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Which Way Was I Going? Contextual Retrieval Supports the Disambiguation of Well Learned Overlapping Navigational Routes

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Groundbreaking research in animals has demonstrated that the hippocampus contains neurons that distinguish between overlapping navigational trajectories. These hippocampal neurons respond selectively to the context of specific episodes despite interference from overlapping memory representations. The present study used functional magnetic resonance imaging in humans to examine the role of the hippocampus and related structures when participants need to retrieve contextual information to navigate well learned spatial sequences that share common elements. Participants were trained outside the scanner to navigate through 12 virtual mazes from a ground-level first-person perspective. Six of the 12 mazes shared overlapping components. Overlapping mazes began and ended at distinct locations, but converged in the middle to share some hallways with another maze. Non-overlapping mazes did not share any hallways with any other maze. Successful navigation through the overlapping hallways required the retrieval of contextual information relevant to the current navigational episode. Results revealed greater activation during the successful navigation of the overlapping mazes compared with the non-overlapping mazes in regions typically associated with spatial and episodic memory, including the hippocampus, parahippocampal cortex, and orbitofrontal cortex. When combined with previous research, the current findings suggest that an anatomically integrated system including the hippocampus, parahippocampal cortex, and orbitofrontal cortex is critical for the contextually dependent retrieval of well learned overlapping navigational routes.

Introduction

The routes people take from their home to work often overlap with other familiar paths, such as the route from home to the grocery store. Overlap between familiar routes can cause interference and lead to navigational errors. To avoid errors, the brain must separate, or “disambiguate,” the two routes. Computational models suggest the hippocampus uses context to retrieve specific episodes, despite interference from other episodes (Hasselmo and Eichenbaum, 2005; Zilli and Hasselmo, 2008a). Research in animals demonstrates that hippocampal neurons uniquely code overlapping navigational trajectories using contextual information (Wood et al., 2000; Ferbinteanu and Shapiro, 2003; Lee et al., 2006; Smith and Mizumori, 2006), and hippocampal lesions impair retrieval of sequences that share common elements (Agster et al., 2002). Based on this animal and

modeling literature, we predicted hippocampal functional magnetic resonance imaging (fMRI) signal increases in humans during retrieval of overlapping compared with non-overlapping navigational sequences.

Like the hippocampus, the parahippocampal cortex plays an important role in navigation. The parahippocampal cortex is important for identification and retrieval of landmarks, their spatial relationships, and their navigational relevance (Epstein and Kanwisher, 1998; O’Craven and Kanwisher, 2000; Burgess et al., 2001; Hartley et al., 2003; Janzen and van Turenout, 2004; Rosenbaum et al., 2004). The parahippocampal cortex, which is connected to the hippocampus directly and via the entorhinal cortex (Suzuki and Amaral, 1994; Kondo et al., 2005; van Strien et al., 2009), processes spatial and nonspatial context (Bar and Aminoff, 2003), and supports source memory (Davachi et al., 2003; Ranganath et al., 2004; Ross and Slotnick, 2008). Modeling suggests that neocortical areas including the parahippocampal cortex may support stable representations like landmarks that appear consistently in multiple episodic memories (McClelland et al., 1995). Therefore, the parahippocampal cortex might play an important, but distinct, role in disambiguation, through the retrieval of stable landmarks and locations that can be used to distinguish between routes.

The orbitofrontal cortex shares strong anatomical connections with the medial temporal lobes, including the hippocampus (Cavada et al., 2000). The orbitofrontal cortex supports flexible response selection and suppression in animals (Murray and

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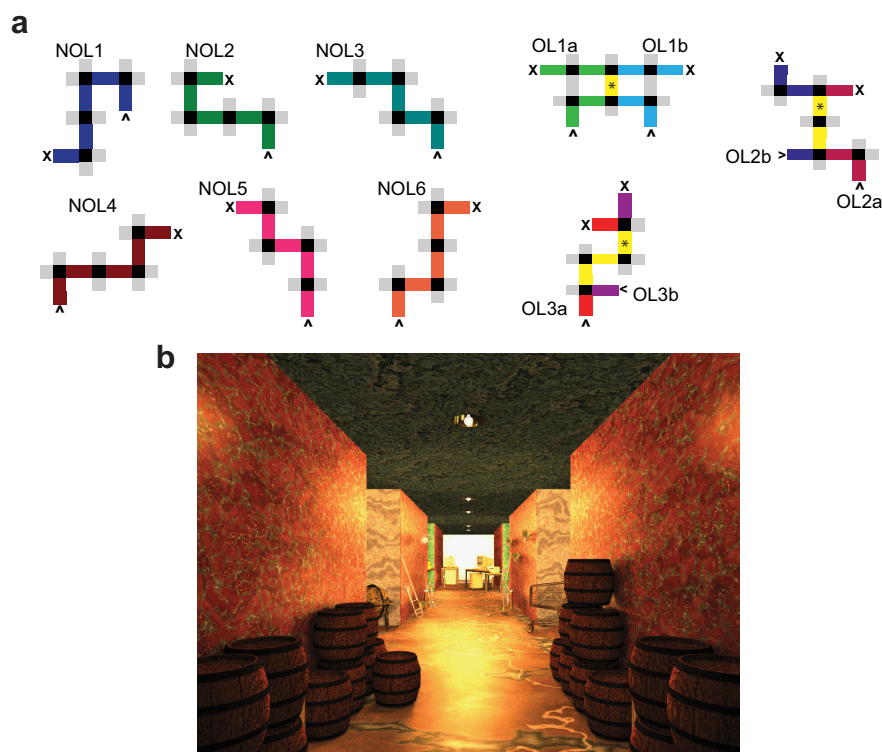


Figure 1. Virtual maze design. *a*, Overhead layout of the 12 mazes used in the task. The non-overlapping mazes (NOL) are depicted on the left and the overlapping mazes (OL) are depicted on the right. Mazes began at the “A” and end at the “X.” The colored, elongated segments represent the hallways of the paths. One color represents one path. The gray segments represent the incorrect “foil” hallways. The black squares represent intersections between hallways. The yellow segments in the overlapping mazes represent overlapping hallways. The final hallway of an overlapping segment before the paths split apart (indicated with “*”) was labeled the critical hall. *b*, Perspective of NOL5 from the beginning of the first hall. This image is representative of how participants viewed the mazes.

