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Distinct Patterns of Functional and Effective Connectivity between Perirhinal Cortex and Other Cortical Regions in Recognition Memory and Perceptual Discrimination

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Traditionally, the medial temporal lobe (MTL) is thought to be dedicated to declarative memory. Recent evidence challenges this view, suggesting that perirhinal cortex (PrC), which interfaces the MTL with the ventral visual pathway, supports highly integrated object representations in recognition memory and perceptual discrimination. Even with comparable representational demands, perceptual and memory tasks differ in numerous task demands and the subjective experience they evoke. Here, we tested whether such differences are reflected in distinct patterns of connectivity between PrC and other cortical regions, including differential involvement of prefrontal control processes. We examined functional magnetic resonance imaging data for closely matched perceptual and recognition memory tasks for faces that engaged right PrC equivalently. Multivariate seed analyses revealed distinct patterns of interactions: Right ventrolateral prefrontal and posterior cingulate cortices exhibited stronger functional connectivity with PrC in recognition memory; fusiform regions were part of the pattern that displayed stronger functional connectivity with PrC in perceptual discrimination. Structural equation modeling revealed distinct patterns of effective connectivity that allowed us to constrain interpretation of these findings. Overall, they demonstrate that, even when MTL structures show similar involvement in recognition memory and perceptual discrimination, differential neural mechanisms are reflected in the interplay between the MTL and other cortical regions.

Keywords: declarative memory, fMRI, medial temporal lobes, object recognition, prefrontal cortex

Introduction

Mechanisms that allow the human brain to create internal representations of objects are fundamental to both memory and perception. For example, in order to recollect an encounter with a previously viewed object successfully, a stored representation of that object must contain sufficient detail so as to avoid confusion with encounters of other similar objects. Likewise, discriminating between similar objects currently in view requires the development of sufficiently detailed internal representations to allow for their differentiation. An important issue of current interest in cognitive neuroscience is whether structures in the medial temporal lobe (MTL), specifically perirhinal cortex (PrC), which interfaces the MTL with the ventral visual pathway, support representations of objects that are critical for perceptual as well as for memory-based discriminations (Baxter 2009; Suzuki 2009).

According to the prevailing view of brain organization, the MTLs act as an integrated modular system that is dedicated to declarative memory (Squire et al. 2004). This memory system is thought to maintain sharp neuroanatomical and functional boundaries with perceptual systems, including lateral and inferior temporal lobe structures that are dedicated to visual object identification, that is, the ventral visual pathway (e.g., Suzuki 2010). MTL mechanisms, including those in PrC, are thought to be critical only for recognition memory, that is, recognition of the prior occurrence of an object after a delay but not for online discrimination of simultaneously presented objects in visual perceptual tasks. This standard view has recently been put into question by several reports of visuoperceptual deficits in association with PrC damage in human and nonhuman primates (Eacott et al. 1994; Buckley and Gaffan 1997; Bussey et al. 2002, 2003; Barense et al. 2005; Lee et al. 2005, 2006; for review, see Buckley and Gaffan 2006; Murray et al. 2007). Studies examining the effects of PrC lesions in nonhuman primates have revealed impairments in a number of tasks that lack an obvious long-term declarative memory component. For example, Buckley et al. (2001) reported that monkeys with PrC lesions were impaired when required to determine the "odd" stimulus from a visual array of simultaneously presented similar objects. These deficits were related the degree of visual similarity between the foil stimuli and the target. Similarly, studies of humans with large MTL lesions that include PrC have uncovered impairments in visual oddity or oddball discrimination tasks when discriminanda are highly similar (Lee et al. 2005, 2006; cf., Shrager et al. 2006). Functional neuroimaging research in healthy participants also supports a role of PrC in oddity or oddball judgments and other perceptual discriminations (Devlin and Price 2007; Lee et al. 2007; O'Neil et al. 2009; Barense et al. 2010).

Although the evidence in support of a role of the MTL in functions beyond declarative memory remains controversial, it has inspired promising alternate theoretical accounts that reject the notion that the MTL acts as a unified, specialized declarative memory system. A radically different proposal is that different MTL structures may be specialized for distinct computations that are tied to the representation of unique classes of stimuli or experiences (Murray et al. 2007; Graham et al. 2010). Within such a framework, PrC has been proposed to constitute an extension of the representational hierarchy within the ventral visual pathway for object identification; it is thought to be recruited in tasks, perceptual or mnemonic, that require discriminations of objects with highly overlapping

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features. It has been proposed that PrC may provide a representation of the conjunctions of features (Murray and Bussey 1999; Murray et al. 2007) or of gestalt-characteristics (Cate and Köhler 2006) that are critical when individual perceptual features are insufficient for unique object identification. Computational modeling has demonstrated that such integrated higher-order representations are particularly important for recognition of prior occurrence of objects following delays. A typical delay is filled with a constant stream of visual input that creates massive interference at the feature level. Highly integrated object representations supported by PrC would allow for resolution of this interference in the assessment of the familiarity of a specific object at the time of its reoccurrence (Cowell et al. 2006, 2010). Complementing the role of PrC, hippocampal contributions would allow for representations that contain contextual information pertaining to a specific object encounter (e.g., Eichenbaum et al. 2007).

We recently reported a functional magnetic resonance imaging (fMRI) study whose findings argue against the classic view of MTL specialization for declarative memory and provide support for the representational account of PrC functioning just discussed (O'Neil et al. 2009). Using morphed faces as stimuli, we compared PrC activity while subjects completed 2 forced-choice tasks, both involving the presentation of 3 highly similar faces. An oddball task required the selection of a face most different from the others in the display, while a recognition memory task required the selection of the item presented in an earlier study phase. A luminance judgment task served as a baseline task of comparable difficulty that did not require referencing the type of complex stimulus representations that PrC is proposed to support. When contrasted with the baseline task, both experimental tasks engaged right PrC to an equivalent degree. Critically, PrC activity was also found to be greater for accurate than inaccurate trials in both tasks. While these findings clearly suggest common PrC involvement in recognition memory and perceptual discrimination, they also raise interesting new questions.

Clearly, tasks that require discrimination of multiple stimuli based on either mnemonic or perceptual information still have processing demands that are distinct from each other, even when the level of representational detail and integration required is considered comparable. Most importantly, recognition memory requires explicit assessment of a memory–strength signal associated with a stimulus currently in view or the recovery of contextual information from a prior related encounter, whereas perceptual discrimination does not. Performing these different tasks also evokes distinct phenomenological experiences; participants typically do not confuse whether their judgment is perceptual or mnemonic in nature. This situation raises the question as to what brain mechanisms differ between recognition memory and perceptual discrimination when PrC is commonly involved. Resolution of this question cannot be achieved by examining the representational role of PrC in isolation. Instead, broader processing dynamics related to processes of integration must be considered at the network level (McIntosh 1999; Friston 2002). Here, we took such an approach and revisited the fMRI data we reported previously (O'Neil et al. 2009) in order to examine whether the functional and effective connectivity of PrC with other cortical regions differed between the perceptual and recognition memory tasks that revealed common PrC involvement.

