Progression from feature-specific brain activity to hippocampal spatial binding during episodic encoding

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ABSTRACT

The hallmark of episodic memory is recollecting multiple perceptual details tied to a specific spatial-temporal context. To remember an event, it is therefore necessary to integrate such details into a coherent representation during initial encoding. Here we tested how the brain encodes and binds multiple, distinct kinds of features in parallel, and how this process evolves over time during the event itself. We analyzed data from 27 subjects who learned a series of objects uniquely associated with a color, a panoramic scene location, and an emotional sound while fMRI data were collected. By modeling brain activity at event onset and event offset, we were able to test how the neural signatures of individual features as well as the integrated event changed over the course of encoding. We observed a striking dissociation between early and late encoding processes: left inferior frontal and sensory signals at event onset tracked the amount of detail subsequently recalled and were dissociable based on distinct remembered features. In contrast, memory-related brain activity shifted to the left hippocampus at event offset, which was particularly sensitive to binding item color and sound associations with spatial information. These results provide evidence of simultaneous feature-specific neural responses at the start of episodic encoding that predict later remembering and show that the hippocampus acts to integrate these features into a spatially-coherent experience at an event transition.

SIGNIFICANCE STATEMENT

Understanding and remembering complex experiences is crucial for many socio-cognitive abilities, including being able to navigate our environment, predict the future, and share experiences with others. Probing the neural mechanisms by which features become bound into meaningful episodes is a vital part of understanding how we view and reconstruct the rich detail of our environment. Our findings show a functional dissociation between initial encoding processes, engaging lateral frontal and sensory regions to prioritize event features, and later encoding processes that recruit hippocampus to embed these features within a contextual framework. Identifying the mechanisms of complex event encoding is an important step toward understanding why many neurological and psychiatric disorders exhibit differences in how the world is perceived and remembered.

INTRODUCTION

Our ongoing perceptual experience of the world includes a stream of disparate, multimodal features unfolding in parallel. Memory-related increases in brain activity during encoding are often found in visuo-perceptual brain regions (Spaniol et al., 2009; Kim, 2011), emphasizing that stronger, more precise representations of perceptual information support memory formation. For instance, comparing encoding of different kinds of information, such as words and pictures, reveals category-selective patterns of sensory activity that predict subsequent recollection of these individual features (Gottlieb et al., 2010; Duarte et al., 2011; Park and Rugg, 2011). Yet natural experience not only involves representing different perceptual features but, crucially, it requires us to encode them simultaneously. Moreover, we later remember this information as a unified event. In this study, we investigated how perceptual features are uniquely represented during encoding and the neural operations that bind them together.

Studies addressing these issues have largely examined memory for simple paired associations studied as short “events”. This research involves presenting subjects with pairs of features within the same trial, such as a location, person, emotion, or color. By predicting subsequent memory separately for each component feature (Uncapher et al., 2006; Staresina and Davachi, 2008; Gottlieb et al., 2012; Ritchey et al., 2018) or contrasting events with overlapping or non-overlapping feature types (Horner et al., 2015), these studies take a step toward understanding how the brain represents and encodes distinct kinds of information in parallel. Moreover, some regions, most notably the hippocampus, show a preference for binding pairs of features during encoding rather than promoting memory for either detail alone (Uncapher et al., 2006; Horner et al., 2015). However, restricting encoding trials to bimodal associations leaves it unclear how distinct feature signals of more complex experiences are simultaneously distinguished, prioritized, and integrated as the event unfolds over time.

The hippocampus has long been considered to be crucial for binding elements of our experience contextual information (Davachi, 2006; Diana et al., 2007; Eichenbaum et al., 2007; Ranganath, 2010), though less is known about how exactly the hippocampus organizes multimodal information. Its involvement might be tied to total memory content, including details and their associations, during event encoding (Addis and McAndrews, 2006; Staresina and Davachi, 2008; Park and Rugg, 2011), such that activity tracks the amount of information subsequently recalled (Qin et al., 2011) regardless of its content or relational structure. Alternatively, hippocampus could be specifically recruited to organize our environment in a structured way, perhaps around a spatial framework (Horner et al., 2015; Deuker et al., 2016; Zeidman and Maguire, 2016). Another outstanding issue is the timing of a binding process: does it proceed throughout the event or occur once all relevant information has been gathered? Interestingly, recent evidence using video stimuli suggests that the hippocampus may be particularly useful for encoding at the end of an event (Ben-Yakov et al., 2014; Ben-Yakov and Henson, 2018). However, research cannot determine if this later signal serves a binding function until specific qualities of the resulting memory are measured. Finally, it is important to distinguish the role of the hippocampus in multimodal event encoding from that of other regions across the brain that also reliably show encoding effects related to organization and integration, such as left inferior frontal gyrus (Ranganath et al., 2004; Addis and McAndrews, 2006; Staresina and Davachi, 2006; Park and Rugg, 2011).

