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Evidence for a gradient within the medial temporal lobes for flexible retrieval under hierarchical task rules

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Abstract

A fundamental question in memory research is how the hippocampus processes contextual cues to retrieve distinct mnemonic associations. Prior research has emphasized the importance of hippocampal–prefrontal interactions for context-dependent memory. Our fMRI study examined the human medial temporal lobes (MTL) and their prefrontal interactions when retrieving memories associated with hierarchically organized task contexts. Participants learned virtual object–location associations governed by subordinate and superordinate task rules, which could be independently cued to change. On each fMRI trial, participants retrieved the correct object for convergent rule and location contextual information. Results demonstrated that hippocampal activity and hippocampal–prefrontal functional interconnectivity distinguished retrieval under different levels of hierarchically organized task rules. In explicit contrast to the hippocampal tail, anterior (body and head) regions were recruited specifically for superordinate changes in the contextual hierarchy. The hippocampal body also differed in its functional connectivity with the prefrontal cortex for superordinate versus subordinate changes. Our findings demonstrate a gradient in MTL for associative retrieval under changing task rules, and advance understanding of hippocampal–prefrontal interactions that support flexible contextual memory.

KEYWORDS

fMRI, hippocampus, human, memory, parahippocampal, prefrontal

1 | INTRODUCTION

Task rules, goal states, and other contextual factors, can be particularly salient for memory retrieval and adaptive behavior. Considerable research has been dedicated to the hierarchical organization of task rule information in the human and nonhuman primate prefrontal cortex (Badre, 2008; Badre & D'Esposito, 2009; Christoff et al., 2009; Kim et al., 2011; Taren et al., 2011). A growing body of research in both animals and humans suggests the medial temporal lobes (MTL) are critical for retrieval of unique associations for the current context, even in the face of interference from overlapping representations (Brown et al., 2010; Brown & Stern, 2013; Fortin et al., 2002; Hasselmo & Eichenbaum, 2005; Hasselmo & Stern, 2014; Zilli & Hasselmo, 2008). Prefrontal interactions have been implicated in

hippocampal-dependent episodic and spatial memory, and planning from memory (Brown et al., 2012, 2016, 2020; Navawongse & Eichenbaum, 2013; Spiers & Gilbert, 2015). However, surprisingly limited research has targeted the intersection between task rule memory, as a contextual construct, and context-dependent hippocampal retrieval in humans.

The hippocampus and its posterior parahippocampal inputs play a fundamental role in processing situational information and contexts, and thus linking mnemonic traces to such states (Ranganath & Ritchey, 2012; Ritchey et al., 2015). Task structures may be represented not just within prefrontal cortex, but also as hierarchical associative “schemas” within the hippocampus (McKenzie et al., 2014), such that the MTL's role in context processing could enable retrieval from (a) *direct* associations between specific perceptual inputs and a unique

memory, as well as (b) convergent cues (task rule, location, etc.) that represent the contextual state associated with a specific memory trace. Therefore, while prefrontal mechanisms may support maintenance of ongoing task rules or goals to guide behavioral selection, prefrontal interactions with the MTL may also be critical for accessing memories for higher-order task contexts and the retrieval of specific associations to accomplish a task. How the human hippocampus supports episodic retrieval within different levels of control hierarchies processed by prefrontal cortex (Badre & D'Esposito, 2009; Badre & Nee, 2018) remains an open question.

If the human hippocampus represents memories within a hierarchical contextual structure (McKenzie et al., 2014), one prediction would be that the hippocampus will be more active for gating context-dependent memory retrieval (Brown, Hasselmo, & Stern, 2014; Hasselmo & Eichenbaum, 2005) when contexts higher in the associative hierarchy change (*activation gradient*). In this theoretical framework, more global contextual cue changes could drive an increasing number of associations for different events to be partially activated. Data also suggest the hippocampus codes for spatial contextual information at a larger/more global scale in the ventral than the dorsal hippocampus (analogous to anterior/posterior axis in humans; Fanselow & Dong, 2010) (Evensmoen et al., 2013, 2015; Komorowski et al., 2013). This has led researchers to theorize that the anterior human hippocampus may code for more global or "coarse" contexts and representations (Poppenk et al., 2013) than the hippocampal tail. In keeping with evidence in rodents and humans (Brown et al., 2012; Brunec et al., 2018; Evensmoen et al., 2013, 2015; Fanselow & Dong, 2010; Komorowski et al., 2013; Sekeres et al., 2018), superordinate and subordinate contextual changes may fall along an anterior-posterior functional gradient. Therefore, another prediction is that more anterior regions of the hippocampus support retrieval based on contextual information of more global scale in a hierarchy (*topographical gradient*), being relatively insensitive to "smaller scale" contextual shifts compared to the tail.

The present study tested these gradient predictions, and examined how the human hippocampus interacts with the prefrontal cortex to support contextual retrieval under changing task rules. Specifically, we designed an fMRI experiment in which healthy young participants were required to flexibly retrieve one of several competing associations for locations in a virtual environment during fMRI scanning. The experiment was designed to examine how context-dependent retrieval activity relates to *changes* in contextual information, and whether the magnitude of activity tracks how global the contextual change is. Task rules were organized hierarchically, such that contextual cues on each trial indicated whether a global task context, subordinate task context, or no task context, had changed. These manipulations allowed us to examine hippocampal-prefrontal contributions to contextual memory at different levels of a contextual hierarchy, and draw connections between our examinations of episodic memory retrieval in the MTL and theories about the organization of the prefrontal cortex (Badre & D'Esposito, 2009; Badre & Nee, 2018) underlying behavioral flexibility.

2 | MATERIALS AND METHODS

2.1 | Participants

Twenty participants with normal or corrected-to-normal vision were recruited from the Boston University community. Two participants were eliminated from analysis, one due to technical issues with the scanner, and one because of poor behavioral performance. Therefore, data from 18 subjects (ages 18–26, mean age \pm SD: 20.89 \pm 2.05; 11 females, 15 right-handed) were used. 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 environment

The contextual memory task was performed using a virtual environment modeled after that used in similar tasks in rodents (McKenzie et al., 2014; Navawongse & Eichenbaum, 2013). Specifically, the environment comprised one hallway connecting two rooms (Figure 1(a)). Each room contained two objects, presented concurrently, that participants would select between on each trial. The correct object on a given trial was selected on the basis of the location and convergent contextual information (described in detail below). The environment was set in a virtual valley, surrounded by distal mountains. The unique shape of the mountains from different perspectives in the environment allowed participants to recognize in which room the current trial was taking place (e.g., "this trial is in the North end of the environment") (Figure 1(b)). The objects were newspaper vending machines, and were rendered in red, blue, green, or yellow paint, and contained either a newspaper, or Time, Fashion, or Sports magazines. This content was clearly identifiable and visible within the boxes (Figure 1(b)). The virtual environment was constructed using POV-Ray Version 3.6 (<http://www.povray.org/>), a 3D ray-tracer modeling program. During the scanning task, participants selected the appropriate object in the different locations from a ground-level first-person perspective and response data were recorded using E-Prime 2.0 (Psychology Software Tools, Inc., Pittsburgh, PA).

2.3 | Experimental task

2.3.1 | General task structure

The experiment was designed to examine how context-dependent retrieval activity relates to *changes* in contextual information, and whether this activity reflects how "global" the contextual change is. To address this aim, we designed the task imposing a hierarchical contextual/associative memory structure on the environment, analogous to that in highly similar study in rodents which motivated this work (McKenzie et al., 2014). Participants first underwent extensive prescan training to enable the learning of the mappings between

