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Cooperative interactions between hippocampal and striatal systems support flexible navigation

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Abstract

Research in animals and humans has demonstrated that the hippocampus is critical for retrieving distinct representations of overlapping sequences of information. There is recent evidence that the caudate nucleus and orbitofrontal cortex are also involved in disambiguation of overlapping spatial representations. The hippocampus and caudate are functionally distinct regions, but both have anatomical links with the orbitofrontal cortex. The present study used an fMRI-based functional connectivity analysis in humans to examine the functional relationship between the hippocampus, caudate, and orbitofrontal cortex when participants use contextual information to navigate well-learned spatial routes which share common elements. Participants were trained outside the scanner to navigate virtual mazes from a first-person perspective. Overlapping condition mazes began and ended at distinct locations, but converged in the middle to share some hallways with another maze. Non-overlapping condition mazes did not share any hallways with any other maze. Successful navigation through the overlapping hallways required contextual information identifying the current navigational route to guide the appropriate response for a given trial. Results revealed greater functional connectivity between the hippocampus, caudate, and orbitofrontal cortex for overlapping mazes compared to non-overlapping mazes. The current findings suggest that the hippocampus and caudate interact with prefrontal structures cooperatively for successful contextually-dependent navigation.

Keywords

fMRI; memory; hippocampus; caudate; human; disambiguation

1. Introduction

The brain's ability to retrieve distinct representations of overlapping information is a critical component of episodic memory and our daily lives. A classic example of what has been

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termed “disambiguation” is the ability to successfully navigate familiar overlapping routes. To avoid navigational errors, the brain must select the appropriate trajectory for the current context, despite interference from other overlapping paths. Models of episodic memory suggest the ability to retrieve specific episodes using contextual information is reliant on the hippocampus (Hasselmo and Eichenbaum, 2005; Zilli and Hasselmo, 2008). Research in both animals (Agster et al., 2002) and humans (Brown et al., 2010; Kumaran and Maguire, 2006; Ross et al., 2009) support a central role for the hippocampus in memory for overlapping sequences, and hippocampal neurons can uniquely code overlapping spatial trajectories using contextual information (Ferbinteanu and Shapiro, 2003; Lee et al., 2006; Smith and Mizumori, 2006; Wood et al., 2000).

While the context-dependent retrieval of mnemonic information is fundamental to disambiguation, navigation of overlapping spatial routes also requires the ability to select between alternative behaviors based on the current context. The orbitofrontal cortex and striatum are both important for the evaluation and selection of behavior, and the hippocampus may interact with these regions in support of the decision-making process (Johnson et al., 2007b). The orbitofrontal cortex is a critical structure for goal-directed behavior, and supports flexible response selection and suppression in animals (Murray and Izquierdo, 2007) and humans (Arana et al., 2003; Elliott et al., 2000; O'Doherty et al., 2003). Orbitofrontal neurons have been shown to encode both rewarding and aversive stimuli (Morrison and Salzman, 2009) and their firing patterns adapt to reflect changes in context (Kravitz and Peoples, 2008; Simmons and Richmond, 2008). The rodent orbitofrontal cortex codes for goal-directed paths and exhibits oscillatory coherence with the hippocampus during goal-directed navigation (Young and Shapiro, 2011). The caudate has received extensive attention in the literature as a cognitive region of the basal ganglia, supporting reasoning, behavioral planning, and shifts in response strategy in humans (Graham et al., 2009; Jankowski et al., 2009; Melrose et al., 2007; Monchi et al., 2001; Monchi et al., 2006). In rodents, the dorsomedial component of the caudate putamen has been implicated in behavioral flexibility (Ragozzino et al., 2002) and contributes alongside the hippocampus to the use of cognitive-spatial information in the water maze (Devan and White, 1999). Both the orbitofrontal cortex and caudate nucleus are more strongly recruited for the successful navigation of overlapping than non-overlapping mazes in humans (Brown et al., 2010). Together, the caudate and orbitofrontal cortex could utilize episodic information provided by the hippocampus to flexibly direct behavior.

There is emerging evidence that the hippocampus and caudate may function cooperatively during tasks which utilize processes attributed to each structure. The hippocampus and caudate have been shown to positively interact during transitive inference tasks where behavioral responses are tied to relational information about the stimuli (Moses et al., 2010). The hippocampus and caudate interact cooperatively during the traversal of cue-rich routes (Voermans et al., 2004), and lesions to the dorsomedial caudate putamen in rodents impair the use of spatial information in navigation, indicating a role for this area in the behavioral expression of hippocampal representations (Devan and White, 1999; Yin and Knowlton, 2004). Although the hippocampus and caudate can support competing strategies in spatial navigation (Bohbot et al., 2007; Hartley et al., 2003; Iaria et al., 2003; Iaria et al., 2008; Packard and McGaugh, 1996), they may cooperate to support spatial disambiguation because the successful navigation of overlapping routes requires the use of contextual signals to flexibly select between alternative behaviors.

The hippocampus and caudate do not share direct anatomical connections, but the primate orbitofrontal cortex receives direct projections from the hippocampus and sends direct projections to the medial caudate nucleus (Cavada et al., 2000; Haber et al., 2006; Roberts et al., 2007). The orbitofrontal cortex also receives widespread sensory input (Barbas, 2000)

and shares strong anatomical connections with reward circuitry including the amygdala and ventral striatum (Cavada et al., 2000; Haber et al., 2006; Roberts et al., 2007; Thierry et al., 2000), supporting its role in reward evaluation of stimuli. Therefore, the orbitofrontal cortex is anatomically positioned to interact with the medial caudate directly as well as indirectly via the ventral striatum. Taken together with previous functional research, the anatomical data suggest the orbitofrontal cortex might integrate sensory input and reward signals with episodic information from the hippocampus to support selection of contextually appropriate behavior by the striatum.

While activity in the hippocampus, orbitofrontal cortex, and caudate has been shown to increase for the navigation of overlapping routes (Brown et al., 2010), such results do not address whether these systems functionally interact in support of spatial disambiguation. In the present study, we tested whether the hippocampus and caudate interact cooperatively, antagonistically, or not at all during successful navigation of overlapping routes, and whether the hippocampus and caudate commonly engage with the orbitofrontal cortex during context-guided behavior. Using seed regions in the head, body, and tail of the hippocampus and the medial caudate nucleus, we contrasted a measure of functional connectivity for the navigation of well-learned overlapping mazes with that of non-overlapping mazes. We hypothesized that the hippocampus and caudate nucleus would have a cooperative functional relationship, becoming more strongly engaged with one-another on successful trials of well-learned overlapping mazes when flexible response planning and expression must be guided by contextual memory. Additionally, we hypothesized that the hippocampus and caudate would commonly engage with the orbitofrontal cortex in the overlapping mazes to support context-guided evaluation of changes in reward contingencies for alternative stimuli and behaviors.

2. Materials and Methods

2.1 Participants

The present study used data acquired from participants for a previous study examining univariate differences in fMRI activations related to spatial disambiguation in humans (Brown et al., 2010). Twenty-two participants (ages 19-31, mean age $\pm$ s.d.: 21.36 ± 3.43 ; nine male) with normal or corrected-to-normal vision were recruited from the Boston University community. Two participants were eliminated from the analysis due to excessive motion during scanning, four because of poor behavioral performance, and two because of signal drop-out 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.

2.2 Virtual Environments

Twelve virtual mazes (see Fig. 1a and b) were constructed using POV-Ray Version 3.6 (<http://www.povray.org/>), a 3D 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, Inc., Pittsburgh, PA). 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 which served as distinguishing features between the locations and were clearly identifiable and distinguishable from one another.

Participants began each maze at a unique starting location (termed the “first hall”) and traveled down each hallway to an intersection. There were four intersections per maze. Using a button box, participants could choose to turn left, right, or continue straight ahead at each intersection. 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 auto-piloted down that hall to the next intersection. The navigational responses at the end of the halls were counterbalanced across conditions.