Here, we presented participants with multimodal features constituting a single event. In line with previous work (Horner and Burgess, 2013; Joensen et al., 2019), we recently showed that successful recall, but not the precision, of event associations encoded in our task - an object with a color, scene location, and sound - exhibits a dependent, integrated structure in memory (Cooper and Ritchey, 2019). Therefore, this paradigm allows us to cleanly test memory for each event dimension, understand how these features are segregated and prioritized at encoding, and assess how they are bound into a unified representation across the brain.

MATERIALS AND METHODS

Portions of this dataset have been previously reported (Cooper and Ritchey, 2019). Whereas the previous paper was focused on functional connectivity analyses of the retrieval phase, the current paper reports on univariate activation analyses of the encoding phase. Methods for MRI data collection, the task procedure, and behavioral analyses have been previously detailed in (Cooper and Ritchey, 2019), and so are summarized here.

Participants

27 participants took part in the current experiment (16 females, 11 males). All participants were 18-35 years of age (mean = 21.7 years, SD = 3.58) and did not have a history of any psychiatric or neurological disorders. Seven additional subjects took part but were excluded from data analyses: two participants did not complete the experiment, one due to anxiety and the other due to excessive movement in the MRI scanner, four additional participants had chance-level performance on the memory task, and one subject was excluded after data quality checks revealed 3/6 encoding functional runs exceeded our motion criteria. Informed consent was obtained from all participants prior to the experiment and participants were reimbursed for their time. Procedures were approved by the Boston College Institutional Review Board.

Experimental Design

Paradigm

Participants were presented with a series of 144 unique object “events” in an MRI scanner, 24 per scan run. Each object was presented in a color from a continuous CIEL*A*B color spectrum, in a scene location within one of 6 panoramic environments, and in conjunction with one of 12 sounds - 6 that were emotionally negative and 6 that were neutral. All sounds contained natural, easily recognizable content and were 6 seconds in duration, corresponding to

the time each event was displayed during encoding. Events were separated by a 1 second fixation. Participants were instructed to integrate the object and its associated features into a meaningful event, but no response was required (Figure 1A). Allocations of features to objects as well as the presentation order of events were randomized within each subject. This memory encoding phase is the focus of all fMRI analyses presented here; see Cooper and Ritchey (2019) for results from the retrieval phase. After encoding 24 events, subjects were tested on their memory for the features associated with each object, presented in grayscale as memory cues. On each retrieval trial, participants attempted to remember all of the features in their mind for 4s, following which they were prompted to remember if the object was paired with a negative or neutral sound (2s), and to reconstruct the object's color and spatial location (6s each). For the sound feature, participants reported their confidence in their decision ('maybe' or 'sure'), whereas, for the visual features, participants changed the object's color and moved it around the panorama to recreate its visual appearance as precisely as possible in 360-degree space.

fMRI Data Acquisition

MRI scanning was performed using a 3-T Siemens Prisma MRI scanner at the Harvard Center for Brain Science, with a 32-channel head coil. Structural MRI images were obtained using a T1-weighted (T1w) multiecho MPRAGE protocol (field of view = 256 mm, 1 mm isotropic voxels, 176 sagittal slices with interleaved acquisition, TR = 2530 ms, TE = 1.69/ 3.55/ 5.41/ 7.27 ms, flip angle = 7º, phase encoding: anterior-posterior, parallel imaging = GRAPPA, acceleration factor = 2). Functional images were acquired using a whole brain multiband echo-planar (EPI) sequence (field of view = 208 mm, 2 mm isotropic voxels, 69 slices with interleaved acquisition, TR = 1500 ms, TE = 28 ms, flip angle = 75º, phase encoding: anterior-posterior, parallel imaging = GRAPPA, acceleration factor = 2), for a total of 466 TRs encompassing encoding and retrieval trials per scan run. Fieldmap scans were acquired to correct the EPI images for signal distortion (TR = 314 ms, TE = 4.45/ 6.91 ms, flip angle = 55º).

Statistical Analysis

Behavioral Data Processing

As previously reported (Cooper and Ritchey, 2019), participants' responses for the object color and scene location questions were measured in terms of error -- the difference between the target (encoded) feature value and the reported feature value in 360-degree space. Responses to the sound question were considered in terms of accuracy and confidence. Each encoding event was characterized in terms of its pattern of memory success (correct vs. incorrect subsequent retrieval) for each of these features. We used a more conservative method for identifying "correct" memory retrieval than in our previous analysis of this data (Cooper and Ritchey, 2019) to ensure that we only included trials associated with confident subsequent recollection, and to more evenly balance the distribution of trials across different remembered feature combinations. Specifically, the sound feature was considered correctly recalled if the participant successfully identified the associated sound as negative or neutral *and* reported this memory with high confidence. For color and scene location features, we first fitted a mixture model (Zhang and Luck, 2008; Bays et al., 2009) to the aggregate group error data, per feature. The mixture model includes a uniform distribution to estimate the proportion of responses that reflect guessing, as well as a circular Gaussian (von Mises) distribution to estimate the proportion of responses that reflect successful remembering. We defined "correct" color and scene memory by the probability that an error had at least a 75% chance of belonging to the von Mises distribution and not the uniform distribution, resulting in a threshold of +/- 42 degrees for color and +/- 24 degrees for scene memory. For each encoding event, a composite measure of memory detail was calculated as the number of features subsequently recalled (0-3). Of note, this is a slightly different composite measure of memory than we have used previously (Cooper and Ritchey, 2019), where we accounted for variations in confidence and precision within "successful" recall. However, we have already restricted our measure of successful memory for each feature to a confident and precise judgment, and, in our previous behavioral analyses, it

was successful recall but not the precision of recall that showed a dependent structure in memory.

