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THE FUNCTIONAL NEUROANATOMY OF CLASSIC DELAYED RESPONSE TASKS IN HUMANS AND THE LIMITATIONS OF CROSS-METHOD CONVERGENCE IN PREFRONTAL FUNCTION

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Abstract—Three classic delay tasks: spatial delayed response, delayed spatial alternation and delayed object-alternation are prototypical experimental paradigms for mapping the functional neuroanatomy of prefrontal cortex in animals. These tasks have been applied in human lesion studies, yet there have been very few studies investigating their functional neuroanatomy in healthy human subjects. We used functional magnetic resonance imaging to investigate the functional neuroanatomy of these classic paradigms (and a fourth: object delayed response) in a single sample of healthy human participants. Consistent with previous animal, human lesion, and functional neuroimaging studies, activity was observed in prefrontal and posterior parietal cortices across all three delay tasks. Task-specific activations, however, were not entirely consistent with predictions drawn from animal lesion studies. For example, delayed object-alternation activated dorsolateral prefrontal cortex, a region not generally implicated in animal lesion reports. Spatial delayed response, classically associated with the dorsolateral prefrontal cortex, did not activate this region; it rather activated posterior premotor cortices involved in response preparation, as did spatial alternation. All three tasks activated the frontopolar cortex, a region not considered crucial in animal research but associated with manipulation of internally generated information in recent human research. While cross-method convergence may be attained for lower level perceptual or motor tasks, the results of this study caution against the assumption that lesion-specific effects in animals generalize to human prefrontal cortex function.

Key words: working memory, delayed response, delayed alternation, prefrontal cortex, fMRI.

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Abbreviations: AFNI, Analysis of Functional Neuroimages; aPFC, anterior prefrontal cortex; BA, Brodmann area; BOLD, blood oxygen level dependent; DLPFC, dorsolateral prefrontal cortex; DOA, delayed object alternation; DR-O, object delayed response; DR-S, spatial delayed response; DSA, delayed spatial alternation; fMRI, functional magnetic resonance imaging; FWHM, full-width-half-maximum; PET, positron emission tomography; PFC, prefrontal cortex; VLPFC, ventrolateral prefrontal cortex.

It is common practice in human neuropsychological research and clinical diagnosis to relate test performance to lesion location. This practice rests on the assumption that lesion location and task effects validated in one experimental platform can be transferred to another context. Such cross-method convergence is readily attained in studies of basic perceptual or motor function. Higher-level processes mediated by the prefrontal cortex (PFC) on the other hand, are more variable across species, individuals, and experimental platforms, challenging assumptions of cross-method convergence.

Three classic delayed response tasks: spatial delayed response (DR-S), delayed spatial alternation (DSA) and delayed object alternation (DOA) are among the best localizing tasks in primate lesion studies of the PFC and have been central to theories of prefrontal function, yet few studies have assessed their validity in human samples using lesion and functional neuroimaging (for exceptions, see Freedman and Oscar-Berman, 1986; Freedman et al., 1998; Curtis et al., 2000; Zald et al., 2002, 2005) methods. To our knowledge, their neural correlates have not been explicitly investigated *in vivo* simultaneously in a single sample of healthy human participants. The purpose of this study was to examine the functional neuroanatomy of these tasks, as well as a fourth, object-based delayed response task (DR-O), in healthy adults using functional magnetic resonance imaging (fMRI).

The classic version of the delayed response task (see Fig. 1a) as devised by Hunter (1913), adopted by Jacobsen (1936), and subsequently widely adapted for research in a variety of animal and human populations involves four primary task components: (i) *stimulus-reward placement* in one of two 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) *motor response* to select the correct location of the stimulus-reward. Starting in the 1950s and 1960s (Pribram et al., 1952; Mishkin and Pribram, 1955, 1956; Pribram and Mishkin, 1956; Mishkin, 1964; Mishkin et al., 1969), investigators began to characterize the role of the PFC in mediating behavior across a brief delay using this simple paradigm. Goldman et al. (1971) reported that deficits on delay tasks following ablations of non-human primate PFC were a function of the delay period and not attributable to primary sensory or motor deficits, demonstrating the *necessity* of PFC in mediating behavior across a delay. Convergent findings from electrophysiological studies of delay-related neuronal activity within the primate PFC (e.g. Fuster and Alexander,

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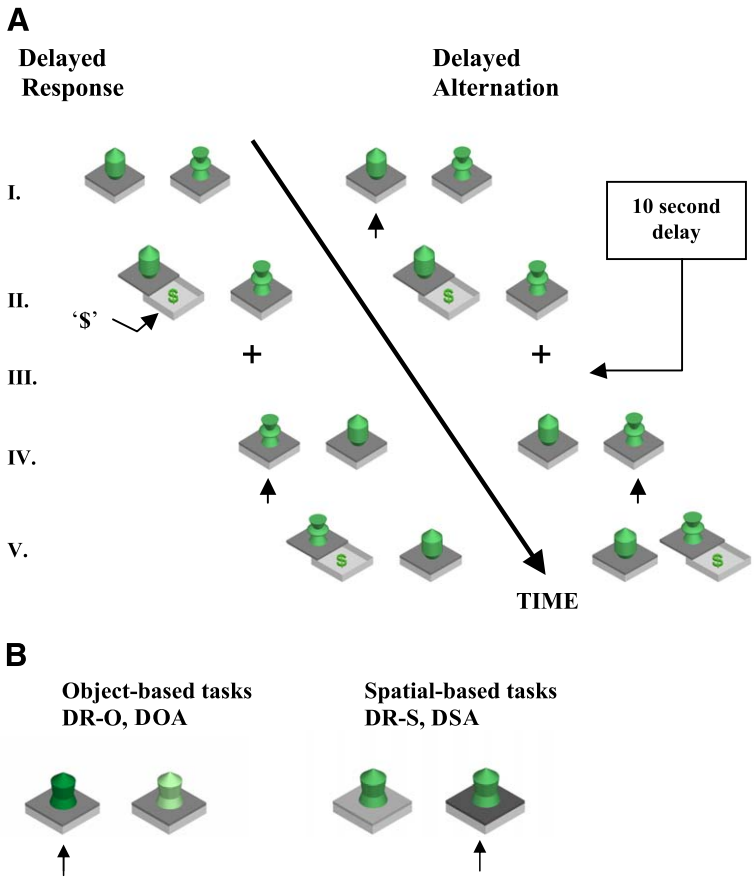

