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Hemispheric Asymmetry of Visual Scene Processing in the Human Brain: Evidence from Repetition Priming and Intrinsic Activity

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Asymmetrical specialization of cognitive processes across the cerebral hemispheres is a hallmark of healthy brain development and an important evolutionary trait underlying higher cognition in humans. While previous research, including studies of priming, divided visual field presentation, and split-brain patients, demonstrates a general pattern of right/left asymmetry of form-specific versus form-abstract visual processing, little is known about brain organization underlying this dissociation. Here, using repetition priming of complex visual scenes and high-resolution functional magnetic resonance imaging (MRI), we demonstrate asymmetrical form specificity of visual processing between the right and left hemispheres within a region known to be critical for processing of visual spatial scenes (parahippocampal place area [PPA]). Next, we use resting-state functional connectivity MRI analyses to demonstrate that this functional asymmetry is associated with differential intrinsic activity correlations of the right versus left PPA with regions critically involved in perceptual versus conceptual processing, respectively. Our results demonstrate that the PPA comprises lateralized subregions across the cerebral hemispheres that are engaged in functionally dissociable yet complementary components of visual scene analysis. Furthermore, this functional asymmetry is associated with differential intrinsic functional connectivity of the PPA with distinct brain areas known to mediate dissociable cognitive processes.

Keywords: conceptual, laterality, parahippocampal place area, repetition suppression, resting-state functional connectivity

Introduction

Specialization of cognitive processes to one or the other hemisphere is a hallmark of healthy human brain development and is thought to be an important evolutionary trait underlying higher cognitive processes in humans (Gazzaniga 2000; Toga and Thompson 2003; Klimkeit and Bradshaw 2006; Corballis 2009). Hemispheric asymmetry of form specificity in perceptual and cognitive processing has been assessed using divided visual field stimulus presentation (Marsolek et al. 1992, 1996; Marsolek 1999), split-brain patients (Metcalfe et al. 1995; Gazzaniga 2000), and repetition priming (Koutstaal et al. 2001; Vuilleumier et al. 2002, 2005; Simons et al. 2003; Eger et al. 2005). While these diverse research approaches provide converging evidence of general right/left hemispheric asymmetry for form-specific versus form-abstract processing, respectively, little is known about the nature of brain organization underlying this functional dissociation. We propose that repetition priming provides a means of assessing form specificity effects across specific cortical regions in the human brain; and furthermore, that analysis of intrinsic low-frequency neural activity correlations across functional-anatomic brain systems can potentially provide insight into the brain organization underlying this hemispheric specialization.

Priming is a nonconscious form of memory (Tulving and Schacter 1990) in which encounters with a stimulus facilitate subsequent processing of the same or a related stimulus. Measures of behavioral priming (BP) include increased accuracy, lower detection thresholds, and faster response time (RT) for identification, production, and classification of primed items. Neuroimaging studies have revealed that BP is typically accompanied by changes in neural activity, referred to here as neural priming (NP), most often characterized by reduced activity (repetition suppression) in cortical regions involved in processing the stimuli (for review, see Schacter and Buckner 1998; Wiggs and Martin 1998; Henson and Rugg 2003; Schacter, Wig, et al. 2007). While BP is often correlated with NP in the prefrontal cortex, most likely reflecting learned stimulus-decision mapping (Dobbins et al. 2004; Wig et al. 2005; Schnyer et al. 2006, 2007; Horner and Henson 2008), it is not typically correlated with NP in posterior cortical regions involved in visual perception (e.g., occipital, fusiform, and parahippocampal regions; for review, see Schacter, Wig, et al. 2007).

Using functional magnetic resonance imaging (fMRI), NP can be indexed as repetition-related changes in the blood oxygen level–dependent (BOLD) signal. Quantifying the magnitude and spatial topography of changes in NP resulting from various experimental manipulations of the stimuli between study (initial exposures) and test (repeated exposures) has proven to be an extremely useful tool for delineating neurocognitive functions across the cortex, such as the hierarchical functional organization of ventral visual cortex (Grill-Spector et al. 1999; Vuilleumier et al. 2002) and regions involved in stimulus-to-decision mapping (Dobbins et al. 2004; Wig et al. 2009). Thus, repetition priming as a tool can provide leverage in efforts to characterize the neural correlates of complex higher cognitive functions in humans, such as perceptual abstraction.

Specificity effects caused by changes in either the perceptual form of stimuli, or the task/behavioral-response performed, reveal cortical sensitivity to the perceptual, conceptual, or stimulus-to-decision mapping properties of primed items (Schacter et al. 2004; Schacter, Wig, et al. 2007). Studies show consistent hemispheric asymmetry in ventral occipitotemporal visual regions, with more pronounced form-specific NP on the right versus form-abstract NP on the left in category-preferential regions (Koutstaal et al. 2001; Vuilleumier et al. 2002, 2005; Simons et al. 2003; Eger et al. 2005). The first demonstration of

this asymmetry by Koutstaal et al. (2001) showed no NP in right object-responsive fusiform cortex at test for different exemplars of primed objects (e.g., a different picture of an umbrella shown at test than at study) but an intermediate degree of NP in left fusiform cortex for these perceptually distinct yet conceptually related items. Subsequent studies reported similar hemispheric asymmetry for NP of nameable objects (Vuilleumier et al. 2002, 2005; Simons et al. 2003) and faces (Eger et al. 2005). However, evidence to date of form-specific versus form-abstract priming effects has been limited to visual processing of individual objects/entities and associated NP in isolated regions of fusiform cortex.

Based on the foregoing consistent evidence across multiple research approaches, we hypothesized that hemispheric asymmetry of form-abstract processing might reflect an important fundamental organizational property of the human brain. If so, then the right and left cerebral hemispheres should play differential roles in processing of stimuli that are characteristic of natural human visual experience: complex visual spatial scenes. Specifically, we predicted a right/left dissociation for form specificity in a region that has been shown to be critical for processing of complex visual scenes: the parahippocampal place area (PPA), a functionally defined region within parahippocampal cortex (PHC) comprising the posterior aspect of the parahippocampal gyrus and adjacent anterior lingual gyrus/medial fusiform cortex along the collateral sulcus (Epstein and Kanwisher 1998; Epstein 2008). To test this hypothesis, we used related exemplar pairs of complex visual scenes in a repetition priming paradigm with simultaneous high-resolution fMRI focused on ventral visual brain regions to assess the magnitude and spatial distribution of NP effects. We selected exemplar pairs that were related conceptually and distinct perceptually (e.g., 2 different beach scenes, 2 different forest scenes, etc.; these conceptually related scenes also had some perceptual overlap, a point we consider fully in the Discussion).

While the foregoing hypothesized results would provide further evidence that asymmetry of form-abstraction is a fundamental property of hemispheric organization, the cortical properties that give rise to this phenomenon remain unknown. One recent suggestion is that cortical organization of category-specialized brain regions might be determined, to some extent, by virtue of their preferential intrinsic functional connectivity with distributed domain-specific brain regions rather than by lower-level "bottom-up" visual properties alone (Martin 2006; Mahon and Caramazza 2011). In support of this hypothesis, recent studies of intrinsic resting-state brain activity have shown that topographically dissociable cortical regions associated with different cognitive functions also show differential intrinsic functional connectivity with distributed domain-specific brain systems that are critical for storing or processing different types of properties or information (Wig et al. 2009; Simmons et al. 2010; Simmons and Martin 2011). These recent advances inspired us to examine intrinsic resting-state brain activity in an attempt understand what gives rise to the right/left hemispheric asymmetry of form-abstraction in the human brain.

We hypothesized that the predicted right/left functional dissociation for scene processing would be associated with different intrinsic functional connectivity of the right versus left PPA with dissociable functional-anatomic brain regions across the cerebral hemispheres. To test this hypothesis, we used resting-state functional connectivity analysis of fMRI data (rs-fcMRI) from independent rest-runs to analyze distributed patterns of intrinsic low-frequency BOLD correlations. Patterns of rs-fcMRI primarily reflect intrinsic activity fluctuations within neuroanatomical networks. Importantly, while rs-fcMRI correlations are highly constrained by anatomical connectivity, they do not exclusively reflect direct anatomical connections (Greicius et al. 2009; Honey et al. 2009; Van Dijk et al. 2010; Wig et al. 2011). In keeping with this, a portion of the variance in these rs-fcMRI patterns can be affected by ongoing (Fransson 2006; Fair et al. 2007; Buckner et al. 2009; Hasson et al. 2009; Wang et al. 2009) or recent behavior or experience (Waites et al. 2005; Albert et al. 2009; Hasson et al. 2009; Lewis et al. 2009; Grigg and Grady 2010; Stevens et al. 2010; Tambini et al. 2010). The latter studies demonstrate that consistent task-related coupling of activity among particular brain regions has subtle enduring effects on the patterns and strengths of spontaneous low-frequency rs-fcMRI correlations between these regions. Based on these findings, we propose that low-frequency BOLD correlations measured by rs-fcMRI reflect, in part, offline functional plasticity, such as motor and perceptual learning (Albert et al. 2009; Lewis et al. 2009) and explicit memory consolidation (Stevens et al. 2010; Tambini et al. 2010), which serves to strengthen functional interconnectivity in a sustained manner that facilitates task-related coupling of distributed brain regions during task performance. Therefore, we hypothesize that the expected right/left functional asymmetry for form-specific versus form-abstract processing in the right versus left PPA, respectively, will be associated with differences in the functional connectivity of these regions with other parts of the brain differentially involved in these processes.