fMRI Data Preprocessing

All data preprocessing was performed using FMRIPrep v1.0.3 (Esteban et al., 2018) with the default processing steps. Each T1w volume was corrected for intensity non-uniformity and skull-stripped. Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c was performed through nonlinear registration, using brain-extracted versions of both the T1w volume and template. All analyses reported here use images in MNI space. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w image. Functional data was slice time corrected, motion corrected, and corrected for field distortion. This was followed by co-registration to the corresponding T1w using boundary-based registration with 9 degrees of freedom. Physiological noise regressors were extracted applying aCompCor. Framewise displacement was also calculated for each functional run. For further details of the pipeline, including the software packages utilized by FMRIPrep for each preprocessing step, please refer to the online documentation: https://fmriprep.readthedocs.io/en/1.0.3/index.html. After preprocessing, the first 116 TRs were selected from each scan run, capturing all encoding trials and extending 6s beyond completion of the final trial. Functional encoding runs were checked for motion and were excluded from data analyses if more than 20% of TRs exceeded a framewise displacement of 0.3 mm. Participants were retained for analyses if at least 4/6 runs passed criteria. One subject was excluded as result of 3 runs having high motion, but no other subjects had runs removed because of movement. Four participants successfully completed only 5 out of the 6 scan runs, 3 as a result of exiting the scanner early and 1 due to a technical problem with the sound system during the first run.

206 ***Whole Brain Parcellation***

207 To test which regions across the whole brain were sensitive to subsequent memory
208 effects, we divided the cortex into 200 functionally homogeneous regions using a recent cortical
209 parcellation (Schaefer et al., 2018; https://github.com/ThomasYeoLab/CBIG). Four medial
210 temporal areas were added to this whole-brain atlas (left and right hemisphere as separate
211 regions). The hippocampus was obtained from a probabilistic medial temporal lobe atlas
212 (Ritchey et al., 2015; https://neurovault.org/collections/3731/) and amygdala was added from the
213 Harvard-Oxford subcortical atlas, consistent with our prior methods (Cooper and Ritchey, 2019).
214 We used a parcellation rather than voxel-based approach to i) utilize what we know about
215 anatomical and functional similarities across the brain to maximise statistical power and ii) allow
216 us to draw conclusions about the function of individual brain regions. The results of all whole
217 brain analyses were displayed using BrainNet Viewer (Xia et al., 2013), where, for visualisation
218 purposes, every voxel within a region was allocated the same t statistic calculated from an
219 analysis of that region's mean activity.

220

221 ***Single Trial Analyses***

222 All analyses were run using single trial estimates of activity during encoding. Single trial
223 betas were computed using MATLAB SPM12, implementing the least squares-separate (LS-S)
224 method (Mumford et al., 2012) where a separate general linear model (GLM) was constructed
225 for each encoding trial. In each single trial GLM, the first regressor corresponds to the trial of
226 interest and a second regressor codes for all other encoding trials in that functional run.
227 Functional data were denoised by including framewise displacement, 6 aCompCor principal
228 components, and 6 movements parameters as nuisance regressors. Spike regressors were also
229 included to exclude data points with high motion (> 0.6mm). Two types of single trial model
230 were constructed: 1) a delta function at stimulus *onset* convolved with the canonical HRF, and
231 2) a delta function at stimulus *offset* convolved with the canonical HRF. Mean single trial onset

and offset beta series were extracted by averaging across voxels within each of the 204 regions per subject. Analyses of these mean single trial betas were conducted using RStudio (RStudio Team, 2016).

Before running any analyses, data were first cleaned by z-scoring the single trial beta values within each subject and region and removing any trials that exceed a z value of |4|. A total of 103 (2.72%) and 113 (2.98%) out of 3792 trials were removed for analyses of event onsets and offsets, respectively. The relationship between each region's encoding beta series and subsequent memory was modeled using linear mixed effects analysis (*lme4*; Bates et al., 2015). In all models, subject was included as a random effect with a variable intercept and variable slopes for all fixed effects. This 'maximal' approach guards against an inflated Type 1 error rate (Barr et al., 2013) but can commonly result in model convergence failures with increasing complexity of the random effect variance-covariance structure (Matuschek et al., 2017). To address this problem, random effect correlations were constrained to zero in all models (Barr et al., 2013; Matuschek et al., 2017) using the formula $lmer(Y \sim X_1 + X_2 + (1 + X_1 + X_2 \,||\, Subject))$. To avoid singular fits for more complex models, the random effects structure of models with more than two fixed effects were additionally simplified using the *lmerTest* package (Kuznetsova et al., 2017) 'step' function, which iteratively removes random slopes that do not improve the model fit. Each fixed effect was tested against zero using *lmerTest*, which implements t-tests with Satterthwaite's approximation method, estimating the effective degrees of freedom for each effect. All p-values reported were FDR-corrected for multiple comparisons across all 204 brain regions within each type of mixed effects model.

