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Dissociating aspects of verbal working memory within the human frontal lobe: Further evidence for a "process-specific" model of lateral frontal organization

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There is now converging evidence that suggests that working memory processes within the dorsolateral and ventrolateral frontal cortices are organized according to the type of processing required, rather than according to the nature (i.e., domain) of the information being processed, as has been widely assumed. For example, recent positron emission tomography (PET) studies have demonstrated that either, or both, of these two lateral frontal areas can be activated in spatial working memory tasks, depending on the precise executive processes that are called upon by the task being performed. Moreover, in a recent study using functional magnetic resonance imaging, performances of visual spatial and visual nonspatial working memory tasks were shown to involve identical regions of the lateral prefrontal cortex when all the factors unrelated to the type of stimulus domain were appropriately controlled. These results concur fully with recent reviews of the imaging literature, which have demonstrated that spatial and nonspatial working memory studies, in general, have produced a widely distributed pattern of overlapping activation foci within these lateral frontal regions. In this study, the effects of varying the executive requirements of a simple verbal working memory task (forward vs. backward digit span) were explored in 8 subjects, using PET, in order to establish whether this model generalizes to the verbal domain. As was expected, during forward digit span, significant activation was observed within the midventrolateral frontal cortex, but not within the middorsolateral frontal cortex. In contrast, during backward digit span, significant activation was observed in both regions. The results provide further evidence that the middorsolateral and midventrolateral frontal cortical areas make distinct functional contributions to memory and that this corresponds, in psychological terms, to a fractionation of working memory processes.

In recent years, the term *working memory* has come to be used in various ways: to describe a cognitive system for both the temporary storage and the manipulation of remembered information (e.g., Baddeley, 1986), to describe the type of memory that is active and relevant only for a short period of time (e.g., Fuster, 1995; Goldman-Rakic, 1995), and most specifically, to describe the process by which a remembered stimulus is held *on line* to guide behavior in the absence of external cues or prompts (Goldman-Rakic, 1987). In part, this descriptive variability reflects the relative interests of those working with different primate species: Psychologists working mainly with humans often emphasize the *organizational* or *higher order* aspects of working memory tasks, whereas those working with nonhuman primates tend to focus on those aspects of task performance related to the on-line retention or short-term storage of information. The problem of comparison between species is further compounded by Honig's (1978) definition of working memory, as applied invariably in rat studies using Olton's radial arm maze (Olton, 1982), which also emphasizes the *organizational* or *executive* component of task performance. Nevertheless, in the absence of a precise definition, few disagree that working memory is a fundamental set of processes and an integral component of many cognitive operations, from complex decision making to selective attention (Baddeley, 1986).

Although evidence from the study of patients with excisions of the frontal cortex, from lesion and electrophysiological recording work in nonhuman primates (for reviews, see Goldman-Rakic, 1994, and Petrides, 1994), and from functional neuroimaging studies in humans suggests that the lateral frontal cortex plays a critical role in certain aspects of working memory, no consensus has been reached regarding the fractionation of functions within this region (e.g., Cohen et al., 1994; Cohen et al., 1997; Courtney, Ungerleider, Keil, & Haxby, 1996, 1997; Funahashi, Bruce, & Goldman-Rakic, 1989, 1990; Gold, Berman, Randolph, Goldberg, & Weinberger, 1996; Goldberg, Berman, Randolph, Gold, & Weinberger, 1996; Jonides et al., 1993; McCarthy et al., 1994; Owen, Downes,

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Sahakian, Polkey, & Robbins, 1990; Owen, Doyon, Petrides, & Evans, 1996; Owen, Evans, & Petrides, 1996; Owen, Morris, Sahakian, Polkey, & Robbins, 1996; Owen, Sahakian, Semple, Polkey, & Robbins, 1995; Petrides, Alivisatos, Evans, & Meyer, 1993; Petrides & Milner, 1982; Rao, Rainer, & Miller, 1997; Smith, Jonides, & Koeppe, 1996; Smith et al., 1995; Stern et al., 2000; Sweeney et al., 1996; Wilson, Scalaidhe, & Goldman-Rakic, 1993; for reviews, see Owen, 1997, Rushworth, Nixon, Eacott, & Passingham, 1997, and Rushworth & Owen, 1998). Until recently, one prevalent view has been that working memory processes are organized according to the type (e.g., domain) of information being processed, with dorsolateral frontal regions being concerned principally with memory for spatial material, whereas the anatomically and cytoarchitectonically distinct ventrolateral frontal regions subserve memory for nonspatial material (Goldman-Rakic, 1987, 1994, 1995; Levy & Goldman-Rakic, 1999; see also Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Courtney et al., 1996, 1997).