It is widely agreed that access to and manipulation of representations recovered through MTL mechanisms depends on control processes supported by prefrontal cortex (PFC; for a discussion, see Moscovitch 1992; Simons and Spiers 2003). Generally speaking, control processes shape the goal of any such attempt, the elaboration of the cue provided (if any), and the monitoring of the outcome of search processes. Functional neuroimaging research has provided considerable evidence that implicates PFC together with MTL structures in declarative memory, including at retrieval in recognition memory tasks (Skinner and Fernandes 2007; Mitchell and Johnson 2009). However, while many efforts have focused on parsing their distinct roles, the direct examination of functional interactions between the MTL and PFC has received much less attention so far (but see Köhler et al. 1998; Habib et al. 2003; McIntosh et al. 2003; Ranganath et al. 2005; Axmacher et al. 2008; McCormick et al. 2010). Thus, at present, it remains unclear whether such functional interactions differ between memory and perceptual tasks that engage PrC equally. Given that PFC has also been implicated in control processes supporting visual attention tasks and perceptual decision making (Desimone and Duncan 1995; Miller and Cohen 2001; Heekeren et al. 2008), it would be oversimplistic to assume that functional interactions between PrC and PFC are simply absent when participants engage in perceptual discriminations. Instead, the unique processing demands that are associated with recognition decisions and perceptual discriminations are more likely reflected in distinct patterns of interaction involving different PFC regions as well as additional posterior cortical structures.

Past fMRI studies have revealed the involvement of a number of different PFC regions in recognition memory. Left frontopolar and dorsolateral PFC regions have been found to be engaged most consistently when participants aim to recollect contextual detail about a prior encounter with the stimulus at hand (e.g., Henson et al. 1999; Rugg et al. 1999; Cansino et al. 2002; Dobbins et al. 2002; Dobbins and Wagner 2005). By contrast, right dorsolateral and ventrolateral PFC regions have more frequently been involved in familiarity-based recognition in the absence of a requirement for contextual recovery (Henson et al. 1999; Dudukovic and Wagner 2007). Involvement of ventrolateral PFC regions has also been linked to the evaluation of perceptual information when it is required for stimulus-based or contextually based recognition (Kostopoulos and Petrides 2003; Dobbins and Wagner 2005). That such an involvement might be more pronounced in memory processing is suggested by findings showing that midventrolateral PFC is differentially associated with mnemonic intentions when complex perceptual stimuli are being viewed (Dove et al. 2006). Based on these findings, we expected that aspects of right ventrolateral PFC would be part of the pattern of cortical regions that show differential coupling with PrC in the forced-choice recognition task and the perceptual oddball task for faces that we used previously. Other cortical regions that might show such differential interactions with PrC are midline structures in posterior cingulate and retrosplenial cortex; these structures have frequently been implicated in recognition memory in prior fMRI research (e.g., Henson et al. 1999; Daselaar et al. 2006; for review, see Wagner et al. 2005; Skinner and Fernandes 2007; Vann et al. 2009) and have been reported to show an increase in activity for recognition memory as compared with visual attention tasks (e.g., Cabeza et al. 2003). The latter finding has led to the suggestion that posterior

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midline structures could be involved in orienting attention to internally generated representations.

We also expected that some cortical regions would show a comparable functional coupling with PrC in recognition memory and perceptual discrimination, including aspects of PFC. A growing number of fMRI findings suggests that some of the control processes supported by PFC, in particular by dorsolateral PFC, in declarative memory tasks may not be unique to the domain of episodic memory (Cabeza et al. 2003; Dobbins and Han 2006; Marklund et al. 2007; Han et al. 2009; Hayama and Rugg 2009; for review, see Naghavi and Nyberg 2005). One prominent idea in the literature is that dorsolateral PFC involvement may be linked to selective visual attention demands that are critical for task performance in many domains (e.g., Cabeza et al. 2003; Mayer et al. 2007). In the current experimental paradigm, for example, such demands would relate to the fact that all experimental trials required processing of multiple simultaneously presented faces and the selection of only one of them as the target for responding.

To examine functional connectivity of PrC, we employed seed-based multivariate partial least square (PLS) analyses in the current investigation (McIntosh et al. 1996, 2004). This method allowed us to assess task-related commonalities and differences in patterns of correlation between activity in PrC and the rest of the brain. In a second analysis, we employed structural equation modeling (SEM) to examine changes in effective connectivity across our 2 tasks for a subset of those regions identified with seed PLS. We performed this analysis to help constrain the interpretation of the PLS findings based on direct consideration of neuroanatomical connectivity in a simplified network model (for rationale, see Mclntosh and Gonzalez-Lima 1994; Protzner and McIntosh 2006). Specifically, we aimed to determine whether within such a model task-related differences in functional interactions would emerge for regions known to be directly connected with PrC.

Materials and Methods

A detailed description of the experimental design and scanning protocol has been presented previously (O'Neil et al. 2009). Thus, only a summary will be provided, in addition to the specific aspects that pertain to the new fMRI analyses presented here.

Participants

Eighteen right-handed healthy individuals, each with normal or corrected-to-normal vision, participated in this study. Each received compensation for their participation. This study received approval from the Health Sciences Research Ethics Board of the University of Western Ontario.

Materials and Procedure

The fMRI study consisted of 2 experimental tasks and a baseline task, intermixed in a fast event-related design. All tasks required the selection of 1 of 3 simultaneously presented visual items; subjects made their selections using an MR-safe keypad. Stimuli for each trial of the experimental tasks were created by morphing a pair of color face photographs of Caucasian individuals with neutral expressions. The original faces of each pair served as endpoints of a continuum on which 3 morphed faces were captured. To create the targets for the perceptual oddball task, 1 of 3 faces was captured at a disproportionate distance to the other two along the morph continuum. Stimuli that composed a memory trial were created in a similar way. However, images were captured at points equally spaced on the morph continuum such that there was no perceptually defined oddball item. Stimuli that served as targets for memory trials were studied in a prescan study session. Memory task difficulty was modulated by manipulating repetition at study exposure (1 or 3 times). Oddball task difficulty was manipulated by changing the degree to which the oddball target was disproportionately positioned along the morph continuum. The baseline task involved presentation of 3 semitransparent white squares of varying luminance overlaid on a visual noise background. On each trial, 1 of the 3 squares possessed 5% greater luminance than the other 2 squares. The baseline task required the selection of the item with the greatest luminance. All experimental stimuli were trial unique.

All participants completed 6 experimental runs, each with 36 trials including all trial types (see Fig. 1*A*). Before each run, the 12 face images that served as targets for the memory task were presented for memorization for 3000 ms each, with a 1000 ms intertrial interval. During scanning, every trial started with presentation of an alphanumeric cue for 1000 ms, which indicated the type of upcoming task (memory, perception, or baseline), followed by a display of 3 critical stimuli for 5000 ms. Participants were required to choose the target item (i.e., studied, oddball, or brightest, respectively) while the stimuli remained on screen. Fixation period between trials was jittered. Trial order and jitter length were determined using Optseq2 (Dale 1999).