Code Accessibility

Single trial encoding data for all subjects and brain regions as well as R scripts to run the analyses described here have been made freely available through GitHub:

http://www.thememolab.org/paper-bindingfmri/. This repository also contains csv and nifti files for all whole-brain linear mixed effects statistics.

RESULTS

Neural correlates of subsequent episodic detail are sensitive to distinct memory features

We first sought to test where across the brain activity at the onset of a multi-feature event was sensitive to the amount of detail later recalled (Figure 1B). Activity of each brain region was predicted from an objective measure of memory detail coding each trial according to whether 0, 1, 2, or 3 features were subsequently recalled.

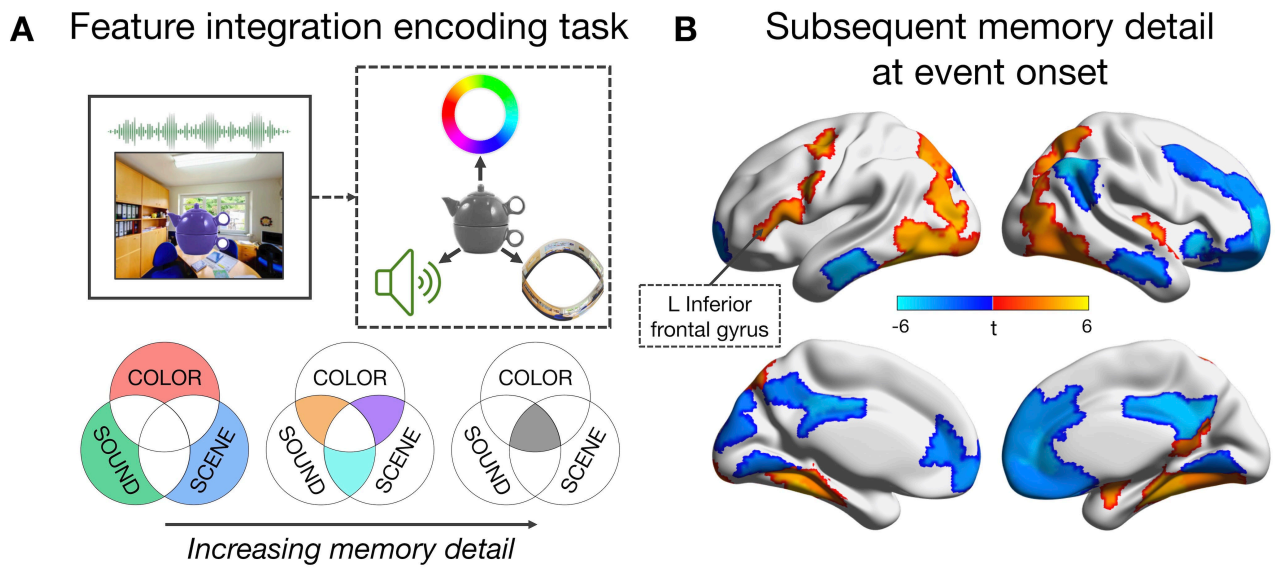

Fig.1. Task design and neural correlates of subsequent memory detail at event onset. A) During encoding, participants learned a series of events presented for 6s, each uniquely associating an object to a color, sound, and scene location. Each event was coded by its level of detail, specified by the number of features (0-3) that were subsequently successfully recollected. B) Brain regions whose activity at event onset is significantly ($p < .05$ FDR corrected) predicted by the number of features subsequently recalled. All voxels within a functionally homogeneous region, defined based on a whole-brain parcellation, are color-coded by the region's t-statistic.

Subsequent memory-related increases in activity at onset were found in a number of sensory regions, including bilateral occipital and ventral visual regions (*t*s > 2.94, *p*s < .047), as well as bilateral parahippocampal cortex (*t*s > 3.07, *p*s < .038), and right retrosplenial cortex (t = 2.96, p = .042), amygdala (t = 3.29, p = .032), and superior temporal cortex (t = 4.54, p = .007). Notably, left inferior frontal gyrus onset activity also tracked memory detail (*t*s > 3.40, *p*s < .024), with this region being frequently associated with successful associative encoding. In contrast, activity of default network regions, including bilateral medial prefrontal cortex (mPFC) (*t*s < -3.35, *p*s < .027) and posterior cingulate (*t*s < -3.14, *p*s < .037), showed a reduction in activity at event onset that tracked increasing memory detail. Therefore, left lateral frontal and sensory regions appear to prioritize event features early on in encoding to support a detailed memory representation.

