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Prefrontal contributions to domain-general executive control processes during temporal context retrieval

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Abstract

Neuroimaging studies have reported increased prefrontal cortex (PFC) activity during temporal context retrieval versus recognition memory. However, it remains unclear if these activations reflect PFC contributions to domain-general executive control processes or domain-specific retrieval processes. To gain a better understanding of the functional roles of these various PFC regions during temporal context retrieval we propose it is necessary to examine PFC activity *across tasks from different domains*, in which *parallel manipulations* are included targeting specific cognitive processes. In the current fMRI study, we examined domain-general and domain-specific PFC contributions to temporal context retrieval by increasing stimulus (but maintaining response number) and increasing response number (but maintaining stimulus number) across temporal context memory and ordering control tasks, for faces. The control task required subjects to order faces from youngest to oldest. Our behavioral results indicate that the combination of increased stimulus and response numbers significantly increased task difficulty for temporal context retrieval and ordering tasks. Across domains, increasing stimulus number, while maintaining response numbers, caused greater right lateral premotor cortex (BA 6/8) activity; whereas increasing response number, while maintaining stimulus number, caused greater domain-general left DLPFC (BA 9) and VLPFC (BA 44/45) activity. In addition, we found domain-specific right DLPFC (BA 9) activity only during retrieval events. These results highlight the functional heterogeneity of frontal cortex, and suggest its involvement in temporal context retrieval is related to its role in various cognitive control processes.

Keywords

episodic memory; working memory; selection; monitoring; face stimuli; fMRI

Introduction

The prefrontal cortex (PFC) has been shown to be important for remembering the relative temporal order of past personal episodes (temporal context retrieval). Patients with damage to

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the PFC exhibit disproportionate deficits in temporal order memory and recency memory, but not recognition memory, compared to healthy controls (McAndrews & Milner, 1991; Milner, Corsi, & Leonard, 1991; Milner, McAndrews, & Leonard, 1990). Functional neuroimaging studies of healthy adults also indicate that the PFC is related to temporal context retrieval. For example, in one functional magnetic resonance imaging (fMRI) study, Suzuki et al (Suzuki et al., 2002) measured brain activity during recognition, between-list recency and within-list recency tasks for pictorial stimuli. It was found that both recency memory tasks engaged bilateral ventrolateral and dorsolateral PFC regions to a greater degree than the recognition memory task. Konishi et al (Konishi et al., 2002) used fMRI to examine temporal order memory retrieval by varying the temporal distance between the two words presented during a recency trial. An increased demand on temporal order recollection (smaller temporal distance) during recency judgments was related to increased activity in bilateral dorsolateral PFC (DLPFC), bilateral medial PFC and left ventrolateral PFC (VLPFC). Therefore, neuroimaging studies have found various regions of PFC to be more active during temporal context retrieval, relative to recognition.

However, functional neuroimaging studies have also reported a distributed pattern of PFC activity during the performance of a variety of cognitive tasks (R.L. Buckner et al., 1995; Cabeza et al., 2004; Cabeza, Dolcos, Graham, & Nyberg, 2002; Cabeza & Nyberg, 2000; Curtis, 2006; D'Esposito, Ballard, Zarahn, & Aguirre, 2000; Duncan & Owen, 2000; Nyberg et al., 2003). For example, in a meta-analysis Duncan and Owen (Duncan & Owen, 2000) reported similar bilateral DLPFC and VLPFC activations across studies examining such diverse cognitive abilities as visual divided attention, auditory discrimination, and task switching, to name a few. In addition, Nyberg et al (Nyberg et al., 2003) examined PFC activity across verbal tasks of semantic, episodic, and working memory, and found there were common left lateralized PFC activations in fronto-polar/anterior PFC (APFC), DLPFC and VLPFC when participants performed these tasks. This overlap in neural activity has been taken to support the prevalent view that the PFC is important for mediating domain-general cognitive control processes (R. L. Buckner, 2003; Stuss & Alexander, 2000; Wagner, Maril, Bjork, & Schacter, 2001). This suggests that increased PFC activity during temporal context retrieval is due to greater demands on cognitive control processes. As such, several neuroimaging studies have focused on examining differences in PFC activity across tasks designed to 'tap into' separate cognitive control processes, and thus identify distinct regions of PFC that are differentially related to specific control processes.

For example, Wagner et al (2001) conducted a functional magnetic resonance imaging (fMRI) study comparing PFC activity during rote verbal rehearsal of three stimuli versus a more elaborate verbal task, in which participants had to mentally reorder triplets of nouns based on subjective desirability. They hypothesized that the rote task engaged phonological working memory (WM) maintenance processes and that the elaborate verbal task engaged these same processes, plus additional monitoring and stimulus/motor selection processes. Monitoring has been broadly defined as the ability to verify that one's behavior is consistent with one's current cognitive or behavioral goal (Henson, Shallice, & Dolan, 1999; Petrides, 2000b). They found that left VLPFC activity was greater during the rote rehearsal task and right DLPFC activity was greater during the more elaborate verbal task. Thus, left VLPFC activity was attributed to WM phonological maintenance processes and right DLPFC activity to monitoring and selection of information from WM. However, it is also possible that other cognitive processes differentiated these two tasks and accounted for the observed PFC activations. For example, the more elaborate verbal task also required the rule-based, controlled, ordering of words; referred to as strategic ordering, which requires WM manipulation (Rajah & McIntosh, 2006). This highlights one of the issues facing neuroimaging studies aimed at identifying specific PFC regions that are differentially related to distinct cognitive processes: often the behavioral tasks contrasted differ on more than one control process.

One way researchers have worked around this problem is to contrast tasks within the same cognitive domain (domain-specific; i.e. within WM or EM), which engage several similar cognitive processes, but differ in the degree to which they engage one or two key processes. For example, in one PET study Nyberg et al (Nyberg et al., 1995) examined brain activity across EM retrieval tasks that differed by how successfully participants performed them, and found a common right VLPFC activity across all tasks, regardless of how successful retrieval was. This result was interpreted as reflecting the importance of right VLPFC in establishing retrieval mode: the cognitive state one has to be in to think back in subjective time while focusing attention on a memory task, which is a domain-specific control process that is active during EM retrieval. Other neuroimaging studies of EM retrieval have linked right APFC and DLPFC activity to domain-specific, EM retrieval-related monitoring processes, since it has been found that activity in these regions differ depending on how successful one performs during EM retrieval (Henson, Shallice, & Dolan, 1999; M.D. Rugg, Fletcher, Frith, Fracowiak, & Dolan, 1996). However, it is not clear from such studies if the executive control processes that engage the PFC are in fact domain-specific or reflect domain-general processes, since the former conclusion would require evidence that similar PFC regions are not related to other domains (i.e. WM).

Therefore, though neuropsychological and neuroimaging studies have highlighted the role of various PFC regions during temporal context retrieval, it remains unclear what control processes these regions are implicated in and if these control processes are specific to temporal context retrieval tasks or not. We propose, in order to gain a better understanding of the roles of distinct PFC regions during temporal context retrieval using the neuroimaging method, it is necessary to examine PFC activity across temporal context retrieval tasks *and tasks from different domains*, in which *parallel manipulations* are included. Moreover, these manipulations should be designed to tap into specific control processes. This was the goal of the current study.

The current event-related fMRI experiment was aimed at dissociating between PFC activations related to domain/task-specific versus domain/task-general cognitive control processes during temporal context retrieval. To do so, we used the following operational definition for temporal context retrieval tasks: *temporal context retrieval tasks involve (i) recognizing the presented stimuli as previously seen (EM retrieval) (ii) maintaining the retrieved mnemonic information in working memory (WM) (iii) the strategic ordering of stimuli, based either on the recollected temporal information or weighted feelings of relative familiarity, (iv) the attentional selection of stimuli, stimulus-response mapping, which inherently involves response selection (collectively referred to as "selection" processes in this paper) and (v) stimulus-guided responding (referred to as " motor control" processes)* (Koechlin, Ody, & Kouneiher, 2003; Moscovitch, 2002; Rajah & McIntosh, 2006; Rowe & Passingham, 2001)). This operational definition does not specify if temporal context retrieval involves temporal recollection or familiarity-based retrieval (Dobbins, Rice, Wagner, & Schacter, 2003; Yonelinas, Otten, Shaw, & Rugg, 2005). Instead, the focus of the current operational definition is on cognitive control processes.

Healthy adults were tested across a series of temporal context retrieval and non-memory ordering tasks while undergoing fMRI scanning. Based on our previous work and that of others (Fuster, 1990; Koechlin, Ody, & Kouneiher, 2003; Koechlin & Summerfield, in press; Rajah & McIntosh, 2006), we hypothesized that some of the PFC activations typically observed during temporal context retrieval reflect their roles in the aforementioned domain-general strategic ordering, selection and motor control processes. Thus, we employed parallel manipulations of stimulus and response number, across memory and non-memory tasks, which were aimed at directly manipulating these specific control processes. By varying the number of stimuli presented, but equating the number of responses required, we manipulated *strategic*

ordering, which is defined as a domain-general, rule-based, controlled sequencing of information (Rajah & McIntosh, 2006); a type of spatio-temporal working memory (WM) manipulation (D'Esposito, Postle, Ballard, & Lease, 1999). By varying the number of responses, but equating the number of stimuli presented, we manipulate *selection and motor control* processes (Hester, D'Esposito, Cole, & Garavan, 2007; Koechlin, Ody, & Kouneiher, 2003; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000; Schumacher, Hendricks, & D'Esposito, 2005). Furthermore, the combined increase in the number of stimuli and responses required across tasks was predicted to increase *task difficulty*. We operationally define task difficulty as a linear, additive, increase in reaction time and decrease in accuracy, within task, as a function of increased stimulus number and response number, that is also correlated with linear increases in neural activity within PFC regions (Koechlin, Ody, & Kouneiher, 2003). Thus, increased task difficulty in the current study context, reflects greater demands on several domain-general control processes, including the aforementioned motor control process. As such, task difficulty could be related to increased activity in PFC overall (Koechlin, Ody, & Kouneiher, 2003), and may interact with PFC activations related to domain-general strategic ordering and selection effects and domain-specific effects. Subjects also performed recognition memory tasks for faces; which served as a retrieval control task. We then examined commonalities and differences in the activation of distinct regions of the lateral PFC (ventral, dorsal and anterior), across these retrieval tasks and non-memory ordering tasks to dissociate between PFC regions that are related to mediating domain/task-general selection, motor control and strategic ordering processes, versus domain/task-specific, retrieval-related, control processes.