Fig. 1. (A) Phases of delayed response tasks: I. Stimulus presentation. II. 'Baiting' of target (in 'alternation' tasks, this depends on accuracy of previous response). III. Delay. IV. Probe stimulus. V. Feedback. The vertical arrow signifies participant response. Feedback provided by appearance of either a happy or sad face between and just above the two wells. During 'spatial' tasks, objects are uninformative (they are placed randomly across locations). During 'object' tasks, location is uninformative. Thus for delayed response (left side of figure) the bait remains in the left well, even though the object switches. For delayed object response (DR-O, not pictured), the bait would remain under the same object, although the location would switch at random. For DSA (right side of figure), the bait is found on the opposite side as on the previous trial, irrespective of object. The alternation trial depicted here would also hold for object alternation (DOA), in which the bait is found under the opposite object as on the previous trial, irrespective of side. Note that the visual stimuli remain constant for all tasks, eliminating variance due to perceptual processing. Total trial length: 17.5 s (DR-S, DR-O); 15 s (DSA, DOA). (B) Left: perceptuomotor control tasks for DR-O/DOA. Participants were instructed to always choose the darker green object (correct response signified by the arrow in this diagram). Right: perceptuomotor tasks for DR-S/DSA. Participants were instructed to always select the side with the darker lid. Feedback as in panel A.

1973), and reports of delayed response deficits in persons with frontal brain disease (e.g. Oscar-Berman and Zola-Morgan, 1980) defined a central role for PFC in what is currently labeled as working (Baddeley, 1986) or representational (Goldman-Rakic, 1987) memory. Moreover, delayed response deficits were sensitive to topographically distributed lesions within PFC depending upon subtle manipulations of the original task (see Mishkin, 1964, for an early review), further enhancing the importance of this delay paradigm as a tool for studying structure–function relationships within PFC.

Early investigators altered the nature of the pre-delay cue (e.g. Mishkin and Pribram, 1955; Goldman et al., 1971; Passingham, 1975), demonstrating that lesions to the principal sulcus in the monkey impacted performance primarily on spatial delay tasks, while inferior frontal convexity lesions in the monkey led to deficits on a non-spatial (i.e. color-matching) delay task (Passingham, 1975). More recent reports have questioned this functional division of the PFC based solely on mnemonic domain. They suggest other factors, including the need to inhibit prepotent responses (Mishkin and Manning, 1978), monitoring/manipulation demands (Petrides, 1996) or attention to and selection from items held on line (Rushworth et al., 1997; Rowe et al., 2000), more than the nature of the stimulus cue, might better characterize regional PFC contributions to delay task performance. Indeed, a second classic manipulation of the delay task paradigm involved reversing the reward contingencies after each correct trial (i.e. delayed alternation). Deficits on these alternation tasks appeared to be disrupted by lesions to ventral regions of PFC, irrespective of the type of pre-delay cue (Mishkin et al., 1969).

Relatively less work has been done using these paradigms in humans. A series of 'comparative neuropsychology' studies has sought to transfer the classic delay tasks

to humans (Oscar-Berman and Zola-Morgan, 1980). Most of these studies, however, have used neuropsychological populations with diffuse or multifocal damage (Oscar-Berman and Zola-Morgan, 1980; Freedman and Oscar-Berman, 1986; Kish et al., 1988). While these studies have illuminated the neuropsychological profile of different syndromes using well-defined tasks, they are less specific as to focal lesion-behavior associations. When these same paradigms have been applied to human subjects with focal lesions, the results have been only partially convergent with reports from animal research (e.g. Oscar-Berman and Zola-Morgan, 1980; Freedman et al., 1998; Muller et al., 2002). These findings raise the possibility that the tasks may have different neural substrates in humans and non-human animals.

Numerous functional neuroimaging reports have employed variants of delay tasks designed to dissociate various components of working memory in healthy human populations (for reviews see D'Esposito et al., 1998a; Cabeza and Nyberg, 2000; Curtis and D'Esposito, 2003), yet we know of only three previous functional neuroimaging studies using the original alternation paradigms (Curtis et al., 2000; Zald et al., 2002, 2005), as well as one other that used a hybrid of the original DR-S and alternation paradigms (Gold et al., 1996).

