



The dependence of span and delayed-response performance on prefrontal cortex

Mark D'Esposito*, Bradley R. Postle

Department of Neurology, University of Pennsylvania School of Medicine, 3400 Spruce Street, Philadelphia, PA 19104-4283, USA

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Abstract

Theoretical and empirical research on the cognitive functions of the prefrontal cortex have established that this region mediates what have been called 'executive' processes that can influence working and long-term memory. Despite the accumulation of such empirical evidence, the dependence of purely mnemonic portions of memory tasks on PFC remains unresolved. To address this issue, we performed an analysis of reports of performance on tests of working memory of patients with lesions of the dorsolateral prefrontal cortex, focusing on published reports in the literature of simple span and delayed-response tasks. We found that none of the eleven studies of forward verbal and spatial span in patients with prefrontal cortical lesions that we reviewed (reflecting the performance of 166 individual patients) demonstrated a statistically significant deficit relative to normal controls. In contrast, our review of the delayed-response literature indicated that there are conditions under which PFC lesions disrupt delayed-response performance. Based on the results of our review of the literature, we present testable hypotheses about the working memory functions of the PFC. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Short-term memory; Working memory; Prefrontal cortex

1. Introduction

An important component of the riddle of frontal lobe function in man [74] is memory. Theoretical and empirical research on the cognitive functions of the prefrontal cortex (PFC) have provided evidence that this region mediates what has been called 'executive' processes that can influence short-term and long-term memory. In the domain of short-term memory, several theorists distinguish between storage and rehearsal processes on the one hand and computational or manipulation processes on the other [3,12]. For example, in one widely cited model of short-term memory, Baddeley [4] distinguishes between a 'slave system' which stores and rehearses speech-based information and a central executive that is an attentional-controlling system. The term 'working memory', which has

evolved to encompass short-term memory, refers to the cognitive function that can include interactions among some or all of these component processes. The 'executive' components of working memory, as conceptualized in these models, have been linked specifically to the PFC in man in both lesion and imaging studies [5,17].

Likewise, the surface manifestations of the long-term memory deficits observed in patients with PFC damage are different than those observed in classic amnesic patients with hippocampal system damage [70]. A common finding in patients with PFC lesions is impairment on multiple-trial list learning tasks, during which they fail on recall measures but have generally normal performance on recognition measures [33]. This has been interpreted as defective retrieval—a function that requires strategy and effort—despite normal storage—a function that is more passive. Thus, patients with PFC damage have been said to be impaired on memory tests as a 'result of disruption of inhibitory control of extraneous activity' [70].

* Corresponding author. Tel.: +1-215-349-8275; fax: +1-215-349-8464.

Despite the accumulation of empirical evidence for the role of PFC in executive processes that can influence memory function, the dependence of purely mnemonic portions of memory tasks on PFC remains unresolved. To address this issue, we performed an analysis of reports of performance on tests of working memory of patients with lesions of the lateral PFC, focusing on published reports with simple span and delayed-response tasks. Considerable behavioral evidence suggests that the *mnemonic* components of tasks such as these can be organized into two classes of processes: storage and rehearsal [6,39,67,69].

Storage is measured in terms of capacity, and can be indexed by span tasks [6]: digit span for verbal working memory [81] and block span for visuospatial working memory [43]. Each of these span tasks assess how much information a subject can recall immediately. However, it is important to note that these span tasks are not perfectly 'pure' tests of storage, because these tests may recruit rehearsal processes. This possibility is manifest in the 'articulatory suppression effect' [38,51] and the 'word length effect' [7]. These are each examples of experimental manipulations believed to tie up articulatory rehearsal resources, and the effect of each is to decrease memory span. Such results are reasonable evidence that rehearsal processes contribute to performance on a span test. Nevertheless, patients with intact articulatory abilities, and thus intact rehearsal, can have severely circumscribed spans [76] suggesting that storage processes make a critical contribution to span performance. Span tests also have an important practical benefit for the kind of retrospective literature review that we report here: Among widely used clinical and experimental measures of working memory, digit and block span tests are the most likely to minimize rehearsal processes because subjects repeat the remembered information immediately following presentation.

Rehearsal refers to the processes necessary to refresh and maintain information held in working memory [3,35]. Tests of delayed-response can typically be considered to rely on rehearsal processes [2,58] to a greater degree than do span tasks, because they tax a subject's ability to maintain information over a longer period of time than do span tasks. Also in contrast to span tests, delayed-response tests rarely require memory of a large number of items, and thus do not provide as good a measure of the capacity working memory storage.

Throughout this report, we do not rely on the assumption that span and delayed-response tasks are

pure measures of either storage and rehearsal processes. We will, however, consider span performance to be an index of working memory *storage* processes (more so than rehearsal), and delayed response performance to be an index of working memory *rehearsal* processes (more so than storage). For the reasons stated above, these measures offer advantages over other working memory tasks, in that they are both relatively unconfounded by nonmnemonic cognitive processes such as inhibition, attention- and set-shifting, strategy formulation and implementation, and others falling under the rubric of 'control' processes.