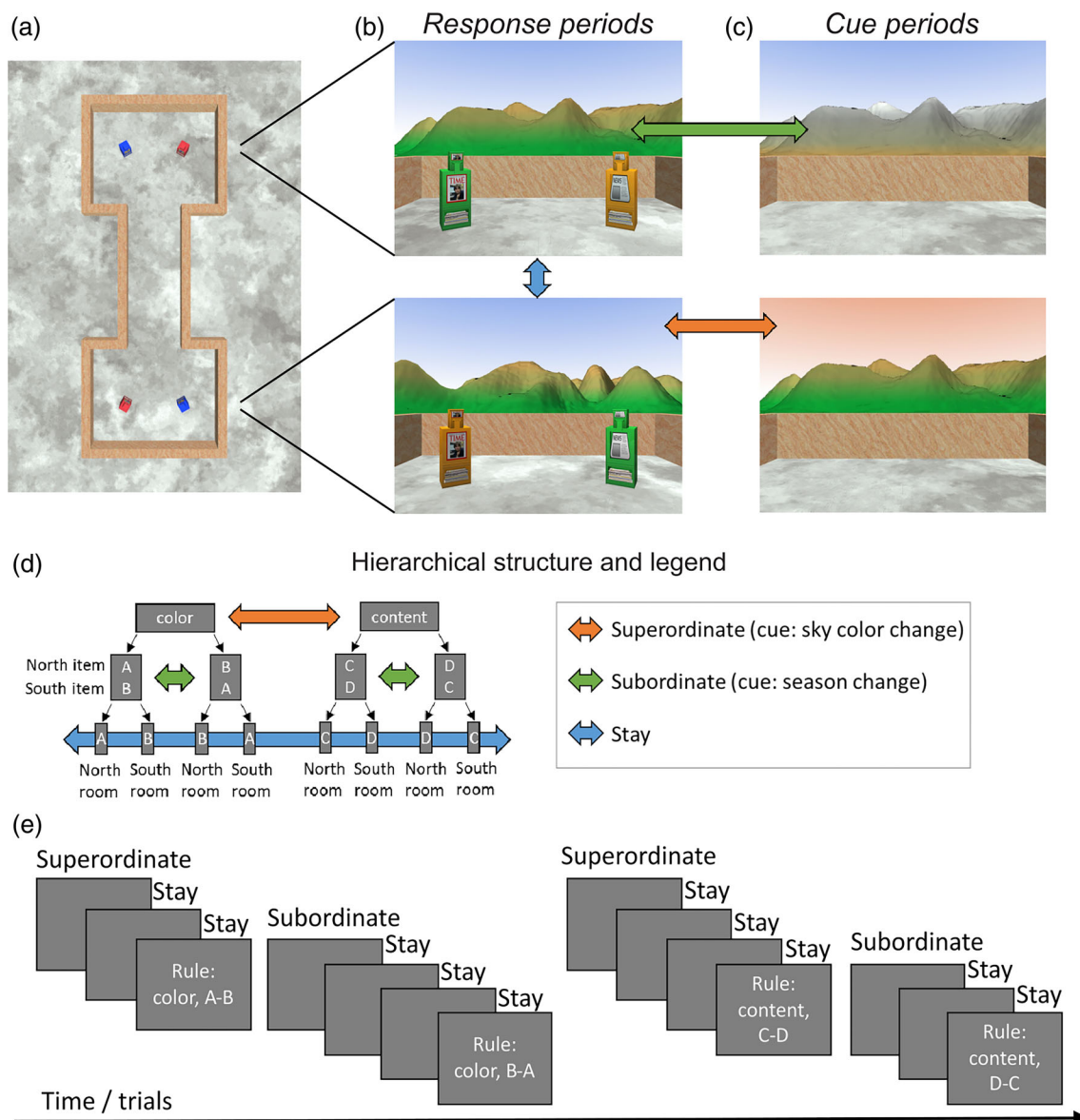


FIGURE 1 Task design. (a) Overhead view of virtual testing environment. On each testing trial, participants chose between one of two objects in the north or south room of the environment. (b) First-person view of example response periods in the north (top frame) and south (bottom frame). (c) Prior to the objects appearing, participants viewed only the contextual cues guiding retrieval: the location, and any changes in season (top frame from b to c) or sky color (bottom frame from b to c). Trials in which neither season nor sky changed were “stay” trials (top to bottom frame in b; note that if a location changed, as shown here, the correct item would alternate [e.g., choose the newspaper instead of the magazine]). Trials in which the season changed were subordinate changes (green arrow; this signaled a remapping of which stimulus was correct in the North and South locations). Trials in which the sky color changed were superordinate changes (orange arrow; this signaled a shift in the correct dimension of the item to retrieve [e.g., switch from retrieving the correct content to the color of the box]). All fMRI analysis were restricted to cue periods. (d) Illustration of the hierarchical structure. For example, a superordinate change might signal participants to retrieve the correct color box, selecting color A in the North and B in the South. After several stay trials a subordinate change would signal a switch to retrieving color B in the North and A in the South. After several more stay trials, another superordinate would signal participants to select content D in the North and C in the South (note that subordinate contingencies never changed during a superordinate, so the season cue carried over from the prior strategy’s trials until another subordinate occurs). (e) Illustration of the hierarchical structure over time—in this example, an initial superordinate switch is followed by two stay trials before a subordinate switch from A in the North and B in the South to B in the North and A in the South. After three stay trials, a superordinate switch occurs changing the higher-order rule to box content, and so on

specific item representations, spatial locations, and two higher-level task rules/contingencies. The task structure branched at the highest level between two “global”/superordinate task rules: (1) retrieve the

correct color vending machine associated with this location (termed the “color strategy”) or (2) retrieve the vending machine content associated with this location (termed the “content strategy”). Critically,

nested within this highest level of task context, was a subordinate task contingency (referred to as a subordinate contingency; described in detail under “task details” below). The task structure branched at this level into two subordinate associations between specific item features and locations (North of South ends of the environment; Figure 1(a)). As such, a global/superordinate task rule was associated with four item-location associations, a subordinate contingency was associated with two item-location associations, and location within a specific set of these two governing task contingencies was associated with one unique item feature (see Figure 1(d) for a visualization of this structure).

This design allowed us to separately manipulate, at retrieval (scanning task), the highest level of the contextual hierarchy (superordinate task rule retrieval) and subordinate, intermediate-level task rule contexts that ultimately combine to govern which specific item feature was correctly associated with a specific location. Given the putative importance of the hippocampus for context-gated retrieval of specific memory traces (Hasselmo & Eichenbaum, 2005), and hierarchical structure of task “schemas” in rodents (McKenzie et al., 2014), these manipulations allowed us to test whether the human hippocampus is more active for context-dependent gating and retrieval when contexts higher in the associative hierarchy, with a greater number of associations for specific item-location events, change. Furthermore, this design enabled us to examine hippocampal–prefrontal contributions to contextual memory at different levels of a contextual hierarchy.

2.3.2 | Detailed information about condition and contextual cues

Participants learned the task ~24 h prior to scanning (training is described in detail in the prescan training section below). During subsequent scanning, participants performed a conditional discrimination where, for a given convergent set of task rules, one object out of a pair was the correct choice in the North room, and the other object would be the correct choice in the South room (transition between top and bottom panels of Figure 1(b), blue arrow). The experiment was designed using “naturalistic” cues that govern behavioral choices in the real world.

During the scanning task, the superordinate level of the contextual hierarchy (color vs. content global strategy) was periodically cued to change (see Figure 1(e) for a snapshot of trial structure over time). These “superordinate” change trials were cued by changes in the sky color (taught to participants as “changes in the time of day”) (transition from bottom panels of Figure 1(b,c), orange arrow). There were three different sky colors resembling early dawn, mid-day, and dusk. Participants learned during prescan training that whenever the sky color changed, they needed to switch to the alternate retrieval strategy. Critically, participants were never guessing during the scanning task, nor was there a learning component. Participants knew, from prescan training, the associations between task contexts and the specific item features, such that when participants were given a “starting strategy” at the beginning of a scan run, they could accurately

perform the task and translate any subsequent sky color changes into a successful strategy shift (see behavioral results below).

Within a given superordinate strategy, the subordinate level of the contextual hierarchy comprised “subordinate” change trials where the correct choice (e.g., color) for a location reversed depending on changes in snow-coverage on the background mountains (transition from top panels of Figure 1(b,c), green arrow). To be explicit, nested within the superordinate context, subordinate changes reflected trials where participants would switch from picking feature A in the North and B in the South, to B in the North and A in the South (the opposite item-location associations). Note that we refer to the superordinate and subordinate rule change events as “superordinate” and “subordinate” conditions throughout.

Participants were instructed to pay very close attention to the environmental background, because they needed to process the convergence of the time of day, season, and location cues in order to retrieve the correct associate on each trial. No one unique combination of background perceptual features deterministically signaled a specific choice on any trial. The cycling of three times of day (sky color) was a critical feature of the task design: without this implementation (i.e., if instead one sky color always mapped to one strategy), the hierarchical associative structure to the task could lose significance for behavior, because instead of participants needing to retrieve and maintain the current task rules, and engage in context-gated retrieval of the correct item association for each trial, performance on each trial of any condition could reduce to a simple pattern-completion of a unique percept-item association. Thus, this design feature encouraged participants to process the changing task rules on a deeper cognitive level rather than selecting unique scene-item associates in a more proceduralized fashion. Therefore, while the specific *perceptual* configuration was not associated with specific memories, the convergent cues signaled a specific contextual state associated with a specific memory trace, such as may be expected in many real-world retrieval scenarios.