The twelve 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 in which each route began and ended at distinct, non-overlapping locations, but converged in the middle to share one, two, or three hallways with the other maze (OL1, OL2, and OL3 pairs, respectively).

Navigational demands were matched between both conditions: all mazes were the same length and the number of left, right, and straight choices counterbalanced across the mazes and conditions (see also the Experimental Task section below). 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 due to spatial navigation alone, allowing us to examine changes in functional connectivity specifically related to processes supporting spatial disambiguation.

2.3 Feedback

After an incorrect choice at the end of a given hall, participants were turned in the selected direction, text reading “Wrong way” in red letters was overlaid on the scene, and a green arrow appeared indicating the correct direction. Participants were then rotated in the correct direction and sent down the correct hallway. To further control the timing of the task, participants were allowed a maximum of five seconds to respond at the end of each hallway. In the case of a “no response,” text reading “Respond” was overlaid on the scene and participants were provided with the same feedback arrows and correctional movement as with an incorrect response. “No response” trials were treated as incorrect for both the training and testing periods of the task. Error feedback was provided during all components of the study.

2.4 Pre-scan Training

Participants were trained to a criterion of 100% correct on all 12 mazes the day before scanning. Participants were initially guided by the experimenter through a sample pair of overlapping mazes (different from those used in the actual task) 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 from one-another. Participants were instructed to attend to the starting hallway as it was the cue for which maze they were following in a given trial, 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. Following individual training on all the mazes, participants performed four training runs in which all twelve 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 mazes and task contingencies.

2.5 Experimental Task

Participants were scanned the day after training took place. Before scanning, participants were given a warm-up run through all twelve 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 second instructional cue image, in which participants viewed the starting perspective of the first hallway of the maze without moving. Overlaid on the cue image were the instructions “Navigate to the end of the maze.” Following the instructional cue image, participants were automatically piloted down the unique starting hallway to the first intersection. At the intersection, participants responded with a button press of 1 to turn left, 2 to continue straight ahead, or 3 to turn right. Following a correct navigational choice, participants were automatically piloted down the next hallway to the subsequent intersection. Incorrect navigational choices were met with the feedback described above. Turns were made in two simulated steps, with each step incorporating 45 degrees 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, each hallway was always followed by the same navigational choice. 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” (Fig. 1a). 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 critical halls were constructed no differently 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 9 POV-Ray generated images, presented to participants as virtual steps in E-Prime. Each image was presented for 0.25 seconds, so that each hallway took 2.25 seconds to traverse. Following the navigational response at an intersection, translation or rotation through the intersection to the start of the next hallway took 1 second. 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 second inter-trial interval (ITI) in which participants viewed a fixation point in the center of a black screen.

2.6 Post-scan 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.

2.7 Image Acquisition

Images were acquired using a 3 T Siemens MAGNETOM TrioTim scanner (Siemens AG, Medical Solutions, Erlangen, Germany) with a 12-channel Tim Matrix head coil. Two high-resolution T1-weighted multiplanar rapidly acquired gradient echo (MP-RAGE) structural scans were acquired using generalized autocalibrating partially parallel acquisitions (GRAPPA) (TR = 2,530 ms; TE = 3.44 ms; flip angle = 7°; slices = 176, field of view = 256; resolution = 1 mm × 1 mm × 1 mm). Functional T2*-weighted BOLD images were acquired

using an echo planar imaging (EPI) 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.

2.8 fMRI Pre-Processing

Imaging analysis was conducted using SPM8 (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 gray and white matter images. The bias-corrected structural images and the coregistered BOLD images were spatially normalized into standard 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.

2.9 Behavioral data analysis

Separate paired-sample *t*-tests were used to assess differences in the fMRI task between the overlapping and non-overlapping conditions for percent accuracy and reaction time for the first halls and critical halls. Because the study was designed to assess functional connectivity effects in 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 less than 75% accuracy for that navigational choice).

Training participants to stable 100% performance on all mazes prior to scanning helped ensure that differential learning effects between the overlapping and non-overlapping conditions would not be a confound for interpreting the fMRI functional connectivity 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.

3. fMRI functional connectivity analysis

3.1 Seed regions and ROI definition

In this experiment we were interested in studying whether the hippocampus and caudate nucleus functionally interact with each other and the orbitofrontal cortex to support the successful navigation of overlapping mazes. There is growing anatomical, genetic, and functional data to suggest various cognitive and behavioral contributions of different hippocampal subcomponents along the anterior-posterior axis (Fanselow and Dong, 2010). Directly related to the present experiment, the posterior hippocampus has been implicated in the formation of non-spatial overlapping sequential memories (Kumaran and Maguire, 2006) and is active for disambiguation during retrieval of overlapping spatial memories (Brown et al., 2010). However, hippocampal regions throughout the anterior-posterior axis have been implicated in cognitive abilities used in the current task. Specifically, sequence processing activates hippocampal clusters ranging from the tail through the body to the anterior hippocampus (Lehn et al. 2009; Ross et al. 2009, Schendan et al., 2003). The anterior

hippocampus is important for spatial processing and flexible navigation (Bohbot et al., 2007; Hartley et al., 2003; Iaria et al., 2003; Wolbers et al., 2007) and interacts with the caudate during route recognition (Voermans et al., 2004). Anatomically, the hippocampal projections to the orbitofrontal cortex are distributed along the rostro-caudal extent of the hippocampus (Barbas and Blatt, 1995; Cavada et al., 2000; Roberts et al., 2007), providing the anatomical framework for potential hippocampal-orbitofrontal cortex interactions along the entire anterior-posterior axis of the hippocampus.

In summary, studies of overlapping sequence disambiguation (Brown et al., 2010; Kumaran and Maguire, 2006) predict posterior hippocampal functional interactions supporting spatial disambiguation, while sequence processing, navigation, and route recognition studies suggest the body and head of the hippocampus might show functional interactions during navigation of overlapping routes. Critically, task-related changes in functional connectivity can manifest differently from activations identified in traditional univariate analyses (e.g. disambiguation-related connectivity may localize to a different part of the hippocampus than disambiguation-related activation differences). Therefore, it remains an open question whether different regions along the rostro-caudal extent of the hippocampus contribute to spatial disambiguation through their pattern of functional connectivity. To better characterize which components of the hippocampus have disambiguation-related changes in functional connectivity, we created distinct seed regions in the head, body, and tail of the hippocampus. We placed our seed regions within these anatomical subdivisions (as defined by Pruessner and colleagues, 2000) using functionally-relevant coordinates implicated in sequence processing and navigation. We created seed regions in the left and right hippocampal tail using coordinates ($\pm 18, -36, 2$) derived from research examining the retrieval of overlapping and non-overlapping sequences (Ross et al., 2009). We created seed regions in the left and right hippocampal body using coordinates ($\pm 30, -24, -15$) from research examining explicit and implicit sequence learning (Schendan et al., 2003). We created seed regions in the left and right hippocampal head using coordinates ($\pm 24, -13, -20$) from a region supporting navigation using spatial information (Bohbot et al., 2007). The left and right caudate nucleus seed coordinates ($\pm 10, 4, 12$) were derived from a medial region active for planning switches in behavioral response strategy (Monchi et al., 2006). The seed regions were created in two steps: we initially created spherical regions of interest (ROIs) of 5 mm radius centered on the above coordinates using the Wake Forest University (WFU) Pick-Atlas (Maldjian et al., 2003) available for SPM. To minimize voxels residing in white matter, cerebrospinal fluid, and other brain areas from being included in our ROIs and adding noise to the functional data, the spherical ROIs were then masked by anatomical boundaries using an intersection between the 5 mm spheres and AAL structural delineations in the WFU Pick-Atlas. These anatomically constrained ROIs were then saved as masks to be used for the connectivity analyses (see Fig. 1c).