The recent advent in human research of neuroimaging technologies has led to an accumulation of empirical evidence for a contribution of many cortical regions, including PFC, to working memory performance [15–17,36]. Two features of such studies, however, impose constraints on their inferential power with respect to the elucidation of a detailed model of mnemonic and nonmnemonic processes that contribute to working memory function. First, many of these studies employ complex working memory tasks that render them unsuitable for a detailed examination of isolated cognitive processes. Second, it is the nature of neuroimaging studies that they support inferences about the *association* of a particular brain system with a cognitive process, but not about its *necessity* to that process [68]. That is, neuroimaging studies cannot, alone, tell us whether the function of a neural system represents a neural substrate of that function, or rather a nonessential process that is associated with that function.¹ Examples of such nonessential processes might include error monitoring and detection, regulation of attention or vigilance, or inhibition of other processes that could potentially compete for the same resources as the process in question. The inference of necessity cannot be made without a demonstration that inactivation of a brain system disrupts the function in question. It has also been noted by Rushworth et al. that: 'The fact that single units in monkeys or populations of cells in imaging studies are more active during delays need not imply that the basic function of the area is to bridge those delays.' [66]. They illustrate this point with the example of dorsal premotor cortex, a structure that displays delay-period activity in electrophysiological studies, but whose lesions disrupt movement selection even in tasks that do not feature a delay [57]. For these reasons we believe that a review of the neuropsychological literature on working memory can serve as an important complement to neuroimaging data.

1.1. Working memory and prefrontal cortex in monkeys

A comprehensive review of the animal literature of studies of working memory is beyond the scope of this paper. The results that have emerged from this

¹ This observation applies to all methods of physiological measurement, including single- and multiunit electrophysiology, EEG, MEG, hemodynamic measures, and measures of glucose metabolism.

research, however, can help guide our predictions regarding the role of human PFC in working memory. Jacobsen was the first to report a link between PFC and working memory [31,32]. He interpreted the results of his experiments, impaired delayed response following large bilateral frontal lesions, as evidence for a memory deficit. Subsequent research, however, challenged this view, postulating instead that deficits on tests of delayed matching-to-sample, delayed response, and delayed alternation arose from deficits of encoding [52], of distractibility [40,53], of stimulus discrimination [47,48], of accessing recently acquired information (despite intact long-term memory) [29], or of set-shifting [46].

Researchers in the 1950s and 60s, by making more circumscribed lesions and using better controlled behavioral experiments, established clearly that PFC lesions cause delayed response deficits in monkeys [24]. For example, lesions of the cortex restricted to the region of the principal sulcus (believed to be homologous to Brodmann areas 9/46 in humans) [10,45] are sufficient to produce working memory deficits. Moreover, it has been demonstrated that narrowly circumscribed lesions in the region of the principal sulcus produce 'mnemonic scotomas' that are revealed in oculomotor spatial delayed response tasks [23]. Results from neurophysiological studies have complemented the findings from lesion studies in that activity is reliably found that is consistent with mnemonic coding in neurons of the principal sulcus, arcuate sulcus, and lateral convexity in monkeys performing delayed response tasks [22,26]. Thus, PFC in the monkey seems necessary for the maintenance of information across short periods of time.

Based on the findings in the monkey literature, we predicted that our review of the human literature would reveal that patients with lateral PFC lesions would exhibit impaired performance on delayed-response tasks. The monkey literature, however, did not allow us to make predictions regarding the necessity of the PFC for the *storage* component of working memory. This is because, to our knowledge, no studies have been performed in monkeys that employ tasks analogous to span tasks in humans. The aim of this critical review is to provide a consensus about the role of PFC in working memory, as well as to generate testable hypotheses.

2. Methods

In the following two sections, we assess the extent and nature of the dependence of performance on two tests of working memory—span and delayed-response—on the integrity of PFC. Our method was to review the relevant literature, to apply, where appro-

priate, statistical and deficit-lesion correlational meta-analyses to it, and to use our conclusions from this effort to formulate testable hypotheses about working memory functions of the frontal cortex. Our literature search was performed using the Medline, PsychLit, and Science Citation Index electronic databases, and by scanning manually the reference sections of papers that we had previously incorporated in our review. Written reports of two of the studies that we have included in this review exist only as unpublished theses [8,60]. Our search covered the years 1960 to the first half of 1998.

2.1. Tasks

Our search was limited to reports of data from one of six categories of working memory tasks: (1) forward digit span, (2) forward spatial (or Corsi) span, (3) spatial delayed response with and (4) without distraction, and (5) nonspatial delayed response with and (6) without distraction. For span tests, we excluded results that were reported as composite scores that might have distorted differences between groups. For example, an index of span that incorporated the number of trials required to achieve a particular span score could communicate a difference between two groups with equivalent spans, if one of the groups consistently needed two attempts at each span length to achieve their maximum score. Such an index would be influenced by factors other than capacity. We also did not include single case reports.

2.2. Patients

We focused only on studies of patients with lesions of lateral PFC. Thus, we excluded studies that included patients whose lesions included medial and/or orbital regions of the frontal lobes, such as patients with anterior communicating artery aneurysm rupture. An additional concern about these types of patients is that their brain lesion often encompasses basal forebrain regions, which include septohippocampal pathways. We also excluded studies that did not report data from matched normal control subjects (NCS).

2.3. Lesions

For reports that presented lesion diagrams, we replotted the lesions onto one of several composite brain diagrams corresponding to each of the six categories of the working memory tasks that we review, and to whether performance was impaired or intact. The purpose of producing these composite diagrams was to assess the extent of PFC damage across all the studies presenting data from a particular category of working memory task. This type of analysis would be

particularly useful in cases in which the meta-analysis indicated that there was no evidence of a behavioral deficit on a particular task. In such a case, one would want to assess the possibility that a region of spared PFC was supporting normal performance in the patients with PFC lesions.