Summary of Behavioral Results

To briefly summarize the previously reported behavioral results (O'Neil et al. 2009), the mean behavioral accuracy (measured as percent correct ± standard error of the mean) for difficult and easy memory conditions was 54.60 ± 2.72 and 66.08 ± 2.80, respectively. The mean accuracy for the difficult and easy perceptual oddball conditions was 50.45 ± 1.98 and 72.90 ± 1.85, respectively. Critically, behavioral performance for the difficult condition of both experimental tasks, as well as overall performance when collapsed across difficulty, was matched in terms of accuracy (*t*-tests; all *P*s > 0.10). In addition,

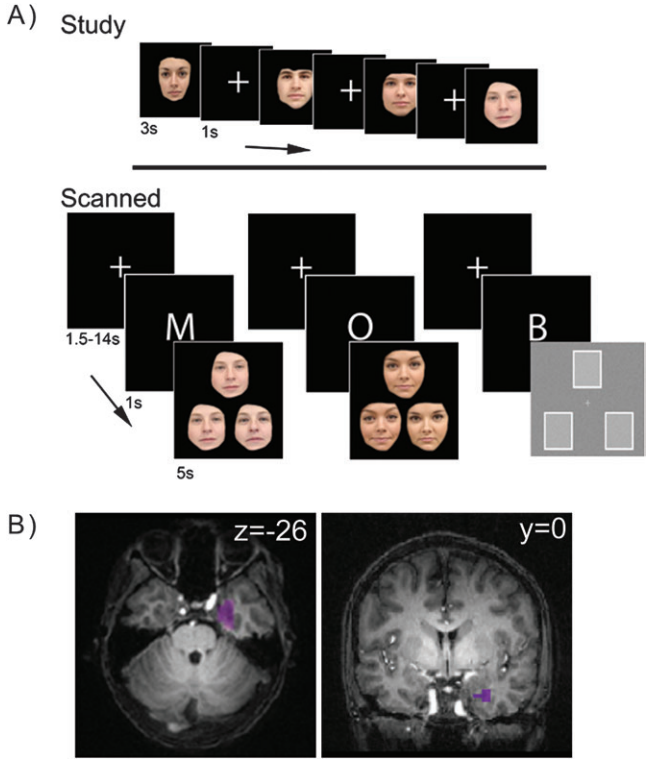

Figure 1. (*A*) Experimental design. Prior to scanning, participants studied a series of faces. During scanning individuals performed 3 different types of judgments. M = forced-choice recognition memory task; O = perceptual oddball task; B = luminance baseline task. (*B*) PrC seed region on transverse and coronal slices of structural MR image in representative participant.

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accuracy for the luminance baseline task (59.23 ± 5.00) did not differ from that of either of these 2 conditions.

Scanning Protocol

Scanning was completed on a 4-T whole body scanner (Varian; Siemens) fitted with a custom head coil. Functional volumes were collected using an oblique coronal slice orientation, roughly perpendicular to the longitudinal hippocampal axis with the constraint that the most anterior slices excluded the eyes. The entire anterior/posterior extent of the brain was covered with the resulting volumes. However, acquisition constraints prevented collection of data for the most superior aspects of the brain, including dorsal aspects of the parietal lobe, as well as the most dorsal aspects of the frontal lobe, which, with the given slice orientation, corresponded only to posterior sections. Thus, most aspects of dorsolateral prefrontal cortex were covered in the functional volumes. All functional scans were acquired using a T_2^*-weighted 4-shot spiral sequence: echo time (TE) = 12 ms, repetition time (TR) = 625 ms yielding a total volume acquisition time of 2500 ms, flip angle = 30°. Each functional volume was composed of 19 contiguous 4-mm slices (22 × 22-cm field of view, 64 × 64 matrix, in-plane resolution of 3.44 × 3.44 mm). Each experimental run involved the collection of 160 functional volumes. High-resolution T_1-weighted structural scans were collected in the same scanning session (144 slices, TR = 45 ms, TE = 3 ms, 256 × 256 matrix, in-plane resolution of 0.86 × 0.86 mm with 1-mm slice thickness) for detailed depiction of brain anatomy. Data preprocessing was completed using Brain Voyager QX 1.8 software (Brain Innovation). Functional images were resampled into 3-mm isotropic voxels, high-pass filtered, coregistered with the anatomical image, and transformed into standardized Talairach space. The resulting images were smoothed using a 3D Gaussian kernel with a full-width at half-maximum value of 6 mm.

Functional Connectivity Analysis

Functional connectivity analyses on PrC were performed using multivariate PLS (McIntosh et al. 1996, 2004). To address our question of interest, we applied seed PLS, a multivariate analysis technique that allows for the identification of spatiotemporal patterns of brain activity, with respect to the experimental conditions, by focusing on the covariance of the blood oxygen level–dependent response between the seed region and the rest of the brain across participants. Put another way, seed PLS allows for investigation of task-related changes in functional connectivity of the seed region. This technique works on the entire group data set at once, flattening spatial and temporal information into a 2D data matrix.

In order to investigate the functional connectivity of PrC with other cortical and subcortical regions, we first defined a seed region in PrC. Our selection was guided by the findings from our univariate GLM-based analyses reported in O'Neil et al. (2009), specifically our observation of shared right PrC involvement in perceptual oddball and recognition memory judgments. Due to differences in data interpolation and definition of cortical boundaries (based on voxel intensity) between BrainVoyager and the PLS platform, it was not possible to use the exact coordinates of the PrC region in the right hemisphere that showed this overlap in our previous analyses. Thus, we used a data-driven version of task PLS aiming to obtain a seed region in close vicinity of the region that we previously reported with a similar common involvement in memory and perception. This type of analysis revealed the major sources of task-related differences in activity across the entire functional volume (independent of any seeds), expressed as latent variables (LVs). Task saliences reflect the loading of experimental tasks; associated patterns of brain activity (i.e., singular images) reveal regions that are sensitive to the task distinction captured by the LV. Nonparametric permutation tests can be used to determine whether the covariance accounted for by the LV differs from chance. In addition, voxel saliences can be tested with nonparametric bootstrap statistics to assess which regions make reliable contributions to the pattern specified in a singular image.

The first LV obtained with this task PLS revealed a distributed activity pattern that differentiated between all experimental conditions on the one hand and the baseline task as well as fixation on the other (explained cross-block covariance = 40.2%, $P < 0.001$ based on 500 permutations). Not surprisingly, brain regions with higher activity in the experimental task as indicated by reliable positive saliences (>3.28 corresponding to $P < 0.001$ as assessed with 100 bootstrap tests) for this LV included large aspects of bilateral occipitotemporal cortex. Critically, a cluster of right-sided PrC voxels was also part of this pattern, replicating results obtained with our prior GLM-based analysis for these data. To specify a seed region in PrC that was well-suited to capture PrC activity across subjects, despite the variable nature of the collateral sulcus (see Pruessner et al. 2002), the 4-voxel cluster that met our salience-based criteria was grown using a 2 nearest-neighbor selection method (centered on Talairach coordinates $x = 25$, $y = 0$, $z = -25$). In this selection process, we ensured, using the anatomical scan averaged across all participants, that no voxels encroached on the hippocampus or amygdala. Due to the documented variability of the anterior collateral sulcus (Pruessner et al. 2002), however, it is impossible to clearly distinguish between the medial and lateral bank of this sulcus on the averaged MR image. Thus, we cannot rule out that aspects of entorhinal cortex were included in the PrC seed in this group-based approach (see Fig. 1*B*). Using univariate *t*-tests on activity averaged across all voxels included in this seed region of interest, we confirmed that, like the PrC cluster identified in our original analyses, this region exhibited no significant difference between the difficult recognition memory and perceptual oddball conditions that were matched for accuracy, $t_{17} = 1.63$, $P > 0.05$ and no overall effect of task difficulty, $t_{17} = 1.77$, $P > 0.05$. Consistent with our previous report, we did find an effect of accuracy across the two experimental tasks, $t_{17} = 3.12$, $P < 0.01$. Although the pattern of activity in the task PLS that allowed us to identify the PrC seed also included bilateral regions in the hippocampus (left $x = -16$, $y = -4$, $z = -11$; right $x = 17$, $y = -4$, $z = -8$), these regions did not exhibit any modulation related to accuracy (all $P > 0.05$). Moreover, when used in exploratory seed analyses, we did not see any differential patterns of connectivity across the perception and memory tasks. Thus, these hippocampal regions were not investigated further (for additional commentary, see Discussion).