Methods

Subjects

Eleven right-handed young adults (four males; mean age = 22.9 yrs old; age range 22–31; mean education = 15.6 yrs) from the San Francisco Bay Area volunteered and were paid to participate in the study. All subjects were screened for any history of major medical, neurological and psychiatric disorders and for a history of substance abuse and psychoactive medication. All participants provided informed consent and the experiment was conducted with approval from the Committee for the Protection of Human Subjects at the University of California, Berkeley.

Behavioral Methods

Stimulus Construction—480 unique black and white photographs of non-famous multi-racial human faces were collected from photograph databases on the internet: 240 age-variant female photographs and 240 age-variant male photographs. The emotional valence/salience and the facial features (including hair) of an individual photograph were randomly varied, and increased how memorable the stimuli used were. Photographs were then grouped into the following age categories: Infant (0–3 yrs old), Child (4–12 yrs old), Teenager (13–19 yrs), Adult (21–39 yrs), Middle Aged to Young Senior Adult (40–65 yrs), Older Senior Adult (66–100 yrs). Each category contained 80 photographs: approximately 40 males and 40 females per age group. The age grouping of each photograph was validated by two separate reviewers and each photograph was labeled by gender and approximate age.

For retrieval and ordering trials requiring only one response, the stimuli were constructed such that there was equal probability that the correct response would appear either on the left, right or center location of the computer screen. For retrieval and ordering trials requiring three serial responses, the stimuli were constructed such that the serial order of button presses varied randomly across trials and across runs.

Task Stimulus/Trial List Construction: Encoding lists for both recognition and recency tasks had a pseudo-randomized sample of 9 stimuli from the six age categories. Each encoding list was screened to ensure that all age groups were represented equally and that there was not a preponderance of males or females in any particular list.

Recognition trials included one photograph from the preceding encoding list and either 1 distracter photograph or 2 distracter photographs. The age and gender of each distracter stimulus was randomized. Recency trials consisted of photographs from the preceding encoding list. The age, gender and temporal 'distance' of each the stimuli included per trial set varied randomly.

Behavioral Tasks—Subjects were told that they would be participating in a visual nonverbal memory experiment in which the stimuli were black-and-white photographs of age variant human faces. Subjects were also informed that they would be asked to perform seven experimental runs, each run consisting of both memory and control tasks, while undergoing fMRI scanning. Each run was 12 min long and there was a brief break between runs. The entire behavioral portion of the experiment took 90 min.

Each run consisted of seven experimental blocks (tasks): one block of recognition (Rg) task, three blocks of recency (R) tasks and three blocks of ordering control (O) tasks; for a total of 7 blocks per run (details of these blocks are presented below). In one run subjects did not have a Rg task to perform. This run consisted of only 6 blocks: three blocks of R tasks and three blocks of O tasks. Blocks were presented in a pseudo-random order, back-to-back. The order of block presentation was counterbalanced across runs and across subjects; for each subject the order in which the runs were administered was randomized. Each block was preceded by a 10 sec instruction screen orienting subjects to which type of retrieval or ordering task would follow. For all retrieval memory tasks, there was a 30 sec break between the encoding and retrieval phases of each task, during which time subjects were reminded what type of retrieval task would follow. The retrieval instructions were on the screen for the entire 30 sec duration to distract participants from using working memory (WM) rehearsal mechanisms to aid subsequent retrieval. Also, the encoding list consisted of nine nonverbal stimuli, which is beyond the maintenance load capacity of the visuospatial scratchpad of 4 visuospatial stimuli (Baddeley & Hitch, 1974; Fougnie & Marois, 2006); thus it is unlikely participants maintained all stimuli within WM during the 30 sec break, prior to retrieval. However, it can still be argued that after reading the retrieval instructions, participants rehearsed and maintained the last four encoding stimuli. Prior cognitive research indicates that, if, there are six or more stimuli between the encoding, and subsequent retrieval, of a particular stimulus, then, the information is being retrieved from secondary/long-term memory (Gershberg & Shimamura, 1994; Simon, Leach, Winocur, & Moscovitch, 1994; Tulving & Colotla, 1970). In the current study 40 % of retrieval events had fewer than six interleaving stimuli between their encoding and retrieval phases. Thus, the behavioral responses to these stimuli may have been based on WM rehearsal and recency effects.

Recognition memory (Rg) tasks: During the encoding phase of these tasks subjects were presented with 9 black and white photographs of age variant human faces, in the center of the computer screen, one at a time. Subjects were instructed to memorize these faces, and that a recognition test would follow. Each encoding stimulus was presented for 2 sec with a variable ITI of either 2.2 or 4.4 or 8.8 sec (mean ITI of 5.13 sec). During the ITI a central white fixation cross was presented on the computer monitor.

After the 30 sec break, the retrieval phase of the task ensued, during which subjects were presented with six retrieval trials. Each retrieval trial was presented for 6 sec with the same variable ITI as that used in the encoding phase. During the retrieval trials of the Rg2s1r task

two black and white photographic stimuli of human faces were presented to the left and to the right of the computer screen, respectively. The center of the computer screen consisted of a centered white fixation cross. Subjects were required to make one button press to indicate whether they recognized the left or the right face from the preceding encoding phase. In the Rg3s1r task each retrieval trial consisted of three black and white photographic stimuli of human faces, which were presented to the left, center, and the right of computer screen, respectively. Subjects were required to make one button press to indicate which one of the three faces they recognized. Subjects were instructed to respond as quickly and as accurately as possible.

Only one Rg block occurred within a given experimental run; with the exception of one run in which there was no Rg block included. Each Rg block had six retrieval trials. Therefore, collapsed across the entire experiment there were 36 Rg retrieval trials for each subject: 18 Rg2s1r retrieval trials and 18 Rg3s1r retrieval trials.

Recency and temporal order memory (R) tasks: Subjects performed the following three types of recency tasks within each run: 2 stimuli-1 response recency task (R2s1r), 3 stimuli-1 response recency task (R3s1r) and 3 stimuli-3 response recency/temporal order memory task (R3s3r). The encoding phases of the three recency tasks were the same as the Rg tasks encoding phases, with the exception that subjects knew they had to memorize the order in which the nine encoding faces were presented.

In the retrieval phase of each recency task, subjects were presented with three retrieval trials per task. Each retrieval trial was presented for 6 sec with the same variable ITI as that used in the encoding phase. Subjects had to make their response during the duration of each trial presentation (6 sec window). During the retrieval trials of the R2s1r task two black and white photographic stimuli of human faces were presented to the left and to the right of the computer screen, respectively. Both faces were from the preceding encoding phase. Subjects were required to make one button press to indicate which of the two faces they remembered seeing most recently. In the R3s1r task each retrieval trial consisted of three black and white photographic stimuli of human faces, which were presented to the left, center, and the right of computer screen, respectively. All three faces were presented in the preceding encoding phase. Subjects were required to make one button press to indicate which one of the three faces they remembered seeing most recently. In the R3s3r task each retrieval trial consisted of three faces presented to the left, center and right of the computer screen, respectively. All three faces were presented in the preceding encoding phase. Subjects were required to make 3 serial responses indicating the reverse temporal order in which the three faces were seen. In all three recency tasks subjects were instructed to respond as quickly and as accurately as possible.

All three R tasks occurred within a given experimental run. Therefore, collapsed across the entire experiment there were 63 R retrieval trials for each subject: 21 R2s1r retrieval trials, 21 R3s1r retrieval trials and 21 R3s3r retrieval trials.

Ordering (O) control tasks: Subjects performed the following three ordering control tasks within each run: 2 stimuli-1 response ordering task (O2s1r), a 3 stimuli-1response ordering task (O3s1r) or a 3 stimuli-3 response ordering task (O3s3r). All ordering tasks consisted of 3 trials per task. Each trial was presented for 6 sec and subjects had to respond during this period of time with the same variable ITI as in previous tasks.

During the O2s1r tasks two black and white photographs of age variant faces were presented on the left and the right of the computer screen, respectively. A fixation cross was presented in the center rectangle. Subjects were required to make one button press corresponding to the photograph depicting the youngest face. During the O3s1r tasks three black and white

photographs were presented on the left, center and right sides of the computer screen, respectively, and subjects were required to make one button press corresponding to the youngest face. In the O3s3r tasks three black and white photographs were presented on the left, center and right sides of the computer screen, respectively. Subjects were required to make three serial button presses ordering the faces according to age, from youngest to oldest. For each ordering task, 2 of the three trials consisted of photographs for which the ages were easily discernible, and one trial consisted of faces that were close in age range. Subjects were told to guess if they could not tell which face was younger than the other. Therefore, all ordering tasks had an equal number of easy and difficult trials. All three O tasks occurred within a given experimental run. Therefore, collapsed across the entire experiment there were 63 O trials for each subject: 21 O2s1r trials, 21 O3s1r trials and 21 O3s3r trials.

Behavioral Analysis—SPSS for Windows (version 11.01) was used to conduct the behavioral analyses. Rg2s1r and Rg3s1r tasks were collapsed to a single Rg task condition because there was no significant difference is subjects accuracy or reaction time (RT; total RT for all responses summed) between these two tasks ($p>0.05$). A within group, repeated measures, one-way Analysis of Variance (ANOVA) was conducted on the subjects RT and accuracy measures to test for a task main effect between Rg, R and O tasks. Post-hoc paired two-tailed t-tests were conducted to clarify ANOVA results at $p<0.05$ corrected for multiple comparisons ($p<0.002$ uncorrected for 21 comparisons).

A within group 2×3 ANOVA was conducted on only R and O tasks to examine task main effects and the significance of the parametric modulation of the number of stimuli (2s vs 3s) and the number of responses across (1 r vs 3r) (referred to as the *task difficulty manipulation* in the remainder of this manuscript), and for task-by-difficulty interactions. Polynomial contrasts were conducted to examine if there was a significant linear change in RT and accuracy as a function of the difficulty manipulation.

fMRI Methods

Data acquisition—A rapid event-related block design was used to acquire fMRI data. Subjects were asked to lie in a supine position in a Varian/Inova (Palo Alto, CA) whole-body 4T scanner equipped with standard radiofrequency (RF) head coil for 2 hrs, while performing seven experimental runs back-to-back. Cushioning was used to restrict head movement. E-prime version 1.1 by Psychology Software Tools Inc. (Pittsburgh, PA, USA) was used to program, run and collect reaction time (RT) and accuracy data for all experimental runs. An LCD projector (Epson, Long Beach, CA) was used to back-project the stimuli onto a projection screen (Stewart, Torrance, CA) in the magnet bore. Subjects viewed the stimuli reflection on a mirror mounted within the head coil (visual angle approx. 4°). Subjects made their motor response using both hands and a four-button fiber optic response system. When responding to stimuli presented on the left side and in the centre of the screen, subjects used their left middle and index fingers, respectively. When responding to stimuli presented on the right side of the screen, subjects used their right index finger to make a button press. Subjects were also outfitted with earphones and a microphone to maintain communication throughout the experimental procedure. After each of the seven experimental runs, subjects had a brief break.

