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FEATURE ARTICLE
The Parahippocampal Cortex Mediates Spatial and Nonspatial Associations

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The parahippocampal cortex (PHC) has been implicated in the processing of place-related information. It has also been implicated in episodic memory, even for items that are not related to unique places. How could the same cortical region mediate such seemingly different cognitive processes? Both processes rely on contextual associations, and we therefore propose that the PHC should be viewed not as exclusively dedicated for analyzing place-related information, or as solely processing episodic memories, but instead as more generally playing a central role in contextual associative processing. To test this proposal, we created a novel learning paradigm to form new associations among meaningless visual patterns. These new associations were created to emulate either spatial or nonspatial contexts. Both spatial and nonspatial associations activated the PHC more than noncontextual items. Moreover, items from spatial contexts activated the posterior part of the PHC, whereas items from nonspatial contexts activated the anterior PHC. Therefore, we show that the PHC plays a role of processing contextual associations in general, and that these associations are not restricted to spatial information. By modifying the existing view of the PHC function accordingly, the seemingly contradicting processes that activate it can be reconciled under one overarching framework.

Keywords: associations, context, episodic memory, parahippocampal, PPA, spatial memory

Introduction

The parahippocampal cortex (PHC) is believed to be involved in several cognitive processes, most prominently in spatial analysis and in episodic memory. Evidence for spatial, place-related processing in the PHC was reported by a variety of studies in which differential activity has been found in this region during tasks involving processing environmental landmarks and scenes (Epstein and Kanwisher 1998; O'Craven and Kanwisher 2000; Levy and others 2001); aspects of spatial memory (Johnsrude and others 1999; Bohbot and others 2000; Ploner and others 2000; Burgess and others 2001); and spatial navigation (Aguirre and others 1996; Maguire and others 1997; Mellet and others 2000). As a result, it has been suggested that at least a portion of the PHC functions as a dedicated module for processing spatial information, and the term parahippocampal place area (PPA) has subsequently been coined to describe this region (Epstein and Kanwisher 1998). In parallel, findings from memory research indicate that the PHC is involved in episodic memory, source memory, and the encoding of novel stimuli (Gabrieli and others 1997; Brewer and others 1998; Wagner and others 1998; Schacter and Wagner 1999; Davachi and others 2003; Ranganath and others 2004; Squire and others 2004). This memory-related activity is often seen in regions that overlap with those implicated in spatial, place-related processing (see Fig. 1). Although one might expect to find PPA activity in memory studies that use place-related stimuli (e.g., encoding indoor scenes), differential activity in this area was sometimes observed even in memory tasks with no direct relevance to place-related information (e.g., Henke and others 1999; Sperling and others 2003; Jackson and Schacter 2004; Kirwan and Stark 2004). The Talairach coordinates reported for the 2 different types of studies can be remarkably close (e.g., remember vs. forgotten face–name associations: −30, −40, −9; Kirwan and Stark 2004; compared with Talairach coordinates for the PPA: −28, −39, −6; Epstein and others 1999). These two independent lines of findings, therefore, present an intriguing paradox: How could the same region of the cortex mediate such seemingly different cognitive processes?

We propose here an expanded viewpoint that bridges these accounts, and we provide critical evidence to support this proposal. Specifically, we propose that the PHC should be viewed not as exclusively dedicated for analyzing place-related information, or as solely processing episodic memories, but instead as more generally mediating contextual associative processing. This proposal for the PHC function emerged from our finding that a large part of the PHC is involved in analyzing contextual associations (Bar and Aminoff 2003; Bar 2004). The idea that associative processing might be a fundamental role of the medial temporal lobe has been suggested before, particularly with respect to the hippocampus (Eichenbaum and others 1999; Eichenbaum 2000; Burwell and others 2004). Associations can be seen as the building blocks both for place-related information and for episodic memories; place-related information relies on associations between identity and location, and episodic memory relies on associations of co-occurring entities. Therefore, by modifying the existing view of the function of the PHC accordingly, to assert that this region mediates the analysis of contextual associations, those seemingly contradicting findings can be explained under one overarching terminology.

Complementing our account of the role of the PHC is previous electrophysiology research by Sakai and Miyashita (1991) and Higuchi and Miyashita (1996). In a series of elegant studies, they found cells within the perirhinal cortex, in a site anteriorly adjacent to the anterior PHC, that are most active for processing the association between 2 stimuli, compared with individual stimuli. Furthermore, it has been shown in rats (Burwell and others 2004) that lesions to the postrhinal/PHC resulted in deficit in acquiring associations related to fear and avoidance, whereas these lesions failed to impair place learning. Finally, Eacott and Gaffan (2005) have demonstrated object–context associations in the postrhinal/PHC of the rat. Taken together, these previous reports are consistent with the proposal tested here.

It might be important at this point to describe our working definition of contextual associations. Context provides a

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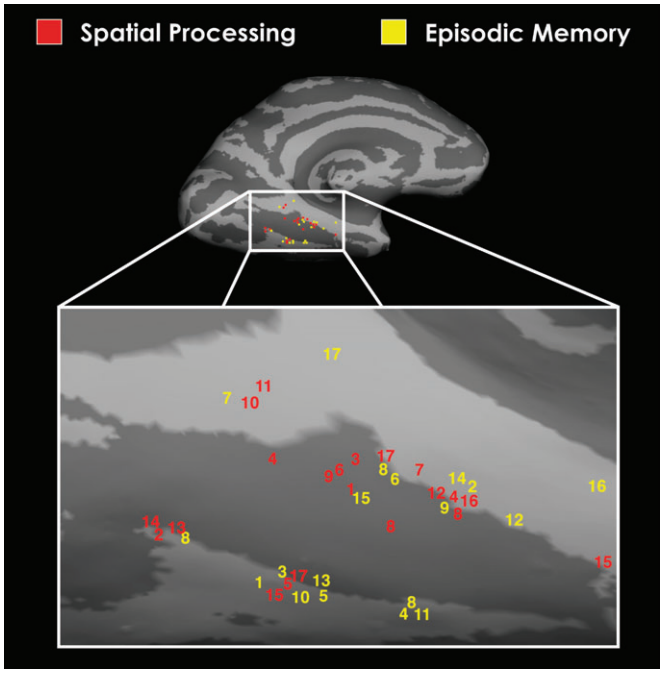