Functional data from the described PrC seed region were extracted for the seed PLS analysis. This region was selected from the third lag of the LV, corresponding to the typical peak of the hemodynamic response function. A data matrix was constructed consisting of voxel intensities capturing a temporal window of 15 s following stimulus onset for each trial. This allowed for the consideration of the relationship between activity in the seed region and the rest of the brain throughout the typical duration of the hemodynamic response. Note, however, that no a priori HR function is modeled in this type of analysis. In data-driven approaches, PLS uses singular value decomposition to rotate the data matrix to identify the strongest effects in the data. Here, we used a nonrotated version of seed PLS, in which a priori contrasts restrict the patterns derived (McIntosh et al. 2004; Protzner and McIntosh 2008). We opted for this nonrotated version as we aimed to test specific hypotheses with 2 contrasts of interest. A singular image is computed for each contrast of interest representing the distributed voxel pattern that embodies it. The strength of the relationship between the singular image and the designated contrast is given by the singular value. In this nonrotated version, the singular image is simply the cross-product of a contrast and the data matrix, and the singular value is the sum of squared voxel values for the singular image. As in the task PLS previously described, statistical assessment was performed using nonparametric permutation tests for the LVs and bootstrap estimation of standard errors for the voxel saliences. The permutation test assesses whether the functional connectivity effect represented in a given LV, captured by the singular value, is sufficiently strong to be considered different from random noise. The standard error estimates of the voxel saliences in each singular image from the bootstrap tests served for assessment of the reliability of the nonzero saliences in significant LVs. Following established criteria for nonparametric tests in PLS analyses (e.g., McIntosh et al. 2004; Protzner and McIntosh 2008; Stevens et al. 2008), results from the permutation tests were considered significant if they survived $P < 0.05$ (as no correction for multiple comparisons is required), and saliences assessed with bootstrap estimates were considered significant if they met a threshold of 3.28, corresponding to approximately $P < 0.001$, at a cluster

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threshold of 5 voxels. All reported coordinates and cluster sizes were obtained for the third lag (TR), corresponding to the typical peak of the hemodynamic response function.

Effective Connectivity Analysis

In an additional analysis, we also employed SEM (LISREL 8.80, Student Edition, Scientific Software Inc.) to examine whether memory and perception tasks involve different patterns of effective connectivity in a simplified, neuroanatomically constrained network that involved a subset of those regions identified with the seed PLS and a connectivity matrix that honored known neuroanatomical connections. Regions included in the model were selected based on theoretical considerations (i.e., prior discussion in the fMRI literature) and robust signs of PrC connectivity as demonstrated by the seed PLS analyses just summarized. All regions were situated in the right hemisphere and included PrC, dorsolateral PFC, ventrolateral PFC, posterior cingulate, superior temporal sulcus, and fusiform gyrus. Corresponding Talairach coordinates for these regions are presented in Tables 1 and 2. The peak voxel of each region was expanded using a 1 nearest-neighbor method, and activity profiles were extracted for the memory and perception task in each participant based on the average obtained over the third and fourth lag (TR from trial onset). This provided us with 72 data points (18 participants; 4 conditions) for each of these 2 tasks for each region. As our main interest focused on the difference between memory and perception, within subject variance related to accuracy and difficulty manipulations was removed with a residualization procedure previously described (McIntosh and Gonzalez-Lima 1991). Anatomical connectivity, including directionality, was specified based on reports from the nonhuman primate literature (Suzuki and Amaral 1994; Morris et al. 1999; Petrides and Pandya 1999, 2006; Lavenex et al. 2002; Petrides 2005; Gerbella et al. 2010). To determine whether effective connectivity differed between the memory and perception tasks, we used a stacked model approach (McIntosh and Gonzalez-Lima 1994). Inferential statistics involved comparing a model in which the path coefficients were constrained to be equal across conditions (null model) with a model in which the coefficients were allowed to differ between conditions (alternate model). For each model, a goodness of fit value, expressed as χ^2, was computed that reflects the extent to which the set of path coefficients reproduced the correlation matrices for all conditions. Inferences were based on the difference in goodness of fit ($\Delta\chi^2$) between the 2 models. Specifically, we examined whether goodness of fit was improved by allowing path coefficients to vary across tasks. Individual paths were examined in 2 different orders to determine whether they contributed to the improved fit of the model. Order of testing was found to have no impact on the results reported.

Results

To address our main question of interest, we first determined whether we could identify a significant LV that would reflect distinct patterns of functional connectivity between the PrC seed region and the rest of the brain for the perceptual oddball and recognition memory tasks. The LV that was associated with this a priori contrast was found to be significant and accounted for 11.0% of cross-block covariance ($P < 0.05$, see Fig. 2). Reliable positive saliences on the corresponding singular image, which reflect an increased positive coupling between PrC and the rest of the brain during the memory as compared to the perceptual task, are listed in Table 1. Consistent with our predictions, the regions that showed the most reliable increase in coupling were right ventrolateral PFC and a posterior midline region in posterior cingulate cortex at the border to retrosplenial cortex. Figure 3 shows the time course of the correlations between PrC and these selected regions. Regions with reliable negative saliences that displayed an increased positive coupling during the perception task were found in bilateral posterior fusiform gyrus and ventral occipital regions as well as in bilateral superior temporal sulcus (see Figs 2 and 3). Visual inspection of the correlation between the brain scores (i.e., the dot product of the voxel salience and fMRI data) and the fMRI signal in the seed region for each experimental condition showed that the task-dependent changes in the correlation between the PrC seed and the regions identified in the singular image of LV 1 were comparable across the easy and difficult task conditions (see Fig. 2). This observation was confirmed statistically by the fact that a targeted task-difficulty contrast did not account for a significant portion of cross-block covariance ($P > 0.05$).

