Similarities in the patterns of prefrontal cortex activity during spatial and temporal context memory retrieval after equating for task structure and performance

M. Natasha Rajah [a,d,*], David Crane [b], David Maillet [b], Darlene Floden [c]

[a] Douglas Mental Health University Institute, QC, H4H 1R3, Canada
[b] Department of Neuroscience, McGill Univ., Montreal, QC, H3A 2T5, Canada
[c] Center for Neurological Restoration, Department of Psychiatry & Psychology, Cleveland Clinic, USA
[d] Department of Psychiatry, McGill Univ., Montreal, QC, H4H 1R3, Canada

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ABSTRACT

Event-related functional magnetic resonance imaging was used to assess healthy adults while they performed spatial and temporal context memory tasks matched in task structure. After equating task structure between spatial versus temporal context tasks, subjects reported using similar strategies across tasks and we observed no significant differences in accuracy and reaction time performance between tasks. We used three methods of statistical analysis to interrogate similarities and differences in whole-brain activity across retrieval tasks, while focussing on prefrontal cortex (PFC) activations: multivariate partial least squares analysis (PLS), univariate statistical parametric mapping (SPM) and conjunction analysis. The PLS and conjunction analyses indicated that the overall pattern of PFC activity was similar across both temporal and spatial context retrieval tasks; but the SPM results indicated that some of these PFC regions exhibited differences in the degree to which they were engaged between tasks. However, none of these methods identified unique PFC activations specific to mediating spatial and/or temporal context retrieval. These results indicate that, overall, similar patterns of PFC activity were observed during temporal and spatial context memory retrieval once task structure and performance were equated.

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Introduction

Lesion studies and functional neuroimaging studies have highlighted the importance of lateral prefrontal cortex (PFC) contributions in retrieving both spatial and temporal contextual details about past personal experiences (spatial context memory and temporal context memory, respectively) (Kopelman et al., 1997; McAndrews and Milner, 1991; Milner et al., 1991). For example, damage to lateral PFC has been associated with deficits in spatial source/context memory events and recency memory events (Kopelman et al., 1997; McAndrews and Milner, 1991; Milner et al., 1991). Moreover, functional neuroimaging studies have reported laterality differences in PFC activation during temporal context retrieval, versus, spatial context retrieval and the retrieval of perceptual details or source information (Cabeza et al., 2000; Dobbins et al., 2003; Mitchell et al., 2004; Rajah et al., 2008; Rajah and McIntosh, 2006; Rugg et al., 1999). For example, fMRI studies have shown that temporal context retrieval engages right lateral PFC to a greater degree compared to baseline

activity, item recognition and spatial context/source memory retrieval (Cabeza et al., 2000; Dobbins et al., 2003; Mitchell et al., 2004; Rajah et al., 2008; Rajah and McIntosh, 2006; Suzuki et al., 2002).

Interestingly, whereas temporal context retrieval has been shown to engage right PFC, spatial context (source) retrieval and the retrieval of perceptual details engage left lateral and anterior PFC to a greater degree compared to baseline, recognition and temporal context retrieval (Ranganath et al., 2000; Slotnick and Moo, 2006; Slotnick et al., 2003). For example, in an event-related fMRI study in which subjects performed recognition (old/new) and spatial-source (left/right) memory events for abstract visual shapes, Slotnick et al. (2003), reported greater activity in left ventrolateral (VLPFC), dorsolateral (DLPFC) and anterior PFC (APFC) during correct spatial source/context judgments compared to correct item recognition judgments. Moreover, a few studies have directly compared PFC activity during retrieval of either source or temporal information (Dobbins et al., 2003; Duarte et al., 2008; Mitchell et al., 2004; Rajah et al., 2010). Although the specific Brodmann Areas varied between studies, in general, these studies have also found differences in the laterality of PFC activation during the retrieval of spatial context and source (left PFC) versus temporal context (right PFC) information and these effects are most often observed in lateral PFC, along the middle frontal gyrus. These effects are apparent for verbal, object and face stimuli, and are observed within the context of both working memory and

* Corresponding author. Douglas Hospital Research Centre, McGill University, 2147 Moe Levin Centre, Memory Clinic, 6875 LaSalle Blvd, Verdun, Quebec, H4H 1R3, Canada. Fax: +1 514 762 3020.
E-mail address: mnrajah@gmail.com (M.N. Rajah).

episodic memory retrieval paradigms (Dobbins et al., 2003; Mitchell et al., 2004; Rajah et al., 2010).

Based on these findings, some researchers have interpreted the laterality of PFC activations during source versus temporal context retrieval as reflecting differences in the type of retrieval-associated cognitive control process engaged during these two task types (Dobbins et al., 2003; Mitchell et al., 2004; Ranganath, 2004). However, it is important to note that the task structure and experimental design typically differed for temporal and spatial context tasks (Dobbins et al., 2003; Mitchell et al., 2004; Rajah et al., 2010) and performance was not equated for accuracy between tasks (Dobbins et al., 2003; Mitchell et al., 2004; Rajah et al., 2010). Thus, the lateralization of PFC activity during source/spatial context retrieval versus temporal context retrieval may be a by-product of these confounding factors. At minimum, differences in task difficulty may have led to the differential recruitment of domain-general PFC-related cognitive control processes associated with increased effort such as error processing, response selection, or response monitoring (Boettiger and D'Esposito, 2005; Garavan et al., 2002; Henson et al., 2000; Petrides, 2000).

A more complicated confound arises if differences in task structure biased subjects to employ different domain-general cognitive strategies at encoding and/or retrieval stages of particular tasks, in which case the laterality differences in PFC activation between source/spatial versus temporal context memory tasks may be explained using more traditional domain-general frameworks of hemispheric specialization of cortical function (Charcot, 1883; Gazzaniga, 2000; Gazzaniga and Sperry, 1967; Geschwind and Levitsky, 1968; Haxby et al., 1995; Hugdahl, 2000; Kosslyn et al., 1992; Milner, 1971; Milner and Petrides, 1984). For example, in previous studies of spatial source memory, the encoding stimuli usually originated from *two* alternate fixed, categorical, source reference points in memory (i.e. left/right spatial location; font X or font Y; presented as picture or word at encoding) and the source retrieval question was also structured categorically (e.g. which stimulus was originally presented in the X or Y spatial location/cognitive context/perceptual context?) (Cabeza et al., 2002; Dobbins et al., 2003; Mitchell et al., 2004; Ranganath et al., 2000). In contrast, in studies investigating temporal context retrieval, the encoding stimuli were presented sequentially, and it was the relative, coordinate, relationship between stimuli that was stressed in the phrasing of the retrieval question asked: for example, "which stimulus was presented most/least recently?" (Cabeza et al., 2000; Dobbins et al., 2003; Rajah and McIntosh, 2006). ==Therefore, it is possible that the PFC laterality effects observed in the previous studies of spatial/source versus temporal context memory may have been related to differences in the use of categorical versus coordinate/continuous strategies at either encoding or retrieval== (Kosslyn et al., 1989; Palermo et al., 2008; Slotnick and Moo, 2006). Indeed, in a recent neuroimaging study it was shown that one can observe either left PFC or right PFC activation during a spatial source memory retrieval, depending on whether a categorical or coordinate strategy was used at encoding or retrieval (Slotnick and Moo, 2006).

The goal of the current study was to determine if previously reported differences in PFC activity during spatial versus temporal context retrieval remained after we equated retrieval performance between task types and equated the cognitive strategies employed by subjects during spatial versus temporal context memory events. To this aim, we conducted an event-related fMRI study for spatial source and temporal context retrieval of non-famous faces in which a similar categorical-based task structure was employed for both events. A parallel manipulation of task difficulty was included within task type and involved increasing retrieval demand and the number of responses made during each trial. Task difficulty was operationalized as increased reaction time and reduced accuracy. We hypothesized that by manipulating difficulty within task type we would have an additional control for prior between-task differences in difficulty. This

would allow us to differentiate between PFC regions that were involved in domain-general control processes related to changes in task difficulty, independent of task type, from PFC regions that were involved in domain-specific cognitive control processes recruited, as a function of task difficulty, during spatial versus temporal context retrieval. Specifically, we predicted that if we saw a common pattern of PFC recruitment as a function of increased task difficulty in both retrieval tasks, which overlapped with previous findings of PFC involvement in source/context memory, we could conclude that these regions were involved in domain-general control processes independent of task type. Alternatively, if we saw a task-by-difficulty interaction in PFC recruitment which overlapped with prior findings, we could conclude that there were domain/task-specific differences in the cognitive control processes recruited during spatial versus temporal context retrieval as a function of difficulty. Therefore, this study design allowed us to discriminate if previous differences in PFC recruitment during spatial versus temporal context were in fact due to differences in the cognitive control processes necessary for retrieving spatial versus temporal context information from memory, or whether these differences were a by-product of differences in task difficulty and task structure.

It is important to note that the pattern of brain activation associated with task-difficulty manipulation during spatial versus temporal events, may be attributable to either increased retrieval demands and/or increased recruitment of domain-general cognitive control mechanisms that related to task effort, such as increased strategic retrieval (Moscovitch and Winocur, 2002; Rajah and McIntosh, 2006), response-selection (Schumacher et al., 2005) and/or monitoring (Henson et al., 1999; Petrides, 2000) processes, to name a few. Our goal was not to discriminate amongst these variable influences that can individually, or in combination, increase the difficulty of a cognitive task. Instead we included this manipulation to determine if increasing task effort had a similar or different impact across task types.

We piloted this task to ensure that subjects reported using similar strategies between task types and exhibited non-significant differences in accuracy and reaction times between retrieval-task types, but exhibited significant differences as a function of the task-difficulty manipulation. We used multivariate spatio-temporal partial least squares (ST-PLS) analysis (McIntosh et al., 2004) to determine if at the image level, the overall patterns of activation in the PFC and other brain regions were similar or different during spatial versus temporal context retrieval events, after equating task structure and performance. In addition, we also examined brain activity in the PFC using a more traditional univariate (statistical parametric mapping) technique to determine if, at the voxel level, distinct regions of the PFC exhibited differential levels of activity between spatial versus temporal context retrieval. Finally, we used conjunction analysis to determine the degree of overlap in the univariate fMRI results between the spatial and temporal context retrieval tasks.

Methods

Subjects

The participants were 16 young adults (7 males, mean age 23.87 years, range 18–34 years, mean education 16 years, education range 12–19 years). All participants were right-handed, English-speaking, reporting normal (or corrected to normal) vision. All subjects were screened for any history of major medical, neurological and psychiatric disorders and for a history of substance abuse and psychoactive medication. The study was approved by the institutional review boards at McGill University, the Douglas Mental Health University Institute and the Montreal Neurological Hospital and all participants provided informed consent.