Numerous studies have demonstrated that critical functions of the lateral PFC include form-abstraction and categorical representation in non-human primates (for review, see Miller et al. 2003), as well as conceptual abstraction in humans (Badre et al. 2010), with a particularly important role of the inferior frontal gyrus (Gotts et al. 2011), predominantly in the left hemisphere (Goldberg et al. 2007; Wang et al. 2010). A recent study of priming for nameable objects (Wig et al. 2009) reported that distinct cortical regions demonstrating sensitivity to stimulus (perceptual) versus decision (conceptual) transformations of stimuli between study and test were correlated with dissociable sets of areas at rest. The authors used a combination of a priori defined brain coordinates, based on previous studies of priming and independent results from their own data set to define regions of interest (ROIs) that consistently (i.e., across multiple independent data sets/studies) demonstrate sensitivity to perceptual versus conceptual manipulations of repetition priming. The 2 ROIs relevant to the current study were: 1) a region in the right middle occipital gyrus (RMOG), which was functionally connected with a network comprising regions associated with visual perception and 2) a region in the left posterior inferior frontal gyrus (LpIFG), which showed functional connectivity with a network comprising regions involved in form-abstract/conceptual processing.

Here, we use the 2 aforementioned regions as a priori seed ROIs in rs-fcMRI analyses of independent resting-state data, as well as an independent task-based functional localizer to define a priori scene-preferential ROIs bilaterally in each participant (i.e., right and left PPA), to demonstrate that this specialized visual processing region (PPA) shows differential functional connectivity in the right versus left hemisphere with

dissociable domain-specific brain systems involved in primarily perceptual versus abstract/conceptual processing, respectively. In a complementary analysis, we explore differences in the brain-wide functional connectivity of the right versus left PPA in an unconstrained data-driven manner.

Materials and Methods

Participants

Participants were 34 healthy, right-handed, young adults (mean age ± standard deviation [SD] = 24.6 ± 3.9; range = 18–33; 16 females/18 males), with normal or corrected-to-normal visual acuity, no history of psychiatric, neurological, or other medical illness, or history of drug or alcohol abuse, which might compromise cognitive functions. All participants were paid for their participation and gave written informed consent prior to participation, in accordance with the guidelines of the institutional review board of Harvard University and the Human Subjects Research Committee at Massachusetts General Hospital. Of the 34 participants that underwent fMRI scanning in this study, 4 were excluded from the analyses presented here due to excessive movement during fMRI scanning. The data and analyses reported here include 30 participants (mean age ± SD = 24.3 ± 3.9; range = 18–33; 14 females/16 males).

Stimuli

Scene stimuli were grayscale images of outdoor scenes and consisted of related exemplar pairs (Fig. 1*A*; Supplementary Fig. 1); half were "MAN-MADE," that is, scenes contained one or more man-made entities; half were "NATURE," that is, scenes contained no man-made entities. Related scene exemplar pairs were pictures of different outdoor locations, chosen to be related within scene pairs but as distinct as possible between different scene pairs (e.g., pictures of 2 different beaches, 2 different city skylines, and 2 different forests, etc.). Scene images were chosen from a variety of sources and were intended to span a wide range of natural visual environments, thus containing potentially recognizable objects/locations in some instances but no humans or other animals. Scene pairs were randomized across different conditions for each participant, with the constraint that half were NATURE and half MAN-MADE in each condition, thus, there was no confound of potentially familiar versus unfamiliar objects/locations across conditions. Face stimuli used in the localizer runs were grayscale images of faces, half were female and half were male (Endl et al. 1998; Jaeger et al. 2005). Stimuli were presented to participants using Presentation software (Neurobehavioral Systems Inc.) run on a Dell Latitude D820 laptop computer, projected onto a screen positioned at the head of the MRI scanner bore using JVC (model SX21/s) D-ILA projector, viewed by participants via a mirror attached to the head coil.

Behavioral Tasks

During the scene priming task, participants viewed pictures of outdoor scenes and identified each scene as MAN-MADE or NATURE as quickly and accurately as possible, with a single 2 alternative forced-choice button-response using the left middle and index fingers, respectively, with an MRI compatible response device. Participants completed 2 study-test sequences. During the study runs (n = 2; not scanned), participants viewed 3 repetitions of only 1 scene from each of the 80 different scene exemplar pairs (half MAN-MADE, half NATURE), presented in random order. During the corresponding test runs (n = 2; fMRI scanned) that followed the study runs, participants viewed 120 scene trials, interspersed with 40 null fixation trials, presented in random order: 40 scenes were repeat presentations of scenes viewed in the previous study runs (SAME); 40 scenes were related exemplars of the other 40 scenes viewed during the previous study runs (EXEMPLAR); 40 scenes were novel scenes not seen during the study runs (NEW). Half of the scenes in each condition were NATURE, half were MAN-MADE. Each test run scene trial (2500 ms) consisted of the presentation of a scene image (800 ms) and an interstimulus fixation crosshair (1700 ms). (See Fig. 1*B* for general depiction of run and trial sequence.) Null fixation-trials consisted of the presentation of a centrally located crosshair (2500 ms). Test session data were collapsed across the 2 study-test sequences for all analyses, as is typical in fMRI studies. To rule out the possibility of differential behavioral strategies or effects across the 2 test sessions, additional analyses were conducted (see Results and Supplementary Table 1). Participants also performed a similar face-priming task either before or after the scene-priming task, which was not analyzed or otherwise reported in the current study. Throughout the experiment, participants were also scanned during 4 "rest-runs." These runs consisted of the continuous

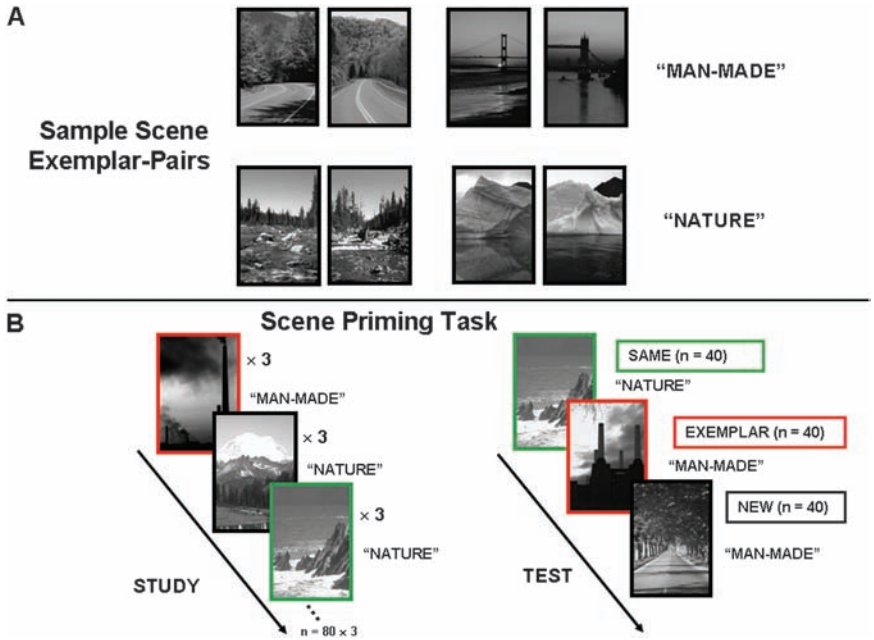

Figure 1. Sample stimuli and priming task design. (*A*) Examples of MAN-MADE (top) and NATURE (bottom) scene exemplar pairs. (*B*) Depiction of the general trial sequence for study and test runs and conditions for the priming test runs. Scenes trials were presented in random order in both study and test runs and were interleaved with fixation null trials in the test runs.

presentation of a centrally located crosshair for the duration of the run (4 min 40 s). Participants were instructed to remain alert and to fixate on the crosshair for the duration of the rest runs; no other specific instructions were given.

At the end of the experiment, participants were scanned during 2 runs of alternating face and scene blocks that served as an independent task-based functional localizer, allowing us to map individual PPA ROIs in the right and left hemisphere for each participant. During the face and scene blocks of the localizer runs, participants performed an incidental recognition memory task; task-based functional localizers typically involve performance of some type of cognitive task to ensure vigilance (Epstein and Kanwisher 1998; Kanwisher et al. 1998) but due to the statistical power and efficiency of block contrasts (Friston et al. 1999), this has negligible bearing on the main contrast of stimulus category, and thus, in no way does this compromise the independence of these runs as functional localizers (Friston et al. 2006). Face and scene blocks were interleaved with short (20 s) "fixation blocks." Each localizer block contained 20 successive face or scene trials (2500 ms: 800 ms face or scene presentation; 1700 ms interstimulus fixation crosshair), consisting of 10 novel pictures and 10 repeated pictures from the priming tasks, presented in random order. For each picture, participants were required to make an "old/new" judgment.

fMRI Scanning

Participants were scanned at the Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital (Charlestown, MA) using a 3-T Siemens Magnetom TimTrio Scanner (Siemens Medical Solutions) equipped with a 12-channel phased-array whole-head coil. All participants were fitted with MRI-compatible corrective lenses (zero-correction control lenses were worn by participants with normal vision). Cushions and clamps were used to minimize head movement during scanning.