Prior to the beginning of each run of the scanning task, participants were explicitly instructed what the starting strategy would be, so that they could interpret the starting sky color/time of day appropriately. Because superordinate changes were singular events, the high degree of performance on these trials (and all conditions) underscores the fact that, despite removing a deterministic association between a specific sky color and a strategy, participants were able to process and maintain their current task state in order to engage in context-guided retrieval.

The superordinate and subordinate levels of change in the contextual task rule hierarchy occurred with equal frequency during scanning, with one change following the other every two to three trials. The intervening trials composed the “stay” condition, which served as a baseline level of the contextual hierarchy (i.e., no rule change) for our analyses. The number of stay trials following superordinate changes and subordinate changes was balanced. The blocks of three to four trials for a given combination of task rules (the initial superordinate or subordinate trial plus the subsequent stay trials) encouraged participants to get into a “cognitive set” before a task rule changed

again. This allowed us to distinguish mnemonic activity for simple conditional discriminations *within* a task rule (stay trials) from retrieval involving a higher-level contextual change.

An important feature of our experiment was the use of repeating, familiar stimuli that had learned associations with specific contextual states. This required participants to engage in context-dependent retrieval of specific information to guide behavior, as opposed to rule-based selection of novel stimuli independent of mnemonic significance. We pseudorandomized on which side of the room the two alternative stimuli appeared in a given trial (equal proportions across the experiment). Randomized pairings of the individual box colors and contents across trials of a given strategy prevented participants from selecting vending machines based on stimulus features relevant to the other strategy.

Importantly, if identical stimuli were used for the color and content strategies, some superordinate trials could suffer interference from the previously chosen (although now irrelevant) stimulus feature, which would impose “reversal”-like cognitive demands. To ensure a clean distinction between superordinate and subordinate trials, a different set of stimuli was used for the color and content strategies (red and blue boxes vs. green and yellow, and sports and fashion content vs. time and news, respectively).

2.3.3 | Run and trial details

Within the scanner, participants performed five runs of the experiment. During each run, participants performed 15 global/superordinate and 15 subordinate trials (with two to three stay trials between each rule change as described above). Therefore, participants performed 75 trials per rule change condition and ~375 stay trials. Run order was randomized across subjects. Prior to the beginning of each run, participants were presented text on a black screen indicating what the starting global strategy (color or content) would be for that run.

At the beginning of each trial, participants appeared in one of the rooms (pseudorandomly assigned to ensure an equal number of trials in the North and South rooms). Each trial began with a variable 2–4 s cue period, during which participants were able to view the critical contextual background information (mountains, season, time of day), but the vending machine objects were hidden. Participants were encouraged to recognize the current context and prospectively retrieve the correct stimulus during this period. Our analyses focused on the contextual cue processing period. Following the cue period, the objects would then appear in the scene for a 2–4 s maximum response period, during which participants selected the correct object with a button box press of 1 or 2 depending on whether the desired object appeared on the left or right side of the room. No error feedback was provided during the scanning task (the associations were very well-learned, such that errors were rare and not attributable to learning). A 2-s intertrial interval (ITI) followed the response period, providing additional separation between subsequent cue events. During the ITI, participants were shown a fixation point in the center of a

black screen. These timing parameters were selected based on pilot data that ensured effects associated with subsequent cue periods were separable. Accuracy and reaction times were recorded for each choice made. The exact timing of behavioral responses as well as the image presentation was logged in E-Prime to allow accurate modeling of the task.

2.3.4 | Prescan training

Participants learned the task ~24 h prior to the scanning experiment. Training was broken into four runs. Two runs were dedicated to learning the associations nested within one strategy at the highest level of the contextual hierarchy, and two were dedicated to the other (i.e., color and content). Runs were presented in an interleaved manner to each participant (e.g., color Run 1, content Run 1, color Run 2, content Run 2). Which strategy was learned first was randomized across participants. Within each run, participants learned the two subordinate contingencies in blocks (i.e., the first half of the trials in a run was dedicated to one contingency, and the other half of the trials to the other contingency). The task was broken down in this manner to help participants understand the mechanics of the task and learn the item-context associations within the hierarchical structure of the task design. Similar to the scanning task, participants were assigned a starting superordinate strategy for the first run (color or content), placed in one of the rooms, and given a cue period followed by a response period. The correct item-context associations were learned organically through feedback for their choices. Feedback entailed overlaying “Correct!” or “Incorrect” on the scene (in blue or red lettering, respectively) immediately following a response.

After receiving feedback for their choice, participants underwent simulated navigation down the hallway into the other room. Simulated alternation between the North and South rooms ensured participants learned the spatial locations as distinct components of one integrated environment, and encouraged binding the North and South item associations as components of the same subordinate contingency. Note that during the scanning task participants did not alternate and were instead pseudorandomly placed in one of the familiar locations on each trial to encourage additional vigilance to the background contextual cues (as described above). Each training run contained 40 trials (20 with each subordinate context). At the start of the next training run, the sky color would be different, signaling a superordinate change to the contextual rule hierarchy (color/content change), and participants would learn the associations of the alternate strategy.

2.4 | Image acquisition

Images were acquired at the Athinoula A. Martinos Center for Biomedical Imaging of the Massachusetts General Hospital in Charlestown, MA, using a 3 Tesla Siemens MAGNETOM TrioTim scanner with a Siemens 32-channel matrix head coil. High-resolution T1-weighted multiplanar rapidly acquired gradient echo structural

scans were acquired using generalized autocalibrating partially parallel acquisitions (TR = 2530 ms; TE = 3.31 ms; flip angle = 7; FOV = 256; slices = 176; resolution = 1 mm isotropic). T2*-weighted BOLD images were acquired using an echo-planar imaging sequence (TR = 2000 ms; TE = 30 ms; flip angle = 85; FOV = 216; slices = 32, resolution = 3.0 × 3.0 × 4.0 mm). Functional image slices were aligned along the anterior/posterior commissure line.

2.5 | fMRI preprocessing

Imaging analysis was conducted using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). 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. Motion correction was conducted, including realigning the BOLD images to the first functional image acquired and unwarping the BOLD images to correct for movement-by-susceptibility artifact interactions (Andersson et al., 2001). The high-resolution structural images were coregistered with the mean BOLD image obtained during motion correction, segmented into white and gray matter images, and bias-corrected. The bias-corrected structural images and BOLD images were spatially normalized into standard Montreal Neurological Institute space using the diffeomorphic anatomical registration using Exponentiated Lie algebra algorithm for improved intersubject registration (Ashburner, 2007). BOLD images were resampled during normalization to 2 mm³ isotropic voxels and spatially smoothed using a 6 mm full-width at half-maximum Gaussian kernel.

3 | DATA ANALYSIS

3.1 | Contextual rule change activity analyses

Twelve separate regressors were created for each participant to model the fMRI data. The task was modeled based on conceptually distinct cognitive experiences; separate regressors were created for the cue periods and response periods of each condition (superordinate, subordinate, and stay trials). We created two sets of cue period and response period regressors for stay trials: one for stay trials that followed subordinate events (Stay_sub), and one for stay trials that followed superordinate events (Stay_sup).

The ITIs were modeled with an 11th regressor, and a 12th nuisance regressor was created to account for variance due to events and elements of noninterest (specifically, incorrect trials). Explicit inclusion of the ITI was conceptually important for the fit of our model. Due to the relatively rapid timing of the paradigm, we considered that modeling the ITIs between events could help improve the accuracy with which variance from the preceding response period, the ITI, and the subsequent cue period (potentially from a different task rule condition) was attributed to the correct cognitive event. Finally, the six motion parameters calculated during motion correction were added to the model as additional covariates of no interest.

Regressors from the task were constructed as a series of square waves or “box-cars.” Box-car onsets were defined by the onset of each event, with the length of each cue period box-car being determined by its variable duration for each trial (2–4 s). These parameters were convolved with the canonical hemodynamic response function in SPM8. The design matrix was then analyzed using the general linear model approach in SPM8.

To address the core question of which regions support context-dependent retrieval under hierarchical task rule changes, T-contrasts between the three conditions were constructed for the cue periods in SPM8. Superordinate changes and subordinate changes were contrasted with their counterpart stay trials (Stay_sup and Stay_sub regressors, respectively). Group averaged statistical parametric maps (SPMs) were created by entering the contrast images into a one-sample *t*-test treating participant as a random factor. Analyses were conducted in a whole-brain mask, with voxelwise statistical thresholds of $p < .001$. To limit the occurrence of spurious clusters, we applied a cluster-extent threshold (k) of 162 to maintain a family wise error rate of $p < .05$, calculated using a 10,000 simulation Monte Carlo analysis in the latest version of 3dClustSim leveraging ACF (for the AFNI software package—<http://afni.nimh.nih.gov/afni/>).