Behavioral methods

Materials

A total of 396 gray-scale unique photos of non-famous multi-racial human faces were used. The faces were collected from photograph databases on the internet. The selected faces characterized the same demographic profile as the study population: aged 18–35 years, varied ethnicity, equal number of males and females. The faces were novel with neutral facial expressions. 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. Participant responses were recorded via a four-buttoned, magnet-compatible fiber-optic keypad; only three of the keys were used and corresponded to the top, middle and bottom of the screen. All subjects were right-handed and used only their right hand to make all motor responses.

Procedure

Preparation. Participants were informed that they would be doing a memory experiment. The participants were informed that there would be two types of tasks (spatial and temporal), at two levels of difficulty (easy and difficult), yielding 4 types of tasks in total: Spatial Easy Task, Temporal Easy Task, Spatial Difficult Task, and a Temporal Difficult Task. They were instructed that each task involved an encoding phase, a break, and then a retrieval phase. During the retrieval phase of Spatial Easy and Temporal Easy Tasks subjects were presented with 3 previously encoded stimuli and required to make one response. During the retrieval phase of Spatial Difficult and Temporal Difficult Tasks subjects were presented with 3 previously encoded stimuli and required to make three responses. Therefore the easy versus difficult versions of the tasks differed in the number or retrieval responses made. Additional information about this difficulty manipulation is provided below.

Participants were given detailed instructions about task events and response requirements, as described below. Participants then completed practice trials of each of the four tasks outside the scanner. Only after subjects stated that he/she understood the tasks and performed above chance were they invited into the scanner. Unique stimuli were used for all practice trials and for each experimental trial. Fig. 1 summarizes the behavioral protocol.

Encoding phase. Each encoding phase began with a 10 sec instruction screen which informed participants which of the four memory tasks would follow: Spatial Easy, Temporal Easy, Spatial Difficult or Temporal Difficult. Apart from this instruction screen, the encoding phase was identical in all 4 tasks. Following the instruction screen, a display indicating "Entering time block 1" appeared for 2 sec, followed by three faces presented one at time, for 2 sec each. Each face was presented either in the left, middle or right region of the visual field. Another display then indicated "Entering time block 2" and three more faces were presented in the same manner. A third display then indicated "Entering time block 3" and three more faces were presented in the same manner. The purpose of the time blocks was twofold. First, we hypothesized it would allow for the encoding of temporal information in a categorical manner, maintaining consistent task structure with the intuitive categorization of spatial location (right/middle/left). Second, it allowed us to equate the number of possible sources in the spatial and temporal tasks (3 in each case). Therefore, the encoding structure was identical for spatial source and temporal context events, for both difficulty levels; only the instructions differed to orient subjects to the type of memory task and level of difficulty that would follow encoding.

Break. A 30-sec break followed the encoding phase, at which point the participant was instructed to alternately press the top and bottom
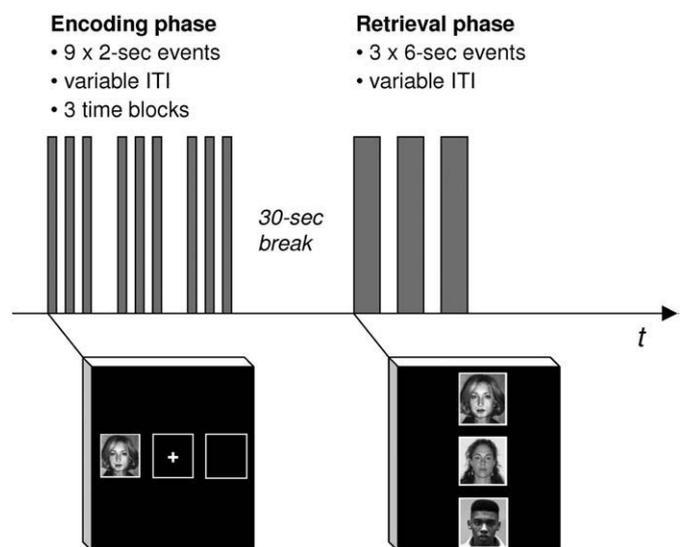
Fig. 1. Behavioral protocol during fMRI scan acquisitions. This figure represents the presentation of stimuli during Task 1 during a single run. Each run consisted of multiple tasks, counterbalanced in order within and between runs. The entire scan session consisted of 8 runs. Total time for fMRI acquisition = 90 min approximately. Each task consisted of an encoding phase, break, and retrieval phase. During the encoding phase first there was a 10 sec instruction screen indicating what type of memory task would be performed, then there were nine encoding events in which a single face was presented either on the right, center or left side of the computer screen, one at a time. The presentation of the nine encoding faces was divided into three temporal blocks (3 stimuli presented per temporal block). Subjects were informed when starting a new temporal block with a slide presented for 2 sec. Following encoding there was a 30-sec break during which subjects alternated using a left–right responses, this was followed by an orienting slide indicating to the subjects that the retrieval phase is about to start (2 sec). During the retrieval phase subjects were presented with three retrieval events. Each retrieval event consisted of 3 simultaneously presented previously encoded faces oriented along the vertical axis. All stimuli are separated by a variable ITI (2.2 sec, 4.4 sec and 8.8 sec, mean IT = 5.13. Instruction slides preceding each phase are not shown in the figure to maintain simplicity.

button on the response keypad. During the first 20 sec of the break a fixation cross was presented, and in the last 10 sec of the break an instruction cue for the upcoming retrieval phase was presented to reorient subjects to the upcoming memory task. This break served to reduce the participant's reliance on working memory and to reduce recency effects. 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. However, previous studies of both WM and EM have reported similar patterns activity during context retrieval (Cabeza et al., 2000; Dobbins et al., 2003; Mitchell et al., 2004; Rajah and McIntosh, 2006), suggesting that PFC activity during retrieval may be similar across domains (Marklund et al., 2007).

Retrieval phase. Three retrieval events occurred during the retrieval phase of every task. In each event, three *previously encoded faces* were presented simultaneously in a vertical array for 6 sec. For each event, one face was present from each time block and each spatial location. For example, for one event the left face would be from time block 1, right face from time block 2, and middle face from time block 3; however, the spatial and temporal pairs would vary across trials, such that during another event the left face would be from time block 2, right face from time block 3, and middle face from time block1. This mix ensured that subjects could not use temporal information to aid spatial source retrieval, and could not use spatial information to aid temporal context retrieval. Faces were oriented along the vertical axis to prevent using simple iconic representations of encoded stimuli in making spatial context judgements and to prevent masking the spatial context of stimuli.

For each of the three retrieval events presented during a Spatial Easy Task subjects were asked to select the face that was initially presented in a particular location (i.e., left, right, or middle). For the three retrieval events in Temporal Easy task subjects were given the parallel instruction to select the face presented in a particular time block (i.e., block 1, block 2, or block 3). Thus, the structure of the retrieval question and response requirements were identical for spatial and temporal tasks: select one of the three faces based on their initial spatial or temporal context. The specific instruction was counterbalanced across runs such that an equal number of "left", "middle" and "right" decisions (in the Spatial tasks) and "block 1", "block 2", and "block 3" decisions (in the Temporal tasks) were made across the experiment.

During the retrieval phase of Spatial Difficult Tasks, subjects were cued to order the three simultaneously presented encoded faces either "from left to right" or "from right to left". Similarly, during the retrieval phase of Temporal Difficult Tasks, subjects were cued to order the three faces either "from most to least recent" or "from least to most recent". Thus, task structure between the Spatial and Temporal Difficult Tasks were identical. The specific instruction for each retrieval phase was counterbalanced across runs such that an equal number of "right to left", "left to right", "most to least recent" and "least to most recent" instructions were presented in the experiment.

Participants performed 8 runs in the fMRI session. Each run included each of the four memory tasks (Spatial Easy, Temporal Easy, Spatial Difficulty, and Temporal Difficult).The run order was randomized across participants and the task order was pseudo-randomized within each run. In each run, there were 9 encoding events and 3 retrieval events for each task, yielding a total of 24 retrieval events for each of the 4 memory tasks.

ITI. There was a variable intertrial interval (ITI) of 2.2, 4.4 or 8.8 sec (average ITI = 5.13 sec) between presentation of each image to add jitter to the fMRI acquisition sequence, allowing for easier dissociations of event-related activity changes (Dale and Buckner, 1997; Friston et al., 1999). Random ITIs ensure that preparatory or anticipatory processing does not confound event-related neural responses.

Rationale

We hypothesized that by presenting stimuli in "3 time blocks" and in either left/middle/right spatial position at encoding, we would bias subjects to use a categorical or labeling strategy during the encoding of both the temporal and spatial contextual elements of each item (Slotnick and Moo, 2006). We also hypothesized that by using a similar format in the retrieval questions posed during spatial versus temporal context retrieval, we minimized differences in the retrieval orientation or strategies employed (Dobbins et al., 2003). Together, by equating task structure at encoding and retrieval we hoped to equate performance between the two context memory events, within difficulty level.

The task-difficulty manipulation. In the current study we manipulated task difficulty by increasing the number of stimuli for which contextual details needed to be recollected and by increasing the number of motor responses needed. The rationale for including the task-difficulty manipulation was to determine if some of the previously reported task differences in PFC recruitment during spatial source versus temporal context retrieval may have been due to the greater recruitment of domain-general cognitive control processes, related to increased task effort and greater retrieval error, in one versus the other task, because one of the tasks were more difficult than the other (usually the temporal context>spatial source task). During Easy Tasks all three events presented were "old" events and depending on the cue presented prior to each retrieval phase, subjects were required to either respond to the face that was on the "left", "middle" or "right" during spatial retrieval tasks, or the face that was

in the "first", "second", or "third" temporal block for the temporal retrieval tasks. Therefore, we would suggest that subjects had to wait for the retrieval phase task cue and then scan all three items prior to retrieving which of the faces was the correct response. Therefore this was a three-alternative response retrieval task in which only one response was required.

The Difficult Tasks were operationally defined as being harder due to pilot subjects exhibiting lower accuracy and slower reaction time during these tasks versus the 3s1r tasks. We rationalized that the increased difficulty of these tasks was because successful performance of these tasks *required* subjects to retrieve, discriminate and monitor the contextual details of a minimum of two of the three retrieval stimuli presented and required more motor responses from subjects. Thus, the Difficult Tasks were constructed to tap into similar cognitive processes across spatial and temporal context retrieval; including task-similar, domain-specific, retrieval-related processes and domain-general cognitive control processes, such as strategic retrieval, response-selection and monitoring (see Introduction for more details).