Anatomical images were acquired using a high-resolution 3D magnetization-prepared rapid gradient echo sequence (MPRAGE: 128 sagittal slices; repetition time [TR] = 2530 ms; echo time [TE] = 3.45 ms; flip angle = 7°; voxel size = 1 × 1 × 1.33 mm). Functional images for the priming test runs (n = 2) were collected using high-resolution T_2^* gradient echo, echo planar imaging sensitive BOLD contrast (TR = 2500 ms; TE = 30 ms; flip angle = 90°; voxel size = 2 × 2 × 2 mm) in sets of 88 volumes per run acquired axially in 27 slices, aligned to the long axis of the temporal lobes, yielding focal coverage of ventral visual processing regions, including the entire occipital lobe and temporal lobes and inferior aspects of the parietal lobes (i.e., "slab coverage"; Supplementary Fig. 2). Functional images for the rest runs (n = 4) and localizer runs (n = 2) were collected in sets of 112 and 138 volumes per run, respectively, using the same parameters as for the priming test runs but with a voxel resolution of 4 × 4 × 4 mm, acquired axially in 36 slices, aligned to the priming test-run images, yielding whole-brain coverage.

Data Analysis

Behavioral Priming

BP was defined as reduced median RT associated with repetition of scenes in the different priming contrasts. Participants' median RT per condition was used to calculate RT differences between conditions rather than mean RT, as the latter is more susceptible to distortion due to anomalous or outlier responses for single or few individual scenes. BP was calculated as the mean percent difference in RT as follows: standard BP = NEW > SAME; form-specific BP = EXEMPLAR > SAME; form-abstract BP = NEW > EXEMPLAR (Fig. 2).

fMRI Preprocessing

All fMRI data were preprocessed using a combination of procedures using both FSL (FMRIB) and SPM2 (Friston et al. 1995; Wellcome Department of Imaging Neuroscience) tools. The first 4 volumes (10 s) in each run were excluded from analyses to allow for T_1-equilibration effects. Data were corrected for slice-dependent time shifts for each whole-brain volume (SPM2) and for head motion within and across runs using a rigid body correction (Jenkinson et al. 2002; FMRIB). Motion parameters generated in the latter process were used later as nuisance regressors in the general linear model (GLM) and rs-fcMRI analyses. Images were then normalized to a standard anatomical atlas space by first computing affine transforms connecting the first image volume of the first functional run with the T_1-weighted structural images (Jenkinson and Smith 2001; FMRIB). Our atlas representative template includes MP-RAGE data from 12 normal individuals and was made to conform to the MNI template using previously described methods (Buckner et al. 2004). The final preprocessing step combined motion correction and atlas transformation in one step to yield a motion corrected volumetric time series sampled at 2-mm cubic voxels, as previously described (Kahn et al. 2008). All anatomical coordinates in this paper are reported in MNI standard atlas space coordinates.

Task-Based Functional Localizer

After preprocessing, fMRI images from the localizer runs were spatially smoothed with a Gaussian kernel with a full-width at half-maximum

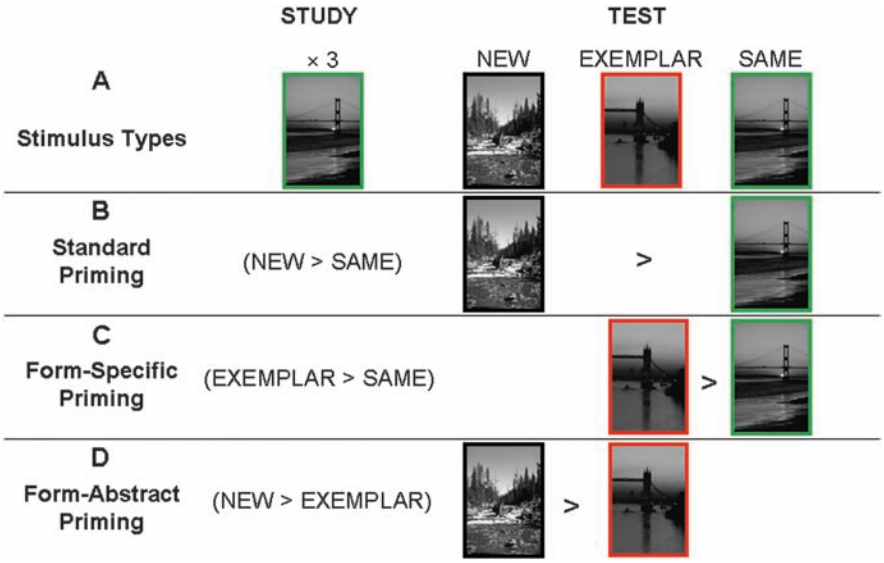

Figure 2. Schematic representation of priming contrasts. (*A*) Example stimulus from a study run (repeated 3 times, randomly ordered, across the run) and corresponding stimulus types in the test runs relative to study runs. Behavioral (mean RT difference) and neural (BOLD signal change) priming contrast for (*B*) standard priming = NEW > SAME; (*C*) form-specific priming = EXEMPLAR > SAME; (*D*) form-abstract priming = NEW > EXEMPLAR.

(FWHM) of 6 mm. The fMRI data were then analyzed using the GLM in SPM2. Regressors of noninterest included run means, linear trends to account for low-frequency noise (e.g., scanner drift), and 6 movement parameters obtained from the previous motion correction procedure. The face blocks and scene blocks were modeled separately with a box-car function convolved with the SPM2 canonical hemodynamic response function (HRF), with the onset and offset points coinciding with the beginning and end of each task block and entered as regressors of interest into the GLM. To identify PPA ROIs, whole-brain voxel-wise statistical parametric maps were computed for each participant for the contrast scenes > faces. Right and left PPA ROIs were defined individually for each participant as all voxels above a given threshold (t = 2.76, P < 0.005) within an approximate sphere with a radius of 8 mm centered on the peak activated voxel within the PHC in each hemisphere in the contrast scenes > faces, as described in previous work (Stevens et al. 2010).

Neural Priming

After preprocessing, fMRI images from the priming test runs were spatially smoothed with a Gaussian kernel (FWHM = 4 mm). The fMRI data were then analyzed using the GLM in SPM2 using the same procedures as for the localizer runs, with the following differences. Onsets for the scene trials were modeled as stick functions convolved with the SPM2 canonical HRF and binned into the 3 different conditions of interest (SAME, EXEMPLAR, NEW), and these conditions were entered as regressors of interest into the GLM. The a priori PPA ROI analyses were conducted as follows: the mean BOLD signal finite impulse response (FIR) time course was extracted separately from the PPA ROI in each hemisphere, for each participant individually, for each condition (SAME, EXEMPLAR, NEW). As is typically done in fMRI studies and based on the fact that there were no behavioral differences between the 2 test sessions (see Results and Supplementary Table 1), data were collapsed across scan sessions to afford sufficient power for a rapid event-related fMRI analysis. Peak BOLD FIR was expected to occur at approximately 6-s poststimulus onset (Miezin et al. 2000); this was confirmed by visual inspection of the BOLD FIR across participants. Thus, peak BOLD signal response for each condition was calculated as the mean percent BOLD signal change across the second and third poststimulus onset time points (i.e., TR 2–3; 2.5–7.5 s poststimulus onset). These values were then subjected to standard random-effects analyses to asses statistical significance across participants at the group level, using repeated measures analysis of variance (ANOVA), and paired-samples comparisons were conducted when indicated by significant main or interaction effects.

We also conducted a whole-volume (slab) analysis exploring NP effects across the entire ventral visual region of the brain covered in our high-resolution scan. Statistical parametric maps were computed for each individual participant for the following contrasts: standard NP = NEW > SAME; form-specific NP = EXEMPLAR > SAME; form-abstract NP = NEW > EXEMPLAR (Fig. 2). These contrast images were then subjected to random effects analyses at the group-level using 1-sample t-tests in SPM2 to assess statistically reliable effects.

rs-fcMRI Analyses of Intrinsic Low-Frequency BOLD Fluctuations

After preprocessing, the fMRI data from the rest runs were subjected to additional processing steps, as described previously (Fox et al. 2005; Vincent et al. 2006), prior to rs-fcMRI analyses. First, a temporal band-pass filter was applied to the atlas-aligned BOLD data, retaining signal within the frequency range of 0.009–0.08 Hz. Data were then spatially smoothed with a Gaussian kernel (FWHM = 6 mm). Then, sources of variance of noninterest were removed from the data by regression of nuisance variables (in addition to first temporal derivatives of each), including: the 6 motion parameters obtained during the motion correction procedure; the mean whole-brain signal; the mean signal from the lateral ventricles; and the mean signal from a region within the deep cerebral white matter.

To analyze patterns of intrinsic low-frequency BOLD correlations, the BOLD data were collapsed across all rest runs (4 runs × 4: 40 = 18: 40 total duration). For each participant, the mean BOLD signal time course was extracted from seed ROIs described below, and the correlation coefficient for each of these time courses with the time course for every other voxel in the brain was computed using Pearson's product-moment formula. These values were then converted to z (r) values using Fisher's r-to-z transformation (Zar 1996).

A Priori ROI Analyses of Intrinsic Activity

For the a priori ROI analyses, the following procedures were followed: First, we replicated the analyses of Wig et al. (2009) that identified 2 distinct brain systems differentially associated with perceptual versus conceptual processing using the 2 a priori seed ROIs as previously described; briefly, an approximate sphere with a radius of 6 mm was centered on an a priori coordinate in the RMOG (MNI transformed coordinates: x, y, z = 40, –86, 18) and in the LpIFG (MNI transformed coordinates: x, y, z = –42, 6, 28). The residual BOLD time course from each of these seed ROIs was correlated with all other voxels in the brain as described above to produce whole-brain voxel-wise correlation maps for each of the seed ROIs for each participant. These maps were then subjected to random effects analysis at the group level, using a 1-sample t-test to assess reliability of the rs-fcMRI maps for each seed ROI (t = 3.4, P < 0.001, uncorrected).

