The Neural Basis for Spatial Relations

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Abstract

■ Studies in semantics traditionally focus on knowledge of objects. By contrast, less is known about how objects relate to each other. In an fMRI study, we tested the hypothesis that the neural processing of categorical spatial relations between objects is distinct from the processing of the identity of objects. Attending to the categorical spatial relations compared with attending to the identity of objects resulted in greater activity in superior and inferior parietal cortices (especially on the left) and posterior middle frontal cortices bilaterally. In an accompanying lesion study, we tested the hypothesis that comparable areas would be necessary to represent categorical spatial relations and that the hemispheres differ in their biases to process categorical or coordinate spatial relations. Voxel-based lesion symptom mapping results were consistent with the fMRI observations. Damage to a network comprising left inferior frontal, supramarginal, and angular gyri resulted in behavioral impairment on categorical spatial judgments. Homologous right brain damage also produced such deficits, albeit less severely. The reverse pattern was observed for coordinate spatial processing. Right brain damage to the middle temporal gyrus produced more severe deficits than left hemisphere damage. Additional analyses suggested that some areas process both kinds of spatial relations conjointly and others distinctly. The left angular and inferior frontal gyrus processes coordinate spatial information over and above the categorical processing. The anterior superior temporal gyrus appears to process categorical spatial information uniquely. No areas within the right hemisphere processed categorical spatial information uniquely. Taken together, these findings suggest that the functional neuroanatomy of categorical and coordinate processing is more nuanced than implied by a simple hemispheric dichotomy. ■

INTRODUCTION

Cognitive neuroscience investigations of semantics traditionally focus on knowledge of objects (Borgo & Shallice, 2001; Moore & Price, 1999; Tranel & Damasio, 1999; Caramazza & Shelton, 1998; Binder et al., 1997; Gonnerman, Andersen, Devlin, Kempler, & Seidenberg, 1997; Tranel, Logan, Frank, & Damasio, 1997; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996; Capitani, Laiacona, Barbarotto, & Trivelli, 1994; Damasio, Damasio, Tranel, & Brandt, 1990). Although these investigations have certainly been fruitful, confining semantics to the study of objects leaves us with an impoverished understanding of the world. Until recently, relatively little attention was paid to our knowledge of how objects act in the world and how they are related to each other. Investigating the neural basis of knowledge of actions, events, and relations between objects would enrich our understanding of the human semantic system.

In this report, we focused on the neural basis for a specific kind of relational knowledge, that is, spatial relations. Spatial relations between objects can be organized in different ways. These relations can be organized in the form of continuous metrics (distance, orientation, etc.) or as a discrete set of relations (such as those that can be labeled verbally by prepositions in English). For exam-

ple, a pen might be 5 or 10 cm to the right of a notebook. These would represent different coordinate relations but not different categorical relations. The pen would have to be on top of the notebook to represent a different categorical relationship. Slobin (1996, 2000) proposed that thinking for speaking might be different than thinking for other reasons. Along these lines, thinking about spatial relationships for speaking might be different than thinking about spatial relations for other reasons. Thus, coordinate (continuous metric) representations are critical to guide movements such as reaching or navigation but may be less relevant to language. They can be described by a large and flexible set of open class terms, such as distance in centimeters, inches, or miles. By contrast, categorical representations form a more coarsely organized set of spatial relations that are encoded in a closed class set of terms such as "on" or "in."

The neural instantiation of spatial relations might be expected to follow naturally from the "what" versus "where" distinction (Ungerleider & Mishkin, 1982). On this central tenet of visual neuroscience from monkey studies, visual processing is divided into dorsal or occipito-parietal and ventral or occipito-temporal streams. The dorsal visual stream specializes in spatial processing, and the ventral stream specializes in object processing (Haxby et al., 1991). Although the streams undoubtedly interact at multiple levels (Schiller, 1996; Ferrera, Rudolph, & Maunsell, 1994), this processing division of labor by

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the nervous system has been corroborated in humans (Chatterjee, 2003; Martin, Ungerleider, & Haxby, 2000; Aguirre & D'Esposito, 1997; Farah, 1990). Occipito-temporal lesions are associated with various visual agnosias, in which individuals have trouble recognizing objects or faces, and posterior parietal lesions are associated with spatial deficits such as hemispatial neglect or simultanagnosia. Imaging studies also confirm this general distinction. Thus, the fusiform gyrus is associated with processing faces (Kanwisher, McDermott, & Chun, 1997), the parahippocampal gyrus with processing places and buildings (Epstein & Kanwisher, 1998; Aguirre & D'Esposito, 1997), and the lateral occipital complex with processing objects in general (Kanwisher, Woods, Iacoboni, & Mazziotta, 1997; Malach et al., 1995). Although the posterior parietal cortex is implicated in shifts of spatial attention (Corbetta, Shulman, Miezin, & Peterson, 1995), relatively little direct functional imaging evidence supports the role of the parietal cortex in processing spatial relations.

Spatial relations relevant to language are likely to be categorical. Kosslyn et al. (1989) initially suggested the distinction between categorical and coordinate spatial relations. They proposed a left hemisphere advantage for categorical visual processing and a right hemisphere advantage for coordinate visual processing (Kosslyn & Ochsner, 1994; Kosslyn et al., 1989). However, the empirical bases for these neural claims were limited, derived primarily from visual hemifield stimuli presentations and computer simulations. The specific results obtained by Kosslyn et al. were subsequently challenged as an artifact of a bias in spatial resolution of sensory processing (Sergent, 1991) or as an artifact of task difficulty (Slotnick, Moo, Tesoro, & Hart, 2001). Furthermore, the approach of using lateralized stimuli presentation to infer lateralized brain function might itself be suspect (Efron, 1990). In a subsequent PET study, Kosslyn, Thompson, Gitelman, and Alpert (1998) failed to find consistent left hemisphere activation for categorical spatial judgments. However, in an fMRI study, Baciu et al. (1999) found that left angular gyrus (AG), within the inferior parietal lobe, displayed greater activity than the right AG when subjects judged whether a dot was located above or below a bar.

Despite the limited evidence for the neural basis for categorical and coordinate spatial processing, this distinction seems plausible (for reviews, see Postma & Laeng, 2006; Jager & Postma, 2003). Damage to right parietal cortex appears to impair performance on tasks that rely on precise metrics (Laeng, 1994; Hannay, 1976; Warrington & Taylor, 1973). Left posterior parietal lesions are associated with left/right confusion, a hallmark symptom of Gerstmann syndrome (Mayer et al., 1999). To our knowledge, patients with Gerstmann syndrome per se have not been tested more comprehensively on categorical spatial judgments. Left–right judgments may be a class of spatial judgment, as evidenced by left hemispatial neglect (Chatterjee, 2003) or mirror reading and writing (Gottfried, Sancar, & Chatterjee, 2003), that implicates a special role for the horizontal axis in processing space. Whether left–right processing generalizes to categorical processing is not known.

Laeng (1994, 2006) has reported data consistent with the hemispheric specialization hypothesis. Patients with focal brain damage were shown drawings of two objects. After a short delay, they were asked to identify the drawing when it was paired with a drawing of the same objects transformed in their categorical or coordinate spatial relations. He found that patients with right hemisphere damage (RHD) were more likely to make coordinate relation errors and patients with left hemisphere damage (LHD) were more likely to make categorical memory errors. The anatomic analyses of patients in this study were rudimentary. Counterintuitively, behavior differences were found when patients had parietal damage only and not when they also had temporal or frontal damage in addition to the parietal damage. More relevant to our study is a report by Tranel and Kemmerer (2004). They examined a large group of patients on a variety of tasks probing knowledge of locative relations. In an "odd man out" task, participants viewed groups of three pictures, each with two objects. They were asked to point to the picture that depicted a different categorical relationship than the other two. They found that damage underlying the white matter of the left parietal and frontal opercula was associated with deficits in matching categorical spatial relations.