Left and right orbitofrontal ROIs were also defined for the extraction of correlation values (detailed in section 3.3). The coordinates for the orbitofrontal volume were derived from a region in which activation during encoding of visual stimuli predicts recognition memory ($\pm 25, 44, -11$) (Frey and Petrides, 2003). The orbitofrontal correlation extraction volumes were defined in the same manner as the connectivity seed region volumes – a 5mm radius sphere was created at the desired coordinates using the WFU Pickatlas, which was then masked to exclude white matter using an orbitofrontal anatomical mask created from the AAL orbitofrontal subdivisions.

3.2 Beta series correlation connectivity analysis

Functional connectivity analyses were conducted using the beta series correlation analysis method (Rissman et al., 2004). The beta series correlation method utilizes the univariate fMRI data analysis so that parameter estimates (betas) reflecting the magnitude of the task-

related blood oxygen level dependent (BOLD) responses are estimated for each trial. Therefore, the beta series correlation analysis requires that the individual trials of events examined in the functional connectivity analysis be modeled separately.

Our functional connectivity analysis was restricted to two key time periods of the task for which we had specific hypotheses: the first hallway cue period and the critical hallways. The individual trials for the first hall cue period and critical hall events were modeled separately with their own regressors for inclusion in the functional connectivity analysis. Because there were 72 trials per condition, a participant with 100% performance on the task would have 72 overlapping first hall regressors, 72 non-overlapping first hall regressors, 72 overlapping critical hall regressors, and 72 non-overlapping critical hall regressors to be entered into the beta series correlation analysis. Because there were no actual overlapping hallways in the non-overlapping condition, “counterpart hallways” were assigned to the overlapping hallway regressors for the non-overlapping mazes. Non-overlapping condition “counterpart hallways” were assigned such that each occupied the same position in the maze as its overlapping hallway counterpart in the overlapping condition.

There were 7 remaining distinct time periods of the task to be modeled: instructional cue images, second halls, non-critical single overlapping halls, non-critical double overlapping halls, fourth halls, fifth halls, and inter-trial interval (ITI) periods. To accurately capture the variance in the task, these 7 factors were each separately modeled with two regressors, one for all correct trials of the overlapping condition, and one for all correct trials of the non-overlapping condition (for a total of 14 regressors), similar to how they might be modeled for a traditional univariate fMRI analysis. The “second halls” and “fourth halls” regressors represented non-overlapping hallways of each condition in that sequential position (excluding overlapping hallways of those positions and non-overlapping condition hallways assigned to “overlapping counterpart hallway” regressors). A single nuisance regressor was created to account for variance due to error trials and feedback, and translation/rotation through the intersections. Finally, the six motion parameters calculated during motion correction were added to the model as additional covariates of non-interest. In total, a subject who made no errors would have a design matrix containing 309 regressors (288 for the beta series correlation analysis of the first hall and critical hall periods, and 21 regressors for remaining task components and noise sources). Because error trials were included in the nuisance regressor, the actual number of regressors varied slightly across participants.

To ensure the regressors captured the navigational decision process, each hallway regressor was modeled as a square wave beginning with the onset time of the first frame of the hallway, and terminating with the response time at the subsequent intersection. Each of the regressors was then convolved with the canonical hemodynamic response function in SPM8 for use in the functional connectivity analysis.

Collinearity between regressors for adjacent hallways was minimal (< 0.24), ensuring a high degree of discriminability between maze segments (e.g. signal in the critical hall is separable from that of its adjoining hallways). An important note is that regressors for the instructional cue image presentation and first hall cue period are correlated due to their temporal proximity. However, the instructional cue and first hall cue period regressors reflect components of the same “contextual cue” event, in that they both represent the same cue location and starting perspective of the environment. The stimulus features of first hall regressors are more similar to other maze components like the critical hall period because there is no instructional text overlaid on the screen and participants are in motion.

Parameter estimates were computed for each regressor using the least squares solution of the GLM in SPM8. Parameter estimates in SPM pertain to the orthogonal components of the

regressors. We made use of SPM's autoregressive AR(1) model during parameter estimation to help account for the effect of aliased biorhythms and other unmodeled signal sources. SPM8 also employs by default a 0.008 Hz high-pass filter during first level model specification to remove very slow drifts in signal over time. The parameter estimates for each trial of a condition of interest were strung together to form a "beta series". Parameter estimates with values above or below 2.5 standard deviations from the mean were considered outliers and excluded from the series correlation. The beta series correlation functional connectivity analysis relies on the assumption that the degree of similarity (correlation strength) between the fluctuations of parameter estimates across trials of two voxels serves as a metric of the functional interaction between the voxels (Rissman et al., 2004). Two brain regions may both significantly increase their activation, on average, across trials for a particular experimental manipulation, but still lack any coherence between their trial-by-trial responses to the task. Conversely, it is possible for a brain region to have significant task-dependent coherence across trials with another region, without necessarily increasing its average activity level. Using a custom MATLAB (MathWorks, Natick, MA) script generously provided by Dr. Jesse Rissman, we determined correlations of our respective seed regions' beta series with the beta series of all other voxels in the brain for the 1st hall and critical hall periods of both conditions. The beta series correlation analysis generates raw correlation (r) maps which are transformed into z maps using an arc-hyperbolic tangent transformation to allow statistical comparisons to be made between correlation magnitudes. For more details and validation of the beta-series correlation method, see Rissman et al., 2004. Group level random-effects statistical parametric maps (SPMs) for the four conditions of interest (first hall and critical hall periods of the overlapping and non-overlapping conditions) were constructed using the z -transformed correlation maps of each individual participant in SPM8.

3.3 Sign of functional correlations between regions of interest

Determining whether the correlations between the hippocampus, caudate nucleus, and orbitofrontal cortex were positive or negative was central to addressing our experimental hypotheses. A positive correlation can be viewed as a cooperative interaction, while a negative correlation is indicative of a competitive relationship. Correlation values were extracted from the raw correlation (r) maps using the Volumes Toolbox in SPM8 (<http://sourceforge.net/projects/spmtools/>). Correlation values were averaged across the voxels within the volumes of our regions of interest. Correlation values between the hippocampus and caudate were extracted from the a-priori defined caudate seed volumes for the respective hippocampal correlation maps. Correlation values with the orbitofrontal cortex were extracted from the respective hippocampal and caudate correlation maps using the a-priori defined orbitofrontal volumes described in section 3.1. To determine whether the correlations were significant, the average correlation values for each participant were entered into one-sample t -tests against zero for each interaction. Because of the large number of statistical comparisons in this analysis, we corrected for false-positives to $p < 0.05$ using Holm's sequential Bonferroni correction for multiple comparisons (Holm, 1979). The least stringent statistical threshold from the sequential Bonferroni correction for our data was $p < 0.00278$.

3.4 Overlapping vs Non-overlapping analysis

Group averaged Statistical Parametric Maps (SPMs) of functional connectivity differences for the overlapping greater than non-overlapping contrast were created by entering the overlapping and non-overlapping condition z -transformed correlation images from each participant into a paired-sample t -test using participant as a random factor. A voxelwise statistical threshold of $p < 0.01$ was applied to the between-condition connectivity maps. To correct for multiple-comparisons, we applied a cluster-extent threshold technique. We used

the AlphaSim program in the AFNI software package (<http://afni.nimh.nih.gov/afni/>) to conduct a Monte Carlo simulation analysis on the whole brain volume (masking out voxels outside the group functional brain space using the ResMS header file). From this analysis, a minimum voxel extent of 140 was determined to maintain a family-wise error rate of $p < 0.01$.

