FUNCTIONAL NEUROANATOMY OF DELAY TASKS
(DELAYED RESPONSE, DELAYED ALTERNATION
AND OBJECT ALTERNATION)

by

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A thesis submitted in conformity with the requirements for the degree of Master of Arts,
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Functional Neuroanatomy of Delay Tasks

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Abstract

The functional neuroanatomy of human performance on 4 delayed response tasks (spatial/object delayed response [DR-S/DR-O] and spatial/object alternation [DA/OA]) was investigated using functional magnetic resonance imaging. Tasks were presented to 5 healthy participants (Mean age = 20 years; 3 males) in a blocked design while in a 1.5T scanner. Dorsolateral prefrontal activations were noted in Brodmann areas 8, 9, 10, 46 for all tasks. Several areas were specifically correlated with object-based task performance and included Brodmann areas 32, 6, 40 (OA) and the thalamus bilaterally (DR-O). Neither mnemonic domain (Goldman-Rakic, 1987) nor processing (Petrides, 1996) theories of functional specialization for working memory within the prefrontal cortex were supported. Findings were consistent with a model of functional dissociation between memory selection and maintenance processes in prefrontal cortex (Rowe et al., 2000). Anterior cingulate activations during OA are consistent with studies implicating this structure in response inhibition and cognitive control.
Acknowledgements

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Functional Neuroanatomy of Delay Tasks

(Delayed Response, Delayed Alternation and Object Alternation)

"I think that we might come to terms with this delayed-response deficit
yet. It has only been around for 30 years now, and we should give it
time." (Konorski and Lawicka, 1964, p.271)

In retrospect, Dr. Konorski's comment, made in 1964 at a conference examining
the functions of the frontal lobes (Warren & Akert, 1964) may have been somewhat
premature. In more than 30 years since his observation researchers have made
considerable progress towards deciphering the functions and structure of what is now
known as the prefrontal cortex using a delay task paradigm. Yet these advances have
also exposed even greater complexities and competing theories with respect to the
behavioural constituents underlying delay task performance and how function and
structure correlate within the prefrontal cortex. (For reviews of prefrontal and delay task
literature see: Fuster, 1985, 1997; Goldman-Rakic, 1987 as well as Petrides, 1996.) The
intent of the present investigation is to examine the role of prefrontal structures in three
delay tasks considered to be behavioural measures of prefrontal function: delayed
response (DR), delayed alternation (DA) and object alternation (OA) (Freedman, Black,
Ebert & Binns, 1998). While performance on these delay tasks has been shown to be
sensitive to prefrontal damage in non-human primates (Mishkin, Vest, Waxler &
Rosvold, 1969; Mishkin, 1964), people with brain injuries (Freedman et al.,1998;
Freedman & Oscar-Berman, 1986; Gansler, Covall, McGrath & Oscar-Berman, 1996;
Verin, Partiot, Pillon, Malapani, Agid & Dubois), neurodegenerative disease (Freedman,
Neuroanatomy of Delay Tasks

1990; Freedman & Oscar-Berman, 1991) and psychiatric disorder (Pribram, Ahumada, Hartog & Roos, 1964; Freedman, 1994), the functional neuroanatomy underlying performance on these tasks in healthy human adults has not yet been directly investigated. To address this issue, functional magnetic resonance imaging (fMRI) techniques will be employed to map the neuroanatomical correlates of human performance on each of these behavioural measures.

Delayed Reaction Tasks as Measures of Frontal Function

As noted above, the delay task paradigm has been employed in investigations of the prefrontal cortex for over 60 years (for a review of pre-1930s exploration of frontal function see: Gross & Weiskrantz, 1964). The modern era of investigating cognitive functions associated with the prefrontal cortex began with Jacobsen (1935, 1936). In his search for a behavioural index of higher mental functions, he revived a delay-task paradigm originally employed by Hunter (1913-1915) to explore whether animals and children could bridge the temporal gap between a stimulus and a later response (Pribram et al., 1964). Hunter’s original test was “aimed at exploring typical mammalian behaviour under conditions where the determining stimulus is absent at the moment of response” (Hunter, cited in Pribram et al., 1964, p.28). Jacobsen was able to utilize this paradigm to show convincingly that delayed-responses were severely impaired after primate frontal lobe injury (Konorski & Lawicka, 1964). Since Jacobsen’s pioneering efforts investigators have employed a range of empirical techniques to explore prefrontal function using the delay-task paradigm. These include animal lesion studies (e.g. Fuster, 1985, 1997; Goldman-Rakic, 1987; Konorski & Lawicka, 1964; Mishkin, 1964; Mishkin
& Manning, 1978; Petrides, 1996; Rushworth, Nixon, Eacott & Passingham, 1993; Wilson, Seamus, Scalaidhe & Goldman-Rakic, 1993), neuropsychological studies (e.g. Chorover & Cole, 1966; Freedman & Oscar-Berman, 1990; Freedman et al., 1998; Gansler et al., 1996), and neurorimagining investigations (e.g. D'Esposito, Aguirre, Zarahn, Ballard, Shin & Lease, 1998; Smith & Jonides, 1998; Courtney, Ungerleider, Keil & Haxby, 1997).

Evidence obtained through these investigations has demonstrated convincingly that the capacity to ‘bridge’ temporal discontinuities between stimulus and response is a hallmark of prefrontal functioning (Goldman-Rakic, 1987; Fuster, 1997) and Jacobsen’s adoption of the delayed-reaction paradigm as an objective experimental methodology to study the functions of the prefrontal cortex is now considered a landmark of neurobiology (Fuster, 1985). His demonstration of an empirically determined link between prefrontal function and behaviour has been referred to alternatively as the ‘fulcrum of behavioural research on the cognitive aspects of prefrontal function’ (Fuster, 1997); a ‘milestone in research concerning the prefrontal areas’ (Konorski & Lawicka, 1964); and ‘the most significant experimental discovery for understanding the functions of the prefrontal cortex’ (Goldman-Rakic, 1987). While it would be difficult to overstate the case for delay tasks as critical behavioural measures of prefrontal function, their utilization has also brought forth new challenges for investigators. Primary among these is mapping the critical behavioural components of delay task performance and their respective neuroanatomic correlates. Owing to their sensitivity to prefrontal damage, efforts to uncover the precise nature of the behaviours measured by delay tasks have now become a critical avenue of inquiry into understanding how and where function maps onto structure
within the pre-frontal cortex (Goldman-Rakic, 1987). However, before continuing with a more in-depth review of the history of delay tasks and their import within the field of experimental psychology, it would be useful to first characterize the various components the delayed response paradigm in more detail by introducing the three tasks which are the basis of the present investigation—delayed response, delayed alternation and object alternation.

**Delayed Response (DR)**

The classic version of the delayed response task (see Figure 1) as devised by Hunter, adopted by Jacobsen, and subsequently widely adapted for research in a variety of animal and human populations involves four primary elements: (i) *stimulus-reward placement* in one of two (or more—see Diamond, 1994; Konorski & Lawicka, 1964) target locations in full view of the participant (ii) a *delay period* during which the target locations are hidden from the participant's view (iii) *presentation of target locations* after the delay and (iv) *participant response* to select the correct location of the stimulus-reward. While the target stimuli in the classic ‘delayed response’ tasks were almost always spatially-based, early experiments also employed other types of pre-delay stimuli including objects and colours (Passingham, 1972, 1975). The present investigation employs both spatial and object stimuli in the classic delayed-response paradigm. These two versions of DR will subsequently be referred within the text as spatial delayed response (DR-S) and object delayed response (DR-O).

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1 In the literature delayed-response tasks have been synonymous with the use of spatial-based stimuli. Paradigms employing non-spatial stimuli are commonly referred to as delayed matching to sample (DMS) tasks. However, there is not always a direct correspondence between the two task categories.
According to Hunter, three cognitive processes are engaged during performance on the delayed response task: (i) sensory attention – to access appropriate stimulus information (ii) short-term memory – to hold the information ‘on-line’ during the delay; and (iii) motor control – to coordinate and initiate a response (adapted from Hunter: cited in Goldman-Rakic, 1987). In addition to these delay task demands originally put forth by Hunter, primate research in the early 1960s suggested a that fourth cognitive operation was also being tapped by delayed response performance (iv) the capacity to suppress, when necessary, whatever response normally prevails in a given situation (Mishkin, Procop & Rosvold, 1962). Mishkin later described this inertial drive as the ‘perseveration of central sets’ (Mishkin, 1964) and the ability to overcome it is commonly referred to in today’s lexicon as response inhibition.

While the sensory and motor aspects of the tasks are critical, it appears that these are, in and of themselves, insufficient to engage the prefrontal cortex. Evidence from studies of prefrontally lesioned monkeys strongly suggests that frontally-mediated deficits on this task are a function of the delay period (Goldman, Rosvold, Vest & Galkin, 1971; Fuster, 1985). Goldman and her colleagues demonstrated that without the insertion of a delay period, frontal animal performance on a delayed response task was comparable to that of normal controls. However, when a delay period occurs between stimulus presentation and response (i.e. the stimulus is no longer present at the time of response) performance of frontal animals declines severely relative to that of normal controls. Fuster and Alexander’s (1971) discovery of so-called ‘memory cells’ in the prefrontal cortex that demonstrated an increased rate of firing during delay periods
provided further evidence for the role of prefrontal cortex in the temporal bridging of delay tasks (see ‘Single-Unit Recordings’ below).

In an effort to further specify the nature of this deficit in frontal animals, Passingham (1975) hypothesized that their poor performance might be attributable to several discrete factors including: visual attention deficits, distractions during delay periods, the type of material to be held ‘on-line’ or the building of proactive interference across trials. His early research into frontally-mediated delay task deficits suggested that, while neither visual attention nor distraction were related to the animal’s poor performance [both the nature of the material to be held on-line and trial-to-trial interference appeared to determine the category of deficit and correlate with lesion location in frontal animals]. These two factors, described by Passingham (1975) and others (Goldman et al., 1971; Pribram, 1961; Mishkin, 1964) over a quarter century ago still serve as pivotal areas of debate within the delay task literature. While the issue of mnemonic category (e.g. spatial, non-spatial) is discussed in more detail below, the contribution of trial-to-trial interference and, more directly, the role of the prefrontal cortex in the suppression or inhibition of such interference has been investigated to a large extent through the use of various delayed alternation paradigms, two of which are described in the next section.

Delayed Alternation (DA) and Object Alternation (OA)

The history of delayed alternation tasks as measures of prefrontal function follows closely that of the classic delayed response tasks (Meyer, Harlow & Settlage, 1951).
Alternation tasks share with classic delay tasks the requirement to perceive and attend to visual stimuli, hold information ‘on-line’ over a delay period and initiate a response based on a cue that is no longer present in the environment. However, unlike a typical delay task, alternation tasks require participants to recall their responses from previous trials in order to guide future responses (i.e. the rewarded stimulus alternates from trial to trial). This additional factor is presumed to increase what Passingham had earlier labeled ‘interference’ from trial to trial, thereby placing a greater demand on the participant to utilize on-line representations to guide behaviour – despite the pull of previous reinforcement to act otherwise (Diamond & Goldman-Rakic, 1989). Mishkin (1964) suggested that the prefrontal cortex was critical in the attenuation of this response conflict.