The studies reviewed served as the backdrop to our investigations of the neural basis of spatial relations using both functional imaging in young healthy participants and behavioral studies in participants with focal brain lesions. Both approaches, now central methods in cognitive neuroscience, have complementary strengths and weaknesses (Chatterjee, 2005; Fellows et al., 2005; Rorden & Karnath, 2004). Imaging studies in young normal subjects offer insights into the processing of the unaltered brain but remain fundamentally a correlational method. Lesion studies are inferentially stronger but are limited by uncertainties of neuronal reorganization, not to mention variables such as age, education, medications, and comorbid conditions in an elderly population. In principle, converging evidence from both methods would provide strong support for brain–behavior relations.

Our first experiment used fMRI to investigate the neural systems activated by the identification of categorical spatial relations, as compared with the identification of objects being located. By categorical relations, we mean between-object relations rather than within-object relations (such as the handle at the top of the briefcase). Our experiment relies on subjects making different judgments on the same set of stimuli. Thus, different neural activation patterns could not arise from differences in the perceptual properties of the stimuli themselves. The second experiment used participants with left or right focal brain lesions to assess their abilities to make categorical and coordinate spatial judgments. We used a variant of voxel-based lesion

symptom mapping (VLSM) (Kimberg, Coslett, & Schwartz, 2007; Bates et al., 2003) to seek evidence consistent with our fMRI results. VLSM is a distinct advance over lesion overlap methods because patients' behavior is considered as a continuous variable rather than being judged as normal or abnormal. Our general hypothesis is that the neural mediation of spatial relations between objects is distinct from that of identification of objects. More specifically, we expected the posterior parietal cortex to be involved in computing categorical and coordinate spatial relations (Chatterjee, 2008). Furthermore, on the grounds that categorical spatial relations are linked more closely to language, we expected behavioral deficits in categorical spatial judgments to be associated with damage to left peri-sylvian regions and deficits in coordinate spatial judgments to be associated with RHD.

FUNCTIONAL NEUROIMAGING

Methods

Participants

Sixteen right-handed participants (10 men and 6 women; mean age = 22 years; range = 18–25 years) were recruited from the University of Pennsylvania. Four subjects were excluded from the analysis because of poor behavioral performance, raising doubts about their engagement in the task. All participants had normal or corrected-to-normal vision and spoke English as their primary language. None had a history of neurological or psychiatric symptoms. All gave informed consent in accordance with the procedures of the institutional review board of the University of Pennsylvania and the Declaration of Helsinki.

Stimuli

Digital pictures of two objects (a mouse, a cassette, a toy monkey, a stapler, a mug, or a spoon) in one of eight spatial relationships (that could be described by above, below, in, on, left, right, in front of, or behind) on a plain background were used. Red arrows were added to denote the figure object to be located.

Behavioral Tasks

In an alternating blocked design, participants performed a one-back matching task. They were instructed to attend to either the spatial relationship between the objects or the identities of the objects. Participants pressed a button press to indicate whether the current image matched the previous image on the basis of either spatial relationship or object identity. In the spatial condition, match trials were those in which the spatial relation was the same, regardless of the objects involved (which alternated from trial to trial; Figure 1A). In the object condition, match

trials were those in which both objects were the same as in the preceding pair and nonmatch trials were those in which one of the objects was different (Figure 1B). Stimuli for both conditions depicted the same set of objects and spatial relations. The behavioral responses (accuracy and RT) across both conditions were not significantly different in off-line pilot testing. Left–right button responses were balanced within and across blocks. For both conditions, the condition not being attended to alternated from trial to trial to avoid the possibility that participants could perform a simple perceptual match on each trial as a tenable strategy. For example, in the object condition, participants were presented with a series of object pairs that might alternate between depicting the spatial relationships of "above" and "below" while the objects themselves varied in such a manner as to produce an equal number of match and nonmatch trials. Baseline perceptual/motor blocks were interspersed between alternating task blocks and consisted of presentations of central fixation points, to which subjects pressed either button.

MRI Acquisition

Data were acquired on a 3.0-T Siemens Trio scanner using a USA Instruments four-channel head coil. BOLD-sensitive, T2*-weighted functional images were acquired in 3-mm isotropic voxels using a gradient-echo, echo-planar pulse sequence (repetition time = 3000 msec, effective echo time = 30 msec). Forty 3-mm slices were acquired during each repetition, with each slice containing a 64×64 matrix within a 192×192-mm field of view. Head motion was minimized by using foam padding, and the scanner performed both prospective (three-dimensional prospective acquisition correction) and retrospective motion correction on-line. One hundred ninety-nine images were collected from each scan. The first six images of each functional scan were discarded to allow for steady-state magnetization to be achieved. High-resolution, T1-weighted anatomical images were also acquired for each subject by using an MPRAGE pulse sequence (repetition time = 1620 msec, echo time = 3 msec, inversion time = 950 msec). One hundred sixty 1-mm slices were acquired, with each slice containing a 256×256 matrix within a 250×250-mm field of view.

Stimulus Presentation

A computer running E-Prime (www.pstnet.com/products/e-prime/) outside the scanner room controlled stimulus timing and response recording. Stimuli were projected onto a screen at the back of the scanner bore and viewed by subjects through a mirror mounted on the head coil. Subject responses were transmitted by a custom-designed fiber-optic response pad. Each subject participated in two functional scans, which were each divided into 12 blocks, 6 for each experimental condition, and 12 blocks of the

Figure 1. Examples of the sequence of stimuli used in the fMRI study, (A) spatial condition and (B) object condition. Images labeled for purposes of this figure; images used in the scanner were unlabeled and in color. The arrow indicated the figure object in the spatial relations condition.
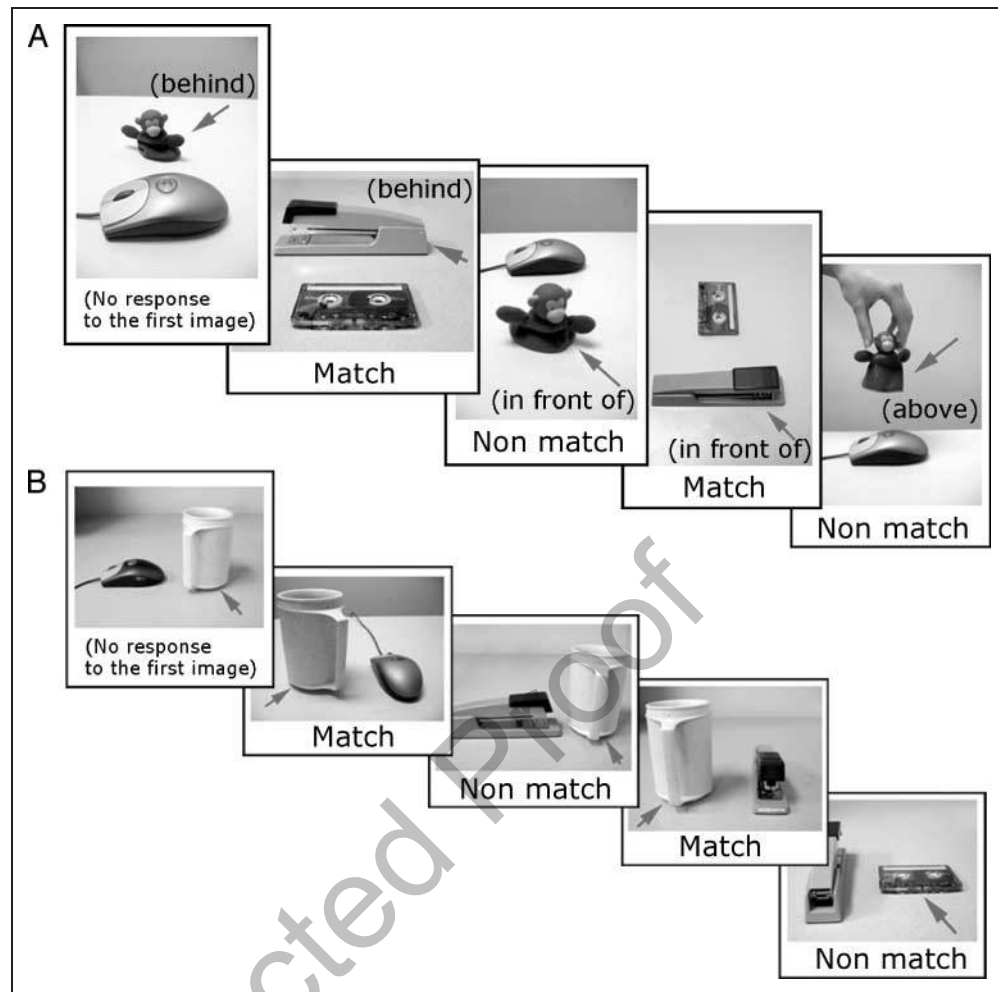
baseline condition. There were 13 stimuli per block, with stimulus durations of 1200 msec, ISIs of 415 msec, and an interval of 3000 msec between blocks.