Functional BOLD MRI scans were acquired during each experimental run using a two-shot, interleaved, gradient echo, echo-planar sequence (TR = 0.9923 ms, total true TR = 2.001 sec; TE = 28 ms; FOV = 22.4 cm2, matrix size = 64 × 64, in-plan resolution = 3.5 × 3.5 mm). Eighteen, 5 mm thick, oblique slices, with 0.5 mm interslice gap, were acquired per scan, allowing for whole-brain coverage in all subjects. For each of the six runs in which subjects performed 7 tasks, 360 fMRI images were acquired per subject. For the run in which subjects only performed 6 tasks, 274 fMRI images were acquired per subject. 20 sec of gradient RF

pulses preceded each experimental run to establish steady-state tissue magnetization and minimize startle-related movement during acquisition. Two T1-weighted structural scans were also acquired per subject. At the beginning of the experiment a gradient-echo multislice sequence (GEMS; TR = 200 msec, TE = 5 msec, FOV =22.4 cm2, matrix size = 256 × 256, in-plane resolution = 0.875 × 0.875 mm) was used to acquire a T1-weighted MRI scan that was coplanar to functional scans. At the end of the experimental session, an oblique magnetization-prepared (MP)-FLASH 3-D sequence (TR = 9 msec, TE = 5 msec, FOV = 22.4 × 22.4 × 19.8 cm, matrix size = 256 × 256 × 128, resolution = 0.875 × 0.875 × 1.54 mm) was used to acquire a high-resolution T1-weighted image, to be used in spatial normalization.

Data processing—Images were reconstructed from raw k-space and between-slice time differences were corrected using a sinc interpolation method. Images were converted to ANALYZE format and subsequent image processing was conducted using SPM2 software (http://www.fil.ion.ucl.ac.uk/spm/) run with Matlab 6.5 (www.mathworks.com) on a Linux platform. First, functional images were spatially realigned to the first image acquired, to correct for movement artifact, using a 6 parameter rigid body spatial transform and a least squares approach; then, the functional images were co-registered with the structural images. These images were then spatially normalized to the T1-weighted Montreal Neurological Institute (MNI) template, using 12 parameter affine and nonlinear transformations, to facilitate group analysis. Volumes were resampled into 2-mm cubic voxels and smoothed using an 8 mm full-width half maximum (FWHM) isotropic Guassian kernel, to minimize inter-subject anatomic variability.

fMRI Data Analysis

Random effects group analysis: Random effects group analysis was conducted to task differences in BOLD response using SPM2 (Friston, 2003). Individual subjects' functional images were analyzed for task-related changes in BOLD response using a general linear model (GLM) for the seven experimental runs in SPM2. The following event types were coded as 6 sec epochs (equal to the length of time each event was presented, see behavioral methods above), and convolved with the SPM canonical haemodynamic response function (HRF), and its temporal derivative, and entered into the GLM: Rg2s1r, Rg3s1r, R2s1r, R3s1r, R3s3r, O2s1r, O3s1r, and O3s3r events. Covariates representing the 2 sec encoding epochs, the 30 sec break during Rg and R tasks, and the 10 sec instructions preceding each task were also included in GLM, but these events were not of experimental interest. In addition, head movement parameters were included as covariates of no interest in the GLM. Parameters estimates were computed for each of the aforementioned covariates and reflected changes in BOLD signal per event-type, relative to baseline.

For each subject, experimental effects of interest were then investigated using weighted t-contrast vectors. Domain-specific PFC activity related to Recency events was examined by comparing the three recency events (R2s1r, R3s1r and R3s3r) versus the three ordering events (O2s1r, O3s1r and O3s3r; contrast 1 = 1 1 1 −1 −1 −1). Domain-specific PFC activity related to Ordering events was examined by coding the inverse of contrast 1. Domain-general PFC activity related to increased demands on visual processing/maintenance and search was examined with a t-contrast comparing activity in 3-stimuli recognition, ordering, and recency events versus 2-stimuli recognition, order, and recency events was conducted (Visual Processing Control). This contrast was used as an exclusive mask ($p = 0.01$ uncorrected, spatial extent = 0) during the evaluation of domain-general PFC activity related to the Stimulus Number manipulation which compared increased activity in 3s1r recency and ordering events versus 2s1r recency and ordering events (since events were concatenated as R2s1r, R3s1r, R3s3r, O2s1r, O3s1r, O3s3r, this contrast was coded: −1 1 0 −1 1 0). In addition, domain-general PFC activity related to the Response Number manipulation was examined by

comparing increased activity during 3s3r recency and ordering event versus 3s1r recency and ordering events (this contrast was coded: 0 −1 1 0 −1 1).

A contrast explicitly coding for a linear increase in activity as a function of increase stimulus number and response number (task difficulty manipulation) was not included, since such a contrast would be redundant with the Stimulus Number and Response Number contrasts. Instead it was assumed that regions sensitive to the task difficulty manipulation would be identified in a post-hoc ROI analysis and by plotting the mean beta values of the activated regions of interest (ROI) from the aforementioned contrasts, by event type (see following section on ROI Analyses and Brain-Behavior Correlations for details).

Whole-brain, random effects, one-tailed, group level, t-tests were then conducted on these contrast images, across subjects, to test the null hypothesis that there were no significant, within group, BOLD activity changes related to the contrast(s) of interest. Regional activations in APFC (frontal pole, Brodmann Area [BA] 10), VLPFC (BAs 44, 45, and 47), DLPFC (BA 46 and 9), and premotor cortex (BA 8 and 6) were considered significant if they had a T-value greater than 4.14 ($p < 0.001$, uncorrected) and spatial extent (k) greater than 15 voxels. In defining these regions of interest (ROIs) we used the nomenclature presented by Miller and Cohen (Miller & Cohen, 2001); with the exception of BA 10, which Miller and Cohen (Miller & Cohen, 2001) include as part of orbital and/or medial PFC along with BA 11, 12 and 13, and we refer to as APFC, consistent with Owen and colleagues (Ramnani & Owen, 2004; Simons, Owen, Fletcher, & Burgess, 2005). Activations within these ROIs were identified by converting the SPM results to Talairach coordinate space and by reference to the Talairach and Tournoux atlas (Talairach & Tournoux, 1988).

Second Level Regions of Interest Analysis: The results from the random effects group analysis were used to define functional regions of interest (ROIs; see Table 1 below). ROIs were created for each activation clusters within DLPFC (BA 9), lateral premotor cortex (BA 6/8) and VLPFC (BA 44/45) activations, listed in Table 1. MRIcro software was used to create functional ROIs consisting of contrast-related supra-threshold voxels within the PFC (http://www.psychology.nottingham.ac.uk/staff/cr1/mricro.html). Marsbar software (http://marsbar.sourceforge.net/) was used to extract each ROI's mean BOLD parameter estimate value (beta value) for each retrieval and ordering event-type, for each subject (ROI plot).

Second Analysis of Task Difficulty and Brain-Behavior Correlations for PFC ROIs related to the Stimulus Number and the Response Number Contrasts from the Random Effects Group Analysis: SPSS for Windows (version 11.01) was then used to conduct 2 (task) × 3 (difficulty) ANOVAs, with linear contrasts, of the mean parameter estimates for frontal cortex ROIs that appeared to exhibit linear increases in activity during recency and/or ordering tasks, as a function of task difficult, based on the ROI plots. The linear contrasts tested if there was a significant linear increase in the mean parameter estimate for a given ROI from 2s1r to 3s1r to 3s3r, collapsed across recency and ordering event types and also if there was a significant task-by-linear contrast interaction, to determine if there were task differences in linearity. In addition, group level correlations between the mean event-related parameter estimate for each ROI, and the mean event-related reaction times and accuracy scores, were computed across recency and ordering event types to determine if there was a significant correlation between ROI activity and behavioral performance, related to the task difficulty manipulation ($df = 4$, $p < 0.05$, $r = 0.811$).

The primary purpose of this post-hoc ROI analysis was to identify those significantly activated frontal cortex regions, from the SPM2 GLM results, that also exhibited a task difficulty effect. A frontal cortex ROI was considered to be related to task difficulty, if it: (a) exhibited

a significant linear effect in activity for ***both*** recency and ordering event types (i.e. a significant linear contrast effect; and non-significant task-by-linear contrast interaction) *and* (b) activity in the region correlated with slower RT and lower accuracy across 2s1r, 3s1r and 3s3r events. Microsoft Excel (2000) was used to plot bar graphs depicting the group averaged activation profiles for ROIs in support of the ANOVA results. Post-hoc paired one-tailed t-tests were conducted to clarify ANOVA results at $p<0.05$.

Second Level Factorial ANOVAs: Examining Dissociations in PFC ROIs related to the Stimulus Number and the Response Number Contrasts from the Random Effects Group Analysis: SPSS for Windows (version 11.1) was used to conduct two sets of factorial ANOVAs to directly compare activity between different ROIs, and determine if there were dissociations in the ROIs' sensitivity to (i) the stimulus number manipulation and (ii) the response number manipulation (Henson & Mouchlianitis, 2007). Four ROIs were identified as being differentially related to the stimulus versus the response number manipulations, based on the random effects analysis (see Table 2): Right BA 6/8 (related to the stimulus number manipulation), and three Left Lateral PFC ROIs that were more related to the response number manipulation (two ROIs from Left BA 9, and one from Left BA 44/45; see Table 1 for exact coordinates of these ROIs). First, overall 4 × 2 × 2 factorial ANOVAs were conducted to compare activity in all four ROIs as a function of task type (Recency memory versus Ordering tasks) and the stimulus or response number condition. In the ANOVAs investigating dissociations in ROI activity related to stimulus number Recency and Ordering 2s1r events were compared to Recency and Ordering 3s1r events. In the ANOVAs investigating dissociations in ROI activity related to response number Recency and Ordering 3s1r events were compared to Recency and Ordering 3s3r events. In addition 2 × 2 × 2 factorial ANOVAs were conducted to compare right BA 6/8 ROI activation with each of the three left lateral PFC ROIs' activations, in relation to the stimulus number and the response number manipulations, respectively, since the random effects analysis indicated that right BA 6/8 was related to stimulus number, whereas the left lateral PFC ROIs were related to response number. For the factorial ANOVAs examining dissociations in ROI activity as a function of stimulus number, a significant ROI*Stimulus number interaction ($p < 0.05$) was taken as support of such a dissociation. Similarly, for the factorial ANOVAs examining dissociations in ROI activity as a function of response number, a significant ROI*Response number interaction ($p < 0.05$) was taken as support of such a dissociation. The rationale for these factorial ANOVAs was to determine if there were regional dissociations in domain-general PFC activity in relation to the stimulus number versus the response number manipulation, which would be supported by directly comparing activity between ROIs.