These contrasts allowed us to test for a systematic increase in recruitment of the hippocampus and prefrontal regions as hierarchical contextual changes increase gated retrieval demands (superordinate > subordinate changes > stay trials). They also allowed us to test predictions from rodent work about functional organization along the rostrocaudal axis of the hippocampus in humans. Specifically, if hippocampal regions anterior to the tail represent more global or higher-level contexts, we would predict these areas to respond comparably for retrieval during stay and subordinate trials (because both trial types require item-level retrieval *within* a higher-level task rule—e.g., vending machine color), and increase activity selectively for retrieving the contingencies and associations when the highest level task contexts change (superordinate trials).

3.1.1 | Conjunction/exclusion activity analyses

To gain leverage on which brain regions are sensitive to the different processing demands of the three conditions, we also examined the contrasts in conjunction and exclusion analyses. Specifically, we masked activations to those common for context-dependent retrieval when task rule contexts change (superordinate > stay and subordinate > stay), and activity that exceeded our statistical threshold specifically when the highest level of the contextual hierarchy changed (superordinate > stay, excluding subordinate > stay). We quantified “superordinate-specific” activity by examining superordinate > subordinate activity within that subordinate > stay-exclusive mask.

3.1.2 | ROI activity analyses

We conducted anatomical ROI-based analysis to explicitly test for regional differences in the degree to which activity in hippocampal regions is sensitive to different degrees of change in task rule context. We extracted mean parameter estimates from the anatomically defined a priori hippocampal

tail and body ROIs used for our connectivity analysis (see below), and used linear mixed-effects modeling in R (R Development Core Team, 2012), to conduct a repeated-measures analysis testing for main effects of region (tail vs. body), condition (stay, subordinate, superordinate), and hemisphere, and region \times condition, region \times hemisphere, condition \times hemisphere, and region \times condition \times hemisphere interactions. Participant was included as the random intercept with random slopes by participant included for region, condition, and hemisphere. Significant interactions between hippocampal region and condition would be indicative of the relationship between rule change and hippocampal activity differing between the tail and the more-anterior delineation of the body. The directionality of significant region \times condition interactions were then characterized by follow-up paired-sample *t* tests. It was of interest to further examine such effects within the hippocampal head, which is anatomically more distal from the tail and may exhibit even greater functional differentiation from the tail than the body does (Fanselow & Dong, 2010). In this study, our scanning parameters (which were designed to balance tradeoffs in signal between MTL and key prefrontal regions such as orbitofrontal cortex), yielded signal dropout in the hippocampal head. Because signal in the anatomical head ROI would be influenced by noise in our data, we excluded the head from our seed-based analyses, and interpret activity in this region with caution—interestingly and importantly; however, we did observe significant differences in the expected direction in the hippocampal head in the voxels surviving SPM's signal strength thresholding (see, e.g., Figure 4).

3.2 | Functional connectivity analysis

To examine whether hippocampal–prefrontal connectivity increases to support context-dependent memory under changing task rules, we used the beta series correlation technique (Rissman et al., 2004). In order to generate the beta-series, we modified the model used for the primary univariate analysis above to obtain betas for individual cue period trials of the superordinate, subordinate, and Stay_sup and Stay_sub events. Because there were two to three stay trials, pseudoblocked, for each subordinate or superordinate, we subsampled one stay trial from each set, such that Stay_sub and Stay_sup regressors had a comparable number of trials (75) to those in the subordinate and superordinate regressors. The subsampling was pseudorandom—because it is possible that switch costs could persist to some degree into the first stay trial, our procedure randomly selected a second or third stay trial (should a third trial be present) per mini block. The remaining stay trials were modeled with two additional cue and response period regressors. Parameter estimates with values above or below 2.5 SDs from the mean were considered outliers and excluded.

Because of our interest in potential functional differences along the rostrocaudal axis of the hippocampus, we defined separate seed regions for this analysis in the left and right hippocampal tail and body—subregions we have shown in a related task (Brown et al., 2012) to have distinct connectivity profiles from each other that support context-dependent retrieval (we excluded the hippocampal head from this analysis, where signal susceptibility in some voxels would limit the ability to quantify interregional correlations). The

hippocampus was manually subdivided using ITK-SNAP (Yushkevich et al., 2006) into tail, body, and head volumes based on established anatomical landmarks (Pruessner et al., 2000).

Using a custom MATLAB (MathWorks, Natick, MA) script generously provided by Dr Jesse Rissman, we calculated correlations between our respective seed regions' trial-by-trial betas and those of all other voxels in our search volume. *z*-Transformed correlation (*r*) maps were created using an arc-hyperbolic tangent transformation to allow statistical comparisons to be made between correlation magnitudes. Group level random-effects SPMs for the three conditions of interest were constructed using the *z*-transformed correlation maps of each individual participant in SPM8. As with the principal univariate activation analysis above, we directly contrasted functional connectivity maps of our hippocampal seed regions for superordinate changes, subordinate changes, and their corresponding stay trials. Due to different underlying autocorrelation/smoothness from the activation analyses, the critical whole-brain cluster-extent threshold (*k*) determined by the simulation analysis was 53 to maintain a family wise error rate of $p < .05$.

4 | RESULTS

4.1 | Behavioral data

Participants performed at a very high level across the three conditions during the scanning task. Accuracies for the response period of the three conditions were 97.1% (stay trials, *SD* 0.03), 93.3% (subordinate changes, *SD* 0.05), and 94.7% (superordinate changes, *SD* 0.06). Reaction times for the response period were 845.2 ms (stay trials, *SD* 152.4), 945.9 ms (subordinate changes, *SD* 200.9), and 1077.7 ms (superordinate changes, *SD* 252.0). We directly compared accuracies and reaction times between the three conditions using paired samples *t* tests. stay trials accuracies were higher than those of subordinate changes and superordinate changes ($t_{(17)} = 4.874, p = .0001$; $t_{(17)} = 3.370, p = .0036$), but accuracy did not differ between the rule switch conditions (subordinate > superordinate: $t_{(17)} = -1.490, p = .1545$). Reaction times were longer for superordinate changes than subordinate changes ($t_{(17)} = 4.957, p = .0001$) and stay trials ($t_{(17)} = 7.255, p = 1.0 \times 10^{-6}$), and longer for subordinate changes than stay trials as well ($t_{(17)} = 4.846, p = .0002$). These results confirm desired ceiling-level accuracy on the task, while also validating desired behavioral switch costs for the cognitive demands of our hierarchical task structure (superordinate > subordinate > stay).

4.2 | fMRI data

4.2.1 | Activity increases with the scale of contextual change

We have previously delineated a broad network of brain regions supporting context-dependent spatial memory (Brown et al., 2010, 2012; Brown & Stern, 2013). The results of the present study demonstrate that components of these networks increase activity for

context-dependent item retrieval as higher levels of the contextual hierarchy changes. The complete pattern of regions is summarized in Table 1 (subordinate > stay), Table 2 (superordinate > stay), and Table 3 (superordinate > subordinate).

Critically, the results supported our prediction that activity in the hippocampus increases with the hierarchical level of the contextual changes, such that superordinate > subordinate > stay in the hippocampal tail (Figure 2).

A similar pattern of activity was observed in parahippocampal cortex, consistent with a role in processing both spatial (Brown et al., 2010; Brown, Hasselmo, & Stern, 2014; Brown & Stern, 2013) and nonspatial context (Turk-Browne et al., 2012). We also observed a similar pattern in the middle frontal gyrus and caudate nucleus, components of a frontostriatal network also implicated in distinguishing between alternative memories in humans (Brown et al., 2010, 2012; Brown & Stern, 2013).

An explicit conjunction analysis of subordinate > stay and superordinate > stay contrasts highlighted the hippocampal tail, parahippocampal cortex, and intraparietal sulcus (Figure 3(a)), the inferior frontal gyrus (IFG) (Figure 3(b)), and the caudate (not shown) as regions commonly active for changes in task rules or context. By contrast, an analysis of superordinate > stay activity, excluding regions significantly active for subordinate changes, demonstrated that regions of the hippocampus anterior to the tail (body, extending into voxels in the head) (Figure 3(c)) and prefrontal cortex (IFG, and frontal pole) (Figure 3(d)) were significantly more active for superordinate than stay trials.