To generate composite lesion diagrams, we first digitized each of the individual lesion diagrams from a paper. Next, we produced two composite lesion diagrams for each study by superimposing diagrams of single cases onto the appropriate brain hemisphere template (left or right). Each lesion was drawn in a low saturation shade of grey, and thus areas representing overlapping lesions appeared darker than regions where a lesion was only in one subject. Next, each composite diagram was transformed to a two-dimensional brain template in standard stereotaxic space [73] using a linear scaling procedure (Morph 2.0, Gryphon Software Corp.). Finally, we superimposed the normalized composite images from each of the studies for which there were data corresponding to a particular working memory task onto two standardized brain templates, one representing each hemisphere.

Each template includes three landmarks: a straight-line facsimile of the central sulcus, derived from [73], and outlines of the 'conservative' boundaries of PFC areas 9 and 46, as described in [62]. The endpoints of the line representing the central sulcus represent the

Table 1

Summary of reports of the effect of frontal-lobe lesions on span tests

Task	Non-spatial (digit span)	Spatial (block span)
	Ghent et al. [27] ($n = 24$)	Canavan et al. [11] ^a ($n = 10$)
	Canavan et al. [11] ^a ($n = 10$)	Owen et al. [54] ^a ($n = 26$)
	Wiegersma et al. [82] ^a ($n = 7$)	Miotto et al. [44] ^b ($n = 20$)
	Pigott and Milner [59] ^a ($n = 22$)	Greenlee et al. [85] ^a ($n = 5$)
	Stuss et al. [72] ^a ($n = 32$)	
	Duncan et al. [83] ($n = 3$)	
	Godefroy et al. [84] ($n = 11$)	
	Mangels et al. [41] ^a ($n = 6$)	

^a Indicates that mean PFC patient score was numerically, but not significantly, inferior to mean NCS score.

^b This study reports a combined score of forward and backward span.

endpoints of the central sulcus as it is represented in [73]. It is drawn as a straight line because this is the extent of detail that is presented in some of the lesion diagrams (and therefore represents the best spatial resolution that we can achieve with this method). The boundaries of areas 9 and 46 were defined in a careful neuroanatomical study of five human brains that was performed expressly to define the extent of these two regions in Talairach coordinates [62].

We were limited, using this technique, to transform-

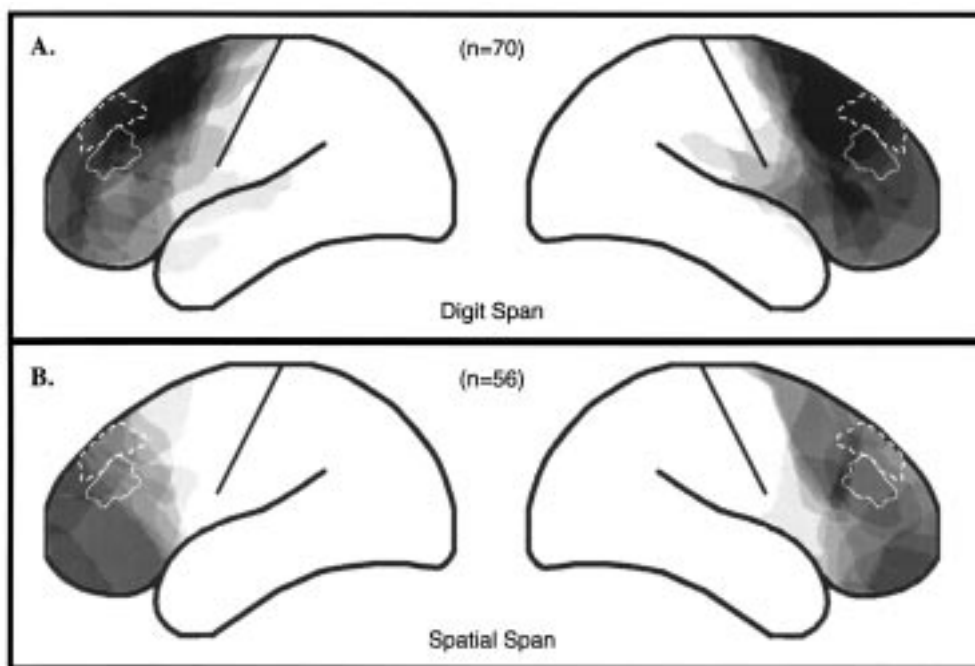


Fig. 1. Composite diagrams illustrating extent of PFC lesions of patients showing no deficit in span performance. (a) incorporates four studies [11,41,59,72]; (b) incorporates three studies [11,44,54]. Areas with overlapping lesions appear darker. Dashed line denotes area 9, dotted line denotes area 46 [62].

ing diagrams that were presented in the original publications as two-dimensional sagittal views. This technique suffers from a lack of spatial resolution because its sources of information are themselves often very low resolution—many of the lesion diagrams from papers included in our review, for example, were created from the estimates of neurosurgeons or of neuroradiologists, rather than directly from high resolution brain scans. The process of transforming each of the diagrams to a common coordinate frame also introduces spatial error into the procedure. Despite these caveats, however, this technique lends to our behavioral meta-analysis the additional power of assessing the contributions of specific subregions of PFC to performance on specific working memory tasks. Whereas not all studies that we reviewed provided lesion diagrams, each of those that did provided a diagram for each patient participating in that study.