We observed significant disambiguation-related (OL>NOL) connectivity for both the hippocampus and caudate with the orbitofrontal cortex and anterior middle frontal gyrus in the critical hall period (see section 4.2.2). To test whether the hippocampus and caudate increased their connectivity with the same regions of the orbitofrontal and lateral prefrontal cortices, we conducted a post-hoc conjunction analysis. Using the caudate seed OL>NOL connectivity contrast maps, thresholded at $p < 0.01$ with a voxel extent of 140, we masked significant clusters of connectivity by the anatomical boundaries of the orbitofrontal cortex and the anterior lateral prefrontal cortex. We then used the anatomically restricted clusters of caudate connectivity in the orbitofrontal cortex and anterior middle frontal gyrus to mask the results of the hippocampal seed OL>NOL contrasts. Contrast maps for the hippocampal seeds were thresholded at $p < 0.01$, and the number of significant voxels, if any, present within the orbitofrontal cortex or anterior middle frontal gyrus volumes reflected the degree of overlap in disambiguation-related connectivity between the hippocampal and caudate seeds.

3.5 Connectivity differences across hippocampal ROIs

To test whether there were differences across hippocampal ROIs (head, body, and tail) in their connectivity with the caudate and the orbitofrontal cortex, we conducted a full factorial analysis in SPM8 with hippocampal ROI, condition (overlapping or non-overlapping), and hallway type (1st hall or critical hall) as factors. We examined the caudate and orbitofrontal cortex for a significant main effect of hippocampal ROI on connectivity, and significant interactions between any such effect with condition or hallway type. This connectivity analysis was conducted with the same statistical criterion used for our primary disambiguation-related connectivity contrast (a voxelwise statistical threshold of $p < 0.01$, with a cluster-extent correction to $p < 0.01$ of 140 voxels).

Following evidence for a significant main effect of hippocampal ROI in both the caudate and the orbitofrontal cortex (see results section), we conducted a series of post-hoc tests to determine which hippocampal subregions differed from one another in connectivity strength. Participants' z-transformed correlation images were entered into separate paired-sample *t*-tests between the hippocampal ROIs in SPM8 (Tail>Body, Body>Head, Tail>Head, and the reverse directions - Head>Body, Head>Tail, and Body>Tail). Applying the same statistical criterion used for the disambiguation-related connectivity and full factorial analyses above, we examined the caudate and orbitofrontal cortex for significant connectivity differences between the pairs of hippocampal ROIs.

4. Results

4.1 Behavioral Data

4.1.1 Training data—Based on behavioral piloting, mazes were initially learned one at a time. We established a criterion of 4 consecutive perfect trials on each maze. Participants reached criterion with the non-overlapping mazes in an average of 5.31 trials with a standard error (s.e.m.) of 0.07. Similarly, participants took an average of 5.65 trials to reach criterion in the overlapping condition mazes (s.e.m. = 0.13). After individually learning all 12 mazes, participants were given 4 training runs of the task (see Methods). In each training run, participants navigated all 12 mazes in a randomized, interleaved order to further familiarize

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

4.1.2 fMRI behavioral data—Prior to 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 percent accuracy between the overlapping condition (mean $\pm$ s.e.m.: 99.40 ± 0.28) and the non-overlapping condition (mean $\pm$ s.e.m.: 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 $\pm$ s.e.m.: 561.75 ± 34.05) and the non-overlapping condition (mean $\pm$ s.e.m.: 529.90 ± 25.10) (Fig. 2b).

Participants navigated the critical halls with near 100% accuracy in both the overlapping condition (mean $\pm$ s.e.m.: 96.51 ± 0.59) and the non-overlapping condition (mean $\pm$ s.e.m.: 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 $\pm$ s.e.m.: 523.98 ± 32.83) and the non-overlapping condition (mean $\pm$ s.e.m.: 530.91 ± 27.54), and were comparable to 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 suggest that overall differences in functional connectivity between the overlapping and non-overlapping conditions are not an artifact of differential effects of practice in the two conditions over time.

4.2 fMRI Connectivity Data

4.2.1 Sign of functional correlations—Although the hippocampus and caudate nucleus are components of dissociable memory systems in the brain, there is evidence that they function cooperatively in supporting behavior which relies on processes attributed to each structure. We hypothesized that the hippocampus and caudate would interact cooperatively during successful performance of our spatial navigation task, facilitating context-guided behavior. In support of our prediction, correlations between task-related signal changes in the hippocampus and the caudate in the first hall and critical hall periods of both conditions were significantly positive, suggesting a cooperative relationship between the hippocampus and caudate. Additionally, signal in both hippocampal and caudate ROIs was significantly positively correlated with orbitofrontal cortex signal in both the first and critical halls of both conditions. Correlation values were sequential Bonferroni corrected for multiple comparisons to $p < 0.05$ with a threshold of $p < 0.00278$. Significant correlation values between ROIs for all hallways and conditions are shown in Tables 1 and 2.

4.2.2 Disambiguation-related functional connectivity—Critical to the experiment, the overlapping and non-overlapping conditions were closely matched to control for navigational features such as motor responses, visual flow due to simulated movement, and movement speed as contributing factors to our results. All functional interactions reported are thresholded at the voxel level at $p < 0.01$ and corrected for multiple comparisons using a cluster extent threshold method. A complete list of significant connectivity differences between the overlapping and non-overlapping conditions is shown in Tables 3 and 4.

Hippocampal-striatal connectivity: Disambiguation-related (OL>NOL) changes in functional connectivity were observed between the hippocampus and the striatum in both the

first hall and critical hall periods of the task. The starting hallways of the mazes were distinct, non-overlapping hallways in both the overlapping and non-overlapping conditions, designed to cue the current route for participants. Despite identical response demands across conditions in the starting hallways, the left hippocampal head was significantly more strongly engaged with the right caudate nucleus in the first halls of the overlapping than the non-overlapping condition. Additionally, the right hippocampal body had significantly greater connectivity with bilateral portions of the caudate head and putamen in the first halls of the overlapping than the non-overlapping condition (Fig. 3a).

The critical halls of the overlapping condition represented the segment where overlapping mazes diverged from one another, with the correct direction at the end of the hallway contingent on which overlapping maze was being followed. The right hippocampal body was significantly more strongly connected with the head and body of the right caudate nucleus in the critical halls of the overlapping than the non-overlapping condition. The left hippocampal body also had significantly greater functional connectivity with the head of the right caudate nucleus in the critical halls of the overlapping condition. Finally, the left hippocampal tail had significantly stronger connectivity with the left caudate nucleus for this contrast (Fig. 3b).

Orbitofrontal connectivity: Disambiguation-related increases in functional connectivity with the orbitofrontal cortex were specific to the critical hall period for both the hippocampus and the caudate. The left hippocampal tail and body were both significantly more strongly connected with the right orbitofrontal cortex in the critical halls of the overlapping than the non-overlapping condition (Fig. 4a). Strikingly, the right caudate nucleus was also significantly more strongly connected with the right orbitofrontal cortex in the critical halls of the overlapping than the non-overlapping condition (Fig. 4b). The conjunction analysis revealed that disambiguation-related connectivity for the left hippocampal tail overlapped with that of the right caudate in the OFC by 30 voxels. The pattern of disambiguation-related functional connectivity for the left hippocampal body also overlapped with that of the right caudate in the OFC by 10 voxels.

Lateral prefrontal connectivity: In addition to the orbitofrontal cortex, the hippocampal and caudate seed regions shared disambiguation-related increases in connectivity with lateral prefrontal regions in the critical hall period. The left hippocampal body, right hippocampal tail, and right hippocampal body all significantly increased their functional engagement with the right anterior middle frontal gyrus in the critical halls for the overlapping greater than non-overlapping contrast. The right hippocampal body also had significantly greater functional connectivity with the right inferior frontal gyrus for this contrast (Fig. 5a). The left and right caudate nuclei were both significantly more strongly connected with the right anterior middle frontal gyrus in the critical halls of the overlapping than the non-overlapping condition (Fig. 5b). Similar to the orbitofrontal connectivity results, the conjunction analysis revealed that disambiguation-related connectivity for the left hippocampal body overlapped with that of both the left and right caudate by 14 voxels in the anterior middle frontal gyrus. The right hippocampal tail overlapped with the left caudate by 40 voxels, and with the right caudate by 30 voxels. The right hippocampal body did not overlap with the caudate in connectivity differences in the middle frontal gyrus.