Preprocessing

Data processing was performed off-line using software developed at the University of Pennsylvania (www.voxbo. org). After reconstructing images from the raw data, data were sinc interpolated in time to correct for staggered slice acquisition, realigned to the first image acquired for each subjects using a six-parameter motion-correction algorithm, and thresholded to excluded extraparenchymal voxels from subsequent analyses. Within each subject, a voxelwise analysis was performed using a modified general linear model that included covariates modeling task conditions as well as sine and cosine regressors for frequencies below those of the task and for frequencies in the elevated range of the noise spectrum. Task covariates were boxcar waveforms convolved with an estimate of the BOLD hemodynamic transfer function, which was empirically derived from motor cortex in a large group of subjects (Aguirre, Zarahn, & D'Esposito, 1998). Data were also smoothed in

time with the hemodynamic transfer function to control the false-positive rate (Aguirre, Zarahn, & D'Esposito, 1997; Zarahn, Aguirre, & D'Esposito, 1997). Group activation maps were constructed by a random-effects analysis of beta-values for each covariate at each voxel.

Definition of ROIs

Anatomical ROIs were derived from the automated anatomical labeling map of the Montreal Neurological Institute (MNI) single-subject brain (Tzourio-Mazoyer et al., 2002). After translation to the appropriate file format, regions were resampled to the correct dimensions and manually adjusted to compensate for resampling errors. Anatomical ROIs were (a) superior parietal lobules, (b) inferior parietal lobules (IPLs) encompassing AG and supramarginal gyrus), (c) lateral occipital cortex, (d) middle temporal cortex, (e) inferior temporal cortex, (f) fusiform gyri (both occipital and temporal portions), and (g) parahippocampal gyri. These ROIs were chosen on the basis of findings in the literature reviewed earlier, suggesting possible roles for these areas in the processing of the cognitive aspects of both of these tasks.
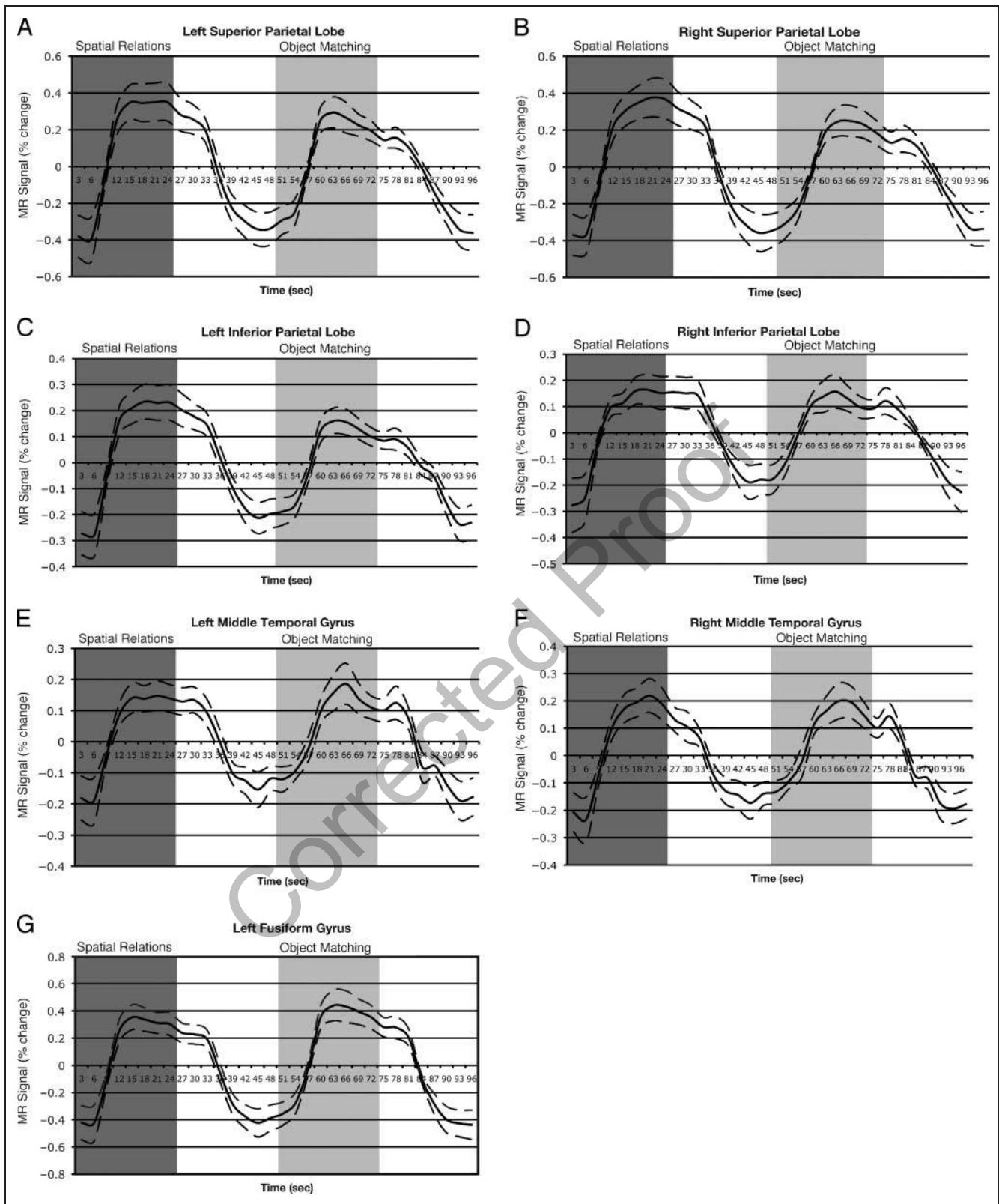
Figure 2. (A–G) Averaged time series for ROIs displaying significant differences between conditions. Time series were averaged across all blocks for each subject and then across all subjects for each experiment. Solid line depicts the average; dotted lines depict average ± *SE*.