Izquierdo, 2007) and humans (Elliott et al., 2000; Arana et al., 2003; O’Doherty et al., 2003). Orbitofrontal cortex activity in humans has also been shown to respond to inter-item (Schon et al., 2008) and proactive interference (Caplan et al., 2007). These data suggest the orbitofrontal cortex might use episodic information to guide response selection between sequences that share common elements in humans, but such a role has yet to be established.

We tested participants on a number of highly familiar virtual mazes. To examine processes related to spatial disambiguation, fMRI signal for overlapping mazes was contrasted with that of closely matched non-overlapping mazes. We hypothesized that, in well learned overlapping mazes, the parahippocampal cortex and hippocampus would be recruited for retrieval of contextual cues and associations that distinguish between the routes, respectively. We predicted this retrieval would occur at the beginning of the mazes, where distinct starting locations cue the current episode, and during critical hallways where overlapping mazes diverge. We hypothesized that the orbitofrontal cortex would be recruited when overlapping mazes diverge for guiding contextually appropriate responses. The current study was designed to specifically examine these regions during different components of spatial disambiguation and elucidate the broader network supporting this behavior.

Materials and Methods

Participants

Twenty-two participants (ages, 19–31; mean age \pm SD, 21.36 \pm 3.43; nine males) with normal or corrected-to-normal vision were recruited from the Boston University community. Two participants were elimi-

nated from analysis because of excess motion during scanning, four because of poor behavioral performance, and two because of signal dropout in the orbitofrontal cortex. Informed consent was obtained from each participant in a manner approved by the Partners Human Research Committee and the Boston University Institutional Review Board.

Virtual environments

Twelve virtual mazes (Fig. 1) were constructed using POV-Ray, version 3.6 (<http://www.povray.org/>), a three-dimensional ray tracer modeling program. Participants navigated the mazes from a ground-level first-person perspective and behavioral data were recorded using E-Prime 2.0 (Psychology Software Tools). The virtual mazes were presented as a series of images rendered in POV-Ray. Every maze was comprised of five hallways, each containing unique objects that served as distinguishing features between the locations and were clearly identifiable and distinguishable from one another.

Participants began each maze at a start point, termed the “cue” and traveled down each hall to an intersection (see Figs. 1, 5). There were four intersections per maze. At every intersection, participants could choose to turn left, right, or continue straight ahead using a button box. The correct choice was the next hall in the sequence of spatial locations comprising a maze. When participants made their navigational responses in a maze, they were autopiloted down that hall to the next intersection. The navigational responses at the end of the halls were counterbalanced across condition.

The 12 mazes were divided into two conditions. Six of the mazes comprised a “non-overlapping” condition, which did not share any hallways with each other and were therefore completely distinct (NOL1–NOL6). The other six mazes comprised the “overlapping” condition. In the overlapping condition, the six mazes were split into three pairs that each began and ended at distinct, non-overlapping locations, but converged in the middle to share some hallways with another maze. The first overlapping maze pair (OL1) shared one hallway between the two mazes. The second overlapping pair (OL2) shared two contiguous hallways between the mazes. The third overlapping pair (OL3) shared three contiguous hallways between the mazes. Inclusion of differing degrees of overlap served two functions: First, it allowed us to test the possibility that responses in our regions of interest might be influenced not only by the contextually dependent retrieval and response demands of the task but also by variation in the extent of overlap, or interference, between representations. Second, examining overlapping segments that precede the hallways where the routes actually diverge allowed us to test the possibility that our regions of interest might respond more generally to the presence of overlap, regardless of whether a contextually dependent response is necessary. Navigational demands were matched between every condition, with the number of left, right, and straight choices counterbalanced across the mazes and conditions. By contrasting one navigational condition (the overlapping condition) with another closely matched navigational condition (the non-overlapping condition), the present study was designed to remove effects attributable to spatial navigation alone, allowing us to examine the effects of contextual retrieval.

Feedback

After an incorrect choice at the end of a given hall, participants were rotated in the selected direction, text reading “Wrong way” in red letters

was overlaid on the scene, and a green arrow indicated the correct direction. Participants were then rotated in the correct direction and sent down the correct hall. To further control the timing of the task, participants were allowed a maximum of 5 s to respond at the end of each hallway. In the case of a “no response,” participants were given a visual prompt and were provided with the same feedback arrows and correctional movement as with an incorrect response. “No responses” were treated as incorrect for both the training and testing periods of the task. Error feedback was provided during all components of the study.

Prescan training

Participants were trained to a criterion of 100% correct on every maze the day before scanning. At the start of training, participants were guided through a sample pair of overlapping mazes (different from those used in the actual task) by the experimenters to ensure participants understood the mechanics of the navigational task and to explain how feedback for incorrect navigational choices worked. Participants were made aware that some mazes would share hallways with other mazes, but that they would all begin and end at distinct locations. Participants were instructed to attend to the starting hallway as it was the cue for which maze they were following, and to attend to the landmark objects to aid in knowing where they were in the mazes.