Other disambiguation-related connectivity changes: Along with marked interactions between hippocampal subregions, the caudate, and orbitofrontal and lateral prefrontal cortices, we also observed significantly greater connectivity with our seed regions during the retrieval of overlapping spatial sequences in areas that have been shown to participate in visual, spatial, and mnemonic processing (see Tables 3 and 4). We observed elevated connectivity between the right caudate and retrosplenial cortex in the first hall period for the

overlapping condition. Retrosplenial involvement in the current task is consistent with an involvement in visualization, construction, and identification of complex visual scenes and spatial information (Addis et al., 2007; Burgess et al., 2001; Epstein and Higgins, 2007; Hassabis et al., 2007). Increased engagement of the caudate nucleus with retrosplenial cortex in the first hallways of the overlapping condition may reflect a use of orientation information or visualization of the critical hallway in planning the upcoming behavioral strategy. Similarly, connectivity between our seed regions and other visual areas may also reflect explicit processing of visuospatial information during planning and retrieval pertaining to the critical hall decision.

4.2.3 Connectivity differences across hippocampal ROIs—Our GLM analysis examining differences in connectivity across hippocampal ROIs (the left and right tail, body, and head) with the caudate and the orbitofrontal cortex revealed a significant main effect of hippocampal subregion. Post-hoc paired-sample *t*-tests revealed a striking posterior bias in functional connectivity, with posterior hippocampal regions tending to have a stronger functional relationship with the caudate and OFC than anterior hippocampal regions (i.e. Tail $\geq$ Body > Head) during navigation of well-learned spatial routes. This bias was most clear between right hippocampal subregions. Significant connectivity differences between hippocampal ROIs are summarized in Table 5.

There were no instances where anterior regions had greater connectivity than posterior regions with two exceptions: for the Body>Tail contrast the left hippocampal body had stronger connectivity than the tail with the left OFC in the 1st and critical halls of the overlapping condition. For the Head>Tail contrast, the left hippocampal head had stronger connectivity than the tail with the left OFC in both halls of the non-overlapping condition, and the critical halls of the overlapping condition (in a different orbitofrontal location than the primary Tail>Head difference).

Interestingly, the omnibus full factorial analysis did not show a significant interaction between experimental condition and hippocampal subregion. This suggests a more general bias in caudate and OFC interaction strength towards posterior hippocampal areas for our spatial sequence retrieval tasks. Although the omnibus full factorial analysis did not show a significant interaction between hippocampal ROI and condition, we did observe a greater number of disambiguation-related functional connectivity differences for hippocampal body and tail seed regions than the hippocampal head seeds (tables 3 and 4, and figures 3-5). The posterior bias of hippocampal functional connectivity is notable because the anatomical connections between the hippocampus and orbitofrontal cortex are densest in the anterior hippocampus in primates (Barbas and Blatt, 1995; Cavada et al. 2000). However, our results are consistent with posterior localization of hippocampal activity for learning and retrieval of both overlapping and non-overlapping sequences (Brown et al., 2010; Kumaran and Maguire, 2006; Ross et al., 2009) and the proposed roles for the posterior and intermediate hippocampus in navigational memory and the translation of such knowledge into motivation and action (Fanselow and Dong, 2010). Our data suggest functional interactions of the mid-posterior extent of the hippocampus may be particularly important for goal-directed navigation.

5. Discussion

It is understood that complex human behaviors emerge from the dynamic involvement of networks of brain regions. A crucial question is which neural systems interact to support a given behavior, and what is the nature of that interaction. Our experimental design allowed us to determine the nature of the functional relationship between the hippocampus, caudate nucleus, and orbitofrontal cortex during the traversal of two key components of well-learned

overlapping mazes. Our functional connectivity results show a significant cooperative relationship between the hippocampus, the caudate, and the orbitofrontal cortex in route navigation, and these regions become more strongly engaged with one another during successful navigation of overlapping mazes.

5.1 Hippocampal-striatal interactions

5.1.1 First hall (cue period)—Every maze began at a unique starting location, serving to cue which route was to be followed. Despite identical navigational response demands between the conditions in the first hall period, our connectivity results demonstrate that the hippocampus had significantly greater functional connectivity with the caudate and an anterior portion of the putamen in the overlapping than the non-overlapping condition. In the post scan interview, participants reported identifying the mazes by these first halls as well as “thinking ahead” to the future critical hall decisions in the overlapping condition. Successful planning of the critical hall decisions in first halls would require retrieval of the specific critical hall associated with the current route so that behavior can be planned within the possible response contingencies of that location.

In the present study, the hippocampus could support retrieval of critical hall locations from the starting hallway. The hippocampus is critical for the formation and retrieval of higher-order, item-context and sequential associations (Eichenbaum et al., 2007; Fortin et al., 2002; Kirwan and Stark, 2004; Lehn et al., 2009; Ranganath et al., 2003; Ross et al., 2009; Schendan et al., 2003; Staresina and Davachi, 2009). The ability of the hippocampus to “look ahead” or bind locations together is exemplified by sequential firing of ensembles of place cells along trajectories from an animal's location (Davidson et al., 2009; Diba and Buzsaki, 2007; Johnson and Redish, 2007a;). The hippocampus has also been shown to be recruited during initial planning of navigational routes through familiar environments in humans (Spiers and Maguire, 2006).

The evaluation of predicted future states and the ability to translate decisions into behavior are critical to the decision-making process, and these functions may lie in prefrontal and striatal circuitry (Johnson et al., 2007b). The caudate nucleus has received extensive attention in the literature as a cognitive region of the striatum. The caudate has been shown to support reasoning (Melrose et al., 2007), the planning of novel behavioral sequences (Jankowski et al., 2009), and cognitive shifts in response strategy due to changes in task rules (Graham et al., 2009; Monchi et al., 2001; Monchi et al., 2006). In rodents, the hippocampus and caudate-putamen exhibit strong oscillatory synchrony during the cue and immediately subsequent decision on a cued spatial alternation T-maze task (DeCoteau et al., 2007). Our experiment separated in time the cue presentation (first hall period) from the contextually-dependent behavior location (critical choice) by at least two intervening hallways and decision points. Our finding that the hippocampus and caudate show significant disambiguation-related functional connectivity during the contextual cue (first hall period) suggests a similar functional interaction occurs in humans, even when the contextually-dependent behavior location is not immediately present. Our findings correspond with participant reports of “looking forward” to the critical hall decision during the first hall period, and support the prediction that the hippocampus and striatum cooperate when planning navigation of the overlapping routes.

5.1.2 Critical hall (overlapping choice point)—In our experiment, the critical halls of the overlapping condition differed from the first halls in that there were two equally-rewarded highly familiar navigational response alternatives associated with each critical hall. There was no visual information within the overlapping critical halls to indicate the correct behavior for a given trial, therefore the context under which participants were

navigating was needed to guide the appropriate navigational response. Our results demonstrate significantly increased hippocampal functional connectivity with the caudate in the critical hall period of well-learned overlapping mazes. Consistent with our results, DeCoteau and colleagues (2007) show evidence in rodents for elevated oscillatory synchrony between the hippocampus and caudate-putamen at the overlapping decision point on a T-maze task. Selection of the contextually appropriate behavior, along with inhibition of the incorrect behavior, may be particularly important for navigation of overlapping critical halls, where visual input can cue both alternative trajectories. The basal ganglia are an inhibitory center of the brain, and may select behaviors through the disinhibition of the desired action coupled with inhibition of competing alternatives (Mink, 1996). As part of its role in flexible behavior shifts (Graham et al., 2009; Monchi et al., 2001; Monchi et al., 2006), the caudate is involved in response suppression (Boehler et al., 2010; Li et al., 2008). Cooperation between the hippocampus and caudate in the critical halls could enable planning and selection of the response associated with the current context and the suppression of the incorrect alternative.