In general, however, both functional neuroimaging studies in humans (for reviews, see D'Esposito, Aguirre, et al., 1998; Owen, 1997, in press, and Rushworth et al., 1997; see also Rushworth & Owen, 1998) and recent electrophysiological recording studies in the monkey (Rao et al., 1997) have failed to support this *domain-specific* model of lateral frontal lobe function. For example, in one recent review of the literature (Owen, 1997), the stereotaxic coordinates of activation foci reported within the dorsolateral and ventrolateral frontal cortices during 14 spatial working memory tasks (Baker, Frith, Frackowiak, & Dolan, 1996; Goldberg et al., 1996; Jonides et al., 1993; McCarthy et al., 1994; McCarthy et al., 1996; Owen, Evans, & Petrides, 1996; Smith et al., 1996; Smith et al., 1995) were compared with those observed during 6 nonspatial (visual) working memory tasks (Baker et al., 1996; Courtney et al., 1996; McCarthy et al., 1996; Owen et al., 1998; Petrides et al., 1993; Smith et al., 1995). In these two sets of studies, widely overlapping patterns of activation foci were observed in both ventral and dorsal regions of the lateral frontal cortex. At the single subject level, the results of recent functional magnetic resonance imaging (fMRI) studies have also demonstrated that formally identical spatial and visual working memory tasks activate identical regions of the lateral frontal cortex when all the factors unrelated to stimulus domain are appropriately controlled (Owen et al., 1998; Postle, Stern, Rosen, & Corkin, 2000). The results of these studies in humans concur fully with the findings from a recent electrophysiological recording study in the monkey, designed to investigate where and how information about object identity is integrated with information about object location within working memory (Rao et al., 1997). In that study, approximately half of the frontal neurons with delay-related activity were tuned to both visual pattern (*what*) and location (*where*). Furthermore, neurons that were tuned only to location or only to visual pattern were equally distributed between the dorsolateral and the ventrolateral prefrontal cortices (Rao et al., 1997; for further discussion, see Rushworth & Owen, 1998).

An alternative general theoretical framework for understanding the role played by the prefrontal cortex in mnemonic processing and its relationship to more posterior cortical association systems has been proposed by Petrides (1994), based largely on lesion studies in the monkey. According to that model, basic memory functions, including storage and immediate processing of incoming and recalled information, are carried out, not within the frontal lobes, but rather within sensory-specific and multimodal posterior association areas in the parietal and temporal cortices. The frontal lobes may, however, receive and act on this information via bidirectional connections between the posterior cortical association areas and the ventrolateral frontal cortex, which, in turn, is closely connected to the middorsolateral frontal cortex, or via direct connections between dorsal regions of the frontal cortex and the medial temporal lobe. Thus, according to this view, the ventrolateral frontal cortex constitutes the first level of interaction between posterior cortical regions and the entire lateral frontal cortex. In this capacity, this region is assumed to be critical for various *second order* memory processes, such as comparisons between or judgments about the occurrence or nonoccurrence of remembered stimuli (have I seen this stimulus before? where were the three locations that I just saw?), the triggering of low-level encoding strategies, such as rehearsal, and the initiation of explicit (i.e., intentional) retrieval of information from long-term memory (Petrides, 1994). In contrast, the middorsolateral frontal cortex is assumed to provide a third level of processing within memory and is recruited when active *manipulation* or *monitoring* of remembered information is required. Manipulation, when used in this context, refers to those processes that are recruited when no direct mapping exists between a particular response and the stimulus that signaled that response; rather, the appropriate response must be computed from information assimilated during the trial and by reference to responses made previously or (planned) responses that remain to be made.

According to this view, therefore, working memory processes within dorsolateral and ventrolateral frontal regions are organized according to the *nature* of the processing required, rather than according to the domain of the information to be remembered (Petrides, 1994, 1995).

One central requirement of this *process-specific* model of lateral frontal organization is that, within a given domain, the dorsolateral and ventrolateral prefrontal cortices can be shown to play distinct functional roles in working memory. Two recent functional neuroimaging studies in humans have addressed this issue in the spatial domain by systematically varying the executive requirements of a spatial working memory task in order to emphasize those processes assumed to depend on each of these two frontal cortical regions (Owen, Evans, & Petrides, 1996; Owen et al., 1999). During one task, modeled on the spatial block-tapping test (or *spatial span*) of Corsi (see Milner, 1971), a significant increase in regional cerebral blood flow (rCBF) was observed in midventrolateral area 47 of the right hemisphere (Owen, Evans, & Petrides, 1996; Owen et al., 1999). No significant rCBF change was observed in the dorsolateral frontal region. In contrast, during two tasks that required both retrieval and, in addition, the manipulation of information within spatial working memory, highly significant activation foci were observed in the middorsolateral (area 9/46) and the midventrolateral (area 47) prefrontal regions.