Next, we tested our hypothesis of asymmetrical intrinsic activity correlations of the right versus left PPA ROI with these perceptual (RMOG) and conceptual (LpIFG) regions, respectively. It was important to rule out the possibility that differences in connectivity between the right versus left PPA with seed ROIs in the right versus left hemispheres, respectively, could be due solely to higher intrahemispheric versus interhemispheric connectivity. Thus, to objectively assess the degree of predicted lateralization of functional connectivity, independent of any potential main effect of hemisphere per se (i.e., intrahemispheric rs-fcMRI > interhemispheric rs-fcMRI), we created 2 additional anatomically homologous ROIs for each of the aforementioned seed ROIs in the opposite hemisphere by inverting the x coordinate to produce seed ROIs in the left MOG (LMOG: x, y, z = –40, –86, 18) and right pIFG (RpIFG: x, y, z = 42, 6, 28) and repeated the whole-brain correlation procedure. In 2 separate analyses, the homologous sets of right and left "seed" ROIs (1: MOG; 2: pIFG) were used to create rs-fcMRI maps, and in both of these analyses, the right and left PPA ROIs were used to extract the seed-to-PPA correlation values. Specifically, we predicted that independent of any main effect of laterality per se, the a priori RMOG ROI would show a higher rs-fcMRI correlation with the right PPA than the left PPA, with no difference in correlation between the LMOG and the right versus left PPA. Conversely, we predicted that the a priori LpIFG ROI would show a higher rs-fcMRI correlation with the left PPA than the right PPA, with no differential correlation between the RpIFG and the right versus left PPA (see Fig. 6 for depiction of hypothetical results under the null [A] and alternative [B] hypotheses). In the first analysis, we extracted the mean rs-fcMRI correlation value (z (r)) of each of the 2 PPA ROIs (right vs. left PPA) with the 2 seed ROIs in the MOG (RMOG vs. LMOG) and subjected these values to a 2 × 2 ANOVA with seed (RMOG vs. LMOG) and PPA hemisphere (right PPA vs. left PPA) as repeated measures variables. A significant seed by PPA–hemisphere interaction effect would indicate hemispheric asymmetry of rs-fcMRI. For significant interaction effects, simple main effects of seed at each level of PPA hemisphere were assessed with paired-samples t-tests. The second analysis was parallel to the first, conducted in exactly the same way, but with the second set of a priori seed ROIs (RpIFG vs. LpIFG). To summarize, in the fist analysis, we predicted higher rs-fcMRI of the RMOG with the right PPA than the left PPA and that this difference would be disproportionately larger than the parallel comparison in the contralateral hemisphere. Likewise, in analysis 2, we predicted higher rs-fcMRI of the LpIFG with the left PPA than the right PPA and that this difference would be disproportionately larger than the parallel comparison in the contralateral hemisphere (see Fig. 6*B*).

Finally, we conducted additional control analyses to assess the possibility that slight systematic differences in the precise average location or shape of the PPA across hemispheres could contribute to the right/left dissociation for intrinsic activity correlations rather than a hemispheric effect per se. First, we created an additional anatomically homologous ROI (x coordinate inverted) for the right and left PPA ROI for each participant. Thus, there were a total of 4 "PPA ROIs" for each participant: 1 ROI in each hemisphere with the "position" (i.e., identical

coordinates [x inverted] and shape) of the right PPA ROI and 1 ROI in each hemisphere with the position of the left PPA. We then conducted a 3-way 2 × 2 × 2 ANOVA with seed (RMOG vs. LMOG), PPA-hemisphere (right vs. left), and PPA-position (left-position vs. right-position) as repeated measures variables. We predicted a significant seed by PPA–hemisphere interaction, but importantly, no seed by PPA–position interaction, which would rule out the possibility that asymmetrical rs-fcMRI of the seed ROIs with the bilateral PPA ROIs was due to differences in their position or shape rather than the hemisphere per se as predicted. Likewise, we conducted a parallel control analysis for the IFG seed ROIs (RpIFG vs. LpIFG).

Whole-Brain Analyses of Intrinsic Activity

The exploratory whole-brain rs-fcMRI analysis was conducted as follows: Typically, rs-fcMRI analysis involves creation of a ROI centered on a given coordinate that is used as a common seed region across multiple participants. Here, in order to account for individual variability and increase functional specificity, we used each participant's own right and left PPA ROIs, defined using the independent localizer, as seed regions for each participant's rs-fcMRI maps, as reported in a previous study (Stevens et al. 2010). These maps were then contrasted with one another in a voxel-wise comparison for each individual participant. Finally, these contrast maps were subjected to random effects analysis at the group-level and displayed at a relatively liberal threshold ($t > 2.76$, $P < 0.005$, uncorrected) to explore the full extent and distribution of intrinsic correlations.

In a similar manner as for the a priori rs-fcMRI analyses, we conducted additional control analyses to assess the relative contribution of laterality effects per se versus potential differential seed-ROI position effects. For the 2 whole-brain "laterality contrasts", we compared rs-fcMRI maps for homologous PPA ROIs in the right versus left hemisphere at the position of the left PPA ROI (i.e., "POSITION 1"; POSITION 1 in the right hemisphere was created by inverting the x coordinate of the left PPA) and at the position of the right PPA ROI (i.e., "POSITION 2"; POSITION 2 in the left hemisphere was created by inverting the x coordinate of the right PPA). For "position contrasts," we compared rs-fcMRI maps for the 2 PPA ROI positions within each of the hemispheres separately (i.e., left hemisphere: POSITION 1 > POSITION 2; right hemisphere: POSITION 1 > POSITION 2).

Figures

For all figures displaying cortical surface maps, fMRI data were projected onto the partially inflated cortical surface (population average landmark surface: PALS-B12) using CARET software (Van Essen 2005).

Results

BP Reveals Form-Specific and Form-Abstract Effects

To assess perceptual specificity of BP for complex visual scenes, we used a semantic classification task in a repetition priming paradigm with a large set of exemplar pairs of outdoor scenes that were selected to be related within pairs but as distinct as possible between pairs (Fig. 1*A*; Supplementary Fig. 1). "Standard" BP was defined as faster RT for REPEAT than NEW scenes; "form-specific" BP was defined as faster RT for SAME than EXEMPLAR scenes; "form-abstract" BP was defined as faster RT for EXEMPLAR than NEW scenes (Fig. 2). A 1-way ANOVA with test condition (SAME, EXEMPLAR, NEW) as a repeated measures factor showed a significant main effect of test condition on RT ($F_{2,58} = 32.43$, $P < 0.001$); paired-samples t-tests showed that RT was significantly faster for SAME than NEW scenes (standard BP: $t_{29} = 6.88$, $P < 0.001$), for EXEMPLAR than NEW scenes (form-abstract BP: $t_{29} = 5.30$, $P < 0.001$), and for SAME than EXEMPLAR scenes (form-specific BP: $t_{29} = 3.52$, $P < 0.001$) (Fig. 3). Thus, a graded BP effect was observed, demonstrating additive form-specific and form-abstract BP.

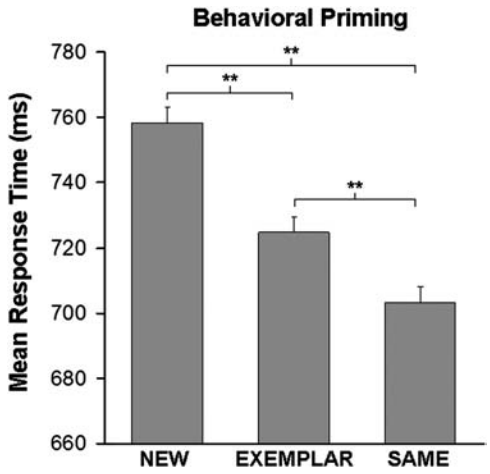

Figure 3. Behavioral priming demonstrates both form-specific and form-abstract effects. There was a graded BP effect, with faster RT for EXEMPLAR than NEW scenes (form-abstract BP) and for SAME than EXEMPLAR scenes (form-specific BP). $^{**}P < 0.001$.

Additional analyses ruled out any behavioral differences between the 2 test sessions (i.e., no main or interaction effects of test session) in terms of both accuracy (MAN-MADE/NATURE decision) and RT across conditions and, moreover, showed the identical pattern of significant priming effects in each of the runs when analyzed separately as when collapsed across sessions (Supplementary Table 1). Thus, there is no evidence that participants' strategy or behavior differed across the 2 test sessions.

Hemispheric Asymmetry of Form-Specific Versus Form-Abstract NP in PPA

An independent task-based functional localizer was used to individually define a priori peak right and left PPA ROIs for each participant (Fig. 4*A*,*B*; Supplementary Fig. 3). We extracted the time course of the BOLD signal response (percent signal change) from each of these ROIs for each of the 3 conditions at test: SAME, EXEMPLAR, and NEW scenes. A 2 × 3 ANOVA with hemisphere (right vs. left) and test condition (SAME, EXEMPLAR, NEW) as repeated measures factors revealed a marginal main effect of hemisphere ($F_{1,29} = 3.83$, $P = 0.06$), and a significant main effect of test condition ($F_{2,58} = 7.81$, $P < 0.001$), the latter confirming that NP did indeed occur. Critically, there was a significant hemisphere by test condition interaction ($F_{2,58} = 5.19$, $P < 0.01$), confirming hemispheric asymmetry of the NP effect. Paired-samples t-tests for simple main effects of condition in each hemisphere revealed a graded NP effect in the right PPA, with peak BOLD response being significantly higher for NEW than EXEMPLAR scenes ($t_{29} = 2.51$, $P < 0.05$) and higher for EXEMPLAR than SAME scenes ($t_{29} = 2.08$, $P < 0.05$). By contrast, NP in the left PPA demonstrated higher peak BOLD response for NEW than both EXEMPLAR ($t_{29} = 2.60$, $P < 0.05$) and SAME ($t_{29} = 2.59$, $P < 0.05$) scenes, and no difference between EXEMPLAR and SAME scenes ($t_{29} = 0.07$, $P = 0.94$). Thus, the significant hemisphere by condition interaction confirmed hemispheric asymmetry of form specificity, marked by relatively more form-specific NP in the right PPA versus form-abstract NP in the left PPA (Fig. 4*C*).