Figure 1. A comparison of reported Talairach coordinates from a spatial processing literature (17 studies) and episodic memory literature (17 studies). **Spatial processing (numbers marked in red)**: 1. Epstein and others 1999; 2. Epstein and others 2003; 3. Levy and others 2001; 4. Goh and others 2004; 5. Gorno-Tempini and Price 2001; 6. O'Craven and Kanwisher 2000; 7. Janzen and van Turennout 2004; 8. Mellet and others 2000; 9. Maguire and others 1997; 10. Rosenbaum and others 2004; 11. Shelton and Gabrieli 2002; 12. Sugiura and others 2005; 13. Yi and Chun 2005; 14. Steeves and others 2004; 15. Goel and others 2004; 16. Suzuki and others 2005; 17. Burgess and others 2001. **Episodic memory (numbers marked in yellow)**: 1. Wagner and others 1998; 2. Medford and others 2005; 3. Sommer and others 2005; 4. Morcom and others 2003; 5. Davachi and others 2003; 6. Kirchhoff and others 2000; 7. Casasanto and others 2002; 8. Brewer and others 1998; 9. Reber and others 2002; 10. Takahashi and others 2002; 11. Dobbins and others 2003; 12. Henke and others 1999; 13. Yonelinas and others 2001; 14. Pihlajamaki and others 2003; 15. Kirwan and Stark 2004; 16. Tsukiura and others 2002; 17. Ranganath and others 2003.

framework of associative relatedness, which can help generate expectations about what might be relevant in the specific situation (Bar 2004). For many, the term "context" implies background information. However, consider the example of a blender in the context of a kitchen. The blender is part of the kitchen, in that the blender is contextually congruent with its surrounding, and thus both the target (foreground) and the background belong to the context. In fact, a foreground object in one instance might be part of the background when another object in the scene is selected as target. A second distinction that we would like to make here is between context and a spatial scene. Indeed, most typical scenes (e.g., street, beach, bedroom) depict a context. This is true because items that tend to appear together are, by definition, associated with each other and share the same context. But the definition of context includes also related objects that do not necessarily appear together in the physical environment, or necessarily appear in a unique place. For example, a heart-shaped chocolate box is contextually related to cupid, though it will be hard to find this pairing in reality. Similarly, confetti and champagne can appear together but in many possible places. Nonspatial associations are therefore also considered contextual; although the associated items may not appear together physically, or in a unique place, they "co-occur" in the brain in that their corresponding representations are strongly linked and coactivate each other. As will be demonstrated here, our proposal for the role of the PHC incorporates these distinctions such that the PHC mediates both spatial and nonspatial contextual associations.

In our previous studies (Bar and Aminoff 2003), we demonstrated that the PHC is particularly sensitive to visual contextual information by comparing the activity elicited by viewing highly associative contextual objects both in a spatial (e.g., a traffic light, strongly associated with a street context) and in a nonspatial domain (e.g., a crown, strongly associated with royalty, but not a specific place) with the activity elicited by objects that have weak contextual associations (e.g., a cell-phone, which is not strongly associated with a single context). Our results revealed differential activity for this contrast in two main sites, one in the PHC and the other in a region we call the retrosplenial complex (RSC) (including portions of the retrosplenial cortex, the posterior cingulate gyrus, subparietal sulcus, and the precuneus). Interestingly, although both contextual conditions elicited greater activity in the PHC compared with objects with weak contextual associations, stimuli associated with spatial contexts elicited activity in the posterior portion of the PHC, similar to areas of the PPA, and extending also into the anterior portion of the PHC. Stimuli associated with nonspatial contexts, on the other hand, elicited activity that was confined exclusively to the more anterior region of the PHC, implying that representations within the PHC are organized along a hierarchy according to spatial specificity. This proposal of a functional organization along a spatial hierarchy has since been supported by other experiments (Düzel and others 2003; Burwell and others 2004; Pihlajamaki and others 2004).

In those previous studies we used pictures of everyday objects (e.g., a parking meter). Such objects are linked to associations that have been formed over a lifetime of visual experience. Disentangling the processing of spatial and nonspatial contextual associations is therefore somewhat hindered by the fact that all real-world objects are encountered in specific locations, even those that are otherwise most strongly associated with nonspatial contexts. For example, although a unicorn might be most strongly related to the nonspatial context of fantasy, one might associate a picture of a unicorn with a place where one read a book or watched a movie with unicorns. That the activity we have observed for the nonspatial contexts did not extend to the posterior PHC (Bar and Aminoff 2003) and that we debriefed the subjects to confirm that the objects did indeed associate with non-spatial contexts supports the presumed qualitative distinction between the spatial and the nonspatial stimuli. Nevertheless, we sought to verify unequivocally that the PHC processes also purely nonspatial associations, using stimuli where associations are tightly monitored. This enabled us to eliminate the possible effect of any uncontrolled knowledge that originates from individual experience.

To achieve this level of control, we developed a novel learning paradigm. Participants underwent extensive training, during which they learned new contextual associations between novel, meaningless shapes (see Methods and Fig. 2*A*). This design not only has ultimate control over spatial and nonspatial associations, but it also controls for the episodic memory associated with each stimulus. Using novel stimuli and novel associations, all participants were exposed equally to all trained stimuli, and therefore the differences in activation observed between the conditions could not be attributed to possible differences in individual experience, but to the