3. Results

3.1. Span tasks

In his seminal report on 'Intelligence in man after large removals of cerebral tissue', Hebb mentioned the case of a woman with incomplete removal of a large bilateral frontal glioblastoma who retained average adult level digit span (Stanford-Binet L-M) despite a constellation of stereotypically 'frontal' behavioral abnormalities [31]. Since that time, surprisingly few studies have focused on simple span tests as a dependent measure of primary interest. Our literature search yielded a total of 11 published studies that reported span performance of patients with PFC lesions and NCS, using the criteria described in the Methods section (Table 1).

Eight studies reported digit span results, each using the standardized procedures of the WAIS-R. None of the reports of digit span reported a statistically significant deficit in patients with frontal-lobe lesions (total n from the eight studies = 115). Although five of these studies reported that the performance of patients with frontal-lobe lesions was numerically lower than that of the NCS, calculation of the binomial probability of this pattern of results indicated that this trend failed to achieve statistical significance ($P = 0.3$; one-tailed Sign Test). Because we did not have access to individual subject data from many of these studies, we believed that a nonparametric statistic would represent a more conservative, less assumption-laden analysis than a parametric statistic derived from z -scored group means.

Four of the eight reports of forward digit span included lesion diagrams [11,41,59,72]. Each of these reports included a diagram for each patient. The composite diagram of the lesions of all the PFC patients

reported in these four studies (Fig. 1a; total n from these four studies = 70) shows that no region of PFC was spared.

Although some of these eight studies also reported data from patients with posterior cortical lesions that spared PFC, meaningful assessment of the performance of posterior-lesioned patients in comparison to PFC-lesioned patients is complicated by the brain regions represented by the posterior-lesioned patients featured in these studies and by the statistical treatment of the posterior-patient data in these reports. We would predict that performance on the digit span test would be particularly sensitive to damage to the inferior parietal lobule in the left hemisphere [19,63,77,79,80]. Span data from posterior-lesioned patients are not reported in each of the eight studies reviewed here, however, and those that are reported are either from patients whose lesions spare left inferior parietal cortex or reflect a group average from all of the posterior-lesioned patients contributing to a particular study. The one study of the eight that provides data for subgroups of posterior-lesioned patients reported a statistically significant impairment of digit span performance in the group with 'nonfrontal injuries in the left hemisphere [$n = 20$]', with the largest error scores within this group contributed by a subgroup of four subjects 'with unilateral injury who had neither visual-field defects nor somesthetic defects; the presumed locus of injury in these subjects was the left parietotemporal region' [27].

Four studies reported results on the block span task that was developed by Corsi [43] as a spatial analogue of the digit span test. Three of these studies reported a numerical, but not statistical, deficit in patients with frontal-lobe lesions. (The study that reported no deficit in patients with PFC lesions [44] reported one combined span score collapsed across forward and backward tests.) This small number of studies precluded meaningful assessment of these data with a sign test.

Three of the four studies that reported spatial span included lesion diagrams [11,44,54]; each of these reports included a diagram for each patient. Fig. 1b presents a composite diagram of the lesions of the PFC patients in these three studies (total n from these three studies = 56). Inspection of the resultant diagram suggests that, as with forward digit span, no subregion of PFC makes a necessary contribution to forward block span performance.

Two other papers have reported nonspatial span performance with tasks that are unique to these studies, and thus are not included in Table 1 or in the composite lesion figures, but that provide additional information about nonspatial span performance in patients with PFC lesions. Ghent and colleagues [27] used a 'form span' task in which subjects studied a linear arrangement of shapes, closed their eyes briefly

while the shapes were placed randomly with a group of additional shapes, and attempted either immediately, or after a delay of 15 s, to reconstruct the series. PFC patients were unimpaired on a form span score collapsed across delays. Pigott and Milner [59] have reported the results of an 'object span' task in which subjects viewed an array of squares with half of the squares illuminated, and indicated, after a delay, which square in the array was no longer illuminated. The number of elements in the array increased by 2 after each correct trial, and testing ended with two consecutive incorrect responses. The task was administered with 2 and 10 s delays, and with and without delay-period distraction. Subjects with right (but not left) frontal lobe lesions were impaired on the measure of span collapsed over time and distraction, but no interactions were significant, indicating that this group was not differently vulnerable to manipulations of delay time or distraction. Additionally, this group was unimpaired on a test of digit span [59]. Pigott and Milner [59] speculated that their object span task may have differed from the digit span test in that formation of a representation of a complex spatial array may have required organizational strategies not required for simple span task performance. Another salient difference between the object span and digit span tests is that object span does not require retention of serial order of stimuli.

3.2. Delayed-response tasks

Whereas meta-analysis of span data is facilitated by the fact that standardized procedures and materials govern the methods of most investigators, comparable analysis of delayed response data is weakened by the absence of such near-universally employed standard methods. Our review encompasses seven studies, each employing a different method and different materials (Table 2). These studies also differ fundamentally from the reports of digit span reviewed above in that these studies were designed explicitly to investigate delayed-response performance in patients with PFC lesions, whereas in all but one of the span studies reviewed above [27], span performance was treated as a baseline psychometric variable of minimal theoretical interest.

