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REVIEW

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Segregation of working memory functions within the dorsolateral prefrontal cortex

Abstract It is now widely accepted that the prefrontal cortex (PFC) plays a critical role in the neural network subserving working memory (WM). At least three related questions are still under debate: (1) is the PFC critical for all constituent processes of WM (i.e., short-term storage, manipulation, and utilization of mental representations) or only in one or a few of them? (2) Is there segregation of function among different cytoarchitectonic subdivisions of the PFC? (3) If this be the case, is this segregation based on the nature of the information being processed or on the type of cognitive operation performed? The present review article describes findings in the monkey supporting a modular "domain-specific" model of PFC functional organization with respect to WM operations. In this model, the dorsolateral prefrontal cortex (DLPFC) is composed of several subregions, based primarily on the nature of the information being processed in WM. Storage and processing functions are integrally related in each area. Future studies designed to map as yet uncharted areas of prefrontal cortex with refined anatomical and physiological approaches may provide a critical test of the model and evaluate the extent to which it applies generally or, instead, mainly to visual domains or only to dorsolateral convexity areas.

Key words Working memory · Cognition · Prefrontal cortex · Rhesus monkey

Introduction

It is widely accepted that the prefrontal cortex plays a major role in the most complex aspects of human thought, such as reasoning and planning. A set of elemental processes, including the maintenance, manipulation, and utilization of mental representations, has been postulated to constitute an operational working-memory (WM) system, which greatly contributes to these higher cognitive functions (Baddeley 1986; Goldman-Rakic 1987). WM involves both a short-term storage capacity for maintaining mental representations in an active state and a capacity for processing or manipulating information held in the WM "buffer", often referred to as the "central executive" (Baddeley 1986) or supervisory attentional systems (Shallice 1982). Experimental studies both in monkeys and humans have clearly demonstrated the critical role played by the prefrontal cortex (PFC) in the neural network subserving WM (Goldman-Rakic 1987; Fuster 1997; Smith and Jonides 1999). In consequence, there is remarkable consensus in the field regarding the association between prefrontal mechanisms and WM capacity. Much less agreement, however, exists on the issue of how the "two-tier" modular model of WM described above is instantiated at the level of brain organization. In particular, a major question pertains to whether the PFC participates in all constituent processes of WM or only in one or a few of them. Moreover, as the PFC is a large territory (including multiple cytoarchitectonic areas), it is of interest to determine the specific contribution to WM of particular areas and subareas within this region. If there is segregation of function among different cytoarchitectonic subdivisions of the PFC, as seems biologically reasonable, is this segregation based on the nature of the information being processed or on the type of cognitive operation performed? The answer to this question holds the key to the general features of the functional architecture of cognition.

This short review article describes findings in the monkey that may contribute to a coherent model(s) of anatomical and functional organization of the PFC for WM. In the following sections, we will review some of the data that has lead to a modular "domain-specific" model of PFC functional organization with respect to WM operations (Goldman-Rakic 1987). This model pos-

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tulates that the dorsolateral prefrontal cortex (DLPFC) is composed of several subregions, based on the sensory nature of the information being processed in WM, regardless of the level of processing. In this view, the cortex surrounding the principal sulcus (Walker's area 46 in the primate) is thought to be specialized for visual-spatial processing, whereas cortex on the inferior convexity below area 46 (Walker's areas 12 and 45) is involved in nonspatial visual (e.g., object/face) processing within WM. Further, sensory input may be only one dimension by which these areas differ; other associated features, such as intrinsic circuitry and efferent mechanisms, may more fully characterize areal specializations. Although several lines of evidence support domain specificity for the rhesus monkey, some caveats are in order: (1) the modular segregation of the visual memory system in the DLPFC may not generalize to other sensory domains; (2) other areas of the prefrontal cortex may play supramodal integrative multiple domain functions; (3) this model might not apply without significant modification to the organization of the human DLPFC; and (4) the model does not specify the type of WM operation processed within each domain-specific module. To place the domain-specific hypothesis in a wider theoretical context, we will briefly describe alternative models of anatomical and organization of the DLPFC vis a vis WM and discuss findings that are not congruent with the domain-specific model.