Hypotheses about activity differences were tested using the following approach. Voxels were initially identified in which activity was significant for the main effect of spatial relations and object matching compared with the baseline condition ($p < .05$, Bonferroni-corrected for multiple comparisons within an ROI). As described previously (Kable, Kan, Wilson, Thompson-Schill, & Chatterjee, 2005; Kable, Lease-Spellmeyer, & Chatterjee, 2002), the baseline condition was not necessarily matched to the conditions of interest; rather, the goal was to reduce the number of voxels within which the contrasts of interest would be queried. The fMRI time series was averaged for all voxels significant for the main effect within a defined ROI in each subject. Next, a measure of the effect size for the orthogonal contrast between conditions of interest (spatial relations–object matching) was extracted from the spatially averaged ROI time series in each subject. We used t values as a measure of effect size rather than percent signal change because the residual error term in the denominator of the t value most effectively corrects the effect size for scaling effects because of differences in signal intensity across scanning sessions (Postle, Zarahn, & D'Esposito, 2000). Finally, paired t tests addressed whether this effect was consistently greater for one condition or the other in that ROI across subjects. This analysis trades spatial resolution for sensitivity by reducing the ef-fect size in each ROI to a single value through averaging across all active voxels within an ROI.

Results

Behavioral Results

Participants did not differ in accuracy (89% ± 3% vs. 87% ± 3%) or RTs (702 ± 32 vs. 661 ± 32 msec) for the spatial relation and object identification conditions, respectively.

Imaging Results

Within each ROI, the averaged time series across all voxels that showed activity for the main effect of both spatial relations and object matching compared with the baseline condition is shown in Figure 2. For each averaged time series, we calculated a measure of the difference in activity between the spatial relation and the object matching conditions and then tested whether this difference was significantly different from zero across subjects for each ROI (a random-effects test, see Table 1).

Across participants, there was consistently greater activation bilaterally for judgments of spatial relations in the superior parietal lobules, left, $t(11) = 3.7$, $p < .005$,

Table 1. Functional MRI Results

Spatial Relations–Object Matching		Average Voxels
Left Hemisphere		
Superior parietal lobe	**1.84 ± 0.49**	**520**
Inferior parietal lobe	**2.07 ± 0.49**	**374**
Lateral occipital complex	−0.78 ± 0.39	520
Middle temporal gyrus	**0.88 ± 0.37**	**149**
Inferior temporal gyrus	0.25 ± 0.49	77
Fusiform gyrus	−0.78 ± 0.28	325
Parahippocampal gyrus	−0.47 ± 0.23	124
Right Hemisphere		
Superior parietal lobe	**2.04 ± 0.62**	**520**
Inferior parietal lobe	**1.39 ± 0.55**	**166**
Lateral occipital complex	−0.39 ± 0.39	414
Middle temporal gyrus	**0.67 ± 0.24**	**189**
Inferior temporal gyrus	0.55 ± 0.41	209
Fusiform gyrus	−0.37 ± 0.28	380
Parahippocampal gyrus	−0.08 ± 0.22	124

Effect sizes are given as mean ± *SE* for contrasts between conditions within each ROI. Effect sizes that are consistently different from zero across conditions ($p < .05$) are in **boldface**.

Figure 3. Effect sizes given as mean ± *SE* for the spatial relations–object matching contrast within each ROI. Dark-outlined columns denote effect sizes that are consistently different from zero across conditions ($p < .05$).
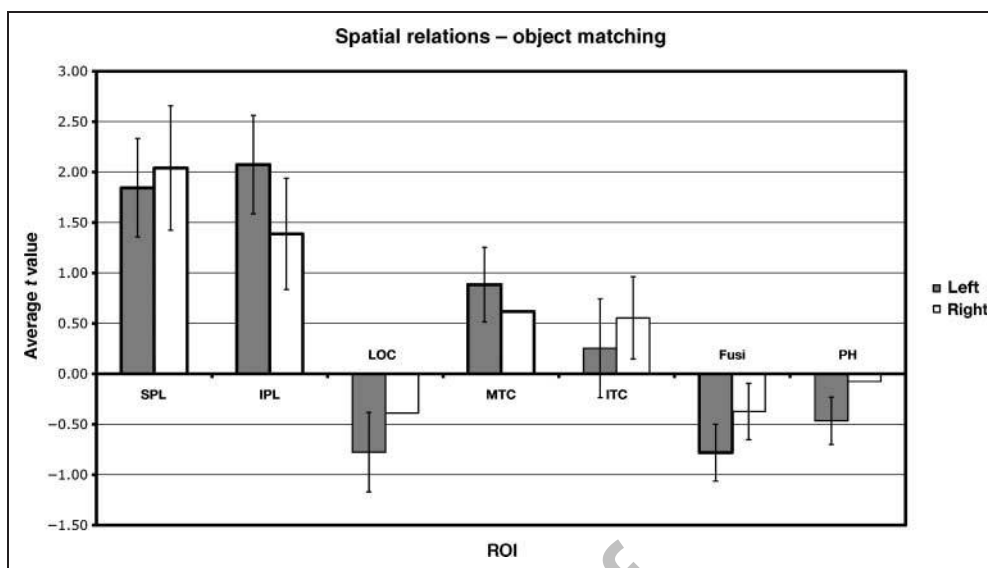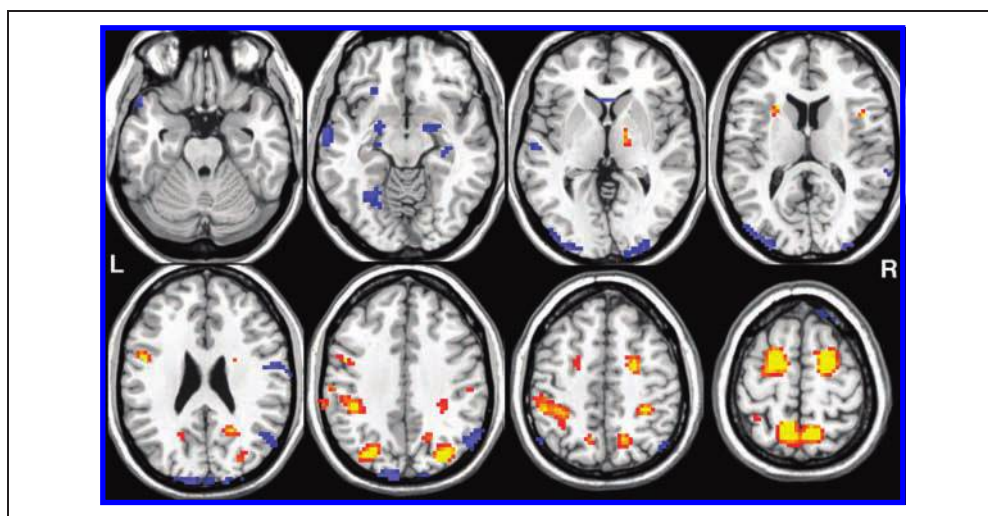
and right, $t(11) = 3.3$, $p < .01$, and the IPLs, left, $t(11) = 4.2$, $p < .005$, and right, $t(11) = 2.5$, $p < .05$, and less robustly within the middle temporal cortices, left, $t(11) = 2.4$, $p < .05$, and right, $t(11) = 2.6$, $p < .05$. Activity was greater for judgments of object identity than spatial relation in the left fusiform gyrus, $t(11) = -2.8$, $p < .05$ (see Table 1; Figures 3 and 4).