Behavioral analysis

SPSS for Windows (version 11.01) was used to conduct the behavioral analyses. Two 2×2 repeated measures analyses of variance (ANOVA) were conducted to examine if there were task main effects, difficulty main effects, and task-by-difficulty interactions in subjects' reaction time (RT) and accuracy performance across Spatial Easy, Temporal Easy, Spatial Difficult and Temporal Difficult tasks. For Difficult events the subjects' response was considered accurate only if he/she made three correct responses per trial. For reaction time of Difficult events we calculated the total RT for making all three responses. For example, the Spatial Difficult RT for a specific subject = (RT for response 1 + RT for response 2 + RT for response 3).

Debriefing of subjects

At the end of the experiment we presented subjects with a debriefing questionnaire. Subjects were asked: "What strategy did you utilize to help you remember the spatial location and temporal order of face stimuli?" If subjects did not report using an explicit strategy we asked them: "How did you go about memorizing the faces?" They were asked if the strategies were similar or different between task types. Subject were also asked if they found one type of context retrieval (temporal/spatial) more difficult. Debriefing was also done to determine if subjects stayed on task throughout the scanning session. All subjects included in the fMRI analysis reported staying on task and performed above chance.

We coded the strategies reported by subjects into the following categories:

1– verbal categorical/grouping strategy (e.g. use of simple categorical verbal labels during encoding of face; such as spatial location, temporal block, feature label, name, occupation) (Kosslyn et al., 1992; Palermo et al., 2008; Slotnick and Moo, 2006)
2– elaborate associative strategy (e.g. used stories to link face stimuli into one schema) (Naveh-Benjamin et al., 2007)
3– other, if the subject either: (i) could not explicitly express the strategy used, (ii) used a combination of strategies which was unclear to the rater to code, (iii) strategy reported was unclear or (iv) reported using a shallow visual memory or working memory strategy (i.e. mental snapshots, rehearsal) (Baddeley, 1992).

fMRI methods

Acquisition

Scanning was performed on a 3.0-T Siemens Trio whole-body MRI system with a standard whole-head coil. Throughout the experiment motion was restricted using a vacuum pillow and foam padding. 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 sessions. An LCD projector (Epson, Long Beach, CA) was used to back-project the stimuli onto a projection screen at the foot of the scanner bed. Subjects viewed the stimuli reflection on a mirror mounted within the head coil (visual angle approx. 4°). When necessary, vision was corrected using MRI-compatible lenses. Participant responses were recorded via a four-buttoned, magnet-compatible fiber-optic keypad; only three of the keys were used and corresponded to the top, middle and bottom of the screen. All subjects were right-handed and used only their right hand to make all motor responses.

At the beginning of a functional neuroimaging session, a structural scan was acquired using the Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol parameters (Jack et al., 2008). This protocol generates T1-weighted image volumes with a 1 mm isotropic resolution. The volumes were acquired using a fast 3D gradient echo sequence (acquisition time: 9 min 35 sec; TR 14 ms, TE 4.92 ms, flip angle 25°, 160 1 mm thick transverse slices, $1 \times 1 \times 1$ mm voxels, FOV = 256 mm²).

Following the acquisition of the structural scan, participants performed the aforementioned behavioral events while BOLD (functional) images were acquired. A mixed rapid event-related experimental design was implemented for this experiment (Amaro and Barker, 2006; Donaldson, 2004; Liu, 2004). A variable intertrial interval (ITI) of 2.2, 4.4 or 8.8 sec (average ITI = 5.13 sec) served to add jitter to the fMRI acquisition sequence, allowing dissociation of event-related changes in BOLD activity. We have successfully used this fMRI design to acquire large amounts of fMRI data with minimal time cost (Rajah et al., 2008). BOLD images were acquired using a single shot T2*-weighted gradient echo EPI pulse sequence (TR = 2000 msec, TE = 30 msec, FOV = 256 mm2, matrix size = 64×64, in-plane resolution = 4×4 mm, 340 whole-brain acquisitions/11:20 min run). Each whole-brain acquisition consisted of thirty-two oblique slices of 4.0 mm thickness, 0.0 mm slice gap, acquired along the anterior–posterior commissural plane. 10 sec of gradient RF pulses preceded each experimental run to establish steady-state tissue magnetization and minimize startle-related movement during acquisition. The functional imaging portion of the study took approximately 90 min. Though this is a long session, we have conducted fMRI studies of the same duration in young and older adult samples in the past with success (Rajah et al., 2008; Rajah et al., 2010; Rajah and McIntosh, 2008).

Pre-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. Images from the first 10 sec of each run were discarded to control for field inhomogeneities. 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. Subjects with head motion greater than 3.5 mm were discarded from the analysis. Individual subjects' functional images were spatially normalized to the MNI EPI-template available in SPM2, placing them in a standard coordinate space based on the atlas of Talairach and Tournoux (1988) which facilitated group analysis and allowed for the reporting of activations in standard Talairach-space (Ashburner and Friston, 2004; Collins et al., 1994). Volumes were resampled into 2-mm cubic voxels and smoothed using 10 mm full-width half maximum (FWHM) isotropic Guassian kernel, to minimize inter-participant anatomic variability (Friston, 2004).

fMRI data analysis

Mean-centered task ST-PLS. Multivariate spatio-temporal partial least squares analysis (ST-PLS, http://www.rotman-baycrest.on.ca/pls) was used to analyze the event-related fMRI data obtained during the encoding and retrieval phases of the four tasks: Spatial Easy, Temporal Easy, Spatial Difficult, and Temporal Difficult (McIntosh et al., 2004). ST-PLS is a powerful tool for identifying whole-brain, task-related changes in brain activity (Addis et al., 2004; Lenartowicz and McIntosh, 2005; McIntosh et al., 2004; Vallesi et al., 2009). In the current study we employed the mean-centered ST-PLS module to identify patterns of whole-brain activity that co-varied with the experimental design. In the following paragraphs we present a brief overview of ST-PLS methods; for a more detailed description of ST-PLS we refer you to the article by McIntosh et al. (2004).

To conduct the ST-PLS analysis, first, each subjects' 3D event-related fMRI data matrix was converted to a 2D data matrix (datamat) by "flattening" the temporal dimension (t), so that time series of each voxel (m) was stacked side-by-side across the columns of the data matrix (column dimension = m*t). In the current analysis, the temporal dimension (time series) consisted of eight time lags (1 time lag = 1 TR of 2 sec) after each event type. This allowed for the full sampling of the hemodynamic response (HR) to each event type, without relying on assumptions about the shape of the HR function (HRF). The jittered ITI and rate of stimulus presentation allowed for adequate separation of event-specific changes in HR.

The rows of each subjects' datamat corresponded to event types of experimental interest: Spatial Easy, Temporal Easy, Spatial Difficult and Temporal Difficult events from both the encoding and retrieval phases of the experiment, respectively. Each subject's datamat was then mean-centered, column-wise, against the overall grand mean, yielding a deviation matrix that underwent singular value decomposition (svd). The svd algorithm outputs a set of mutually orthogonal paired latent variables (LVs) and singular values, in descending magnitude. LVs are comparable to eigenvectors from principle components analysis (McIntosh et al., 2004). The number of LVs and singular values produced is equivalent to the number of event/task types included in the analysis; in this analysis there were eight. Each LV pair consists of a vector representing the weighted contributions of each event type (design LV or salience; which is similar to a data-driven based contrast effect) to the pattern of brain activity represented by its' paired singular image (brain LV or salience). A singular image (s.i.) consists of negative and positive brain saliences, which are numerical weights assigned to each voxel at each temporal lag, and represents a spatio-temporal pattern of whole-brain activity for the entire time series (eight 2 sec TRs/time lags after event onset). Brain regions with positive voxel saliences are positively related to the contrast effect identified by a given design LV, and those with negative voxel saliences are negatively related to the contrast effect identified by a given design LV. Thus the relationship between the singular image and contrast effect is symmetrical.

Additional results obtained from the ST-PLS analysis are temporal brain scores, which represent the degree to which each subject expresses the pattern of brain activity identified by the s.i., in relation to its paired design LV, at each time lag. The temporal brain score can be used to indicate at which time lag the experimental event-related/task effect is maximally differentiated within the temporal window sampled (McIntosh et al., 2004). We used this temporal score to identify the subset of time lags which maximally represented the effects of interest, and only report activations from those time lags (McIntosh et al., 2004; Vallesi et al., 2009).

The statistical significance of each LV pair was determined by conducting 500 permutation tests, on the singular values, which represented the proportion of the covariance matrix accounted for by each LV pair (McIntosh et al., 2004; McIntosh and Lobaugh, 2004; McIntosh et al., 1998; McIntosh et al., 1999). Permutations were conducted with sampling without replacement so that the event-type order was rearranged for each subject. The probability that the permuted singular values exceed the observed singular values was calculated and only LVs for which this probability was $p < 0.05$, were deemed significant. To identify dominant and stable voxels within a dot product image, a bootstrap analysis of standard errors was

conducted (Efron and Tibshirani, 1986). The bootstrap method allowed us to identify voxels that consistently contributed to the experimental effect within each LV. Only local maxima with bootstrap ratios $= \pm 4.0$ or greater (p<0.0001) and a spatial extent greater than 15 voxels were considered significant. All local maxima coordinates were converted to Talairach space and the Talairach and Tournoux atlas was used to localize these maxima and identify the Brodmann area (BA) label for each significant activation (Talairach and Tournoux, 1988).