Evidence for the "domain-specific" model

Anatomical definitions

As this review focuses on anatomical and functional relationships, it is important to define the main regions of interest and their connectivity. Our reference for PFC subdivisions is Walker's (1940) cytoarchitectonic map, recognizing that it may be only an approximation to functional subdivisions being established by contemporary neurophysiological methods. Area 9 represents the most superior and dorsal part of the DLPFC. It has both a lateral and a medial aspect within the prefrontal cortex. For purposes of this review, we refer to this area as "dorsomedial" (DM). Area 46 is entirely included in the DLPFC. It lies beneath area 9, and it encompasses the principal sulcus, the major sulcus in the DLPFC. It is noteworthy that this area has been the most-studied part of the DLPFC (Goldman-Rakic 1987; Fuster 1997), and we refer to it as "dorsolateral" (DL). Areas in the inferior part of the DLPFC, beneath area 46 and above the lateral orbital prefrontal cortex, are Walker's area 12 and 45, referred to here as the "inferior convexity" (IC). Two other areas, Walker's area 8 and a part of 10 (the frontal pole) occupy the lateral aspect of the prefrontal cortex. Area 8 should be briefly mentioned. It is subdivided into area 8A, in the arcuate concavity, caudal to area 46, and area 8B, dorsomedial and caudal to area 9. The most caudal part of the principal sulcus merges with the anterior extension of area 8A. Thus, numerous lesions or electrophysiological studies focused on the principal sulcus region have also included the most anterior part of area 8A. The frontal eye field (FEF) is generally not included in this anterior cortex, as it is located more caudally within the rim and fundus of the arcuate sulcus (Goldberg and Bushnell 1981).

Extrinsic connections

The extrinsic connections of the PFC provide essential information regarding the issue of regionalization of function. Numerous anatomical studies have shown that DL and IC prefrontal cortices receive differential connections from posterior association cortices. The dorsolateral areas receive dense projections from the inferior parietal association cortex (Mesulam et al. 1977; Petrides and Pandya 1984; Andersen et al. 1985; Barbas and Mesulam 1985; Cavada and Goldman-Rakic 1989), a region involved in visuospatial processing (Pohl 1973; Batuev et al. 1985; Friedman and Goldman-Rakic 1994; Chafee and Goldman-Rakic 1998). By contrast, IC cortex is networked with the inferotemporal association cortex (Kuypers et al. 1965; Jones and Powell 1970; Chavis and Pandya 1976; Jacobsen and Trojanowski 1977; Kawamura and Neito 1984; Shiwa 1987; Barbas 1988; Seltzer and Pandya 1989; Ungerleider et al. 1989; Distler et al. 1993; Webster et al. 1994; Bullier et al. 1996), a region involved in the representation of visual objects (Bruce et al. 1981; Fuster and Jervey 1981; Perret et al. 1982; Desimone et al. 1984; Baylis et al. 1985; Fuster 1990; Miller et al. 1991, 1993; Rodman et al. 1993). The fact that DL and IC prefrontal cortices are the recipients of differential projections from areas that are themselves specialized visual processing areas (spatial vs. feature) is highly suggestive of a parallel organization of domain-specific modules within the PFC. It would be reasonable to expect, and we have proposed, that regions receiving these differential visual system inputs are functionally related to and are extensions of the dorsal and ventral visual-processing streams with which they are selectively connected (Goldman-Rakic 1987, 1996).

Selective lesions and behavior

The delayed-response (DR) tasks have been a primary instrument for assessing WM capacity in the nonhuman primate. Their main feature is that they require monkeys to maintain a mental representation during a delay period and then use this representation to guide the choice of response at the end of the delay (Hunter 1913). DR tasks can be formatted to examine WM for various informational domains (e.g., spatial DR, spatial or object delayed alternation, object/color delayed matching or nonmatching to sample, oculomotor DR). For this reason, they have long been used to study the possible areal specializations of the prefrontal cortex (for a review, see