Results

Behavioral Results

Reaction time—Due to computer malfunction, we only had behavioral data for 10 of the 11 subjects tested. Figure 1(A) presents the within group, mean reaction time (RT) in msec per event type. There was significant differences in RT across event types (one-way repeated measures ANOVA, $F(6,54) = 85.77$, $p<0.001$). The paired t-tests show that recognition (RG) RT was significantly faster than R3s1r, R3s3r and O3s3r, but slower than O2s1r RT ($p<0.05$ corrected for multiple comparisons). R3s3r RT was longer than all other event type RTs and there was not a significant difference in RT between R2s1r and R3s1r events. In addition, O3s3r RT was not significantly different from R3s1r and R2s1r RT, but was slower than O2s1r and O3s1r RT. O2s1r RT was not significantly faster than O3s1r RT.

The 2×3 repeated measures ANOVA comparing recency and ordering tasks indicated there were significant task ($F(1, 9) = 94.03$, $p < 0.001$) and difficulty ($F(2, 18) = 146.90$, $p< 0.01$)

main effects, but not a significant task-by-difficulty interaction ($F(2,18) = 1.63$, $p > 0.05$). In addition, there was a significant linear increase in RT across 2s1r, 3s1r, and 3s3r, versions of tasks, collapsed across tasks type ($F(1,9) = 194.05$, $p<0.001$) and no significant task-by-difficulty linear effect ($F(1,9) = 2.78$, $p>0.05$). Therefore, RT increased as a function of increased stimulus number and increased response number, indicating that these parametric manipulations successfully increased RT and thus task difficulty.

Accuracy—A bar graph depicting the average percent correct (accuracy), per event type, is presented in Figure 1(B). There was a significant difference in accuracy across task ($F(6,54) = 30.33$, $p < 0.001$). The post-hoc paired t-tests indicate that in general O2s1r events were significantly easier than all other event-types, except O3s1r events. R3s3r and R3s1r events were significantly more difficult than all other event types, but were not significantly different in difficulty from one another. Recognition (RG) accuracy was not significantly different from 2s1r recency and ordering accuracy or O3s1r accuracy, but was significantly better than O3s3r, R3s1r and R3s3r events. These results indicate that RG accuracy was not significantly different from R2s1r, but was significantly better than R3s1r and R3s3r events.

The 2×3 repeated measures ANOVA of accuracy during recency and ordering tasks indicated there were significant task ($F(1,9) = 72.07$, $p < 0.001$) and difficulty ($F(2,18) = 32.62$, $p < 0.001$) main effects, and a significant task-by-difficulty interaction ($F(2,18) = 4.30$, $p = 0.03$). There was also a significant linear decrease in accuracy across 2s1r, 3s1r and 3s3r tasks, collapsed across task types ($F(1,9) = 76.82$, $p < 0.001$), and a significant task-by-difficulty linear effect ($F(1,9) = 10.11$, $p = 0.011$). These results indicate that the parametric manipulations significantly impacted task accuracy during both recency and ordering tasks; however, the recency tasks were on average more difficult than ordering tasks and the parametric manipulations increased recency task difficulty to a greater degree.

fMRI Results

The statistically significant ($p <0.001$, uncorrected) SPM2 random effects group analysis results are presented in Table 1 n for each of the pre-specified contrasts. At the thresholds specified there were no significant frontal cortex activations related to the Ordering > Recency retrieval events contrast or related to the Visual Processing Control contrast. Significant group mean correlations between ROI activity and accuracy and RT are also highlighted in Table 1.

Recency Retrieval > Ordering Contrast—The random effects group analysis identified greater activity in bilateral DLPFC (BA 9) during Recency Retrieval versus Ordering events (see Figure 2A). Figure 2B presents a bar plot depicting the mean beta values for the right DLPFC ROI (BA 9) during recognition, recency and ordering events (ROI plot). The ROI plot for the left DLPFC ROI is presented in a later section.

The post-hoc ROI ANOVAs and linear contrasts indicate that there was as a marginally significant linear increase in right DLPFC activity across 2s1r, 3s1r and 3s3r events ($F(1,10) = 3.89$, $p = 0.08$), and no significant task-by-linear contrast interaction ($F(1,10) < 1$). However, the ROI plot presented in Figure 2B indicates that the near significant linear increase in right DLPFC activity was driven by the recency event types, since activity in this region was near to zero during both 3 stimulus ordering events; consistent with the random effects group results. Brain-behavior correlations for right DLPFC indicated that increased activity in this region was negatively correlated with task accuracy and positively correlated with RT. Given the random effects results and the ROI bar plot in Figure 2B indicating that this region was related to recency retrieval; we also examined brain-behavior correlations within even type, to determine if right DLPFC activity was correlated to task accuracy and RT for *both* recency and ordering events. We observed a significant correlation between right DLPFC activity and

recency accuracy ($r = 0.99$, $p < 0.05$, with $df = n-2 = 1$), but not ordering accuracy ($r = -0.69$, $p > 0.05$). A marginally significant correlation was observed between right DLPFC activity and recency RT ($r = 0.95$, $p > 0.05$) and no significant correlation was observed between right DLPFC activity and ordering RT ($r = 0.47$, $p > 0.05$). These correlations suggest that right DLPFC activity was related to recency accuracy and RT, but not ordering accuracy and RT.

Figure 2B also indicates that activity within right DLPFC was similar during both recognition and R2s1r events, which is consistent with post-hoc one-tailed paired t-tests results indicating that recency retrieval-related activity in right DLPFC did not significantly differ between recognition and R2s1r ($p = 0.50$), even though the latter event type in each comparison contained a greater number of familiar events than the former.

Post-hoc one-way ANOVAs with simple contrasts were conducted to examine if right DLPFC activity was modulated by either the stimulus or response number manipulations within ordering event types and within recency event types. No significant difference in mean right DLPFC activity was observed across O2s1r, O3s1r and O3s3r events ($F(2,20) = 1.04$, $p = 0.37$). Similarly, no significant difference in meant right DLPFC activity was observed across R2s1r, R3s1r and R3s3r events ($F(2,20) = 1.95$, $p = 0.17$). These post-hoc ANOVAs indicate that right DLPFC activity was not modulated by the stimulus number nor the response number manipulations within either recency or ordering event types; and that the observed variance in right DLPFC activity within ordering events and within recency events in Figure 2B were not significantly different. Therefore, right DLPFC activity was: (i) related to retrieval events (ii) increased linearly across R2s1r, R3s1r and R3s3r events (iii) correlated negatively with recency accuracy and positively with recency RT and (iv) similar during recognition and R2s1r event types.

The post-hoc ROI analysis indicated that left DLPFC exhibited a significant linear increase in activity across 2s1r, 3s1r and 3s3r events ($F(1,10) = 9.07$, $p = 0.01$), and a marginally significant task-by-linear contrast interaction ($F(1,10) = 3.57$, $p = 0.09$). Within task, linear contrast analysis indicated that this latter interaction effect was due to left DLPFC exhibiting a non-significant linear effect across recency events ($F(1,10) < 1$), but a significant linear effect across ordering events ($F(1,10) = 11.58$, $p = 0.007$). The brain-behavior correlations indicated that increased activity in left DLPFC was negative correlated with task accuracy and positively correlated with task RT. Therefore, on average left DLPFC activity was greater during recency events versus ordering events; however, this region also exhibited a strong linear increase in activity across 2s1r, 3s1r and 3s3r ordering events. Furthermore, Table 1 shows that a similar region left DLPFC region was also identified in the response selection, random effects results. This is discussed further in Response Selection Contrast section below.

Stimulus Number Manipulation—The random effects group analysis identified greater domain-general activity in right anterior lateral premotor cortex (BA 6/8) during 3 stimuli recency and ordering events versus 2 stimuli recency and ordering events. Figure 3A presents the spatial location of this ROI super-imposed on structural MRI template, and also the ROI plot for this region. The ROI plot corroborates the random effects contrast result. Furthermore, post-hoc paired t-tests found that right BA 6/8 activity was significantly different between 3s1r and 2s1r recency and ordering event-types ($p<0.05$), but not between 3s3r and 3s1r ($p>0.05$). Therefore, right anterior lateral premotor cortex activity was related to the domain-general stimulus number manipulation in the current experiment.

Response Number Manipulation—The random effects group analysis indicated that the response number manipulation was related to increased activity in left DLPFC (BA 9) during recency and ordering tasks, which was significantly correlated with reduced task accuracy, and increased RT. This ROI is similar in spatial location to the left DLPFC (BA 9) ROI identified

from the aforementioned Recency/Familiarity Retrieval contrast. Figure 3B shows these two left BA 9 ROIs superimposed on a T1-image template, to highlight their similar spatial locations, and the mean activity plot for these two ROIs. The activation patterns of these two left DLPFC ROIs were similar. For example, the post-hoc linear contrast analysis of the left DLPFC ROI identified in the response number contrast showed there was a significant linear increase in left DLPFC activity across 2s1r, 3s1r and 3s3r events ($F(1,10) = 11.70$, $p = 0.007$), and a marginally significant task-by-linear contrast interaction effect ($F(1,10) = 3.17$, $p = 0.11$). Within task, linear contrast analysis indicated that this latter interaction effect was due to left DLPFC exhibiting a significant linear increase in activity across 2s1r, 3s1r and 3s3r events during ordering events ($F(1,10) = 10.65$, $p = 0.01$), but only a marginal linear effect during recency events ($F(1,10) = 4.07$, $p = 0.07$). This pattern of linear effects is similar to that observed in the Recency Retrieval contrast left DLPFC ROI.

Post-hoc one-tailed paired t-test showed that activity in both left DLPFC ROIs was not significantly different between R3s3r versus O3s3r ($p > 0.05$). In addition, activity in both left DLPFC ROIs was correlated with lower task accuracy and longer task RT. Taken together, these findings indicate that activity in left DLPFC (BA 9) may have been related to a domain general task difficulty effect since activity in both ROIs increase across 2s1r, 3s1r and 3s3r events and correlated with reduced task performance. However, given that in both left DLPFC ROIs there was: (i) a near significant task-by-linear contrast interaction effect, due to left DLPFC activity not exhibiting a linear effect across recency events (ii) greater left DLPFC activity, on average, during recency events versus ordering events (Recency Retrieval-related main effect) (iii) greater left DLPFC activity during 3 response versus 1 response events during ordering events (response number manipulation) and (iv) there was no significant difference in left DLPFC during O3s3r versus R3s3r events, suggest that left DLPFC activity in this experiment was not related to task difficulty but may instead be related to the response number manipulation.