Many recent functional neuroimaging studies of working memory have employed verbal stimuli, such as numbers or letters (presented either visually or auditorily), and provide additional material for assessing models of lateral frontal organization in humans. In one recent review (Owen, in press), the stereotaxic coordinates of activation foci reported within the dorsolateral and ventrolateral frontal cortices during 27 verbal working memory studies (Andreasen et al., 1995; Awh et al., 1996; Barch et al., 1997; Becker et al., 1994; Braver et al., 1997; Callicot et al., 1999; Cohen et al., 1994; Cohen et al., 1997; Collette et al., 1999; Coull, Frith, Frackowiak, & Grasby, 1996; D'Esposito, Aguirre, et al., 1998; D'Esposito, Ballard, Aguirre, & Zarahn, 1998; de Zubicaray et al., 1998; Fiez et al., 1996; Goldberg et al., 1998; Grasby et al., 1993; Grasby et al., 1994; Jonides, Schumacher, et al., 1998; Jonides et al., 1997; Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998; Paulesu, Frith, & Frackowiak, 1993; Petrides et al., 1993; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999; Salmon et al., 1996; Schumacher et al., 1996; Smith et al., 1996; Van der Linden et al., 1999) were compared. Like studies of spatial and visual working memory, widely distributed patterns of activation foci across both dorsal and ventral frontal areas were observed.

One logistic problem, however, with comparing the results of unrelated studies is that the tasks used often differ both in terms of their mnemonic (e.g., processing) requirements and in terms of the nature of the material to be remembered (e.g., domain: verbal, spatial, or visual). In addition, as was discussed above, the precise definition of working memory and various component processes varies widely from investigation to investigation. In the present positron emission tomography (PET) study, a direct analogue of the spatial span task described above (Owen, Evans, & Petrides, 1996; Owen et al., 1999) was employed to investigate whether evidence for the process-specific model of lateral frontal organization can be found within the verbal domain. During one experimental task, subjects were required to hold a sequence of auditorily presented numbers in memory (e.g., 7, 3, 8, 2, 9) and then, after a short delay, to respond by (verbally) producing those numbers, in order (e.g., 7, 3, 8, 2, 9). Since the emphasis of this verbal working memory task was on the active (i.e., conscious) retrieval of remembered information and not on the manipulation of that information, it was predicted that the midventrolateral, but not the middorsolateral, prefrontal cortex would be activated. During the second experimental task, the subject was required to listen to similar sequences of numbers, reproducing each sequence *in reverse order* (e.g., 9, 2, 8, 3, 7) after a short delay. Since, like the forward digit span task, this task involved the continuous retrieval of information from working memory, it was predicted that the midventrolateral prefrontal cortex would be similarly activated during the two conditions. In addition, however, the backward digit span task places significant demands on the manipulation of the information within working memory; thus, the task requires that the remembered information be reordered in order to program the appropriate sequence of responses. On this basis, the backward digit span task was expected to additionally activate the middorsolateral prefrontal region.

METHOD

Image Acquisition and Data Analysis

PET scans were obtained with the General Electrics Advance system, which produces 35 image slices at an intrinsic resolution of approximately 4.0 × 5.0 × 4.5 mm. Using the bolus $H_2{}^{15}O$ methodology, rCBF was measured during two separate scans for each of the three experimental and control conditions (total of six scans). For each scan, the subjects received a 20-sec 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}. With this method, each scan provides an image of rCBF integrated over a period of 90 sec from the time at which the tracer first enters cerebral circulation. The six PET scans were realigned, using the first scan as a reference, normalized for global CBF value, and averaged across the 8 subjects for each activation state. The images were then smoothed using an isotropic Gaussian kernal at 16 mm. Finally, a simple analysis of covariance model was fitted to the data at each voxel, as implemented by the method of statistical parametric mapping (SPM 96, provided by the Wellcome Department of Cognitive Neurology, London), with a condition effect for each of the conditions, using global CBF as a confounding covariate.

For each subject, 3-D MRI volume (256 × 256 × 128 pixels, 3 mm thick) was acquired and resliced so as to be coregistered with the PET data. Composite stereotaxic MRI and PET volumes were merged to allow direct anatomical localization of regions with statistically significant rCBF changes between conditions.

The significance of a given rCBF difference was assessed by application of an intensity threshold to the SPM images (Worsley, Evans, Marrett, & Neelin, 1992; Worsley et al., 1996). This threshold, based on 3-D Gaussian random field theory, predicts the likelihood of obtaining a false positive in an extended 3-D field.