Goldman-Rakic 1987). Lesions of the DLPFC, and more specifically those restricted to the principal sulcus or the middle third of its sulcus, are sufficient to produce a deficit as severe as larger PFC lesions in performance on spatial-DR and spatial-alternation tasks (Mishkin and Pribram 1955; Butters and Pandya 1969; Butters et al. 1971, 1972; Goldman-Rakic 1987; Fuster 1997). An important point is that the deficits which follow dorsolateral lesions are not necessarily modality-specific, i.e., the stimuli to be recalled need not be visual. Delayed-response tasks with spatial auditory cues or somatic stimulation as memoranda may also be impaired after lesions of the DLPFC cortex (Shindy et al. 1994). The spatial deficits are also independent of the mode of response. Thus, in an oculomotor analog of the classical spatial DR tasks, Funahashi and colleagues (Funahashi et al. 1993a) demonstrated that a unilateral lesion of DLPFC, sparing the FEF area, disrupted performance of memory-guided eye movements to spatial cues in the visual field contralateral to the hemisphere in which the lesion was placed. The deficit was delay-dependent and not present in a sensory-guided version of the task. Finally, monkeys with DLPFC are unimpaired in nonspatial DR tasks in which the physical features (patterns, shapes, or colors) of objects are the behaviorally relevant memoranda. Thus, monkeys with DL prefrontal lesions perform as well as intact monkeys in performance on delayed object alternation and object or color matching or nonmatching-to-sample tasks (Stamm and Rosen 1973; Passingham 1975; Mishkin and Manning 1978; Bachevalier and Mishkin 1986). Thus, there is little evidence to indicate a role of the DL prefrontal sector in object recognition or in basic short-term memory for object features. The fact that so many studies clearly indicate that one given subregion of the PFC – the principal sulcal area – is specialized in the processing of one given sensory domain – the visuospatial domain – provides strong evidence for the concept of a domain-specific module within the PFC, even if lesion studies have not yet shown the same degree of specialization for other PFC areas (for instance, see Mishkin et al. 1969). Taken together, these findings attest to the critical role played by the principal sulcal region in the most elementary WM operation, i.e., the "on-line" maintenance and utilization of mental representations of visuospatial coordinates within the spatial domain.

By contrast to DL, lesions of IC cortex cause impairments in tasks based on the identity or features of object rather than their spatial location. This impairment is seen in classical WM tasks, such as delayed object alternation (Mishkin and Manning 1978) and "recognition memory" like the object/color delayed matching or non-matching-to sample tasks (Iversen and Mishkin 1970; Passingham 1975; Mishkin and Manning 1978; Kowalska et al. 1991), tasks which include a short-term memory component. The impairment produced by IC lesions on the non-matching tasks is sometimes described as small and transient (Passingham 1975; Bachevalier and Mishkin 1986; Kowalska et al. 1991), unlike the severe impairment in these tasks after ventromedial prefrontal lesions (Bachevalier and Mishkin 1986; Meunier et al. 1997). Thus, in a recent study, Rushworth et al. (1997) have found that lesions restricted to the anterior part of IC cortex (Walker's area 12) were without lasting effect on the relearning of various cognitive tasks based on color and shape discrimination (visual pattern association, delayed, or simultaneous color matching to sample tasks). However, larger lesions incorporating the caudal IC (Walker's area 45A) and the lateral orbital prefrontal cortex produced impairments of various degree on these tasks. Although the nature of the underlying impairment after such lesions remains unclear, a deficit specific to features of objects could account for the behavioral impairments observed after inferior prefrontal lesions. Moreover, some studies have shown that neither spatial DR or delayed alternation tasks are impaired following IC lesions (Mishkin and Manning 1978; Passingham 1985). However, impairments on spatial DR tasks have occasionally been observed following large IC lesions (e.g., Mishkin et al. 1969). These deficits have been long been attributed to nonsensory difficulties in shifting-response strategies rather than to sensory processes per se (Mishkin 1964). Indeed, selective deficits on spatial tasks have never been demonstrated in monkeys with IC lesions. It is also possible that deficits on spatial tasks arise from inadvertent damage to portions of the inferior arcuate sulcus, affecting a portion of the spatial system. One should thus acknowledge that, though there is a strong case from lesion and single-unit-recording studies favoring a specific role of IC cortex in "object-cognition", no clear-cut double dissociation (as the one evidenced in DL cortex for "spatial cognition") has yet been demonstrated. Consequently, the precise role of IC cortex with respect to WM domains deserves further examination. Single-unit-recording studies designed to map this region more precisely should provide a clearer basis for future lesion studies.

The DM, or superior portion of the prefrontal promontory, is the least understood of its main divisions. Performance on the classical spatial DR, delayed alternation, and delayed non-matching to sample tasks is not impaired following DM lesions (Goldman et al. 1971; Levy and Goldman-Rakic 1999). Moreover, in more complex spatial or nonspatial WM tasks, the involvement of DM cortex remains in question (see discussion below).