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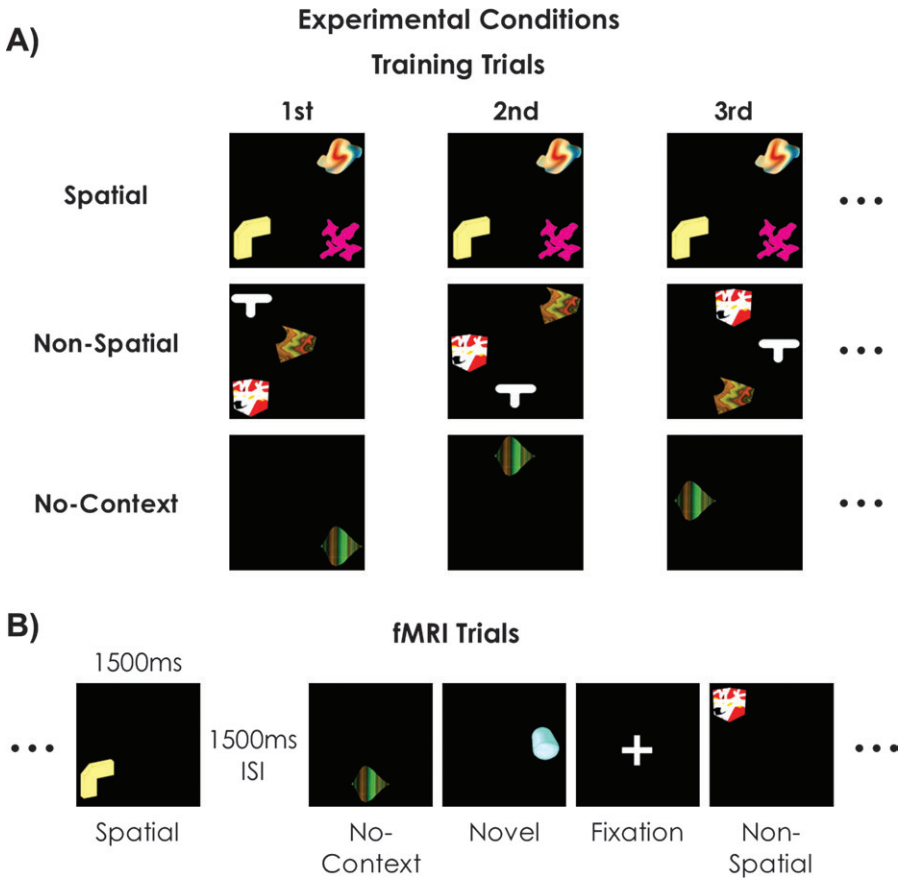

Figure 2. Experimental design. (*A*) Examples of displays in training trials from different sessions (first presentation, second presentation, third presentation, etc.) within the training phase for each of 3 conditions. In the spatial condition, 3 shapes were always shown together in the same spatial location. In the nonspatial condition, 3 shapes were always shown together in random locations. In the no-context condition, a single shape was always presented alone in a random location. (*B*) During the fMRI trials, only 1 shape was presented at a time. Thus, the only difference between trials in different conditions was the prior experience subjects had with the shapes during the training. In addition to the 3 main conditions, novel shapes with which the subjects had no prior experience (novel condition) were presented at random locations.

differences in contextual associations. Special care was taken to ensure that these shapes do not resemble any real object. Two-thirds of the shapes were grouped into triplets, where each triplet represented a "context." In half of these contextual triplets, the 3 shape members of the triplet were always presented in the exact same spatial location on the screen. This was considered the spatial context condition (see Fig. 2*A*, top). The members of the second half of the contextual triplets consistently appeared together during training, but the location of each member within the triplets was randomized among 9 possible locations on the screen across different training presentations. This was the nonspatial context condition (see Fig. 2*A*, middle). For the third, no-context, condition, participants were trained with individual shapes, always appearing alone and in a random location (see Fig. 2*A*, bottom). The individual shapes were not associated with any other shape, and thus did not belong to any context. They were used as control items, analogous to the objects used in the weak context condition in our previous experiments. Stimuli in all conditions appeared for the same number of times during training to equate level of experience.

Once participants reached a training criterion that indicated a sufficient level of fluency with the novel associations (see Methods), their brain activity was studied with functional magnetic resonance imaging (fMRI) while they were viewing each shape in isolation (see Fig. 2*B*) and were required to perform a memory task on each (whether the associated shapes were single- or multicolored for contextual targets, and whether the presented target was single- or multiplecolored for the no-context and novel patterns; see Methods). To determine whether the PHC processes contextual associations in general, we compared the activity elicited by individual shapes from the spatial context condition and the shapes in the nonspatial context condition with the activity elicited by the control, no-context shapes. To assess how much of the activity associated with these 3 conditions was attributable to familiarity, we included a fourth condition in the fMRI portion of the experiment: shapes with which the participants had no experience (i.e., completely novel shapes).

The use of this tightly controlled design allowed us to address the function of the PHC in 2 ways. First, it provided a means for testing directly whether the PHC mediates the processing of contextual associations in general, or is it limited to spatial information. Second, it allowed us to test our hypothesis that the PHC is hierarchically organized, with spatially bound stimuli eliciting greater activity in the posterior portions of the PHC and nonspatial but nonetheless contextually associative stimuli evoking greater activity in the anterior PHC. By using novel shapes, we maximized the distinction between spatial and nonspatial targets. In general, the stimuli used here may be seen as highly impoverished versions of real-word contexts and scenes. By deliberately avoiding the richness of realistic scenes,

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however, we have minimized the chances of confounds that might stem from sources such as background information, individual experience, and so on, allowing us to concentrate on the specific questions that emerged from our proposal regarding the role of the PHC in spatial and nonspatial contextual processing.

Finally, to be able to localize the activation elicited by these conditions in relation to the previously defined PPA, we also ran a "PPA localizer" task. Blocks of different categories of stimuli (indoor and outdoor scenes, weak contextual objects, faces, and scrambled pictures; adapted from Epstein and others 2003) were presented to the participants while they performed a 1-back memory task, requiring participants to decide whether a picture was repeated. By comparing activity elicited by the indoor and outdoor scenes with the activity elicited by the other stimulus categories (weak contextual objects, faces, and scrambled pictures), we could localize the PPA in each of the participants. Once localized, we compared the area of the PHC sensitive to the contextual shapes with the area defined as the PPA.

Materials and Methods

Participants

Fourteen participants participated in this experiment (7 females, mean age 26.6). All participants had normal or corrected-to-normal vision. Informed written consent was obtained from each of the participants prior to the scanning and training sessions. All procedures were approved by Massachusetts General Hospital Human Studies Protocol number 2001-001754.

Stimuli

Novel colorful shapes on a black background were used in this experiment. The shapes were specifically selected to have no explicit semantic meaning. Two- and 3-dimensional shapes were used. The shapes spanned were of 4° of visual angle and were presented within a black square spanning 12°. The surrounding screen was gray. The black square was divided into 9 sections in which a shape could be presented.