Table 1
Regions exhibiting differential functional connectivity with the PrC seed region during the memory and perceptual task

Region	Hemisphere	Talairach coordinates			Ratio	Cluster size
		x	*y*	*z*		
Memory > perception						
Posterior cingulate cortex[a]	R	5	−28	22	5.07	31
Inferior frontal gyrus (VLPFC)[a]	R	44	32	10	4.38	19
Anterior cingulate cortex	L	−7	47	4	4.37	7
Cerebellum	L	−28	−52	−41	4.37	9
Posterior cingulate cortex	L	−22	−37	16	4.32	13
Thalamus	R	11	−16	19	4.28	14
Perception > memory						
Fusiform gyrus[a]	R	17	−58	−20	−6.64	164
Middle frontal gyrus (DLPFC)	R	47	−1	40	−5.20	17
Superior temporal gyrus	L	−49	20	1	−5.10	12
Superior temporal sulcus[a]	R	38	−16	−11	−4.88	23
Superior frontal sulcus	L	−28	44	43	−4.88	12
Middle frontal gyrus (DLPFC)	L	−25	32	34	−4.76	32
Fusiform gyrus	L	−25	−70	−26	−4.50	21
Fusiform gyrus	L	−43	−34	−20	−4.35	7
Cerebellum	B	2	−43	−11	−4.16	8

Note: Talairach coordinates indicate peak voxel. Bootstrap ratios all reflect a significance of $P < 0.001$, minimum cluster size of 5 voxels, lag 3. VLPFC = ventrolateral PFC; DLPFC = dorsolateral PFC.
[a]Regions selected for SEM.

Table 2
Regions exhibiting common increased functional connectivity with the PrC seed region during both experimental tasks as compared with the baseline task

Region	Hemisphere	Talairach coordinates			Ratio	Cluster size
		x	*y*	*z*		
Middle frontal gyrus (DLPFC)[a]	R	29	35	25	7.48	80
Superior frontal gyrus (DLPFC)	L	−22	65	10	6.22	9
Cerebellum	R	38	−64	−29	5.60	18
Pons	L	−1	−25	−17	5.54	19
Middle frontal gyrus (DLPFC)	R	41	20	28	5.29	83
Medial superior frontal gyrus	R	8	50	34	5.27	6
Thalamus	L	−4	−22	1	4.65	12
Cerebellum	L	−37	−55	−29	4.55	8
Superior frontal gyrus	R	23	53	10	4.54	11
Middle frontal gyrus (DLPFC)	L	−43	20	37	4.51	19
Cerebellum	L	−16	−67	−35	4.44	11
Caudate	R	8	20	16	4.44	7
Superior temporal gyrus	L	−40	17	−23	4.43	17
Retrosplenial cortex	L	−7	−40	7	4.40	7
Lingual gyrus	L	−4	−73	−20	4.34	44
Retrosplenial cortex	R	14	−40	13	4.32	17
Medial superior frontal gyrus (DLPFC)	L	−13	50	34	4.32	6
Fusiform gyrus	L	−28	−79	−23	4.28	8
Fusiform gyrus	L	−28	−40	−20	4.27	22
Middle temporal gyrus	L	−34	−55	10	4.13	11
Temporal pole	L	−4	65	4	4.12	6
Cerebellum	L	−22	−28	−32	3.93	6
Middle frontal gyrus (DLPFC)	R	38	47	7	3.72	5

Note: Talairach coordinates indicate peak voxel. Bootstrap ratios all reflect a significance of $P < 0.001$, minimum cluster size of 5 voxels, lag 3. DLPFC = dorsolateral PFC.
[a]Region selected for SEM.

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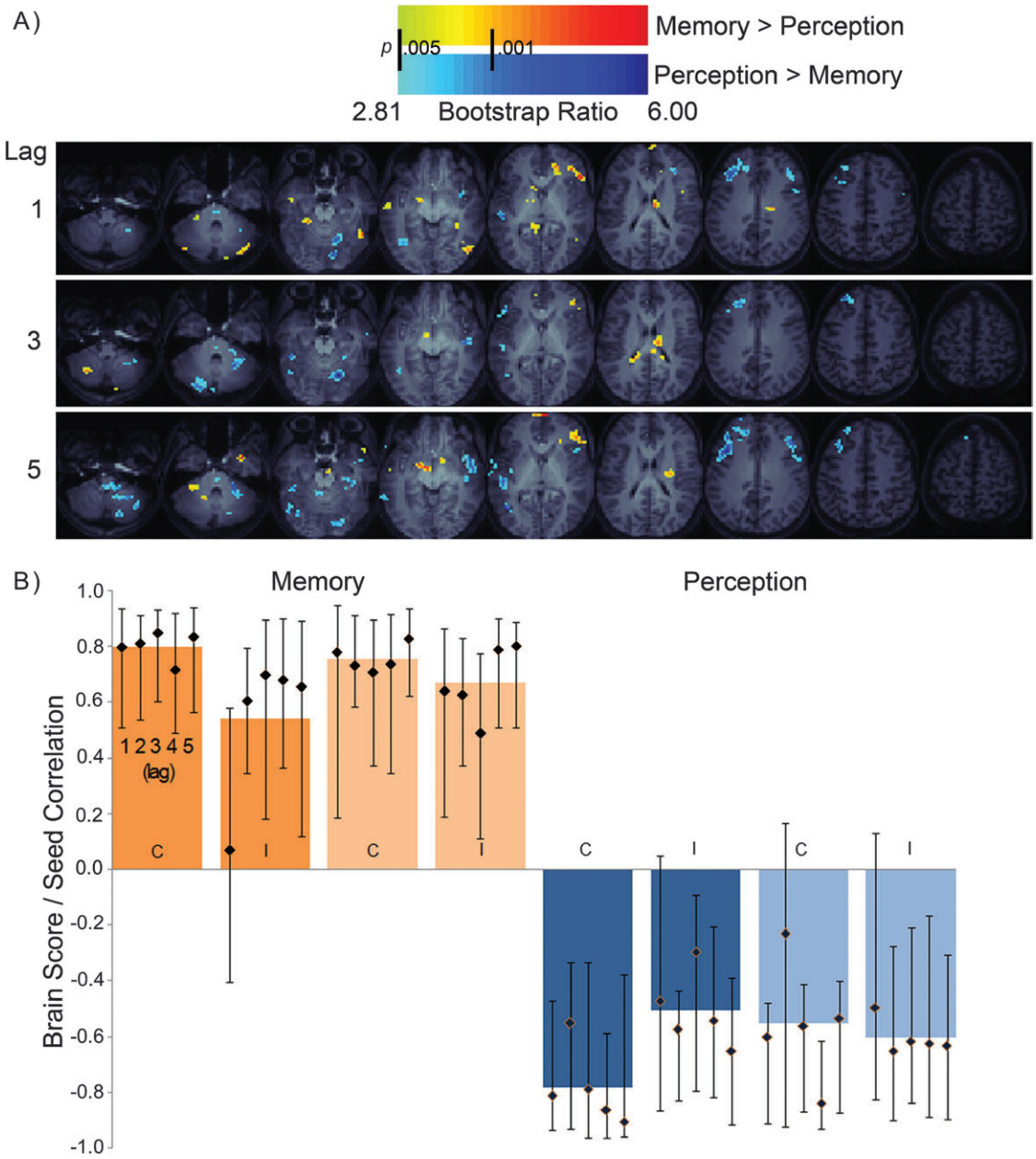

Figure 2. (*A*) Pattern of distinct functional connectivity revealed with the contrast between recognition memory and perceptual discrimination for the PrC seed region. Maps are thresholded at $P = 0.005$ for visualization purposes. (*B*) Associated LV demonstrating how this pattern of activity mapped onto experimental conditions. Bar plot depicts correlation between brain scores and PrC seed activity. Dark colors = difficult trial conditions, light colors = easy trial conditions, C = correct trials, I = incorrect trials. Lags 1–5 correspond to 2.5-s intervals encompassing the duration of the hemodynamic response within a trial. Error bars represent 95% confidence intervals derived by bootstrap estimation.

