginning of each trial (encoding phase) was tightly coupled to the timing of the scanning sequence and jittered in 500 ms increments around the start of the TR (from 1500 ms prior to the TR onset to 1000 ms past the TR onset). The length of the delay phase, which immediately followed the encoding phase, was pseudo-randomly varied in 500 ms increments from 6 to 10 s. The intertrial interval (ITI), which commenced immediately after the fourth response (or after 7 s if fewer than four responses were made), was pseudo-randomly varied in 500 ms intervals between 8 and 12 s in order to allow the blood oxygen level-dependent (BOLD) response to return to baseline between trials.

All fMRI data were processed and analyzed using SPM99 software (Wellcome Department of Cognitive Neurology, London, UK). Prior to analysis, all images were corrected for slice timing, with the first slice in each scan used as a reference. Images were realigned with respect to the first image using sinc 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. 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 hemodynamic response with the time series of the events and removing low-frequency noise with a high-pass filter. Group data were analyzed with a random effects analysis. All reported peaks passed a whole-brain false detection rate (FDR) (Benjamini and Hochberg, 1995; Genovese et al., 2002) threshold of $p < 0.01$. 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 (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 and Tournoux (1988).

For the ROI analysis, DLPFC and VLPFC regions were specified by taking the mean of a range of published coordinates for these regions in harder versus easier versions of an array of tasks, as listed in a recent review (Duncan and 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 coordinates 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, a t test was carried out to compare the mean voxel value during the structured versus the unstructured trials.

Control Study

11 neurologically normal participants (3 males, 8 females; ages 21–33) were scanned using exactly the same experimental, scanner, and analysis parameters as in the previous fMRI study. However, instead of being required to remember the sequence, the participant was instructed to observe each sequence and decide whether the stimuli had formed a regular shape or not. Following the same delay as in the previous experiment, at the onset of the yellow dots on the red squares, participants were required to make a binary response repeated four times on a button box to indicate whether they had perceived a regular shape within the stimuli. For six subjects, 60 trials in total were presented over three scanning runs, while for the remaining five, only 20 trials were collected, during one scanning run. For the analysis, the trials for each subject were separated into structured and unstructured sequences, exactly as in the previous study.

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