5.2 Prefrontal interactions

There are no known direct anatomical connections linking the hippocampus and caudate in humans. However, the hippocampus and caudate are anatomically linked through other structures which may support interactions between the episodic memory and behavioral control systems. The prefrontal cortex has been suggested as a pathway by which the hippocampus and caudate interact (Burianova et al. 2009; Graham et al., 2009). Anatomically, the orbitofrontal cortex (OFC) is ideally situated for overseeing memory-directed flexible behavior. The OFC receives direct anatomical projections from the hippocampus (Barbas and Blatt, 1995; Cavada et al, 2000; Roberts et al, 2007), and sends projections to the entorhinal cortex, the gateway of information into the hippocampus (Cavada et al., 2000; Rempel-Clower and Barbas, 2000; Roberts et al., 2007). Therefore, the OFC can both receive and influence information processed in the hippocampus. Similarly, the OFC sends direct projections to the caudate nucleus (Cavada et al., 2000; Haber et al., 2006; Roberts et al, 2007) and, by virtue of cortico-striatal loops, the striatum can influence processing within the orbitofrontal cortex (Alexander et al., 1986; Middleton and Strick, 2002). Among prefrontal structures, the OFC is a unique site of convergence for sensory and reward information, receiving input from every sensory modality (Barbas, 2000) and sharing strong connections with the amygdala and the nucleus accumbens (Cavada et al., 2000; Roberts et al., 2007; Thierry et al., 2000). This distinct pattern of anatomical connections supports the functional role of the OFC in processing contextual information, flexible behavior, guiding response selection, and the resolution of interference (Arana et al., 2003; Caplan et al., 2007; Elliott et al., 2000; Frey and Petrides, 2002; Kravitz and Peoples, 2008; LoPresti et al., 2008; Murray and Izquierdo, 2007; O'Doherty et al., 2003; Schon et al., 2008; Young and Shapiro, 2011).

In the present study, we provide evidence that both the hippocampus and the caudate interact cooperatively with the orbitofrontal cortex in humans. Importantly, the hippocampus and medial caudate increase their engagement with a shared region of the OFC specifically during the critical hall component of our task, when contextual information is necessary for evaluating which alternate behavior will be correct on a given trial. Our findings provide a functional correlate of known anatomical connections between the hippocampus, caudate, and the OFC and support the hypothesis that the orbitofrontal cortex may serve as a common link between the hippocampus and caudate which facilitates goal-directed behavior. Interestingly, the hippocampus does have other anatomical paths through which it can interact with the striatum. Specifically, the hippocampus sends projections to the ventral striatum (Thierry et al. 2000) and the orbitofrontal cortex projects strongly to ventral striatal

areas (Haber et al., 2006; Roberts et al., 2007). The hippocampus also projects to the medial prefrontal cortex, which in turn projects to the striatum (Thierry et al., 2000; Roberts et al., 2007). It is critical to note that fMRI functional connectivity results cannot be attributed to specific anatomical pathways. Anatomical pathways through the ventral striatum and medial prefrontal cortex may facilitate cross-talk between the hippocampus and medial caudate in our experiment alongside direct projections from the orbitofrontal cortex to the medial caudate. However, because our data demonstrate increased hippocampal and caudate functional connectivity with the same region of the OFC during correct critical hall trials, but no such effects in the ventral striatum or medial prefrontal cortex, our results support a particularly important role for orbitofrontal cortex interactions in context-dependent navigation.

Another key finding in the present study was a common increase in functional connectivity for the hippocampus and caudate with an anterior portion of the middle frontal gyrus in the critical hall period for the overlapping condition. Anatomically, the lateral prefrontal cortex is connected with the caudate nucleus, but unlike the OFC, has very limited, if any, anatomical connectivity with the hippocampus proper (Barbas and Blatt, 1995; Haber et al., 2006; Roberts et al., 2007). However, lateral prefrontal areas do share connections with other medial temporal lobe subregions including the presubiculum, parasubiculum, entorhinal cortex, and perirhinal cortex (Barbas and Blatt, 1995; Roberts et al., 2007). There are also anatomical connections between the OFC and lateral prefrontal cortex (Cavada et al., 2000). Therefore, functional connectivity between the hippocampus and anterior middle frontal gyrus may result from indirect anatomical connections via other medial temporal lobe structures and the OFC, similar to the hippocampal-caudate connectivity we report. Rostral and dorsal lateral prefrontal areas have been associated with cognitive control and decision-making, with more anterior lateral prefrontal areas functioning on a more abstract or integrative level (Badre, 2008; Kuo et al., 2009; Ramnani and Owen, 2004). Lateral prefrontal areas are recruited during the receipt of ambiguous navigational information (Janzen and Jansen, 2010), and lateral frontopolar cortex supports cognitive set switching (Kim et al., 2011). Therefore, the anterior middle frontal gyrus may relate to the hippocampus and caudate more for the planning and cognitive control demands of the current task, while the OFC could more specifically support the contextually-based evaluation of the trial-by-trial changes in reward contingencies (Rudebeck and Murray, 2008; Tsuchida et al., 2010; Walton et al., 2010).

Measures of functional connectivity such as the beta series correlation analysis cannot indicate the direction in which information travels between brain regions. As described above, the anatomical connections linking the hippocampus and caudate with the orbitofrontal cortex are reciprocal. The existence of bidirectional connections between the OFC and the medial temporal lobes as well as reciprocal cortico-striatal loops suggests a complex interplay between these systems in support of flexible behavior. For example, the orbitofrontal cortex could integrate contextual input from the hippocampus while directing hippocampal place representations along the correct trajectory, as suggested by Young and Shapiro (2011). We suggest the present study could guide future research in animals, where simultaneous recording of neuronal activity within the hippocampus, caudate, and the prefrontal cortices could evaluate the temporal dynamics of the functional relationships demonstrated by the current fMRI results.

5.3 Relationship to other navigation studies

In navigation research, the hippocampus and caudate are often viewed as components of competing systems, with the hippocampus associated with the use of spatial information during navigation, while the caudate has been shown to support response-based navigation using local cues (Bohbot et al., 2007; Hartley et al., 2003; Iaria et al., 2003; Iaria et al.,

2008; Packard and McGaugh, 1996). We propose that the results of the present study are not in conflict with the “spatial” versus “response-based” experimental dichotomy, but rather extend our understanding of route navigation to the traversal of specific, cue-rich, well-learned routes which must nevertheless be guided by contextual information due to their overlapping nature. We build on prior evidence of a positive correlation between the hippocampus and caudate during traversal of navigational routes (Voermans et al., 2003) by demonstrating a dynamic increase in the cooperation between these two structures in supporting flexible, contextually-dependent response shifts in the overlapping mazes.

6. Conclusions

The navigation of highly-familiar routes in the real world often requires the use of contextual information to disambiguate the intended path from others with which it overlaps. We demonstrate that successful disambiguation of well-learned overlapping routes involves a cooperative interaction between the medial temporal lobe and striatal memory systems, congruent with the need for episodic information to guide the planning and execution of appropriate behavioral responses. The hippocampus and caudate both show disambiguation-related increases in connectivity with key prefrontal areas, particularly the orbitofrontal cortex, when there is a need to flexibly determine and execute a contextually appropriate response. These interactions are consistent with the proposed role of the prefrontal cortex as an anatomical and functional intermediary between the hippocampus and dorsal striatum. Our findings are critical to understanding flexible navigation in humans, demonstrating that successful disambiguation of overlapping trajectories involves a cooperative functional network comprised of the episodic memory system, frontal regions important for flexible decision-making and reward-evaluation, and the behavioral planning circuitry in the striatum.