The only difference in hemispheric activity between ROIs was seen in the left IPL, which displayed significantly greater activity than the right IPL, $t(11) = 2.5$, $p < .05$, for the spatial relations, and in the left fusiform gyrus, which displayed significantly greater activity than the right fusiform gyrus for the object identity condition, $t(11) = -2.9$, $p < .05$.

Figure 4 displays whole-brain activation maps for the spatial relations versus object identity contrast. Because the purpose of these figures is to display general trends in brain activity rather than the results of strict statistical tests, these maps are thresholded at $t = 3.5$. The direct-contrast maps largely overlap with our ROIs of interest.

However, bilateral posterior middle frontal gyri, not included in our original ROI analyses, also displayed greater activity in the spatial than in the object condition.

LESION STUDY

Methods

Participants

Thirty-four patients ranging from 48 to 85 years of age with chronic (at least 6 months duration) unilateral hemispheric lesions were recruited from the Focal Lesion Patient Database (Fellows, Stark, Berg, & Chatterjee, 2008). They were evenly divided between those with left and those with right brain damage. By design, participants were not selected on the basis of specific behavioral criteria, except that patients with a history of other neurological disorders affecting the CNS or psychiatric disorders are excluded from the patient database. Twelve

Figure 4. fMRI results in the whole-brain analysis for the contrast of spatial relations–object matching, $t = 3.5$.

elderly control subjects ranging from 58 to 79 years of age were also tested on these tasks.

All participants were native English speakers and right-handed. Written informed consent in accordance with the procedures of the institutional review board of the University of Pennsylvania and the Declaration of Helsinki was obtained for each participant. A native English speaker delivered all spoken materials. If a participant was unable to complete testing in one session, additional sessions were scheduled at least one week later.

Stimuli

Images consisted of digital color photographs (specific stimuli may be obtained from the corresponding author). The objects in these images consisted of small set of relatively common household/office items that could function as figure and/or ground objects for the locative relations being tested. In the images, a red arrow pointed to the figure object. Spatial relationships that could be

Figure 5. Example stimuli for the (A) categorical matching and the (B) coordinate matching tasks. Figure object being located indicated by the arrow. Original in color.

described by *in* and *on*, which are considered topologic relations, and those that could be described by *above*, *below*, *to the left of*, and *to the right of*, which are considered projective relations, were used as stimuli. We recognized the polysemous nature of prepositions. With topological relationships, each exemplar for "in" depicted a containment relationship and for "on" a contact relationship of the figure to ground along the vertical *y*-axis. For the topological relationships, the verbal descriptors refer to an allocentric reference frame (note that the stimuli themselves only used pictures; for examples, see Figure 5).

Screening Tasks

All patients were screened for unilateral neglect. Although neglect usually recovers within 3 months (Chatterjee, 1995), we wanted to ensure that severe attentional biases would not impair their ability to see or to respond to specific stimuli. All patients were given the gray scale test for neglect (Mattingley et al., 2004). We also wished to ensure that subjects recognized the objects being pictured. All subjects identified the series of objects that were used in the spatial tasks. Twenty-six trials were presented in which the name of an object was presented along with four photographic images (one image depicting the object named). Participants indicated which one of the four pictures depicted the correct answer either by pointing or by reading the letter underneath a particular image. The location of correct response (top/bottom and left/right) was counterbalanced across the trials.

Categorical Spatial Matching

This task was designed to assess patients' ability to match categorical spatial concepts across different photographic representations. The patients were presented with 40 trials in which a probe image containing one pair of objects in a particular spatial relationship was to be matched with one of four images containing a different pair of objects. Of the four choices, one depicted the correct categorical spatial relationship, and the foils could depict within- or across-class categorical relations (Figure 5A). Twenty-four items had a correct topological match (12 with pictures that could be described by *in* and 12 that could be described by *on*). Sixteen items had a correct projective match (4 that could be described by *in front of*, 4 *behind*, 4 *above*, 2 *to the left of*, and 2 *to the right of*). Subjects indicated which of the four pictures depicted the correct answer either by pointing or by reading the letter underneath the image of their choice.

Coordinate Spatial Matching

This task was designed to assess patients' abilities to match images on the basis of metric spatial distance. The patients were presented with 32 trials in which a
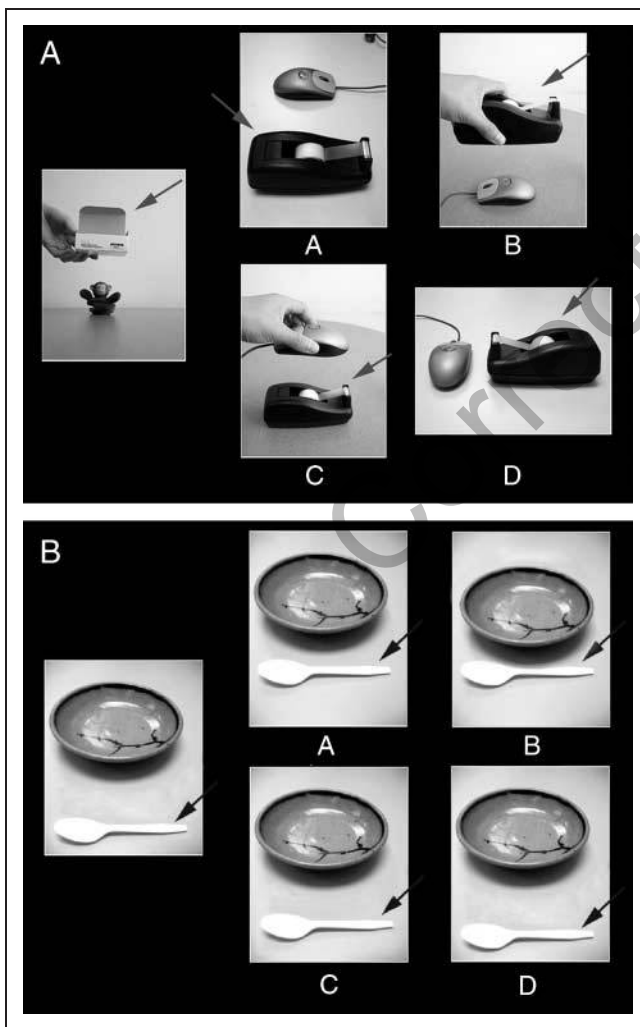
probe image containing one pair of objects in a particular spatial relationship was to be matched with one of four images containing the same pair of objects in the same coordinate spatial relationship (Figure 5B). Subject indicated which of the four pictures depicted the correct answer either by pointing or by reading the letter underneath the image of their choice.

Neuroanatomical Analysis

Lesions were segmented and coregistered using a manual procedure with MRIcro (Rorden & Brett, 2000). A T1-weighted MNI template image was first rotated pitchwise to correspond with the patient's scans. An experienced neurologist outlined the lesions on the rotated template, resulting in a map in which each voxel was labeled either 0 (intact) or 1 (lesioned). Finally, the lesion maps were rotated back into a canonical MNI orientation, using nearest-neighbor interpolation to restrict the map values to 0 and 1 using an automated feature of MRIcro. For most of the subjects, lesions were drawn on a 2 × 2 × 2-mm template. For those originally drawn at higher resolution, the lesions were resampled to 2 × 2 × 2 mm for the purposes of this test. All of the thresholds below correspond to an alpha criterion of .05.