To characterize activations specific to the superordinate level of contextual change in the hierarchy, as opposed to the subordinate rule changes, we directly contrasted superordinate and

subordinate activity in the exclusive mask of subordinate > stay responses. This analysis demonstrated that not only does task context change activity in the body and head exceed our significance threshold solely for the superordinate > stay contrast, but activity anterior to the tail was significantly more active for superordinate changes than subordinate changes (Figure 4(a)). This suggests the body and head are sensitive to computational costs specific to higher-level (superordinate) changes in the contextual hierarchy.

In fact, in the hippocampus, activity anterior to the tail did not differentiate between the subordinate changes and stay trials. We observed this in the analysis of our a priori ROIs, as well as in our voxel-wise analysis even when using a substantially reduced threshold of $p < .05$ to understand the regional specificity. Using mean parameter estimates from the anatomically defined a priori hippocampal tail and body ROIs (also used for our connectivity analysis), linear mixed-effects modeling revealed a significant main effect of hierarchical condition on hippocampal activity ($F_{(2,17)} = 19.239$, $p = 4.304 \times 10^{-5}$), no significant effect of hemisphere ($F_{(1,17)} = 3.062$, $p = .098$), and, critically, a significant region \times hierarchical condition interaction ($F_{(2,119)} = 8.243$, $p = 4.439 \times 10^{-4}$). This result indicates that the relationship between hippocampal activity and contextual changes significantly differed between the tail and the body. There were no significant region \times hemisphere ($F_{(1,119)} = 0.376$, $p = .541$), condition \times hemisphere ($F_{(2,119)} = 0.596$, $p = .553$), or region \times condition \times hemisphere ($F_{(2,119)} = 0.393$, $p = .676$) interactions. These findings indicate that the region \times condition interaction did not differ by hemisphere. Although we interpret results from the hippocampal head with caution, exploratory mixed effects modeling of activity in this area corroborated voxel-wise evidence that the hierarchy effect extended to the head (main effect of condition:

TABLE 1 Subordinate > stay

Region	Left		Right	
	t-Value	Coordinates	t-Value	Coordinates
Middle frontal gyrus (anterior)	7.49	-38, 52, 10	—	—
Inferior frontal sulcus (posterior)	11.32	-44, 14, 26	11.07	44, 10, 34
Anterior insula	11.17	-30, 20, 2	12.42	32, 22, 0
Hippocampus (tail)	6.69	-18, -38, -2	9.82	20, -34, 0
Parahippocampal cortex	9.53	-16, -42, -8	9.36	28, -32, -24
Medial putamen and caudate	9.59	-12, 10, 8	8.62	8, 4, 8
Midbrain	9.69	-8, -16, -8	7.02	12, -14, -10
Thalamus	15.39	-8, -12, 0	11.13	12, -20, 10
Intraparietal sulcus	12.15	-30, -68, 40	12.14	34, -54, 54
Retrosplenial cortex	6.22	-8, -40, 8	7.08	10, -44, 14
Posterior cingulate	10.67	-8, -32, 30	6.39	6, -32, 30
Fusiform cortex	13.38	-34, -60, -14	10.17	30, -72, -10
Angular gyrus	—	—	11.42	34, -66, 36
Cingulate body	9.80	-2, 14, 46	7.78	4, 16, 42
Lateral occipital gyrus	13.83	-38, -84, -12	—	—

Note: Coordinates reflect MNI coordinates of peak values from a cluster.
Abbreviation: MNI, Montreal Neurological Institute.

TABLE 2 Superordinate > stay

Region	Left		Right	
	t-Value	Coordinates	t-Value	Coordinates
Frontal pole	6.36	-22, 60, -2	4.81	22, 54, -2
Middle frontal gyrus (anterior)	10.12	-44, 30, 20	7.75	52, 32, 24
Inferior frontal sulcus (posterior)	9.87	-46, 10, 30	10.01	44, 12, 32
Anterior insula	10.54	-30, 20, 0	13.30	32, 22, -4
Hippocampus (tail)	10.73	-22, -40, -4	12.87	20, -32, -6
Hippocampus (body)	8.84	-18, -28, -16	6.29	26, -28, -16
Parahippocampal cortex	12.87	-16, -42, -8	10.68	20, -34, -18
Medial putamen and caudate	12.11	-14, 4, 0	10.71	16, 12, 2
Midbrain	15.02	-8 -16 -10	10.90	8, -14, -14
Thalamus	11.92	-6, -16, -4	12.60	8, -24, -4
Intraparietal sulcus	8.66	-28, -48, 38	12.50	34, -52, 48
Middle temporal gyrus	6.15	-58, -46, -2	13.03	54, -46, -6
Retrosplenial cortex	9.48	-6, -42, 14	10.25	14, -48, 12
Fusiform cortex	10.22	-36, -50, -20	10.00	42, -52, -16
Collateral sulcus	12.90	-28, -68, -6	—	—
Lingual gyrus	13.17	-22, -58, -4	—	—
Cingulate body	9.50	-2, 18, 40	9.36	6, 26, 36

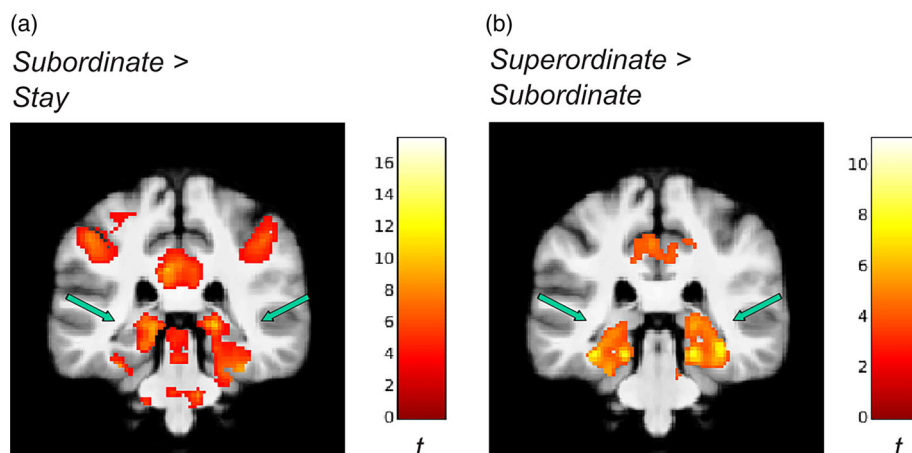
Note: Coordinates reflect MNI coordinates of peak values from a cluster.
Abbreviation: MNI, Montreal Neurological Institute.

TABLE 3 Superordinate > subordinate

Region	Left		Right	
	t-Value	Coordinates	t-Value	Coordinates
Anterior insula	4.26	-38, 16, -8	5.60	40, 26, 0
Hippocampus (body)	5.26	-28, -30, -10	5.08	32, -30, -14
Parahippocampal cortex	7.68	-18, -34, -16	10.97	18, -38, -14
Putamen and caudate	6.33	-18, 2, -8	4.92	10, 16, 6
Cuneus	—	—	5.04	8, -84, 24
Lingual gyrus	8.64	-16, -66, -10	5.72	18, -60, -10

Note: Coordinates reflect MNI coordinates of peak values from a cluster. Regions exclude clusters from subordinate > stay contrast.
Abbreviation: MNI, Montreal Neurological Institute.