In summary, in the visual domain, lesion studies in the non-human primate provide compelling evidence for a model of anatomical and functional segregation of the PFC, based at least in part on sensory processing, in which the DL prefrontal cortex (i.e., Walker's area 46 including the principal sulcus) is specialized for spatial cognition involving a WM process, whereas the IC/ventrolateral prefrontal (i.e., Walker's area 12/45) plays a role in object cognition involving WM. The DM and the prearcuate regions do not seem to participate in this domain-specific processing within WM.

Single-unit-recording studies

The "domain-specific" model is also supported by a wealth of single-unit-recording studies. Recordings of area 46/8a neurons during spatial DR, spatial alternation, or memory-guided oculomotor-saccades and anti-saccades tasks have demonstrated that a significant proportion of these neurons is engaged in short-term spatial-mnemonic functions (Fuster and Alexander 1971; Kubota and Nikki 1971; Kojima and Goldman-Rakic 1982; Funahashi et al. 1989, 1990, 1991; Carlson et al. 1990, 1997; Wilson et al. 1993). Indeed, many DL neurons have receptive fields ("memory field") depending on the spatial location of relevant stimuli (Funahashi et al. 1989). These memory fields can be defined as maximal and constant (from trial to trial) firing of a neuron to the representation of a visual target in one or a few locations of the visual field (Goldman-Rakic 1996). Although many DL neurons may respond to various sensory stimuli (visual, somatosensory, auditory) (Tanila et al. 1992, 1993; Carlson et al. 1997; Rao et al. 1997), the large number of DL neurons engaged in DR tasks seem to be exclusively responsive to maintenance of spatial information in short-term memory (Funahashi et al. 1993b; Carlson et al. 1997). By contrast, it appears that neurons tuned specifically to the identity or features of objects are very few in DL area compared with other PFC areas (Wilson et al. 1993; O'Scalaidhe et al. 1997; Rao et al. 1997), as might be expected from the fact of the preferential dorsal pathway input to DLPFC. Moreover, a recent study (Romo et al. 1999) has shown that neurons engaged in a vibrotactile WM task without a visuospatial component are located in the IC cortex; importantly, none of these neurons were found in the DL region. Neuronal responses to vocalizations are currently being mapped in this laboratory, and preliminary evidence is revealing circumscribed territories dedicated to auditory processing in the vicinity of the object processing areas of IC cortex (Romanski and Goldman-Rakic 1999). Wilson et al. (1993) have recorded single units in DL and IC regions while monkeys performed two different oculomotor DR tasks varying with respect to pattern or location as relevant cues. Differential neuronal activity during the delay depended on site of recording within the DLPFC, i.e., neurons in DL cortex were responsive to spatial, whereas neuronal activities in IC cortex were related to object features. Finally, in a recent mapping of PFC, covering Walker's areas 8, 9, 12, 45 and 46, O'Scalaidhe et al. (1999) tested over 2000 neurons and discovered that a subset of these neurons responded selectively to monkey faces – visual stimuli that may be considered prototypical of object vision. Careful reconstruction of electrode tracks in each of three monkeys located these neurons to the IC cortex and the lateral orbital prefrontal region; none were found in the principal sulcal region (O'Scalaidhe et al. 1999).

Taken together, the combined data obtained from anatomy, lesions, and electrophysiological studies in the rhesus monkey support a model of anatomical and functional segregation of the DLPFC in the non-human primate, based on the sensory domain of the information processed in WM.