This study was designed to test two anatomically specific hypotheses based directly on the results of previous imaging studies that have employed (spatial) working memory tasks analagous to those used here (Owen, Evans, & Petrides, 1996; Owen et al., 1999). Accordingly, it was predicted that during one verbal working memory task (forward digit span), significant activation would be observed in area 47 of the midventrolateral frontal cortex, but not in areas 9 and 9/46 of the middorsolateral frontal cortex, whereas in another working memory task that required manipulation of the memoranda (backward digit span), both regions would be significantly activated. On this basis, two directed searches were conducted for activation foci located within these two frontal regions, and the threshold for significance was set at $p = .001$, uncorrected. For the rest of the brain, an exploratory search involving all peaks within the gray matter (volume, 600 cm^3) was conducted, and the threshold for reporting a peak as significant was set at $p < .05$, corrected for multiple comparisons.

Subjects

Eight healthy right-handed female volunteers participated in the study (mean age, 55 years; range, 50–58). Previous behavioral and imaging studies of working memory processes have confirmed that individuals in this age group perform similarly to younger volunteers (e.g., Robbins et al., 1998) and exhibit changes in blood flow that are distinguishable from younger subjects (e.g., Owen, Doyon, et al., 1996). Accordingly, since the age range was narrow, age was not considered to be an important variable in the analyses of results. Each subject underwent six PET scans and one MRI scan within a single session. All the subjects gave informed, written consent for participation in the study after its nature and possible consequences had been explained to them.

Stimuli and Testing Conditions

The stimuli used in all three conditions of this study were digits from the set 1–9, presented directly to the subject via in-ear headphones. The nine digits were recorded previously, digitized, and presented in a fully automated time-controlled fashion, using a VisualBasic 6 program running on a personal computer based on Windows 95. Each of the three conditions was performed twice, making six scans in all. The order in which the three conditions were administered was randomly arranged across subjects, with the restriction that no 2 subjects performed all the tasks in the same order. Each PET scan lasted 90 sec, and testing on the task was initiated 15 sec before scanning began. All the subjects completed the same fixed number of trials in each condition, total performance lasting for approximately 2 min. Performance data were collected during this 2-min period. The scans were separated by 8 min, during which time the requirements of the next task to be performed were explained to the subject.

There were two experimental conditions and one control condition in this study. The three tasks involved identical stimuli and, during the course of the scan, required an identical number of similar responses from the subject. In the first experimental task (backward digit span), which we consider to exemplify those tasks that require both retention and manipulation of information within verbal working memory, the subjects heard strings of digits (such as 3, 7, 2, 1, 8) presented at a rate of one digit per second and, at the end of each string, were required to respond verbally by reproducing the digit sequence in reverse order. In the second experimental condition (forward digit span), which also requires the retention and reproduction of information stored in working memory but places minimal demands on the manipulation of that information, the subjects heard similar digit strings and were required to respond by reproducing them in the *same* order in which they were presented. In a third, control condition, each trial involved an identical digit string, (1, 1, 1, 1, 1), and the subjects were required to respond by repeating the sequence. In all three conditions, the stimuli were presented at a paced rate of one digit per second, with 1 sec allowed for each response. If all responses were not made within the allowed time period, the program would move on to the next stimulus automatically, although once the subjects had received sufficient practice prior to scanning, this occurred extremely rarely.

To control for the nonspecific effects of task difficulty, each subject underwent a pilot testing session prior to scanning, in order to determine their individual forward and backward digit spans. During scanning, the number of digits presented in the two experimental conditions was set according to the maximum number of digits that could be recalled accurately in three successive trials. In general, therefore, for each subject the *forward digit span* condition involved more stimuli and more responses during each trial than did the *backward digit span* condition. Every trial of the control task involved five stimuli and 5 responses. It is important to point out, however, that the overall amount of information that had to be remembered and retrieved and the total number of responses made during the scanning window were equivalent for all three conditions. For example, during 1 min of performance of the forward digit span task with, say, six digits per trial, the subject would be required to remember 30 items (six digits in each of five trials) and, correspondingly, to make 30 responses. During the same time frame for the backward digit span task with, say, 5 items per trial, the subject would also be required to remember 30 items (five digits in each of six trials) and, correspondingly, to make 30 responses. Thus, these settings also ensured that the subjects were exposed to the same number of stimuli and made the same number of responses during each of the three conditions.

RESULTS

Pilot testing established that the subjects' mean forward and backward digit spans were 5.88 (*SEM* = 0.23) and 4.93 (*SEM* = 0.32), respectively. Thus, on average, the subjects were given six digits to remember in the forward digit span condition and five digits in the backward digit span condition. Consequently, their performances during the two experimental conditions, as indexed by the mean number of correctly recalled digit sequences (forward, 95%; backward, 91%), were not significantly different [$F(1,7) = 3.78, p > .05$]. No errors were made during the control condition.