Post-hoc SPM data analysis. The PLS analysis did not identify an LV related to a differential pattern of brain activity during spatial versus temporal context memory retrieval nor any task-by-difficulty inter-actions. Given our a priori goals of this study (to explore task differences and task-by-difficulty interactions during spatial and temporal context retrieval after equating task structure and difficulty) we conducted a post-hoc univariate analysis of the same data using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/) to examine if we could observe task differences in PFC activity during spatial versus temporal context retrieval and task-by-difficulty interactions in PFC activity at retrieval. Random effect group analysis was conducted to identify within group task differences in BOLD response in the PFC 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 eight experimental runs in SPM2. The following encoding and retrieval event types were entered into the GLM as stick-function events, and convolved with the SPM canonical hemodynamic response function (HRF), and its first temporal derivative (Hopfinger et al., 2000): Spatial Easy, Temporal Easy, Spatial Difficult and Temporal Difficult events from both the encoding and retrieval phases of the experiment. This yielded eight regressors of interest and eight of no interest (HRF temporal derivatives). In addition, parameters for four additional experimental conditions that were not relevant to the current experimental question and movement parameters were included as covariates of no interest in the GLM. Parameter 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 investigated using weighted t-contrast vectors (Friston, 2003). These contrasts were designed to identify brain regions differentially engaged during spatial versus temporal context retrieval events. Contrasts 1 and 2 examined differences in brain activity during spatial>temporal (contrast 1) and during temporal>spatial (contrast 2) context memory at retrieval, collapsed across levels of difficulty. Contrasts 3 and 4 examined task-by-difficulty at retrieval interactions. Whole-brain, random effects, one-tailed, group level, t-tests were then conducted on these contrast images, across participants, to test the null hypothesis that there was no significant, within group, BOLD activity change related to the contrasts of interest (Friston, 2003; Worsley and Friston, 1995; Worsley et al., 2002). Regional activations were considered significant if they had a t-value greater than 3.73 (p<0.001, uncorrected) and spatial extent (k) greater than 15 voxels. In defining activations within the PFC we used the nomenclature presented by Miller and Cohen (2001); with the exception of BA 10, which Miller and 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 and Owen, 2004; Simons et al., 2005). Localization of activated regions was determined by converting the SPM results to Talairach coordinate space and by reference to the Talairach and Tournoux atlas (Talairach and Tournoux, 1988).

MRIcro (http://www.psychology.nottingham.ac.uk/staff/cr1/mricro.html) was used to create functional ROIs of all suprathreshold voxels activated within PFC from the SPM results. Marsbar software (http://marsbar.sourceforge.net/) was used to extract each ROI's mean BOLD parameter estimate value (beta value) for each encoding and retrieval event type, for each participant. Mean beta plots were then created depicting the mean beta value for each ROI during spatial and temporal context retrieval event types (ROI plots) to visualize the SPM results.

Post-hoc conjunction analysis. Finally, we conducted a conjunction analysis using SPM2 and Marsbar to bridge the ST-PLS results which highlighted the similarities in image-level brain activity between events, and the SPM results which highlighted the differences in voxel-level brain activity between events (Nichols et al., 2005). Conjunction analyses were conducted to examine percent overlap in significant activations observed during spatial and temporal context retrieval, versus baseline, within each difficulty level (conjunction within 3s1r and within 3s3r), since we knew that there was a significant difference in activation between levels of difficulty from the ST-PLS results. The conjunction image was achieved by saving a whole-brain image of the suprathreshold voxels (p<.001, uncorrected, spatial extent threshold, k>5) for each spatial and temporal task type vs. baseline (S_{img}, T_{img}), then using Marsbar software (http://marsbar.sourceforge.net/) to perform an AND transformation on these images ($S\&T_{img}$). This operation identifies regions activated by spatial and temporal events by creating a new image composed of voxels that have minimum significance for both of the input images (Nichols et al., 2005). The percent overlap is then calculated by dividing the number of resulting voxels in $S\&T_{img}$ ($S\&T_{num}$) by the number of suprathreshold voxels from one of the original suprathreshold input images (S_{num} or T_{num}) to obtain either a spatial or a temporal percent overlap value (e.g.: Temporal % overlap $= S\&T_{num}/T_{num}$). In addition, S_{num} and T_{num} were used to directly compare spatial and temporal activation throughout the brain. This is calculated as a percentage for each respective task by dividing the difference between S_{num} and T_{num} by the number of suprathreshold voxels of either task image (e.g.: Spatial recruits χ% more voxels than temporal, where $\chi = (S_{num} - T_{num})/T_{num} \cdot 100\%$).

Results

Behavioral results

We only had RT data for 14 out of the 16 subjects due to a computer program error for the first two subjects scanned; RT was not collected, but accuracy was. Table 1 presents the task accuracy (proportion correct) and total reaction time results for Spatial Easy, Temporal Easy, Spatial Difficult and Temporal Difficult Tasks. The 2-by-2 repeated measures ANOVA for accuracy indicated that there was a significant difficulty main effect ($F(1,15) = 48.20$ p<.001), but there was no significant task main effect ($F(1,15) = 1.1$, p>.05) nor a significant task-by-difficulty interaction (F<1). Similarly, the 2-by-2 repeated measures ANOVA for RT yielded a significant Difficulty main effect ($F(1,13) = 178.44$, p<.001), but no significant task main effect (F<1) and no significant task-by-difficulty interaction ($F(1,13) = 3.93$ p>.05) effect. Therefore, by equating task structure at encoding and retrieval subjects performed equivalently during spatial and temporal context retrieval events, within a specific difficulty level.

Table 1
Mean behavioral data with standard error.

	Spatial	Temporal	Chance
Accuracy (N=16)			
Easy	.81 (.03)	.79 (.04)	0.33
Difficult	.59 (.04)	.56 (.04)	0.17
Reaction time (N=14)			
Easy	3321.25 (161.17)	3178.76 (199.21)	n/a
Difficult	4506.14 (96.50)	4585.57 (108.34)	n/a

Note. Accuracy values shown are the proportion correct per task type with SE.
The task mean reaction time values shown are in msec with SE. For two subjects there was a computer error and RT data was not collected.

Debriefing results

Of the 16 subjects included in the fMRI analysis, two subjects reported finding the spatial source retrieval trials more difficult and two subjects reported finding the temporal context retrieval trials more difficult. The remaining 12 subjects did not report finding one type of retrieval task to be more difficult than the other.

Table S(supplementary)-1 is included in the appendix and presents each subject's verbal report of his, or her, strategy employed during encoding and retrieval. Eight of the subjects explicitly reported using a categorical strategy to memorize faces during all spatial and temporal events, such as labeling subjects based on a physical attribute or gender or race. One of these subjects explicitly reported using temporal block as a grouping variable. Six subjects combined categorical strategies with relational strategies or with visual memory strategies; such as using a feature label and then associating a face with a family member or using a feature label and then taking a mental snapshot. One subject reported not using any specific strategy and the description of the strategy used by another subject was unclear to the rater. Therefore, overall subjects reported explicitly using categorical strategies, either in isolation, or in combination with another strategy. It is also important to note that the majority of subjects reported using the same strategy for encoding and retrieving both spatial and temporal context events.

fMRI results

ST-PLS results

The first two LVs from the PLS analysis were significant (p<.05), neither of these LVs identified differences in whole-brain activity during spatial versus temporal events at encoding or at retrieval, nor did they reflect task-type-by-difficulty interactions. Fig. 2A presents a bar graph of the design salience for each event type for the first LV (LV1; p<.001; percent cross-block covariance accounted for = 67.92%), which indicates that this LV identified brain regions that were differentially activated during retrieval versus encoding events. In addition, the bar graph indicates this LV effect was also modulated by task difficulty at retrieval. The temporal brain score for LV1 indicated this experimental effect was most strongly expressed 6 to 10 sec after event onset; see Fig. 2B. Moreover, the temporal brain score indicates that Difficult events exhibited the pattern most strongly.

Fig. 2C presents the bootstrap results for the s.i. of LV1 (BS ratio≥±4.0, p<0.0001), reflecting stable and significant activations at 6 to 10 sec after event onset. Table 2 lists the local maxima from LV1. Brain regions of positive voxel salience in the s.i. (areas in red/orange/yellow), reflected areas that were more active during retrieval versus encoding events, and were also more active during difficult versus easy retrieval events. Brain regions of negative voxel salience (areas in blue) reflected the inverse effect. Therefore there was greater activity during retrieval versus encoding events in bilateral ventrolateral PFC (VLPFC; BA 47 and 45), right dorsolateral PFC (DLPFC; BA 9 and 46), right anterior/superior PFC (BA 10), bilateral dorsal occipital cortices (BA 19), and bilateral precuneus (BA 7), in addition to other regions (see Table 2). In contrast there was more activity during encoding versus retrieval events in bilateral ventral visual cortices (BA 19/18), bilateral inferior temporal cortex (BA 20, 21), bilateral inferior parietal cortex (BA 40, 39) and left VLPFC (BA 47), in addition to other brain regions.

Fig. 3A presents a bar graph of the design salience for each event type for the second LV (LV2; p<.005; percent cross-block covariance accounted for = 13.61%), which indicates that this LV identified brain regions that were differentially activated during difficult versus easy retrieval events. Fig. 3B shows the temporal brain score plot which shows the differentiation in brain activity during difficult versus easy retrieval events was maximal between time lags 4 to 5 (8 to 10 sec after event onset). Fig. 3C shows the significant bootstrap results for the s.i. for LV2 at lags 4 and 5. Table 3 lists the local maxima for LV2.

During difficult versus easy retrieval events there was greater activity in brain regions related to motor processing (Halsband and Lange, 2006; Hammond, 2002; Paus et al., 1998; Timmann et al., 2010) including: bilateral precentral gyrus, post-central gyrus and cerebellum. In addition, during difficult>easy retrieval events there was greater activity in bilateral VLPFC (left BA 44 and right BA 44/45), left temporal pole (BA 22) and left hippocampus. In contrast, during easy>retrieval events, more activity was observed in left occipital cortex (BA 18 and 19), right temporal cortex (BA 21 and 22), right posterior cingulate (BA 30), right anterior/superior PFC (BA 10) and right supramarginal gyrus (BA 40). Interestingly, the right BA 10 activation related to easy>difficult memory retrieval events, overlapped with a region related to context retrieval>encoding, and performance on easy events was better than performance on difficult events. However, a post-hoc bivariate correlation analysis conducted in SPSS indicated there was no significant correlation between right BA 10 activity during retrieval and task accuracy during either easy or difficult context memory task.

Post-hoc SPM results

There were no significant activation in any brain region, at the threshold used, related to a task-by-difficulty interaction at retrieval. Table 4 presents the results from the post-hoc SPM analysis of PFC regions that were significantly more active during spatial versus temporal context retrieval, collapsed across levels of difficulty (p<.001, spatial extent>15 voxels).The majority of the PFC activations observed were also identified in the PLS results as being related to retrieval>encoding: bilateral VLPFC (BA 47 and 44) and right DLPFC (BA 46). Moreover, the PLS analysis indicated that these regions were also modulated by task difficulty. One of the PFC regions that was identified in this contrast, and was more associated with encoding vs. retrieval in PLS LV1, was the left anterior PFC (BA 10). There were no significant voxels that were more active during temporal versus spatial context retrieval at the thresholds specified.