In their positron emission tomography (PET) study, Gold and colleagues (1996) reported extensive prefrontal activation associated with performance on a hybrid delayed response task; a pattern that was attenuated in strength but topographically stable even after a subset of the participants was trained on the task and re-scanned. Curtis et al. (2000) also used PET to investigate performance on the original spatial and object delayed alternation tasks using a brief (1 s) delay interval. They reported prefrontal activity only in a region of orbitofrontal cortex. In a follow-up report, Zald et al. (2002) employed a longer delay (5 s) and again observed activity in orbitofrontal regions associated with both alternation tasks. However, at this longer delay interval they also reported activation within dorsolateral prefrontal cortex (DLPFC) associated with DSA performance. In a recent report, Zald et al. (2005) compared activity during both rule acquisition and practiced performance phases of the object alternation task. The authors found activity in ventral prefrontal and, more specifically, pre-supplementary motor areas was associated with rule acquisition on the object alternation task.

We adopted the original two-alternative delay task paradigm and implemented the two manipulations which have been most commonly reported in the animal lesion literature: mnemonic domain (spatial, object) and alternation demand (high: delayed alternation; low: delayed response). This approach allowed us to map the functional neuroanatomy of healthy human performance across each of the tasks individually, while also enabling us to characterize content- and process-related differences in activity in the PFC and other brain regions. The balanced factorial design allowed us to assess how these task manipulations, which have been so influential in our understanding of structure-functional relationships within PFC, are both commonly and differentially represented in healthy human participants. Given the requirement of equivalent performance across tasks and time limitations in the scanning session, we chose to examine the functional neuroanatomy of practiced performance rather than learning.

EXPERIMENTAL PROCEDURES

Subjects

Ten healthy, right-handed volunteers (mean age: 24.5 years, range: 19–32 years; five males) with no reported history of neurological, psychiatric or significant general medical disease participated in the study. Informed consent was obtained from the subjects according to institutional guidelines established by Baycrest Centre for Geriatric Care. Subjects were compensated for their time.

Experimental tasks

Each participant completed the four experimental and four matched perceptuomotor control tasks during a single scanning session. Three of the experimental tasks (DR-S, DSA, DOA) were designed to replicate delayed response paradigms employed in primate lesion studies (e.g. Mishkin et al., 1969) and human neuropsychological investigations (e.g. Oscar-Berman and Zola-Morgan, 1980; Freedman et al., 1998). A fourth task, DR-O, was included to balance the design across mnemonic domains (spatial, object) and alternation demands. Computerized presentation displays, developed using E-Prime software (Psychology Software Tools, Pittsburgh, PA, USA) (Schneider et al., 2001), reproduced essential parameters of the Wisconsin General Testing Apparatus (adapted for use with human participants as described previously, Oscar-Berman and Zola-Morgan, 1980, and see Fig. 1a). Visual stimuli were presented with the 'Visible Eye' system (Avotec, Inc., Jensen Beach, FL, USA, and SensoMotoric Instruments GmbH, Berlin, Germany), which consists of a pair of lightweight, binocular glasses linked by a flexible fiber optic image guide to an LCD projector.

Visual components of the display were identical across all four experimental tasks (see Fig. 1a). Two covered wells, rendered in three dimensional format, and aligned horizontally, were centered on the video display screen. Objects rendered as facsimiles of those used in the standardized behavioral testing apparatus (Freedman, 1990; Freedman et al., 1998) appeared atop each of the wells in all four tasks. The same objects appeared in all trials across each of the four tasks.

The stimulus display for the perceptuomotor control tasks was as described above with two exceptions: (i) one of the objects (DR-O/DOA control tasks) or well covers (DR-S/DSA) was always darker during the probe and participants were asked to 'always select the darker object (well cover)' (ii) the same (novel) object appeared atop both wells, replacing the two original delay task objects (Fig. 1b.). These modifications to the stimulus display precluded the need for stimulus evaluation, mnemonic processing, decision-making, or response selection while maintaining a tight match to the experimental tasks for visual and motor processing demands.

All trials consisted of four primary components: a visual cue, 10 s delay, response probe and feedback display (see Fig. 1a). Non-alternating task (DR-S/DR-O) trials began with placement of a target stimulus in one of the wells that were then replaced by a black fixation cross on a white background for 10 s. At the end of the delay the original wells re-appeared with lids closed. Subjects selected the location/object where they saw the target appear prior to the delay by pressing one of two response buttons on a keypad held in their right hand (Lumitouch, Lightwave Technologies, Inc., Surrey, BC, Canada). On 'hit' trials the selected well

opened to reveal the target and a happy face appeared to reinforce the correct response. On 'miss' trials the well appeared empty and a sad face was presented. Subjects were asked to respond as quickly and as accurately as possible. If a response was not registered in 3 s, the correct response was shown and a red warning clock appeared to remind participants that they should respond more quickly on subsequent trials. To initiate the alternation tasks, subjects randomly selected a location/object. First trials were always correct and target placement subsequently alternated between locations/objects based on a 'win-shift/lose-stay' rule. Subjects were pre-trained on each experimental task, outside of the scanner, to a 95% criterion level (minimum of 20 trials for DR-S/DR-O; 30 for DSA/DOA).