Other models of anatomical and functional organization of the PFC

Although it is widely accepted that the PFC is involved in WM functions, and generally that its functional organization is modular as we have proposed, there is disagreement as to the particulars of this organization . For example, Petrides and Owen have postulated a segregation within the PFC based on the nature of processing within WM rather than a sensory domain-specific modularity (Petrides 1995; Owen et al. 1996a, 1998, 1999; Owen 1997). In this model, the PFC is divided into two subregions: the superior convexity, or – as they have referred to it – the "mid-dorsolateral" cortex (the cortex above the principal sulcus-Walker's area 9 and upper 46), and the IC, referred to as " ventrolateral " cortex (cortex below the principal sulcus-Walker's areas 12/45 and lower 46). According to Owen (1997), the ventrolateral prefrontal cortex is "concerned with the active organization of sequences of responses based on conscious, explicit retrieval of information and active comparison about stimuli held in short-term memory". By contrast, the mid-dorsolateral region is viewed as an executive processor that allows active manipulation and monitoring of information within WM. This view differs from the "domain-specific model" in that different subregions are devoted to storage and processing, respectively, and each processes several sensory domains, whereas in the "domain-specific" model one given subregion processes only one informational domain (be it visual, auditory, or somatic spatial input), but subserves both storage and processing operations. Although recent functional-imaging studies in humans have been interpreted as supportive of the Owen/Petrides model (Petrides et al. 1993a; Owen et al. 1996a, 1996b, 1998; Owen 1997), evidence for this model from experimental studies in monkeys is sparse. Indeed, only one study in the monkey (Petrides 1995) may support this hypothesis. In this study, monkeys were trained to perform self- or externally ordered tasks and, thereafter, were subject to lesions either of the superior convexity (Walker's area 9 and upper 46) or the prearcuate regions (Walker's area 8). Monkeys with bilateral superior-convexity lesions were profoundly impaired in re-learning a three-object self-ordered task, suggesting that lesions in this region disrupt performance on tasks requiring the monitoring of nonspatial visual information in WM. However, our recent attempt to replicate this finding (in monkeys with DM lesions trained on an similar nonspatial and three-item self-ordered task) produced a different result, which we discuss below in comparison with the Petrides et al. study.

Another model of DLPFC functional organization that needs to be considered is that of a unitary association cortex that integrates information in a supra-modal fashion. Fuster and co-authors have shown that cooling the principal sulcal region produced both spatial and nonspatial short-term memory deficits and also impairment on a delayed matching task with cross-modal (visual and somesthetic sensory modalities) contingencies (Fuster and Bauer 1974; Bauer and Fuster 1976; Quintana and Fuster 1993). However, as recognized by the authors (Fuster 1989, p 77), this method could not rule out a functional dissociation within the DLPFC because of the large area of the PFC cooled in these studies. Several authors have found neuronal activation in the DLPFC in response to nonspatial stimuli (Tanila et al. 1992, 1993; Bodner et al. 1996; Carlson et al. 1997; Rao et al. 1997). Moreover, some neurons throughout the DLPFC are activated by both spatial and nonspatial visual stimuli during WM tasks if these stimuli are presented within central vision (Quintana et al. 1988; Rao et al. 1997; Rainer et al. 1998; Miller 1999). Neuronal responses in DLPFC for both spatial and nonspatial items are not necessarily inconsistent with a domain-specific model for several reasons. The nonspatial stimuli may, by prior association, immediately signify the spatial response to be made at the end of the delay, so that the neuronal response may actually be related to the impending movement rather than to the features of the stimulus. Again, it must be stressed that the domain-specific hypothesis is not a modality-specific hypothesis: several sensory modalities feed into the perceptual/mnemonic mechanisms related to spatial WM. Further, the specificity of the DL region for spatial WM operations could be relative and some neurons within this area may be linked with other domain-specific regions. Finally, the presence of such responses apparently does not specify their functional importance for that area. Lesion studies emphasize this concept: DL lesions consistently produce a deficit restricted to visuo-spatial cognition (for a review, see Goldman-Rakic 1987). Rarely, if ever, have monkeys with DL lesions exhibited strong or permanent impairments on object-based tasks.