We extracted the mean beta value for each of the PFC ROIs listed in Table 4 during Spatial and Temporal retrieval events, averaged across difficulty level. Fig. 4 presents the mean beta plots for the four PFC ROIs: left BA 10, left BA 44, right BA 47 and right BA 46. Examination of Fig. 4 indicates that there were variations in the level of activity, relative to baseline, between event/events types. During temporal context retrieval there was less activity, relative to baseline, in right BA 47 and left BA 10, compared to spatial context retrieval. In addition, there was more activity in right BA 46 and left BA 44 during spatial versus temporal context retrieval, relative to baseline.

Post-hoc conjunction analysis

Table 5 presents the conjunction analysis results. Within the Easy events, there were 26,055 voxels that exhibited overlapping activity during correct spatial and correct temporal context retrieval. The overlapping activations accounted for 69% of the activations uniquely observed during spatial context retrieval versus baseline and for 88% of the activations uniquely observed during temporal context retrieval versus baseline. Within the Difficult events, there were 34,420 voxels that exhibited overlapping activity during correct spatial and correct temporal context retrieval. The overlapping activations accounted for 79% of the activations uniquely observed during spatial context retrieval versus baseline and for 94% of the activations uniquely observed during temporal context retrieval versus baseline.

Fig. 5 contains the conjunction of the activation maps for Spatial and Temporal Easy retrieval events, and for Spatial and Temporal Difficult retrieval events. It is notable that there is striking similarity in the conjunction maps for easy versus difficult events, with the difficult events activating regions with larger spatial extent and much more motor-related areas. Interestingly, within difficulty level there was overlapping activation during spatial and temporal context retrieval events in most of the PFC regions identified in the SPM analysis as
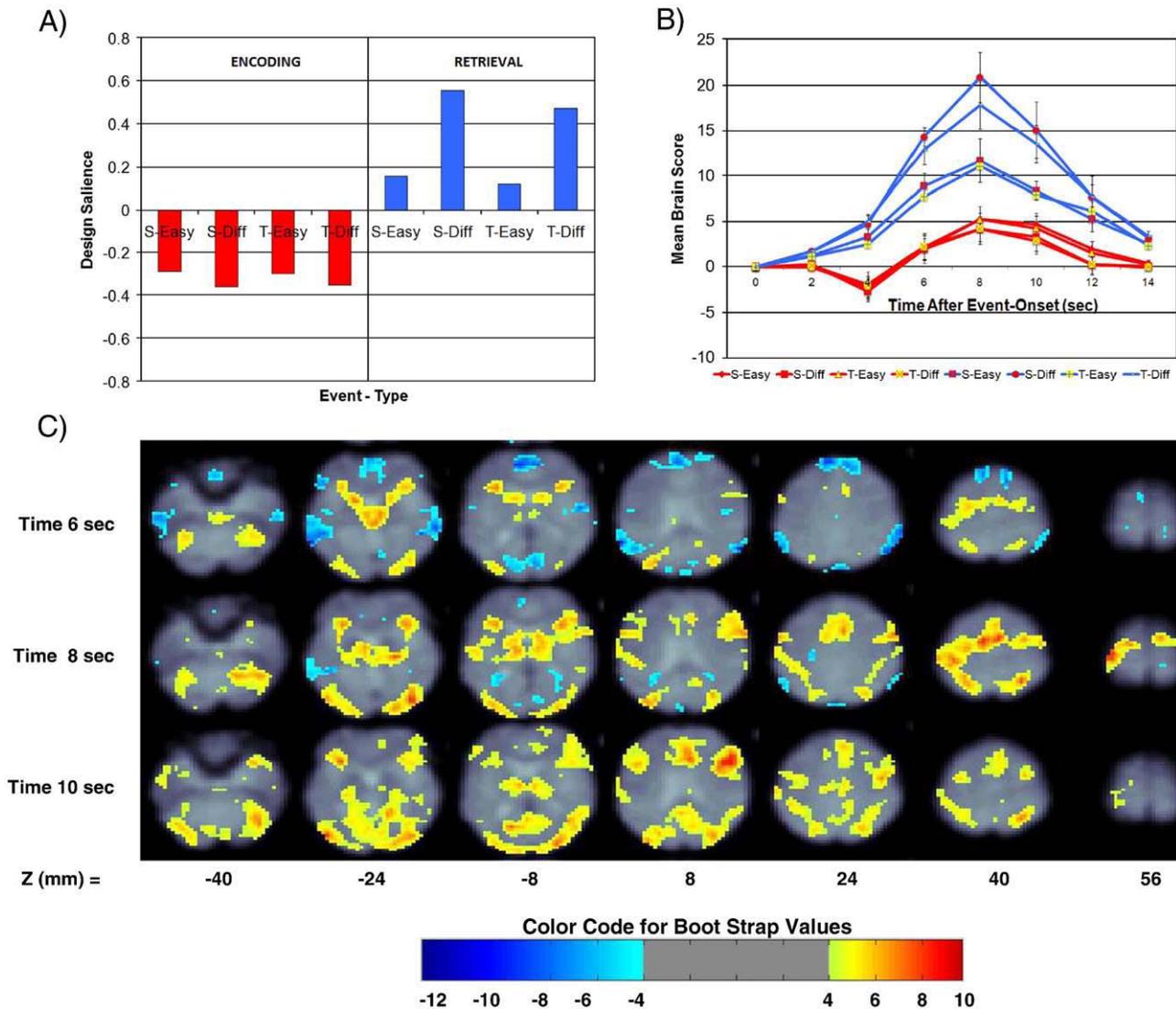
Fig. 2. Latent Variable 1 (LV1) — regions differentially activated during context retrieval versus encoding. A) Bar graph of design salience for each event type entered into the PLS analysis. This graph indicates the experimental effect identified by LV1. The bars colored in red represent the design salience for encoding events and the bars colored in blue represent the design salience for retrieval events. B) The temporal brain score graph for each event type indicates that the experimental effect (retrieval versus encoding) was maximally represented 6–10 sec after event onsets. C) The singular image for LV1 at bootstrap ratio threshold of ±4.0 (p<.0001), which reflects stable and significant activations at 6 to 10 sec after event onset. The color-bar at the bottom represents the color code for the colorized activations on the singular image. Regions colored in red–orange–yellow are positively related with the experimental effect presented in (A) and reflect regions that are more active during retrieval versus encoding events, and are also more active during difficult versus easy retrieval events. Regions colored in blue are negative related with the experimental effect presented in (A) and reflect regions that are more active during encoding versus retrieval events. There were four different event types: SE = spatial encoding, SR = spatial retrieval, TE = temporal encoding, TR = temporal retrieval, conducted at two levels of difficulty (difficulty (Diff) and easy). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

being significantly more active during spatial>temporal context retrieval: right BA 47 (Easy Conjunction Map coordinates X = +42 mm, Y = +23 mm, Z = −5 mm; Difficult Conjunction Map coordinates X = +42 mm, Y = +20 mm, Z = +2 mm), left BA 44/45 (Easy Conjunction Map coordinates X = −45 mm, Y = +19 mm, Z = +22 mm; Difficult Conjunction Map coordinates X = −46 mm, Y = +16 mm, Z = +22 mm), and right BA 46 (Easy Conjunction Map coordinates X = +48 mm, Y = +26 mm, Z = +15 mm; Difficult Conjunction Map coordinates X = +48 mm, Y = +27 mm, Z = +15 mm). However, there was no overlap at either difficulty level between spatial and temporal context retrieval in left BA 10 ROI indentified in the SPM results. Interestingly, left BA 10 was identified as being more related to encoding versus retrieval processing. Therefore, the conjunction analysis indicates there was considerable overlap in the pattern of brain activity observed during spatial and temporal context retrieval during both easy and difficult events. Moreover, several of the PFC ROIs identified as being more active during spatial>temporal context retrieval from the

SPM results also appeared in the conjunction maps. These results corroborate the PLS results and suggests that within difficulty level, there was considerable similarity in the overall activation results during spatial versus temporal context retrieval. These results also indicate that across difficulty level similar PFC regions were engaged, although to a greater extent during difficult>easy events.

Discussion

The primary goal of the current study was to determine if previously reported differences in PFC activity during spatial versus temporal context retrieval would be observed after we successfully equated retrieval performance between task types, and equated the cognitive strategies employed by subjects during spatial versus temporal context memory events (Dobbins et al., 2003; Mitchell et al., 2004; Rajah et al., 2008; Rajah et al., 2010; Slotnick et al., 2003). We equated the cognitive strategies employed by subjects during

Table 2
Local maxima for LV1 EM retrieval versus EM encoding.

Temporal lag (sec)	Bootstrap ratio	Spatial extent	Talairach coordinates			HEM	Gyral location	BA
			X	Y	Z			
Local maxima of positive salience (EM retrieval > EM encoding)								
6	12.54	954	36	19	−1	Right	Insula and inferior frontal gyrus	13/47
6	8.09	375	−28	−80	30	Left	Middle occipital gyrus	19
6	7.62	358	36	−80	22	Right	Middle occipital gyrus	19
6	7.31	420	−20	−1	55	Left	Superior frontal gyrus	6
6	7.26	70	0	−56	−31	Right		Cerebellum
6	6.39	39	28	−51	58	Right	Superior parietal lobule	7
6	6.30	21	−59	6	33	Left	Precentral gyrus	6 and 44
6	5.60	52	−20	−59	55	Left	Superior parietal lobule	7
6	5.49	44	67	9	25	Right	Middle frontal gyrus	9
6	5.38	36	24	−68	48	Right	Superior parietal lobule	7
8	13.23	4610	8	6	48	Right	Middle cingulate gyrus	6 and 24
8	10.94	1324	40	−82	−3	Right	Inferior occipital gyrus	19
8	5.54	30	67	−10	30	Right	Postcentral gyrus	1 and 3
8	5.52	23	67	−38	20	Right	Superior temporal gyrus	22
10	11.46	6884	48	20	21	Right	Middle frontal gyrus	45 and 46
10	10.14	685	−36	19	−11	Left	Inferior frontal gyrus	47
10	5.38	38	59	−16	−16	Right	Middle temporal gyrus	21
10	5.30	45	20	63	8	Right	Superior frontal gyrus	10
Local maxima of negative salience (EM encoding > EM retrieval)								
6	−10.15	217	67	−37	42	Right	Supramarginal gyrus	40
6	−9.77	876	−8	52	38	Left	Superior medial gyrus	9
6	−9.62	291	67	−35	−8	Right	Middle temporal gyrus	21
6	−9.46	197	−63	−53	28	Left	Inferior parietal lobule	40
6	−7.99	281	−12	−89	4	Left	Lingual gyrus	17
6	−7.47	31	−48	6	−37	Left	Inferior temporal gyrus	20
6	−7.31	76	−51	27	−5	Left	Inferior frontal gyrus	47
6	−4.88	17	−12	−92	30	Left	Superior occipital gyrus	19
8	−7.30	207	−63	−36	−12	Left	Inferior temporal gyrus	20
8	−6.71	87	40	−47	−1	Right	Middle temporal gyrus	21
8	−6.06	48	0	−92	34	Left	Cuneus	18
8	−5.89	48	−55	−60	40	Left	Angular gyrus	39
8	−5.84	15	−8	55	5	Left	Superior medial gyrus	10
8	−5.73	36	59	−56	43	Right	Inferior parietal lobule	40
8	−5.22	15	12	−81	11	Right	Calcarine gyrus	17