The two delayed alternation tasks utilized in the present investigation, one spatial (DA), the other non-spatial (OA), have been specifically employed as behavioural measures of prefrontal function in both monkeys (Mishkin, 1964; Mishkin et al., 1969) and humans with brain disease (Freedman et al; 1998; Freedman & Oscar Berman, 1990). Standard administration of the spatial delayed alternation task (DA) employed in this study is similar to that of the classic delayed response task with two important procedural differences: (i) the participant does not witness the baiting of the target location and (ii) the location of the stimulus-reward is alternated after each correct response. This latter condition demands that participants to recall their response from the previous trial and make the opposite selection in the current trial, effectively requiring them to update information from trial-to-trial based upon their previous responses (Curtis, Zald, Lee & Pardo, 2000) and thereby temporally interlocking all trials within a task block (Fuster,
1997). The object alternation task is identical to delayed alternation in terms of task structure, however the nature of the target stimuli differs between the two tasks with 'objects' replacing 'locations' as the relevant mnemonic category. As with DA, the trials are interlocked as placement of the stimulus is alternated between objects after each correct response, thus making response selection contingent upon the response made one trial earlier (Mishkin et al., 1969). As summarized in Table 1, the four delay tasks described above may be indexed along two key dimensions that, according to Passingham (1975), may be used to predict both the nature and extent of prefrontal engagement: (i) mnemonic domain and (ii) trial-to-trial interference (referred to here as response conflict — the degree of influence of previous responses on future responding).

Table 1

<table>
<thead>
<tr>
<th>Mnemonic Domain</th>
<th>Spatial</th>
<th>Non-spatial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>DR-S</td>
<td>DR-O</td>
</tr>
<tr>
<td>High</td>
<td>DA</td>
<td>OA</td>
</tr>
</tbody>
</table>

Note: Functional Task Descriptions. Four behavioural tasks employed in the present investigation are categorized along two dimensions (i) mnemonic domain: the stimuli to be held 'on-line' are either locations (Spatial) or objects (Non-spatial) (ii) response conflict: response selection is independent from trial to trial (Low), response selection requires active avoidance of previously rewarded stimuli (High).

Determining the efficacy of these delay task manipulations in differentially engaging regions within the prefrontal cortex and subsequently localizing these areas of suspected cortical engagement has been a principal approach to the study frontal lobe function since Jacobsen’s pioneering investigations. The application of functional
neuroimaging techniques to study the performance of human participants on these tasks \textit{in vivo} is a direct extension of this approach.

\textbf{Dissociating Frontal Involvement In Delay Task Performance (Early Perspectives)}

With the considerable similarity in the design of the delay tasks described above, it is not surprising that early investigators considered them to be interchangeable in assessing the effects of selective cortical and subcortical lesions (Mishkin, 1964; Oscar-Berman, Zola-Morgan, Oberg & Bonner, 1982). In fact, the delayed alternation paradigm was considered by Jacobsen to be as sensitive to frontal injury as the original delayed response task (Pribram, 1964). Yet, the precise nature of the performance deficits on these tasks (and whether or not they were dissociable) remained elusive almost three decades after Jacobsen's initial observations. The topic was the subject of considerable debate particularly with respect to the categorization of the cognitive processes engaged by these tasks and the lack of geographical precision in lesion location (i.e. dorsal vs. ventral regions) within the monkey prefrontal cortex (Gross & Weiskrantz, 1964).

In a landmark series of experiments in the 1950s and 1960s (Pribram, Mishkin, Rosvold & Kaplan, 1952; Mishkin & Pribram, 1955, 1956; Pribram & Mishkin, 1956 and see Mishkin, 1964 for a broad review of these early experiments) the performance of frontally lesioned monkeys and sham-operated controls were compared on a wide variety of tasks in which they varied both the nature of the stimulus characteristics (spatial vs. non-spatial) and the nature of the task demands (e.g. visual discrimination, delayed
response, reversal learning). The results of these investigations strongly suggested to Mishkin and his colleagues (1964) that performance deficits on delay tasks could be principally attributed to an impairment in the ability of frontal animals to suppress a maladaptive response tendency (e.g. repeatedly responding to the previously reinforced location in a reversal learning task). Their conclusion was consistent with other reports (e.g. Brutkowski & Mempel, 1961; Milner, 1964) that identified similar patterns of maladaptive perseverative responding in frontal animals and frontally lobotomized humans. Two of the tasks that were critical to Mishkin’s final conclusions were the place and object reversal tasks. Of particular relevance to the present investigation, he employed several versions of each of these tasks in which he manipulated the number of trials that preceded a reversal of the reinforced response (from as many as 32 to as few as 2 trials/reversal) and found that there was no impact on performance. He concluded that the “impairment on double (i.e. two trial) alternation was simply a reflection of the frontal animal’s difficulty with reversal learning per se: no additional factor was needed to account for the poor performance on tests requiring a high frequency of reversal” (Mishkin, 1964, p.230). In this sense, Mishkin’s reversal tasks are analogous to the alternation tasks used in this study – both of which have been demonstrated to be measures of perseverative responding (Freedman et al., 1990; Freedman et al., 1998). He described this condition as an impairment in behavioural adaptation to shifting environmental contingencies and, through this and subsequent series of studies (Mishkin, 1964; Jones & Mishkin, 1971; Iversen & Mishkin, 1972; Mishkin & Manning, 1978) clearly showed it to be a consequence of frontal lesions.
But was this one factor responsible for all of the observed deficits in delay task performance of frontally-lesioned monkeys? Mishkin, aware that severe DA and DR deficits resulted from lateral frontal lesions, was curious to determine whether lesion location within the frontal cortex could predict performance on the other tasks in his investigation. The original set of experiments was repeated with two frontally lesioned groups of animals - one with lateral and a second with orbital frontal ablations (Mishkin, Vest, Waxler & Rosvold, 1969). In this second investigation (considered to be one of the earliest frontal localization experiments) the orbital group was more severely impaired than the laterals on all tasks with one critical exception. On the place reversal task (analogous to delayed alternation) both lateral and orbital groups were equally impaired even though on a non-spatial object reversal task (analogous to object alternation) laterally lesioned animals performed significantly better than the orbital group. From these findings Mishkin suggested that a second factor, specifically related to the spatial nature of the task, was affecting the performance of the lateral lesion group (Mishkin, 1964, p. 237).

For the first time, Mishkin and his colleagues demonstrated empirically that deficits on delay tasks following frontal lesions might be attributable to dissociable cognitive demands. He surmised that the poor performance of the orbital-frontal group was primarily related to the reversal component of the tasks, as these animals clearly had difficulty alternating responses between trials in both the spatial and non-spatial paradigms. Deficits of the lateral-frontal group, on the other hand, appeared to be more related to the spatial aspects of the tasks. This ‘two-factor theory’ of frontal function (Brutkowski, 1964) broadened the scope of investigation into prefrontal function
considerably. Investigators now began to examine not simply the general role of the prefrontal cortex in 'temporal bridging' (i.e. Jacobsen's (1935) 'immediate memory' or Fuster's (1997) 'working memory') but the contribution of specific structures within the prefrontal cortex to the effective mediation of temporal discontinuities depending on (i) the nature of the content to be held on-line (e.g. spatial vs. non-spatial) and (ii) the cognitive processes engaged during a delay (e.g. inhibition of prepotent response tendencies).

**Mapping Prefrontal Involvement in Delay Task Performance**

As described in the previous section, the delay task paradigm has been a crucial tool in elucidating and mapping functions mediated by the prefrontal cortex. Since Mishkin's pioneering studies, a vast corpus of knowledge pertaining to prefrontal involvement in delay task performance has been built upon contributions from almost every discipline within the cognitive neurosciences, including animal lesion studies, neurophysiology (i.e. single-cell recordings), human neuropsychology and, more recently, functional neuroimaging. Several of the seminal findings in each of these areas are reviewed briefly below. This immense body of research is subsequently distilled further into several leading (and often conflicting) accounts of delay-related prefrontal function in the following section and these generalized accounts then provide the theoretical backdrop against which the present study design and predicted outcomes are described.

**Primate Lesion Studies**
Had exploration of prefrontal involvement in delay tasks ended with Mishkin’s early primate studies (Mishkin, 1964; Mishkin et al., 1969), predicting the outcome of the current neuroimaging study – a loosely-based replication of his earlier work – may have been quite straightforward. Consistent with his two-factor theory (1964 and described above), and presuming an acceptable degree of cytoarchitectural congruence between the primate and human prefrontal cortex (Pandya & Petrides, 1996), one might reasonably predict patterns of activation to follow a dorsolateral (Brodmann areas 9/46) to ventrolateral/orbitofrontal (Brodmann areas 45/47/11) progression across the prefrontal cortex as subject performance shifted from DR-S (a spatial, non-reversal task), to DA (a spatial, reversal task) to OA (a non-spatial, reversal task). Such a pattern of cortical activation would also be consistent with later findings from primate lesion studies that suggested a ‘functional duality’ (Goldman-Rakic, 1996) between the dorsolateral cortex (particularly areas surrounding the principal sulcus in primates) and the ventrolateral cortex. As originally suggested by Mishkin (1964) and upheld by later investigators (Goldman-Rakic, 1987, 1996; Wilson, Schlaaidhe, Goldman-Rakic, 1993) the dorsolateral prefrontal cortex region is implicated primarily in spatial working memory while ventral regions are presumed to be preeminently engaged in non-spatial (i.e. object) working memory – a prefrontal extension of the hypothesized dorsal/ventral posterior visual streams for spatial and object processing (Ungerleider and Mishkin, 1982). In fact, since the ground-breaking work of Mishkin and his contemporaries, primate lesion studies have demonstrated that both ablations or reversible lesions restricted to the lining

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2 Mishkin didn’t employ a non-spatial delayed response task as part of these early studies. However, he did contend that working memory for objects was mediated by regions below the principal sulcus lying within the ventral frontal regions of the monkey (Mishkin, 1964).
of the sulcus principalis in the dorsolateral frontal lobe impair performance on delayed response and delayed alternation tasks (e.g. Bauer & Fuster, 1976; Goldman & Rosvold, 1970; Gross & Weiskrantz, 1964). Even small lesions of the sulcus principalis have been shown to severely disrupt delayed response performance (Funahashi, Bruce & Goldman-Rakic, 1993). While these findings strongly implicated the dorsolateral prefrontal cortex in tasks that require the integration of spatially and temporally discontinuous elements of cognition – features of both the DR-S and DA tasks (Fuster, 1997), an analogous locus for object working memory functions within the ventral prefrontal cortex was somewhat more elusive.

Unconvinced that such a clear delineation existed for working memory domains in the prefrontal cortex, Petrides (1994, 1996) in more recent work with primates has suggested an alternative dissociation of working memory functions within the PFC. In contrast to the information domain theory put forth by Goldman-Rakic and her colleagues (1993), Petrides’ (1996) processing theory proposes that prefrontal regions are differentially engaged as a function of the processing demands of the delay task being performed. In this model, dorsolateral structures are presumed to mediate on-line monitoring and manipulation of information while ventrolateral prefrontal areas are engaged in more simple on-line maintenance processes (Petrides, 1996). Unfortunately, this theory of prefrontal involvement in working memory processes does not lead to clear predictions of neural activation patterns in the present study. While the delayed response tasks (DR-S, DR-O), are presumed to primarily involve simple maintenance (D’Esposito, Aguirre, Zarahn, Ballard, Shin & Lease, 1999) and might therefore be associated with more ventral prefrontal activity, it is unclear where the alternation tasks (DA/OA) might
fall along Petrides’ maintenance/manipulation continuum. This debate between the information domain and information processing theories is revisited again in the neuroimaging section below.