Each scan series consisted of 16 experimental and 16 control trials for a single condition presented alternately in blocks of four trials following a standard boxcar design. Two consecutive scan series were acquired in each condition for a total of 32 trials per condition. Condition order was pseudo-randomized across participants. A 'blocked' fMRI experimental design was necessitated by the temporal structure of the alternation tasks wherein responses on DSA/DOA trials (other than the first) are contingent upon the results of the immediately preceding trial in the series, precluding the insertion of the intertrial interval necessary for an event-related design.

fMRI

A 1.5-T MRI scanner (Signa, CV/i hardware, LX8.3 software; General Electric Medical Systems, Waukesha, WI, USA) with a standard quadrature birdcage transmit/receive head coil was used for all experiments. A three-dimensional fast spoiled gradient echo pulse sequence (TR=12.4 ms, TE=5.4 ms, flip angle 35 deg, 22×16.5 cm FOV, 256×192 acquisition matrix, 124 axial slices 1.4 mm thick) was used to acquire a T1-weighted volumetric anatomical MRI for each participant. Functional imaging was performed to measure brain activation by means of blood oxygenation level-dependent (BOLD) effect (Ogawa et al., 1992) with optimal signal contrast. Twenty-six axial slices 5 mm thick were obtained using a single shot T2*-weighted pulse sequence with spiral readout, and offline gridding and reconstruction (Glover and Lai, 1998) (TR=2000 ms, TE=40 ms, flip angle 80°, 90×90 effective acquisition matrix, 20 cm FOV). To allow magnetization to reach equilibrium, stimulus presentation was delayed by 20 s after the onset of repetitive fMRI scanning.

fMRI recording and analysis.

Data pre-processing and analyses were performed using Analysis of Functional Neuroimages (AFNI) software. In the pre-processing stage, time series data were spatially co-registered to correct for head motion using a 3D Fourier transform interpolation. Each volume in the time series was aligned to an early fiducial volume from the first imaging run in the scanning session. The alignment parameters were computed by an iterative weighted least square fit to the base volume (19 iterations). The peak range of head motion was less than 1.7 mm for all subjects. Implementation was done using 3dvolreg plugin, part of AFNI software. All data were normalized by deriving the mean for each voxel, across each functional run, and dividing it by the values within that voxel to derive the percent signal change at each time point.

Task-specific and factor-level analyses

The realigned and normalized functional datasets (one per task condition) were submitted to a deconvolution analysis utilizing 3dDeconvolve, part of AFNI software. For each participant, stimulus timing was defined for each task and used to construct a stimulus input waveform. General Linear Tests (GLT's) with one linear constraint were conducted to test whether the statistical model incorporating the stimulus input waveform for each condition (i.e. the full model) was a significantly better predictor of the variance associated with estimated BOLD hemodynamic response than a baseline model (i.e. BOLD response during performance of a perceptuomotor control task+motion correction parameters). For each task condition, the response across task epochs was estimated at four lag times (0–3 TR) to account for variability of hemodynamic characteristics across brain regions and participants. The magnitude of the stimulus response was computed by summing the response parameters over all of these lagged epochs. Only the stimulus-input waveform was modeled from the experimental design; the data themselves determined the functional form of the estimated BOLD hemodynamic response, and as a result the shape of this response varied from voxel-to-voxel. The output consisted of the estimated full model response, along with the statistical significance of the fit of this response to the original functional data, for each voxel in the dataset. In addition to the regression coefficients, F statistics and t statistics for each response parameter and partial F statistics for the task condition were computed.

The resulting individual task activation maps were then transformed into Talairach stereotaxic space (Talairach and Tournoux, 1988; Cox and Hyde, 1997) to account for individual variation of the anatomical landmarks and spatially smoothed with a Gaussian filter of 6 mm full-width-at-half-maximum (FWHM) to increase the signal-to-noise ratio. These last two steps were performed to facilitate the subsequent group analysis, which consisted of a voxel-wise, mixed model, two-factor ANOVA with participants as a random factor and conditions as a fixed factor. Output datasets included mean task vs. control activation maps; task-specific contrast maps (e.g. DR-O vs. DR-S) and factor-level contrast maps (e.g. high vs. low alternation demand). Because the ANOVA was performed on the task vs. baseline contrast images, the degrees of freedom were based on the number of subjects rather than the number of scans. For all comparisons, the statistical cut-off for individual voxel probability was set at $P<0.001$, uncorrected. A Monte Carlo simulation program included with the AFNI software package (Alphasim) was used to determine minimum cluster sizes in order to statistically correct for multiple comparisons across brain regions. Areas of activation with a minimum cluster size of seven acquisition voxels (approximately 350 μl) are reported, representing a probability value of $P<0.05$, corrected for multiple comparisons across the whole brain. Because of our a priori expectations regarding the role of the PFC in these tasks, we also created a mask containing only voxels within PFC. We used this mask to generate a corrected cluster size threshold of >100 μl within PFC following the methods outlined for whole-brain correction as described above.

Global patterns of delay-task related activity

We conducted a conjunction analysis to identify areas of general delay task related activity (i.e. voxels demonstrating evoked response during all four delayed-response task). Conjunction maps of evoked response common to all four delay tasks (contrasted with their respective perceptuomotor control) were produced according to the technique described by Cabeza et al. (2002). Masks were created for each participant, containing only those voxels activated above an individual probability threshold of $P<10^{-5}$. These maps were subsequently transformed into Talairach stereotaxic space (Talairach and Tournoux, 1988; Cox and Hyde, 1997) and spatially smoothed with a Gaussian filter of 6 mm FWHM. Each of the 10 participant conjunction maps was overlaid onto a common conjunction map for the entire sample (Fig. 2). This group conjunction map represents voxels where activation was observed across all tasks ($P<10^{-5}$) in a majority of our participants.