Note. Temporal lag represents the time (sec) after event onset, when a cluster of voxels exhibited a peak bootstrap ratio reflecting the contrast effect of interest (EM encoding versus retrieval main effect).
The bootstrap ratio threshold was set to ≥ + or −4.0, and identified dominant and stable activation clusters.
The spatial extent refers to the total number of voxels included in the voxel cluster (threshold ≥ 15). The stereotaxic coordinates are measured in mm and gyral location and Brodmann Areas (BA) were determined by reference to Talairach and Tournoux (1988). HEM refers to the cerebral hemisphere in which the activation occurred.

both events by controlling for the task structure of the two memory events at both encoding and retrieval (see Methods for details). Debriefing reports obtained from the fMRI subjects indicated that the majority of them used categorical strategies alone, or in combination with other strategies during encoding and retrieval of *both* spatial and temporal context memory tasks. We defined a categorical strategy as: the use of simple categorical verbal labels during encoding of faces; such as spatial location, temporal block, feature label, name, occupation (Kosslyn et al., 1992; Palermo et al., 2008; Slotnick and Moo, 2006). This suggests that we successfully controlled for task differences in the cognitive strategies employed by subjects by equating task structure.

In addition, we successfully controlled for accuracy and reaction time differences between spatial versus temporal context retrieval, *within each of the two levels of task difficulty*. There was no significant task effect in either retrieval accuracy or RT within difficulty level, nor was there a significant task-by-difficulty interaction for accuracy and RT. However, there was a significant difficulty effect for both accuracy and RT: difficult Spatial and Temporal events yielded lower accuracy and longer RTs than easy Spatial and Temporal events. These results indicate that the difficulty manipulation was successful and that it had an equivalent impact on the performance of both spatial and temporal context events, since there was no significant task-by-difficulty interaction in accuracy or RT. This is the first behavioral and/or neuroimaging study in which performance of spatial source retrieval and temporal context retrieval tasks has been equated. This indicates

that by controlling for task structure and the cognitive strategies employed during spatial versus temporal memory tasks, we were able to equate performance between task types, within difficulty level. Furthermore, the behavioral results suggest that the task-difficulty manipulation had a similar impact on both task types, indicating the current manipulation may have engaged only task-similar, domain-general cognitive processes.

PLS results: similarities in PFC contributions to spatial and temporal context retrieval

The PLS analysis of the fMRI data indicated that there was no significant whole-brain pattern of brain activity that distinguished spatial versus temporal context events during either encoding or retrieval, within a difficulty level. Nor at the whole-brain image level was there evidence of a task–by–difficulty interaction. However, the PLS analysis did identify significant effects that highlighted the overlap in brain activity during spatial and temporal context memory tasks which were modulated by the task-difficulty manipulation.

LV1 from the PLS analysis, identified regions in bilateral VLPFC, right anterior PFC (APFC) and right DLPFC that were more active during all retrieval events versus encoding events. These task-general retrieval-related activations were also modulated by task difficulty, and were more active during difficult versus easy retrieval events. Conversely, encoding was related to increased activity in distinct regions of left VLPFC, relative to retrieval. Several posterior cortical
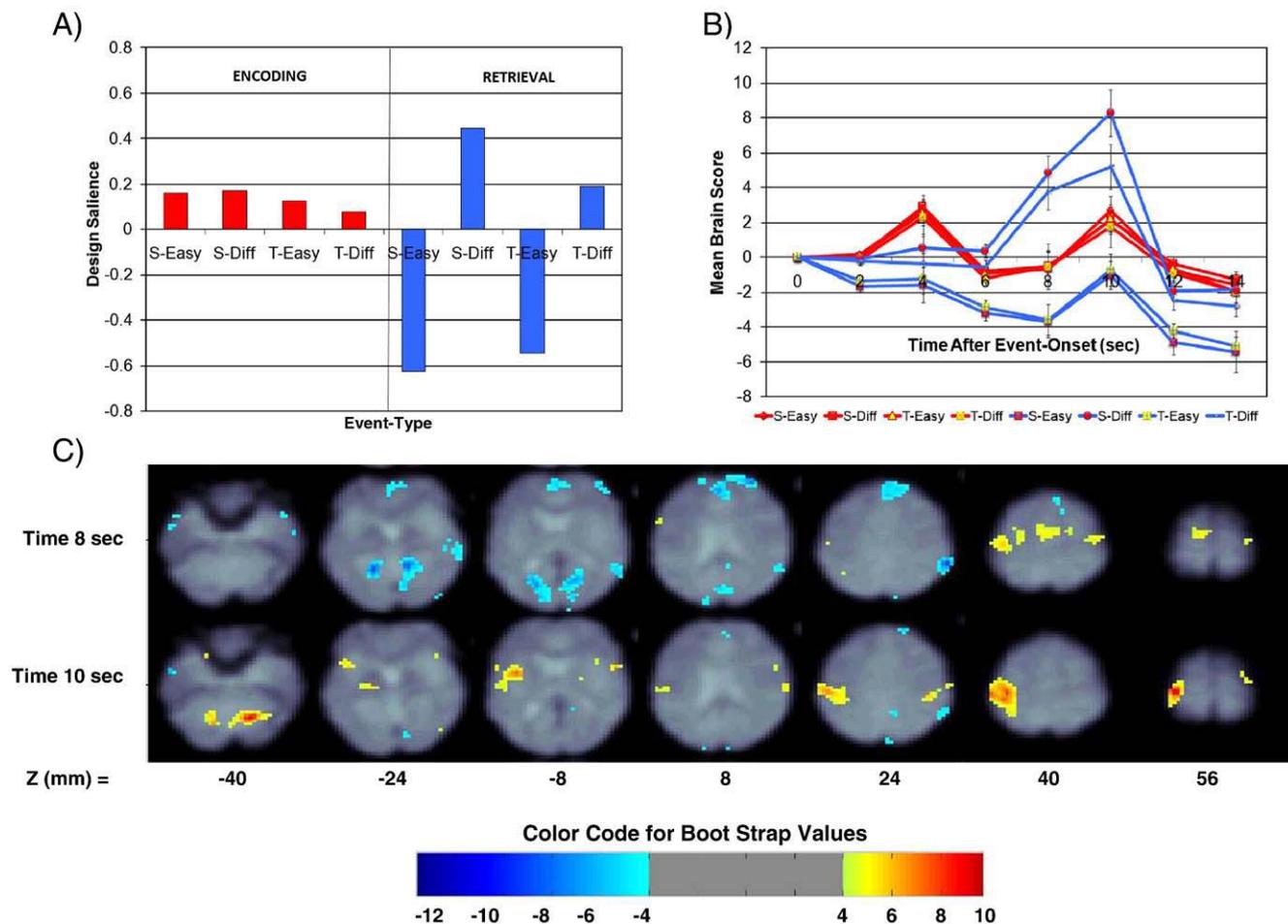
Fig. 3. Latent Variable 2 (LV2) — regions differentially activated during difficult versus easy context retrieval events. A) Bar graph of design salience for each event type entered into the PLS analysis. This graph indicates the experimental effect identified by LV2. The bars colored in red represent the design salience for encoding events and the bars colored in blue represent the design salience for retrieval events. B) The temporal brain score graph for each event type indicates that the experimental effect (difficult versus easy retrieval events) was maximally represented 8–10 sec after event onsets. C) The singular image for LV1 at bootstrap ratio threshold of ±4.0 (p<.0001), which reflects stable and significant activations at 6 to 10 sec after event onset. The color-bar at the bottom represents the color code for the colorized activations on the singular image. Regions colored in red–orange–yellow are positively related with the experimental effect presented in (A) and reflect regions that are more active during difficult versus easy retrieval events. Regions colored in blue are negative related with the experimental effect presented in (A) and reflect regions that are more active during easy versus difficult retrieval events. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

regions were also differentially activated during retrieval versus encoding (see Table 2); however, in the current paper we focus on PFC contributions to context memory encoding and retrieval.

The patterns of PFC retrieval-related activations and of PFC encoding-related activations in the current study are consistent with prior studies of episodic memory (Cabeza and Nyberg, 2000; Nyberg et al., 2000; Rajah and D'Esposito, 2005; Tulving et al., 1994). For example, studies of episodic memory retrieval have reported increased retrieval-related activation in bilateral VLPFC (Lepage et al., 2000; Nyberg et al., 2003), right DLPFC (Buckner, 2002; Rugg et al., 2003; Wagner et al., 2001) and right APFC (Dobbins et al., 2003; Henson et al., 2000). Similarly encoding-related activity has been consistently reported in left VLPFC (Fletcher et al., 1998; Kahn et al., 2005). In the current study, we did not manipulate the variables necessary to infer the precise retrieval– or encoding–related functions functions of each of the PFC activations. Therefore, one must be cautious in interpreting the functions attributed to the activations observed in LV1 (Poldrack, 2006).

However, we did directly manipulate the level of task difficulty. We hypothesized that the difficulty manipulation employed in the current study would increase demands on both memory retrieval processes and domain-general cognitive control mechanisms that

related to task effort, such as increased strategic retrieval (Moscovitch and Winocur, 2002; Rajah and McIntosh, 2006), response-selection and motor processing (Schumacher et al., 2005) and/or monitoring (Henson et al., 1999; Petrides, 2000), to name a few. As noted in the Introduction, our goal was not to discriminate amongst these variable influences that can individually, or in combination, increase the difficulty of a memory task. Instead we included this manipulation to determine if increasing task difficulty would have a similar or different impact during spatial versus temporal context retrieval.