We next wanted to determine which of these regions were associated with subsequent memory in a feature-specific way-- that is, to what extent does encoding a multi-feature event involve the parallel activation of feature-specific patterns? To this end, mixed effects models were used to identify patterns of event-onset activity that were *uniquely* predicted by subsequent memory for color, sound, or scene perspective, with memory coded according to whether the feature was subsequently correct or incorrect (Figure 2). Whereas deactivation of default regions was generally important for remembering any feature, regardless of its modality, more pronounced feature-specific effects emerged in terms of positive subsequent memory correlates. Successful encoding of the object's color was associated with enhanced activity of right ventral visual cortical areas (*t*s > 3.25, *p*s < .030), whereas subsequent memory for the sound was positively related to activity in bilateral superior temporal (auditory) cortex (*t*s > 4.16, *p*s < .014). Neural correlates of successful scene memory were more widespread, suggesting a dominance of spatial information during episodic encoding. Positive changes in activity with subsequent scene recall were observed in right lateral frontal cortex (*t*s = 3.49, p = .018), bilateral dorsal medial parietal and occipital cortex (*t*s > 2.98, *p*s < .049), as well as bilateral

retrosplenial and parahippocampal cortex (*t*s > 3.49, *p*s < .032), frequently reported to be sensitive to specific representations of spatial locations and perspectives (Epstein, 2008; Robin et al., 2018; Berens et al., 2019). Even though spatial information appears to be prioritized across the brain, we were able to detect unique patterns of brain activity at the onset of an event that track different kinds of episodic features encoded simultaneously.

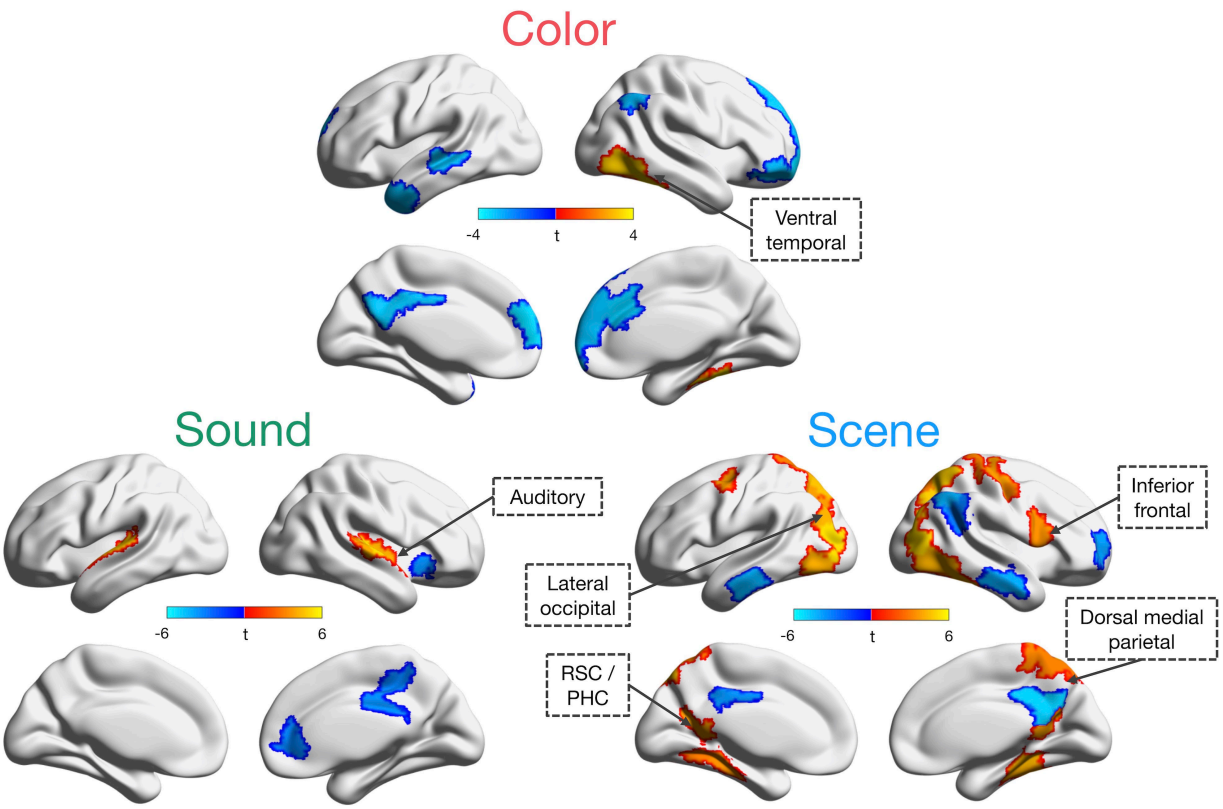

Fig.2. Regions whose activity at event onset is uniquely predicted by subsequent color, sound, or scene memory while these features are encoded in parallel. Task-positive effects are labeled, which show mostly distinct patterns across the three features. Effects shown are FDR-corrected for multiple comparisons at $p < .05$, and all voxels within a region are color-coded by the region's t-statistic.