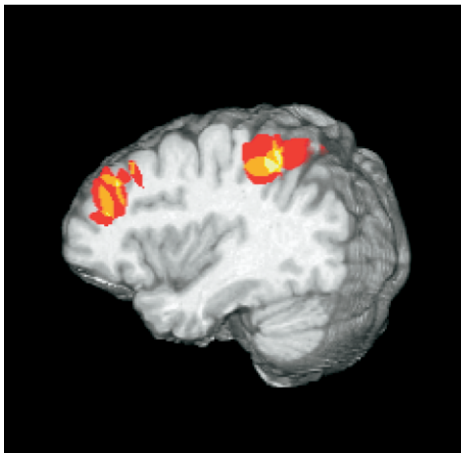

Fig. 2. Conjunction map of delay-task related activity across all tasks and participants. Color scheme indicates percentage of participant sample demonstrating conjunction pattern (red=50%; orange=60%; yellow>70%. X=−37 (left sagittal slice as represented in the grid of Talairach and Tournoux (1988). Maxima reported in Table 2. Details of conjunction analysis in text.

RESULTS

Performance data

The mean percentages of correct trials as well as average reaction time data for each of the experimental tasks are presented in Table 1. Performance differences between tasks were analyzed using repeated measures ANOVA. Significant differences were observed only on reaction time measures across the four tasks, $F(3,36)=4.09$; $P<0.05$. Reaction times were significantly faster for spatial as compared with object tasks (DR-S<DR-O, $t(9)=-3.42$; $P<0.01$; DSA<DOA, $t(9)=-5.91$; $P<0.001$). No reaction time differences were observed when alternation and non-alternation tasks were compared within spatial and non-spatial domains (i.e. DR-S vs. DSA; DR-O vs. DOA).

Functional imaging data

Global patterns of activity related to delayed response performance. Fig. 2 and Table 2 present a conjunction of activations common to all four delay tasks (as compared with perceptuomotor control tasks). Activation peaks, representing voxels where significant evoked response was measured during all four delayed tasks in a majority of our sample, were observed in left anterior prefrontal cortex (aPFC; BA 10), left DLPFC (BA 9) and left inferior parietal lobule (BA 40).

Table 1. Percentage correct and reaction times for delay task performance

Task	% Accuracy (SD)	Reaction time (SD)
DR-S	97.19 (05)	680.93 (242.67)
DR-O	97.19 (05)	881.64 (291.92)
DA	98.44 (03)	625.32 (195.66)
OA	95.62 (06)	932.42 (306.78)

Table 2. Conjunction of BOLD signal increases across all delay tasks relative to perceptuomotor control tasks

Region	Lat.	BA	X	Y	Z
Frontal cortex					
Middle frontal gyrus	L	10	−37	38	20
Middle frontal gyrus	L	9	−32	35	34
Posterior cortices					
Parietal cortex					
Inferior lobule	L	40	−37	−52	47

Coordinates represent voxels of maximal conjunction across tasks and participants. Individual voxel probability threshold of $P<10^{-5}$ (see Experimental Procedures). Coordinates are in standardized space of Talairach and Tournoux (1988). Lat.=lateralization; L=left; R=right.

Task- and factor-specific patterns of activation. Table 3 lists brain regions where significant increases in neural activity were observed when performance on each of the four delay tasks (DR-S, DR-O, DSA, DOA) was compared with their respective perceptuomotor control conditions. DR-S was associated with activity in the aPFC bilaterally (BA 10), bilateral premotor cortex (BA 6), left lingual gyrus (BA 18), lentiform nucleus bilaterally and the anterior lobe of the cerebellum. DR-O was associated with activity in the insular region bilaterally (BA 13), right cingulate gyrus (BA 24) and the right caudate nucleus. DSA evoked activity in the right aPFC (BA 10) and DLPFC (BA 8) as well as in the precentral gyrus bilaterally (BA 6). Posterior activity associated with DSA included the left superior parietal lobule (BA 7) and right middle occipital gyrus (BA 37). Finally, DOA was associated with increases in the bilateral aPFC (BA 10) as well as the left DLPFC (BA 9/46). Posterior activity was observed in left precuneus (BA 7) and the caudate nucleus bilaterally.

Contrasting spatially-cued tasks across levels of alternation demand revealed no significant differences. In a similar contrast involving the object-cued tasks, only a single cluster of activation in right aPFC (BA 10; DOA>DR-O) was observed. This individual task contrast drove an overall main effect of alternation demand observed in the right aPFC (BA 10) associated with high alternation demand. Within mnemonic domain, there were no significant differences observed when DR-S and DR-O tasks were contrasted. A similar contrast at high levels of alternation demand revealed significant differences between DSA and DOA in the right premotor cortex (BA 6; DSA>DOA). An overall main effect of mnemonic domain was observed in the left premotor cortex (BA 6; Object>Spatial).

DISCUSSION

We used fMRI to investigate the functional neuroanatomy of healthy human performance on classic delayed response paradigms. Broadly speaking, our data are in agreement with previous findings of PFC involvement in the classic delay tasks. It appears, however, that different experimental instantiations of these tasks (e.g. animal vs. human, lesion vs. functional imaging) can produce divergent brain-behavior associations within PFC regions.