In Table 1, all the activation foci reaching statistical significance according to the criteria outlined in the Method section above are provided, together with stereotaxic coordinates as reported by SPM 96. When the backward digit span condition was compared with the control task, a significant increase in rCBF was observed in the right midventrolateral frontal cortex (area 47), slightly more anterior ($y = 34$) to the coordinates of rCBF changes within the same region than have been reported previously (Owen, Evans, & Petrides, 1996; Owen et al., 1999) during tests of spatial working memory (Table 1 and Figure 1). A similar focus was observed in the left ventrolateral frontal region (area 47), although this was rather smaller and only just reached significance according to our anatomically defined threshold for this region. As was predicted, a significant rCBF change was also observed in area 9/46 of the left middorsolateral frontal region during the backward digit span task. An rCBF change was detected in the right middorsolateral frontal cortex ($x = 58$, $y = 36$, $z = 20$), although this failed to reach statistical significance ($z = 2.21$, $p = .014$, uncorrected). Other significant rCBF changes during this task were observed in the right orbitofrontal cortex (area 11), the right posterior parietal cortex (area 7), the left anterior cingulate cortex (area 24), and the cerebellum (see Table 1). The reverse subtraction yielded no significant rCBF changes within the entire gray matter volume.

When the forward digit span condition was compared with the control task, similar increases in rCBF were observed in right midventrolateral area 47 (Table 1 and Figure 1). An rCBF increase was also detected in the left

Table 1
Regions Exhibiting Task-Related Activity Across the Main Comparisons

Region	Stereotaxic Coordinates x	y	z	z Statistic	p value
Backward Digit Span Minus Control					
Right hemisphere					
Orbitofrontal cortex	−22	50	−28	5.01	.004
Mid-ventrolateral frontal cortex (area 47)	56	34	−16	4.39	.000
Posterior parietal cortex (area 7)	34	−64	48	4.84	.009
Left hemisphere					
Mid-ventrolateral frontal cortex (area 47)	−28	40	0	3.01	.001
Mid-dorsolateral frontal cortex (area 9)	−36	50	20	4.73	.000
Anterior cingulate cortex (area 24)	−6	24	20	4.45	.046
Cerebellum	−2	−58	−20	6.11	.000
Forward Digit Span Minus Control					
Right hemisphere					
Orbitofrontal cortex (area 11)	22	42	−28	4.55	.032
Mid-ventrolateral frontal cortex (area 47)	60	30	−12	3.26	.001
Mid-ventrolateral frontal cortex (area 47)	62	36	−4	3.21	.001
Backward Digit Span Minus Forward Digit Span					
Left hemisphere					
Mid-dorsolateral frontal cortex (area 9/46)	−36	44	20	3.33	.000

Note—All significant activation foci are reported.

hemisphere ($x = -32, y = 20, z = -8$), although this failed to reach statistical significance ($z = 2.27$, $p = 0.012$, uncorrected). No significant blood flow changes were observed in the middorsolateral frontal region. In fact, the only other significant rCBF change observed during this task was located in the orbitofrontal cortex (area 11). The reverse subtraction yielded no significant rCBF changes within the entire gray matter volume.

In summary, relative to the control task, significant rCBF changes in the left middorsolateral frontal cortex were only observed during the backward digit span task, whereas significant changes were observed in the right ventrolateral frontal cortex during both of the digit span conditions.

A final comparison was made between the two working memory conditions to confirm, more directly, that the additional requirements of the backward digit span task were responsible for the significantly increased activity in the middorsolateral frontal cortex, rather than a more general aspect of verbal working memory processing that would be expected to produce similar activity patterns in both tasks (and would, therefore, be subtracted out when the two conditions were compared directly). When rCBF in the forward digit span task was subtracted from that in the backward digit span condition, only one significant rCBF change emerged, in area 9/46 of the left middorsolateral frontal cortex (Table 1 and Figure 2). This focus is at almost identical stereotaxic coordinates within the left hemisphere as the residual activation produced in the right hemisphere when tasks that require manipulation of information within *spatial* working memory are compared with tasks that require simply the retention and reproduction of spatial information (see Figure 2; also see Owen et al., 1999). The reverse subtraction yielded no significant rCBF changes within the entire gray matter volume.

DISCUSSION

The results presented here provide further evidence that the middorsolateral and the midventrolateral frontal cortices make distinct functional contributions to spatial, visual, and verbal working memory and that this corresponds, in psychological terms, to a fractionation of working memory processes. Thus, during one variant of a general verbal working memory paradigm (forward digit span), which simply required active (i.e., conscious) retrieval and reproduction of stored information, rCBF increases were observed in the midventrolateral prefrontal cortex, predominantly in the right hemisphere. In contrast, both the midventrolateral and the middorsolateral prefrontal regions were significantly activated during a variant of the task that required on-line manipulation of information within working memory (backward digit span).