Primate lesion studies have also been critical to progress in the study of the second of Mishkin’s ‘two-factors’ that contribute to delayed response performance—response inhibition. Lesions of the ventrolateral frontal cortex that extend below the sulcus principalis, have been shown to severely impair performance on tasks that involve reversing (or inhibiting) a previously rewarded response (Iverson & Mishkin, 1970; Mishkin, 1964; Mishkin et al., 1969; Passingham, 1972). Similar findings have also been reported by Diamond and Goldman-Rakic (1989) and Diamond (1991). However, such precision in the localization of a response inhibition function has been recently questioned by Dias, Robbins and Roberts (1997). These authors suggest that inhibitory control may be operating across a number of distinct functional regions within the prefrontal cortex (p. 9285), depending upon the nature of the cognitive process being inhibited. From their study on marmoset monkeys, the authors demonstrated that while rapid reversals of ‘affective’ associations for visual stimuli (analogous to Mishkin’s ‘reversals’ or ‘alternations’ within the DA and OA tasks) are mediated by orbitofrontal structures, the inhibitory capacity necessary to switch between higher-order response sets (such as rule-shifting between spatial and object cueing in DA and OA), may be mediated by regions within the lateral prefrontal cortex (Dias et al., 1997).

In summary, deficits have been observed in the ability of prefrontally lesioned animals to hold stimuli ‘on-line’ (i.e. working memory) and to inhibit prepotent
responses; two critical features of successful delayed response performance (Diamond & Goldman-Rakic, 1989). However, efforts to map these functions onto dissociable areas within the prefrontal cortex have been controversial and the evidence emerging from primate studies with respect to a more precise functional topography underlying either working memory or response inhibition remains equivocal.

**Neurophysiology (Single-Unit Recordings)**

Perhaps one of the most exciting findings in the modern study of prefrontal function was the discovery of cells, primarily in the primate dorsolateral prefrontal cortex, that increase and sustain their rate of firing during the delay period of a delayed response task (Fuster & Alexander, 1971). Since these early investigations (e.g. Fuster & Alexander 1971; Kubota & Niki, 1971), both the high spatial and temporal resolution offered by microelectrode recording techniques have led to numerous advances in understanding of the neuroanatomy and neurophysiology of the prefrontal cortex (for a review see Fuster, 1997, Goldman-Rakic, 1987; 1996). The earliest prefrontal single-cell recordings were obtained within the sulcus principalis region of the dorsolateral prefrontal convexity in monkeys during performance of delayed response and delayed alternation tasks (Fuster, 1997). Since this initial discovery, more features of these so-called ‘memory cells’ have been described (Fuster, 1995; 1997), two of which are of particular relevance to the present investigation: (i) their topographic distribution within the prefrontal cortex and (ii) their contingency-dependent pattern of activation.
Delay dependent memory cells have been found across the prefrontal cortex (Fuster, 1973), however, they are particularly prevalent in the banks and depth of the sulcus principalis in the monkey (Fuster, 1997, Wilson et al., 1993). Studies by Quintanna, Yajeya & Fuster (1988) and Fuster, Bauer & Jervey (1982) have demonstrated that memory cells in this region are equally activated by both spatial and non-spatial delay tasks. In contrast, Wilson and his colleagues (1993) reported findings that suggest the presence of selective, delay-related neuronal activity for non-spatial stimuli in the ventral-lateral prefrontal cortex with neurons exhibiting spatial sensitivity concentrated in more dorsal-lateral regions. Yet Fuster (1997) suggests that caution is warranted before considering the dorsolateral/sulcus principalis region as a circumscribed and specific functional area for spatial working memory (p. 135) citing his earlier investigations (Fuster & Alexander, 1973) which failed to find evidence of clearly identifiable topographic specificity.

The presence of a behavioural contingency – i.e. the requirement to respond at the end of a delay period based upon a pre-delay cue – is considered the most critical factor for the delay-related activity observed in some memory cells (Fuster, 1997). The removal of the contingency associated with the cue, while preserving the general delay task paradigm (i.e. non-informative cue + delay + response) has been shown to eliminate the prefrontal activation pattern previously observed in these delay-related cells (Fuster, 1973). This ability to ‘shut down’ prefrontal memory cells by eliminating the contingency between the pre-delay cue and a subsequent response is the basis of the perceptuomotor control for the three delay tasks in this investigation (see Methods below).
In summary, the neurophysiological findings pertaining to prefrontal involvement in the working memory (i.e. delay) component of delay tasks are generally consistent with those of the lesion studies discussed above. Delay-related neuronal activity has been recorded primarily in the dorsolateral prefrontal cortex and specifically around the sulcus principalis in the monkey. However, as with the lesion studies, results from single-cell recordings with respect to the dissociability of prefrontal areas mediating spatial and non-spatial delay-related processing are equivocal.

**Human Neuropsychological Findings**

Delayed response, delayed alternation and object alternation tasks have been used as measures of prefrontal dysfunction in both neurological and psychiatric populations (Freedman et al., 1998; Freedman, 1990; 1994; Gansler et al., 1996; Levine, Freedman, Dawson, Black & Stuss, 1999). Specifically, delayed response and delayed alternation paradigms have been used to assess frontal involvement in Korsakoff's syndrome (Freedman & Oscar-Berman, 1986), Huntington's disease (Oscar-Berman et al, 1982) and to identify differing patterns of prefrontal degeneration in Parkinson's and Alzheimer's-type dementia (Freedman, 1990). Delay tasks have also been used with psychiatric illnesses such as schizophrenia (Pribram et al., 1964) and depression (Freedman, 1990). Although early applications of delay tasks as measures of frontal damage following brain injury were not successful (Chorover & Cole, 1965), later more tightly controlled studies found DR, DA and OA to be sensitive measures of prefrontal
damage following head trauma (Freedman & Oscar-Berman, 1986; Gansler et al., 1996; Verin et al., 1993; Levine et al., 1999).

In a recent study Freedman and his colleagues (1998) investigated the functional neuroanatomy of the DR, DA and OA tasks using brain-injured subjects. Specifically, the authors found that bilateral lesions of Brodmann areas 24, 32 (in the medial frontal lobes), area 10 on the orbital frontal surface as well as a left frontal lesion in ventrolateral area 47 were most related to deficits on OA performance (Freedman et al., 1998). Findings that orbital/ventrolateral damage predicted performance deficits on OA – presumed to be a measure of response inhibition – aligns well with the animal lesion reports of Mishkin suggesting a orbital/ventrolateral contribution to reversal deficits on both place and object tasks (1964; 1969). Yet, the substantial impact of medial frontal damage was somewhat unexpected, although Pribram, Wilson & Connors (1962) and, more recently, Meunier, Bechevalier & Mishkin (1997) did find evidence of medial frontal contribution to alternation performance in primates. Freedman and colleagues’ findings with respect to the two spatial-based tasks (DA and DR) were also somewhat surprising. Damage to areas 33 (medial frontal) and 25 (medial frontal with an extension onto orbitofrontal cortex) resulted in the greatest performance deficits on DA while no areas of prefrontal damage were specifically correlated with delayed response deficits. While the requirement for the resolution of response conflict in DA might explain the medial/orbitofrontal involvement (see Garavan, Ross & Stein, 1999; Meunier et al., 1997), the absence of any performance correlation with dorsolateral prefrontal damage appears inconsistent with the vast primate lesion literature (e.g. Pribram et al., 1964; Mishkin, 1964, Mishkin & Manning, 1978).
The overall experimental approach adopted by Freedman and his colleagues (1998) is known as comparative neuropsychology (Oscar-Berman et al., 1982) and describes the application of a reliable and valid methodology for measuring and understanding the behaviour of non-human animals to identify impairments in brain damaged patients (Oscar-Berman et al., 1982). While this has proven to be an effective strategy in assessing human prefrontal dysfunction, the value of this approach in the mapping of prefrontal structure and function is circumscribed by difficulties in (i) extrapolating from behavioural test data to neuroanatomy (Freedman, 1994) (ii) conducting interspecies comparisons of the cytoarchitecture of the prefrontal cortex (Pandya & Petrides, 1996) and (iii) assessing the impact of human verbal abilities on both behavioural strategy and concomitant prefrontal involvement in task performance (i.e. the impact of verbal rehearsal strategies during tests of non-spatial working memory). Fortunately, advances in functional neuroimaging techniques now provide a means of examining, in vivo, the performance of healthy human participants, thereby overcoming the limitations associated with animal models of cognitive function and providing cognitive neuroscientists with a powerful new tool to explore the functional neuroanatomy of behaviour. While the application of functional neuroimaging techniques to the study of these four classic delay tasks in a single study is novel, there does exist a rapidly expanding body of neuroimaging literature focusing on the functional neuroanatomy of human delayed response capacities more generally.

**Neuroimaging of Delay Tasks**
Many of the neuroimaging studies (either positron emission technology – PET or functional magnetic resonance imaging – fMRI) involving delay-task paradigms have focused on exploring the neuroanatomical correlates of spatial and non-spatial working memory (for reviews see Cabeza & Nyberg, 2000; D'Esposito et al., 1998). The results of these efforts to map the functional neuroanatomy of working memory have provided converging evidence supporting earlier animal lesion and electrophysiological reports implicating dorsolateral prefrontal cortex (BA 9/46) and, in particular, those cortical areas surrounding the middle frontal gyrus (e.g. Cohen, Perlstein, Braver, Nystrom, Noll et al., 1997; Courtney et al., 1997, D'Esposito et al., 1998, 1999; Owen et al., 1998; Zarahn, Aquirre & D'Esposito, 1999) in the temporal bridging of a stimulus and a future response. Yet a review of these studies also reveals that they, as with earlier animal and human neuropsychological reports, are somewhat more equivocal with respect to the identification of further areas of functional specialization for working memory processes. The work of D'Esposito and his colleagues (1998) as well as reviews by Fuster (1997) and Petrides, (1996) implicate ventrolateral prefrontal regions (BA 45/47) while a recent report from Petit, Courtney, Ungerleider and Haxby (1998) also suggest that medial prefrontal structures including the supplementary motor area and the caudal portion of the anterior cingulate cortex may be involved in mediating delay-related task performance.

To date, neuroimaging reports have not produced a unifying theory of prefrontal involvement in working memory. However, two recent, extensive reviews of the delay task neuroimaging literature (Cabeza & Nyberg, 2000; D'Esposito et al., 1998) concluded that, on balance, neuroimaging findings do not support the information domain theory of prefrontal involvement in working memory (described above and see Goldman-Rakic,
1987) wherein dorsolateral prefrontal regions are theorized to mediate spatial working memory tasks while ventrolateral prefrontal regions mediate non-spatial tasks. These reviews do, however, present convincing evidence that the functional heterogeneity underlying delay task performance may be better characterized by the type of processing required during the delay period – supporting the processing model of prefrontal involvement working memory (Petrides, 1996; Owen, Stern, Look, Tracey, Rosen & Petrides, 1998). However, before abandoning the information domain model, it should be noted that Courtney, Petit, Maisog, Ungerleider & Haxby (1998) found evidence of an area around the superior frontal sulcus (Brodmann area 8) that appeared to be specialized for spatial working memory. This finding has also recently been supported in a report by Rowe et al. (2000) who have, in direct contrast to the Petrides model, found evidence of localized activation in Brodmann area 8 correlating with the simple maintenance of spatial stimuli across a delay.