Given that our PrC seed was selected based on its common involvement in the memory and perception tasks, we also investigated whether activity in PrC showed a pattern of coupling with other brain regions that was common to both tasks. Toward this end, we examined the contrast between the luminance baseline task and all perceptual and memory conditions. The corresponding LV was significant and accounted for 39.7% of cross-block covariance ($P < 0.001$). The pattern of regions that showed an increased positive coupling with PrC in both tasks, as compared with the luminance baseline, is displayed in Figure 4 (see also Table 2). This pattern included several foci in bilateral dorsolateral PFC, with the largest cluster and the highest bootstrap ratio present in the right hemisphere (as shown in Table 2).

In a final step of our functional connectivity analyses, we aimed to determine whether the differential coupling we observed between PrC and other cortical regions for the memory versus perception task was related to interindividual differences in behavioral accuracy. To examine this possibility, we assessed the correlations between the strength of the relationship between the seed region and the brain scores with behavioral performance for the memory and oddball tasks. Put another way, we determined whether behavioral performance was related to how strongly the pattern between the seed and

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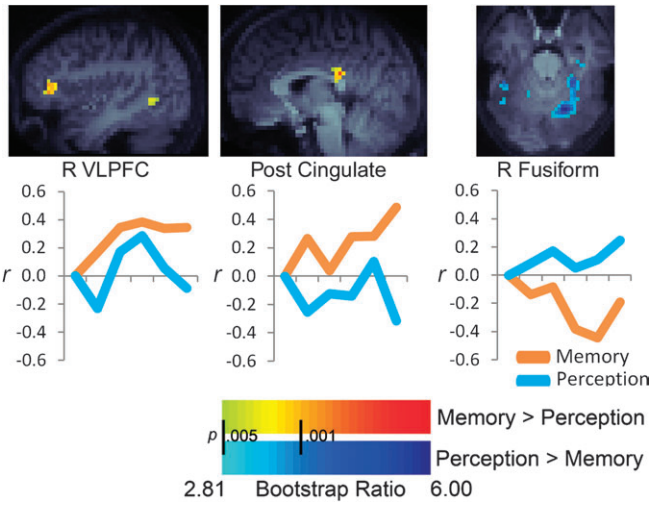

Figure 3. Functional coupling between PrC and selected regions that were part of the pattern showing differential connectivity for memory and perception illustrated in Figure 2. Time courses show correlations of activity between the seed and a 9-mm cube centered on the peak voxel of each region over the course of a trial (hatch marks on *x*-axis indicate 2.5-s lag intervals following stimulus onset). Note that such coupling is not constrained to follow the typical hemodynamic response function.

the singular image was expressed in each participant. Brain scores offer an index of how strongly individual participants express the pattern captured by a given LV in a given task. Collapsing across easy and difficult conditions, we observed that participants with higher behavioral accuracy in the memory task also showed stronger functional connectivity between the PrC seed and the pattern of brain regions identified with our first LV, showing a tighter positive coupling in the memory task, $r_{16} = 0.451$, $P < 0.05$. No such relationship was found for behavioral performance on the perceptual task $r_{16} = -0.209$, $P > 0.05$.

In a follow-up analysis, we employed SEM to examine changes in effective connectivity for a subset of regions that were identified with seed PLS and that are of particular interest in the context of the functional neuroimaging literature reviewed in the Introduction (see Fig. 5). Generally speaking, we aimed to explore connectivity in a model that probed interactions between PrC, prefrontal regions implicated in executive control, and regions implicated in face processing. The model included regions with differences in functional connectivity with PrC across tasks (ventrolateral PFC, posterior cingulate, superior temporal sulcus, and fusiform gyrus), as well as a region in dorsolateral PFC with a common pattern of connectivity. In the first step of model assessment, an omnibus test revealed that the alternative model provided improved fit over the null model, suggesting memory and perception tasks were associated with differential patterns of effective connectivity, $\Delta\chi^2(13) = 34.97$, $P < 0.001$. In a second step, we explicitly tested whether task-related differences in the pattern of effective connectivity would also emerge when only direct connections with PrC were considered, that is, were allowed to vary across tasks, with all other connections forced to maintain fixed values. In comparison with the null model, we again found a significant increase in model fit, $\Delta\chi^2(5) = 15.67$, $P < 0.01$. Finally, testing of individual path coefficients (Fig. 5) revealed that connections with the most noticeable (i.e., individually significant) changes across tasks involving PrC were those between PrC and ventrolateral PFC as well as between PrC and posterior cingulate cortex (Fig. 5 and Table 3). Other connections with significant task-related differences were found between ventrolateral PFC and dorsolateral PFC and between ventrolateral PFC and superior temporal sulcus (see Table 3).

Discussion

Using a multivariate seed-correlation approach, we examined task-related modulations of functional connectivity between PrC and the rest of the brain that pertain to recognition memory and perceptual discrimination of faces. Although right PrC showed a comparable involvement in our forced-choice memory and perceptual oddball tasks, as previously reported (O'Neil et al. 2009), it exhibited distinct patterns of functional connectivity during execution of these tasks. SEM-based examination of PrC connectivity within a network of selected regions identified with our seed analysis also revealed that distinct patterns of effective connectivity can be detected for regions known to be directly connected with PrC.

Right ventrolateral PFC and posterior cingulate cortex were part of the network of brain regions that exhibited stronger functional connectivity with PrC in recognition memory than in perceptual discrimination. Conversely, ventral occipital regions, aspects of bilateral posterior fusiform gyrus, as well as bilateral superior temporal sulcus were part of the network of regions that displayed stronger coupling with PrC in perceptual discrimination than in recognition memory. Furthermore, the strength of the coupling in the memory condition for the pattern of regions that discriminated between memory and perception was related to interindividual differences in behavioral accuracy on that task. Contrasting with these differences between recognition memory and perceptual discrimination, we also identified a pattern of PrC functional connectivity common to these experimental tasks, when compared with the luminance baseline task; this pattern included several foci in right dorsolateral PFC. To our knowledge, these findings are the first to reveal that PrC dynamically supports performance in mnemonic and perceptual tasks through shared and distinct patterns of functional interactions with other cortical regions.

The current investigation was guided by a representational theory of PrC functioning that contrasts with the classic view, which holds that the MTL operates as an integrated system that is dedicated to declarative memory. The representational view posits MTL contributions to a task are related to computational demands involved in creating specific types of representations, and that a common, highly integrated representation in PrC supports both memory and perception when discrimination of stimuli cannot be based on simple perceptual features (Murray and Bussey 1999; Murray et al. 2007). Within such a framework, the question emerges as to how the neural correlates of perceptual discrimination and recognition memory differ when representational demands are closely matched. The present findings suggest that such differences are reflected in distinct patterns of functional interactions between PrC and other cortical regions. In functional terms, such differences in connectivity likely pertain to processes of cross-cortical integration given they are also related to the resulting quality of the discrimination process, that is, its accuracy.