The delayed-response tasks reviewed here can be fit into a 2×2 matrix with the factors of stimulus-material (spatial, nonspatial) and distraction-type (no-distraction, distraction) (Table 3). Orthogonal to the experimental design factors is the factor of lesion location. Only two of the delayed-response studies reviewed here [9,61] controlled lesion locus as an independent variable, however, so we could not categorize delayed response results according to this factor in Table 3. Because many of the reports that we reviewed presented data from more than one condition of a delayed response task (e.g., with and without distrac-

Table 2
Summary of tasks represented by delayed-response studies

Study	Tasks
Ghent et al. [27]	Spatial: visual point localization (judgment of when a moving dot occupies the position of the target, following a 15 s delay). Nonspatial: form span (reconstruct a series of shapes after a 15 s delay)
Prisko ^a [60]	Nonspatial: delayed response with nonsense figures (60 s delay with and without distraction; based on [37])
Chao and Knight [13]	Nonspatial: delayed response with auditory stimuli (stimuli were [nonspeech] environmental sounds; 5 s delay with and without distraction)
Baldo [8]	Spatial: delayed response (point with computer mouse to location of target; 3 and 9 s delay conditions with and without distraction) Nonspatial: delayed response with color stimuli (point with computer mouse to portion of a color spectrum that matches the target color; 3 and 9 s delay conditions with and without distraction)
Ptito et al. [61]	Spatial: delayed response (point with computer mouse to location of target; 30 s delay with and without distraction)
Verin et al. [78]	Spatial: delayed response (15 s delay)
Bechara et al. [9]	Spatial: delayed response with playing card stimuli (select two target stimuli from among four stimuli total; stimulus identity defined by position; 15, 30, and 60 s delays with distraction) Nonspatial: delayed nonmatching to sample with color stimuli (select two playing cards featuring the nonmatching color from among two red and two black cards; 15, 30, and 60 s delays with distraction)

^a We have limited our interpretation of the Prisko [60] data to those data that are not contaminated by proactive interference (PI), i.e., to the nonsense figures. PI, the phenomenon of stimuli presented earlier in the course of testing interfering with the processing of subsequently presented stimuli, can be exaggerated in patients with PFC lesions [49]. The presence of PI in neuropsychological studies complicates the interpretation of the mnemonic component of delayed response performance, because it can reflect the differential operation of inhibitory or filtering mechanisms that do not, in strict terms, contribute to memory storage or retrieval. For a discussion of the role of proactive interference in this study, see [42].

Table 3
Summary of reports of the effect of frontal-lobe lesions on delayed-response tests

Task	No distraction	Distraction
Non-spatial	Ghent et al. [27] ($n = 24$) Prisko [60] ^c ($n = 10$) Chao and Knight [13] ^{b,c} ($n = 10$) Baldo [8] ^c ($n = 11$)	Prisko [60] ^{a,c} ($n = 10$) Chao and Knight [13] ^{b,c} ($n = 10$) Baldo [8] ^{b,c} ($n = 11$) Bechara et al. [9] ^{b,c} ($n = 4$) Bechara et al. [9] ^f ($n = 6$)
Spatial	Ghent et al. [27] ($n = 24$) Ptito et al. [67] ^{a,d} ($n = 8$) Ptito et al. [61] ^{b,c} ($n = 12$) Verin et al. [78] ^{b,c} ($n = 10$) Baldo [8] ^c ($n = 12$)	Ptito et al. [67] ^{b,d} ($n = 8$) Ptito et al. [67] ^{b,c} ($n = 12$) Baldo [8] ^c ($n = 12$) Bechara et al. [9] ^{b,c} ($n = 4$) Bechara et al. [9] ^f ($n = 6$)

^a Indicates that mean PFC patient score was numerically, but not significantly, inferior to mean NCS score.

^b Indicates that mean PFC patient score was significantly impaired.

^c Indicates that patients in this observation have lesions including area 9 and/or 46.

^d Indicates that patients in this observation have lesions that spare areas 9 and 46.

^e Indicates that patients in this observation have right hemisphere lateral PFC lesions.

^f Indicates that patients in this observation have left hemisphere lateral PFC lesions.

tion, or with different stimulus materials), we organized Table 3 by 'observation' rather than by publication. Following this convention, for example, results from the Chao and Knight [13] delayed response-*without*-distraction condition and the Chao and Knight [13] delayed response-*with*-distraction condition are assessed as separate observations. Similarly, results from the two lesion groups studied by Ptito et al. [61] are assessed as discrete observations, as are the two lesion groups studied by Bechara et al. [9]. This method permitted us to group together individual experiments that used similar stimulus materials and testing procedures, even though these observations came from separate reports.