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Figure 1.

Virtual maze design. (a) Overhead layout of the 12 mazes used in the task. The overlapping mazes (OL) are depicted on the left and the non-overlapping mazes (NOL) are depicted on the right. Mazes began at the “^” 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 during the turn into the fourth hall. This image is representative of how participants viewed the mazes. (c) Connectivity seed regions. The hippocampal head, body, and tail are indicated by red, green, and purple dots, respectively. Depictions of hippocampal seed locations are approximate, due to curvature of the structure. The seed regions in the medial caudate nucleus are shown in light blue.

Figure 2. Scanning day behavioral performance. Error bars reflect the standard error (s.e.m.). The overlapping (OL) condition is represented in dark gray, the non-overlapping (NOL) condition is represented in light gray. **(a)** Proportion of correct trials for the 1st hall and Critical hall periods. **(b)** Reaction times (RT) in milliseconds for the 1st hall and Critical hall periods.

Figure 3.

Changes in connectivity between hippocampal subregions and the striatum during 1st hall and Critical hall periods for the overlapping compared to the non-overlapping condition (OL > NOL). The images are thresholded to $p < 0.01$, corrected for multiple comparisons with a voxel extent of 140. The specific seed region is labeled above each connectivity map. The 1st hall period (**a**) had greater functional connectivity between the hippocampus and the caudate head and body (blue arrows), and the hippocampus and the putamen (green arrows). The Critical hall period (**b**) had greater functional connectivity between the hippocampus and the caudate head and body (blue arrows).

Figure 4.

Changes in connectivity for the hippocampus and caudate with the orbitofrontal cortex during the Critical hall period for the overlapping compared to the non-overlapping condition (OL > NOL). The images are thresholded to $p < 0.01$, corrected for multiple comparisons with a voxel extent of 140. The specific seed region is labeled above each connectivity map. The left hippocampus (a) and right caudate (b) had significantly greater connectivity with the orbitofrontal cortex.

Figure 5. Changes in connectivity for hippocampus and caudate with the lateral prefrontal cortex during the Critical hall period for the overlapping compared to the non-overlapping condition (OL > NOL). The images are thresholded to $p < 0.01$, corrected for multiple comparisons with a voxel extent of 140. The specific seed region is labeled above each connectivity map. The hippocampus (a) and caudate (b) had significantly greater connectivity with the middle frontal gyrus (blue arrows) and the inferior frontal gyrus (green arrows).

Table 1

Correlations for hippocampal seeds (columns) with the orbitofrontal cortex (OFC) and the caudate nucleus (Cd).

	Left hippocampus				Right hippocampus			
	Tail	body	head	tail	body	head	tail	head
Left OFC	1 st hall	NOL	0.27 (0.04)	0.27 (0.03)	-	0.29 (0.03)	0.24 (0.03)	0.19 (0.05)
	1 st hall	OL	0.21 (0.03)	0.3 (0.03)	-	0.25 (0.03)	0.24 (0.05)	-
	Crit hall	NOL	-	0.23 (0.04)	-	0.22 (0.05)	0.18 (0.04)	-
	Crit hall	OL	0.24 (0.04)	0.26 (0.04)	-	0.25 (0.03)	0.23 (0.05)	-
Right OFC	1 st hall	NOL	0.25 (0.03)	0.29 (0.03)	-	0.25 (0.03)	0.22 (0.03)	-
	1 st hall	OL	0.25 (0.03)	0.3 (0.03)	-	0.28 (0.03)	0.23 (0.04)	-
	Crit hall	NOL	0.18 (0.04)	0.22 (0.04)	-	0.20 (0.05)	0.19 (0.05)	-
	Crit hall	OL	0.27 (0.03)	0.23 (0.03)	-	0.26 (0.03)	0.22 (0.05)	0.14 (0.03)
	Left hippocampus				Right hippocampus			
	tail	body	head	tail	body	head	tail	head
Left Cd	1 st hall	NOL	0.36 (0.05)	0.33 (0.04)	0.26 (0.06)	0.35 (0.05)	0.26 (0.04)	0.22 (0.05)
	1 st hall	OL	0.4 (0.04)	0.34 (0.03)	0.27 (0.03)	0.39 (0.04)	0.3 (0.04)	0.27 (0.03)
	Crit hall	NOL	0.32 (0.06)	0.26 (0.03)	0.23 (0.04)	0.33 (0.04)	0.19 (0.04)	0.19 (0.05)
	Crit hall	OL	0.33 (0.04)	0.3 (0.04)	0.18 (0.04)	0.35 (0.05)	0.25 (0.05)	-
Right Cd	1 st hall	NOL	0.35 (0.05)	0.35 (0.04)	0.27 (0.05)	0.36 (0.05)	0.3 (0.03)	0.25 (0.05)
	1 st hall	OL	0.4 (0.04)	0.37 (0.04)	0.3 (0.03)	0.43 (0.04)	0.33 (0.04)	0.28 (0.03)
	Crit hall	NOL	0.32 (0.06)	0.28 (0.03)	0.25 (0.04)	0.34 (0.04)	0.21 (0.03)	0.21 (0.05)
	Crit hall	OL	0.34 (0.05)	0.33 (0.05)	0.19 (0.04)	0.4 (0.05)	0.27 (0.04)	-

All correlations shown are significantly greater than 0, corrected for multiple comparisons to $p < 0.05$ significance with Holm's sequential Bonferroni correction. Correlations are separated by rows into the hallway (1st hall or Critical hall) and condition (NOL – non-overlapping, or OL – overlapping). Each cell contains the average correlation followed by the standard error (s.e.m.) in parentheses.

Table 2

Correlations between caudate seeds (columns) and the orbitofrontal cortex (OFC).

			Left Caudate	Right Caudate
Left OFC	1 st hall	NOL	0.33 (0.03)	0.33 (0.02)
	1 st hall	OL	0.32 (0.03)	0.3 (0.02)
	Crit hall	NOL	0.35 (0.03)	0.32 (0.03)
	Crit hall	OL	0.34 (0.03)	0.3 (0.03)
Right OFC	1 st hall	NOL	0.25 (0.04)	0.29 (0.04)
	1 st hall	OL	0.3 (0.05)	0.27 (0.04)
	Crit hall	NOL	0.33 (0.04)	0.3 (0.04)
	Crit hall	OL	0.32 (0.05)	0.3 (0.04)

All correlations shown are significantly greater than 0, corrected for multiple comparisons to $p < 0.05$ significance with Holm's sequential Bonferroni correction. Correlations are separated by rows into the hallway (1st hall or Critical hall) and condition (NOL – non-overlapping, or OL – overlapping). Each cell contains the average correlation followed by the standard error (s.e.m.) in parentheses.