The random effects response number contrast also identified an ROI in left VLPFC (BA 44/45; see Figure 3C). The post-hoc analysis indicated there was a significant linear contrast effect in this region ($F(1,10) = 20.19$, $p = 0.001$); there was no significant task-by-linearity interaction effect ($F(1,10) = 1.79$, $p = 0.22$). Therefore, activity in left BA 44/45 increased linearly across 2s1r, 3s1r and 3s3r events; however, group mean activity in this region was *not significantly correlated with group mean task accuracy or RT*. Post-hoc one-tailed paired t-tests indicate that left BA 44/45 activity was greater during 3s3r versus 3s1r for both recency and ordering event-types ($p<0.05$), but was not significantly greater during 3s1r versus 2s1r recency events ($p > 0.05$); confirming that activity in this region was sensitive to the response number manipulation. A post-hoc 2 (task) X 3 (difficulty) ANOVA of this region confirms that mean activity was not significantly different during recency versus ordering events ($F < 1.0$ for task main effect), which is why this region was not identified in the Recency/Familiarity Retrieval contrast. Thus activity in left BA 44/45 exhibited a response number effect.

Second Level Factorial ANOVAs: Direct Comparison of PFC ROIs related to the Stimulus Number and the Response Number Contrasts from the Random Effects Group Analysis—Table 2 presents the results from the factorial ANOVAs conducted to directly compare activity in each ROI selected from Table 1 in order to determine if there were simple dissociations between the ROIs' sensitivity to the stimulus number manipulation versus the response number manipulation. The Stimulus Number factorial ANOVAs indicate that overall there was no significant ROI*Stimulus interaction ($p>0.05$); however, the $p = 0.12$ can be considered marginally significant given the small sample size. This suggests that there were dissociations amongst the four ROIs sensitivity to the stimulus number manipulation. The comparisons of the right BA 6/8 ROI with each of the left PFC ROIs, indicate that there was a significant ROI*Stimulus interaction between right BA 6/8

versus left BA 9 (selected from the recency > order random effects contrast) and a marginal ROI*Stimulus effect between right BA 6/8 and left BA 9 (selected from the response number contrast). There was no significant ROI*Stimulus interaction effect for right BA 6/8 versus left BA 44/45. These results suggest that there was no dissociation in right BA 6/8 and left BA 44/45 sensitivity to the stimulus number manipulation; however there was dissociation in right BA 6/8 versus left DLPFC sensitivity to the stimulus number manipulation. Given that the random effects analysis indicated that right BA 6/8 activity was related to stimulus number manipulation and left DLPFC activity was related to the response number manipulations; the Stimulus Number factorial ANOVA results indicate that right BA 6/8 ROI was more sensitive to the stimulus number manipulation compared to the left DLPFC ROIs.

The Response Number factorial ANOVAs indicate that overall there was a significant, ROI*Response interaction effect ($F(1,3) = 8.27$, $p < 0.0001$). The 2 ×2 ×2 Response Number ANOVAs comparing right BA 6/8 to each of the three left PFC ROIs, indicate there was a significant ROI*Response interaction effect between right BA 6/8 and left BA 44/45 and between right BA 6/8 and left BA 9 (selected from the response number contrast). In addition, there was a marginally significant ROI*Response interaction between right BA 6/8 and left BA 9 (selected from the recency > ordering contrast). Taking the random effects results into consideration, these ANOVA results indicate that there was a dissociation between the right BA 6/8 ROI and all three left PFC ROIs' sensitivity to the response number manipulation: right BA 6/8 activity was not sensitive to this manipulation, whereas all three left PFC ROIs were (see Figure 3 and Table 2).

Discussion

Neuroimaging studies have highlighted the role of various PFC regions during temporal context retrieval (Cabeza, Anderson, Houle, Mangels, & Nyberg, 2000; Dobbins, Rice, Wagner, & Schacter, 2003; Dudukovic & Wagner, 2007; Konishi et al., 2002; Suzuki et al., 2002). However, it remains unclear which of these PFC activations are related to mediating domain or task-specific cognitive control processes such as, recollection-based retrieval monitoring, familiarity-based retrieval monitoring, retrieval success and establishing retrieval mode (Dobbins, Rice, Wagner, & Schacter, 2003; Henson, Shallice, & Dolan, 1999; Nyberg et al., 1995; Yonelinas, Otten, Shaw, & Rugg, 2005) and which are related to mediating domain-general cognitive control processes including strategic ordering and controlled selection processes, to name a few (Moscovitch, 2002; Rajah & McIntosh, 2006; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000; Schumacher, Elston, & D'Esposito, 2003).

To effectively dissociate domain-specific versus domain-general frontal cortex activity during temporal context retrieval we examined frontal cortex activity across temporal context retrieval and a non-memory ordering task, in which parallel parametric manipulations, targeted at modulating specific cognitive control process, were included. Parallel increases in stimulus number (with response number maintained), and in response number (with stimulus number maintained) were incorporated across task domains to determine which frontal regions that were active during recency retrieval were related to mediating domain-general cognitive control processes that may be related to these parametric manipulations. It was hypothesized that increasing stimulus number would increase demands on strategic ordering processes that are defined as a domain-general, rule-based, controlled sequencing of information (Rajah & McIntosh, 2006) requiring spatiotemporal working memory (WM) manipulation (D'Esposito, Postle, Ballard, & Lease, 1999). Similarly, increasing response number was hypothesized to increase demands on controlled selection processes required for the attentional selection of stimuli and stimulus-response mapping (which inherently involves response selection) (Boettiger & D'Esposito, 2005; Fuster, 1990; Hester, D'Esposito, Cole, & Garavan, 2007; S.L. Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997) and motor control processes (Koechlin,

Ody, & Kouneiher, 2003). Participants also performed recognition tasks while undergoing scanning. Stimulus number, but not response number, was increased during recognition to identify frontal regions that may respond to increased demands on on-line visual search and processing during retrieval. In addition, by including the recognition task we were able to ascertain which frontal activations were related to domain-specific retrieval-related control processes, such as familiarity-based retrieval monitoring (Dobbins, Rice, Wagner, & Schacter, 2003; Dudukovic & Wagner, 2007).

The effect of increasing both stimulus and response number across temporal context retrieval and ordering tasks was predicted to manipulate task difficulty. In general, increased task difficulty was expected to increase demands on several cognitive control processes, and increase activity in frontal cortex, overall (Koechlin, Ody, & Kouneiher, 2003). Thus, it was likely that regions related to domain-general strategic ordering and response selection and to domain-specific processes would exhibit these effects *and* a task difficulty effect. However, in the current study we employed a more restrictive operational definition for identifying regions that were solely related to the task difficulty manipulation: PFC regions related to task difficulty were those that exhibited a linear increase in activity, as a function of increased stimulus and response number, across *both* recency and ordering event types, which *also* correlated with slower RT and lower accuracy. In the following sections we will discuss those frontal regions that were differentially related to domain-general strategic ordering and selection and motor control processes and those related to domain-specific recency retrieval-related control processes.

Stimulus Number Manipulation: Right Lateral Premotor Cortex

In the current study we observed greater right lateral premotor activity (BA 6/8) during 3 stimuli versus 2 stimuli events during both recency retrieval and ordering events. Activity in this region was not related to increased demands on visual processing during the presentation of three versus two stimuli, since this region was observed after exclusively masking out activations related to this possible confound; nor was activity in this region sensitive to the response number manipulation, as shown by the second level Response Number factorial ANOVA directly comparing activity in this ROI with activity in left PFC ROIs and by the post-hoc paired t-test results (see Figure 3A and Table 2).

Previous fMRI studies of recency memory have also reported greater activity in right BA 6/8 during recency memory tasks (Dobbins, Rice, Wagner, & Schacter, 2003; Dudukovic & Wagner, 2007). Moreover, Dudukovic and Wagner (2007) found that greater right BA 6/8 activity during correct recency decisions, versus correct novelty decisions; indicating that activity in this region is related to processes important for making correct recency judgments. In the current study, activity in right BA 6/8 was found to be related to the stimulus number manipulation. As mentioned above, the stimulus number manipulation during recency retrieval and ordering events was incorporated into the experimental design to identify domain-general PFC activations related to strategic ordering processes (defined above) (D'Esposito, Postle, Ballard, & Lease, 1999; Rajah & McIntosh, 2006); since increasing stimulus number, but not response number, was assumed to result in subjects sequentially ordering, and/or manipulating, a greater number of events, based on temporal recency or age, prior to making a single response. Unfortunately, due to the small number of events in the current study, and the relatively poor performance on the more difficult recency events-types, we were unable to determine if right BA 6/8 activity was greater for correct versus incorrect recency and ordering events in the current experiment. However, the results from the current study do show that increased activity in this region was not specific to recency retrieval, but instead reflects the importance of this region in *domain-general* cognitive control processes that are sensitive to increasing stimulus, but not response, number in tasks requiring sequential ordering of stimuli. Therefore, right BA

6/8 activity in the current experiment may reflect its role in rule-based sequential ordering of visual stimuli (strategic ordering processes) which would involve spatiotemporal WM manipulation.

Interestingly, in a previous fMRI study using a delay task with spatiotemporal stimuli Rowe et al (Rowe & Passingham, 2001) found premotor cortex (BA 8, more posterior and dorsal to our current activation foci) activity during the delay period, while subjects were required to maintain the relative temporal order and spatial location of the stimuli presented, prior to selecting a response. In the current study the spatial information necessary for selecting a correct response did not need to be maintained in WM, since stimuli were on the screen during recency and ordering events; however, during recency retrieval maintenance of temporal order information in WM would have been necessary. Although, it can be argued that in the current study the mental representations of the spatial location of stimuli on the computer screen needed to be maintained and manipulated in WM whilst subjects performed the serial ordering demands of these tasks, and that right lateral premotor activity in the current study may reflect this spatiotemporal WM maintenance and/or manipulation. Therefore, it is possible that right lateral premotor cortex activity was related to spatiotemporal WM maintenance. Alternatively, it is possible that in the previous study by Rowe et al. (2001), premotor cortex activity was not simply related to passively maintaining spatiotemporal information but to rehearsing the relative temporal and spatial order of the stimuli. Thus, in both the current study and the study by Rowe et al. (2001) it is possible that premotor cortex (BA 6/8 and 8) activity was related to the visual spatiotemporal WM manipulation and/or maintenance processes required for the rehearsal of stimuli and for the rule-based sequential ordering of stimuli (strategic ordering processes). Future studies need to be conducted to distinguish whether this regional activation was more related to the spatiotemporal WM maintenance demands of recency and ordering events or to the spatiotemporal WM manipulation demands of these events.