FIGURE 2 Posterior medial temporal lobe (MTL) activity scales with contextual change. The hippocampal tail and parahippocampal cortex are more active for retrieval during subordinate changes than stay trials (a), and during superordinate changes than subordinate changes (b)



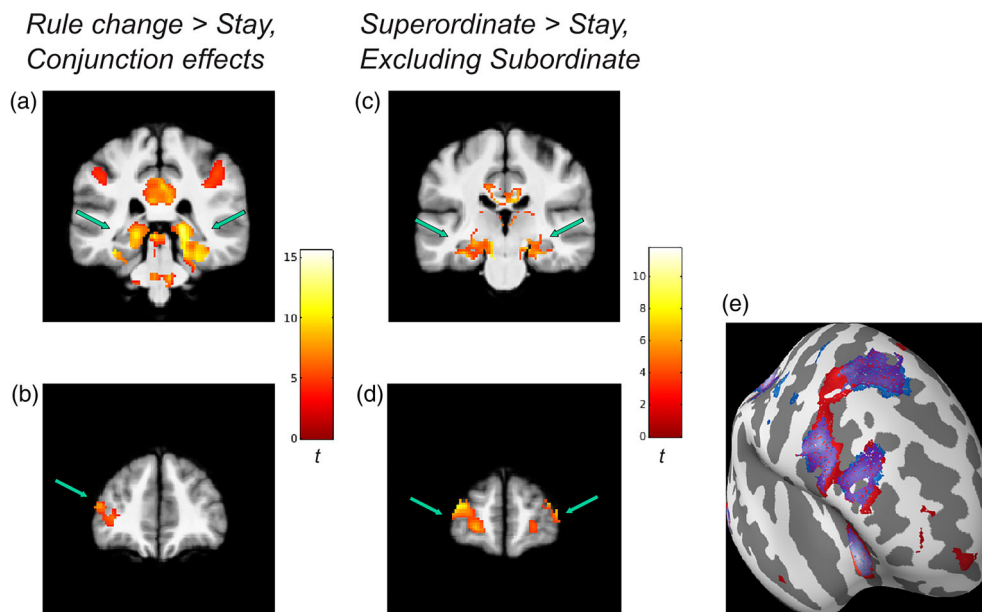


FIGURE 3 Conjunction (a,b) and exclusion (c,d) analyses for superordinate and subordinate rule change activity. Superordinate and subordinate trials shared activity in more posterior regions of the medial temporal lobes (MTL) and IFS relative to stay trials, but activity in more anterior hippocampal and prefrontal regions only reached significance in the superordinate > stay contrast. Surface mapping of rule change > stay (e) illustrates the lateral profile in significant prefrontal cortex (PFC) activation (rendered with PySurfer; blue = subordinate, red = superordinate, purple = conjunction)

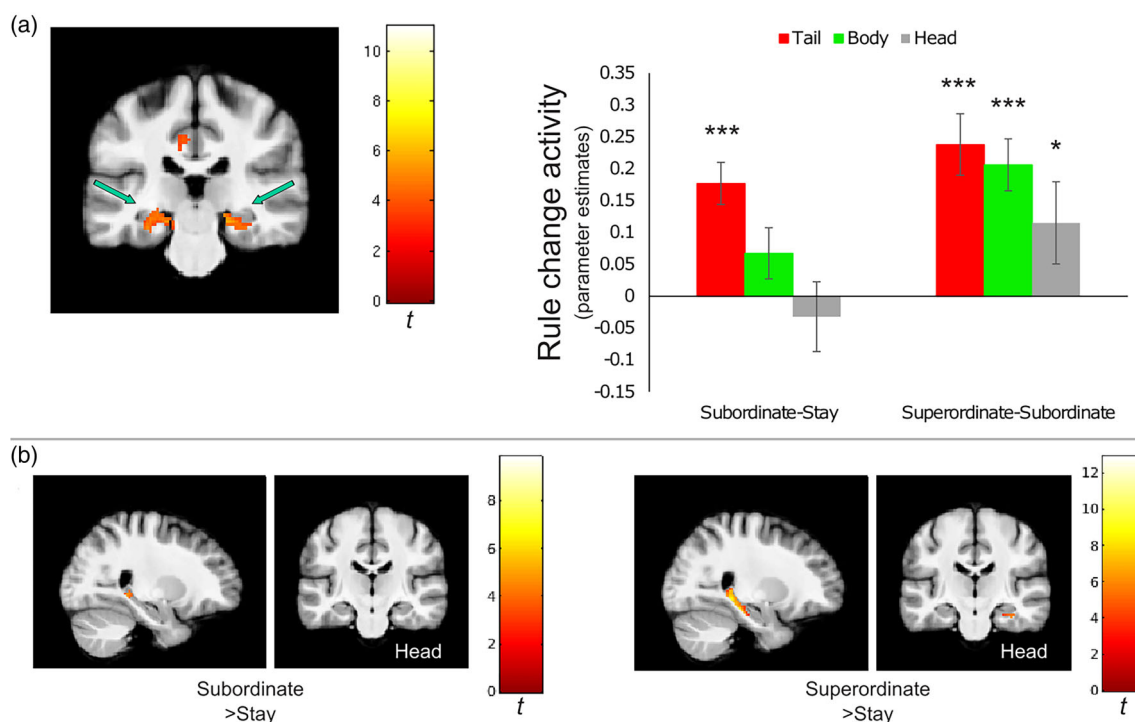


FIGURE 4 Superordinate-specific responses. Activity greater for superordinate changes than subordinate changes in regions where subordinate activity did not differ from that of stay trials. (a) The anterior hippocampus was among a handful of regions (including parahippocampal and retrosplenial cortical areas) to exhibit this difference. Right plot: explicit ROI-based test of anterior versus posterior distinctions in hierarchical rule-based activity changes (parameter estimate differences between conditions) from left hippocampus, illustrating the highly significant interaction (see Section 4) between the body and tail in the relationship between activity and contextual change. Although anatomically adjacent to the tail, the ROI-based tests reveal no difference, unthresholded, between subordinate and stay in the body (by contrast, the body was significantly more active for superordinate than subordinate [and stay]). For completeness, we show that the same activation profile as the body was present in the head (gray). Subordinate-stay differences in the hippocampal body and head were $p > .1$. (b) Illustration of rostral spread of activity for hierarchical rule changes ($p < .001$, corrected, masked to hippocampus). *** $p < .001$ pairwise parameter estimate difference, * $p < .05$

$F_{(2,68)} = 4.130, p = .020$; nonsignificant interaction with hemisphere: $F_{(2,68)} = 0.907, p = .408$). Full model output also visualized in Table 4.

In order to formally characterize the directionality between conditions underlying the significant region \times condition interaction, we conducted follow-up paired-sample t tests. These demonstrated that the hippocampal body responses did not differ between the subordinate changes and stay trials (left: $t_{(17)} = 1.668, p = .114$; right: $t_{(17)} = 1.562, p = .137$). By contrast, hippocampal body responses were significantly greater for the superordinate changes than subordinate changes (left: $t_{(17)} = 5.066, p = 9.540 \times 10^{-5}$; right: $t_{(17)} = 4.503, p = 3.138 \times 10^{-4}$) (see Figure 4(a), right-hand graphs). Hippocampal tail responses were significantly greater for superordinate changes than subordinate changes (left: $t_{(17)} = 4.940, p = 1.242 \times 10^{-4}$; right: $t_{(17)} = 5.135, p = 8.268 \times 10^{-5}$), and for subordinate changes than stay trials (left: $t_{(17)} = 5.366, p = 5.138 \times 10^{-5}$; right: $t_{(17)} = 5.014, p = 1.063 \times 10^{-4}$)—consistent with a more continuous gradient in recruitment for the tail beginning at subordinate contextual changes. Superordinate activity was greater than stay activity in both the hippocampal body (left: $t_{(17)} = 5.121, p = 8.509 \times 10^{-5}$; right: $t_{(17)} = 4.049, p = 8.331 \times 10^{-4}$) and the tail

(left: $t_{(17)} = 6.636, p = 4.209 \times 10^{-6}$; right: $t_{(17)} = 7.195, p = 1.500 \times 10^{-6}$). These pairwise differences also survive Bonferroni correction for multiple comparisons.

Similar results were observed in the exploratory analysis of hippocampal head across voxels, despite weak signal in the area: (subordinate>stay $t_{(17)} = -0.597, p = .553$; superordinate>subordinate $t_{(17)} = 2.136, p = .036$) (although this test unpacking the main effect of condition in the head does not survive correction for multiple comparisons). We further visualize the corresponding rostral hippocampal activity in Figure 4(b). All told, the ROI analyses provide clear evidence that the body (and head) differ from the tail, despite anatomical adjacency and that this cannot be simply attributed to a thresholding concern (as one might raise for SPM maps).