When learning the mazes, participants would repeatedly navigate one maze until they met a training criterion of four perfect consecutive trials. When criterion was met for one maze, participants would learn the next maze. The order in which mazes were learned was randomized for each participant. After individual training on all the mazes, participants performed four training runs in which all 12 mazes were presented in an interleaved, randomized order, just as they would be presented the following day during scanning. The final three training runs were required to be error-free to ensure participants had mastered the task contingencies along with the individual mazes.

Experimental task

Before scanning, participants were given a warm-up run through all 12 mazes in an interleaved, randomized order. Within the scanner, participants performed 12 runs of the experiment. Each run contained all 12 mazes presented in a counterbalanced order across runs. The order of the runs was randomized across subjects. Each maze began with a 2 s cue period, in which participants viewed the first perspective of the starting point in the maze without moving. Overlaid on the cue image were the instructions “Navigate to the end of the maze.” After the cue, participants were automatically piloted down the first hallway to the first intersection. At the intersection, participants responded with a button press of 1 to turn left, 2 to continue straight ahead, and 3 to turn right. After a correct navigational choice, participants were automatically piloted down the next hallway to the next intersection. Incorrect navigational choices were met with the feedback described above. Turns were made in two simulated steps, with each step incorporating 45° of rotation, such that the participant would come out of the turn centered and facing directly down the next hallway.

In the non-overlapping condition, the landmark objects within each hallway were always associated with the same navigational choices. In the overlapping condition, both the non-overlapping and overlapping hallways were also always associated with the same navigational choices except for the “critical halls” (see Figs. 1, 5). The critical halls were the last hall within an overlapping segment before the two mazes diverged. These hallways were termed critical halls because the navigational choice at the end of the hallways differed depending on which route was being followed. Because every maze began at a distinct location, correctly navigating beyond a critical hall required knowledge of the starting point and the hallways traveled before having entered the overlapping component. Importantly, the construction of the critical halls was no different from any other hallway, ending at an intersection with three possible navigational choices leading to hallways containing uniquely identifiable objects. Only knowledge of the routes distinguished the critical halls as important. Accuracy and reaction times were recorded for each navigational choice made.

Each hallway was comprised of nine POV-Ray-generated images, presented to participants as virtual steps in E-Prime. Each image was presented for 0.25 s, so that each hallway took 2.25 s to traverse. The exact timing of behavioral responses as well as the image presentation was logged in E-Prime to allow accurate modeling of the task. The total duration of a maze varied with the response times at each intersection. Each maze was followed by an 8 s intertrial interval (ITI) in which participants viewed a fixation point in the center of a black screen.

Postscan interview

After scanning, participants were interviewed about their experience with the mazes, including their use of the landmark objects, how they identified the mazes, and their strategy for accurately navigating the periods of overlap.

Image acquisition

Images were acquired using a 3 T Siemens MAGNETOM TrioTim scanner (Siemens) with a 12-channel Tim Matrix head coil. Two high-resolution T₁-weighted MP-RAGE (multiplanar rapidly acquired gradient echo) structural scans were acquired using GRAPPA (generalized autocalibrating partially parallel acquisitions) [repetition time (TR), 2530 ms; echo time (TE), 3.44 ms; flip angle, 78°; slices, 176; field of view, 256; resolution, 1 × 1 × 1 mm]. Functional T2*-weighted blood oxygen level-dependent (BOLD) images were acquired using an echo planar imaging sequence (TR, 2 s; TE, 30 ms; flip angle, 90°; acquisition matrix, 64 × 64; field of view, 256; slices, 32; resolution, 4.0 mm isotropic). Slices were aligned along the anterior/posterior commissure line.

fMRI preprocessing

Imaging analysis was conducted using SPM5 (Wellcome Department of Cognitive Neurology, London, UK). All BOLD images were reoriented so the origin [i.e., coordinate $xyz = (0\ 0\ 0)$] was at the anterior commissure. Images were then slice-time corrected to the first slice acquired in time. Motion correction was conducted and included realigning and unwarping the BOLD images (Andersson et al., 2001). The high-resolution structural images were then coregistered with the mean BOLD image from motion correction and segmented into white and gray matter images. The bias-corrected structural images and the coregistered BOLD images were spatially normalized into standard Montreal Neurological Institute (MNI) space using the parameters derived during segmentation with resampling of the BOLD images to 2 mm³ isotropic voxels and then smoothed using a 6 mm full-width at half-maximum Gaussian kernel.

Data analysis

Behavioral analysis

Overlapping versus non-overlapping analysis. Separate paired-sample *t* tests were used to assess differences in the fMRI task between the overlapping and non-overlapping conditions for percentage accuracy and reaction time for the first halls and critical halls. Because the study was designed to assess activation for well learned environments, a stringent criterion was applied such that participants were excluded from the study if they made more than three errors at any intersection in either condition (yielding <75% accuracy for that navigational choice).

Training participants to stable 100% performance on all mazes before scanning helped ensure that differential learning effects between the overlapping and non-overlapping conditions would not confound the interpretation of the fMRI data. To demonstrate that behavioral performance in the scanner did not change across time differently for the two conditions as a result of continued practice, accuracies and reaction times were examined across runs for both the first hall and critical hall periods. Accuracies for the first halls and critical halls in both conditions remained markedly stable across runs at near 100%. Since reaction times can demonstrate practice effects even when accuracy is invariant, the individual reaction times of participants across trials were entered into a repeated-measures general linear model (GLM) analysis testing for influences of condition and run number on performance.