Table 3. Regions showing BOLD signal increases for each delay task relative to its perceptuomotor control task

Region	Lat.	BA	Delayed response						Delayed alternation					
			Spatial			Object			Spatial			Object		
			x	y	z	x	y	z	x	y	z	x	y	z
Frontal cortex														
Frontopolar														
Medial frontal gyrus	R	10										20	41	11
Inferior frontal gyrus	L	10										−47	52	0
Middle frontal gyrus	R	10	38	49	−5							26	55	−2
Superior frontal gyrus	R	10							33	59	−2			
Superior frontal gyrus	L	10	−26	51	0									
Dorsolateral														
Middle frontal gyrus	L	46										−45	44	29
Middle frontal gyrus	L	9										−52	29	36
Middle frontal gyrus	R	8							36	35	40			
Premotor														
Middle frontal gyrus	R	6	21	−8	51									
Middle frontal gyrus	L	6	−22	−11	49									
Precentral gyrus	R	6							48	0	48			
Precentral gyrus	L	6							−32	−17	65			
Cingulate gyrus	R	24				2	−8	24						
Insula	R	13				31	19	13						
	L	13				−36	17	11						
Posterior/subcortical														
Parietal cortex														
Precuneus	L	7										−28	−45	38
Superior lobule	L	7							−32	−50	60			
Occipital cortex														
Lingual gyrus	L	18	−15	−77	3									
Middle occipital gyrus	R	37							56	−73	3			
Basal ganglia														
Putamen	R		18	23	−1									
Globus pallidus	L		−11	4	0									
Caudate nucleus	R					18	16	14				17	22	0
	L											−18	−9	27
Cerebellum														
Anterior lobe	L		−34	−50	−26	−2	−60	−21						

Individual voxel probability threshold of $t>3.69$; $P<.001$. Only clusters surviving correction for multiple comparisons to $P<.05$ are reported (see Experimental Procedures). All other criteria as in Table 2.

Many of our results would not have been predicted from the animal work, yet, as will be argued below, they are generally consistent with human work, particularly other functional neuroimaging findings.

Global delayed response activity and its modulation by mnemonic domain and alternation demands

Having each of the participants complete all tasks in a single scanning session provided us with the opportunity to examine common patterns of activation during performance of the classic delay tasks. As observed in numerous animal lesion, electrophysiological and human neuropsychological and functional imaging reports, general delay task performance preferentially engaged regions within PFC and posterior parietal cortices. The pattern of activation common to all of the delay tasks employed here closely replicates those found in meta-analyses of human performance on working memory tasks (e.g. D'Esposito et al., 1998a; Cabeza and Nyberg, 2000), supporting the notion that although these tasks were designed for use with non-human primates, they nonetheless engage a well-established pattern of neural activity that is associated with working memory performance in healthy humans.

The general delay task activity observed within DLPFC is consistent with previous findings suggesting a role for this region both in working memory maintenance (Courtney et al., 1998; Rowe et al., 2000; Leung et al., 2002) and executive control processes within working memory (e.g. Petrides, 1996; Owen, 2000). The pattern of left lateralized activity across tasks raises the possibility that our participants may have adopted verbal mnemonic strategies during all four delay tasks. The common left inferior parietal lobule activity—an area considered to be the neural instantiation of Baddeley's 'phonological store' (Awh et al., 1996)—provides further support that our participants may have employed verbal codes to store information across the delay.

While aPFC has been observed in previous functional imaging (Gold et al., 1996; Zald et al., 2002, 2005) and

human neuropsychological studies (Freedman et al., 1998), research on its contribution to working memory performance is in the early stages. Our findings are consistent with an emerging consensus surrounding the role of the aPFC in higher cognitive functions. In a recent review, Ramnani and Owen (2004), expanding on conclusions from existing models of aPFC function (e.g. Koechlin et al., 1999; Christoff and Gabrieli, 2000; Gusnard and Raichle, 2001), proposed that the aPFC is principally engaged during tasks requiring coordination of information processing and information transfer between cognitive operations. In a similar proposal, Burgess et al. (2005) have proposed a more circumscribed coordination function for the aPFC, that of coordinating between stimulus-oriented and stimulus-independent thought.

Each of our tasks requires participants to parse the current contents of working memory from recent trials and to shift their attention from the probe display to the current contents of working memory in order to select a correct response. This coordination is particularly important when responses cannot be made on the basis of novelty, when memoranda are frequently repeated within a task, or when salient but potentially misleading information is present in the environment. In each of our tasks participants were presented with only two stimuli repeated randomly across multiple trials, requiring isolation of the current trial from past trials, which were identical in all aspects except their temporal sequencing. Indeed, anecdotal evidence collected at the time of scanning indicated that participants found that dissociating current from recent trials to be the most challenging aspect of the tasks. Henson et al. (2002) have demonstrated aPFC involvement in the resolution of proactive interference, a specific instantiation of the cognitive coordination role ascribed to the aPFC by Burgess et al. (2005) and Ramnani and Owen (2004). In this respect, our findings of common aPFC activity across all tasks are consistent with these hypotheses regarding the role of the aPFC in higher cognitive functions.

While the role of the aPFC is increasingly investigated in both functional imaging and human neuropsychology reports, little has emerged from the study of non-human primates with respect to function-structure correlations in this region (Ramnani and Owen, 2004). While, aPFC was included in ventral prefrontal resections in earlier delay task studies (Mishkin, 1964; Mishkin et al., 1969), this was not always so (Mishkin and Manning, 1978). In any case, aPFC did not receive much attention in the interpretation of animals' delay task performance. Indeed current theories of aPFC function are derived from studies of humans, who show a greatly expanded BA 10 as compared with other species (Semendeferi et al., 2001).

Task-specific patterns of activation

The following sections review findings associated with each of the delay tasks. In interpreting these findings, however, we are mindful of the fact that direct contrasts of these tasks yielded relatively few differences (see Results) calling into question the convergence of animal lesion and human functional neuroimaging data. Possible explanations for this are discussed below.