Voxel-based Lesion Symptom Mapping/Analysis

We used permutation analyses to establish VLSM (Bates et al., 2003; Nichols & Holmes, 2002). In contrast to fMRI, where the dependent value is the signal value in a given voxel and behavior the independent value, VLSM switches the roles, with lesion status comprising the independent variable and behavior the dependent variable. However, as with fMRI, the problem of multiple comparisons remains. Given the large number of comparisons across the brain, it is likely that voxels will display as significantly associated with impairment strictly by chance. Extant methods of correcting for this problem, such as Bonferroni correction, yield overly conservative thresholds and do not account for the spatial coherence of lesion data (the lesion status of one voxel is well predicted by neighboring voxels). Permutation testing provides a solution to this by correcting exactly for the number of independent comparisons within a volume, without making assumptions about the spatial structure of the data. Generally, the permutation method entails the creation of a null distribution for a given test statistic (here, a t statistic) by generating a large number (>1000) of random permutations of the independent and dependent variables (in this case, lesion status and behavioral data, respectively) and by recalculating the test statistic for each permutation. A maximum statistic across the brain is calculated for each permutation, and thresholds for significance are calculated from the 95th percentile of this distribution to ensure a family-wise error rate of 0.05. This yields a threshold t value that would be exceeded
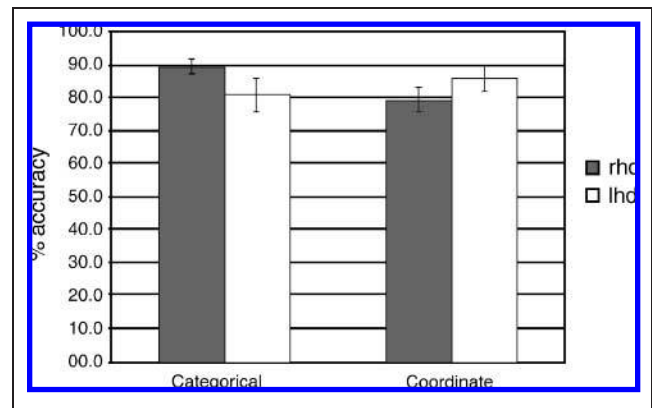

Figure 6. Behavioral performance of patient groups on the categorical and coordinate spatial tasks (mean ± *SEM*).

somewhere in the brain in only 5% of the permutations (Nichols & Holmes, 2002). When the empirically obtained pairing results in an extreme t value relative to the other permutations and exceeds this threshold, the null hypothesis is rejected. To eliminate effects produced by a single participant outlier, only voxels that were damaged in at least two participants were queried. For further details of this logic, see Kimberg et al. (2007), and for a recent application, see Wu, Waller, and Chatterjee (2007).

Results

Screening Tasks

As a group, RHD and LHD subjects displayed mild attentional biases on the gray scales test. None of the patients had obvious neglect. All participant groups performed at ceiling in the object identification task, ensuring that errors on subsequent tasks were not influenced by object recognition deficits.

Categorical and Coordinate Spatial Matching: Behavioral Analyses

The elderly control subjects generally performed well on both tasks, 89% accurate for categorical matching and 93% accurate for coordinate matching. These performances showed a trend toward being significantly different (Wilcoxon signed ranks test, $p = .08$).

With Group (LHD and RHD) as the between-subject factor and Task (categorical vs. coordinate spatial relations) as the within-subject factor, we found no significant effects of either group or task on percent accuracy in an ANOVA. However, there was a significant interaction in the expected direction with the LHD performing relatively better on the coordinate task than the categorical task and the RHD performing relatively better on the categorical task than the coordinate task, $F(1, 32) = 9.59$, $p < .005$. Behavioral data for the groups is shown in Figure 6. Error analysis for the categorical relations (topological vs. projective) showed that participants were most
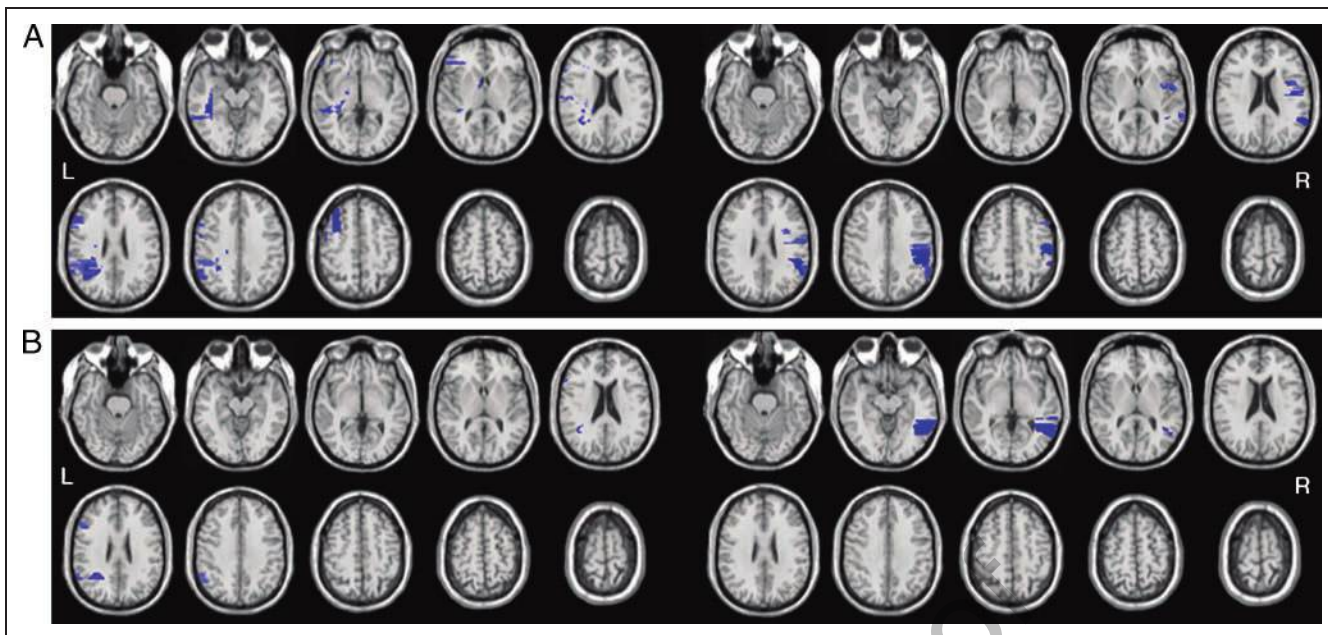
Figure 7. VLSM maps for LHD and RHD groups on the (A) categorical matching task and (B) coordinate matching task. These maps are colored depictions of *t* scores significant at a level of *p* < .05 on tests evaluating behavioral performance on a voxel-by-voxel basis. Colored areas thus represent areas where damage is predictive of the behavioral deficit observed in that group.

likely to make within-class errors (84.2% as compared with 45.8% if choosing randomly) than across-class errors (*p* < .001 using test of proportions).