The exploratory whole-volume analysis was consistent with the foregoing a priori ROI analysis, showing right-left asymmetry for form specificity of NP: 1) standard NP effects were

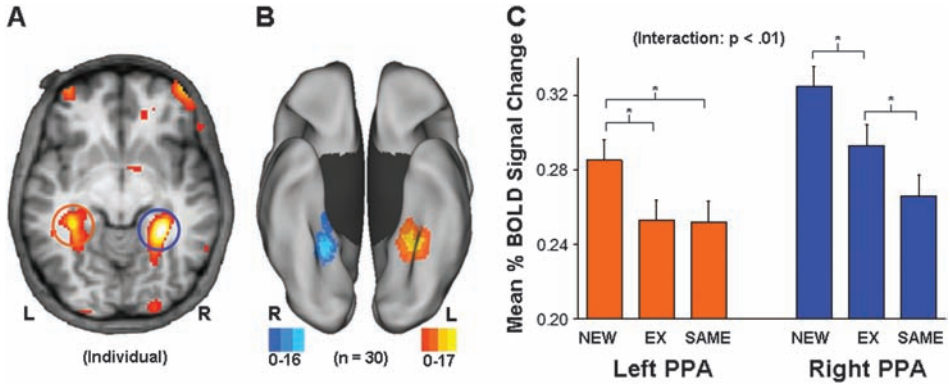

Figure 4. Hemispheric asymmetry of form-abstract neural priming in left versus right PPA. (*A*) Scene-preferential activation for the localizer contrast scenes > faces, used to define individual a priori right and left PPA ROIs, shown for a representative participant overlaid on their normalized anatomical image. (*B*) Right (blue) and left (orange/yellow) PPA ROIs of all participants ($n = 30$) overlaid on the partially inflated ventral cortical surface show the spatial distribution and overlap of PPA ROIs across individuals; voxel values (graded blue and orange/yellow scale bars) represent the number of participants whose PPA ROIs encompassed a given voxel. (*C*) Mean peak percent BOLD signal change relative to fixation baseline for scenes in each of the test conditions: A significant hemisphere by test condition interaction ($P < 0.01$) indicated hemispheric asymmetry of NP. A graded NP effect in the right PPA was indicated by lower BOLD response for EXEMPLAR than NEW scenes and for SAME than EXEMPLAR scenes. Purely form-abstract NP in the left PPA was indicated by equivalent suppression of the BOLD response for EXEMPLAR and SAME scenes relative to NEW scenes. EX, EXEMPLAR; R, right; L, left. $^*P < 0.05$.

widespread within posterior and anterior ventral visual regions bilaterally, including transverse occipital sulcus, fusiform, and PHC regions; 2) the peak form-specific NP effect across the entire volume occurred within posterior right PHC (collateral sulcus); 3) the peak form-abstract NP effect occurred within the left anterior PHC. For the purposes of exploring the distribution and extent of regions showing NP effects, maps are displayed at a relatively liberal threshold ($t_{29} = 2.76$, $P < 0.005$, uncorrected; Supplementary Fig. 4).

Hemispheric Asymmetry of Intrinsic Activity Correlations of Right Versus Left PPA with Perceptual Versus Conceptual Regions

We hypothesized that there would be hemispheric asymmetry of the functional connectivity of the right versus left PPA with regions involved primarily in visual processing versus regions involved primarily in abstract/conceptual processes, respectively. We tested this hypothesis using a priori seed ROIs in the RMOG and LpIFG (Fig. 5, upper left), based on the study by Wig et al. (2009).

First, we replicated the rs-fcMRI correlation maps reported by Wig et al. (2009) with a high degree of reliability, such that the anatomical distribution of the rs-fcMRI maps is strikingly consistent (Fig. 5). The RMOG showed significant rs-fcMRI correlations primarily with regions involved in visual perception, including the majority of the lateral occipital lobes, the cuneus, lingual gyrus, occipitotemporal/posterior fusiform gyrus, superior parietal lobule, and the posterior extent of the inferior and middle temporal gyri. Conversely, the LpIFG showed significant rs-fcMRI correlations primarily with regions involved in more abstract/conceptual processes, including the majority of the IFG bilaterally; dorsal medial PFC; frontal operculum/anterior-insula (left), lateral and medial banks of the intraparietal sulcus, and mid inferior and middle temporal gyri (Both maps: $t_{29} = 3.41$, $P < 0.001$; Fig. 5).

In the first a priori ROI analysis of predicted lateralization, a 2 × 2 ANOVA with seed (RMOG vs. LMOG) and PPA-hemisphere (right PPA vs. left PPA) as within-subjects factors revealed no significant main effects of seed ($F_{1,29} = 0.32$, $P = 0.58$) or PPA-hemisphere ($F_{1,29} = 0.40$, $P = 0.53$), but

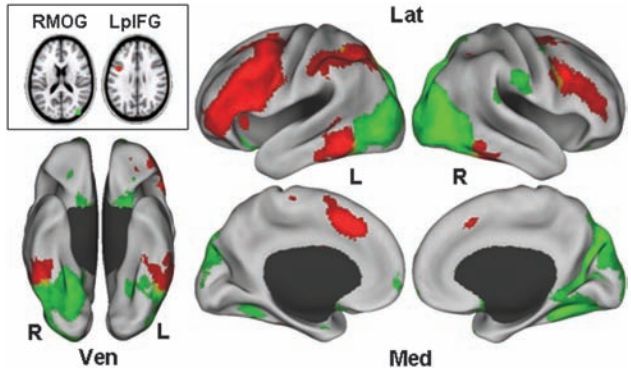

Figure 5. Seed regions in frontal and occipital cortex are intrinsically correlated with distinct brain systems. A priori seed ROIs (upper-left panel) in the RMOG (green) and LpIFG (red) that are sensitive to perceptual versus conceptual components of repetition priming (Wig et al. 2009), respectively, show intrinsic activity correlations with distinct cortical systems. RMOG is correlated with cortical regions (green) involved in primarily perceptual processes, including: The majority of the posterior and lateral occipital lobes, lingual gyrus, medial and lateral fusiform cortex, superior parietal lobule, and posterior inferior and middle temporal gyri. The LpIFG is correlated with cortical regions (red) involved in more abstract/conceptual processes, including: The majority of the inferior frontal gyrus and superior frontal sulcus, bilaterally; dorsal medial PFC; medial and lateral banks of the intraparietal sulcus; and mid inferior and middle temporal gyri. These results replicate the findings of Wig et al. (2009). The whole-brain group statistical rs-fcMRI maps for the RMOG (green), LpIFG (red), and overlap of these 2 (yellow) are displayed on the partially inflated ventral (Ven), lateral (Lat), and medial (Med) cortical surfaces (random effects: $t_{29} = 3.4$, $P < 0.001$). L, left; R, right.

critically, there was a significant seed by PPA–hemisphere interaction ($F_{1,29} = 19.92$, $P < 0.001$). Paired-samples contrasts of the simple main effects showed that, as predicted, RMOG had a higher rs-fcMRI correlation with the right PPA than the left PPA ($t_{29} = -2.18$, $P < 0.05$), with no differential correlations of the LMOG with the right versus left PPA ROIs ($t_{29} = 0.90$, $P = 0.37$) (Fig. 6*C*). Conversely, in the second a priori ROI analysis, a parallel ANOVA with the LpIFG versus RpIFG seed ROIs showed a significant main effect of seed ($F_{1,29} = 7.79$, $P < 0.01$), no main effect of PAA-hemisphere ($F_{1,29} = 0.69$, $P = 0.41$), but critically, there was a significant seed by PPA–hemisphere interaction ($F_{1,29} = 6.26$, $P < 0.05$). Paired-samples contrasts revealed that, as predicted, there were no differential

correlations of the RpIFG with the right versus left PPA ROIs (t_{29} = –0.35, P = 0.73), but there was a marginally higher correlation of the LpIFG with the left PPA relative to the right PPA (t_{29} = 1.94, P = 0.06) (Fig. 6*C*).

Regression of the global signal during rs-fcMRI analysis was used to remove sources of variance of noninterest (e.g., physiological and motion-related sources of variance). We note that there is debate in the literature concerning the effects of this procedure on the interpretability of an absolute zero-correlation baseline and negative correlation values per se (Fox et al. 2009; Murphy et al. 2009). However, we are concerned in these analyses only with relative differences in the rs-fcMRI correlation values, and thus, we do not interpret negative correlation values as such or the absolute zero-correlation baseline. Accordingly, relative difference in rs-fcMRI correlation values between the right versus left PPA ROIs (i.e., Δ rs-fcMRI: left PPA—right PPA) are plotted in Figure 6 (for plots of raw correlation values and additional discussion see Supplementary Fig. 5).

To summarize, significant interactions in both of the forgoing rs-fcMRI analyses confirmed hemispheric asymmetry of intrinsic activity correlations of both sets of a priori seed ROIs (RMOG vs. LMOG and LpIFG vs. RpIFG) with the left versus right PPA ROIs. Paired-samples contrasts of the simple main effects indicated that these differences were in the predicted directions (note the striking similarity between the predicted and actual results in Fig. 6*B*,*C*, respectively).