Association of storage and processing within the visuo-spatial domain

Regarding the functional specialization of the different subregions of the DLPFC with respect to their spatial and nonspatial specificity or to their involvement in simpler or more complex aspects of WM (e.g., maintenance versus processing and/or monitoring functions), we have undertaken a study to determine the degree of anatomic segregation for WM functions within the DLPFC in the rhesus monkey (Levy and Goldman-Rakic 1999). The monkeys were trained to perform several WM tasks according to two dimensions: sensory modality (visual spatial and nonspatial modalities) and level of processing (low vs. high executive demand within WM). Tasks with low executive demand within WM were considered to be represented by the conventional DR format, in which monkeys store and use only one item of information. WM tasks with higher executive processing demand were self-ordered (SO) tasks (Petrides and Milner 1982; Petrides et al. 1993a; Petrides 1995) (Fig. 1). The SO tasks require the same basic WM processes engaged by the DR tasks (i.e., maintenance and utilization of internal representations), but impose a larger memory load (three items versus one) than do the DR tasks and also require the monkey to compare his current choice with previous choices, i.e., to serially self-order internal representations. This additional monitoring process is conceptually an important upgrade in the level of processing over the classical DR tasks, requiring as it does a supplementary executive operation. In the present study, we employed a nonspatial SO task (OBJ-SO) based on Petrides (1995) and designed a new spatial version (POS-SO) expressly for this study (Fig. 1). Once the tasks were learned, one group of monkeys was given a bilateral resection of Walker's areas 9/8B, namely the dorsomedial (DM) aspect of the PFC, whereas a second group received a bilateral lesion of Walker's area 46/8A, namely the dorsolateral (DL) aspect of the PFC. We reasoned that, if a "modality-specific" model prevailed, DL lesions would produce a selective spatial WM deficit. Alternatively, if areal segregation were based on the nature of operation performed, regardless of the sensory information processed, then DM and/or DL lesions should produce a supra-modal impairment (in both the spatial and nonspatial domain), particularly in the SO tasks with high executive demand.

In fact, lesions of DL region produced a significant and stable impairment in the two spatial WM, but little or no impairment in the two nonspatial WM tasks. As the spatial SO task requires the same basic WM processes as the spatial DR task, it is not possible to determine, from this study, the contribution to this deficit of the components that differentiate the SO task from the DR task. Therefore, two interpretations of this result are possible: (1) the DL area is involved both in elementary WM operations (maintenance) and in more executive operations (self-ordering) and indeed, the maintenance of single items in short-term memory is a constituent operation of sequential processing; or (2) the DL region is mainly involved in storing spatial information (for both DR and SO tasks), while still another area of the PFC may be selectively involved in the executive aspects of WM. If this were the case, it would be necessary to demonstrate that there exists a cortical area, damage to which causes deficits on the spatial SO task, but not the DR task. No such executive area has yet been discovered in monkeys and the requisite double dissociation remains to be demonstrated. At present, a parsimonious interpretation of our data is that the storage and processing components of WM are inextricable within informational domains. It is, thus, reasonable and appealing that each prefrontal module, networked with sensory, motor, limbic, and association areas (Selemon and Goldman-Rakic 1988), can support domain-specific executive operations. And, indeed, a wide range of operations integral to WM, including preparation, inhibition, or sequencing of motor responses and context-contingencies, have been consis-