Behavioral effects of differing degrees of overlap. Individual critical hall accuracies and reaction times were separated into three factors represent-

ing the varying levels of overlap in a maze (one, two, or three overlapping hallways) and entered into a repeated-measures GLM analysis constructed to test for significant effects of the differing degrees of overlap on behavioral performance.

fMRI analysis

Overlapping versus non-overlapping analysis. Twenty-three separate regressors were created for each participant to model the fMRI data. Maze components were modeled based on their conceptually different cognitive experience. Separate regressors were created for the following eight elements in both conditions (for a total of 16): cue periods, first halls, main halls, single noncritical overlapping halls, double noncritical overlapping halls, critical overlapping halls, fifth halls, and ITI periods (see Fig. 5). To ensure the regressors captured the navigational decision process, each hallway regressor contained both the hallway period and the time at the subsequent intersection preceding the response.

Non-overlapping “counterpart” hallways were assigned to the critical and noncritical overlapping hall regressors because there were no actual overlapping halls in the non-overlapping condition. Non-overlapping critical and noncritical hallways were assigned such that each occupied the same position in the maze as its overlapping counterpart. The “main halls” regressors represented the non-overlapping hallways in each condition other than the first, fifth, and overlapping-counterpart halls. A 17th nuisance regressor was created to account for variance attributable to events and elements of noninterest (specifically, incorrect trials and feedback periods). Finally, the six motion parameters calculated during motion correction were added to the model as additional covariates of noninterest.

Regressors from the task were constructed as a series of square waves or “boxcars.” Boxcar onsets were defined by the onset of each event, with the length of each hallway boxcar being determined by the time to traverse each hallway (2.25 s) and the reaction time of participants for that particular trial. These parameters were convolved with the canonical hemodynamic response function in SPM5. The design matrix was then analyzed using the general linear model approach in SPM5.

The t contrasts between the overlapping and non-overlapping conditions for the seven modeled trial components (cue, first halls, main halls, critical halls, single overlapping halls, double overlapping halls, fifth halls) were constructed for each participant. Group-averaged statistical parametric maps (SPMs) were created by entering the overlapping greater than non-overlapping condition contrast images from each participant into a one-sample t test using participant as a random factor. The group SPMs were corrected for multiple comparisons across the whole brain using a false discovery rate (FDR) correction to a threshold of $p < 0.05$ with a voxel extent of 30.

Parametric modulation by degree of overlap. A separate parametric modulation analysis was conducted to test whether the degree of overlap between mazes modulated the BOLD responses in the critical halls. For this analysis, the data were modeled in the same manner as above, except critical halls were modeled separately for the three degrees of overlap. The critical hall signal was entered into a parametric modulation analysis to test for a linear relationship with overlap. We also directly compared the different degrees of overlap with t contrasts for the three pairings of critical hall types, to evaluate the possibility of a nonlinear difference between the three degrees of overlap.

Results

Behavioral data

Training data

Based on behavioral piloting, mazes were initially learned one at a time. We established a criterion of four consecutive perfect trials on each maze. Participants reached criterion with the non-overlapping mazes in an average of 5.31 trials with a SEM of 0.07. Similarly, participants took an average of 5.65 trials to reach criterion in the overlapping condition mazes (SEM, 0.13). After individually learning all 12 mazes, participants were given four training runs of the task. In each training run, they navigated all 12 mazes in a randomized, interleaved order to further familiar-

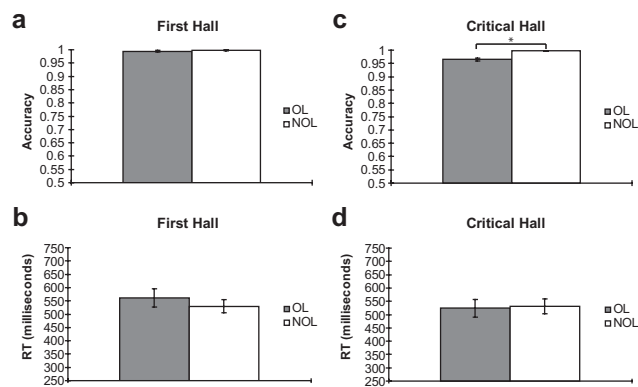


Figure 2. Scanning day behavioral performance. Error bars reflect the SEM. Significant differences are indicated with an asterisk. The OL condition is represented in gray, and the NOL condition is represented in white. **a**, Proportion of correct trials for the first hall period. **b**, Reaction times (RTs) in milliseconds for the first hall period. **c**, Proportion of correct trials for the critical hall period. **d**, RTs in milliseconds for the critical hall period.

ize participants with the mazes as well as expose them to the structure of the task used during scanning the following day.

fMRI behavioral data

Before scanning, participants were given a warm-up run of all 12 mazes in a randomized order. During scanning, participants navigated the first halls with no significant difference ($t_{(13)} = 1.47$; $p = 0.165$) in percentage accuracy between the overlapping condition (mean \pm SEM, 99.40 ± 0.28) and the non-overlapping condition (mean \pm SEM, 99.80 ± 0.14) (Fig. 2a). Reaction times (in milliseconds) did not differ significantly ($t_{(13)} = -1.89$; $p = 0.081$) between the overlapping condition (mean \pm SEM, 561.75 ± 34.05) and the non-overlapping condition (mean \pm SEM, 529.90 ± 25.10) (Fig. 2b).