While there is now a substantial body of neuroimaging literature with respect to working memory, the collection of imaging studies addressing response inhibition processes or the ‘perseveration of central sets’ in the context of delay task paradigms remains comparatively small. As described above, the inhibition of prepotent responses has been shown to be impaired by ventrolateral and orbital prefrontal ablations in monkeys (Butters, Butter, Rosen & Stein, 1973; Iversen & Mishkin, 1970; Miskin et al., 1969) and hence it must be noted that the working memory and inhibition components of these tasks may be confounded in the object-based tasks – as both object working memory and response inhibition are posited to engage ventral prefrontal regions according to the model of working memory put forth by Goldman-Rakic (1987).
However, this potential confound would not be predicted for the spatial-based tasks wherein a dorsal (DR-S)/ventral (DA) dissociation would be predicted. In fact, this theoretically-derived prediction of a dissociation between dorsal and ventral PFC mediation of spatial- but not object-based delay task performance highlights the utility of the delayed-response paradigm in mapping structure and function with the prefrontal cortex. Importantly, damage in ventral prefrontal areas has also been correlated with performance deficits on delayed/object alternation and set shifting tasks that require the inhibition of prepotent response tendencies in humans (Freedman & Oscar Berman, 1986; Freedman et al., 1998; Levine et al., 1999; Milner, 1964). Neuroimaging evidence to date converges with these findings implicating ventrolateral prefrontal regions (BA areas 45/47) in the inhibition of prepotent response tendencies (e.g. Jonides, Smith, Marshuelz, Koeppke & Reuter-Lorenz, 1998; Konishi, Nakajima, Uchida, Kikyo, Kameyama & Miyashita (1998); D'Esposito, Postle, Jonides & Smith, 1999).

While ventrolateral prefrontal regions have been primarily implicated in response inhibition, a recent report by Garavan, Ross & Stein (1999) has suggested that this inhibitory function is mediated by a more distributed, right-lateralized, cortical network that includes middle and inferior frontal gyri, limbic areas, anterior insula and inferior regions of the parietal lobe. Activations associated with response inhibition processes in regions outside of the ventrolateral prefrontal cortex have also been reported by Casey, Trainor, Orendi, Schubert, Nystrom, Giedd et al. (1997). In their fMRI study of what they considered to be response inhibition in children and adults they report that activation volume within the middle frontal gyrus was the only frontal region to correlate
significantly with age, suggesting that this region is an important neural mediator of developmental improvements in response inhibition.

In summary, evidence emerging from neuroimaging investigations of delay tasks is generally concordant with that of animal lesion, neurophysiological and human neuropsychological studies in assigning a critical role to the prefrontal cortex in delay task performance. To date, greater support is found for the process theory of functional specialization than for the information domain theory (Cabeza & Nyberg, 2000; D'Esposito et al., 1998), although considerable debate remains with respect to the precise nature of dorsolateral and ventrolateral prefrontal involvement in bridging the temporal gap during delay task performance. There is somewhat greater convergence between the imaging literature and earlier animal and human neuropsychological reports with respect to the neuroanatomical correlates of response inhibition processes wherein a specialized role for the ventrolateral prefrontal cortex in inhibiting prepotent responses sets' has been posited through the use of both delay (OA/DA; Mishkin, 1964; reversal; Dias et al., 1996) and non-delay type (Go-No/Go; Konishi et al., 1999) paradigms (but see Garavan et al., 1999).

Summary and Research Hypotheses

As is readily apparent from this brief review of the delay task literature, the mapping of the cognitive functions assumed to underlie delay task performance onto the prefrontal cortex has become considerably more complex and controversial since the time of Mishkin's early investigations. There are, however, several key findings emerging out
of this literature that have guided hypothesis formulation and predictions for the present investigation.

First, the delay task paradigm has been shown to be a valid and reliable behavioural measure of prefrontal function. This was convincingly demonstrated by Goldman et al. (1971) who reported that lesioning of the primate prefrontal cortex impaired performance on delayed response tasks while performance on equivalent tasks without the delay was preserved. Subsequently, the discovery of delay-related neural cell activity within the prefrontal cortex, evidence from persons with frontal brain disease and almost unanimous functional neuroimaging reports of prefrontal activations during delay task performance has confirmed the importance of the prefrontal cortex in mediating delayed responding.

Second, two psychologically dissociable cognitive demands, working memory and response inhibition have been shown to be associated with successful performance on delayed response-type tasks. This finding, originally labeled by Mishkin and his colleagues (1964) as the two-factor theory of prefrontal involvement in delay tasks, has been more eloquently described by Diamond & Goldman-Rakic (1989) who characterize delayed-response performance as an “ability to hold a goal in mind in the absence of external cues, and to use that remembered goal to guide behaviour despite the pull of previous reinforcement to act otherwise” (p.24).

Third, attempts to map these two components of delayed response function onto areas within the prefrontal cortex have met with remarkably differing degrees of success.
Efforts to find a unifying theory of prefrontal involvement in working memory has produced at least two (or perhaps more – see Rowe et al., 2000) competing models of prefrontal function. While both the information domain and process theories postulate a dorsal/ventral dissociation within the PFC, they differ dramatically with respect to the basis of this dissociation. In contrast, the evidence is more conclusive with respect to the neuroanatomical basis of response inhibition which has been postulated to be localized within the area of the ventral prefrontal cortex (i.e. below the inferior frontal sulcus in humans (Passingham, 2000) corresponding to Brodmann areas 45, 47 and 44. (Although several recent studies suggest that there may be a broader network of cortical areas implicated in response inhibition – see Garavan, 1999 for a recent report).

The overlay of these generalized findings onto the four delayed response tasks under investigation in the present study (and their respective task characteristics – see Table 1), has lead to the formulation of three hypotheses concerning the functional neuroanatomy of healthy human performance on these delayed response tasks.

**Hypothesis 1:** Performance across all delay tasks will be associated with significant activity within the prefrontal relative to posterior cortices.

Given the well-established role of the prefrontal cortex in mediating response contingencies across delays, performance on each of the delayed response tasks in the present investigation will be associated with areas of relatively greater neuronal activity within the prefrontal cortex than in more posterior cortical regions (when contrasted with a perceptuomotor baseline task).
**Hypothesis 2:** Areas of activation associated with the performance of spatial and object delayed response tasks will overlap within a region ventral to the inferior frontal sulcus.

This prediction is derived from the processing theory of prefrontal involvement in working memory and is supported by the recent findings of Cabeza et al. (2000) as well as D'Esposito et al. (1998) who have found convincing support for the processing theory of PFC involvement in working memory in two recent reviews of the functional neuroimaging literature. While the balance of evidence does favour this prediction, it is important to note that an alternate outcome, aligning with the mnemonic domain theory, cannot be ruled out as recent reports have proposed the existence of an area specialized for spatial working memory in the dorsolateral PFC (see Courtney et al., 1998; Rowe et al., 2000).

**Hypothesis 3:** Alternation task performance will be correlated with activity within ventral regions of the prefrontal cortex.

Performance on the two alternation tasks will produce areas of activation that mirror those associated with the non-alternation tasks, reflecting similar task demands for working memory. However, an additional area of activation will be observed within the ventral prefrontal cortex reflecting a higher degree of response conflict associated with these tasks (see Table 1) and a concomitantly greater demand to suppress or inhibit previously rewarded responses. In-keeping with previous reports, it is predicted that
these additional areas of activation will be observed ventral to the inferior frontal sulcus in the region of the inferior frontal gyrus.

**Methods**

**Study Design**

It is important to reiterate that the present investigation represents the initiation of a third line of inquiry with respect to the neuroanatomy of performance on these classic delay tasks. As discussed above, these tasks have already been extensively employed with non-human primates (Mishkin et al., 1969) as well as humans with brain disease (Freedman, 1990; Freedman et al., 1998). To enhance the possibility of inter-study comparisons, the design of the behavioural paradigms have been matched as closely as possible. However, there is one important exception. The participants in our study will learn the response rules for each task outside of the fMRI scanner. The rule acquisition phase has been excluded from the scanning protocol for two primary reasons. First, pre-training to an established accuracy criterion equates the tasks on overall difficulty (Object alternation has been shown to be more difficult for normal controls – see Freedman et al., 1998). This facilitates a more ‘process-pure’ mapping of activation patterns across all tasks and, by proxy, a more direct comparison of the functional neuroanatomy underlying task performance (hypothesis #1). Second, as only the two alternation tasks involved a ‘rule learning’ phase, its exclusion from the design facilitates a direct comparison of the functional neuroanatomy of performance on alternation versus non-alternation tasks – the central line of inquiry for hypothesis #3. However, the contribution of rule acquisition to the patterns of human and non-human primate performance on these tasks (reviewed
above) is an important area of inquiry and one that must be addressed in future research if
the functional neuroanatomy of these tasks is to be completely understood. Nonetheless,
the pedigree of the current protocol, arising from the methods employed by Freedman
and his colleagues (1998), serves as a reminder that this investigation is not an isolated
experimental exercise but one component of a broader exploration of function and
dysfunction in the human prefrontal cortex. It is hoped that the results of this study of
normal human functioning will improve our conceptualization of the functional deficits
associated with poor performance on these three delay tasks – thereby advancing our
understanding of their overall efficacy in assessing and perhaps predicting prefrontal
dysfunction.

Participants

Five normal, healthy, young adults (aged between 19 and 26 years; 3 males) participated in the study. All were right-handed and reported no history of neurological, psychiatric or significant general medical disease. Each participant signed an Informed Consent Form approved by the Baycrest Geriatric Centre and the Sunnybrook and Women’s College Health Sciences Center ethics committees. Data from a sixth participant was collected but is not reported here due to excessive head motion during the scan.3

Tasks

3 motion greater than one millimeter recorded between scans on at least one task
A computerized display was designed to replicate the essential parameters of the Wisconsin General Testing Apparatus adapted for use with human participants (described previously: Oscar-Berman et al., 1980; Freedman, 1990; Freedman et al., 1998). Stimulus presentation programs were developed using E-Prime, Beta 5 software and individual stimulus images were developed using Adobe Dimensions graphics software.

Each participant completed four experimental tasks which may be categorized along two primary task dimensions (i) mnemonic domain (i.e. object vs. spatial working memory) and (ii) response conflict (see Table 1).

Three of the experimental tasks: spatial delayed response (DR-S), delayed alternation (DA) and object delayed alternation (OA) replicate delayed response tasks which have been well described previously (see: Oscar-Berman et al., 1982; Freedman et al., 1998). The fourth task, object delayed response (DR-O), was included to balance the design across mnemonic domains (spatial, object) and response inhibition demands (alternation, non-alternation).