4.2.2 | Functional connectivity results

Posterior hippocampus exhibited elevated functional connectivity for subordinate relative to stay trials with ventral attention circuitry in the anterior insula, and the IFG, implicated in cognitive control and

TABLE 4 Hierarchical condition activity by hippocampal region

LMER output—analysis of variance table of Type III with Satterthwaite approximation for degrees of freedom						
	Sum Sq	Mean Sq	NumDF	DenDF	F.value	Pr(>F)
Region (tail vs. body)	0.00208	0.00208	1	17	0.2562	0.61927
Condition	0.31224	0.15612	2	17	19.2385	4.30E-05
Hemisphere	0.02485	0.02485	1	17	3.0624	0.09815
Region:condition	0.13379	0.06689	2	119	8.2431	0.00044
Region:hemisphere	0.00305	0.00305	1	119	0.3758	0.54102
Condition:hemisphere	0.00967	0.00483	2	119	0.5956	0.55286
Region:condition:hemisphere	0.00638	0.00319	2	119	0.3934	0.67566
Exploratory head analysis						
	Sum Sq	Mean Sq	NumDF	DenDF	F.value	Pr(>F)
Condition	0.356	0.178	2	68	4.1296	2.03E-02
Hemisphere	0.00652	0.00652	1	17	0.1512	0.70226
Condition:hemisphere	0.07822	0.03911	2	68	0.9073	0.40843

TABLE 5 Hippocampal functional connectivity

Seed	Region	Left		Right	
		t-Value	Coordinates	t-Value	Coordinates
Contrast: superordinate > subordinate					
Left hipp. body	Frontal pole	10.18	−20, 58, −4	—	—
Contrast: superordinate > stay					
Left hipp. tail	Inferior frontal gyrus	7.11	−48, 16, 16	7.15	52, 28, 6
Contrast: subordinate > stay					
Right hipp. tail	Anterior insula	6.09	−40, 22, 4	5.46	40, 22, 8

Note: Coordinates reflect MNI coordinates of peak values from a cluster.
Abbreviation: MNI, Montreal Neurological Institute.

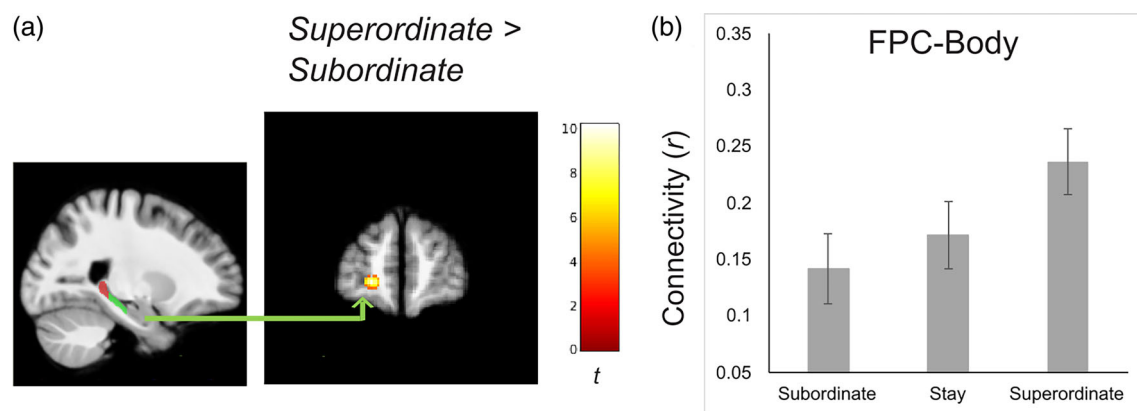


FIGURE 5 Prefrontal functional connectivity of hippocampal subregions that differentiated rule change conditions. (a) Only one region of the brain had differential connectivity with the hippocampus for our rule change conditions: the same region of left frontal pole cortex (FPC) observed in our superordinate versus subordinate exclusion analysis (Figure 3) had greater functional connectivity with the left hippocampal body for superordinate changes. Left panel: illustration of anatomically defined seed regions. (b) Connectivity estimates (r) extracted from the FPC (with hippocampal body) for subordinate changes, stay trials, and superordinate changes. These extracted data illustrate a selective increase of hippocampal connectivity for this prefrontal region for superordinate trials

goal-directed memory for superordinate trials (Yeo et al., 2011) (Table 5). Interestingly, the only difference in functional connectivity of the hippocampus for subordinate and superordinate trials manifest more anterior, with the body demonstrating stronger functional connectivity with the frontal pole cortex (FPC) for superordinate than subordinate trials. Because this FPC functional connectivity difference for the superordinate versus subordinate contrast did not overlap with connectivity results from task rule change vs. stay contrasts, one intriguing possibility was that the difference between the rule change conditions was characterized in part by a pattern of *reduced* functional connectivity. To explore this possibility, we extracted and plotted the mean raw connectivity estimates (r values) from the FPC cluster. The connectivity data revealed that hippocampal–prefrontal connectivity for stay trials was intermediate between superordinate and subordinate trials (Figure 5(b)).

4.3 | Discussion

The present research demonstrates several key findings: the hippocampus and related structures are recruited for retrieving distinct memories in the face of overlapping features (e.g., the same location) on the basis of task rules. Moreover, their recruitment increases during retrieval when more global levels of a contextual hierarchy change (i.e., stay < subordinate changes < superordinate changes). More anterior hippocampal regions, and more anterior regions of the prefrontal cortex (PFC), responded similarly to trials involving subordinate rules in the task, increasing activity selectively for superordinate contextual changes (superordinate changes). Not only did this activity precede the response period, but activity in these core regions did not track RT, indicating the correlates of retrieval are discriminable from the mechanisms governing behavioral selection. Finally, the hippocampus had greater functional connectivity with key PFC regions for retrieval

during any rule change relative to stay trials, and altered its engagement with distinct PFC networks when processing different hierarchical levels of contextual change. Together, our data provide novel evidence that the hippocampus supports hierarchical context-dependent memory retrieval through its activity level and a rostrocaudal topographical organization.

4.3.1 | Contextual changes modulate recruitment of the MTL

The hippocampus and MTL cortex have been implicated in disambiguating overlapping memories in humans (Bakker et al., 2008; Brown et al., 2010, 2012; Brown, Hasselmo, & Stern, 2014; Brown & Stern, 2013; Brown, Whiteman, et al., 2014; Newmark et al., 2013) and rodents (Agster et al., 2002; Ferbinteanu & Shapiro, 2003; Ginther et al., 2011; Lee et al., 2006; MacDonald et al., 2011; Smith & Mizumori, 2006; Wood et al., 2000). The present data corroborate these findings, demonstrating that both the hippocampus proper and parahippocampal cortex are recruited to support context-guided retrieval of overlapping memories. We demonstrate that this role extends beyond basic forms of context (e.g., spatial) to support more abstract task rule-based contextual memory. Given the hierarchical structure of the task rules, if the hippocampus leverages contextual signals to gate potential associative output (Hasselmo & Eichenbaum, 2005), one would predict increased recruitment of the hippocampus to resolve specific item memories under greater contextual changes (particularly given that a more global context has a greater number of associates than a subordinate context). Consistent with this framework, we demonstrate that recruitment of the hippocampus scales with the magnitude of the contextual change.

Interestingly, we observed the same pattern of recruitment in the parahippocampal cortex (PHC). Prior work has strongly implicated

PHC in processing spatial context, its associations, and relational-structure (e.g., Brown et al., 2010; Brown, Hasselmo, & Stern, 2014; Brown & Stern, 2013; Burgess et al., 2001; Ekstrom & Bookheimer, 2007; Janzen & van Turenout, 2004; Libby et al., 2014), but recent evidence suggests that PHC is also sensitive to nonspatial contextual signals (Aminoff et al., 2013; Turk-Browne et al., 2012). The present findings are broadly consistent with the “PMAT” framework (Ranganath & Ritchey, 2012; Ritchey et al., 2015) in which the collective functional and anatomical data implicate posterior parahippocampal cortex as a critical structure for processing situational information and contexts, which can be linked to mnemonic traces. The present study was not designed to directly compare the contributions of the hippocampus and PHC to contextual memory, but one possibility is that PHC interacts with the hippocampus to retrieve the contextual significance of scene/location changes. The fact that PHC activity increases from subordinate to superordinate trials, despite both conditions being cued by a single change in scene content, supports this view.

Prior research has implicated frontostriatal regions in cognitive set shifting and flexibility (for reviews, see Yin & Knowlton, 2006; Robbins, 2007; Badre & D'Esposito, 2009) and in retrieval of competing memories (Brown et al., 2012; Ross et al., 2011). We demonstrate a role in rule-guided memory where retrieval of a correct item places increased demands on the PFC and basal ganglia when task contexts change, with some evidence that more rostral PFC regions interact with response-guiding memory for more global changes. Importantly, our design controlled for response demands across conditions, suggesting frontostriatal activity supports the cognitive processes associated with task context-guided retrieval.