DR-S. The bilateral premotor activity observed in relation to DR-S performance (Table 3) is consistent with this region's role in working memory processes (for a review see: Cabeza and Nyberg, 2000), yet DLPFC activation was absent, and we observed bilateral frontopolar activity. Although DR-S is classically associated with the DLPFC in the animal literature (Goldman et al., 1971; Passingham, 1975), lesions restricted to DLPFC do not always disrupt human performance on these tasks (Freedman et al., 1998; Muller et al., 2002). Furthermore, human functional imaging studies do not support domain specificity for the DLPFC in spatial working memory tasks (D'Esposito et al., 1998a; Cabeza and Nyberg, 2000; Owen, 2000), indicating that DLPFC recruitment may not be necessary for human performance on the classic DR-S task.

As discussed above, the aPFC activation is thought to reflect resolution of proactive interference (Henson et al., 2002) and the coordination of cognitive operations more generally (Ramnani and Owen, 2004). Posterior activity was observed in the vicinity of the lingual gyrus, a finding consistent with previous meta-analyses of DR-S performance (D'Esposito et al., 1998a; Cabeza and Nyberg, 2000). Activity was also observed in the basal ganglia, a region implicated in working memory performance in monkeys (Levy et al., 1997) and previous functional imaging reports (Postle and D'Esposito, 1999, 2003).

DSA. DSA was associated with activity in right aPFC, the posterior aspect of the right middle frontal gyrus (BA 8) and posterior premotor cortex (BA 6) bilaterally. Again, aPFC activation is likely related to attenuation of proactive interference and mediating internally-guided responses. Area 8 activity has been demonstrated repeatedly in association with spatial working memory tasks (Rowe et al., 2000; Leung et al., 2002) and working memory for face stimuli (Courtney et al., 1998). Activation in premotor cortices is commonly reported in functional imaging studies of working memory and has been attributed to general working memory processes (Cabeza and Nyberg, 2000) and, more recently, the conversion of working memory into motor programs in monkeys (Ohbayashi et al., 2003). The premotor activations associated with DSA (also significant in comparison to DOA) surround the precentral sulcus (particularly on the right) and may therefore fall within the frontal eye fields, which have been implicated in both working memory and visually-guided saccadic activity in humans and monkeys (see D'Esposito and Postle, 1999). Again, activity was observed in the posterior parietal region (BA 7) consistent with many previous imaging reports (Cabeza and Nyberg, 2000).

Our findings are generally consistent with the observation of DLPFC and pre-motor activity recently reported in imaging studies of human performance on DSA, even after rule acquisition (Gold et al., 1996; Curtis et al., 2000; Zald et al., 2002). However, our center of activation in DLPFC occurred on the right in BA 8 whereas that of Zald et al. (2002) was centered in left BA 9. While the authors pro-

pose that this DLPFC activity may be related to motor preparation rather than working memory processes per se, we did not observe similar DLPFC activity (either left or right) during a DR-S task which has very similar motor preparation demands. Moreover, we did observe activity in left DLPFC during DOA performance, a task in which pre-probe motor preparation was impossible. These disparate findings vis-à-vis the role of DLPFC in DSA and DOA are explored in more detail in the next section.

DOA. DOA performance was related to activation in the aPFC bilaterally. Zald et al. (2005) reported right aPFC activation in association with DOA acquisition proximal to the peak reported here. Our data extend this finding by demonstrating that the aPFC may be involved in alternation task performance post-rule acquisition, consistent with the report of Gold et al. (1996). These researchers directly investigated this effect of practice using a hybrid delayed spatial response/alternation paradigm. They found that while the overall strength of the activation pattern was somewhat attenuated following practice, the spatial patterns of activity remained consistent across practiced and novel task conditions. Practical considerations governed our decision to study practiced performance rather than learning effects. Inter-individual variability in learning curves with these tasks would significantly confound data analysis, as would variability in the rate of acquisition of the response pattern across tasks. Given that this was the first study to investigate this particular configuration of delay tasks using functional neuroimaging, training subjects to an equal performance standard on all tasks was necessary to reduce these confounds, allowing us to focus on task effects uncontaminated by inter-individual or task difficulty. In this respect our data complement the work of Zald et al. (2005) and may serve as a benchmark for the evaluation of future studies assessing learning effects. It is of note that the same focus emerged (right lateralized) in a direct comparison of DOA to DRO.

The absence of ventrolateral prefrontal cortex (VLPFC) activity during DOA performance was unexpected given animal lesion studies implicating the inferior convexity of the monkey brain (homologous to the human VLPFC). The lack of activation in this region may be due to low statistical power or signal drop-off in the vicinity of orbito-frontal and ventrolateral PFC, a region notorious for susceptibility artifact in fMRI scanning. Although the DLPFC activation in association with DOA stands in contrast to previous reports (Curtis et al., 2000; Zald et al., 2002), the findings are consistent with a model of PFC involvement in response selection implicating the middle frontal gyrus (anterior to BA 8) in the *selection* of internal representations held within working memory to guide a subsequent response (Rowe et al., 2000). Additionally, Curtis et al. (2000) and Zald et al. (2002) used a shorter delay epoch (1–5 s), reducing the likelihood of prefrontal activation (Barch et al., 1997). Friedman and Goldman-Rakic (1994), have also reported DLPFC involvement in monkeys during DOA performance with long delays.

Consistent with the findings from DR-S and DSA, a large area of posterior cortical activation was observed in posterior parietal cortex (BA 7). As noted above, left-lateralized posterior activations suggest recruitment of verbal working memory (e.g. D'Esposito et al., 1998b). Caudate activity was observed bilaterally during OA performance, consistent with a recent imaging report in monkeys (Levy et al., 1997).