The features of the stimulus display were identical for all four tasks (see Figure 1a, 1b). The display for the experimental trials consisted of two grey boxes, rendered in 3 dimensional format, aligned horizontally and centered on the video display screen. Each box had a darker grey lid cover that would open or close to reveal the target ($) or an empty box depending upon response accuracy. Atop each of the boxes were two green objects designed to resemble objects used in the standardized behavioural testing apparatus (Freedman et al., 1998; Freedman, 1990). The target would be found either (i)
on the left or right or (ii) under one of the two objects, depending upon the rules of each task. A question mark appearing between the two boxes served as a response prompt for each of the trials. After a response was made, the question mark was replaced by a feedback object (not presented in Figures 1a, 1b) consisting of a yellow ‘happy’ or ‘sad’ face indicating a correct or incorrect response. If the participant failed to respond within the allotted time (3 seconds), the question mark was replaced with a red clock to indicate that too much time had elapsed. Participants were informed that when the red clock appeared they would be shown the correct answer but they should endeavor to respond more quickly on subsequent trials. Representative trials and event times are detailed in Figures 1a, 1b.

Participants also completed perceptuomotor control trials in which they were required to simply respond to a clearly demarcated target after each delay (e.g. “always choose the darker green object” – see Figure 1c). The control tasks were designed to reproduce the visual and motor components of the experimental tasks without tapping the mnemonic or processing demands presumed to subserve delayed response/delayed alternation performance. For the control trials the stimulus display was exactly as described above with two exceptions: (i) to attenuate any established tendency to hold the stimuli on-line over the delay during control trials, the two original objects were replaced with a single novel object, placed atop both boxes, for all control tasks and (ii) to increase correspondence between the perceptual demands of the experimental and perceptuomotor control tasks, participants were asked to (a) “always select the darker green object” during the object-based experimental and control tasks and (b) “always select the side where the darker lid appears” during the spatially-based experimental and control tasks.
Pre-scan training

All participants were trained to a 95% criterion level on each task prior to the scanning session. Participants were required to complete a minimum number of (DR-S/DR-O = 20; DA/OA = 30). The variance in pre-training trials for alternation and non-alternation tasks was based upon performance of control subjects in previous studies (see Freedman, 1990; Freedman et al., 1998). All participants achieved criterion in a single training session of approximately 45 minutes duration. Training instructions for both the spatial and the object delayed response (DR-S, DR-O) were identical with the exception of references to 'location' and 'object'.

LOCATION [OBJECT] MEMORY
1. You will see two boxes with objects on top.
2. Money ($) will appear in one of the boxes.
3. After you see where the money has been placed the boxes will disappear.
4. When they reappear select the LOCATION [OBJECT] where the money was placed.

The goal is to get as much money as you can!

The following instructions were provided for the control tasks:

LID [OBJECT] COLOUR TASK
(This task is a little different than the last one.)
1. Once again, you will see money placed in a box before the delay.
2. This time the money will ALWAYS be found under the darker lid [green object].
3. When the boxes reappear choose the darker lid [green object] every time.
Participants also completed two short task blocks of two DR-S/DR-O trials followed by two trials of their respective baseline tasks. This last phase of the training session was included to familiarize participants with the presentation format to be used while they were in the scanner (i.e. experimental trials alternating with baseline trials).

Immediately prior to the scan session, participants completed one additional block of trials (four task + four control) to reacquaint them with the task instructions and provide them with a chance to respond via the response button system to be used to record responses during scanning. While in the scanner participants were provided with the following ‘refresher’ instructions before each task began:

**Location [Object] Memory Task:**
- Money stays in the same LOCATION [under the same OBJECT] as it was placed.

**Lid Colour Task:**
- Always choose the DARKER LID [GREEN OBJECT].

Training for the alternation tasks (DA/OA) was conducted in the same manner. Again, participant instructions for both the spatial and the object alternation versions of the task were identical with the exception of references to ‘location’ and ‘object’:

**LOCATION [OBJECT] SWITCHING TASK**

1. You are going to see two boxes with objects on top.
2. There is money ($) hidden in one of them.
3. You must find the money every time the boxes appear.
4. Two rules will help you find the money:
   - it will switch between LOCATIONS [OBJECTS] if you find it.
   - it will stay in the same LOCATION [under the same OBJECT] if you don't.

Get as much money as you can!
Once positioned in the scanner, they were provided with the following 'refresher instructions' before each scan series:

Location [Object] Switching Task:
- Money switches from one LOCATION [OBJECT] to the other after you find it.
- Money stays in the same LOCATION [under the same OBJECT] if you do not find it.

A total of sixteen task and sixteen control trials were completed during a single scanning series (four blocks of 4 task followed by 4 control trials in a standard 'on-off' blocked design). A single scan series of 32 trials lasted for approximately 10 minutes with only a single task type (i.e. DR-S, DR-O, DA or OA) performed within a single series. Two series (for a total of 32 task + 32 control trials) were run consecutively for each task and task order was pseudo-randomized for each participant.

fMRI Parameters

Functional magnetic resonance imaging was conducted using a whole-body scanner operating at 1.5 T magnetic field strength (Signa, General Electric Medical Systems). Visual stimuli were presented with the "Visible Eye" system (Avotec, Inc., Jensen Beach, FL, and SensoMotoric Instruments GmbH, Berlin Germany), which consists of a pair of lightweight, binocular glasses linked by a flexible fibre optic image guide to an LCD projector. Participant responses were acquired using response pads (Lumitouch, Lightwave Technologies, Inc., Surrey, BC, Canada) that are connected to a computer outside the magnet room by fiber optics.
During the functional scan twenty-six axial slices, 5 mm thick were obtained. Scans were obtained using a single shot T2-weighted pulse sequence with spiral readout, offline gridding and reconstruction (Glover, 1998) (TR=2000, TE=40 ms, flip angle 80 degrees, 90x90 effective acquisition matrix). For each participant, volumetric anatomical MRI was performed prior to functional scanning using standard three-dimensional T1-weighted pulse sequence (TR = 12.4 ms, TE = 5.4 ms, flip angle 35 degrees, 22x16.5 field of view, 256x192 acquisition matrix, 124 axial slices, 1.4 mm thick).

fMRI Analyses

Data processing and analyses were performed using Analysis of Functional Neuroimages (AFNI) software (Cox, 1996). Time series data were spatially coregistered to correct for head motion using a 3-dimensional Fourier transform interpolation, and detrended using a fifth order polynomial. Percent changes in signal intensity with respect to baseline were analyzed using voxel-wise correlations of the task series with square-wave reference vectors shifted to account for the delay in hemodynamic response (Bandettini, 1993). The square wave vectors modeled the 10 second delay period and 3 second probe period of each trial. This produced four activation images for each participant (one each for DR-S, DR-O, DA and OA) which were then transformed into Talairach coordinates (Talairach, 1988; Cox, 1996), and smoothed with a Gaussian filter FWHM of 6 mm to increase the signal to noise ratio. The latter step was also performed to facilitate the group analysis, which consisted of a voxel-wise 2-factor ANOVA with tasks as within participant factors.
Results

Behavioural Results

Overall, group performance during scanning remained at the pre-training threshold criterion of 95% accuracy ($M = 95.2$, $SD = 6.27$) with little variability in mean performance across tasks (range: 94.2% – 96.4%). However, ceiling effects on these tasks likely any obscure any differences in task difficulty. Low power ($N=5$) precludes meaningful analysis of variance. The object alternation task was reported by participants during debriefing to be the most demanding of the four tasks. These self-reports are consistent with data reported by Freedman et al. (1998) wherein normal control participants produced a greater number of errors on the OA task in comparison to DR or DA.

fMRI Results

Only clusters of significant voxels ($p < .001$) with a minimum size of 300 μm were preserved (roughly equivalent to 6 original 3.125mm x 3.125mm x 5mm voxels). A $t$ value threshold was set that established an estimated false-positive statistical threshold of $\alpha = .01$ (Ward, personal correspondence, 2000) and accounts for the multiple comparisons that have been performed. The threshold $t$ value was set at 3.83 with an associated $p$ value of $4.0 \times 10^{-6}$. The advantages of combining a voxel-based threshold with a minimal cluster size have been described elsewhere (Forman, Cohen, Fitzgerald, Eddy, Minton & Noll, 1995). Performance on each the four tasks was contrasted with
their respective control tasks which were designed to match the experimental tasks as closely as possible on perceptuomotor demands. The resulting areas of significant activation are presented in Tables 2 & 3 and Figures 2 (a-d).

When activity recorded during performance of the spatial delayed response task was compared to its baseline only a single area of significantly increased blood oxygen-level (BOLD) signal intensity in the superior frontal sulcus (Brodmann Area 8) on the right surpassed the cluster threshold criterion (see Figure 2a). In contrast, when a similar comparison was performed on the object-delayed response task, increases in signal intensity were much more widespread particularly within the medial and dorsolateral prefrontal cortex (see Figure 2b). Significant areas of signal intensity increase included the right medial frontal gyrus (area 32), areas within the dorsolateral prefrontal cortex on the left throughout the middle frontal gyrus (areas 9, 46 and 10) as well as on the right within area 10 (see Table 2 for specific cluster coordinates according to the map of Talairach and Tournoux 1988). In addition to these prefrontal activations, significant increases were noted in the left temporal lobe laterally (area 21) as well as within the medial temporal lobe surrounding the uncus with above-threshold activity extending into the anterior hippocampal formation. Large clusters of significantly ‘activated’ voxels were also evident in the thalamus bilaterally with maximal intensity localized within the ventrolateral thalamic nuclei. Two areas of significant activation were also noted in the posterior lobe of the cerebellum on the left.

When the delayed alternation task was compared with its perceptuomotor control task (i.e. ‘always choose the darker lid’), significant increases in signal intensity were
evident in the middle frontal gyrus bilaterally within area 8 (Figure 2c). As was the case with the non-alternating, delayed response tasks, performance of the object-based alternation task (OA) was associated with more widespread signal intensity changes than was spatial alternation performance (Figure 2d and Table 2). Specifically, BOLD signal increases were significant in the area of the anterior cingulate gyrus on the right (area 32) and the middle frontal gyrus bilaterally (area 8 on the right; area 9 on the left). A large area of significant activation was also noted in the medial frontal gyrus (BA 6). More posterior areas of signal intensity increases were evident in the inferior parietal lobule on the left (area 40) as well as in the area of the posterior inferior longitudinal fasciculus, extending into posterior hippocampal regions bilaterally.

Areas of significant reductions in BOLD signal activity during task performance relative to baseline were also evident across three of the four tasks (no areas of significant signal decrease were evident for the delayed alternation task) and are reported in Table 3. Interpretation of these ‘deactivation’ areas is complicated by an inability to dissociate those areas in which signal intensity decreased during experimental task performance or increased during perceptuomotor control task performance. Areas of a significant decrease in signal intensity during spatial delayed response relative to control included the right superior temporal gyrus (area 38) right anterior cingulate (BA 25) and left cingulate gyrus (BA 24); right hippocampus and posterior parahippocampal gyrus (BA 19) and the left fusiform gyrus (area 19). For the object delayed response task two areas of relative signal decrease included the anterior cingulate on the left (area 24) and the right pre-central gyrus (area 4). Relative reductions in BOLD signal during object alternation included the left inferior frontal gyrus (BA 44), left middle temporal gyrus
(area 21) and inferior parietal lobule (area 40), the left precuneus (areas 7, 19), and the cuneus bilaterally (area 19 on the right, area 18 on the left).