Previous functional neuroimaging studies of verbal working memory have yielded a diffuse pattern of activation foci across both dorsal and ventral regions of the prefrontal cortex (Andreasen et al., 1995; Awh et al., 1996; Barch et al., 1997; Becker et al., 1994; Braver et al., 1997; Callicot et al., 1999; Cohen et al., 1994; Cohen et al., 1997; Collette et al., 1999; Coull et al., 1996; D'Esposito, Aguirre, et al., 1998; D'Esposito, Ballard, et al., 1998; de Zubicaray et al., 1998; Fiez et al., 1996; Goldberg et al., 1998; Grasby et al., 1993; Grasby et al., 1994; Jonides, Schumacher, et al., 1998; Jonides et al., 1997; Jonides, Smith, et al., 1998; Paulesu et al., 1993; Petrides et al., 1993; Rypma et al., 1999; Salmon et al., 1996; Schumacher et al., 1996; Smith et al., 1996; Van der Linden et al., 1999). The present results suggest that these anatomically and cytoarchitectonically distinct regions can be functionally dissociated within the verbal domain if the

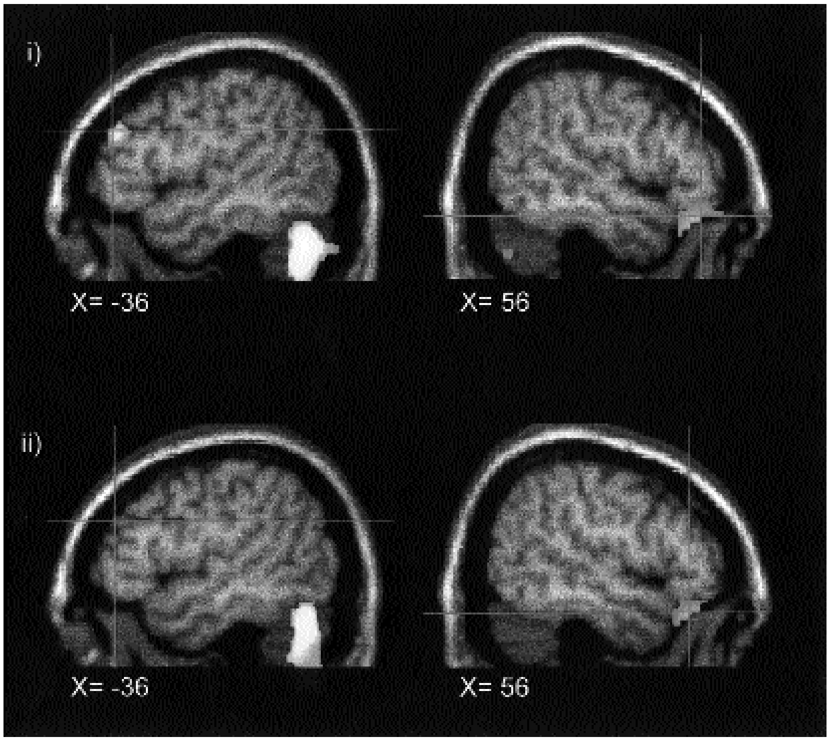

Figure 1. Schematic illustration of the averaged PET subtraction images superimposed onto corresponding slices from a standard three-dimensional MRI (SPM 96). The left hemisphere is shown on the left side of the figure. i) Backward digit span minus control. Within the prefrontal cortex, significant regional cerebral blood flow (rCBF) changes are shown within mid-dorsolateral area 9 (left hemisphere) and within ventrolateral area 47 (right hemisphere). ii) Forward digit span minus control. Within the prefrontal cortex, a significant rCBF change is shown within ventrolateral area 47 (right hemisphere). No changes were observed in the mid-dorsolateral frontal cortex (see the left side of the figure).

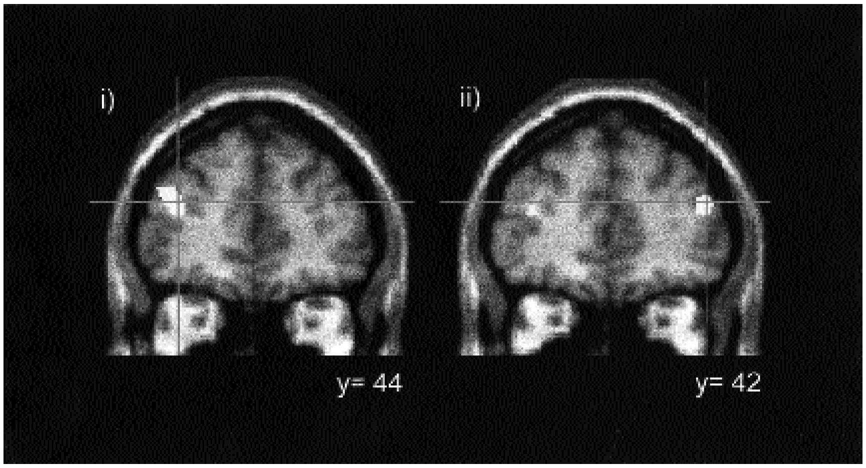

Figure 2. Schematic illustration of the averaged PET subtraction images superimposed onto corresponding slices from a standard three-dimensional MRI (SPM 96). Left hemisphere is shown in the left side of the figure. i) Backward digit span minus forward digit span. The two working memory conditions differ only with respect to regional cerebral blood flow (rCBF) changes in the left mid-dorsolateral frontal cortex (area 9/46). ii) For comparison, data are shown from Owen et al., 1999. In that study, comparison of a spatial span condition with a condition that required manipulation of spatial information within working memory yielded significant changes in rCBF in a similar region of the right mid-dorsolateral frontal cortex only.