As predicted, the anatomical locations of the functionally defined peak PPA regions in the right and left hemisphere appeared to be essentially homologous across participants. Accordingly, control analyses confirmed that the right/left asymmetry of intrinsic activity correlations of the PPA with perceptual versus conceptual regions, respectively, is a hemispheric dissociation per se and not attributable to systematic differences in the position (as defined by standard MNI coordinates), size, or shape of the individually defined PPA ROIs (for full details, see Supplementary Results). Nevertheless, we consider the relevance of potential local anatomical asymmetries (Toga and Thompson 2003; Lyttelton et al. 2009) to these differences in the discussion.

Whole-Brain Analyses Confirm Hemispheric Asymmetry of Intrinsic Activity Correlations of Right Versus Left PPA

Finally, to explore the general pattern and extent of differential correlations between the right versus left PPA across the entire

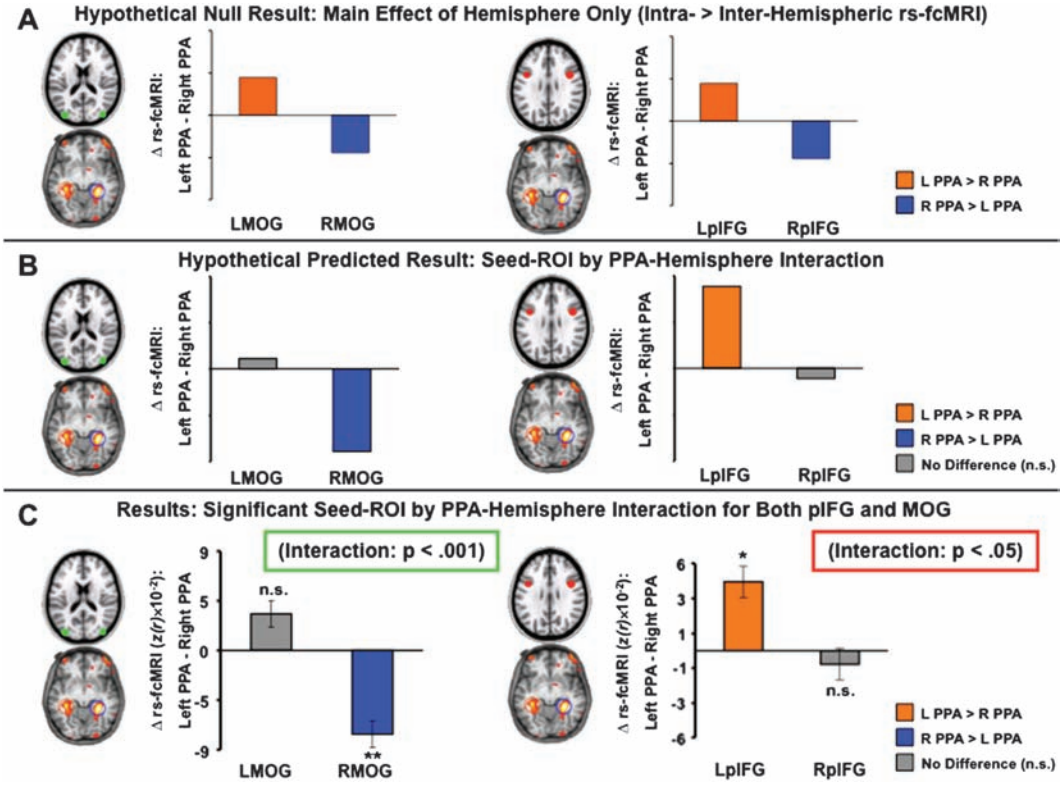

Figure 6. A priori rs-fcMRI analyses demonstrate hemispheric asymmetry of intrinsic functional connectivity of the PPA. Plots represent the difference between left PPA and right PPA correlations with the a priori seed regions (i.e., Δ rs-fcMRI: Left PPA—Right PPA); positive values (orange bars) indicate higher correlation with left PPA than right PPA; negative values (blue bars) represent higher correlation with right PPA than left PPA; gray bars indicate no statistically significant difference between correlations with the left and right PPA. Brain images illustrate locations of the MOG seed regions (green), pIFG seed regions (red), right PPA (blue circle), and left PPA (orange circle). (*A*) Hypothetical pattern of expected results under the null hypothesis of only a main effect of hemisphere per se, that is, higher intrahemispheric relative to interhemispheric rs-fcMRI correlations. (*B*) Hypothetical pattern of results if, as predicted, there were a seed ROI (MOG or pIFG) by target-hemisphere (right PPA vs. left PPA) interaction (predicted alternative hypothesis). (*C*) Actual results mirrored the hypothetical predicated results depicted in panel *B*: An ANOVA with 2 a priori seed ROIs (RMOG and LMOG) and 2 PPA ROIs (right PPA vs. left PPA) showed a significant interaction, demonstrating hemispheric asymmetry of intrinsic activity correlations, with relatively higher functional connectivity of the RMOG with the right PPA than the left PPA and no differential connectivity of the LMOG, as predicted. A parallel analysis using RpIFG and LpIFG seed ROIs also revealed a significant interaction, confirming hemispheric asymmetry, with no difference in functional connectivity of RpIFG but marginally higher connectivity of LpIFG with the left PPA relative to the right PPA, as predicted. MOG, middle occipital gyrus; pIFG, posterior inferior frontal gyrus; R, right; L, left; $z(r)$ = Fisher's r-to-z transformed correlation values; n.s., not statistically significant; $^*P = 0.06$; $^{**}P < 0.01$.

cortex, we seeded the individually defined PPA ROIs (see Fig. 4*A,B*) to create rs-fcMRI maps for each participant individually. The overall rs-fcMRI correlations of the right and left PPA ROIs were markedly similar Supplementary Fig. 6), as expected given their virtually homologous positions. However, consistent with the previous a priori ROI analyses, exploratory whole-brain analyses revealed that the right PPA showed relatively higher functional connectivity with posterior perceptual regions, including: posterior and lateral occipital regions; lingual gyrus and medial fusiform cortex (right); superior parietal lobule (right); and bilateral superior temporal gyrus (Fig. 7). Conversely, the left PPA showed relatively higher functional connectivity with regions involved in abstract/conceptual processes (Fig. 7), including aspects of the frontoparietal control network (left rostrolateral PFC; bilateral inferior frontal gyrus and anterior superior frontal sulcus; and left posterior/mid cingulate cortex) and, additionally, with aspects of the default network (left angular gyrus and bilateral ventromedial PFC. See Discussion).

In a similar manner as for the a priori rs-fcMRI analyses, we conducted additional control analyses to assess the relative contribution of laterality effects per se versus potential differential seed-ROI position effects (for details, see Materials and Methods). These whole-brain maps (Supplementary Fig. 7) confirmed that there were strong laterality effects accounting for the rs-fcMRI asymmetry (Supplementary Fig. 7*A,B*). By contrast, there was little evidence that systematic position effects could account for our findings (Supplementary Fig. 7*C,D*), with very few foci demonstrating significant differences in the position contrasts, relative to the laterality contrasts.

Discussion

In this study, we provide novel evidence of hemispheric asymmetry for form-abstraction in the human brain, using both high-resolution task-related fMRI and rs-fcMRI analyses of intrinsic low-frequency BOLD correlations. In a priori ROI analyses, we demonstrated that the left PPA is involved in relatively more form-abstract processing of complex visual scenes, while the right PPA is involved in relatively more form-specific processing (Fig. 4). We predicted that the functional right/left asymmetry would be associated with underlying differential intrinsic functional connectivity of these regions with areas mediating perceptual versus conceptual processing, respectively. We confirmed these predictions by using rs-fcMRI analyses of intrinsic activity in independent rest data with both whole-brain analyses (Fig. 7) and a priori ROI analyses (Fig. 6). We conclude that the PPA comprises lateralize subregions across the cerebral hemispheres that play complementary roles in visual scene analysis, possibly determined by differential intrinsic functional connectivity with distributed brain systems critically involved in perceptual versus conceptual processes.

While a number of experimental techniques have provided behavioral evidence of general hemispheric asymmetry of form-abstraction, including divided visual field presentation of stimuli (Marsolek et al. 1992, 1996; Marsolek 1999) and studies