Inspection of Table 3 suggests an effect of distraction-type on performance: only three out of nine *no-distraction* observations were significantly different from NCS, as contrasted with significant impairment in six out of ten *distraction* observations. We created composite lesion diagrams for the two spatial cells in Table 3, grouping studies by performance (spared vs impaired), in order to assess whether systematic differences across studies in locus of lesion might explain differences in performance on similar tasks (Fig. 2). Four of the five studies of spatial delayed response included lesion diagrams. Each of these reports included a diagram for every patient. (We did not attempt a similar analysis for the nonspatial studies, because the heterogeneity of stimulus material used in different studies in this group would render the results of such an analysis difficult to interpret.) Inspection of the composite lesions of spatial/no-distraction studies suggests that the PFC lesions of subjects in the observations reporting intact performance on such tests

[8,27,61] largely spare areas 9 and 46 of dorsolateral PFC in the right hemisphere, as compared to lesions of subjects in the impaired group [61,78] (Fig. 2a,b). Assessment of the composite diagram of the studies making up the spatial/distraction cell in Table 3 reveals a similar pattern: The lesions of the subjects in the studies reporting intact performance [8,9] tend to spare areas 9 and 46 of lateral PFC in the right hemisphere in comparison to the lesions of subjects in the impaired group [9,61] (Fig. 2c,d).

The lesions in patients with intact performance on spatial delayed response tasks with and without distraction may also spare a more posterior and superior region of lateral prefrontal cortex located along the superior frontal sulcus (Brodmann's area 8), which has recently been implicated as being critical for spatial working memory in humans [50]. These investigators argue that this more posterior region, rather than area 9/46, is more likely the human homologue of the principal sulcus in monkeys. However, with our method it is difficult to assess with any certainty the location of this more posterior region.

Direct examination of the results of three of the delayed response studies incorporated in our review also suggest a particularly important role for the cortex of Brodmann's area 46 (located on the middle frontal gyrus and often considered to be homologous to the principal sulcus region of monkeys) in mediating performance on tests of spatial delayed response. Two studies in our review that controlled locus of frontal-lobe lesion as an independent variable [9,61]. Ptito and colleagues [61] found intact performance in *sparing-area-46* patients in the spatial/no-distraction condition, but impaired performance of *sparing-area-46* patients

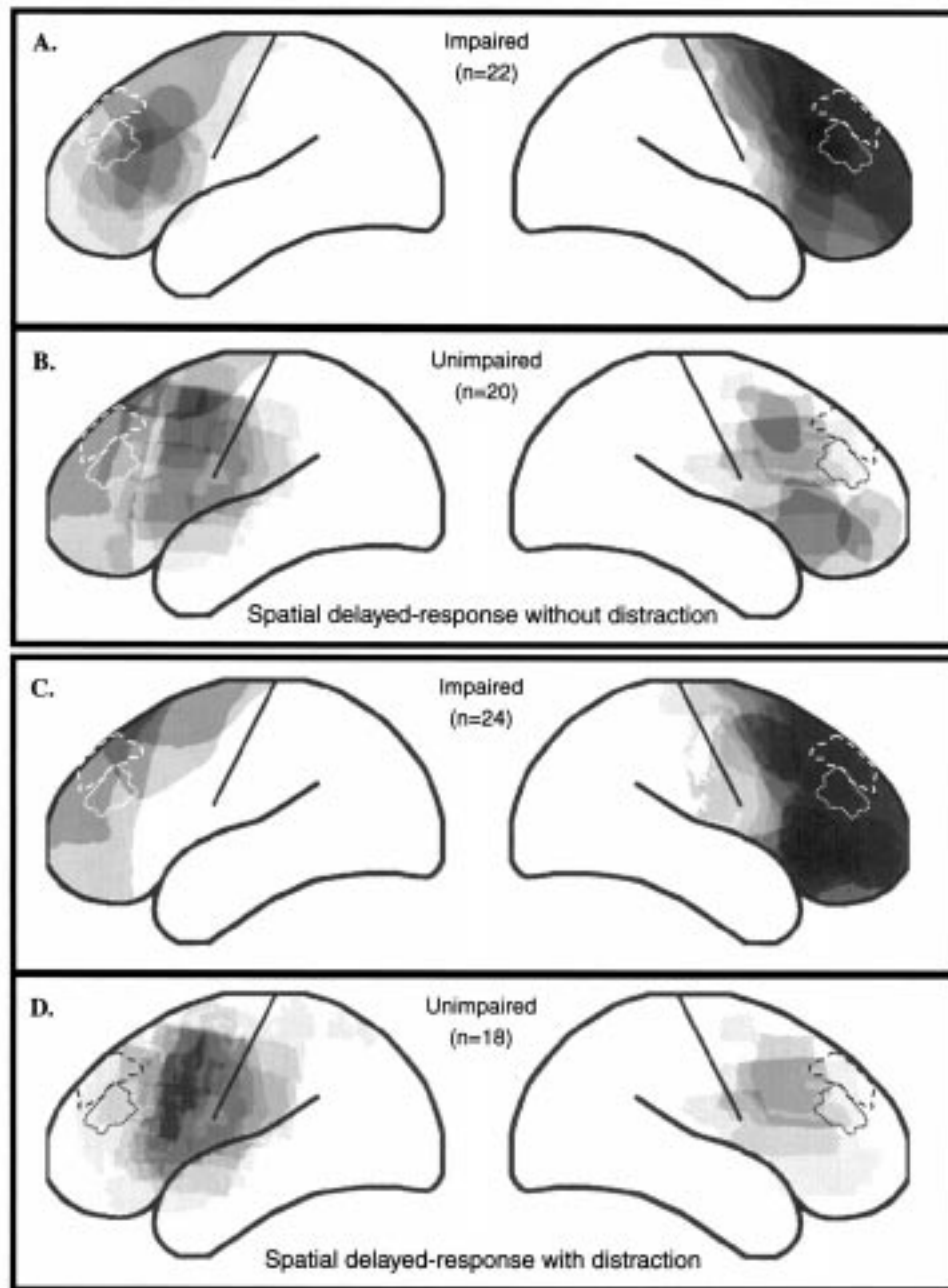


Fig. 2. Composite diagrams, organized by performance, of PFC lesions of patients tested on spatial delayed-response tasks with or without distraction. (a) incorporates two observations (from [61,78]); (b) incorporates three observations (from [8,27,61]); (c) incorporates three observations (from [8,61,78]); and (d) incorporates two observations (from [8,9]). Dashed line denotes area 9; dotted line denotes area 46 [62].