There were 4 conditions in this experiment: spatial-context, nonspatial-context, no-context, and novel. There were 96 shapes in each condition. The perceptual properties of the shapes, such as 2-dimensional versus 3-dimensional, and simple- versus multicolored, were balanced between conditions. In the spatial and nonspatial conditions, shapes were grouped in triplets. The 96 shapes were divided into 32 triplets per condition. During the training period, the shapes were always presented as a triplet. In the spatial condition, the groups of 3 shapes were always presented together, and always in the same location within the black square. Assignment of the spatial configuration for each spatial triplet was defined using a random permutation function in Matlab prior to the commencement of the training phase and was different across participants. Participants had to learn not only that the 3 shapes were grouped together but also their location within the square. In the nonspatial condition, the groups of 3 shapes were always presented together, but their location varied randomly. In the no-context and novel conditions, shapes were not grouped into triplets. In both conditions, only 1 shape was presented at a time in a random location. The novel condition was only used at the time of scanning, and was not presented during the training phase, therefore those shapes were only presented to the participant once.

Training

The training period was determined by the performance of the participant and therefore the schedule of training varied based on the individual. The mean training period necessary to learn the shape associations was 7 days, with an hour-long session each day (not including weekends). There were 3 possible tasks in the training session divided into a study phase and a testing phase.

In the study phase participants passively viewed the stimuli, either the whole triplet (for the spatial and nonspatial condition) or the single shape (for the no-context condition) within the black square. The viewing was self-paced. There were 3 repetitions of the stimuli on average for the first half of training. Once participants became more proficient with the stimuli, they only had one repetition of the stimuli during the study phase. After the study phase of each training session, participants proceeded to the testing phase.

The testing phase consisted of 1 of 2 types of quizzes. Participants began being tested with a categorical quiz. In this quiz, 1 shape was presented (regardless of condition), and the participant had to press a button to report whether the shape was spatial, nonspatial, or no-context. After each decision, feedback was provided to the participants on whether their response was correct. After participants became more proficient with the stimuli, they were required to take a more difficult test. This test was a multiple-choice test that consisted of a 5-part trial. One shape was presented in the black square on the right side of the screen. On the left side of the screen were 9 other shapes. Participants first had to report which of the 9 shapes was associated with the shape on the right side of the screen. If the shape presented on the right side of the screen was in the no-context condition, they would answer "none" and move on to the next trial. If the shape belonged to the context conditions, after selecting the associated shape, the participants had to report the correct location *if* the shape was from the spatial context condition. If the shapes belonged to a nonspatial context, the participant would be required to report "no location." After the location was decided, the participant would be presented with another selection of 9 shapes, and would pick the remaining shape that belonged to the context. If the participant had previously answered "no location," the participant would move on to the next trial. If the participant had given a location for the previous picked shape, then they would be asked to state the location of the second shape they selected, and then move on to the next trial. At the end of each trial, the whole triplet would be presented to give feedback to the participant. If the presented shape was from the no-context condition, just that shape would be presented during the feedback portion. Once participants performed consistently at >95% correct in all portions of the test, we deemed the associations well learned, and the participants continued on to the fMRI portion of the experiment.

fMRI Experimental Details

There were 3 runs of functional acquisition for each participant. Trials were designed in a rapid event-related paradigm in which task-related trials were intermixed with fixation trials. The order of trials was optimized for hemodynamic response estimation efficiency by using OptSeq of the FS-FAST toolbox. There were 84 trials per condition. Four conditions were used in the fMRI experiment, spatial, nonspatial, no-context, and novel. Novel shapes were stimuli that participants had not been previously exposed to and employed as a control for familiarity. Each trial consisted of displaying 1 shape alone (regardless of condition), on the black square, and in the appropriate location for the spatial contextual shapes. The shape was presented for 1500 ms, with 1500 ms interstimulus interval, thus the total length of each trial was 3 s. Each run contained 150 trials, of which there were 28 trials per condition, and 38 fixation trials. The participants' task was to determine whether the single shape presented was part of a triplet, and if it was, to determine how many shapes within the whole triplet were single colored (note that only 1 shape was actually presented during each trial, thus task performance was based on memory of the associated triplets). If the shape was a no-context or a novel shape, the participant had to press a button determining whether the shape presented was single colored or multicolored. Participants had a practice test outside the scanner with 12 trials in each condition with feedback. Once in the scanner, the participants performed the practice with the same trials to make sure that they were comfortable with the timing and button presses. No shape presented was ever repeated.

PPA Localizer Scan

After the participants had completed the experiment, they were scanned in an additional 3 runs in which we used the PPA localizer task to find the PPA in our participants. The design of this localizer was adapted from Epstein and others (2003). The localizer was a block design in which task-related blocks alternated with fixation blocks. Each block had a length of 20 s. In each task-related block, 20 pictures of the same kind of stimulus were presented. We used 5 types of stimuli:

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indoor scenes, outdoor scenes, weakly contextual objects, faces, and scrambled colorful pictures. In each block, a picture was presented for 400 ms, with a 600-ms interstimulus interval. Each run consisted of 2 blocks per stimulus type, except for the scrambled pictures, which were presented in only 1 block. Participants had to perform a 1-back task, and pressed a button to indicate whether the picture repeated the previous picture or did not repeat. There were 2 repetitions per block randomly interspersed within the trials. Altogether, there were 120 trials, or 6 blocks, per stimulus type, presented in 3 runs; except for the scrambled pictures that were shown for 60 trials, or 3 blocks. Fixation blocks consisted of a black fixation cross in the middle of the screen that was presented for 1700 ms with a 300-ms interstimulus interval. On the last presentation of each fixation block, the fixation cross changed to a red color to alert the participant a picture block was going to begin next. There were 8 blocks, or 80 trials, of fixation trials per run, with a total of 24 fixation blocks, or 240 fixation trials used.

Imaging Parameters

Participants were tested in a 3-Tesla Siemens Trio scanner (Erlangen, Germany). All images were acquired with a custom-built head coil. For each participant, a series of conventional high-resolution structural images (3D T_1-weighted images) was first collected for cortical surface reconstruction. A series of functional images was then collected using a gradient echo-planar imaging sequence (time repetition [TR] = 3.00 s for the shape task runs, and TR = 2 s for the localizer runs, time echo = 25 ms, flip angle = 90°, field of view = 200, slice thickness = 3 mm, 1 mm gap, 33 interleaved slices oriented parallel to the anterior commissure—posterior commissure line). Each functional acquisition run for the shape experimental runs lasted 7 min and 48 s, and the functional acquisition run for the localizer lasted 5 min and 8 s. Each scanning session, including the structural and functional sequences, lasted 1–1.5 h.