4.3.2 | Posterior–anterior gradient in hippocampal regions processing contextual changes

A striking characteristic of the rodent hippocampus is the increase in the scale of place cell firing fields as you move from the dorsal to the ventral hippocampus (analogous to the posterior–anterior axis in primates) (Kjelstrup et al., 2008). Recent evidence suggests that the dorsal–ventral/posterior–anterior axis is characterized by differential contextual coding, such that there is a gradient with increasingly ventral/anterior hippocampal neurons supporting representation of events at broader, behaviorally meaningful, spatial contextual levels (Brunec et al., 2018; Evensmoen et al., 2013, 2015; Komorowski et al., 2013). Neurons in the dorsal rodent hippocampus represent tasks similar to ours in hierarchically organized neural schemas (McKenzie et al., 2014), with neural populations overlapping based on contextual similarity (e.g., reward valence and local or broader spatial context). These findings suggest that specific item-level memories in the dorsal hippocampus (Komorowski et al., 2013) can be linked by the complex associative structure of such tasks, potentially mediated through more global coding schemes in more ventral regions. Given these data, we hypothesized that behaviorally relevant task contexts may be reflected in similar organizational principles in the human

hippocampus, such that there would be a graded increase in the hippocampal tail as the scale of contextual state changes. More anterior regions of the hippocampus would only be expected to show such a graded profile if the area represents subordinate context with similar precision to superordinate—but one prediction from the above literature is that the more ventral/rostral areas would instead be relatively insensitive to smaller scale contextual changes. Because of this, our prediction was that rostral hippocampal areas would not register subordinate task changes as contextual changes to the same degree as the posterior hippocampus.

We provide novel evidence that activity in the hippocampal tail parametrically increased with hierarchical rule changes (stay < subordinate changes < superordinate changes), consistent with a framework wherein an increasing number of associations for specific item–location events may be activated for more global contextual changes. Strikingly, moving anterior into the hippocampal body, activity increases specifically for retrieval during superordinate changes in the contextual hierarchy, consistent with a more global coding scheme.

One interesting point for consideration is that, to the best of our knowledge there is no precedent in the literature for where the threshold would be for anterior hippocampus to be less sensitive to a subordinate contextual change (as in our design). We suggest this is not a fixed quantity and such thresholds will be dependent on the task and learning parameters themselves. In our task, the subordinate rule change signals a reversal, within the same stimulus dimension, on which of the items are currently correct for a given spatial location. However, in variants of this task it may be possible for such a change to represent a more substantial contextual shift (for example, it could accompany a shift from reward to error punishment in a reward version of our task). It will be interesting to test this idea in future work, and to examine whether anterior hippocampal areas are more sensitive to changes in some task/context dimensions than others (given, for example, greater connectivity between anterior hippocampal areas and emotion and reward circuitry (Fanselow & Dong, 2010)). Here, we targeted the anterior vs. posterior dimension in our current study, but it is known that in rodents the hippocampal CA3 subfield processes environmental contextual changes in a “thresholded” manner as we discuss above—remapping to more marked changes that could be interpreted as a different environmental context, but not to more modest changes that could be interpreted as modifications to the same environment (e.g., Leutgeb et al., 2007; Vazdarjanova & Guzowski, 2004). Therefore, differences between subfields as well as along the rostrocaudal extent may be of interest. Our paradigm could be modified to map gradations in contextual change in a more continuous manner and along different dimensions.

Our data may also lend some support for growing body literature suggesting a hierarchical topographic organization of the lateral PFC (Badre & D'Esposito, 2009), demonstrating that significant activity spread rostrally from the inferior frontal sulcus for subordinate changes to the PFC, which was active for the superordinate > stay contrast, but not subordinate changes (however, we stress that at $p < .001$, activity in this region did not differ in direct contrast between the two rule-change conditions). Stronger evidence favoring

such a hierarchical functional organization manifest from convergence of this pattern with that from our functional connectivity analysis. Specifically, across the brain, the hippocampus shared rule-change related connectivity with more posterior prefrontal regions—but the FPC significantly increased functional connectivity with the hippocampal body specifically for superordinate changes relative to subordinate changes.

Interestingly, connectivity estimates extracted from the FPC revealed this increase was selective for superordinate changes—with no evidence for increased interaction for subordinate changes relative to the baseline condition of stay trials. This pattern suggests that FPC may increase its functional interaction with hippocampal memory processes depending on whether (a) higher-level or (b) less-abstracted contingencies have changed. Potentially, this may indicate FPC is important for updating and control of memory retrieval over alternative stimulus dimensions (as opposed to resolving competition from memory between stimuli within the same dimension, as in the subordinate condition—a response conflict problem that may be supported by prefrontal areas more directly tied to response shifts (Allman et al., 2001; Barbas et al., 1999; Beckmann et al., 2009; Botvinick et al., 2004; Braver, 2001; Brown, Whiteman, et al., 2014; Bunce & Barbas, 2011; Kerns et al., 2004; Rushworth et al., 2011)), although future research is needed to further test this theory.

Across several studies now, we have observed functional links between the hippocampus and FPC (Brown et al., 2012, 2016, 2020) when people are making (spatial) context-dependent choices. The lateral prefrontal cortex has very limited, if any, direct anatomical connectivity with the hippocampus proper (Barbas & Blatt, 1995; Haber et al., 2006; Roberts et al., 2007). However, lateral prefrontal areas do share connections with other MTL subregions including the presubiculum, parasubiculum, entorhinal cortex, and perirhinal cortex (Barbas & Blatt, 1995; Roberts et al., 2007). There are also anatomical connections between the lateral prefrontal cortex and orbital medial areas also engaged in our task, which in turn are directly linked to the hippocampus (Barbas & Blatt, 1995; Cavada et al., 2000; Roberts et al., 2007). Another possible route could be via the nucleus reuniens of the ventral midline thalamus (Bokor et al., 2002; Ferraris et al., 2021; Herkenham, 1978), a prefrontal-hippocampal pathway which has recently been mechanistically linked to goal-directed memory output in rodents (which do not have a direct analog of BA10, complicating such speculation) (Ito et al., 2015). Therefore, this striking functional connectivity shift between the hippocampus and FPC in our task may result from indirect anatomical connections via other pathways.

One interesting point of connection for the present study is its similarity to the AX continuous performance task (CPT) (Badre & Frank, 2012; Frank et al., 2001; Frank & Badre, 2012), where the theoretical framework emphasizes gating of task representations via PFC–striatal interactions. Similar fMRI paradigms in that framework (Chattham et al., 2014; Nee & Brown, 2012, 2013) show important consistencies with our present results—particularly the graded frontostriatal association with higher-order contextual updates versus lower. Our current design, however, revealed robust effects of the higher-order changes in MTL that were not observed in that prior work. One

important distinction with our design is its emphasis on long-term memory—although participants could maintain the current global contextual state in working memory to perform, their responses to each scene cue critically depended on the convergence of the actively processed contextual state and learned associations in long-term memory. Moreover, our use of environmental cues to guide contextual state, rather than arbitrary symbolic cues, could be a major factor for increased sensitivity of MTL areas (perhaps, in particular, the scene-sensitive posterior parahippocampal cortex) to our state manipulations.

A related consideration is competition between task sets—in our design, different superordinate task sets targeted different stimulus dimensions, which contrasts with the implementation of the same targets for both task sets in the above work. In our case, this was an important feature to enable long-term association retrieval to guide behavior, but it potentially pushes the burden from resolving contextual interference between target-task set associations in PFC more toward MTL-dependent processing. Indeed, using nonoverlapping targets for the superordinate sets in our design could facilitate “dropping” the contingencies of the current irrelevant dimension from working memory until they are needed (a superordinate shift)—at which point they may be reaccessed from long-term memory (with retrieval according to the current contextual state informed by working memory for the prior state).

In this sense, our findings may illustrate how memory gating demands in the MTL may be induced by changes in the task design and/or how it is learned. This is an important consideration to be explored in research using CPTs, because in complex real-world scenarios the relative burden of hierarchical contextual-response gating on WM and LTM may vary continuously depending on the properties of response targets, cue availability, and the strength of prior associations that link cues to behaviors.

5 | CONCLUSIONS

The results of our experiment provide novel evidence that activity in the hippocampus not only scales with the magnitude of nonspatial contextual changes, but that subdivisions along the anterior–posterior axis of the hippocampus are recruited differently for memory retrieval when superordinate, more global task rules change. Moreover, the hippocampal body differed in its functional interaction with rostral cognitive control circuitry in the PFC for retrieval when task rules change, depending on whether the change was of a higher order or not. Together, our findings provide a novel demonstration that different regions of the hippocampus contribute to contextual retrieval at different hierarchical levels of a memory structure (or “schema”). These findings provide novel insight into the brain regions that enable us to flexibly access and act on our memories in a complex, ever-changing world.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

DATA AVAILABILITY STATEMENT

The data supporting this manuscript will be made available upon reasonable request.

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