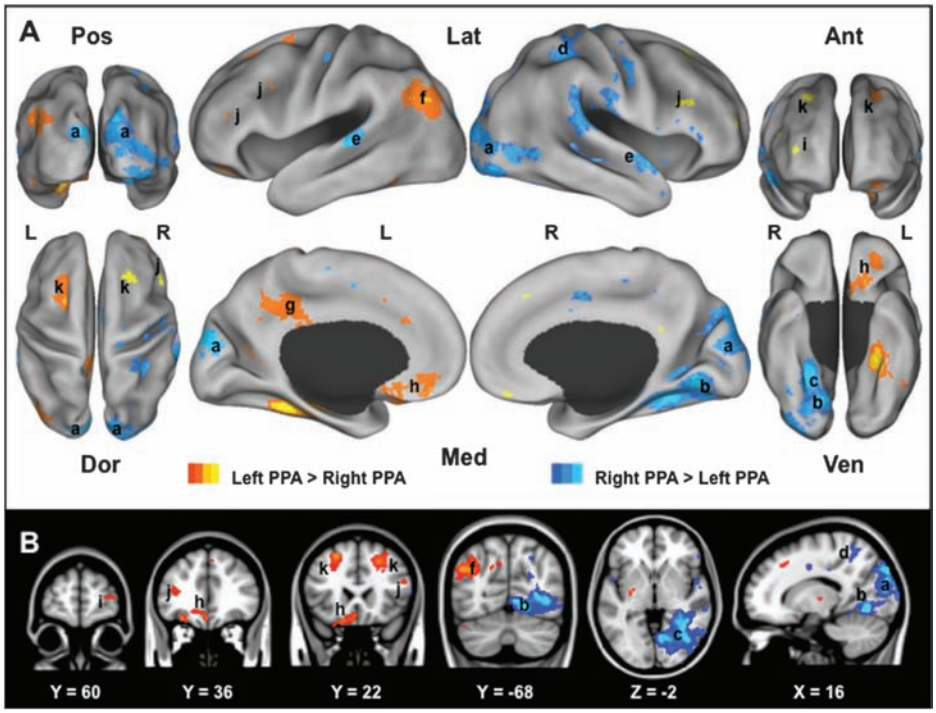

Figure 7. Whole-brain analyses confirm hemispheric asymmetry of intrinsic activity correlations. An exploratory whole-brain voxel-wise analysis ($t_{29} = 2.79$, $P < 0.005$) was used to explore the general pattern and extent of relative differential intrinsic activity correlations of the right (blue scale) versus left (yellow/orange scale) PPA ROIs. Group statistical rs-fcMRI maps for the contrast right versus left PPA are displayed on: (*A*) the partially inflated posterior (Pos), dorsal (Dor), lateral (Lat), medial (Med), anterior (Ant), and ventral (Ven) cortical surfaces and (*B*) coronal (*y*), axial (*z*), and sagittal (*x*) slices. The right PPA showed differentially higher correlations with primarily visual perceptual brain regions, including: posterior and lateral occipital regions (a); right lingual gyrus (b) and medial fusiform cortex (c); right superior parietal lobule (d); and bilateral superior temporal gyrus (e). The left PPA showed differentially higher correlations with regions primarily involved in abstract/conceptual processes, including aspects of the frontoparietal control and default networks, including: angular gyrus (f); posterior/mid cingulate cortex (g); ventromedial/orbitofrontal (h) and rostrolateral (i) PFC; and bilateral inferior frontal gyrus (j); and anterior superior frontal sulcus (k). R, right; L, left.

of split-brain patients (Metcalfe et al. 1995; Gazzaniga 2000), fMRI studies of NP were the first to allow mapping of form-specificity effects across specific cortical regions in the human brain. However, hemispheric asymmetry of form-specificity reported in previous priming studies (Koutstaal et al. 2001; Vuilleumier et al. 2002, 2005; Simons et al. 2003; Eger et al. 2005) has been limited to visual processing of individual entities in fusiform cortex. Here, we have demonstrated hemispheric asymmetry for visual processing of complex scenes in distinct brain regions thought to be specialized for navigating our spatial environment (Aguirre et al. 1998; Epstein and Kanwisher 1998; Epstein 2008).

Repetition priming has proven to be an invaluable tool for delineating the neural correlates of perceptual and conceptual cognitive processes (for review, see Schacter, Wig, et al. 2007; Stevens et al. 2008). Here, we used a paradigm with related scene pairs that allowed us to parse general repetition priming effects, both BP and NP, into their dissociable constituent form-specific and form-abstract components. The PPA showed relatively more form-abstract NP in the left hemisphere, and conversely, relatively more form-specific NP in the right hemisphere.

Our results provide new information about the nature of the PPA, a much-studied category-preferential brain region. Rather than functioning as a monolithic visual processing unit, the PPA may comprise lateralized subregions engaged in functionally dissociable yet complementary components of visual scene analysis, coordinated across the cerebral hemispheres. This parallel organization may underlie 2 crucial roles of visual scene analysis. While, it is essential that one be able to accurately distinguish one's specific location at any given time from other similar environments (form-specific analysis), one must also be able to abstract certain common elements, properties, and regularities across similar environments in order to guide behavior and predict what sorts of entities and events are likely to be encountered. We provide evidence that differential intrinsic functional connectivity with dissociable brain systems, specialized for detailed visual analysis versus processing and integration of abstract or conceptual knowledge, may underlie this important functional specialization.

While NP in the right PPA was more form-specific relative to the left PPA, the former region showed a graded reduction of the neural responses to NEW versus EXEMPLAR versus SAME scenes. This observation differs from the pattern of lateralization first reported by Koutstaal et al. (2001) for differential object priming within the right versus left fusiform cortex, in that they reported purely form-specific priming on the right but graded priming for EXEMPLAR relative to SAME objects on the left. However, differences inherent in the stimulus-types across studies might explain the different patterns of lateralization. Whereas exemplars of objects representing the same concept can be very perceptually dissimilar (e.g., an antique rotary telephone may share very little visual similarity with a modern cell phone), though they are not necessarily so (e.g., 2 hammers will always share considerable perceptual overlap), conceptually related complex visual scenes are by definition much more likely to share visual properties (Oliva and Torralba 2001)—for example, 2 desert scenes consisting of sand dunes are likely to share lower frequency visual information relative to 2 forest scenes containing trees and leaves which would share higher frequency visual information. Therefore, while it is possible that processing in the right PPA might be somewhat form-abstract, given the reduced neural response to SAME relative to EXEMPLAR scenes, it is likely that the scenes were more visually similar within scene-exemplar pairs than between pairs. Thus, it is possible that the graded NP effect in the right PPA reflects a graded reduction of visual similarity between the SAME, EXEMPLAR, and NEW scenes relative to previously studied scenes. This question suggests an important direction for future research, with studies explicitly designed to test NP in the PPA across a controlled range of visual similarity between stimulus repetitions. One approach would be to use objective measures of the degree of visual similarity between scene pairs, such as independent participant ratings and/or automated computer algorithm estimates (cf. Gotts et al. 2011), as a parametric modulator in an fMRI analysis to quantify the extent to which NP in the PPA is sensitive to the degree visual similarity. While the latter is beyond the scope of the current study, the striking finding here was the significant asymmetry of form-specificity across the hemispheres, with markedly more form-abstract responses in the left PPA than the right.

The latter explanation fits with findings of previous studies that have investigated priming effects for complex scenes (Epstein et al. 2003, 2007; Blondin and Lepage 2005; Xu et al. 2007). These studies all reported some degree of NP for different exemplars of previously viewed scenes, but none reported the degree of form-abstract NP or the hemispheric dissociation reported here. Several differences in experimental designs most likely account for these discrepancies. First, an important methodological feature of the current study was the definition and analysis of the PPA ROIs in the right versus left hemispheres independently; by contrast, some previous studies have reported scene-related activation of the PPA as a whole, collapsed across hemispheres (Epstein, Higgins, et al. 2007; Xu et al. 2007). Other studies have reported that there were no significant laterality differences in PPA activation across similar conditions (Epstein, Parker, et al. 2007; Park and Chun 2009). In these cases, the PPA results were collapsed across hemispheres for presentation; thus, it is not clear whether the pattern of PPA activity in these studies might have shown a trend toward lateralization despite this null finding.

Furthermore, there is evidence that a number of experimental parameters are instrumental in eliciting distinct forms of repetition effects, such as stimulus duration, as well as lag time and number of intervening stimuli between critical stimulus repetitions (e.g., differences between "fMRI adaptation" vs. "repetition suppression"; Ganel et al. 2006). For example, previous studies have reported purely viewpoint-specific NP in the PPA for repetition of scenes (same vs. different viewpoint) within adaptation trials (successive scene presentations without intervening stimuli) but partially view-invariant NP for scene repetition between trials (lagged repetition of scenes with intervening stimuli) (Epstein et al. 2008; Park and Chun 2009). Finally, in all the foregoing studies, scenes within each exemplar pair were drawn from the same scene, such as nonoverlapping "panels" (i.e., subsections) of the same larger scene (Blondin and Lepage 2005), overlapping panels of the same larger scene (Park and Chun 2009), different viewpoints of the same location (Epstein et al. 2003; Epstein, Higgins, et al. 2007) and different "zoom-level" views of the same larger scene (Xu et al. 2007). Perceptual specificity for lower level visual parameters, such as illumination, image size, and viewpoint, is known to vary across even posterior to mid

ventral visual cortex (Grill-Spector et al. 1999; Vuilleumier et al. 2002) and likely reflects a fundamentally different form of abstraction (i.e., lower level perceptual) than that which is tested using completely different exemplars that are more perceptually distinct, yet share abstract visual properties (Oliva and Torralba 2001), as in the current study.

A number of previous studies have also highlighted an important role of a region within retrosplenial cortex (RSC) in processing scenes or contextual associations, and these studies have consistently supported the following 2 ideas: while the PPA is involved in visual processing of the physical characteristics of scenes, the RSC is involved in more abstract conceptual-level processing (Epstein and Higgins 2007; Epstein, Parker, et al. 2007; Park and Chun 2009; for a similar distinction pertaining to contextual associations, see also Bar and Aminoff 2003; Bar 2004). Because the high-resolution fMRI method we used allowed only partial brain coverage focused on ventral visual regions, the RSC was not reliably covered in all participants, depending on intersubject variability of brain size and shape (see Supplementary Fig. 2). Thus, a complete and reliable analysis of activity in the RSC was not possible in the current study. The specific role of the RSC in scene processing is an ongoing topic of active research (see Epstein 2008) and must be elucidated further by future studies.