Statistical Analysis

Functional data were analyzed using the FS-FAST analysis tools. The methods used here have been used and elaborated previously (Bar and others 2001; Bar and Aminoff 2003). Data from individual fMRI runs were first corrected for motion using the AFNI package (Cox 1996) and spatially smoothed with a Gaussian full-width, half-maximum filter of 5 mm for the group average, and 4.5 mm for the region of interest (ROI) analysis. The intensities for all runs were then normalized to correct for signal intensity changes and temporal drift, with global rescaling for each run to a mean intensity of 1000. Signal intensity for each condition was then computed, excluding trials with incorrect behavioral responses, and averaged across runs. The estimated hemodynamic response was defined by a gamma function of 2.25 s hemodynamic delay and 1.25 s dispersion for the group average. A finite impulse response model was used for the individual ROI analysis. To account for intrinsic serial correlation in the fMRI data within participants, we used a global autocorrelation function that computes a whitening filter (Burock and Dale 2000). The data were then tested for statistical significance and activation maps were constructed for comparisons of the different conditions. Both group average activation maps and ROIs are random effect analysis.

Cortical Surface-Based Analysis

Once the data from all trials were averaged, the mean and variance volumes were resampled onto the cortical surface for each participant. Each hemisphere was then morphed into a sphere in the following manner: First, each cortical hemisphere was morphed into a metrically optimal spherical surface. The pattern of cortical folds was then represented as a function on a unit sphere. Next, each individual participant's spherical representation was aligned with an averaged folding pattern constructed from a larger number of individuals aligned previously. This alignment was accomplished by maximizing the correlation between the individual and the group, while prohibiting changes in the surface topology and simultaneously penalizing excessive metric distortion (Fischl and others 1999).

ROI Analysis

The ROIs chosen for this analysis were constrained both structurally and functionally. The structural constraint, of the PHC (encompassing the collateral sulcus and the parahippocampal gyrus), was based on a hand labeling of different brain structures for each participant, chosen a priori on the basis of previous studies showing their involvement in contextual analysis (Bar and Aminoff 2003). The PHC and perirhinal cortex were defined using procedures elaborated in Insausti and others (1998) and Reber and others (2002). The PHC was then split in half to run a ROI analysis on the anterior half and posterior half of the area. Using the data from the localizer we were able to define the PPA by finding the active voxels in the contrast of indoor and outdoor scenes versus house, faces, objects, and scrambled pictures. Once defined, we were able to use the PPA as a functional ROI. For all ROIs, a functional constraint was based on a mask selecting the subset of voxels within each of these labels that was activated by any component of the task, as revealed by the main effect (i.e., all vs. fixation contrast), with a threshold of $P < 0.05$. Only voxels that elicited signal change in a positive direction when compared with baseline were included in the final definition of each of the ROIs for analysis. Voxels that fell in an area of signal dropout, most often found within the perirhinal ROI, were removed from the analysis. All of the voxels that met these constraints were then averaged, allowing the contrasts of interest to be computed across the resulting time courses. A 1-way repeated-measures analysis of variance (ANOVA) was performed for experimental conditions on the mean percentage of peak signal change calculated for each condition.

Results

Participants were trained on the stimuli for hour-long sessions for an average of 7 days (range 4–11 days). Participants proceeded to the fMRI portion of the experiment once they had consistently performed above 95% in the training tests for all conditions (see Methods for details).

During the fMRI portion of the experiment 1 shape was presented on each trial, and therefore the only difference between trials of the different conditions was the previous experience that the participant had acquired with each stimulus (i.e., its associations, if any, with other stimuli or locations; see Fig. 2*B*). The task was relatively difficult, and resulted in an average of 75% correct trials (range 61–96%). Accuracy in performance was highest for the no-context condition (context vs. no-context $t(13) = 10.13$, $P = 0.00000008$). This might be expected given that in the context conditions the perceptual judgment pertained to the associated patterns from memory, whereas in the no-context condition it pertained to the presented items. Accuracy was also significantly better in the spatial condition compared with the nonspatial condition ($t(13) = 3.11$, $P = 0.0004$). The addition of spatial associations may have helped participants retrieve a more descriptive visual memory and therefore increase their accuracy in forming the perceptual judgment. However, incorrect trials were excluded from further statistical analysis and therefore performance accuracy was equated between the different conditions. Analysis of the reaction times revealed a significant difference between the context and no-context trials (1557 vs. 1208 ms, respectively, $t(13) = 10.33$, $P < 0.0000001$), implying that the judgment task was more difficult for items that participants had previously seen in a context (spatial and nonspatial) than those they had seen without a context. Again, we might expect this difference given that in the context conditions the perceptual judgment pertained to the associated patterns from memory, whereas in the no-context condition it pertained only to the presented item. Critically, there was no significant difference in reaction time between the spatial context and the nonspatial context trials (1561 vs. 1554 ms, respectively, $t(13) = 0.337$), suggesting that the 2 contextual conditions were of equivalent difficulty level.

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Context-Related Neural Activity in the PHC

To identify the brain regions involved in contextual processing, we compared the activity elicited by the shapes that were associated with either a spatial or a nonspatial context with the activity elicited by the shapes that were not associated with any other shape or location. The group-averaged statistical activation maps for these contrasts (i.e., spatial condition vs. no-context condition; and nonspatial condition vs. no-context condition) can be seen in Figure 3(*A*,*B*). Significant differential activity was found in the PHC for these contrasts. A ROI analysis was conducted to investigate the fMRI relative signal change in the PHC for each condition. The PHC ROI was defined anatomically on each individual using detailed procedures with instructions for defining the boundaries of the entire PHC (Insausti and others 1998; Reber and others 2002). The ROI analysis demonstrated significant contextual activation in the PHC, both in the left and right hemispheres (LH: spatial vs. no-context $t(13) = 3.48$, $P < 0.002$, nonspatial vs. no-context $t(13) = 3.41$, $P < 0.002$; RH: spatial vs. no-context $t(13) = 3.07$, $P < 0.004$, nonspatial vs. no-context $t(13) = 3.45$, $P < 0.002$; all *t*-tests are presented with 1-tailed significance) (Fig. 3*C*). Note that although the richness of associations that a given target in this study possesses is substantially smaller than this of an associative everyday-object (e.g., a traffic light), these findings help generalize the results of Bar and Aminoff (2003) in revealing the importance of the PHC in processing of both spatial and nonspatial contextual information.