Response Number Manipulation: Left Lateral PFC

The response number manipulation in the current study was included to identify PFC activity related to selection processes, which was defined as a domain-general control processes related to the attentional selection of stimuli and stimulus-response mapping, and to motor control processes. Two left lateral PFC regions were related to response selection processes: left DLPFC (BA 9) and left VLPFC (BA 44/45; Broca's Area). However, left BA 9 also exhibited a recency task main effect, and activity in this region was negatively correlated with better task performance. In addition, the second level Stimulus Number factorial ANOVA indicated that left BA 9 activity was relatively insensitive to increases in stimulus number, but was significantly sensitive to increases in response number, compared to the right BA 6/8 ROI discussed above. In contrast, activity in left BA 44/45 was *not* correlated with task performance and was *not* greater during recency retrieval events versus ordering events. Furthermore, the second level Stimulus Number factorial ANOVA indicated that left BA 44/45 was not significantly different from right BA 6/8 in sensitivity to the stimulus number manipulation, but was significantly different from right BA 6/8 in sensitivity to the response number manipulation. This suggests that left BA 44/45 activity was impacted by both stimulus and response number manipulations whereas left BA 9 activity was only impacted by the response number manipulation; indicating that these two left lateral PFC regions may be related to mediating different components of selection and/or motor control processes.

The observed left BA 44/45 activation, in Broca's area, was strongest during 3 stimuli and 3 response events, which required the attentional selection of three stimuli and three stimulus-response mappings. Given, that Broca's area is important for both overt and covert language production (Mayer, Xu, Pare-Blagoev, & Posse, 2006), it is likely that activity in this region reflected covert verbalizing during stimulus selection and stimulus-response mapping.

Alternatively, activity in left BA 44/45 may have been related to verbal WM maintenance (D'Esposito, Postle, Ballard, & Lease, 1999; Roth, Serences, & Courtney, 2006). Considering that activity in this region was sensitive to both the stimulus number and response number manipulations supports the possibility that left BA 44/45 was related to increased verbal WM maintenance necessary for the use of verbal 'labels' (Binkofski & Buccino, 2004; Henson, Burgess, & Frith, 2000) during the attentional selection of stimuli (S. L. Thompson-Schill, D'Esposito, & Kan, 1999). Due to limitations in our experimental design we are unable to distinguish between possibilities that left BA 44/45 activity in the current study was related to covert verbalizing, WM maintenance, stimulus selection or to establishing stimulus-response associations. However, given that DLPFC is generally more associated with establishing stimulus-response associations (Boettiger & D'Esposito, 2005; Fuster, 1990; Hester, D'Esposito, Cole, & Garavan, 2007) we feel it is likely that left BA 44/45 activity in the current study was related to covert verbalising which would inherently engage stimulus selection and possibly verbal WM maintenance.

We also observed left BA 9 activity to be greater during 3 response recency and ordering events. Activity in this region was: (i) on-average greater during recency retrieval events versus ordering events (Recency Retrieval random effects group analysis result), (ii) greater during 3 versus 1 response events (Response Number random effects group analysis result) and (iii) correlated with task performance, but was *not* differentially active during R3s3r versus O3s3r events. In addition, post-hoc linear contrast analysis indicated activity in left BA 9 increased across 2s1r, 3s1r and 3s3r ordering events. The behavioural results show that on average recency events were more cognitively complex and demanding. Given that left BA 9 was in general more active during recency events and activity in this region was negatively correlated with better task performance, one may argue that increased left BA 9 activity reflected monitoring and errors processing (Petrides, 2000a). However, activity in left BA 9 did not differ between R3s3r and O3s3r (post-hoc t-test $p > 0.05$) even though subjects performed very poorly on R3s3r compared to O3s3r events (see Figure 1, post-hoc t-test $p<0.05$, corrected). This observation is inconsistent with the possibility that left BA 9 activity was related to error processing or to monitoring processes since more difficult R3s3r tasks should engage these processes, and thus left BA 9, to a greater extent than easier O3s3r.

Alternatively, left BA 9 activity in the current study may have reflected increased demands on the stimulus-response mapping (Boettiger & D'Esposito, 2005; Fuster, 1990; Huettel & McCarthy, 2004; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000). This explanation is consistent with the observed increase in left BA 9 during three-response events and the non-significant activation difference within left BA 9 during R3s3r versus O3s3r events; but, it is not obvious how this explanation could account for the recency task main effect observed in this region. One way to reconcile this finding is to note that stimulus-response mapping is an internally-guided, top-down, cognitive control process that would be more involved during recency events and O3s3r events compared to the simple O2s1r and O3s1r events, since responses made in these latter events could be performed using a relatively automatic, perceptually-driven, bottom-up processes. More recently, Hester and colleagues (2007) conducted a verbal WM study in which they dissociated stimulus selection from response selection and found left BA 9/46 to be related to response selection, which would require instantiating stimulus-response associations. Therefore, based on our current findings and those of others (Boettiger & D'Esposito, 2005; Fuster, 1990; Hester, D'Esposito, Cole, & Garavan, 2007; Huettel & McCarthy, 2004; Quintana & Fuster, 1993) we suggest that left DLPFC activity in the current experiment may be related to stimulus-response mapping; however it is also possible that activity in the region was related to motor control processes, such as response preparation, since these processes would also be more engaged during 3s3r events compared to 2s1r and 3s1r events. Further studies need to be conducted in which stimulus-response mapping, response selection, and response preparation are dissociated.

Retrieval-related Activity in Right DLPFC

In addition to domain-general PFC activity, domain or task-specific, right DLPFC (BA 9) activity was observed during recency retrieval events compared to ordering events. Figure 2 shows that activity in this region was significantly greater during recognition and recency events compared to ordering events. Moreover, post-hoc one-way ANOVAs, with simple contrasts, of right DLPFC activity, within recency and within ordering event types, indicated that activity in this region was not significantly different across 2s1r, 3s1r and 3s3r event types. This suggests that despite the variance in right DLPFC activity as a function of stimulus and response number within recency and ordering event types (as seen in Figure 2B), activity in this region was not significantly impacted by the stimulus and response number manipulations; although, this may be due to a lack of power. In addition, activity in right DLPFC was significantly correlated with recency accuracy, and marginally correlated with recency RT. In general, our findings of greater right DLPFC activity during retrieval events versus ordering events are consistent with studies that have found greater right PFC during EM retrieval in general (Habib, Nyberg, & Tulving, 2003;Nyberg, Cabeza, & Tulving, 1996) and during temporal context retrieval specifically (Dobbins, Rice, Wagner, & Schacter, 2003;Konishi et al., 2002;Rajah & McIntosh, 2006;Suzuki et al., 2002). However, due to the relatively short delay (30 sec) between encoding and retrieval in the current study design, it may be argued that the retrieval tasks employed in this study reflected retrieval from WM and not from EM. Therefore, right BA 9 activity in the current study may not reflect the importance of these regions in EM-specific retrieval processes, but may reflect the importance of these regions for WM-specific retrieval processes. However, previous studies of both WM and EM have reported greater right DLPFC activity during temporal context retrieval (Cabeza, Anderson, Houle, Mangels, & Nyberg, 2000;Dobbins, Rice, Wagner, & Schacter, 2003;Mitchell, Johnson, Raye, & Greene, 2004;Rajah & McIntosh, 2006), suggesting that right DLPFC activity may reflect the importance of this region in mediating retrieval-related executive control processes across domains (Marklund et al., 2007).

It has been argued that increased right DLPFC activity during both EM and WM recency tasks reflects the role of this region in familiarity-based retrieval monitoring (Dobbins, Rice, Wagner, & Schacter, 2003; Dobbins, Simons, & Schacter, 2004; Mitchell, Johnson, Raye, & Greene, 2004; Yonelinas, Otten, Shaw, & Rugg, 2005). According to this perspective recognition and temporal context retrieval tasks can be performed by making judgments about the relative feelings-of-familiarity of retrieved stimuli, wherein more recent stimuli are inherently more salient and thus more familiar. Recently, Dobbins and Han (2005) have raised the issue of whether familiarity-based retrieval monitoring activations in right DLPFC reflects the role of this region in evidence-based verification that the retrieved familiarity information is appropriate for the retrieval task at hand (referred to as evidence-based familiarity monitoring) or reflects the role of this region in the implementation of a specific type of decision rule or retrieval orientation. If right DLPFC activation was related to evidence-based familiarity monitoring, activity in this region would be impacted by the quality of the mnemonic information available at retrieval and be related to behavioral accuracy (Dobbins & Han, 2005; Dudukovic & Wagner, 2007; Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Petrides, 1996). Alternatively if right DLPFC activation was related to the implementation of a specific decision rule, then one would not predict activity in this region to correlate with task accuracy (Dobbins & Han, 2005).

Our results show right DLPFC was consistently activated across all retrieval event types, suggesting that activity in this region may reflect its role in a specific decision process (Dobbins & Han, 2005; Dobbins, Rice, Wagner, & Schacter, 2003). However, we observed a near significant linear increase in right DLPFC activity across recency event types; in addition, activity in this region correlated with reduced recency accuracy. If right DLPFC involvement

in retrieval reflected its' role in mediating a specific rule, common to all retrieval events, it is unclear why activity in this region would exhibit a linear increase across recency events, but no significant difference in activity between recognition and R2s1r events (which were behaviorally equivalent). Moreover, the fact that the decision rule between R3s1r (3 alternative forced choice) and R2s1r (2 alternative forced choice) was the same, yet right DLPFC activity exhibited a linear increase across these event-types, which was correlated to the reduced success rates between these two event types, is not consistent with a rule-based account of right DLPFC activity.

Alternatively, it could be argued that these results indicate that right BA 9 activity was related to the number of errors made (Huettel & McCarthy, 2004); however, since the random effects analysis indicates that activity in this region was specific to retrieval events, and was near zero across ordering events, it is unlikely right BA 9 activity was related to a domain-general error processing. Yet another possibility is that, since, in the current study, subjects were aware of the type of retrieval task to be performed at the time of encoding; it can be argued that subjects used different encoding strategies for each retrieval task type and that the quality of the mnemonic information encoded differed across tasks. Thus differences in right DLPFC activity across different retrieval events may be due to the use of different retrieval operations reflective of the qualitative differences in the encoded information. However, one would assume, based on prior work (R. L. Buckner, 2002; Dobbins, Rice, Wagner, & Schacter, 2003; M. D. Rugg, Henson, & Robb, 2003), that different retrieval operations/orientations would be related to differences in regional PFC activity. Instead, we observed the same region of right DLPFC activated across the different retrieval events. In addition, activity in this region did not differ between recognition and R2s1r events, which one would not expect if this activation was related to the implementation of different retrieval operations since recognition encoding likely differed from R2s1r encoding. So, activity in this region does not appear to be related to differences in encoding histories nor to the use different operations/rules at retrieval; instead, activity in this region was greater during recency versus ordering events and correlated with retrieval accuracy.