Participants navigated the critical halls with near 100% accuracy in both the overlapping condition (mean \pm SEM, 96.51 ± 0.59) and the non-overlapping condition (mean \pm SEM, 99.70 ± 0.16), although these differences did reach statistical significance ($t_{(13)} = 6.28$; $p < 0.001$) (Fig. 2c). Reaction times did not differ significantly ($t_{(13)} = 0.26$; $p = 0.798$) between the overlapping condition (mean \pm SEM, 523.98 ± 32.83) and the non-overlapping condition (mean \pm SEM, 530.91 ± 27.54), and were comparable with those of the first hall period (Fig. 2d).

The results of the GLM analysis of reaction times across runs confirmed there was no significant difference between the reaction time slopes of the overlapping and non-overlapping conditions for either the first hall ($F_{(11,110)} = 1.37$; $p = 0.199$) or critical hall period ($F_{(11,110)} = 1.28$; $p = 0.245$). These data strongly suggest that overall changes in fMRI activity between the overlapping and non-overlapping mazes are not an artifact of differential effects of practice in the two conditions over time.

Behavioral effects of differing degrees of overlap

No significant effect of degree of overlap in the critical halls was observed for either accuracy ($F_{(2,22)} = 1.43$; $p = 0.868$) or reaction time ($F_{(2,22)} = 0.993$; $p = 0.387$). These results demonstrate that, in well learned routes, manipulating the degree of overlap before the critical halls did not significantly alter the difficulty of the critical hall choices.

Postscan interview

All 14 participants reported using the landmark objects to identify the hallways and aid in navigation of the mazes. All 14 partic-

Table 1. Significant areas of activation from the overlapping > non-overlapping contrast in the first hall period

Area	Left		Right	
	t value	MNI x, y, z	t value	MNI x, y, z
Posterior hippocampus (bilateral)	3.77	−18, −36, −2	4.04	18, −34, −2
Parahippocampal cortex (bilateral)	7.88	−28, −36, −22	5.83	24, −38, −18
Caudate (bilateral)	5.44	−8, 4, 12	4.33	12, 2, 12
Medial globus pallidus (bilateral)	5.08	−12, −4, −2	4.69	14, −2, −2
Lateral globus pallidus (right)	—	—	5.01	26, −14, −4
Thalamus (bilateral)	6.55	−12, −20, 14	6.44	10, −20, 14
Cingulate cortex (bilateral)	5.79	−4, 8, 52	5.92	10, 12, 50
Inferior frontal gyrus (bilateral)	8.89	−34, 48, 6	5.2	24, 56, −8
Inferior frontal sulcus (right)	—	—	4.59	38, 22, 26
Middle frontal gyrus (bilateral)	11.3	−30, −2, 54	6.57	36, 48, 26
Superior frontal sulcus (right)	—	—	11.83	26, 10, 54
Insular cortex (bilateral)	3.86	−30, 24, −2	5.81	36, 26, 0
Inferior temporal gyrus (bilateral)	8.12	−46, −66, −10	6.08	44, −62, −14
Fusiform gyrus (bilateral)	4.72	−28, −44, −12	8.64	28, −60, −14
Superior parietal lobule (left)	6.61	−26, −62, 54	—	—
Angular gyrus (bilateral)	10.01	−28, −76, 34	7.18	42, −70, 32
Precuneus (bilateral)	6.78	−6, −54, 54	8.29	12, −62, 56
Retrosplenial cortex (bilateral)	2.93	−10, −46, 2	5.68	8, −48, 2
Lingual gyrus (bilateral)	7	−12, −62, 2	11.97	6, −70, 2
Lateral occipital gyrus (bilateral)	4.43	−44, −76, 12	4.39	46, −76, 10
Cuneus (bilateral)	3.49	−4, −98, 2	7.15	10, −64, 18
Cerebellum (bilateral)	4.78	−30, −56, −30	5.07	36, −52, −32

MNI coordinates reflect cluster-center voxels. The t values reflect FDR correction to $p < 0.05$.

ipants also indicated that they identified the overlapping mazes and retrieved the appropriate critical hall decisions to reach the end of the mazes using the starting points (i.e., first halls). Participants indicated two strategies for correctly navigating critical halls in the overlapping condition. Nine of 14 participants reported their predominant strategy was to prospectively “think forward” by maintaining the starting hallway in their memory until the critical hall. The remaining five participants reported their predominant strategy was retrospective, and reported “remembering back” to where they began the maze to correctly navigate out of the critical hall.

fMRI data

Overlapping versus non-overlapping analysis

Critical to the experiment, the overlapping and non-overlapping conditions were closely matched in navigational demands, such that the only difference between the mazes was that some hallways were shared between paths in the overlapping condition. By comparing activity between the overlapping and non-overlapping conditions, we controlled for navigational features such as motor responses, visual flow attributable to simulated movement, and movement speed as contributing factors to our results. Direct comparison between the overlapping and non-overlapping experimental conditions revealed activity across multiple brain regions. All activations reported are FDR corrected to a statistical threshold of $p < 0.05$ with a voxel extent of 30. Significant differences in activation between the overlapping and non-overlapping conditions were restricted to the first hall and critical hall periods. We focus our report on the hippocampus, parahippocampal cortex, and orbitofrontal cortex because of their respective anatomical connections and their demonstrated roles in contextual and spatial mnemonic processing, and guiding flexible behavior.