Patterns of PrC functional connectivity in the current study were found to be related to demands that were both distinct and common for the 2 experimental tasks. In both cases, these

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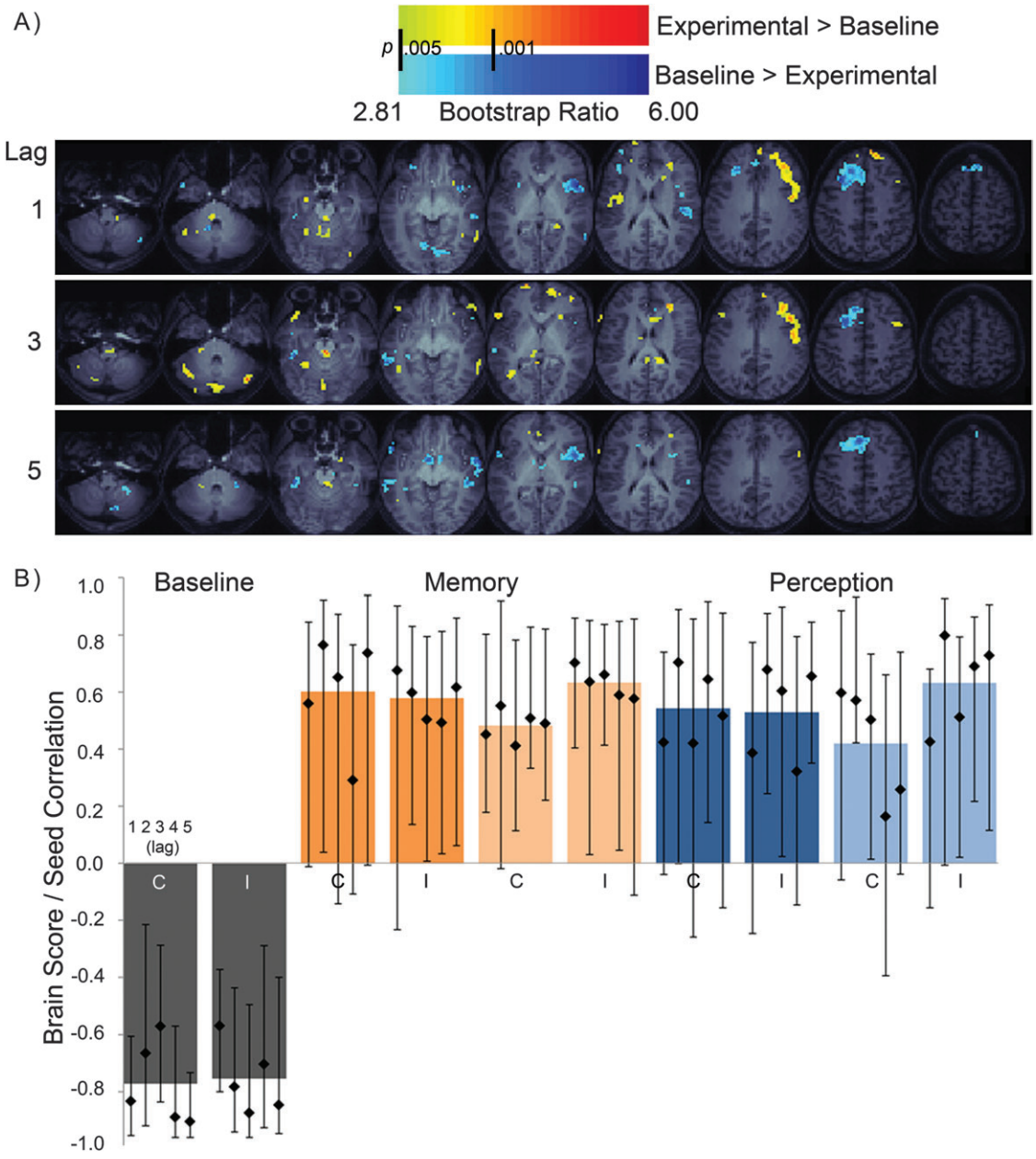

Figure 4. (*A*) Pattern of common functional connectivity revealed with the contrast between the two experimental tasks and the luminance baseline task for the PrC seed region. (*B*) Associated LV demonstrating how this pattern of activity mapped onto experimental conditions. Bar plot depicts correlation between brain scores and PrC seed activity. For additional information, see Figure 2 caption.

patterns included regions of PFC. While the current experiment was not designed to pinpoint the specific control processes that are distinct and those that are shared, the fMRI literature reviewed in the Introduction allowed us to make some predictions concerning task-related involvement of PFC. One of the regions we anticipated to exhibit differential coupling with PrC during performance of the recognition memory versus the perceptual oddball task was right ventrolateral PFC; this region has previously been linked to the evaluation of perceptual information when the latter is required for stimulus-based or contextually based recognition (Kostopoulos and Petrides 2003; Dobbins and Wagner 2005) and to mnemonic intentions when complex perceptual stimuli are being viewed (Dove et al. 2006). Theories that emphasize the role of PFC in behavioral control processes suggest that such control may come about through top-down biasing of posterior cortical regions involved in perceptual analyses (e.g., Desimone and Duncan 1995). In forced-choice recognition memory tasks, like the one used in the present study, such top-down control may be critical for increasing subtle differences in perceived memory signal associated with the perceptually highly similar choices in the display (as an index of familiarity). Right ventrolateral PFC, specifically, has been proposed to amplify the gain on signals activated by retrieval probes in recognition memory tasks (Dobbins and Wagner 2005). As memory signals are irrelevant for the oddball task, the corresponding negative path coefficients for the connections between ventrolateral PFC and PrC, as well as between

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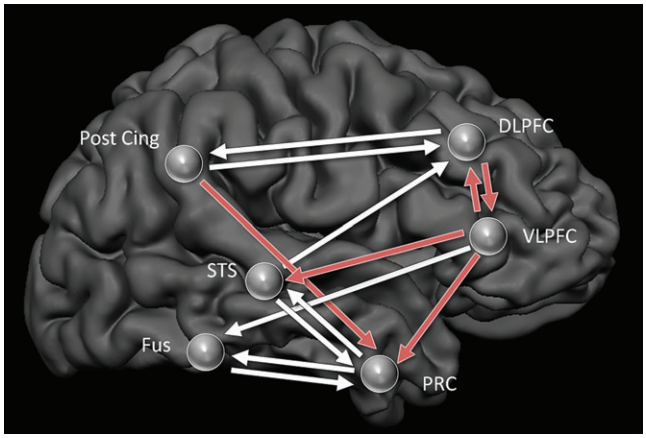

Figure 5. Anatomical model and effective connectivity changes across tasks in the SEM analyses. Connections exhibiting significant task-related changes in effective connectivity are shown in red. Corresponding path coefficients are listed in Table 3. Generally, the pattern of change was such that coupling was more positive in memory than in perception. For ventrolateral PFC and PrC, the change was in the same direction but the path coefficients took on negative values in both cases.

Table 3
Path coefficients derived from SEM analyses for connections that showed significant differences between memory and perception conditions

Region		Memory	Perception
Ventrolateral PFC	→PrC	−0.19	−0.38
Ventrolateral PFC	→Dorsolateral PFC	0.13	−0.06
Ventrolateral PFC	→Superior temporal sulcus	0.09	−0.17
Dorsolateral PFC	→Ventrolateral PFC	0.12	−0.08
Posterior cingulate cortex	→PrC	0.28	−0.04

Note: All other path coefficients did not differ significantly.

ventrolateral PFC and the superior temporal sulcus, revealed though our SEM analyses can be interpreted as reflecting a process of inhibition. Such a process would be of particular importance in the context of a task design that mixes memory and perceptual trials, as in the current study. That the introduction of explicit memory demands led to a switch from a negative to a positive coupling in effective connectivity between ventrolateral PFC and the superior temporal sulcus, a region frequently implicated in the perceptual representation of faces in past fMRI research (Ishai 2008; Liu et al. 2010), is also in line with this notion. For PrC, however, the SEM findings for the memory condition appear less clear-cut. That the coefficient for the connection between ventrolateral PFC and PrC shifted toward smaller negative values could suggest that PFC mediated gain of memory signals may also come about through partial release from inhibition.