Discussion

The primary objective of the present investigation was to describe the functional neuroanatomy of healthy human performance on three delay tasks (delayed response, delayed alternation and object alternation) that have been proposed as measures of prefrontal function in non-human primates and persons with brain disease. Overall, the results presented here represent an important contribution to the delayed response literature by providing a third convergent line of evidence in support of the long-standing tenet that healthy human performance on each of these tasks is subserved, at least in part, by the prefrontal cortex.

There are several notable and perhaps surprising trends apparent within the data. The most important, with respect to the overall objective of the present study, is the striking degree of correspondence between task performance on all tasks and localized activity within the frontal lobes (15 of 22 significant clusters were located within the frontal cortex). Although areas negatively correlated with task performance are not discussed in further detail here, it is perhaps of interest, within this context, to note that only 3 of the 13 clusters of negative activations that surpassed threshold were located in the frontal lobes, suggesting either that the control tasks engaged more regions within the posterior cortex or that there may have been a decrease in cortical activation posteriorly associated with task performance.
Within the frontal lobes two patterns of activity are also readily identifiable – one predicted, the second somewhat more surprising. First, as has been demonstrated in numerous functional neuroimaging studies using delayed response paradigms, prefrontal activity is predominantly observed within the dorsolateral region in the area of the middle frontal gyrus. This is observed across all tasks irrespective of mnemonic domain or alternation demands. Cabeza and Nyberg (2000) found a similar predominance of dorsolateral prefrontal activity in their recent review of neuroimaging literature wherein 29 out of 45 working memory studies (including spatial, non-spatial and verbal/numeric tasks) reported activity in Brodmann areas 9/46 – regions encompassing the middle frontal gyrus. The second, unpredicted finding is the absence of any suprathreshold activations within the region of the ventral prefrontal cortex (one cluster, correlated with DR-O performance, fell just below threshold cluster size and was located in the area of Brodmann 45). Both of these results are discussed in greater detail below.

Two other general trends apparent within these results are worth noting before proceeding with a more detailed comparison of these findings with our predictions. First, there is no general lateralization trend apparent within either within the frontal or the posterior cortices or across tasks. This is consistent with a recent report by D’Esposito et al. (1998) who found little evidence of laterality reported in the working memory literature. It is of note, however, that right lateralization of a network of areas subserving response inhibition has been reported by Garavan et al. (1999). A single area of left lateralization is evident in the cerebellum associated with DR-O performance and this might have been predicted as the cerebellum is known to play a critical role in the
modulation of movement (Kandel, Schwartz, & Jessel, 2000). However this explanation does not address either the left lateralization nor the absence of similar supra-threshold cerebellar activations associated with performance on the other three tasks. Finally, one of the most obvious features of the data set, apparent upon even a brief scan of Table 2, is the rather dramatic imbalance between spatial and object-based tasks in the number of significant activation clusters surviving threshold. There is no obvious precedence for such an imbalance based upon mnemonic domain within the neuroimaging literature. One potential explanation may be related to differing levels of task difficulty between the object and spatial tasks (as assessed by participant debriefing). While such a difference may be manifest through differing attentional demands, superior parietal activations, which have associated with attentional processing (Pardo, Fox & Raichle, 1991) are not observed in the present study. Cabeza and Nyberg (2000) report that anterior cingulate activations may also be associated with increased task effort. While there is evidence of anterior cingulate activity associated with performance of the object alternation task (considered by participants to be the most difficult task), this explanation does not address the prevalence of activation clusters associated with performance of the object delayed response task wherein no anterior cingulate activations were evident. Further exploration of this apparent imbalance in activations will need to be addressed in future research.

Having discussed the broad trends apparent within the data set, the following sections will proceed with a more detailed analysis of the results. In-keeping with the hypothesis-driven approach of the present investigation, each of the three predictions flowing from the hypotheses outlined earlier will be contrasted with the actual findings
reported in Table 2 and interpretations proffered to help explain the various areas of convergence and divergence of the data with our expectations.

**Delayed Response Tasks as *Bona Fide* Measures of Prefrontal Function**

Looking back to the earliest studies by Jacobson (1935) and Harlow and his colleagues (1945), these findings contribute to the broad arc of investigative efforts which have identified the delayed response paradigm as a *bona fide* measure of human prefrontal function. Developed originally as measures of the human capacity to guide behaviour by cues no longer present in the environment, the tasks became central to investigations of frontal lobe function in non-human primates (Mishkin, 1964; Mishkin et al., 1969; Pribram, 1962). Subsequently, these tasks were the first measures of primate behaviour to be successfully employed as measures of prefrontal deficits in persons with brain disease and this approach has been used successfully to map the course of brain disease in human neurodegenerative illnesses affecting frontal regions (Freedman & Oscar-Berman, 1986a; Freedman & Oscar-Berman, 1986b; Freedman, 1990). While others have studied the functional neuroanatomy of variants of these tasks (Curtis et al., 2000, Gold, Berman, Randolph, Goldberg, Weinberger, 1996), the present study is, to our knowledge, the first to utilize direct facsimiles of these three early paradigms (delayed response, delayed alternation and object alternation) in order to investigate the neural basis of healthy human performance within a single study. We have attempted to replicate, to the extent possible, the essential parameters across all three tasks and, as a result, our findings provide converging evidence from a neuroimaging study of healthy
human participants suggesting a critical role for frontal lobes in the mediation of successful performance on these classic delayed response paradigms.

While these paradigms have played an important role in describing the critical involvement of the frontal lobes in bridging temporal gaps between stimulus and response (Goldman & Rosvold, 1970; Goldman-Rakic, 1987; Fuster, 1997), they have been employed primarily, from the early investigations of Mishkin and Pribram (1955, 1956) and Pribram and Mishkin (1956), to more precisely map function onto structure within the prefrontal cortex. Having confirmed our first prediction with respect to the role of delayed response tasks as bona fide measures of prefrontal function, we turn now to our subsequent predictions concerning functional specificity within the prefrontal cortex.

Process And Mnemonic Domain Hypotheses Of Working Memory Within The PFC

Predictions of hypothesis 2

The data provides no support for the mnemonic domain hypothesis as there was no dissociable dorsolateral/ventrolateral pattern of activation that distinguished spatial and object delayed response performance. In fact, no significant areas of activation were recorded within ventrolateral PFC (defined as areas lying ventral to the inferior frontal sulcus and including Brodmann areas 44, 45, 47 (D'Esposito et al., 1998; Passingham, 2000)) for any of the tasks in this study. As a result these findings would not appear to support the model of ventrolateral prefrontal involvement for object working memory.
and dorsolateral mediation of spatial working memory proposed by Goldman Rakic (1987; 1996) and Wilson et al. (1993). These negative findings are consistent with two recent reviews of the literature (Cabeza & Nyberg, 2000; D'Esposito et al., 1998) which did not find support for dissociable prefrontal involvement in working memory based upon mnemonic domain. However, the absence of any significant areas of activation within the ventrolateral prefrontal cortex for either the spatial or object delayed response tasks (as compared to their respective perceptuomotor control tasks) in the present investigation is also inconsistent with a processing account of working memory specialization within the PFC and, as such, fails to support hypothesis 2(b). However, both Cabeza and Nyberg (2000) and D'Esposito et al. (1998), in their reviews of the literature, found strong support for the memory process model of prefrontal involvement in working memory put forth by Petrides (1996) and Owen et al. (1998). Both of the reviews place the delayed response tasks utilized in this study within the ‘maintenance’ category of working memory tasks (Cabeza & Nyberg, 2000, p. 17; D’Esposito et al., 1998, see chart. p.4) and both report extensive engagement of ventral prefrontal regions (areas 44, 45, 47) during performance of these delayed response type tasks. The failure to find similar activation patterns within the current study may attributable to several factors. 

**Methodological constraints**

The ventral prefrontal cortex is a region that has been associated with reductions of functional signal owing to the magnetic susceptibility artifact that arises at air-tissue interfaces within the cranium (Garavan et al., 1999). The ventral areas of the prefrontal
cortex, in particular anterior, orbitofrontal and ventromedial regions lie adjacent to the sinus cavities resulting in substantial susceptibility artifacts and signal loss in these regions. This potential signal reduction within ventral prefrontal regions may have reduced sensitivity within the present study to detect changes in functional signal in these areas (Garavan et al., 1999). This hypothesis is substantiated to an extent by the absence of significant activation clusters within the ventral prefrontal cortex (i.e. areas lying below the inferior frontal sulcus) in any of the four task conditions. Somewhat related to this issue of sensitivity to detect signal change is the possibility that the statistical power in the present design may not have been sufficient to detect relatively smaller changes in ventrolateral prefrontal signal intensities. This possibility is further strengthened by noting that as the threshold for significance is lowered, an area of activation correlating with DR-O performance is evident within the ventrolateral prefrontal white matter (adjacent to area 47 on the left). However, this cluster falls just below the voxel probability/cluster volume significance threshold of 300 µl, \( p < .01 \) (corrected for multiple comparisons) established for the present study. The cluster volume for this ventral activation was 266µl, equivalent to approximately 5 original voxels with a corrected, false positive probability level of \( p > .05 \). It is worth noting, however, that no similar sub-threshold activation clusters appeared within the ventral prefrontal cortex when the significance threshold was lowered for the spatial analogue of the object delayed response task – a mnemonic dissociation that would not have been predicted by Cabeza and Nyberg (2000) or D'Esposito et al. (1998). This suggests that inadequacies in the sensitivity of the present design, owing to either a susceptibility artifact or deficient statistical power, may provide only a partial explanation for the inconsistency of the present findings with those of the recent reviews, thereby necessitating an alternate
explanation for the null findings with respect to ventral prefrontal activity relating to
either maintenance processes within working memory (Petrides, 1996) or object-based
working memory (Goldman-Rakic, 1987).

Alternative interpretations of PFC engagement in working memory

Although reviews of the functional neuroanatomy of working memory cited
above align with Petrides' (1996) model of dissociable working memory processes within
ventral (maintenance related activity) and dorsolateral (monitoring/manipulation activity)
prefrontal regions, several studies have failed to find such a clear dissociation. Elliott and
Dolan (1999) failed to find evoked neural activity within the ventrolateral PFC when
delayed match to sample tasks (categorized as 'maintenance-only' by D'Esposito et al.
1998) were contrasted with perceptuomotor control tasks. Similarly, Courtney et al.
(1996, 1998) found left ventral (area 44) activation during a face working memory but
not during its spatial analogue - even though both were categorized as 'maintenance'
tasks (see D'Esposito et al., 1998 for further discussion of this result). Rowe, Toni,
Josephs, Frackowiak and Passingham (2000) reported that activity specifically associated
with the 'maintenance' epoch in a spatial working memory task was localized to the
dorsolateral and not the ventrolateral prefrontal cortex, specifically within a region in and
around the superior frontal sulcus (area 8); an area close to that reported by Courtney and
her colleagues (1998). In addition to these neuroimaging findings, primate lesion studies
conducted by Rushworth et al. (1997) demonstrated that while animals with inferior
convexity lesions were severely impaired on a delayed matching task immediately after
surgery, they were able to relearn delay tasks with extended training. This result led
Rushworth and his colleagues (1997) to conclude that ventral prefrontal lesions did not interfere with working memory in the non-human primate. These finding led Passingham (2000) to recently conclude that the ventral prefrontal cortex is not essential for working memory per se, a conclusion that lies in direct contrast with Petrides earlier model (1996).