The behavioral results indicated that there was a significant difficulty main effect in both behavioral measures, but there was no significant task-by-difficulty interaction in either accuracy or RT, suggesting that the difficulty manipulation had a similar impact on both task types. At the whole-brain level, the PLS results corroborated these behavioral results: a significant LV related to a task-by-difficulty interaction was not observed. Instead, the positive salience from LV2 of the PLS analysis reflected activation differences during easy versus more difficult retrieval-task conditions, that were *common to both spatial and temporal context retrieval events*. This suggests that LV2 identified brain regions that were involved in mediating similar, domain-general, retrieval and cognitive control processes related to task difficulty during both spatial and temporal context retrieval

Table 3
Local maxima LV2 difficult versus easy retrieval events.

Temporal lag (sec)	Bootstrap ratio	Spatial extent	Talairach coordinates			HEM	Gyral location	BA
			X	Y	Z			
Local maxima of positive salience (difficult>easy retrieval)								
8	8.69	252	−4	−5	59	Left	Supplementary motor area	6
8	5.48	50	40	−12	63	Right	Precentral gyrus	6
8	5.36	19	−59	9	25	Left	Inferior frontal gyrus	44
10	9.42	670	−40	−20	64	Left	Precentral gyrus	6
10	9.03	226	20	−59	−17	Right		Cerebellum
10	7.53	27	55	4	11	Right	Inferior frontal gyrus	44 and 45
10	6.66	56	44	−33	42	Right	Postcentral gyrus	2
10	6.63	47	−16	−67	−17	Right		Cerebellum
10	5.92	19	−48	11	−4	Left	Temporal pole	22
10	5.82	23	16	−68	−40	Right		Cerebellum
10	5.70	30	44	−5	63	Right	Middle frontal gyrus	6
10	5.33	36	67	−15	19	Right	Postcentral gyrus	1 and 3
10	5.22	24	−24	−20	−6	Left	Hippocampus	
10	5.20	22	40	12	3	Right	Insula	13
Local maxima of negative salience (easy>difficult retrieval)								
8	−9.28	497	−20	−54	−1	Left	Lingual gyrus	18
8	−7.97	141	63	−45	39	Right	Supramarginal gyrus	40
8	−7.14	376	32	63	15	Right	Superior frontal gyrus	10
8	−6.79	87	63	−16	−13	Right	Middle temporal gyrus	21
8	−6.11	22	44	58	1	Right	Superior frontal gyrus	10
8	−5.04	18	−16	−96	31	Left	Superior occipital gyrus	19
8	−4.97	24	59	6	−27	Right	Medial temporal pole	22
10	−6.60	17	8	−53	36	Right	Posterior cingulate gyrus	31
10	−5.16	27	59	−49	32	Right	Supramarginal gyrus	40

Note. Temporal lag represents the time (sec) after event onset, when a cluster of voxels exhibited a peak bootstrap ratio reflecting the contrast effect of interest (EM encoding versus retrieval main effect).
The bootstrap ratio threshold was set to ≥ + or − 4.0, and identified dominant and stable activation clusters.
The spatial extent refers to the total number of voxels included in the voxel cluster (threshold ≥ 15). The stereotaxic coordinates are measured in mm and the gyral location and Brodmann Areas (BA) were determined by reference to Talairach and Tournoux (1988). HEM refers to the cerebral hemisphere in which the activation occurred.

events (Dobbins and Han, 2005; Dobbins and Wagner, 2005; Rajah et al., 2008). For example, the easier retrieval events were related to increased activity in right APFC, in the same right APFC region as that exhibiting increased activity during retrieval versus encoding. Given that subjects performed more accurately on easy versus difficult events, it is possible that increased right APFC activity in the current study tracked retrieval success (Henson et al., 1999; Rugg et al., 1996). However, we did not observe a direct correlation between activity in this region, and performance, in this study.

Table 4
Post-hoc SPM analysis results.

| T-value	Spatial extent	Talairach coordinates			HEM	Gyral location	BA
		X	Y	Z			
Regions more active during spatial versus temporal context retrieval							
6.53	315	−50	−55	−2	Left	Middle temporal gyrus	BA 37
5.66	619	−59	−35	37	Left	Inferior parietal lobule	BA 40
5.58	177	−53	13	18	Left	Inferior frontal gyrus	BA 44/45
5.46	130	−32	−15	19	Left	Insula	
5.32	21	−26	44	22	Left	Superior frontal gyrus	BA 10
4.76	48	−24	1	50	Left	Middle frontal gyrus	BA 6
4.23	42	−30	−64	33	Left	Angular gyrus	BA 39
6.15	85	50	−51	−4	Right	Inferior temporal gyrus	BA 37
5.55	51	46	39	−5	Right	Inferior frontal gyrus	BA 47
5.13	92	44	16	5	Right	Insula	
4.94	145	26	−79	13	Right	Cuneus	BA 17
4.51	17	55	10	7	Right	Precentral gyrus	BA 6
4.48	20	40	38	15	Right	Middle frontal gyrus	BA 46

Note. This table presents the random effects 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 (threshold ≥ 15). The stereotaxic coordinates are measured in mm and gyral location and Brodmann Areas (BA) were determined by reference to Talairach and Tournoux (1988). HEM refers to the cerebral hemisphere in which the activation occurred.

The more difficult memory retrieval events were associated with increased activity in bilateral lateral PFC, with peaks reported in bilateral VLPFC (BA 44 and 45), compared to the easy retrieval events. Although, the focus of this study was on examining PFC contributions to spatial versus temporal context memory retrieval; given the vast literature associating hippocampal contributions to context memory (Addis and McAndrews, 2006; Cabeza and Nyberg, 2000; Davachi, 2006; Henson, 2005), we found it interesting that in addition to observing increased bilateral lateral PFC activity during difficult versus easy events, we also observed greater left hippocampal activation during difficult versus easy retrieval events. The difficult retrieval events required subjects to recollect the spatial location and or temporal order of three stimuli and make three motor responses using their right hand. Thus the difficult events placed greater demands on: semantic processing during stimulus selection, response inhibition, and recollection processes, compared to the easier retrieval events. Therefore, the increased activity in bilateral VLPFC and left hippocampus during difficult versus easy events may reflect the involvement of these brain areas in mediating these aforementioned cognitive processes. This interpretation is consistent with previous studies of left VLPFC involvement in stimulus selection and response selection, of right VLPFC involvement in response inhibition and of hippocampus in source memory recollection (Nadel and Moscovitch, 2001; Rosenbaum et al., 2001; Rowe et al., 2000; Schubotz and von Cramon, 2003; Thompson-Schill et al., 1997).

Previous studies have observed increased right DLPFC activity during temporal context retrieval and recognition retrieval events and have interpreted this as reflecting a role for right DLPFC in cognitive control processes important for mediating familiarity-based retrieval decisions (Dobbins et al., 2003; Duarte et al., 2004; Yonelinas, 2001). In addition, it has been argued that right DLPFC activity during memory retrieval may be related to a role for this region in domain-general cognitive control processes such as error processing and monitoring (Cabeza et al., 2003; Dobbins et al., 2004; Hayama and
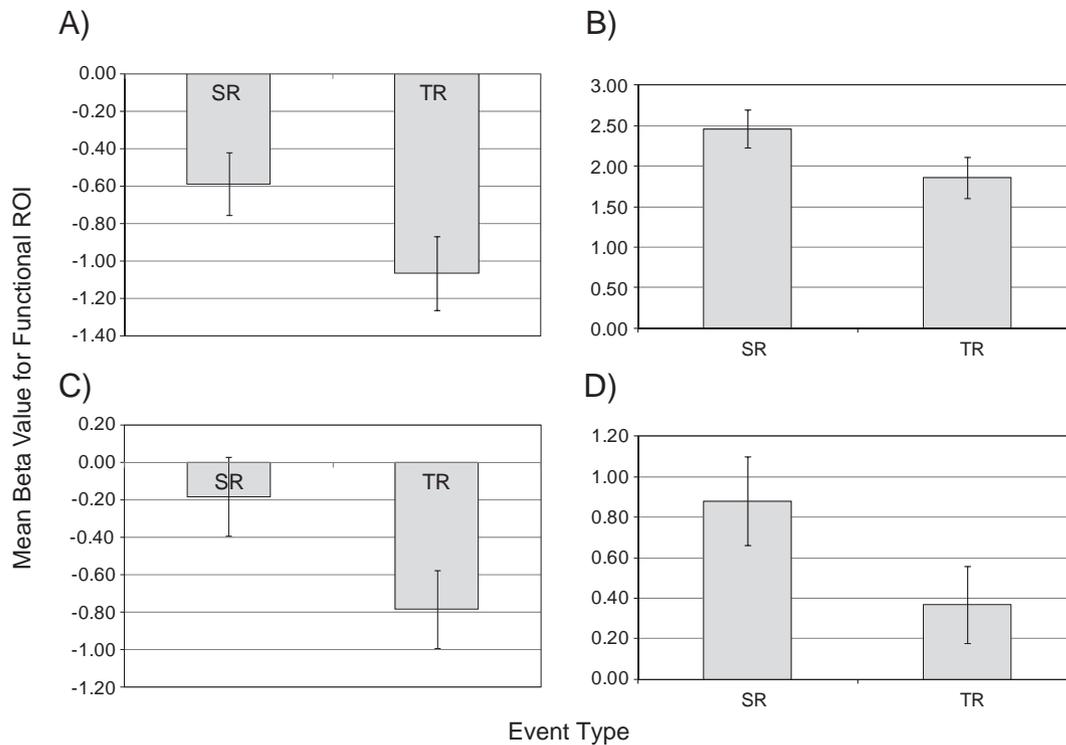
Fig. 4. Mean beta plots for PFC ROIs from SPM results. Mean beta value for A) left BA 10. B) left BA 44. C) right BA 47 and D) right BA 46, during spatial (SR) and temporal (TR) context retrieval events.

Rugg, 2009; Henkel et al., 1998; Henson et al., 2005; Petrides, 2005; Rugg et al., 1999; Swick et al., 2006). Although a right DLPFC activation was not observed in LV2, right DLPFC activations were observed in LV1. The temporal brain score for LV1 indicates that all retrieval-related activations were also greater for the difficult versus easy retrieval events (see Fig. 2). Therefore, even though right DLPFC was more active during all retrieval events, it was more strongly engaged during difficult versus easy retrieval events. This result is consistent with previous reports of right DLPFC involvement in difficult memory retrieval tasks which may reflect this regions' importance in error processing and retrieval monitoring demands (Chevrier et al., 2007; Hayama and Rugg, 2009; Henson et al., 2005; Henson et al., 1999; Petrides, 2000; Rugg et al., 1999).