In addition to showing that the PHC is generally sensitive to contextual associations, we wanted to substantiate further our proposal that the PHC is organized along a hierarchy of spatial specificity. Consequently, we conducted an additional ROI analysis in which the PHC was divided into anterior and posterior subregions (see Methods). ROI analyses were performed separately within each subregion, for each participant, to verify that spatial contextual information is mainly processed in the posterior portions of the PHC, whereas nonspatial contextual information is processed in more anterior regions of the PHC (Fig. 3*C*). We computed the interaction of contextual condition (spatial, nonspatial) by subregion (anterior, posterior PHC). This interaction was statistically significant in both hemispheres (LH: $F_{1,13} = 10.12$, $P < 0.007$; RH: $F_{1,13} = 5.54$, $P < 0.035$; all ANOVAs are presented with 2-tailed significance). The simple main effects for the specific contrasts of interest were also computed within each portion of the PHC, in each hemisphere. Results from the LH revealed significantly greater activity for spatial compared with nonspatial contextual shapes in

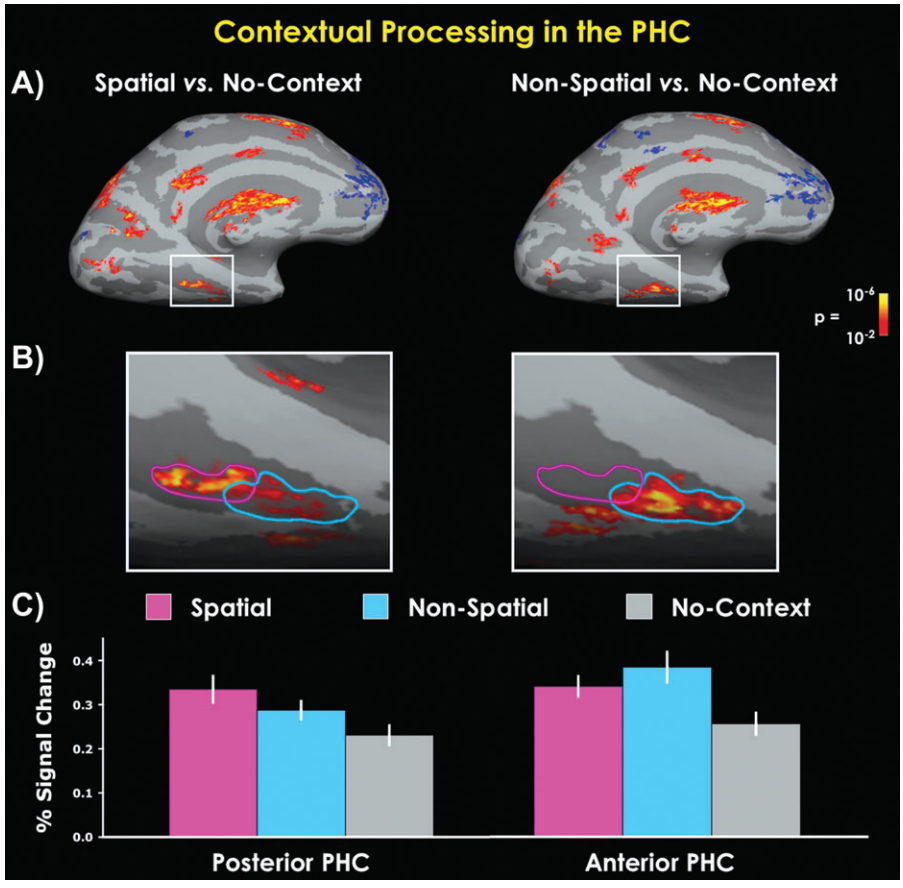

Figure 3. Spatial and nonspatial context-related activity compared with no-context activity within the LH. (*A*) Random effects statistical activation maps representing the difference between perceiving shapes associated with a spatial context (left) and shapes associated with a nonspatial context (right) compared with shapes in the no-context condition. Both spatial and nonspatial conditions significantly activated the PHC more than shapes in the no-context condition. (*B*) Activation in the PHC enlarged: Activity elicited for the spatial shapes was concentrated in a posterior subregion of the PHC (left), whereas activity elicited for the nonspatial shapes was concentrated in a more anterior subregion (right). (*C*) For each subject, separate ROI analyses were conducted within the posterior (left) and anterior (right) subregions of the PHC (here shown averaged across subjects). The ROI analyses clearly demonstrated a spatial hierarchical organization within the left PHC, with greatest activation for the spatial context condition in the posterior PHC, and for the nonspatial condition in the anterior PHC. Results in the RH showed a similar pattern but were less robust. Error bars represent a single standard error.

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the posterior PHC ($t(13) = 2.15$, $P < 0.03$), whereas an opposite pattern was found in the anterior PHC (nonspatial vs. spatial, $t(13) = 1.92$, $P < 0.04$). In the RH, even though the overall interaction of contextual condition by subregion was significant, the simple main effects did not reach significance (spatial vs. nonspatial in posterior PHC: $t(13) = 1.23$; nonspatial vs. spatial in anterior PHC: $t(13) = 0.9$). In summary, our results demonstrate a hierarchical organization of spatial sensitivity within the PHC, which was most robustly expressed in the LH.

To study the effect of mere experience and familiarity on PHC activity, we compared activity elicited by the shapes in the no-context condition with activity elicited by the novel shapes that participants had not seen before. There was no significant difference between these 2 conditions in either the left or the right PHC ROIs (LH: $t(13) = 1.25$; RH: $t(13) = 0.25$), suggesting that the PHC is not sensitive to familiarity or novelty per se, at least under the conditions of this study. Rather, it seems more reasonable that the PHC is activated by the mere associations between representations.