Hippocampal offset signals bind episodic features within a spatial framework

The previous analysis showed that there are partially distinct patterns of encoding activity that support memory for individual features in parallel. Yet a fundamental aspect of episodic memory is the binding of multimodal features into a coherent event representation. How does this emerge over the course of encoding? Most models of episodic memory assume that the hippocampus supports this binding process. Interestingly, we found that hippocampal onset activity was not predicted by subsequent memory detail (ts < 0.60, ps > .77), or memory for any individual feature (ts < 0.71, ps > .68), despite being frequently reported in this context (Ranganath et al., 2004; Addis and McAndrews, 2006; Ritchey et al., 2018), specifically for encoding multiple episodic features (Horner et al., 2015). Yet this onset-locked analysis does not capture the full temporal dynamics of episodic encoding. We reasoned that feature-specific brain regions might be important for prioritizing features early on whereas other regions, such as hippocampus, might be engaged later in encoding to integrate such features into a coherent memory representation. Thus, we tested whether the pattern of subsequent memory effects would shift from event onset to event offset, with the hippocampus playing a binding role that is especially apparent at offset (Figure 3A).

First, activity of each brain region at event *offset* was predicted from a continuous measure of memory detail. Overall, we found that fewer regions exhibited sensitivity to the number of features subsequently recalled at the end of an event (Figure 3B), although the sensitivity of some default regions to memory detail was sustained over encoding, with an overlapping subset of mPFC regions showing decreased activity with greater subsequent memory detail at both onset (ts < - 3.35, ps < .027) and offset (ts < -2.78, ps < .038). A transition of subsequent memory effects was particularly the case for left inferior frontal and sensory regions that tracked later memory detail and feature-specific recall early on during event learning -- these regions did not sustain their sensitivity to memory over the full course of encoding. Importantly, enhanced activity at event offset in left hippocampus was predictive of

the number of event details subsequently remembered (t = 3.25, p = .034), reflecting the emergence of a hippocampal memory effect over the course of the encoding trial. Of note, the same pattern was also present in right hippocampus, but it did not reach significance after correction for multiple comparisons across the brain (t = 2.23, p = .13). Positive correlates of memory detail at event offset were also seen in left inferior parietal cortex (t = 3.29, p = .017) and middle temporal gyrus (t = 3.58, p = .018). This temporal transformation in the neural correlates of memory detail during encoding is unlikely to be influenced by the proximity of each event offset to the onset of the next trial. Specifically, a mixed effects model predicting subsequent memory detail on the next trial from subsequent memory detail on the current trial, accounting for nested random effects of subject and task run, revealed no statistical dependency between encoding success on successive trials (t = 1.16, p = .26).