DR-O. DR-O was not one of the original delayed response tasks, yet the ability to hold non-spatial stimuli (e.g. objects, words, scents) in mind over a delay interval has been investigated extensively in both humans (e.g. Elliott and Dolan, 1999; Dade et al., 2001) and non-human primates (e.g. Passingham, 1975; Wilson et al., 1993; Meunier et al., 1997). When contrasted with a perceptuomotor control task, we found activation in anterior insular cortex bilaterally (BA 13) as well as the cingulate gyrus (BA 24). Insular activity has been reported in two previous studies involving object alternation (Curtis et al., 2000; Zald et al., 2002) and has been associated with voluntary saccadic eye movements as well as voluntary movements of the hand and arm, however, the exact role of this region in delayed response or alternation performance remains uncharacterized. We also observed activity in the caudate nucleus associated with DR-O.

Conclusions and implications for cross-method convergence in PFC

Functional imaging has provided an opportunity to replicate, *in vivo*, in healthy human participants, findings from other experimental platforms, including human lesion studies or investigations with experimental animals. Convergence across lesion and functional neuroimaging studies of basic visual, perceptual, and motor processes is expected; indeed, such studies were important in the original validation of functional neuroimaging applications in humans. For other tasks, convergence has been more elusive. Whereas hippocampal damage is reliably associated with amnesia in humans and animals (Scoville and Milner, 1957; Squire and Zola-Morgan, 1991), hippocampal activation is often not observed in functional neuroimaging studies of memory (Brewer and Moghekar, 2002). This problem is compounded in polymodal cortex (such as the PFC), where brain–behavior associations are less reliable (Mesulam, 1998, see Levine et al., 2005, for a related example concerning convergence across different types of human lesion studies).

The sensitivity of classic delay tasks and their variants to specific lesion sites in animal studies has been highly influential in theories of prefrontal function. These findings have only been partially replicated in human lesion studies (Freedman et al., 1998; D'Esposito and Postle, 1999; Muller et al., 2002). Using fMRI, we found that the classic delay tasks relate systematically to patterns of brain activity in humans, yet these patterns bore more resemblance to other human studies than to findings from the animal literature.

The assumption of cross-method convergence is confounded by a multitude of factors, some technical and some conceptual. In the case of convergence across animal lesion and human functional neuroimaging studies, both species and experimental platform variance must be bridged. A rather ambitious approach to cross-species convergence, eliminating method variance, is to scan healthy monkeys and humans during performance of the same task, as was recently demonstrated for the Wisconsin Card Sorting Test (WCST, Nakahara et al., 2002). With respect to differences in experimental platforms, functional neuroimaging data may identify multiple areas involved in a task without distinguishing among those that are necessary for performance. Moreover, it is not a foregone conclusion that activity in regions critical to task performance will be significantly greater than baseline (Price and Friston, 2002). Functional neuroimaging and behavioral studies, be they human or animal, rely on entirely different dependent measures (i.e. brain activity vs. behavior, regarded as a proxy for brain function). An assumption of convergence across imaging and lesion platforms presumes a correspondence between activity in the healthy human brain is directly related to behavioral output in a lesioned brain, an assumption that is only recently being tested by scanning patients with focal lesions (Price et al., 1999, 2001).

Technical differences aside, tasks reliant on prefrontal function are likely to be performed quite differently in humans as compared with animals because the human PFC is greatly elaborated relative to animals. Beyond the obvious distinction of verbal rehearsal capacity, humans are capable of higher cognitive operations such as episodic recall and self-referential processing. Interestingly, we observed activity common to all four tasks within aPFC, a region previously associated with self-referential processing (e.g. Christoff and Gabrieli, 2000; Ranganath et al., 2003) and coordination of internally-mediated and externally-guided behaviors (Ramnani and Owen, 2004; Burgess et al., 2005; Gilbert et al., 2005). To the extent that such strategies are common across subjects and tasks, patterns of activation in relation to these strategies converge. Accordingly, the commonalities in fronto-parietal activations across tasks in this study (see Fig. 2) overshadowed differences in direct task contrasts. This was particularly true for the aPFC, an area greatly elaborated in humans relative to lower species, and one particularly implicated in higher level strategic operations unique to humans (Christoff and Gabrieli, 2000; Stuss and Levine, 2002).

An example of successful convergence across animal lesion and functional neuroimaging platforms can be found in the self-ordered pointing and conditional associative learning working memory tasks designed by Petrides (1989), who replicated lesion location effects from monkey research in human functional neuroimaging studies (Petrides et al., 1993a,b) (although even with these tasks additional premotor, parietal, frontopolar, and cingulate activity was observed). An important difference between these studies and those involving the delay tasks is that the paradigms used for the former studies were modified and refined for use in humans (for example by increasing stimuli), whereas the classic delay tasks were applied to humans without modification. It is possible that some of our findings (particularly in aPFC) may be attributable to 'noise' introduced by human information processing not fully engaged by these relatively simple tasks. Moreover, variability in human performance on these tasks leaves open the possibility that larger sample-sizes may be required in order to demonstrate reliable differences on tasks developed for use with non-human animals.

Our findings should not be taken to mean that the classic delay tasks cannot be useful in human neuropsychological studies. Indeed, these tasks have already proven useful in multiple comparative neuropsychology experiments (Oscar-Berman and Zola-Morgan, 1980; Freedman and Oscar-Berman, 1986; Kish et al., 1988). Rather, our data caution against the assumption that these tasks are mediated in humans by the same regions implicated in animal studies.

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