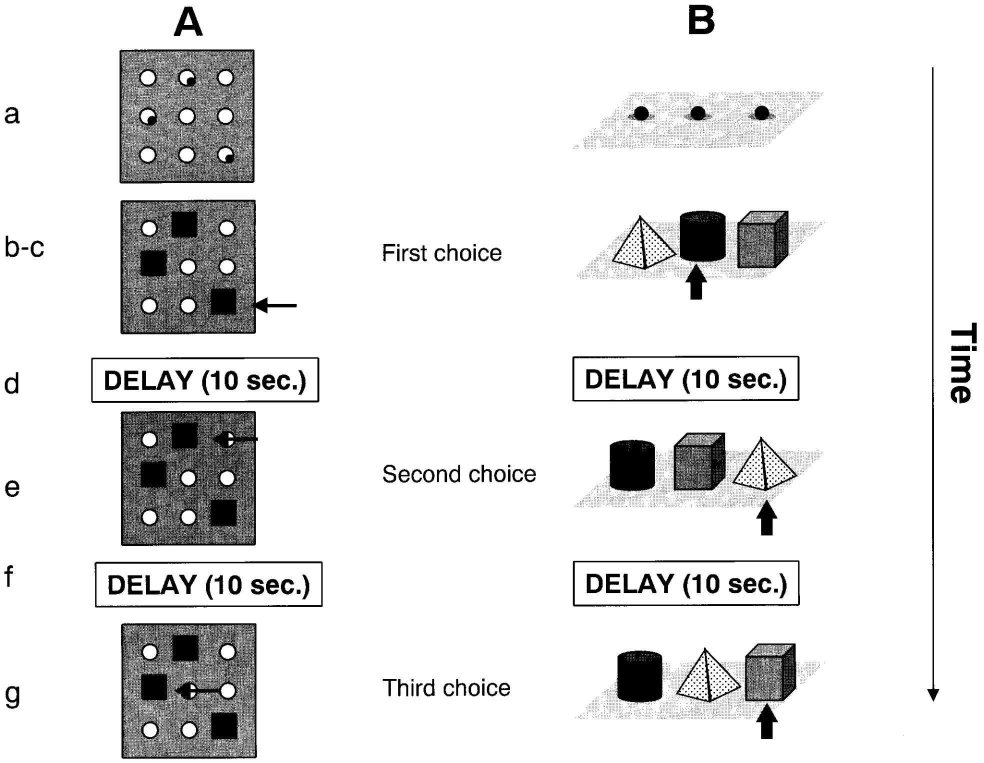

Fig. 1A,B The spatial (POS-SO) and object (OBJ-SO) self-ordered tasks. **A** The POS-SO task. The monkey views a testing tray with nine foodwells (*a*), three of which are covered by identical blue plaques (*b*), each plaque covering a reward; the monkey is allowed to displace any one of the three plaques to retrieve a reward (*c*); an opaque screen is lowered for a 10-s delay period, during which the plaque is replaced over the empty well (*d*). After this first delay, the monkey is allowed to make his second choice by displacing any of the three plaques (*e*); however, to receive a reward, he must choose one of the two remaining plaques that cover baited wells. After the second choice, the opaque screen is again lowered for a second 10-s delay period (*f*). To complete the trial, the monkey has to displace the one remaining plaque over the foodwell that still contains a reward (*g*). The trial is completed only when the monkey has found all rewards. Thus, a trial could consist of a minimum of three choices, but choice of an incorrect foodwell prolongs the current trial until all rewards are retrieved (all choices being separated from each other by a 10-s delay). Monkeys received ten trials a day. Positions of plaques were pseudo-randomly distributed in order to discourage the monkeys from adopting spatial strategies. **B** The OBJ-SO task. The testing procedure is similar to the POS-SO task except that: (1) the position of the object is changed following a pseudorandom order during the delay periods; (2) the test tray contains three foodwells, each covered by an object distinctive for shape, color, and size and containing a reward. New sets of three objects were used on each trial. Monkeys received ten trials a day

tently observed in DL cortex (Funahashi et al. 1993b, 1997; Williams and Goldman-Rakic 1995; Watanabe 1996). Thus, the intrinsic neuronal circuitry within the DL area provides for a spectrum of functions compatible with all levels of WM operations, including executive operations.

Monkeys with DM lesions were not impaired either on spatial or nonspatial WM tasks, whether the task engaged a higher executive component or not. Our failure to demonstrate impairment in the spatial SO task following DM lesions (areas 9 and 8B) indicates that this region is no more essential for self-ordering spatial information than it is for the simple maintenance of spatial information. These results are in accord with a study by Passingham (1985), in which monkeys were taught to retrieve rewards hidden behind 25 small doors without returning to the same location twice, thus engaging self-monitoring and serial organization of mental representations. Yet, lesions of the principal sulcus produced a marked impairment in this task, whereas dorsomedial frontal convexity lesions (similar to our DM lesions and to the mid-frontal lesion of Petrides) failed to do so.

The fact that neither DL nor DM lesions produced impairments on the nonspatial SO task suggests that neither subregion is critical for accomplishing this task. This result differs from those obtained by Petrides (1995), in which monkeys with “mid-frontal” lesions were profoundly impaired on a non-spatial SO task similar to that used in the present study. It appears that no formal explanation can be provided so far to explain the differences between the two studies. It should be noted that our tripartite separation of the lateral prefrontal cortex (DM-area 9/8B, DL-46/8A, and IC-12/45) differs from Petrides’s approach, in which the lateral prefrontal cortex is subdivided into a dorsolateral (above the principal sulcus) and a ventrolateral (below the principal sulcus) parts. Nevertheless, the resection in the Petrides (1995) study corresponds closely to our DM lesion, as it removed mainly areas 9 and 8B and largely spared the principal sulcus in two of three animals. An alternative explanation of the difference between our study and Petrides’ may arise from the different types of stimuli used in the two studies. In Petrides' study, the same three stimuli were used from trial to trial, whereas, in our study, a different set of objects was used from trial to trial. However, this difference would have been more than offset by the fact that, in Petrides' study, monkeys were given only one trial a day in order to reduce intertrial interference.