Our results, in regards to right DLPFC involvement during retrieval, are inconsistent with recent results obtained in an fMRI study of EM retrieval by Dobbins and Han (2005). In this previous study, subjects performed verbal two-alternative forced choice (2AFC) recognition tasks, three-alternative forced choice (3AFC) recognition tasks and a 2 alternative same-different (2ASD) tasks. The rationale for this study was to dissociate PFC activations during EM retrieval that may be related to the implementation of different decision rules, by comparing AFC to ASD tasks, from those related to evidence-based familiarity monitoring, by comparing 3AFC to 2AFC tasks. Dobbins and Han (2005) found greater bilateral DLPFC (BA 46/9) activity in relation to the 2ASD tasks, compared to both 2AFC and 3AFC tasks; but did not find any activation differences between 3AFC versus 2AFC tasks. A similar pattern of results were obtained for 2AFC lexical decision task versus a 2ASD lexical decision rule. Therefore, it was concluded that PFC involvement in EM retrieval was not evidence-based, but reflected domain-general rule-based processing. In a similar vein, a recent fMRI study comparing PFC activity during a verbal recognition memory task and a spatial judgment visual perception task Fleck et al (Fleck, Daselaar, Dobbins, & Cabeza, 2006) observed activity in right PFC (BA 46/10) during both the retrieval and perceptual tasks. Moreover activity in this region was correlated with reduced confidence in the accuracy of one's behavioral response, but was not related to RT. The correlation between right PFC activity and task accuracy was not reported. The brain-behavior relationship reported by Fleck et al (2006) was domain-general, and since right BA 46/10 activity was not related to task RT (a continuous variable), but to response confidence (a categorical variable), the authors interpreted right BA 46/10 activity to be related to a discontinuous decision process such as selection of a response, as opposed to a retrieval-related continuous process, such as post-retrieval monitoring. However, monitoring is a general

cognitive process engaged when one evaluates his/her behavioral performance as being 'off-task' or not and may also be categorical since this process is more engaged under conditions of low confidence (Henson, Rugg, Shallice, & Dolan, 2000).

In contrast to Dobbins and Han (2005) and Fleck et al's (2006) evidence of domain-general activity in right DLPFC, we observed a domain/task-specific effect for right DLPFC. Considering that subjects performed worse on recency versus ordering tasks, it is possible that they were also less confident in their performance of these events, and that right DLPFC activity in the current study was related to this effect. However, a lack of confidence in one's judgment could be related to increased demands on monitoring processes, especially in the current study since activity in this region was also marginally correlated with recency RT and significantly correlated with recency accuracy. It is also important to note that the localization of right PFC activity reported by Dobbins and Han (2005) and Fleck et al (2006) extended more ventral and anterior to the current right DLPFC ROI; thus, it is possible that these studies reflect different functional regions in right PFC, and that this may account for the different results observed between studies.

Therefore, based on our results and those of others, we suggest that our current results *do not imply* that right DLPFC involvement in cognitive operations is *retrieval-specific*; instead, we suggest that our results show that right DLPFC was more involved in a cognitive control process that was more engaged during memory retrieval versus ordering events, and that activity in this region was inversely related to retrieval performance. Given that there were several cognitive control processes that were not directly manipulated in the current experiment, it is possible that right DLPFC activity in this study may be related to any of these control processes. However, our current results are consistent with previous studies implicating right DLPFC in monitoring processes engaged during familiarity-related retrieval processing (Dobbins, Simons, & Schacter, 2004; Dudukovic & Wagner, 2007; Henson, Rugg, Shallice, & Dolan, 2000; Petrides, 2000b)

Conclusions

Multiple frontal cortical regions were involved during the retrieval of temporal context information. Brain activity in several of these regions exhibited greater activity during recency versus ordering events, which is not surprising since recency events were more difficult and likely increased demands on multiple cognitive control processes. However, several of these regions also exhibited domain-general experimental effects. We found left VLPFC and DLPFC activity to be related to domain-general changes in the response number, which may reflect a role for these regions in selection processes such as: covert labeling and/or stimulus selection and stimulus-response mapping, respectively. Similarly, activity in right lateral premotor cortex (BA 6/8) activity was sensitive to the domain-general stimulus number manipulation, which suggests this region may be involved spatiotemporal WM manipulation required for strategic ordering. Only right DLPFC exhibited a domain-specific effect during retrieval, wherein domain/task-specific refers to the memory-domain (both EM and WM); perhaps reflecting its role in retrieval-related cognitive control, possibly in monitoring responses during familiarity-based retrieval events. In conclusion, our study highlights the functional heterogeneity of frontal cortex involvement in temporal context retrieval. Moreover, our results show that frontal cortex involvement in temporal context retrieval is related to its various roles in cognitive control; some of which were recruited to a greater degree during retrieval versus ordering events, and thus play a greater role during memory versus non-memory tasks.

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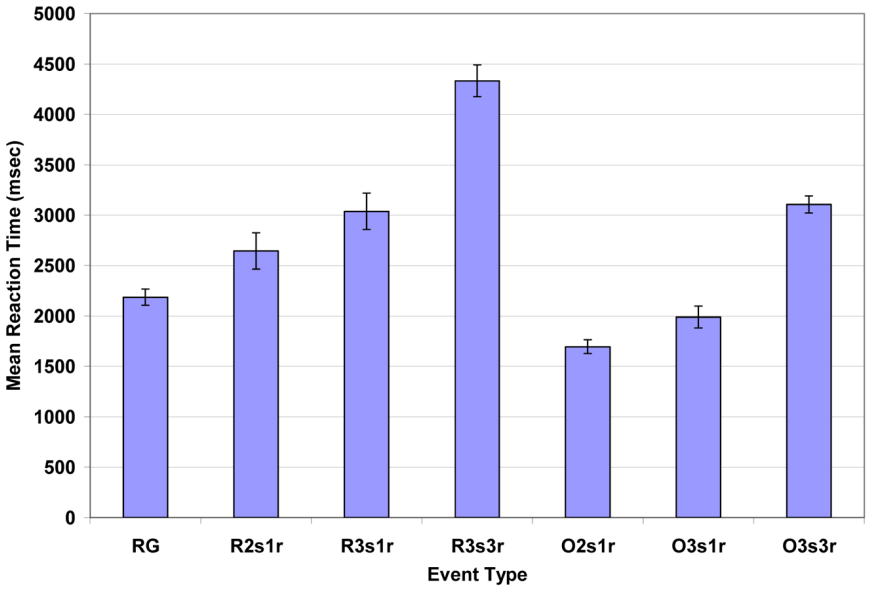

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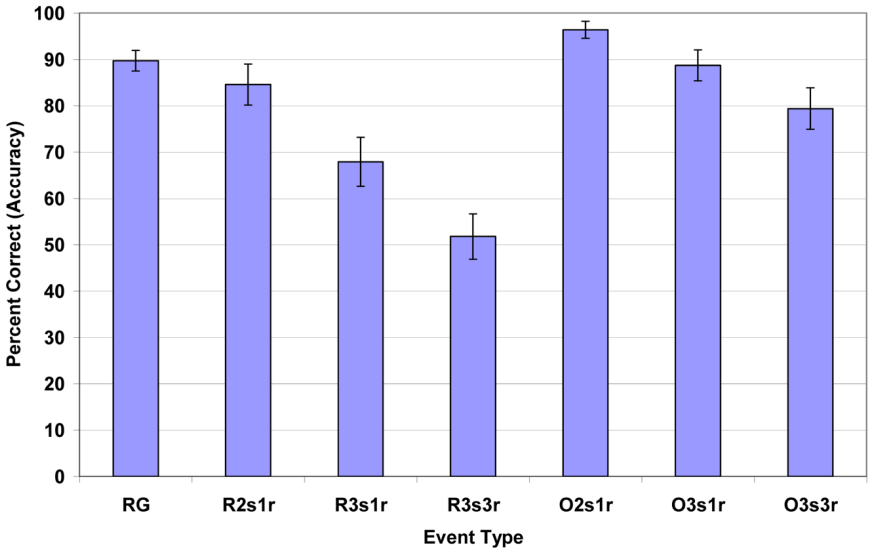
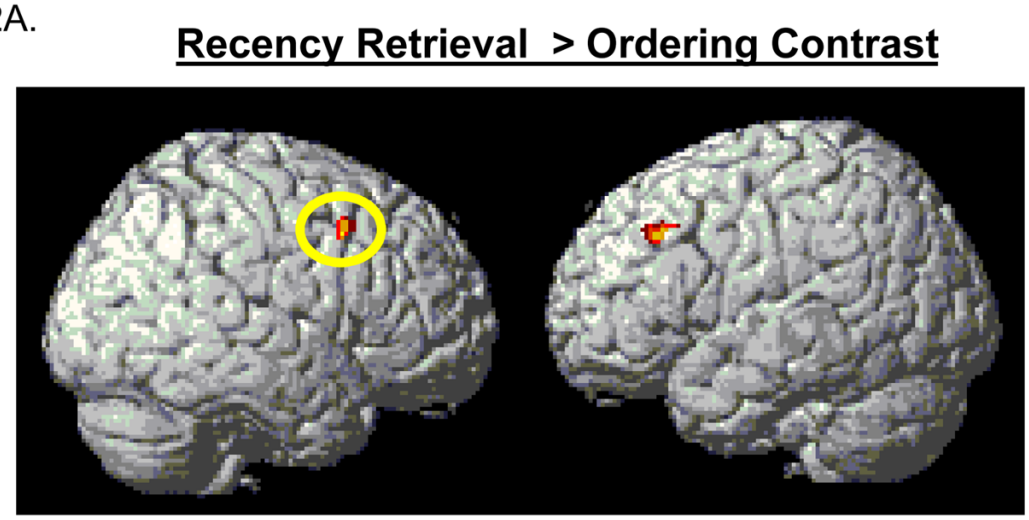


Figure 1. Behavioral Results

Figure 1A. Mean reaction time (RT), in msec, for participants (n = 9) across all behavioral tasks, with standard error bars. Figure 1B. Mean accuracy data (percent correct) for participants (n = 9) across all behavioral tasks, with standard error bars. Rg = Recognition; R2s1r = Recency 2 stimuli, 1 response; R3s1r = Recency 3 stimuli, 1 response; R3s3r = Recency 3 stimuli, 3 responses; O2s1r= Ordering 2 stimuli, 1 response; O3s1r = Ordering 3 stimuli, 1 response; O3s3r = Ordering 3 stimuli, 3 responses.

2A.