Therefore, to summarize, the PLS results identified a network of brain regions that were more active during the retrieval versus encoding of spatial and temporal contextual details which included: bilateral VLPFC, right APFC, right DLPFC and left hippocampus. These brain regions were also modulated by task difficulty in a similar manner across spatial and temporal memory tasks. This overlap in neural activity between task types and across difficulty levels, particularly in the PFC, was corroborated by the conjunction analysis, which indicated a high degree of similarity in activity between tasks, within difficulty (see Table 5) and indicated that similar PFC regions were recruited across difficulty levels (see Fig. 5). Thus, the PLS and

conjunction results suggest that after equating task performance within levels of difficulty, similar PFC regions were recruited during spatial and temporal context retrieval. Furthermore, the manipulation of task difficulty within task type resulted in a similar pattern of increased PFC and hippocampal recruitment between task types. This indicates that the task differences in PFC activity previously reported during spatial versus temporal context retrieval, may have been due to differences in task performance and task structure; and that once these factors are controlled both tasks similarly engage the PFC. This argues that PFC involvement in spatial and temporal context memory tasks reflect this regions' role in domain-general cognitive control processes (Rajah et al., 2008).

Comparison of PLS and SPM results: differences in degree of PFC activity during spatial versus temporal context retrieval events

Previous studies have reported task differences in the laterality of PFC activity during spatial source versus temporal context retrieval (Dobbins et al., 2003; Dobbins et al., 2004; Mitchell et al., 2004) but these studies used univariate fMRI data analytic techniques, such as statistical parametric mapping (SPM; Frackowiak, Friston, Frith, Dolan, & Mazziotta, 1997). SPM can yield different results than that observed by ST-PLS due to computational differences between the two methods (see Addis et al., 2009; Chen et al., 2009; McIntosh and

Table 5
Conjunction analysis results.

Image 1		Image 2		Image1 AND Image 2	Image 1% overlap with Image 2	Image 2% overlap with Image 1
Name	Suprathreshold voxel #	Name	Suprathreshold voxel #	Conjunction voxel #	(Image 1 AND 2/Image 1)	(Image 1 AND 2/Image 2)
Spatial easy	37,613	Temporal easy	29,658	26,055	69	88
Spatial difficult	43,413	Temporal difficult	36,745	34,420	79	94

Note. We examined the % overlap in voxels activated during spatial and temporal context retrieval events, within each level of difficulty. Conjunctions were defined as overlap in significantly activated voxels (p<.0001, spatial extent >5) observed during spatial and temporal context retrieval events, relative to baseline, identified by using the "AND" transformation in Marsbar (http://marsbar.sourceforge.net/). This operation identifies regions activated by spatial and temporal events by creating a new image composed of voxels that have minimum significance for both of the input images (Nichols et al., 2005).

A) Conjunction Map for Spatial Easy and Temporal Easy Retrieval Activity
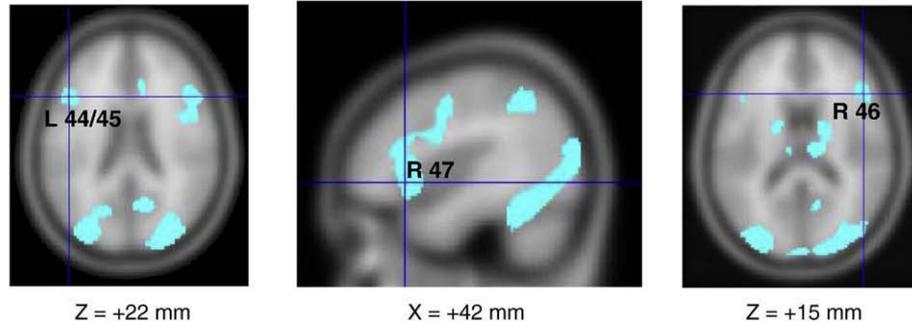
B) Conjunction Map for Spatial Difficult and Temporal Difficult Retrieval Activity
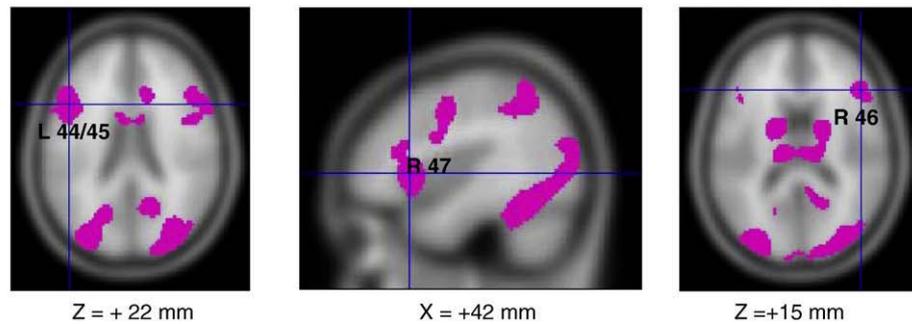
Fig. 5. Conjunction map for activity during spatial context retrieval and temporal context retrieval. A) Conjunction of activity during spatial and temporal context retrieval, during easy events, super-imposed on the SPM T1-template brain. B) Conjunction of activity during spatial and temporal context retrieval, during difficult events, super-imposed on the SPM T1-template brain. In both conjunctions there was overlap in activity in right BA 47, left BA 44 and right BA 46 during spatial and temporal context retrieval events, for both event types and difficult levels.

Lobaugh, 2004). One of the main differences between PLS and SPM methods that can contribute to different results, is that PLS focuses on the multivariate level of data analysis, and thus the inference is at the whole-brain image level; whereas SPM is focused on the individual voxel level. Therefore, with PLS and random assignment (permutation) there may not be any differences in activation between spatial versus temporal context retrieval, at a whole-brain image level; however it may remain possible that individual voxels exhibit task differences. As such, it would not be surprising if the SPM analysis could identify task differences in brain activity during spatial versus temporal retrieval, that the ST-PLS analysis did not identify. To determine if this was the case in the current data set, we conducted a post-hoc univariate analysis of the same data using SPM2 to examine if we could observe task differences in the relative level of brain activity in specific regions identified in the PLS analysis.

The results from this analysis indicated that there were differences in brain activity in the following PFC regions during spatial>temporal context retrieval: left APFC (BA 10), bilateral VLPFC (left BA 44, right BA 47) and right DLPFC (BA 46). Interestingly, these same regions were also indentified in the PLS results. The PLS results indicated that most of these PFC regions were more active during retrieval>encoding and were more engaged during difficult>easy retrieval events. Examination of the mean beta plots for these PFC ROIs (see Fig. 4) indicates that none of these regions were uniquely activated or deactivated for one task versus the other, or exhibited different directions of activation (i.e. positive versus negative slope), relative to baseline. Specifically, the pattern of recruitment in these PFC regions were parallel during both tasks, but there was less suppression of left BA 10 and right VLPFC and more recruitment of left VLFPC and right DLPFC during Spatial versus Temporal context retrieval. Interestingly, the SPM results did not identify any brain regions that exhibited a task-by-difficulty interaction in activity at the thresholds specified.

These SPM results indicate that *qualitatively* the activations were similar between tasks, and that the difficulty manipulation had a parallel effect on both tasks. This interpretation of the SPM results is consistent with the interpretations of the PLS and conjunction results. However, the SPM results also indicate that there were *quantitative* differences in PFC recruitment, at the voxel level, between tasks types. This latter observation raises the issue of how one interprets univariate task differences *in the "degree" of brain activity* within the context of multivariate results which highlight the overall similarity in neural activity, at the whole-brain level, between tasks.

In considering the SPM, PLS, and conjunction results together, we interpret the SPM results as reflecting quantitative modulations within nodes of a large-scale neural network (identified in the PLS and conjunction analyses) that was similarly engaged during spatial and temporal context memory tasks, and was similarly modulated by task difficulty (Rajah and McIntosh, 2005). Moreover, based on the PLS results we conclude that the increased recruitment of bilateral VLPFC and right DLPFC during spatial>temporal context retrieval suggests that at a neural-level spatial retrieval tasks may have remained more difficult than temporal retrieval tasks, despite behavioral equivalence in accuracy and RT between task types. This interpretation is consistent with the observation that the PLS results indicated that these PFC regions were modulated by task difficulty.

Conclusions

In conclusion, previous studies have reported laterality differences in PFC activity during spatial and temporal context retrieval (Dobbins et al., 2003; Duarte et al., 2008; Mitchell et al., 2004; Rajah et al., 2010). However, it remained unclear from these previous studies if the lateralization of PFC activity during spatial versus temporal context retrieval reflected inherent differences in PFC-related cognitive control

contributions to retrieving spatial versus temporal context information, or if they were a by-product of the different task structure employed in the two tasks, and differences in task performance (Dobbins et al., 2003; Mitchell et al., 2004; Rajah et al., 2010). After matching for these variables in the current study we did not observe significant differences in the laterality of the PFC regions activated during spatial versus temporal context retrieval. Instead the current PLS and conjunction results suggest once task structure and performance were matched a similar network of brain regions were engaged during both spatial and temporal context retrieval, and were similarly modulated by the task-difficulty manipulation during both tasks. These results suggest that PFC contributions to spatial and temporal context retrieval may not reflect *inherent differences* in the cognitive control processes important for retrieving spatial versus temporal context information, per se. Instead, the current results suggest that PFC contributions to both spatial and temporal context retrieval tasks may reflect this regions' importance in various domain-general cognitive control processes (Stuss and Knight, 2002).

One may argue against this conclusion by stating that one can never accept the null hypothesis (no significant differences in activity between spatial and temporal context events) as being true since failure to reject the null hypothesis may be due to low statistical power (Nickerson, 2000). However, it is notable that the SPM analysis did in fact detect differences in the degree to which brain regions were more or less active between spatial and temporal context retrieval; suggesting there was adequate power in the current study to detect differences. The activation differences identified from the SPM analysis furthered the multivariate results by indicating that even though equating task structure resulted in behavioral equivalence between tasks, and significant overlap in the domain-general PFC contributions between tasks at a whole-brain level; at a quantitative level there remained differences in the degree to which some nodes within this network were engaged during spatial versus temporal context retrieval. This may reflect differences in the amount to which some PFC-related domain-general cognitive processes may be recruited to perform spatial versus temporal context retrieval tasks (Rajah and McIntosh, 2005), which may account for why one experiences encoding and retrieving spatial *versus* temporal contextual details from episodic memory as cognitively distinct phenomena. Furthermore, based on prior research, it remains possible that these experiential differences are also mediated by the interaction between the PFC and other brain regions involved during encoding and/or retrieval (Gazzaley et al., 2004; McIntosh, 2004; Rajah et al., 1999). Future studies will need to explore this possibility.

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Disclosure statement

Acknowledgments

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