in the spatial/distraction condition, as well as impaired performance of the *including-area-46* group in both of these conditions, suggesting that distraction interacts with integrity of area 46 on tests of spatial delayed re-

sponse.² Bechara and colleagues [9] reported that the one subject of their right hemisphere-lesioned group who demonstrated normal performance on the spatial delayed response task was also the only subject whose lesion was restricted to *inferior* dorsolateral PFC. Additionally, although Baldo [8] did not find statistically significant group differences between PFC patients and NCS in any condition of any of the three spatial delayed response tests that she administered, she did find a significant, positive correlation between

² Interpretation of the results of this study, however, must be tempered by the fact that the lesions of most of the patients in the including-area-46 group also invaded the frontal eye fields (Ptito, personal communication). The same caveat may also apply to the results of Verin et al. [78].

number of errors and percentage of damage to area 46 in the PFC group in two of the three studies presented in her thesis. These results, which were independent of total lesion volume, suggested a dependence of spatial delayed response performance on integrity of area 46. Interestingly, Baldo [8] did not find evidence for dependence of *color* delayed response performance on area 46 integrity, despite finding an overall impairment in color delayed response in the PFC group.

Four of the studies of delayed response that we reviewed included patients with postcentral cortical lesions that spared PFC [14,27,60,78].³ Three of these studies found no evidence of delayed-response impairment in the posterior-lesioned patients [14,27,78]. The fourth, which tested delayed response for nonsense figures with a 60 s, distraction-filled delay, found an impairment in patients with right temporal lobectomy, but no impairment in patients with left temporal lobectomy [60]. The right temporal lobectomy patients were not impaired, however, on analogous tests that employed clicks, flashes, tones, and colors as stimuli. Their memory impairment was thus interpreted as a reflection of the privileged role that this structure was believed to play in the learning and retention of visual patterns.

4. Discussion

4.1. The effect of PFC lesions on span performance

Prisko, upon reviewing the neuropsychological literature through 1963, concluded that: “memory defects after frontal-lobe damage are more apparent than real” [60], a view that echoed the conclusion of Ghent and colleagues published one year previously [27]. This observation holds up well in our updated review of span literature: none of the 11 studies of forward verbal and spatial span in patients with PFC lesions that we reviewed (reflecting the performance of 166 individual patients) demonstrated a statistically significant deficit. The non-significant results of a sign test of a trend toward lower performance by PFC patients across digit span studies permitted us to reject the possibility that PFC lesions cause a subtle deficit in digit span performance that only emerges when data are compared across a large number of studies. Additionally, the construction of composite diagrams

of the lesions represented by several of the papers reporting digit span scores indicated that there was no strong bias among subregions of PFC lesions in these studies. That is, there was no evidence of regions that were spared in the majority of these studies that might, themselves, have made a necessary contribution to digit span performance. These results establish clearly that the PFC does not make a necessary contribution to forward digit span performance. Our interpretation of the spatial span data, although tempered by the smaller number of observations in our review, is similar: We found no evidence of a necessary contribution of any region of the PFC to spatial span performance.

We conclude from our findings that PFC lesions do not cause a reduction in working memory *capacity* as indexed by span task performance. Evidence from the neuropsychological and neuroimaging literature suggests that passive working memory storage of the kind required for performance on a span task is supported by the distributed systems in posterior cortical regions that represent semantic information (e.g., digits) and that process sensory information (e.g., visuospatial). For example, lesions in left inferior parietal cortex are associated with disrupted working memory for auditory verbal stimuli [19,63,77,79,80], and in right inferior parietal cortex with disrupted working memory for visuospatial stimuli [1,20,30,43]. Patients with parietal lobe lesions have been shown to have markedly reduced span (e.g., digit span = 2.3 in patient KF [86]) as compared to the normal span of patients with frontal lesions. Corroborating neuroimaging evidence also implicates inferior parietal cortex as an important site of information storage [71].

4.2. The effect of PFC lesions on delayed-response performance

Our review of the delayed response literature, in contrast with the span literature, indicated that there are conditions under which PFC lesions disrupt delayed response performance. These findings suggest several possibilities: (1) PFC may be necessary for some rehearsal processes; (2) PFC-mediated processes may make important contributions to elements of the delayed-response task that are not present in span tasks, such as the discrimination and decision-making processes recruited by a forced-choice testing procedure; (3) PFC-mediated attentional and/or inhibitory mechanisms may play a more prominent role in delayed response than in span tasks.