In summary, our study demonstrated a functional dissociation between the dorsomedial and dorsolateral prefrontal cortex with respect to WM processes: only lesions of dorsolateral areas 46/8A impaired WM processes, whereas lesions of the dorsomedial areas 9/8B were without lasting consequences. Second, the deficit following the dorsolateral lesion was confined to the spatial domain and did not encompass object WM. The present finding of a dissociation of deficits on nonspatial and spatial tasks after DL lesions, and the marked impairment observed in both simple and complex spatial WM tasks, confirm and extend the evidence for a specialization in DL cortex for spatial WM, regardless of the level of processing within this domain. Finally, the findings revealed that dorsolateral cortical areas are no less critical for tasks with low WM demand than for more complex sequential processing with higher WM load. These results support an anatomical-functional segregation of the PFC for WM based on the type of information being processed rather than on the nature of the operations performed. Although the present study does not specify a particular area for nonspatial WM processing, several studies indicate that the inferior convexity (mainly Walker's area 12/45) may be specialized for nonspatial processing (see discussion above).

Do experimental studies in humans support the "domain-specific" model?

By adapting tasks conceptually derived from the DR tasks used in monkeys, functional-imaging studies of human cognition have repeatedly shown significant increases of activity in the DLPFC in WM tasks (for a review, see Owen et al. 1997; Ungerleider et al. 1998; Smith and Jonides 1999), confirming that this region plays a crucial role in WM processes in humans. The issues of anatomical-functional segregation and the specific role played by the DLPFC in WM have been, of course, raised using functional imaging as a tool. Although several studies by Petrides, Owen, and their collaborators suggest a division of the lateral frontal cortex based on the level of operation performed, according to the two-stage model described above (Petrides et al. 1993a; Owen et al. 1996a, 1998). Thus, Petrides and colleagues (1993a, 1993b) reported that self-ordering tasks activate BA 9/46 (mid-dorsolateral region), whether they require monitoring of verbal or visuospatial materials. In addition, Owen (1997) performed a meta-analysis of activation studies that employed both spatial and nonspatial WM tasks and failed to dissociate peaks of activation for these tasks within the DLPFC. Owen and colleagues have also reported the engagement of different PFC regions with different levels of executive demand (Owen et al. 1998, 1999). However, for each of the negative findings in the literature, there are numerous functional-imaging studies that strongly support a domain-based segregation of function within the PFC (Smith et al. 1995, 1996; Courtney et al. 1996, 1997, 1998; McCarthy et al. 1996; Belger et al. 1998; Kelley et al. 1998; Kohler et al. 1998; Smith and Jonides 1999; R. Adcock, T. Constable, J. Gore, and P.S. Goldman-Rakic, unpublished observations). For instance, Courtney and colleagues have found that object WM activates an inferior frontal region, whereas activation for spatial WM activated a caudal portion of the superior frontal gyrus (Courtney et al. 1996, 1998). Others have reported double dissociations between loci of activation within the prefrontal cortex based on hemispheric lateralization, the right PFC being predominantly activated by spatial WM tasks and the left PFC by object WM tasks (Smith et al. 1995; McCarthy et al. 1996). Although disparities exist between studies with respect to the exact loci for different tasks, the main point is that tasks equated for WM demand, but formatted for different domains activated different areas in these studies. The visuospatial and feature domains may be particularly difficult to dissociate as tasks described as "spatial" often can be performed as "object" if stimuli are presented foveally, as is commonly the case. Further, the spatial/temporal resolution of fMRI may yet not be sufficient to detect segregation in closely adjacent areas. Clearly, more studies are indicated to overcome the technical and design issues in this difficult area. However, clear evidence for domain specificity comes from studies on WM for verbal material. A number of studies have demonstrated that Broca's area (left BA 45/47) is crucial for verbal WM and especially for subvocal rehearsal (Cohen et al. 1994, 1997; Demb et al. 1995; Awh et al. 1996; Smith et al. 1996, 1998; Wexler et al. 1999). Broca's area and other areas related to semantic processing are distant and distinct from activation peaks found in most studies of spatial WM (see Owen 1997). That verbal-, spatial-, and object-based WM each depend on a distinct area(s) within the PFC provides evidence for the predicted homology in functional architecture of the DLPFC in humans and monkeys and for "domain-specificity".

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