Context-Related Activity in Respect to the PPA Borders

To understand the relation between activity related to general contextual associations and place-related activity typically attributed to the PHC, we further compared the activity elicited by contextual shapes with activity elicited by images of scenes that were presented in a separate PPA localizer task. Because we were interested in investigating the role of the PHC proper (Insausti and others 1998; Reber and others 2002), we limited the PPA definition to voxels that were within the boundaries of the PHC (see Fig. 4, top, for group activation map). Once the PPA was defined for each participant, it was used as an ROI in which activation for the different shape conditions was compared. An ROI analysis showed that shapes in the spatial contextual condition elicited significantly more activity inside the PPA borders than both the shapes in the nonspatial (LH: $t(13) = 1.98$, $P < 0.034$, RH: $t(13) = 2.25$, $P < 0.02$) and the no-context condition (LH: $t(13) = 2.29$, $P < 0.019$; RH: $t(13) = 2.88$, $P < 0.006$). These results suggest that the PPA is associated mainly with processing of spatial contextual associations; in contrast, the activation for the nonspatial condition was centered in a region anterior to the PPA (see Fig. 4). This further supports our proposition that the posterior portion within the PHC (encompassing the PPA) is most sensitive to spatial and location information, whereas the anterior portion is responsive to nonspatial associative information.

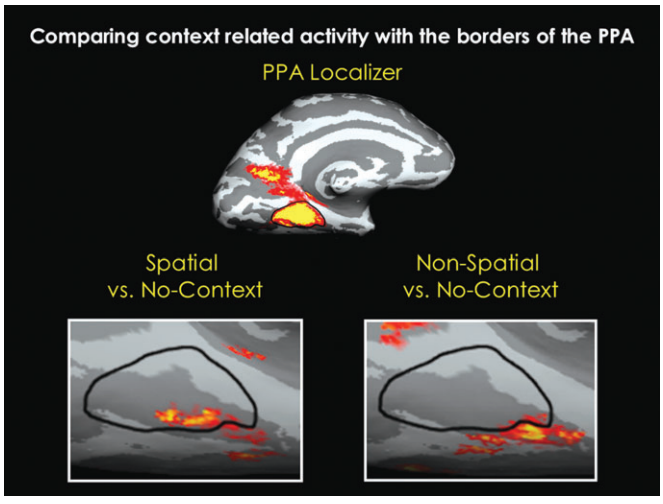

Figure 4. Comparison of PPA activation with contextually related activation within the PHC. Top brain shows the group average PPA, defined by comparing activity elicited by indoor and outdoor scenes within the activity elicited by weak contextual objects, faces, and scrambled objects. As can be seen, the activity elicited by the shapes associated with a spatial context extends well into the borders of the PPA (illustrated by the black outline), whereas the activity elicited by the shapes associated with a nonspatial context does not, and is located in the portion of the PHC anterior to the PPA.

Medial Temporal Lobe Activations beyond the PHC

Hippocampal and perirhinal ROIs were also analyzed to compare contextual activation in the PHC with contextual activity within the greater medial temporal lobe. The hippocampus showed a significant spatial context effect in the LH (spatial vs. no-context, $t(13) = 2.37$, $P < 0.018$) and a significant spatial and nonspatial context effect in the RH (spatial vs. no-context, $t(13) = 2.91$, $P < 0.006$; nonspatial vs. no-context $t(13) = 2.83$, $P < 0.007$). No significant differences were found comparing spatial context with nonspatial context. However, unlike the PHC, which showed no differential activity for the no-context shapes compared with the novel shapes, the left hippocampus was significantly more active for the no-context shapes compared with the novel shapes that had not been presented prior to the scan (no-context vs. novel $t(13) = 1.8$, $P < 0.048$) and the right hippocampus was significantly more active for novel shapes compared with no-context shapes (no-context vs. novel $t(13) = -1.72$, $P < 0.05$). This suggests that the hippocampus, although sensitive to contextual information, is sensitive to familiarity.

The perirhinal ROI (as defined by Insausti and others 1998) yielded significant contextually specific activity. One participant was considered to be an outlier in the left perirhinal ROI because the average percent signal change was above 2 standard deviations from the mean, which was specific to this ROI and did not demonstrate such a strong deviation from the mean in any of the other ROIs. Furthermore, a different participant had to be removed from the right perirhinal ROI due to signal dropout. Both the activity elicited for shapes of a spatial context and activity elicited for shapes of a nonspatial context were significantly higher than what was elicited for no-context shapes (LH: spatial vs. no-context, $t(12) = 2.71$, $P < 0.01$; nonspatial vs. no-context, $t(12) = 3.27$, $P < 0.004$; RH: spatial vs. no-context. $t(12) = 2.75$, $P < 0.009$; nonspatial vs. no-context $t(12) = 2.752$, $P < 0.009$). There were no significant differences between the activity elicited for the no-context and novel shapes in either hemisphere, nor any significant differences between the activity elicited for spatial and nonspatial shapes. It is important to note, however, that because our primary focus pertained to PHC activation, scanning parameters were not optimized for signal in the perirhinal (and hippocampus), which are known to require tailored optimization in fMRI. This might have led to signal dropout (although those areas without signal were removed from the ROI, see Methods) and less voxels than optimal in the analysis. We present these results here mainly as a report, and future research will be required before strong conclusions about the role of the perirhinal and the hippocampus in such tasks can be made.

Modulation of Activity by Amount of Days in Training

We were interested to see if the overall duration of individual training correlated with any of the differential activity found in the ROIs. We ran a Pearson's correlation between the number of

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days the individual participant was in training and the difference in blood oxygen level dependent activity for spatial context versus no-context. Nonspatial context versus no-context, and spatial versus nonspatial context. This analysis further distinguished the responses in the PHC and the hippocampus. There were significant positive correlations in the left PHC for numbers of days in training and increased activity for the spatial condition compared with the no-context condition ($r(14) = 0.632$, $P < 0.016$), and for increased activity for the nonspatial condition compared with the no-context condition ($r(14) = 0.706$, $P < 0.004$). These positive correlations indicate that the longer a participant was in training, the greater the neural response was for contextual stimuli over noncontextual stimuli. Similar trends were found in the RH PHC but did not reach significance. Days in training did not correlate with differential activation in the left or right hippocampus or perirhinal cortex.

Finally, in the comparisons we conducted in these analyses, other regions besides the PHC showed differential activity. These regions included the RSC, fusiform gyrus, intraparietal sulcus, the parietal–occipital junction, caudate, lateral-occipital complex, the inferior frontal cortex, and medial prefrontal cortex. Given that the main purpose of this study was to test a well-defined hypothesis about the role of the PHC in contextual associations, and its relation to the PPA, the design of the present study was geared to address these questions, and future experiments will be needed to address the role of other cortical regions in such experiments.