First hall period

The starting points of the mazes (termed the “first halls”) were distinct, non-overlapping hallways in both the overlapping and non-overlapping conditions, and served to cue which path was to

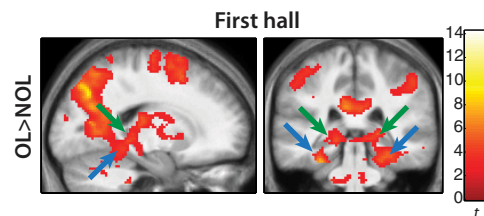


Figure 3. Medial temporal lobe activation during the overlapping first hall period. Statistical parametric map of the OL > NOL contrast for the first hall period. The image is FDR corrected to $p < 0.05$ with a voxel extent of 30. The green arrows indicate bilateral hippocampal clusters of activation. The blue arrows indicate bilateral parahippocampal clusters of activation.

be followed in a given trial. For a summary of all regions activated in the first hall period for the overlapping greater than non-overlapping contrast (OL > NOL), refer to Table 1. Of particular interest, the first halls of the overlapping mazes elicited significantly greater bilateral activity in the posterior hippocampus than the first halls of the non-overlapping condition (Fig. 3). Significantly greater bilateral activity in the parahippocampal cortex was also present for the OL > NOL contrast (Fig. 3). Greater activation in the hippocampus and parahippocampal cortex for the overlapping condition suggests these regions are particularly important for the retrieval of the starting locations (spatial context) and associated components in the spatial sequences when the maze representations must be kept separate from one another.

Critical hall period

The critical halls of the overlapping condition represented the final hallway of an overlapping segment, with the correct choice at the end of the hallway contingent on which overlapping maze was being followed. The critical halls of the overlapping mazes elicited significantly greater activity in the right posterior hippocampus and right parahippocampal cortex (Fig. 4a). There was also significantly greater bilateral activity in the orbitofrontal cortex for the OL > NOL contrast (Fig. 4b). These findings suggest that the hippocampus and parahippocampal cortex are impor-

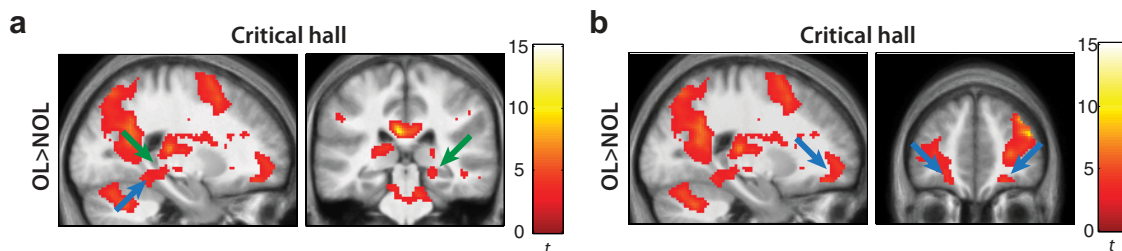


Figure 4. Greater activation in the critical hall period for overlapping mazes. *a*, Statistical parametric map of the OL > NOL contrast for the critical hall period. The image is FDR corrected to $p < 0.05$ with a voxel extent of 30. The green arrow indicates the right hippocampal cluster of activation. The blue arrow indicates the right parahippocampal cluster of activation. *b*, Statistical parametric map of the OL > NOL contrast for the critical hall period. The image is FDR corrected to $p < 0.05$ with a voxel extent of 30. The blue arrows indicate bilateral orbitofrontal clusters of activation.

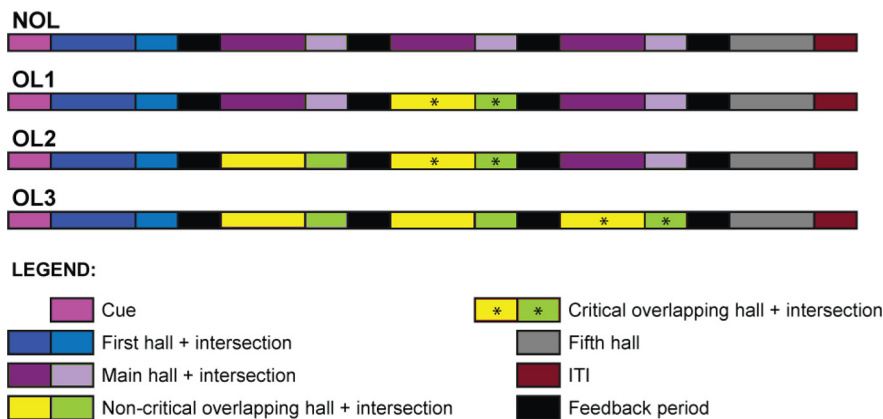


Figure 5. Breakdown of the individual components of the non-overlapping and overlapping mazes. The same colors denote comparable components across mazes (i.e., both the overlapping and non-overlapping mazes contain non-overlapping first halls). Note that the OL1 mazes only have one overlapping hallway, and therefore they do not have any noncritical overlapping halls.

tant for the retrieval of distinguishing features, such as the starting points of the mazes, and the associated series of hallways to support the critical hall choice. Additionally, greater activation in the orbitofrontal cortex for the critical halls of the overlapping condition suggests the orbitofrontal cortex is important for selecting the correct navigational response based on the contextual information and associations retrieved by the medial temporal lobes. For a summary of all regions activated in the critical hall period for the OL > NOL contrast, refer to Table 2.