tasks employed differentially tax those processes that are assumed to depend crucially on these areas, a view that concurs with contemporary reviews of the verbal working memory literature (Smith & Jonides, 1999). In the case of the midventrolateral frontal regions, the requirements of the forward digit span task are very similar to those of the spatial span tasks used in previous investigations (Owen, Evans, & Petrides, 1996; Owen et al., 1999), and accordingly, similar activation foci were observed within the midventrolateral prefrontal cortex. In contrast, the backward digit span task, which produced a significant increase in rCBF more dorsally, in areas 9 and 9/46, required the subject to monitor or manipulate an ongoing series of verbal stimuli, reordering them within working memory before programming an appropriate series of responses. These requirements are more similar to those of spatial working memory tasks that have been shown to activate similar regions within the middorsolateral frontal cortex (e.g., McCarthy et al., 1994; McCarthy et al., 1996; Owen, Evans, & Petrides, 1996; Smith et al., 1996; for further description, see Owen, 1997). There was some, albeit tentative, evidence from the present results to suggest that the backward digit span task preferentially activated the *left* middorsolateral frontal cortex, consistent with the known dominant role of this hemisphere in the processing of verbal information (Milner, 1971). Phonological processes with no specific relationship to memory *per se* may be recruited during many working memory tasks in order to facilitate normal memory function, through mechanisms such as verbal rehearsal. However, a *right*-sided change in rCBF was also observed during the backward digit span task, although this failed to reach significance according to our criterion. Both left- and right-sided activation foci within this area have been reported in previous studies of verbal working memory processes (for a recent comprehensive review, see Smith & Jonides, 1999). Similarly, although recent spatial working memory studies using analogous tasks have tended to emphasize right dorsolateral frontal regions (e.g., Owen et al., 1999), bilateral activity is frequently reported during such tasks (for a review, see Owen, 1997).

The present results, therefore, add further support to the hypothesis that, at the area level at least, the lateral frontal cortex is organized topographically according to the nature of the process being carried out, rather than according to the nature of the material being processed, as was previously thought (Courtney et al., 1998; Goldman-Rakic, 1995; Wilson et al., 1993; also see Courtney et al., 1996, 1997). In this respect, the results concur with recent event-related fMRI studies employing similar types of stimulus materials (e.g., D'Esposito, Postle, Ballard, & Lease, 1999; Postle, Berger, & D'Esposito, 1999). For example, in one study by D'Esposito et al. (1999), subjects performed a delayed-response task with two types of trials in which they were required to either retain a sequence of letters across the delay period or reorder the sequence into alphabetical order. Activity during the delay period was found in both dorsolateral and ventrolateral prefrontal regions in both types of trials, although dorsolateral activity was greater during the reordering task.

It is important to emphasize that the findings reported in the present study do not rule out the possibility that some functional differentiation based on stimulus material might still exist *within* the dorsolateral and ventrolateral frontal cortical regions. For example, it is plausible that the functional neuroimaging methods used in current studies have sufficient spatial resolution to detect differences *between*, but not *within,* these anatomical regions. Certainly among the middorsolateral activation foci discussed in recent reviews (Owen, 1997, in press; Rushworth et al., 1997), there is considerable overlap between studies of spatial, nonspatial, and verbal working memory in all three planes (x, y, and z). In the ventrolateral cortex, however, there does appear to be some reasonably consistent evidence for differences between those studies that have used spatial stimuli and those that have used nonspatial stimuli in the anterior–posterior (y) plane. For example, spatial working memory tasks used by Jonides et al. (1993), Owen, Evans, and Petrides (1996), Owen et al. (1999), and Smith et al. (1995) have all yielded rather posterior ventrolateral activation foci at y coordinates of between 14 and 24 mm. In two nonspatial studies that employed face stimuli, ventrolateral activation foci were reported rather more anteriorly at y coordinates of between 33 and 40 mm (Courtney et al., 1996; Haxby, Ungerleider, Horwitz, Rapoport, & Grady, 1995). In the present verbal working memory study, the ventrolateral activation foci were also observed rather more anteriorly ($y = +30$ to $+40$) than those reported in spatial working memory studies that have employed directly analogous tasks (e.g., Owen, Evans, & Petrides, 1996; Owen et al., 1999). Nevertheless, even if such subtle differences in activation were to be confirmed in later studies, it would still not be evidence to support a functional separation between the dorsolateral and the ventrolateral frontal lobe regions that are the central focus of the present study. Moreover, as was noted above, this general pattern of overlapping activation foci concurs fully with the results of a recent electrophysiological recording study in the monkey (Rao et al., 1997).