Discussion

The PHC has previously been implicated in the processing of place-related information (i.e., PPA; Epstein and Kanwisher 1998), as well as in episodic memory (for review see Schacter and Wagner 1999). Motivated by our previous findings and the intention to bridge the seemingly incongruent functions attributed to this medial temporal region, we tested a specific hypothesis about the possible function of the PHC: that the PHC is sensitive to contextual associations in general, regardless of whether they pertain to spatial or nonspatial information, and these associations are organized within the PHC along a hierarchy dictated by their spatial specificity.

By using a novel paradigm that optimally separated spatial from nonspatial contextual associations, we showed that the PHC indeed processes both types of associations, and processes them in separate subregions. Specifically, our results show that the functional organization of the PHC varies along a hierarchal posterior–anterior axis of spatial specificity; representations in the anterior portions of the PHC rely on nonspatial associations, whereas those in the posterior portions of the PHC rely on spatial associations. Moreover, the locus of activity related to the processing of spatial contexts overlaps with the region known as the PPA, thus help linking the present findings with previous reports. Taken together, it seems reasonable to propose that the anterior PHC is involved in the representation of constituent identities of a particular context, regardless of the spatial position of these constituent parts within a scene, whereas the posterior PHC represents the spatial relations between these specific members. Note that within the realm of spatial information, one can distinguish between spatial relations (e.g., where is the hat relative to the head) and spatial location (e.g., where is the Tower of Pisa). From our results, it would seem that spatial relations are mediated by the posterior part of the PHC, whereas spatial locations, which combine space and identities, will be expected to recruit both the posterior and anterior portions of the PHC. This also implies that the representation of items that are associated contextually without being linked by space, such as a champagne and confetti that both belong in the nonspatial context of celebration, will be mediated by the anterior PHC without recruiting the spatial, posterior PHC. It is further encouraging that the anterior PHC, which we argue might be emphasizing objects' identity independent of spatial information, is immediately adjacent to the perirhinal cortex, which is often perceived as processing "what" information (Murray and Bussey 1999).

In addition, that the anterior PHC serves to process nonspatial associations is supported by previous studies that have implicated the anterior medial temporal lobe in relational processing (Henke and others 1999; Schacter and Wagner 1999; Sperling and others 2003; Jackson and Schacter 2004). These studies have looked at associative processing of nonspatial stimulus properties such as associating abstract nouns (Henke and others 1999) or face–name pairs (Sperling and others 2003). Furthermore, associations between nonrelated objects (e.g., monkey-umbrella) activate a similar region in the PHC as we observed here (Henke and others 1997; Rombouts and others 1997). In addition, associative encoding of visual scenes, but not match-to-sample of these scenes, activates the PHC (Montaldi and others 1998). Finally, in a recent study of associative and recognition memory, object–color associations elicited significantly more parahippocampal activation than old/new object judgments (Yonelinas and others 2001). These findings, therefore, converge with the present results that the anterior PHC processes nonspatial properties of associations. If these studies had also used stimuli that required the association of spatial properties, we would have expected more activation in posterior portions of the PHC, as we have shown here and previously (Bar and Aminoff 2003), and has been shown by others since (Düzel and others 2003; Pihlajamaki and others 2004). The current study ties these findings together to reveal the posterior–anterior spatial hierarchical organization of the PHC with maximal control over all associations by using novel meaningless shapes.

The PHC showed a significant effect of context versus no-context but did not show a significant difference between previously encountered no-context items and novel, unlearned items. This suggests that the PHC was not sensitive to mere familiarity in the present study, but to whether the items are part of a familiar context. Previous studies have implicated the PHC in familiarity processing (Brown and Aggleton 2001; Weis and others 2004; Gonsalves and others 2005; Daselaar and others 2006; Montaldi and others 2006), although this implication might be inconclusive (Squire and others 2004). It is possible that a familiar item elicits a larger number of associations compared with a new item, giving the impression of familiarity signal, whereas instead it could be a result of increased contextual activity in the PHC. The lack of PHC sensitivity to familiarity is in contrast with the hippocampus, which showed differential activity based both on context and on previous exposure (i.e., demonstrating differential activity for no-context and novel items). The perirhinal cortex also elicited significant differential activity for context shapes compared with no-context shapes but did not show the novelty effect previously reported in this region (e.g., Daselaar and others 2006).

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However, we take our results of the perirhinal cortex cautiously because of susceptibility artifacts in this region.

Previous studies have also suggested that the PHC is involved in single item processing, rather than associative processing (Davachi and Wagner 2002; Preston and others 2004). Indeed, also in our previous studies (Bar and Aminoff 2003) individual items elicited activation in the PHC. It is possible that although the PHC is not specifically sensitive to individual items per se, it will show increased sensitivity if these objects are highly associated with other objects. In addition, some studies (Davachi and Wagner 2002; Preston and others 2004) have found that the hippocampus, and not the PHC, seems to be sensitive to associative processing. We suggest that this discrepancy may be a result of the length of the experience the participants had with the associations. In those studies in which associative processing was not found in the PHC, participants learned associations between 2 familiar items over the course of a couple of hours, whereas in our study participants trained on average for 2 weeks to learn the associations. It has been reported that hippocampus may be more involved in rapid learning of new associations, whereas the parahippocampal region may be more involved in learning over time (McClelland and others 1995). Indeed, a substantial experience might be required for consolidating contextual associations between individual members of a context and eventually to support a robust *context frame* (Bar and Ullman 1996; Bar 2004) that links all the items together.

In conclusion, our findings support the hypothesis that the PHC processes contextual associations in general, thus providing a unified framework that bridges different accounts of spatial processing and episodic memory in the PHC. Taking advantage of contextual regularities in our environment can provide a powerful source for facilitation of visual cognition (Bar 2004). We have shown that these regularities are processed in the posterior and anterior PHC, along a posterior–anterior axis of spatial specificity. We have proposed in the past that typical contexts are represented in context frames (Bar and Ullman 1996; Bar 2004) that store both the identity of the objects likely to appear in the specific context as well as the typical spatial relations among them. The findings we report here indicate that the anterior PHC is involved in processing information about the identity of the associated members participating in a certain context, and the posterior PHC processes the spatial relations among these members. The functional benefit from such representational hierarchy remains an important open question for the future. It might be related to integration of multiple sources, possibly in the hippocampus and the prefrontal cortex, and it can clearly be beneficial in coactivating contextual information for facilitating recognition and other associative operations.

Notes

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