Table 3
Significant differences in functional connectivity for the overlapping > non-overlapping contrast in the First hall period

Seed region	Connected area	Left		Right	
		(<i>t</i> -value)	(MNI <i>x,y,z</i>)	(<i>t</i> -value)	(MNI <i>x,y,z</i>)
Right hippocampal tail	Supplementary motor cortex (bilateral)	4.18	-8, 14, 60	3.68	8, 12, 60
	Superior temporal sulcus (bilateral)	3.74	-52, -40, 0	-	-
	Insula body (bilateral)	5.01	-42, 8, 2	3.98	40, 6, -2
Left hippocampal body	Middle temporal gyrus (left)	6.61	-56, -66, 2	-	-
	Inferior temporal gyrus (left)	3.94	-52, -60, -10	-	-
	Caudate head (bilateral)	2.86	-12, 22, -6	3.25	16, 22, -8
Right hippocampal body	Putamen (bilateral)	3.09	-20, 18, -6	3.70	22, 20, -8
	Posterior inferior frontal gyrus (right)	-	-	3.76	50, 30, 0
	Supplementary motor cortex (bilateral)	4.03	-4, 10, 42	5.08	4, 6, 48
	Anterior insula (bilateral)	5.40	-32, 30, -4	5.14	36, 28, -4
	Posterior cingulate sulcus (bilateral)	4.24	-10, -38, 54	4.01	10, -38, 50
	Middle temporal gyrus (left)	6.24	-54, -66, 2	-	-
	Supramarginal gyrus (bilateral)	5.69	-60, -28, 24	6.53	60, -30, 30
	Intraparietal sulcus (right)	-	-	5.01	40, -42, 50
	Lateral occipital gyrus (left)	6.68	-44, -62, -12	-	-
Left hippocampal head	Caudate body (right)	-	-	3.95	18, 8, 20
	Middle temporal gyrus (right)	-	-	5.83	56, -66, 0
Right hippocampal head	Middle temporal gyrus (left)	5.10	-54, -64, 6	-	-
	Supramarginal gyrus (right)	-	-	4.34	64, -26, 34
Left caudate	Inferior frontal sulcus (bilateral)	4.18	-38, 32, 20	3.53	32, 36, 16
	Precentral gyrus (left)	4.44	-42, -6, 34	-	-
	Middle temporal gyrus (left)	3.70	-54, -70, 4	-	-
	Supramarginal gyrus (left)	4.52	-60, -30, 36	-	-
Right caudate	Inferior frontal sulcus (bilateral)	4.58	-34, 32, 20	3.92	32, 40, 18
	Middle temporal gyrus (bilateral)	4.88	-52, -70, 2	4.06	56, -64, -2

Seed region	Connected area	Left		Right	
		(<i>t</i> -value)	(MNI x,y,z)	(<i>t</i> -value)	(MNI x,y,z)
	Retrosplenial cortex (right)	-	-	3.22	20, -56, 12
	Post-central gyrus (bilateral)	4.86	-56, -12, 32	4.85	62, -10, 34
	Calcarine fissure (left)	4.14	-10, -66, 10	-	-
	Lingual gyrus (left)	4.28	-10, -60, -2	-	-
	Lateral occipital gyrus (right)	-	-	5.70	48, -68, -14

*MNI coordinates reflect cluster-center voxels. *t*-values reflect a statistical threshold of $p < 0.01$. Functionally connected areas survived cluster-threshold correction for multiple comparisons to $p < 0.01$ with a minimum cluster size of 140 voxels

Table 4
Significant differences in functional connectivity for the overlapping > non-overlapping contrast in the Critical hall period

Seed region	Connected area	Left		Right	
		(<i>t</i> -value)	(MINI x,y,z)	(<i>t</i> -value)	(MINI x,y,z)
Left hippocampal tail	Caudate body (left)	2.87	-16, 16, 16	-	-
	Orbitofrontal cortex (right)	-	-	3.87	28, 38, -6
	Anterior inferior frontal gyrus (right)	-	-	4.08	36, 46, 0
	Anterior insula (right)	-	-	4.99	38, 16, -2
	Cuneus (right)	-	-	3.35	14, -68, 18
	Cerebellum (left)	3.53	-10, -72, -20	-	-
Right hippocampal tail	Anterior middle frontal gyrus (right)	-	-	5.02	30, 52, 8
	Cingulate sulcus (bilateral)	5.57	-14, -24, 48	4.42	18, -24, 46
	Cerebellum (right)	-	-	4.74	22, -44, -30
Left hippocampal body	Caudate head (right)	-	-	3.72	12, 24, -2
	Orbitofrontal cortex (right)	-	-	2.69	28, 38, -6
	Anterior middle frontal gyrus (right)	-	-	2.95	34, 46, 18
Right hippocampal body	Caudate head (right)	-	-	3.34	12, 24, 0
	Caudate body (right)	-	-	3.36	18, 4, 24
	Anterior inferior frontal gyrus (right)	-	-	4.65	34, 50, -2
	Anterior middle frontal gyrus (right)	-	-	5.94	34, 56, 24
	Premotor cortex (bilateral)	4.95	-20, 6, 66	5.51	18, 8, 64
	Supplementary motor cortex (bilateral)	5.17	-2, 6, 56	4.84	4, 10, 46
	Pre-central sulcus (bilateral)	4.74	-30, -66	4.05	34, -6, 62
	Anterior insula (right)	-	-	3.67	44, 8, -8
	Intraparietal sulcus (left)	5.61	-26, -50, 50	-	-
	Cerebellum (bilateral)	4.61	-44, -58, -36	4.10	44, -66, -30
Left hippocampal head	Hippocampal body (left)	3.36	-36, -24, -14	-	-
	Hippocampal tail (left)	2.89	-28, -38, 0	-	-
Right hippocampal head	Supramarginal gyrus (left)	3.77	-62, -42, 34	-	-

Seed region	Connected area	Left		Right	
		(<i>t</i> -value)	(MNI x,y,z)	(<i>t</i> -value)	(MNI x,y,z)
Left caudate	Anterior middle frontal gyrus (right)	-	-	3.56	26, 44, 6
	Posterior cingulate (bilateral)	4.85	-4, -32, 32	3.58	4, -34, 28
	Anterior insula (bilateral)	3.57	-32, 18, 10	3.48	38, 16, 4
	Parieto-occipital sulcus (bilateral)	4.50	-12, -66, 28	4.16	16, -66, 28
	Cuneus (right)	-	-	3.90	4, -84, 28
Right caudate	Orbitofrontal cortex (right)	-	-	3.77	26, 42, -6
	Anterior middle frontal gyrus (right)	-	-	4.04	30, 48, 8
	Anterior insula (bilateral)	3.24	-32, 18, 0	4.31	38, 20, -2
	Intraparietal sulcus (right)	-	-	4.60	32, -52, 38
	Parieto-occipital sulcus (bilateral)	3.96	-14, -64, 26	4.02	14, -66, 30
	Cuneus (right)	-	-	3.36	4, -82, 26
	Thalamus (bilateral)	4.62	-4, -6, 8	3.47	6, -14, 14

*MNI coordinates reflect cluster-center voxels. *t*-values reflect a statistical threshold of $p < 0.01$. Functionally connected areas survived cluster-threshold correction for multiple comparisons to $p < 0.01$ with a minimum cluster size of 140 voxels

Significant differences between hippocampal subregions in their connectivity with the caudate nucleus (Cd) and orbitofrontal cortex (OFC).

Table 5

Contrast	Condition	Left Hippocampal Seeds				Right Hippocampal Seeds			
		Cd		OFC		Cd		OFC	
		Left	Right	Left	Right	Left	Right	Left	Right
Tail>Body	NOL	1 st				+			
		—							
		Crit				+			
	OL	1 st				+		+	+
		—							
		Crit							+
Body>Head	NOL	1 st	+	+	+	+	+	+	+
		—							
		Crit	+	+	+	+			
	OL	1 st	+	+	+	+	+	+	+
		—							
		Crit	+	+	+	+	+	+	+
Tail>Head	NOL	1 st	+		+	+	+	+	+
		—							
		Crit				+		+	+
	OL	1 st	+			+	+	+	+
		—							
		Crit	+	+	+	+	+	+	+

Columns under the hippocampal seed headings indicate significant connectivity differences between hippocampal subregions with the left and right Cd and OFC. Significant connectivity differences between hippocampal regions are denoted with a “+”. Connectivity differences were significant at a statistical threshold of $p < 0.01$, surviving a cluster-threshold correction for multiple comparisons to $p < 0.01$ with a minimum cluster size of 140 voxels.