It is important to consider the nature of the behavioral task used in our experiment and how this might or might not interact with priming effects used to assess the nature of visual processing in the PPA. We have previously discussed at length both top-down attentional effects on priming and its interaction with explicit memory processes in a comprehensive review (Stevens et al. 2008). To summarize here, while some studies suggest that BP and NP can occur independent of shifts in attention (Badgaiyan et al. 2001; Schott et al. 2005; Hasson et al. 2006; Voss and Paller 2006), there is also considerable evidence that they are sensitive to top-down attentional modulation (Henson et al. 2002; Eger et al. 2004; Ishai et al. 2004; Murray and Wojciulik 2004; Yi and Chun 2005; Yi et al. 2006; Thoma and Henson 2011). Likewise, the evidence regarding potential interactions between NP and explicit memory is mixed: Some studies have proposed a link between these processes (Wagner et al. 2000; Gonsalves et al. 2005; Turk-Browne et al. 2006; Chee and Tan 2007; Kompus et al. 2011; for review, see Dew and Cabeza 2011). However, others have explicitly argued that NP effects are associated with implicit processes that can occur independently of explicit memory processes and that their neural signature is distinct from brain activity associated with explicit memory (Schott et al. 2005, 2006). Particularly relevant to the current results, several studies report that NP in ventral visual regions is not directly correlated with BP and/or is not critically affected by behavioral task variables (Dobbins et al. 2004; Maccotta and Buckner 2004; Wig et al. 2005; Sayres and Grill-Spector 2006; McMahon and Olson 2007; Horner and Henson 2008) including the PPA specifically (Bunzeck et al. 2006; Turk-Browne et al. 2006; Xu et al. 2007). Furthermore, a recent study by Kravitz et al. (2011) convincingly demonstrates that the PPA is specifically involved in visual-perceptual processing per se, representing both form-specific and form-abstract visuospatial information (cf. Oliva and Torralba 2001) rather than conceptual/semantic representations (although see Walther et al. 2009). Based on the foregoing facts, we conclude that the NP effects in the PPA of particular interest here are primarily driven by scene repetition per se rather than any particular aspect of the behavioral paradigm used, and as such, reveal form-specific versus form-abstract visual scene analysis in the right versus left hemisphere, respectively.

Conversely, we propose that the BP effects we observed might reflect stimulus-decision associations, given that the same task was used at study and test across all stimulus repetitions; improved performance related to learned "stimulus-decision" associations tends to be highly specific to the particular task and perceptual features of the stimuli (Schnyer et al. 2006, 2007). Because our NP analyses were constrained to ventral visual regions using high-resolution fMRI, we could not assess NP effects in the PFC. However, we propose that stronger intrinsic functional connectivity among brain regions, revealed in the whole-brain rs-fcMRI analyses, may facilitate, as well as reflect a history of, task-related coupling of these regions during visual scene analysis. In this way, connectivity of a critical left PFC region, previously shown to be instrumental in stimulus-decision associations (Wig et al. 2009), with the left PPA, a region demonstrated here to be specialized for processing relatively more form-abstract visual information, might facilitate higher level abstract or conceptual scene analysis. Likewise, preferential functional connectivity of the rMOG with the right PPA, a region specialized for more form-specific visual processing, facilitates more detailed scene analysis involving finer-grained visual distinctions. Finally, the studies reviewed above suggest that while the PPA is involved in visual scene analysis per se, the RSC may play a complementary role in more abstract scene analysis as well—whether this is at the visual or purely conceptual level remains to be definitively established.

The current results are also relevant to an ongoing debate within the literature as to whether hemispheric asymmetry of form-abstraction fundamentally reflects conceptual/semantic processes (e.g., Curby et al. 2004) or a purely visual form of abstraction (e.g., Marsolek and Burgund 2008). The observed dissociation in the PPA is consistent with the dissociable neural subsystems theory (Marsolek 1999; Marsolek and Burgund 2008). However, the primary aim of the current study was to assess whether asymmetry of form-specificity would exist at all in this higher order visual processing region for complex visual scene processing, which we report here for the first time; as such, we did not include an explicit manipulation to test a purely conceptual level of abstraction (cf. Marsolek 1999; Curby et al. 2004; Marsolek and Burgund 2008). Thus, our results cannot definitively confirm or eliminate one possibility or the other. Nonetheless, an interesting hypothesis is that while the organization of posterior visual processing regions is consistent with the dissociable neural subsystems theory (asymmetry of NP), left lateralization of intrinsic functional connectivity between an abstract visual processing region and remote conceptual processing regions facilitates behavioral performance and possibly underlies BP effects to some extent. This hypothesis, which will require more extensive testing in the future, suggests a critical link between abstract visual processing and semantic/conceptual processing, both apparently lateralized within the left hemisphere, possibly reconciling these theories.

It is unsurprising that the overall patterns of rs-fcMRI correlations for the bilateral PPA ROIs were markedly similar Supplementary Fig. 6), given that they were functionally defined and virtually symmetrically positioned across the hemispheres (i.e., nearly anatomically homologous). However,

a direct comparison of differential connectivity of these regions demonstrated that, as predicted, functionally defined PPA regions in the right versus left hemispheres showed differential intrinsic activity correlations with distributed perceptual versus conceptual brain systems, respectively. The left PPA also showed higher correlations with aspects of the default network, consistent with a previous study showing that posterior parahippocampal gyrus regions generally fall within the confines of the default network (Kahn et al. 2008), which is significantly left lateralized (Liu et al. 2009). However, the latter cannot alone explain the overall pattern of asymmetry observed here. First, the bilateral PPA regions showed brain-wide patterns of rs-fcMRI correlations that were distinct from that previously reported for posterior parahippocampal regions (Kahn *et al.*, 2008), likely due to the fact that the PPA comprises more caudal cortex, including anterior lingual gyrus/medial fusiform cortex along the collateral sulcus in addition to the adjacent posterior-most aspect of the parahippocampal gyrus (Aguirre et al. 1998; Epstein and Kanwisher 1998; Epstein 2008). Second, in addition to default network regions, the left PPA showed relatively increased intrinsic correlations with components of a frontoparietal control network (Vincent et al. 2008; Wig et al. 2009; Spreng et al. 2010) as well, including rostrolateral PFC, bilateral regions in the middle frontal gyrus and anterior superior frontal sulcus, and a mid/posterior cingulate cortex region. Third, the right PPA showed not only relatively lower correlation with default network regions but instead showed relatively increased intrinsic functional connectivity with visual perceptual regions, including lateral, medial, and ventral occipital regions, as well as the right superior parietal lobule. Finally, our a priori ROI analyses (RMOG and LpIFG) confirmed our prediction that these regions would show relatively higher intrinsic functional connectivity with the right versus left PPA, respectively.

A recent study using rs-fcMRI to quantify lateralization of independent functional-anatomic systems showed that asymmetry of distinct brain systems, as defined by relatively higher intrahemispheric than interhemispheric functional connectivity between nodes of a given network, is determined by multiple independent factors (Liu et al. 2009) rather than a single general factor as has been previously suggested (Annett 1964). Four independent factors revealed lateralization of 4 corresponding putative systems: "visual/perceptual" and "attentional" systems in the right hemisphere; "default" and "language/controlled semantic processing" systems in the left hemisphere. These results fit with our hypothesis that asymmetry of form-abstraction is a fundamental property of hemispheric specialization in the following way: The 2 putative systems lateralized to the right hemisphere are fundamentally perceptual in nature: the "visual" system and an "attentional/monitoring" system. Conversely, the 2 putative systems shown to be lateralized within the left hemisphere are both systems fundamentally involved in conceptual abstraction: language/controlled semantic processing, which are inherently conceptual by nature and the "default network," which is known to be fundamentally involved in abstraction across time or beyond "the here and now" (e.g., remembering the past, imagining the future; imaging the thoughts and feeling of others) (Andrews-Hanna et al. 2010; Spreng and Grady 2010; for review, see Buckner and Carroll 2007; Schacter, Addis, et al. 2007; Buckner et al. 2008; Spreng et al. 2009). Similarly, we demonstrated that the right PPA showed perceptually specific processing and had relatively higher functional connectivity with visual perceptual regions, while the left PPA showed form-abstract processing and had relatively higher functional connectivity with frontopartietal control and default network regions.

The results from several control analyses demonstrated that our findings reflect functional connectivity asymmetry effects per se rather than potential differences in the position of ROIs across the hemispheres. However, one must consider the extent to which local anatomical asymmetries, such as those associated with petalia and Yakovlevian torque (Toga and Thompson 2003; Lyttelton et al. 2009), could contribute to observed asymmetries of functional connectivity. Based on consideration of the relevant literature (for full details, see Supplementary Discussion) and the particular methods used in the current study, we conclude that it is unlikely that anatomical asymmetries could explain the current results. Nonetheless, an interesting direction for future research will be to explicitly assess whether, and to what extent, asymmetrical intrinsic activity correlations across the brain are associated with local anatomical asymmetries.

To conclude, we provide novel evidence of functional asymmetry for processing of complex visual scenes in the PPA, with form-abstract processing in left hemisphere versus relatively more form-specific processing in the right hemisphere. Based on our results, in combination with previous behavioral evidence of general asymmetry of form-abstraction and recent work showing lateralization of brain systems as measured by intrinsic activity correlations, we propose that this functional dissociation reflects a fundamental organizing principle of cerebral hemispheric asymmetry. Critically, our demonstration of asymmetrical intrinsic functional connectivity of the PPA across hemispheres with dissociable areas critical for perceptual versus abstract/conceptual processing provides new insight into the nature of cortical organization that underlies this important neurocognitive specialization. Our results suggest avenues for future research, investigating form-abstraction across other domains, sensory modalities, and brain systems, at multiple levels of abstraction, ranging from first level perceptual abstractions to higher level concepts.

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Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

Notes

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