Finally, recent findings suggest that further insights about the role of the human prefrontal cortex in working memory are likely to emerge from comparisons with studies of other types of mnemonic processes assumed to be similarly dependent on the frontal lobe, such as episodic memory. For example, Fletcher, Shallice, et al. (1998) have reported activation in the midventrolateral frontal cortex during a paired-associates task that required subjects to retrieve previously learned category exemplars in response to a series of category names. In contrast, during a second condition that required subjects to free recall items from a previously learned list, activation in the middorsolateral frontal cortex was observed (Fletcher, Shallice, et al., 1998). This dissociation within the frontal lobes is almost identical to that described above for two types of spatial *working* memory tasks (Owen et al.,

1999) and in the present study for two variants of a general verbal working memory task, suggesting that any general theoretical framework for understanding the role of the prefrontal cortex in mnemonic processing will have to be sufficiently comprehensive to incorporate the main findings from ostensibly different types of mnemonic task, but divorced from a strict localizationalist perspective. In this respect, a fruitful approach may be to assume that the various *frontal* processes involved in working memory, episodic memory encoding and retrieval, and related mnemonic functions not discussed here are drawn from a single set of underlying components, although they may be differentially represented in different tasks. Thus, a general role for the ventrolateral frontal cortex in memory may be to trigger active low-level encoding strategies, such as rehearsal, and to initiate explicit (i.e., intentional) retrieval of information from long-term memory. In the case of working memory tasks, this would correspond to a relatively straightforward mapping of stimuli to responses, such as that which is assumed to occur in the digit span task described in this study and in spatial span tasks described previously (e.g., Owen, Evans, & Petrides, 1996; Owen et al., 1999), or even in simple delayed matching-to-sample paradigms (e.g., Elliott & Dolan, 1999). In the case of long-term episodic memory (e.g., verbal paired associate learning), these *active* encoding and retrieval processes might correspond to the active mapping and implementation of a somewhat arbitrary learned response (e.g., a category exemplar) to a specific stimulus (e.g., a category name; see Fletcher, Shallice, & Dolan, 1998; Fletcher, Shallice, et al., 1998). Indeed, a number of recent verbal episodic memory tasks that have produced predominantly ventral frontal activation have involved fairly *low-level* mnemonic processes, such as word pair encoding (Kapur et al., 1996) and short-term word recognition (Andreasen et al., 1995).

In contrast, the mid-dorsolateral frontal cortex may mediate more complex types of processing within memory and will be recruited when active manipulation or monitoring of remembered information is required. For example, in one of the earliest demonstrations of dorsolateral frontal activation during a verbal working memory task, subjects were required to generate the numbers 1 to 9 in random order without making repetitions (Petrides et al., 1993). To perform this task successfully, a strategy for determining an appropriate sequence of choices is required that must be constantly updated, or monitored, during its execution by reference to responses that have already been made and responses that may still be chosen (for further discussion, see Owen, Morris, et al., 1996). One key component of the verbal "*n*-back" tasks that have repeatedly been shown to activate dorsolateral frontal regions (e.g., Cohen et al., 1994; Jonides, Schumaker, et al., 1998; Jonides et al., 1997; Schumacher et al., 1996; Smith et al., 1996) is that responses are not made directly to any particular (remembered) stimulus but, rather, are generated by comparing each stimulus with others seen earlier in an ongoing sequence. Similarly, one key component of the free recall task described by Fletcher, Shallice, et al. (1998), which activated the dorsolateral frontal cortex, is that each response cannot be made in isolation but, rather, can only be made by monitoring responses made and information assimilated earlier in each trial. For example, the subject knows, in this case, that there are a specific number of items to be recalled and has to check with each new item produced that it has not been produced before. At this level, the task becomes indistinguishable from that employed by Petrides et al. (1993) to assess verbal *working* memory.

In conclusion, the results of the present study suggest that stimulus domain may not be a critical dimension for understanding the contribution of the lateral frontal cortex to the component *processes* of human memory. Rather, it is suggested that a more productive line of inquiry may be to relate specific regions within the lateral frontal cortex to specific polymodal processes that may be recruited during a variety of tasks, involving many different types of memoranda. This will enable data from the functional neuroimaging paradigm to be more readily integrated into findings from cognitive neuropsychological studies in patients and theoretical approaches to human memory.

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