The suggestion that ventral prefrontal regions are not essential for working memory performance is consistent with the results of the present study wherein no significant clusters of activation were evident ventral to the inferior frontal sulcus for any of the four working memory tasks. Furthermore, the specific region proposed by Rowe et al. (2000) and Courtney et al. (1998) to mediate maintenance processes pertaining to spatial working memory lay in and around the superior frontal sulcus (area 8); an area overlapping with the sole area of significant activation reported for the spatial delayed response task in the present study. While clusters of significant activations falling within Brodmann area 8 were also evident during the delayed alternation and object alternation tasks, these activations were situated on the middle frontal gyrus bordering Brodmann area 9, lying somewhat inferior and anterior to the superior frontal sulcus activations described by Passingham (2000) and Courtney et al. (1998). Whether the absence of ventral prefrontal cortical activations within the present study is attributable to methodological deficits or whether the data are suggestive of an alternative model of prefrontal involvement in working memory, these results clearly do not align well with either the mnemonic domain or the process models of the functional neuroanatomy of working memory that have been so extensively debated in the literature. There is,
however, some support within the data for a model recently proposed by Rowe et al. (2000).

An emerging model

Rowe et al. (2000), in their model, assert that the role of the middle frontal gyrus (specifically area 46), traditionally thought to subserve working memory, is involved in the selection of internal representations held within working memory to guide a subsequent response while maintenance activities are assumed to be mediated by regions within Brodmann area 8 around the superior prefrontal sulcus (see above). By definition, all of the tasks employed in the present study may be categorized as having a maintenance requirement (i.e. they all require information be held ‘on-line’ across a 10 second delay period) and, as would be predicted by Rowe and his colleagues, performance on three of the four tasks in the present study (and see note 5) correlated with significant activations within Brodmann area 8. However, the tasks may be differentiated in terms of their requirement for response selection as defined by Rowe et al., (2000).

Performance of the spatial-based tasks may be seen as necessitating little internal response selection at the time of the probe given that the correct response (i.e. a left or right button push) may be set from the time of the initial target presentation. Put another way, the relation between the target stimulus and the correct response for the spatial tasks

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4 An activation cluster within Brodmann area 8 was also evident during the object delayed response task. However the cluster-volume of 275 µl fell below the significance threshold of 300µl (p < .01).

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is both direct and invariant ("see target on the left – at probe press button #2"). While the alternation rule adds a switch component, the essential task elements remain the same (see target on the left; press button #1). Performance on the object-based tasks, on the other hand, requires more effortful scanning of internal representations in order to guide responses at the time of the probe stimulus. This difference owes to the task design wherein placement of the object stimuli is randomized across locations from the stimulus presentation to the probe display, thereby severing the direct relation between stimulus presentation and response. As a result, the algorithm for performance of object delayed response contains an added contingency relative to the spatial delayed response task. (i.e. see target object A on left; hold object A on line; at probe match on-line representation to location of the target stimulus; guide response).

Allowing that there may be differing response selection demands between object and spatial-based tasks leads directly to a prediction, using the model of Rowe et al. (2000), of differing patterns of activation for the two task categories in and around the middle frontal gyrus within Brodmann area 46 – the area identified by the authors as underlying response selection. This is in fact the pattern of activation observed in the present study. While the significant activations associated with the two spatial-based tasks (DR-S and DA) are restricted to Brodmann area 8, the object-based tasks have additional activations located both inferiorly and anteriorly within the middle frontal gyrus around Brodmann areas 9/46. These activations may represent additional demands within these tasks to select from internal representations to guide responses.
While the model proposed by Rowe et al. (2000) does provide a theoretical framework within which the results of the present investigation may be interpreted, it is important to acknowledge that the analysis is being conducted post hoc and represents only one possible interpretation of these data. It is interesting, nonetheless, to consider that while neither of the widely accepted hypotheses of dissociability between the ventral and dorsolateral prefrontal cortex pertaining to working memory performance were supported here, a third, more recently proposed theory of dissociation between working memory maintenance and response selection within the dorsolateral PFC did align well with the results obtained in the present study. A more precise delineation of this theorized dorsolateral dissociation will have to await future research.

**PFC and the Resolution of Response Conflict**

**Predictions of Hypothesis 3**

As reviewed earlier, Mishkin (1964), and others (D'Esposito, Postle, Jonides & Smith, 1999; Diamond & Goldman-Rakic, 1989; Garavan, Ross & Stein, 1999; Jones & Mishkin, 1970; Mishkin et al., 1969; Passingham, 1975), have suggested that successful performance on delayed response tasks is contingent not only upon the maintenance of information across a delay, but also upon the capacity to successfully select representations held within working memory in the face of competition from other representations (of varying degrees of salience) that may also be active within the short-term memory store. The neural correlates of such a capacity – described both as prepotent response inhibition (Garvan et al., 1999; Konishi et al., 1999; Dias et al., 1996)
and suppression of proactive interference (D'Esposito et al., 1999) have been the source of considerable debate. Early animal lesion studies with both delayed alternation and object alternation tasks (Jones & Mishkin, 1970; Mishkin et al., 1969), reviewed previously, demonstrated that the capacity to inhibit a prepotent response towards a previously rewarded stimulus was disrupted by lesions of the inferior prefrontal convexity in monkeys. Similar findings of ventral prefrontal involvement in similar response inhibition processes were more recently demonstrated in monkeys using a set-shifting paradigm (Dias et al., 1996) and in healthy human adults using a Go-No Go task (Konishi et al., 1999). These findings, in addition to the reported performance deficits on alternation tasks observed in persons with ventral frontal brain disease (Freedman, 1990) led to the hypothesis that performance on the alternation tasks (DA, OA) but not the non-alternation tasks (DR-S, DR-O) in the present study would be correlated with activity within the ventral prefrontal cortex. As reported above, however, no significant areas of activation were evident within the ventral prefrontal cortex for any of the tasks, thus failing to support this prediction. Once again, this null finding must be considered both in terms of the methodological constraints within the present study and alternative interpretations drawn from a broader review of the response inhibition literature.

A broader network for response inhibition

The methodological problems of signal loss in areas of the ventral prefrontal cortex and statistical thresholding issues have been discussed above and may once again underlie the absence of predicted ventral prefrontal activations. A summary review of the activation clusters presented in Table 2 clearly illustrates that the majority of frontal
cortical activity found in the present study is predominantly focused within the middle
and, to a lesser extent, the superior frontal gyri. While this pattern of activation has been
discussed previously in terms of mnemonic processing (maintenance, manipulation,
monitoring within working memory) and response selection components of delayed
response tasks, it is interesting to note that these same regions have also been implicated
in so-called response inhibition processes (Casey, Trainor, Orendi, Schubert, Nystrom
Giedd et al., 1997). In addition, Garavan et al. (1999) reported that most the prefrontal
activity observed in their study of what they conceived as being response inhibition
demands was found within the middle frontal gyrus.

Involvement of the anterior cingulate gyrus in response conflict and inhibition

In addition to those activations recorded in the middle frontal gyrus, however, the
pattern of activations reported in the present study suggest a second prefrontal region, the
anterior cingulate cortex, that may be implicated in the identification and/or mediation of
response conflicts arising during alternation delay task performance. In addition to the
right anterior cingulate, significant medial frontal activations were also reported along the
border of the medial frontal gyrus and right medial cingulate gyrus (area 32) correlating
with DR-O performance and the left superior medial wall (area 6 just superior to area 32)
correlating with OA. The specific location of the cingulate activation associated with
performance on the object alternation task in the present investigation lay anterior to the
anterior commissure, within an area referred to as the pre-supplementary motor area
(Picard & Strick, 1996) and which has been associated with response inhibition and/or
the monitoring of response conflict in neuroimaging studies by Barch, Braver, Sabb and

These anterior cingulate activations appear to be distinct from the more posterior and superior medial/cingulate activity evident during performance of object delayed response which is situated caudal to the anterior commissure within the region of the supplementary motor area (Picard & Strick, 1996). This anterior/posterior distinction is an important one as Garavan et al (1999) reported that activations in the post-AC region recorded during performance of their response-inhibition task were highly correlated with response execution, while anterior cingulate activity was more strongly related to the inhibition of prepotent responses. More specifically, they observed that all medial wall activation rostral to the anterior commissure (as observed in OA here) was associated with response inhibition while medial wall activation caudal to the AC (as observed in both OA and DR-O) was associated with response execution. There remains a significant debate in the literature with respect to the role of the anterior cingulate as an ‘evaluator’ of response conflicts (Botvinick et al., 1999) or as an active node within a broad prefrontal response inhibition network (Garavan et al., 1999). While the results reported here are unable to contribute directly to this debate, the finding of anterior cingulate involvement in object alternation nonetheless strongly suggests that (i) the resolution of response conflict is a cognitive demand tapped by the ‘alternation’ and not by other components of OA (as evidenced by an absence of similar activity in the otherwise
cognitively-matched object delayed response task) and (ii) that the anterior cingulate region is preferentially engaged by this cognitive demand in healthy human adults.

While it would be tempting, based on this analysis, to more categorically confirm the role of the anterior cingulate in mediating alternation performance, two cautionary notes are warranted. As reiterated several times, the susceptibility artifact may have occluded any ventral or orbitofrontal areas of activation associated with task performance and this is of particular concern for the alternation tasks where previous studies have found activations relating to the performance of object and spatial alternation (Curtis et al., 2000) and a similar ‘working memory + response inhibition’ paradigm, delayed non-matching to sample (Elliott & Dolan, 1999). Caution must also be taken in extrapolating these results across mnemonic domains given the somewhat glaring absence of similar medial wall activity in the spatial analogues of the object-based tasks. Even with a significantly reduced statistical threshold, no similar cingulate activations are evident in either the spatial delayed response or delayed alternation tasks – a discrepancy that runs somewhat counter to the interpretation that dissociations within the anterior/posterior cingulate may be used to directly infer differing task demands for response inhibition and/or response execution.

Delayed Response: Memory Representation and Associative Learning

Task performance vs. rule acquisition
As reported, one of the more striking findings emerging from the present study is the absence of ventral prefrontal (or, more specifically, ventrolateral and orbitofrontal) activations. This is particularly surprising given that the experimental tasks utilized here have been employed extensively to investigate dorsal and ventral prefrontal function (and dissociations between these regions) in non-human primates (for example Pribram, 1962; Mishkin et al., 1969, Mishkin & Manning, 1978) and humans (Curtis et al., 2000; Freedman, 1990; Freedman et al., 1998). While several methodological and theoretical accounts of this finding have been addressed above specifically in terms of prefrontal involvement in mnemonic processing and response inhibition, an alternative account pertaining to the particular design of the present study must also be considered.