The lack of group differences in performances of the RHD and LHD groups on the categorical or coordinate tasks does not necessarily disconfirm the hypothesis that the left hemisphere is biased toward categorical spatial judgments and the right to coordinate spatial judgments. By design, greater behavioral variability within groups is desirable for VLSM methods to identify specific brain behavior correlations. This greater behavioral variability within each group maximizes the likelihood of finding statistically robust differences within the group and minimizes the likelihood of finding differences across groups.
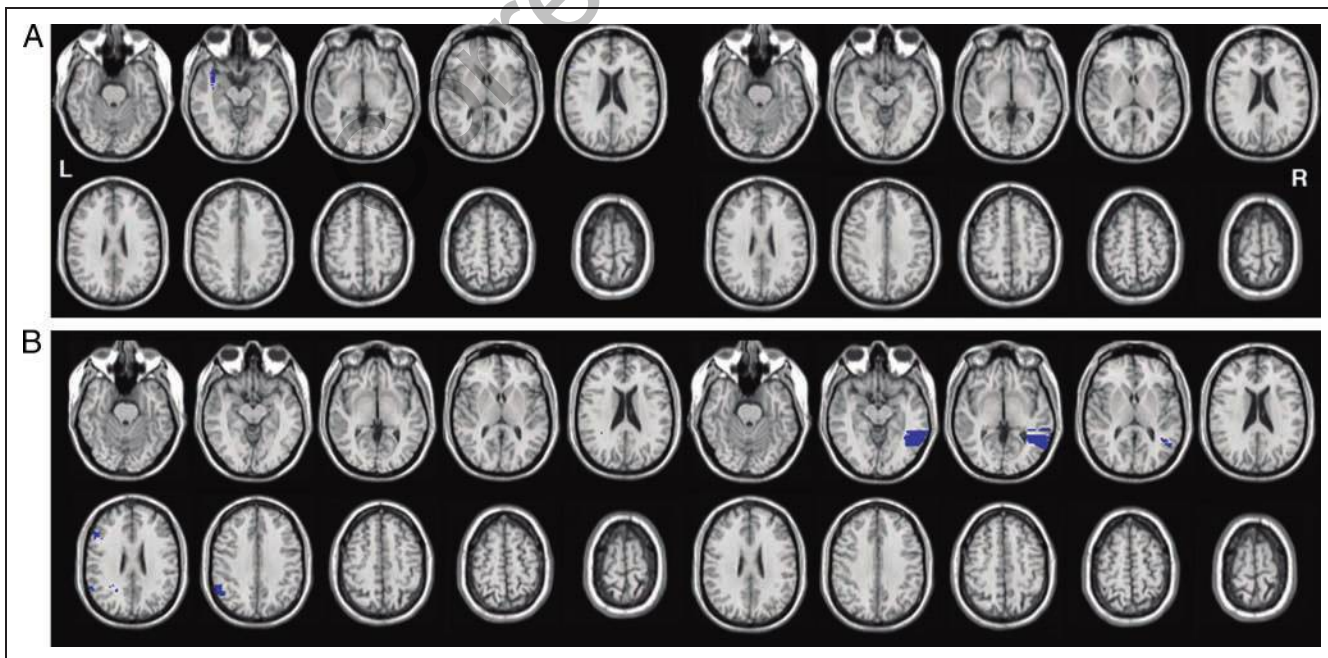

Figure 8. VLSM maps for LHD and RHD groups using residual analyses (A) deficits on categorical matching not accounted for by coordinate matching performance and (B) coordinate matching not accounted for by categorical matching. These maps are colored depictions of *t* scores significant at a level of *p* < .05 on tests evaluating behavioral performance on a voxel-by-voxel basis. Colored areas thus represent areas where damage is predictive of the unique behavioral deficit.

Performances on the categorical and coordinate tasks correlated across groups ($r = .50$, $p < .005$). We tested the hypothesis of hemispheric differences in categorical and coordinate processing by conducting residual analyses. When performances on the categorical task were regressed onto performances on the coordinate task, the LHD had significantly lower categorical residuals scores than the RHD group, $t(32) = 2.43$, $p = .02$. Analogously, when performances on the coordinate task were regressed onto performances on the categorical task, the RHD group had significant lower coordinate residual scores than the LHD group, $t(32 = 2.73$, $p = .01$.

Our fMRI results revealed greater left than right IPL activations for categorical spatial relation judgments. To link those findings more closely to these lesion results, we sorted our patients into those with ($n = 9$ LBD and $n = 9$ RBD) and without ($n = 8$ LBD and $n = 8$ RBD) IPL damage. Using residual analyses, we found the left IPL group performed worse than the right IPL group (Mann–Whitney U test; $p < .01$) on categorical matching tasks when performance on coordinate matching tasks was factored out. Similar hemispheric differences were not found for the patients in whom lesions spared the IPL (Mann–Whitney U test; $p = .75$).

Categorical and Coordinate Spatial Matching: Functional-anatomic Analyses

Representative slices from VLSM maps for both groups are shown in Figure 7. For categorical spatial matching, empirically derived t statistic thresholds with a significance level of $p < .05$ were 2.83 for the RHD group and 3.00 for the LHD group. In the LHD group, impairments on categorical matching correlated with lesions to the posterior middle and inferior frontal gyri, the supramarginal gyrus and AG, and the white matter undercutting to the anterior superior temporal gyrus. In the RHD group, impairments on the task correlated with damage to the superior temporal gyrus, supramarginal gyrus, and AG. For coordinate matching, t statistic thresholds with a significance level of $p < .05$ were 3.51 for the RHD group and 2.48 for the LHD group. In the RHD group, impairments on coordinate matching correlated with damage to the middle temporal gyrus. In the LHD group, impairments on the coordinate matching task correlated with damage to the AG and the inferior frontal gyrus.

Representative slices from VLSM maps for both groups, using residual scores, are shown in Figure 8. For categorical residual analyses, empirically derived t statistic thresholds with a significance level of $p < .05$ were 2.79 for the LHD group and 5.15 for the RHD group. In the LHD group, categorical deficits were uniquely associated with damage to the white matter undercutting the anterior superior temporal gyrus. No such areas were identified in the RHD group. For coordinate residual analyses, empirically derived t statistic thresholds with a significance level of $p < .05$ were 3.32 for the RHD group and 2.26 for the LHD group. In the

RHD group, coordinate deficits were uniquely associated with damage to middle temporal gyrus. In the LHD group, coordinate deficits were uniquely associated with damage to the AG and the inferior frontal gyrus.

DISCUSSION

What is the neural basis for representing spatial relations? We addressed this question using both functional neuroimaging and lesion methods. Despite nontrivial differences generally inherent in these methods and particular aspects of the actual experiments conducted, we found largely consonant results. Taken together, our findings suggest that a distributed neural network mediates spatial relations organized around fronto-temporo-parietal circuits, with left–right hemispheric differences. We first discuss the fMRI findings comparing categorical spatial and object processing. We then discuss the lesion study findings for categorical processing and relate them to the fMRI results. Then, we reviewed the neural instantiation of coordinate processing and highlight interactions of categorical and coordinate processing. These interactions reveal that the functional-anatomic organization of spatial relations is more nuanced than generally appreciated. Finally, we placed our results in a broader context as they relate to spatial language.

Categorical Spatial and Object Processing: Imaging Evidence

Our fMRI findings confirm the hypothesis that fronto-parietal networks are important in representing categorical spatial relations in contrast to the representation of object identities. We are not aware of previous fMRI studies that have directly compared object identification and categorical spatial relations using identical stimuli. Young healthy participants activated the posterior parietal lobules bilaterally as they processed categorical spatial relations more than when they processed the identity of objects. Activity in the IPLs was greater on the left than on the right. The greater left hemisphere activation within the posterior inferior parietal cortex is consistent with the claim that the left hemisphere is biased to processing categorical spatial relations (Kosslyn et al., 1989), but the bilateral activations raise questions about the relative contributions of each hemisphere. Thus, these imaging results confirm a dorsal–ventral distinction for processing spatial relations, but not necessarily a left–right distinction for categorical spatial processing.