Other hallways

We did not see any differences between the overlapping and non-overlapping conditions in any other hallways besides the first halls and critical halls. In particular, because the noncritical overlapping halls (Fig. 5) were directly associated with both mazes in the overlapping condition, this result suggests that differential activity in the first halls and critical halls is not an artifact of a perceived increased complexity of the overlapping environments, or a more general response to the presence of overlap regardless of whether a contextually dependent response is necessary.

Parametric modulation by degree of overlap

No significant modulation was found in the critical hall activity by the three degrees of overlap (Figs. 1, 5), either in the form of a linear trend or significant differences between critical hall types. These data, along with the finding that behavioral performance was equivalent across the three degrees of overlap, suggest that, in well learned representations, the flexible retrieval and response selection demands are the primary contributors to differential activity observed between the conditions. It may be that varying

levels of interference have more significance for these brain regions during the formation of new overlapping memories, when stable, orthogonal representations have not yet formed, but a subsequent study examining learning-period activity would be required to test this.

Other regions recruited

Along with hippocampal, parahippocampal, and orbitofrontal cortical activation, we also saw significantly greater activity during the retrieval of overlapping sequences in regions that have been shown to participate in visual, spatial, and mnemonic processing (Tables 1, 2). In particular, we observed medial parietal activity, including some retrosplenial cortical activation, for the first hall period. Retrosplenial involvement in the current task is

consistent with studies examining visualization, construction, and identification of complex visual scenes and spatial information (Burgess et al., 2001; Addis et al., 2007; Epstein and Higgins, 2007; Hassabis et al., 2007). Retrosplenial cortical activation, along with other medial and lateral parietal activations observed, may contribute to the successful disambiguation of overlapping spatial routes through explicit processing of visuospatial information necessary for the successful planning of the critical hall decision.

Discussion

When we navigate familiar routes in daily life, we typically begin with a goal, such as a need to go to the grocery store. Using this objective, we retrieve the route we must then follow. Theoretical models propose it is the context under which we are traveling (e.g., “I am going to the store for milk”) that we use to successfully navigate beyond points where the route overlaps with other routes we commonly follow (e.g., the route we take to work every day). Our experimental design allowed us to examine responses in the hippocampus, parahippocampal cortex, and orbitofrontal cortex, for distinct components of well learned overlapping mazes. Our fMRI results show increased activity in the hippocampus and parahippocampal cortex in the first halls and critical halls of overlapping mazes, when participants identify and retrieve the critical features of the current episode. The orbitofrontal cortex was specifically active during the critical halls, when participants need to use the context under which they are traveling to make correct navigational responses.

Table 2. Significant areas of activation from the overlapping > non-overlapping contrast in the critical hall period

Area	Left		Right	
	t value	MNI x, y, z	t value	MNI x, y, z
Posterior hippocampus (right)	—	—	3.44	22, -32, -8
Parahippocampal cortex (right)	—	—	4.73	18, -40, -12
Caudate (bilateral)	5.43	-8, 6, 16	6.1	14, 4, 14
Thalamus (bilateral)	4.84	-6, -6, 4	4.27	10, -8, -4
Orbitofrontal cortex (bilateral)	3.65	-20, 46, -16	4.52	22, 44, -14
Cingulate cortex (bilateral)	4.4	-10, 30, 22	7.71	6, 20, 44
Precentral sulcus (left)	6.78	-44, 2, 54	—	—
Inferior frontal sulcus (left)	11.44	-36, 30, 20	—	—
Middle frontal gyrus (bilateral)	4.6	-34, 48, 8	9.47	42, 46, 22
Superior frontal gyrus (right)	—	—	7.85	12, 12, 58
Superior frontal sulcus (left)	5.63	-24, 4, 60	—	—
Insular cortex (bilateral)	6.12	-32, 26, 0	7.91	34, 26, -2
Superior parietal lobule (left)	8.46	-36, -66, 48	—	—
Intraparietal sulcus (left)	12.77	-34, -52, 44	—	—
Angular gyrus (bilateral)	7.06	-30, -82, 34	8.02	36, -72, 42
Supramarginal gyrus (right)	—	—	5.88	46, -42, 46
Precuneus (bilateral)	10.72	-4, -70, 44	13.18	8, -66, 46
Lingual gyrus (bilateral)	9.01	-6, -70, 4	7.49	4, -72, 4
Cerebellum (bilateral)	9.22	-8, -76, -32	8.41	10, -72, -30

MNI coordinates reflect cluster-center voxels. The t values reflect FDR correction to $p < 0.05$.

First hall period

From the reports collected in the postscan interview, we found evidence that participants identified the mazes by the first halls with the help of the landmark objects and then retrieved the appropriate future critical hall decision necessary to reach the end of the maze. The first halls provided a spatial context indicating which route was to be followed, since the mazes always began in distinct locations. Such contextual information was necessary to correctly navigate the critical halls because the overlapping locations themselves provided no information indicating which route was currently being followed. Although the present design does not permit dissociation of the respective functions of the parahippocampal cortex and hippocampus, a large body of existing literature would strongly suggest distinct roles for these medial temporal lobe structures in supporting spatial disambiguation. The parahippocampal cortex is important for object identification and retrieval of spatial context (Epstein and Kanwisher, 1998; O'Craven and Kanwisher, 2000; Burgess et al., 2001; Bar and Aminoff, 2003; Hartley et al., 2003; Rosenbaum et al., 2004; Eichenbaum et al., 2007; Hasselmo, 2009). The strong bilateral parahippocampal cortex activations observed within the first halls of the overlapping mazes could correspond with the identification and retrieval of the spatial context reported by participants.