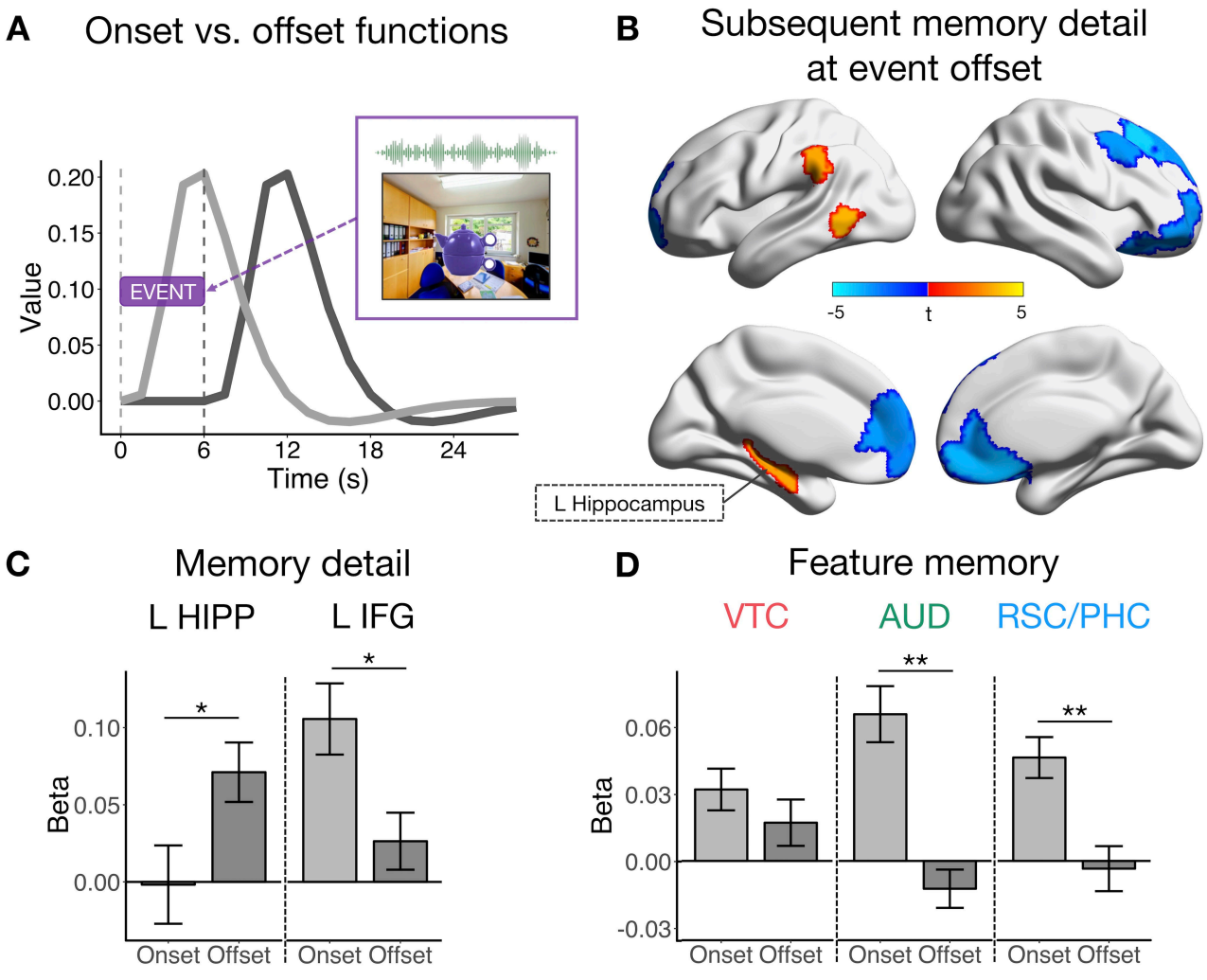

Fig.3. Whole brain correlates of subsequent memory detail at event offset and the change memory-related activity in 5 ROIs between event onset and offset. A) Single trial estimates were constructed by convolving either the event offset (dark gray), compared to event onset (light gray), with the canonical HRF (TR=1.5s). B) Brain regions whose offset activity is significantly ($p < .05$ FDR corrected) predicted by the number of details subsequently recalled (0-3). All voxels within a region are color-coded by the region's t-statistic. C-D) Visualization of the change in memory-related activity between onset and offset, for subsequent memory detail (C) in left hippocampus (L HIPP) and left inferior frontal gyrus (L IFG), and for subsequent color, sound, and scene memory (D) in bilateral ventral temporal cortex (VTC), auditory cortex (AUD), and

retrosplenial/parahippocampal cortex (RSC/PHC), respectively. Bars = fixed effect beta estimates of memory-modulated activity, error bars = SEM. ** $p < .005$, * $p < .05$.

To complement the previous onset-related analyses, we next tested the unique influence of memory for each feature - color, sound, and scene - on offset activity across the brain. Whereas there were no significant increases in activity with subsequent color or sound memory, some regions did, however, track subsequent scene memory. These effects were not present in retrosplenial/parahippocampal cortex and occipital regions as previously seen; rather, activity of left hippocampus ($t = 3.91$, $p = .006$), bilateral inferior frontal gyrus ($ts > 3.16$, $ps < .034$), and left temporoparietal junction ($ts > 3.17$, $ps < .034$) tracked scene encoding at the end of the event. To visualize the transformation of memory-related activity between event onset and offset, we focused on 5 regions (Figure 3 C-D) -- left hippocampus (L HIPP), left inferior frontal gyrus (L IFG), showing sensitivity to total memory detail at event offset and onset, respectively, as well as ventral temporal cortex (VTC), auditory cortex (AUD), and retrosplenial/parahippocampal cortex (RSC/PHC), which tracked color, sound, and scene encoding, respectively, at event onset. To confirm, sensitivity to memory detail was significantly greater at event offset than onset in L HIPP ($F(1,52.9) = 4.95$, $p = .030$), whereas the opposite was true in L IFG ($F(1,61.3) = 6.63$, $p = .012$). AUD and RSC/PHC also showed significantly greater sensitivity to later sound ($F(1,50.5) = 24.30$, $p < .001$) and scene memory ($F(1,60.3) = 12.18$, $p < .001$), respectively, at event onset than offset, but this pattern was not significant for VTC and color encoding ($F(1,59.4) = 1.02$, $p = .32$). Therefore, lateral frontal and sensory memory-related onset signals transition to a hippocampal offset signal that is sensitive to later scene recollection and the amount of information recalled.

The observed pattern of hippocampal activity raises two possibilities about its memory-related function: 1) it may promote memory for the spatial context at an event transition regardless of other episodic features, or 2) it could reflect a binding signal, integrating event

features within a spatial framework after the individual features have been processed. To distinguish these explanations, we predicted the mean activity of left hippocampus with all combinations of features recalled (each feature remembered alone, each possible pair of features remembered together but the third forgotten, or all three features remembered), and tested if hippocampal offset activity is greater in situations where space was bound to either color or sound features, or both, than when space was recalled in the absence of other information (Figure 4). Indeed, hippocampal activity was only increased at offset for trials where scene information was successfully remembered in conjunction with color, sound, or both features (*t*s > 3.06, *p*s < .003) and not when scene was the only feature subsequently recalled ($t = 1.29$, $p = .20$; scene-alone vs. scene-binding fixed effects: $F(1,2553.9) = 3.51$, $p = .061$, two-tailed). Hence, although hippocampal activity was uniquely predicted by subsequent memory for space, it seems particularly sensitive to binding other event features within a spatial framework at the end of a studied event.