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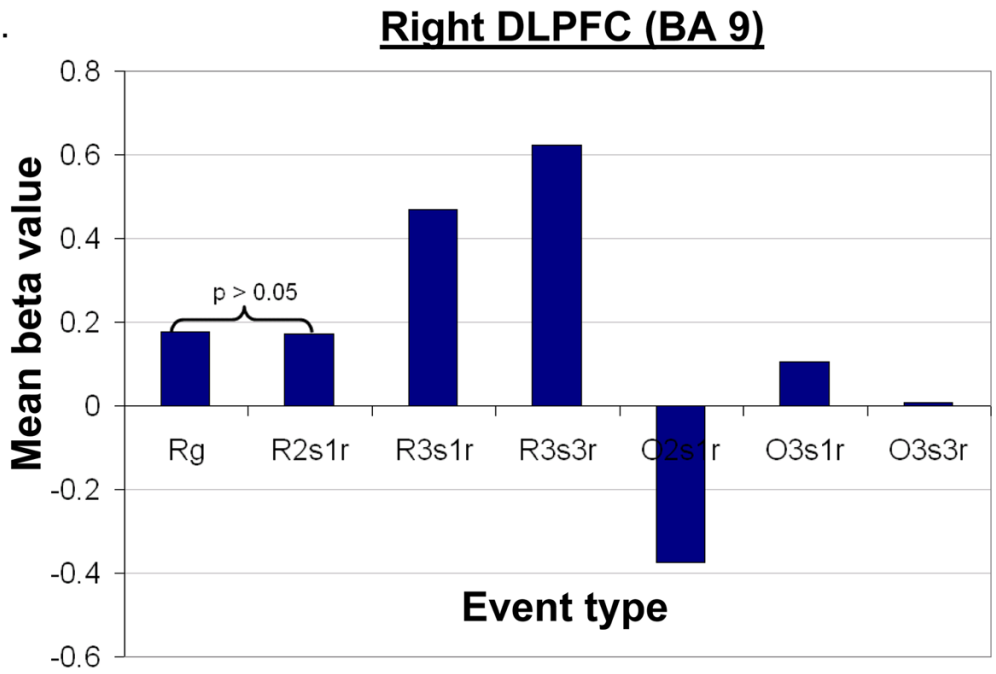

Figure 2. Recency/Familiarity Related Activations

Figure 2A. Presents the PFC activations identified in the random effects analysis for the Recency Retrieval > Ordering evnts contrast rendered onto a single subject anatomical template ($p<0.001$, uncorrected; spatial extent, $k = 15$). A yellow circle is drawn around the right DLPFC (BA 9) activation for which a mean activity plot is present in Figure 2B. Figure 2B. Presents a bar plot depicting the mean beta values, by event type, for right DLPFC ROI (BA 9). The central peak coordinates and the spatial extents of this ROI is listed in Table 1. This graph also presents some of the post-hoc paired t-test results comparing activity differences between retrieval event types for this region ($p = 0.05$), the details of which are presented in the results section. In general, this graph indicates there was no significant difference in right DLPFC activity as a function of the number of familiar events presented at retrieval (e.g. no significant difference between Rg and R2s1r events).

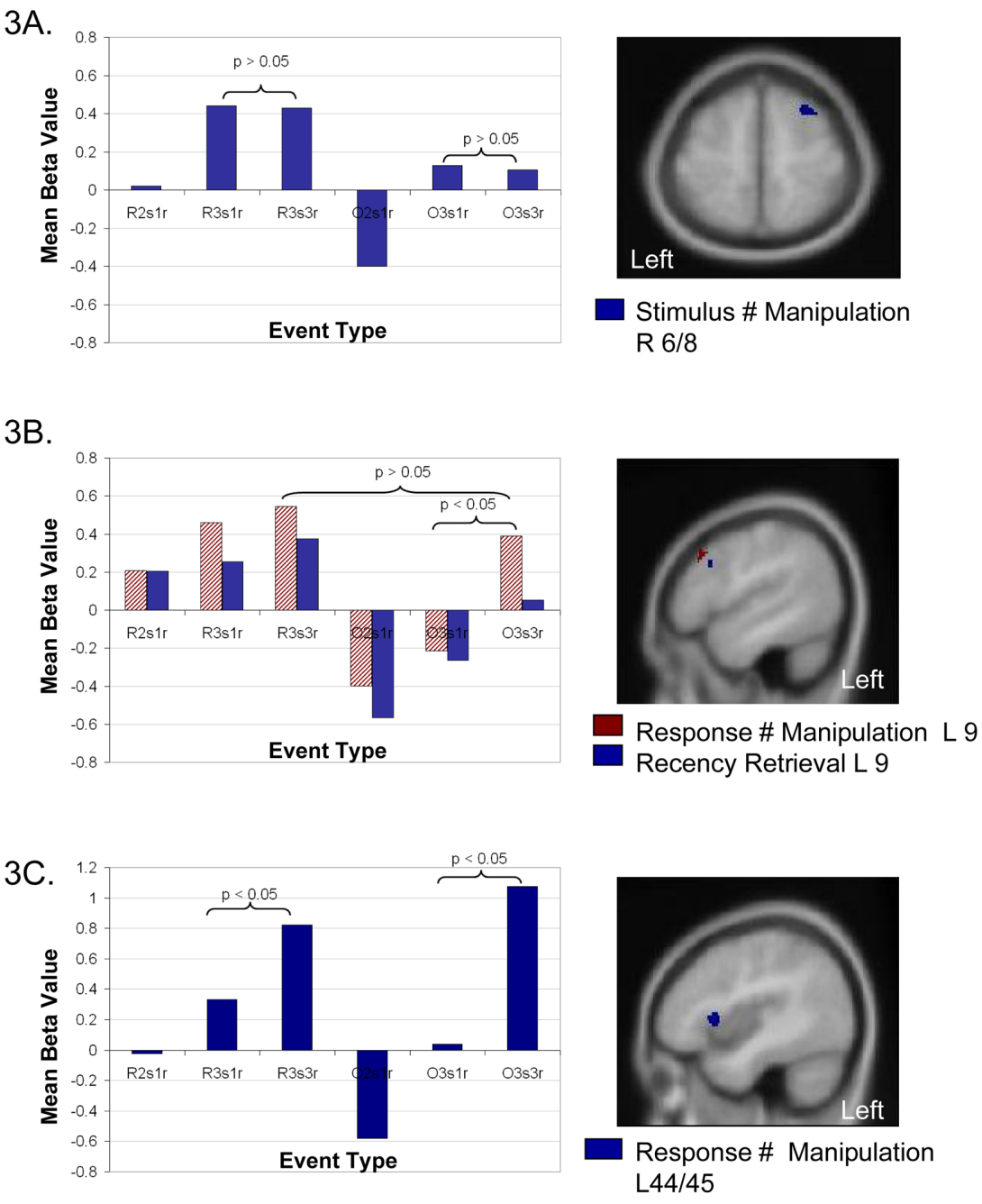

Figure 3. PFC ROI Mean Activity Plots

Figure 3A. The right side of this figure shows the right lateral premotor (BA 6/8) ROIs identified from Stimulus number manipulation contrast, overlaid on a MRI template. The left side of this figure shows the mean activity plot for this ROI, with some of the summary post-hoc paired t-test results. Right BA 6/8 activity was sensitive to increase stimulus, but not response, number. Figure 3B. The right side of this figure shows the two left DLPFC (BA 9) ROIs, identified from the Recency Retrieval > Ordering contrast and the Response number manipulaton contrast, overlaid on a MRI template. The left side of this figure shows the mean activity plot for both ROIs, with some of the summary post-hoc paired t-test results, discussed in detailed in the Results section. Figure 3C. The right side of this figure shows the left VLPFC

(BA 44/45) ROI, identified from the Response number manipulation contrast, overlaid on a MRI template. The left side of this figure shows the mean activity plot for this ROI, with some of the summary post-hoc paired t-test results which are discussed in detail in the Results section.

Table 1

Domain-specific and Domain-general PFC Activations

Contrast Name	Spatial Extent	Voxel T-value	Talairach Coordinates			HEM	BA	Brain-Behavior Correlation	
			x	y	z			Accuracy	RT
Domain - Specific Activations									
Recency > Ordering Events									
	36	5.43	−46	31	33	Left	9	−0.84	0.87
	34	5.25	36	14	40	Right	9	−0.91	0.83
Domain - General Activations									
Stimulus Number**									
	53*	4.22	30	22	54	Right	6/8	−0.86	-
Response Number									
	25	5.66	−51	18	32	Left	9	−0.86	0.91
	117	5.51	−42	14	9	Left	44/45	-	-

Note. This table presents the random effects within group SPM2 results.

The T-values represent the value for local maxima which had a $p < 0.001$. The spatial extent refers to the total number of voxels included in the voxel cluster.

* The peaks in these clusters were significant at $p<0.001$; however, the spatial extent listed was identified at $p<0.005$.

** After exclusiving masking out activations related to the Visual Processing Control Contrast. The stereotaxic coordinates are measured in mm. Brodmann Areas (BA) were determined by reference to Talairach & Tournoux (1988). HEM refers to the cerebral hemisphere in which the activation occurred.

Table 2

Factorial ANOVA results, ROI* Task*Stimulus or Response Number Manipulation

	Stimulus Number Manipulation (2s1r versus 3s1r)		Response Number Manipulation (3s1r versus 3s3r)	
ROIs Compared	**ROI*Stimulus Interaction**		**ROI*Response Interaction**	
	F-statistic	**p-value**	**F-statistic**	**p-value**
All 4 ROIs:				
Right 6/8, Left 44/45, Left $9^{Recency}$, Left $9^{Selection}$	2.12	0.12	8.27	p<0.0001
Right 6/8, versus Left 44/45	< 1.00	-	10.13	p = 0.01
Right 6/8, versus Left $9^{Recency}$	5.06	0.05	3.36	p = 0.1
Right 6/8, versus Left $9^{Selection}$	2.86	0.12	6.74	p = 0.03

Note: The random effects analysis identified right lateral premotor (Right BA 6/8) as being related to the stimulus number manipulation. Left lateral PFC regions Left 44/45 and Left 9 were identified as being more related to the response number manipulation. Another Left 9 activation foci exhibited greater activity during recency versus ordering events, but was similar in location to the Left 9 ROI related to the response number manipulation. These ROIs were selected from the random effects group analysis. To directly test if these ROIs exhibited single dissociations in activity related to the stimulus number versus the response number manipulations we conducted post-hoc ANOVAs directly comparing ROI activity X task X parametric manipulation. ANOVAs comparing all 4 ROIs were conducted to assess if there was an overall ROI*Stimulus effect and an overall ROI*Response effect (df = 3,1). Then pair-wise comparison between Right BA 6/8 ROI and each of the Left Lateral PFC ROIs were conducted since Right BA 6/8 was related to stimulus number (according to the random effects analysis) whereas the left lateral PFC ROIs were related to response number (df = 1,1). The results from these ANOVAs are presented in this Table. The F-statistic and the significance value are shown.