The finding that humans with PFC lesions are impaired on delayed-response tasks is consistent with the monkey literature [24]. However, it may be surprising that there were several human studies in which patients with PFC lesions were not impaired on certain

³ Although Chao and Knight have recently published two studies that examine delayed response performance in PFC patients [13,14], these two reports use many of the same patients and we therefore only included the study with the larger *N* [13] in our meta analysis. It is the other study, however, that includes patients with posterior cortical lesions [14]. The behavioral results of the PFC groups in these two studies are qualitatively comparable.

delayed-response tasks [8,9,27,60,61]. There are several possible explanations for this observation. First, this disparity may reflect important differences in the role of PFC in working memory function across species. Second, it may be that nonmnemonic demands of the delayed-response task, such as attentional and strategic demands, rely to a greater extent on PFC mediation in the monkey than they do in the human. Third, methodological differences across tests may have contributed to the variability across studies. Finally, differences between studies in the site of the PFC lesions in patients may explain a great deal of the variance in the delayed-response studies reviewed here. This last explanation gains support from the results of our comparison of loci of lesions in the spatial/no-distraction and spatial/distraction delayed-response studies, illustrated in Fig. 2. Also, Baldo [8] found that performance on a *spatial* delayed-response task correlated with the extent of area 46 damage, although the PFC group as a whole was not impaired.

We also found more reports of impaired delayed response performance when the delay period was filled with a distractor than when it was unfilled, suggesting that the dependence of delayed-response performance on PFC may increase with the insertion of distraction into delay periods. The variation of dependence of delayed-response performance on PFC with manipulation of delay can be understood as a reflection of the effects of this manipulation on information processing demands. The rehearsal/maintenance processes that suffice to support undistracted delayed response function may require the mediation of other PFC-supported processes when distraction during the delay interval presents a source of interference or attentional salience. These PFC-supported processes may include inhibition of prepotent responses [21,64], gating behaviorally irrelevant stimuli [14], shifting attention among stimuli and/or among different components of a task [65], maintaining/refreshing information in a noisy environment [34] or selection among competing responses [75].

The results of this review are generally consistent with the view that PFC supports the maintenance and manipulation of information that is no longer available in the environment, in the service of planning and guiding behavior [25,28]. Delayed-response tasks, particularly those that feature interference during the delay period can tax these functions. Span tasks, in contrast, engage only minimally these processes that are believed to be supported by PFC.

4.3. *The neural basis of the components of STM—converging evidence from lesion and neuroimaging studies*

Our review of the literature is consistent with the

idea that working memory is not a unitary process, but rather, is a function that can recruit many dissociable processes that may be subserved by distinct neural circuitry. We demonstrated that capacity, to the extent that it is indexed by span tasks, is not dependent on PFC function, whereas rehearsal and manipulation processes show greater dependency on PFC. This conclusion is bolstered by the subset of the studies reviewed that also reported data from patients with lesions of posterior cortex, because the posterior-lesioned patients demonstrated the reverse pattern of impairment and sparing: the three studies of delayed response that included patients with posterior lesions found no evidence of delayed-response impairment in these patients [14,27,78], whereas the one study of digit span that reported data for a group of patients with lesions of left temporoparietal cortex reported impairment in this group [27]. Collectively, these studies form an anatomical double dissociation consistent with our functional neuroanatomical model.

A question that our review did not address is the potential contribution of selective regions of the PFC to rehearsal and manipulation processes. The evidence for anatomical distinctions among PFC subregions supporting these processes derives from neuroimaging research. For example, two recent PET studies have presented data that suggest that the storage (i.e. retention) components of *verbal* working memory are associated with activation in inferior parietal cortex whereas the rehearsal components of these same tasks are associated with activation in ventral PFC [2,58]. Other studies have observed that working memory tasks that place demands on the processing or manipulation of information often elicit greater activation in dorsolateral PFC (Brodmann's areas 9 and 46), whereas working memory tasks that do not place demands on such processes tend to activate only ventral PFC [16,18,55]. This model of PFC organization is also consistent with the results of one of the lesion studies that we reviewed, that reported that area 46 lesions caused greater impairment of delayed-response performance than did lesions that spared this area [61].

4.4. *Proposal of hypotheses*

The critical review of working memory data presented in this paper can serve as a useful guide for hypothesis formulation. Interpretation of the meta-analysis itself, however, should be tempered by at least two factors. Comparison of Tables 1 and 3, for example, indicates that there is increased variability in delayed-response performance as contrasted with span performance. This increased variability of delayed-response performance may reflect the increased variability in *methods* across delayed-response studies, as contrasted with the methodological homogeneity of

studies assessing memory span. Alternatively, the increased variability of delayed-response performance may reflect legitimate interactions between stimulus type and processing requirements that differed between these tasks. We have also observed that the variability in performance across studies may be due in part to differences across studies of the specific regions that are damaged in PFC patients.

Our review presents us with an opportunity to articulate hypotheses about the nature and degree of dependence of working memory task performance on the integrity of subregions of the PFC:

1. Simple verbal and spatial span performance is not dependent on PFC integrity.
2. Performance on delayed-response tasks without distraction will be differentially dependent on PFC integrity, depending on damage to specific regions of PFC. For example, left ventrolateral PFC lesions (incorporating areas 44 and 45) will impair verbal, but not spatial, delayed response performance. Alternatively, dorsolateral lesions to areas 9 and 46 (and possibly to area 8), especially in the right hemisphere, will impair spatial delayed-response performance.
3. Performance on delayed-response tasks with distraction is dependent on the integrity of dorsolateral PFC within Brodmann's areas 9/46. Impairments on such tasks will be comparable regardless of the type of information being retained.

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