Another brain region that showed differential coupling in functional and effective connectivity for recognition memory as compared with perceptual oddball discrimination was found in posterior cingulate cortex. Activation in this region has previously been reported in other studies involving recognition memory for faces. For example, increases in posterior cingulate activity have been found to track increases in familiarity induced through multiple exposures of faces over the course of an experimental session (Kosaka et al. 2003). Evidence for a critical role of this region in the discrimination between familiar and unfamiliar faces has also come from research on individuals with congenital prosopagnosia, that is, individuals who exhibit consistent and lasting impairments in face recognition. Specifically, although such individuals were reported to show normal effects of repetition in the fusiform gyrus, posterior cingulate regions did not discriminate between previously familiar and novel faces as demonstrated in healthy control participants (Avidan and Behrmann 2009). While neither these findings nor those from the present study offer insight as to the specific functional contributions of the posterior cingulate to the recognition of familiar faces, one possibility raised in the context of other research is that it could be involved in orienting attention to internally generated representations (Cabeza et al. 2003). Regardless of whether this particular interpretation holds to be true, the observed task-related changes in patterns of functional and effective connectivity between posterior cingulate cortex and PrC indicate that integration of cortical signals involved in recognition judgments extends beyond the interplay between the MTL and PFC.

At first glance, it may seem surprising that the pattern of PrC connectivity that differentiated recognition memory from perceptual discrimination did not include the hippocampus. However, although it is well established that the hippocampus plays a critical role in recognition memory, recent research suggests that its contributions are specific to processes of recollection, that is, the recovery of contextual associations pertaining to a prior encounter with the stimulus that is being judged, rather than to recognition more broadly (Brown and Aggleton 2001; Eichenbaum et al. 2007). Forced-choice recognition memory tasks that require discrimination between perceptually highly similar stimuli, such as the one used in the current experiment, encourage recognition decisions based on a comparison of subtle differences in the relative familiarity of all concurrently presented items in the display (Migo et al. 2009). This retrieval process has been linked to PrC functioning and has been proposed to rely on specific computational mechanisms that are different from those that support hippocampally mediated recognition (Norman and O'Reilly 2003; Norman 2010). In line with this notion, human lesion research has shown that some individuals with selective hippocampal damage are not impaired in making recognition judgments in forced-choice memory tasks with high perceptual similarity between targets and lures, while clearly showing deficits in recollection (Holdstock et al. 2002; cf., Jeneson et al. 2010). From this perspective, the lack of hippocampal involvement in the current set of results is in fact expected.

Our functional connectivity analyses also revealed brain regions that exhibited stronger coupling with PrC in the perceptual discrimination as compared with the recognition memory task. Such increased functional connectivity was observed in posterior cortical regions previously characterized as being part of a face processing network (Gobbini and Haxby 2007; Barbeau et al. 2008; Ishai 2008), including the superior temporal sulcus and the fusiform gyrus, as well as in bilateral dorsolateral PFC. The higher overall similarity of the faces in the oddball as compared with memory displays, which was introduced to equate task difficulty, may have contributed to an increased requirement for integration of activity in ventral visual pathway structures with PrC. Furthermore, to identify the oddball in our perceptual discrimination task, the perceptual similarity between all stimuli must be compared explicitly. This places heavy demands on maintenance of multiple faces in working memory; by contrast, a direct assessment of perceptual similarity in the display is not

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required in forced-choice recognition tasks (for discussion, see Dobbins and Han 2006). Prior research on the effects of working memory load for faces on activity in the posterior fusiform gyrus suggests that the increased functional connectivity between this region and PrC in the current study may be related to working memory demands (Druzgal and D'Esposito 2001, 2003). However, given that our effective connectivity analyses did not reveal any significant differences in path coefficients for these particular connections across tasks, it remains a possibility that the differences in functional connectivity we observed are indirect and reflect influences mediated by other structures. Further research is needed to elucidate how PrC, fusiform gyrus, and the superior temporal sulcus jointly support the representation of faces under varying perceptual and working memory demands, and how their activity is influenced by other regions.

Turning to the pattern of PrC connectivity common to both experimental tasks, we found that it included right dorsolateral PFC as predicted. Again, the design of our study does not allow us to specify the exact role that this region plays across domains. Common coupling with PrC in both memory and perceptual oddball tasks may reflect a role of dorsolateral PFC in attentional processes that are shared across domains (e.g., Cabeza et al. 2003). In the current experimental paradigm, all trials required processing of multiple simultaneously presented faces and the selection of a single target. Prior research using a visual target detection task, involving the presentation of complex visual stimuli from different categories, indicates that right dorsolateral PFC responds comparably to the presentation of both target and same-category foil stimuli but less so to stimuli categories irrelevant for the search at hand (Hampshire et al. 2007). This finding suggests a broad attentional tuning of dorsolateral PFC to the stimulus category relevant for the task goal, rather than to a specific target item. Connectivity of dorsolateral PFC with PrC during the experimental tasks could thus reflect the interplay between regions supporting attention to items within a stimulus class and those supporting individual item representations, respectively. Such interplay was reduced in the luminance baseline task as PrC-based representations would be ill-suited for supporting discrimination of simple features, such as brightness. While this attentional account of shared connectivity across our memory and perception task is appealing, we acknowledge that it remains speculative at present, and that other interpretations are viable as well. An alternate view, for example, that has been suggested, assigns dorsolateral PFC a role in integrating information distributed over many cortical regions into complex but unified representations (e.g., Naghavi and Nyberg 2005). Theoretical consideration aside, as neuroanatomical findings suggest only sparse if any direct connections between dorsolateral PFC and PrC in primates (Petrides and Pandya 1999, 2006), a full account of interactions between these regions must ultimately also take into consideration the role of other mediating structures.

In closing, we would like to emphasize that our general finding of task-dependent modulations of functional connectivity does not imply that the regions we identified to be differentially connected with PrC in our recognition memory and perceptual oddball tasks are uniquely specialized for declarative memory and perceptual processing, respectively. It also does not entail that these regions are always recruited together with PrC in a fixed manner when recognition memory or perceptual discrimination tasks are being performed. Rather, the patterns of functionally connected regions may be better understood as flexibly deployed network configurations that are optimized for specific processing goals dictated by many different task demands and parameters (e.g., McIntosh 1999; Fuster 2009). Further research is necessary to determine how these patterns change, for example, when the format of the recognition task is changed from forced choice to yes/no or when the perceptual task requires matching of stimuli rather than detection of an oddball. Regardless of the outcome of such future research, the current findings offer critical first evidence that, even when MTL structures show a similar involvement in recognition memory and perceptual discrimination, differential neural mechanisms are present at the level of interplay between the MTL and other cortical regions.

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Notes

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