In adapting the delay task behavioural paradigms to the fMRI scanning protocol, substantial import was given to replicating the standardized administration of these tasks within the scanner to the extent possible given both the physical constraints imposed by the scanning apparatus and the limitations imposed by the transient nature of the BOLD signal. While the former placed few actual constraints on the design (e.g. response buttons replaced actual reaching for the target), the latter, in the conjunction with the empirical issues discussed in ‘Methods’, prompted the decision to implement the ‘rule acquisition’ phase for the tasks outside of the scanner. As a result, the activations reported here provide direct data only with respect to the neural correlates of ‘performance’ for each of the delay tasks and not for the ‘rule learning’ which would normally precede performance on each of the tasks. This represents a significant departure from the standardized administration of these tasks as employed in both primate lesion (for example Mishkin et al., 1969) and human neuropsychology studies.
(for example Freedman, 1990). Yet the approach, which has provided important insight into the neural correlates of delay task performance, may also, through comparative analyses, provide indirect, yet valuable, insights into the neural correlates of rule acquisition for these delay tasks.

**Associative learning and the ventral PFC**

The ventral prefrontal cortex has been shown to mediate the learning of rules that govern the production of responses based on visual cues (Murray, Bussey & Wise, 2000). Similarly, lesions of the inferior prefrontal convexity in primates have been shown to impede relearning of the delayed non-matching to sample principle (Kowalska, Bechevalier & Mishkin, 1991) and Passingham et al. (2000) recently proposed that the ventral prefrontal cortex (areas lying inferior to the inferior frontal sulcus in humans) ‘constitutes part of the circuitry via which associations are formed between visual cues and the actions or choices that they specify’ (p. 103). These findings are of relevance to the present investigation as they suggest that the failure to observe ventral prefrontal activations in the present study may be an artifact of the decision to train participants on each of the tasks prior to scanning, thereby reducing task demands for associative learning. This learning of visuo-motor associations has been linked to prefrontal function in humans (Toni & Passingham, 1999) and non-human primates (Kowalska et al., 1991; Meunier et al., 1997; Passingham, 1975).

In this respect, the results of present investigation appear to align well with the findings of Meunier and colleagues (1997) who describe a network subserving object
memory processes that includes primarily the rhinal and orbitofrontal cortices and the magnocellular division of the medial dorsal thalamus in monkeys. The authors have found evidence for dissociable contributions of the ventromedial prefrontal cortex (specifically orbitofrontal regions) and the rhinal cortex (in the area of the rostral, medial temporal lobe) to associative learning and representational memory, respectively. They describe this dissociation functionally, using a delayed non-matching to sample task, wherein the orbitofrontal cortex is preeminently engaged by associative memory requirements across trials (i.e. critical for the learning of the DNMS principle that novel stimuli are related to reward) while the rhinal cortex is critical for representational memory within individual trials (p. 1011). This finding (assuming a homologous network exists within the human cortex) might provide an explanation for the null findings with respect to ventral prefrontal activity in the present study.

In short, the associative learning components of the tasks, which might be expected to engage ventral prefrontal regions, were not measured in the present study as all participants were pre-trained on the rules of each task and performed at a 95% criterion level prior to the scanning session. However, representation memory, as defined by Meunier et al. (1997) would likely support performance on the object-based tasks utilized in the present investigation. In this respect, it is of particular interest that the areas these authors identify as subserving recognition memory ‘from trial to trial’ included regions within the rostral, medial temporal lobe and the dorsal medial thalamus — overlapping with two areas of significant activity evident during performance of the object delayed response task. This partial neuroanatomical convergence with the findings of Meunier et al. (1997) is informative for the present investigation in two respects: (i) it
provides a theoretical interpretation of two areas of significant activation (thalamus and medial temporal regions) associated with performance on the object delayed response task and (ii) it provides an indirect interpretation of the null results found within the present study for activations within ventrofrontal PFC in that the associative learning component of the tasks which would normally be mediated by this region was absent in the present study. In other words, the absence of ventral PFC activity may be a direct manifestation of the decision to pre-train participants prior to scanning, therefore reducing the associative learning demands, which, according to Meunier et al. (1997) and Passingham et al. (2000) is a specialized function of the ventral prefrontal cortex.

Conclusion

The delayed response paradigm that has been at the centre of this investigation has served as an essential, empirical tool to investigate what may seem to be rather simple and somewhat abstract human talents. In fact, delay tasks measure what are, in actuality, fundamental aspects of higher cognitive function – abilities that allow us to guide our behaviour, not only in response to the world around us, but by our own internal milieu. Our ability to hold information ‘on-line’ affords us the capacity to retain not just phone numbers or names of friends but thoughts and ideas and, in turn, to use those ideas to guide our behaviour into the future. Likewise ‘the ability to resist the strongest response of the moment endows us with extraordinary flexibility and freedom to choose our actions – it gives us all the option of not being solely creatures of habit’ (Diamond & Goldman-Rakic, 1989). An effort to better understand these fundamental building blocks of a rich, human existence has served as the impetus for the present study.
Within this broader context, the present investigation has provided the first direct evidence that healthy human performance on three classic delay task paradigms: delayed response, delayed alternation and object alternation, is mediated to a large extent within the frontal cortex. This finding is the last of three converging lines of evidence that implicate the frontal lobes in the performance of these versions of the delayed response paradigm and further confirm the import of this region in the guidance and control of behaviour. However, as the results of this study would suggest, the story of frontal lobe involvement in these tasks will not end here. The failure of the present study to find support for the prevailing theories of prefrontal involvement in working memory and, to some extent, response inhibition has raised many more questions for future research. It does seem clear, however, both in the grand theoretical debates that have remained unsolved and in the plethora of emergent (and divergent) models of delayed response performance, that the quotation from Dr. Konorski, presented at the beginning of the text remains is as applicable today as it was in 1964.
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Neuroanatomy of Delay Tasks


Neuroanatomy of Delay Tasks


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<th>Task</th>
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<th>Region</th>
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</table>

Note.

1 Significant areas of activation corrected for multiple comparisons using a cluster size/voxel probability threshold (alpha < .01, p < 1x10⁻⁵)
2 Probable Brodmann areas based upon the atlas of Talairach and Touroux
3 Minimum cluster volume threshold = 300 microlitres
4 Cluster threshold t-value = 3.88, p < .001 uncorrected.
Table 3

<table>
<thead>
<tr>
<th>Task</th>
<th>Lobe</th>
<th>Region</th>
<th>Side</th>
<th>Brodmann's area$^a$</th>
<th>Volume$^b$ mm$^3$</th>
<th>Max thresh t-value$^b$</th>
<th>Max. Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spatial Delayed Response</strong></td>
<td>Limbic Lobe</td>
<td>Anterior Cingulate</td>
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<td>Limbic Lobe</td>
<td>Parahippocampal Gyrus</td>
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<td>Parahippocampal Gyrus</td>
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<td>Fusiform Gyrus</td>
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<td>Anterior Cingulate</td>
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<td>Inferior Frontal Gyrus</td>
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<td>Left</td>
<td>18</td>
<td>312</td>
<td>-5.16</td>
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</tr>
</tbody>
</table>

**Note.**

1 Significant areas of activation corrected for multiple comparisons using a cluster size/voxel probability threshold (alpha < .01., p < 1x10$^{-4}$)
2 Probable Brodmann areas based upon the atlas of Talairach and Touroux
3 Minimum cluster volume threshold = 300 microlitres
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Figure 1a

Schematic of delayed response tasks. Figures 1b, 1c describe spatial-based tasks and control stimuli respectively.

<table>
<thead>
<tr>
<th>Delayed Response Task (Object)</th>
<th>Object Alternation Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. inter-trial marker</td>
<td>a. initial probe*</td>
</tr>
<tr>
<td>(gray screen-not shown)</td>
<td>b. initial feedback *</td>
</tr>
<tr>
<td>b. placement of target</td>
<td>c. fixation</td>
</tr>
<tr>
<td>c. fixation (delay)</td>
<td>d. probe</td>
</tr>
<tr>
<td>d. probe</td>
<td>e. feedback</td>
</tr>
<tr>
<td>e. feedback</td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td></td>
</tr>
</tbody>
</table>

*subjects are always correct on the initial trial in both DA & OA.

Note: Delayed response task sequence (a-e) is presented on the right; Alteration task sequence is presented on the left. Each sequence denotes one trial (initial response on the alternation tasks is not counted as a trial). Arrows denote responding (angled arrow represents the target “popping in” as the well is “baited”). Critical events and related times are listed below the respective task displays.
**Figure 1b**

Spatial Delayed Response (DR-S) | Spatial Alternation (DA)
---|---

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>inter-trial marker 1000</td>
</tr>
<tr>
<td>b.</td>
<td>placement of target 2250</td>
</tr>
<tr>
<td>c.</td>
<td>fixation (delay) 10000</td>
</tr>
<tr>
<td>d.</td>
<td>probe 3000</td>
</tr>
<tr>
<td>e.</td>
<td>feedback 1250</td>
</tr>
</tbody>
</table>

**Delayed Response Task** (Spatial) | **Delayed Alternation Task**
---|---
| a. | initial probe* 3000 |
| b. | initial feedback 2000 |
| c. | fixation 10000 |
| d. | probe 3000 |
| e. | feedback 2000 |

*subjects are always correct on the initial trial in DA.

**Note:** Delay task schematic: Delayed response task sequence (a-e) is presented on the right; Alternation task sequence is presented on the left. Each sequence denotes one trial (initial response on the alternation tasks is not counted as a trial). Arrows denote responding (angled arrow represents the target “popping in” as the well is “baited”). Critical events and related times are listed below the respective task displays.

**Figure 1c**

Object-based tasks | Spatial-based tasks
---|---
DR-O, OA | DR-S, DA

**Note.** Stimuli for control tasks. Figure on the left is control stimuli for object-based tasks; Figure on the right is control stimuli for spatial-based tasks (participants were discouraged from attending to the ‘object’). Task sequences and timings are as described in Figure 1a. Arrows here denote the correct response.
Object Alternation

Significant ($p < 0.01$, corrected) activations correlated with performance of object alternation. Activation is located in the area of right anterior cingulate (Brodmann area 32). Maximal intensity coordinates: $x = 14$, $y = 27$, $z = 14$. Colour scale represents % change.

(Note: areas of negative correlation are not displayed but are listed in Table 3.)
Figure 2 (c)

Delayed Alternation

Significant ($p < .01$, corrected) activation correlated with performance of delayed alternation. Activation is located on right middle frontal gyrus (Brodmann area 8). Maximal intensity coordinates: $x = 34, y = 26, z = 40$. Colour scale represents % change.

(Note: areas of negative correlation are not displayed but are listed in Table 3.)
Object Delayed Response

Significant (p < .01, corrected) activations correlated with performance of object delayed response. Frontal pole activation is located on right middle frontal gyrus (Brodmann area 10). Maximal intensity coordinates: $x = 39$, $y = 58$, $z = 13$. Colour scale represents % change.

(Note: areas of negative correlation are not displayed but are listed in Table 3.)
Spatial Delayed Response

Significant ($p < .01$, corrected) activation correlated with performance of spatial delayed response. Activation is located on right superior frontal gyrus (Brodmann area 8). Maximal intensity coordinates: $x = 28$, $y = 35$, $z = 53$. Colour scale represents % change.

(Note: areas of negative correlation are not displayed but are listed in Table 3.)