Categorical and Coordinate Spatial Processing: Lesion Evidence

Our lesion study broadly confirmed and extended the results of the imaging experiment. Paralleling the imaging results, VLSM analyses revealed that damage to the left

supramarginal gyrus and AG, the posterior middle and inferior frontal gyri, and the white matter undercutting the superior temporal gyrus was associated with deficits in categorical spatial judgments. Damage to the right superior temporal gyrus, supramarginal gyrus, and AG produced milder deficits in categorical spatial judgments. VLSM analyses also revealed that damage to the right middle temporal gyrus produced deficits in coordinate spatial processing, whereas damage to the left AG and inferior frontal gyrus produced milder deficits in coordinate spatial processing. Thus, damage to the left AG and inferior frontal gyrus produced deficits in both coordinate and categorical processing.

In our brain-damaged participants, performances on categorical and coordinate spatial tasks were correlated. Thus, some variance in performance on each of these tasks could be accounted for by deficits on the complementary task. To test the hypothesis that damage to some brain regions contributes uniquely to categorical or to coordinate deficits, we conducted residual analyses. Specifically, performances on categorical tasks were regressed on coordinate performances, and the derived residuals were subjected to analysis. Analogously, coordinate performances were regressed on categorical performances to derive residuals then subjected to analysis.

The LHD patients were more impaired than the RHD group on the categorical task beyond the variance in performances accounted for by coordinate deficits. Analogously, the RHD patients were more impaired than the LHD group on the coordinate tasks beyond variance in performance accounted for by categorical deficits. These relative impairments cannot be explained by difficulty in recognizing stimuli, nor can they be explained by the hypothesis that the left hemisphere processes relatively easy spatial relations and the right more difficult ones (Slotnick et al., 2001).

Can our lesion results be linked more directly to the fMRI data? The fMRI study revealed greater activity in the left IPL than that in the right for categorical spatial processing than for object identity. If these relative activations are causally related to categorical processing, then patients with left IPL damage should be worse than patients with right IPL damage on categorical tasks. We tested this hypothesis by first sorting patients on the basis of whether they had IPL damage. Nine patients had left IPL damage and nine had right IPL damage. Using residual analyses, we found that patients with damaged left IPL had greater deficits than patients with damaged right IPL on categorical spatial tasks. The same analysis with the other patients ($n = 8$ each) did not reveal similar differences. Thus, we have strong converging evidence for the importance of the left IPL on categorical spatial processing.

Our VLSM results demonstrate that the functional neuroanatomy of categorical and coordinate spatial relations is more nuanced than that suggested by the straightforward hypothesis that the left hemisphere processes categorical spatial information and the right processes coordinate spatial information. Damage to left posterior parietal and dorsolateral prefrontal structures produced deficits in both categorical and coordinate processing. However, damage within the left AG and inferior frontal gyrus produced deficits in coordinate processing (although these were mild deficits) not explained by categorical deficits. Similarly, damage to the white matter undercutting the left anterior superior temporal gyrus uniquely produced deficits in categorical processing not accounted for by coordinate deficits. Although RHD also produced deficits in both categorical and coordinate processing, no damaged areas were uniquely associated with categorical deficits. By contrast, damage to the right middle temporal gyrus uniquely produced coordinate spatial deficits.

These patterns of lesion and behavioral correlations suggest that categorical and coordinate spatial processing are quite intertwined. The right hemisphere processes coordinate spatial information preferentially within the posterior temporal cortex. By contrast, the left hemisphere processes both categorical and coordinate information conjointly within fronto-parietal circuits as well as distinctly within the AG, inferior frontal gyrus for coordinate processing, and anterior superior temporal gyrus for categorical processing.

Our categorical spatial task used stimuli that depicted both topological and projective spatial relations. We noted that when subjects erred on this task, they were likely to choose within-class foils. That is, if the target was topological, they were more likely to choose a topological foil and vice versa for projective spatial relations. Thus, despite categorical spatial deficits, some knowledge of the kind of categorical spatial relationships appears to have been retained. These observations raise the possibility that the neural underpinnings of topological and projective spatial relations might segregate further within networks instantiating categorical spatial relations. Future studies designed and powered to test this hypothesis will be needed.

Categorical Spatial Processing and Language

A major motivation for anticipating that the left hemisphere is biased to processing categorical spatial relations is its relationship to language (Chatterjee, 2008; Kemmerer, 2006). Prepositions comprise only a small set of the infinite possible spatial relations. As Landau and Jackendoff (1993) and Talmy (1983) pointed out some years ago, prepositions discard much of the geometric richness of objects in favor of relatively coarse spatial notions like "containment" or "contact." They suggested that any aspect of space that could be expressed in language must have nonlinguistic spatial representations. Similarly, Regier (1995) used computational models to argue that spatial language is grounded in spatial perception. Thus, one might infer that categorical spatial relations, which are limited in number and in which details of object features are reduced to general shapes and axes, would serve as the perceptual counterpart to

locative prepositions. At an anatomic level, one would expect the processing of these discrete spatial representations linked to language, to be instantiated in the left hemisphere of right-handed individuals, close to or overlapping with the processing of spatial prepositions.

As an aside, we recently reported a fronto-parietal network involved in processing paths of movement (Wu, Morganti, & Chatterjee, 2008). This finding is relevant to the current study because path of motion in English is described using prepositional phrases (e.g., running *through* the fields, jumping *across* the puddle). Thus, the perceptual counterparts of locative prepositions, whether dynamic or static, may be instantiated in similar fronto-parietal networks.

Few studies have examined the neural bases of locative prepositions directly. Using PET imaging, Emmorey et al. (2002) and Damasio et al. (2001) found that naming spatial locations was associated with the left supramarginal gyrus and the inferior prefrontal cortical activations. Noordzij, Neggers, Ramsey, and Postma (2008) also found left supramarginal gyrus activity in subjects who were asked to process terms denoting left and right, but whether left–right judgments generalize broadly to other categorical relations is not known. Limited electrophysiologic data are consistent with the view that the parietal cortices instantiate the use of spatial terms (Carlson, Robert, Taylor, & Herndon, 2002). Occasional case studies of deficits with prepositions in aphasics have been reported, but these have not been informative about their neural underpinnings (Miozzo, Simon, & Postman, 2008; Chatterjee & Maher, 2000; Grodzinsky, 1988; Frederici, 1982; Schwartz, Saffran, & Marin, 1980). An important exception in this regard is a study by Tranel and Kemmerer (2004), which directly examined the neural correlates of deficits in locative prepositions in a large group of brain-damaged individuals. They found the greatest overlap of lesions in patients with such deficits within the left supramarginal gyrus and subjacent white matter as well as the frontal opercula. We also found that damage to the posterior temporo-parietal cortex, anterior superior temporal gyrus, and inferior pFC was most closely associated with deficits in matching locative sentences to pictures depicting categorical spatial relations (Wu et al., 2007). The emerging view from these studies is that left peri-sylvian cortices involving the supramarginal gyrus, the anterior superior temporal gyrus, and the inferior prefrontal regions mediate locative prepositions. Areas mediating spatial categorical relations overlap or are closely aligned with these regions, consistent with the view that these regions serve as perceptual points of entry for their lexicalizations (Chatterjee, 2008; Wu et al., 2007).

In summary, we found converging evidence from both imaging and lesion investigations of the neural basis for spatial relations. A bilateral network comprising the posterior parietal, posterior middle and superior temporal, and posterior middle and inferior frontal gyri mediates spatial relations. The left hemisphere is biased toward processing categorical spatial relations and the right toward processing coordinate spatial relations, but these distinctions are relative rather than absolute. The left hemisphere appears to mediate both categorical and coordinate processing, whereas we did not find evidence that the right hemisphere processes categorical relations independent of its coordinate processing.

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