Once a maze was identified by its starting position, participants reported thinking ahead to the critical hall and retrieving the future navigational response that would be made to reach the end of that particular maze. The hippocampus has been shown to play a key role in the formation and retrieval of both higher-order and item–context associations (Kirwan and Stark, 2004; Ranganath et al., 2004; Eichenbaum et al., 2007; Staresina and Davachi, 2009), as well as sequences of information (Fortin et al., 2002; Schendan et al., 2003; Lehn et al., 2009; Ross et al., 2009). Ensembles of hippocampal place cells have been shown to fire sequentially along trajectories from an animal's physical location, which may be important for the association between distal locations (Diba and Buzsáki, 2007; Johnson and Redish, 2007; Davidson et al., 2009). Additionally, there is evidence in humans that the hippocampus is active during initial planning of navigational routes through familiar environments (Spiers and Maguire, 2006). In the present study, posterior hippocampal activity ob-

served in the first halls could support a sequential retrieval of visuospatial information linking contextual information provided by the starting location with the associated critical hall choice. Hippocampal lesions in humans generally leave representations for well learned environments intact (Teng and Squire, 1999; Rosenbaum et al., 2000), but impair retrieval of their most-detailed features (Rosenbaum et al., 2000) and impair navigation of more ambiguous or complex roadways (Maguire et al., 2006). Our results corroborate these findings, demonstrating significantly greater hippocampal activity when details supporting successful navigation of overlapping routes are retrieved compared with the general navigation of non-overlapping routes.

Critical hall period

There was no visual information within the critical halls of the overlapping condition to indicate the correct navigational response for any given trial; therefore, retrieval of the context under which participants were navigating was needed to discriminate between the overlapping routes. The parahippocampal and hippocampal activation seen in the critical hall period could underlie the retrieval of the starting hallway, which participants identified as the contextual cue indicating which route was to be followed, and the associated critical hall response.

In our study, the orbitofrontal cortex is bilaterally activated within the critical hall period. Of the three navigational choices at the end of the critical hall, two are equally rewarded over the course of the experiment. The anatomical connections of the orbitofrontal cortex are ideal for integrating perceptual information with contextual information to enable the navigator to select the correct response for a given trial. The orbitofrontal cortex receives input from every sensory modality (Barbas, 2000) and is anatomically connected with the hippocampus directly (Barbas and Blatt, 1995; Cavada et al., 2000; Cateñoix et al., 2005; Roberts et al., 2007) and through connections with the adjacent entorhinal and perirhinal cortices (Cavada et al., 2000; Kondo et al., 2005; Roberts et al., 2007). An emerging body of literature in both animals (Murray and Izquierdo, 2007; Kravitz and Peoples, 2008) and humans (Elliott et al., 2000; Frey and Petrides, 2002; Arana et al., 2003; O'Doherty et al., 2003; Caplan et al., 2007; LoPresti et al., 2008; Schon et al., 2008) suggests that the orbitofrontal cortex

processes contextual information and is important for promoting flexible behavior, guiding response selection, and the resolution of interference. One patient with a lesion that included the orbitofrontal cortex was unable to suppress habitual responses at intersections in favor of the correct direction, despite being able to recall the correct destination (Ciaramelli, 2008). In the present study, contextual information and the associated items retrieved in the medial temporal lobes could be used by the orbitofrontal cortex to flexibly select the correct response for execution in a given trial.

Together, our results suggest that the processes underlying spatial disambiguation may occur in several stages: an initial identification of the spatial context in the first hallway enables retrieval of the appropriate navigational responses to reach the present goal. When navigating the critical hall, the unique information identifying the episode is retrieved to allow navigators to select the appropriate direction and suppress the alternative response. Recent computational models predict that similar tasks might be solved by an initial retrieval of the sequence that is maintained in working memory until the choice point (Zilli and Hasselmo, 2008b), or, alternatively, retrieval of the necessary information is cued at the critical choice point itself (Zilli and Hasselmo, 2008a). Our results suggest that retrieval occurs at both points in the present task, in agreement with participants' verbal reports. It is possible that intervening intersections between the first halls and critical halls serve to disrupt the active maintenance of the starting location in working memory, encouraging the episodic retrieval strategy at the critical choice.

A central element of the disambiguation literature is that subjects are distinguishing between sequences of information. Although near 100% accuracy on all mazes in the present task demonstrates participants knew the elements of the spatial sequences very well, it is not possible to show that participants retrieved every element of a maze in each trial. Indeed, the retrieval of some elements of the maze might not be necessary for successful disambiguation in the critical hall. Participants explicitly reported recalling the first hall, the critical hall, and the correct hallway choice following the critical hall to reach the end of the path. Although it is possible that other elements of the maze were included in this retrieval (such as the final hall itself), given the overlearned nature of the overlapping mazes we suggest that the medial temporal lobe activity observed here is related to a more focal retrieval of episodic information relevant for the correct critical hall decision.

Conclusions

We provide evidence that, in well learned overlapping environments, recruitment of the hippocampus and parahippocampal cortex is specific to periods requiring the retrieval of features of the current navigational episode, and the orbitofrontal cortex is recruited specifically when there is a need to flexibly prepare and execute a contextually appropriate response. These findings are critical to our understanding of human navigation, as countless routes that we follow in our daily life have some degree of overlap with another route. Successful navigation of well learned routes in the real world often involves more than the simple execution of a habitual path, and requires the retrieval of contextual information to disambiguate the intended route from others with which it overlaps or intersects. We illustrate a pattern of activity recruited for the context-dependent retrieval of highly familiar routes in humans that includes brain regions shown to be critical for this behavior in parallel studies in animals.

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