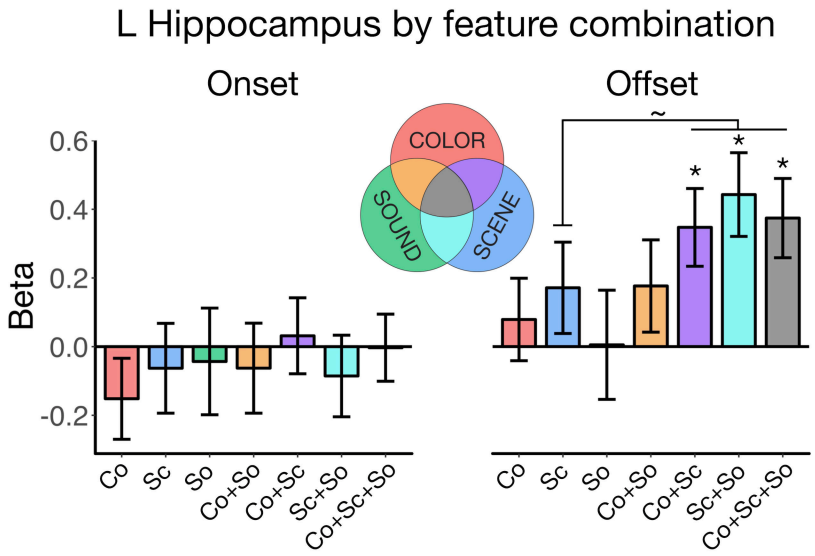

Fig.4. The pattern of L HIPP activity based on all possible feature conjunctions in memory, relative to an implicit baseline of no features recalled. Hippocampal activity at event onset (left) was not sensitive to memory for any combination of features. In contrast, hippocampal activity at

offset (right) was increased when spatial information was successfully bound with other episodic features in memory. Co = Color, Sc = Scene, So = Sound. Bars = fixed effect beta estimates of activity in each condition, error bars = SEM. * $p < .05$, ~ $p < .1$.

DISCUSSION

This study tested the neural correlates of distinct features encoded in parallel within a complex event, and how those features are integrated into a coherent representation. First, we found that left IFG and visuo-perceptual regions were sensitive to the amount of detail encoded at the onset of each event. Whereas IFG selectively tracked the number of associations recalled, we uncovered unique variance in sensory brain activity predicted by subsequent memory for color, sound, and scene features. In contrast, modeling activity at event offset revealed a shift in the positive neural correlates of successful encoding. Specifically, activity in left hippocampus at the end of each event was predicted by the amount of detail later recalled as well as memory for spatial information. Probing specific feature combinations revealed that these hippocampal effects were driven by binding color and sound information with an associated scene.

Our findings of feature-specific encoding effects demonstrate that multimodal details of complex episodes can be decomposed in the brain, even when encoded simultaneously. The specific pattern of our results converges with univariate and multivariate decoding studies previously using these types of features, including color (Uncapher et al., 2006; Favila et al., 2018), sounds (Gottlieb et al., 2012), and scenes (Park and Chun, 2009; Morgan et al., 2011; Staresina et al., 2011) to study perception and encoding. Moreover, by modeling the unique variance of each feature, we found that scenes showed the most prominent subsequent memory effects. This suggests that spatial information may be prioritized during encoding and serve as the dominant framework for integrating other features within memory (Robin et al., 2016; Robin, 2018). In fact, complementary work using multivariate pattern analysis of multi-

428 feature mental imagery also found more widespread neural sensitivity, primarily in posterior
429 medial cortex, to distinct spatial environments compared to different people or objects (Robin et
430 al., 2018). We additionally showed that these visuo-perceptual neural correlates were only
431 present early on in the encoding trial, which is consistent with relatively earlier subsequent
432 memory effects in ventral visual areas shown using intracranial EEG (Long and Kahana, 2015).
433 Therefore, while the strength of sensory signals predicts feature-specific encoding, the
434 importance of this activity for memory generally decreases over the trial. In contrast, we
435 observed that deactivation of default network regions, particularly medial prefrontal cortex,
436 correlated with subsequent memory at both the onset and offset of multi-feature events,
437 suggesting that reallocation of task resources to the external stimulus (Daselaar et al., 2004) is
438 consistently important for memory encoding.

439 In addition to feature-specific encoding effects showing an early, transient profile, left
440 IFG also showed an early relationship to total memory detail that diminished over time. Notably,
441 its onset activity was not sensitive to memory for any feature alone. This pattern supports the
442 proposal that IFG processes goal-relevant information and initiates an organizational framework
443 (Blumenfeld and Ranganath, 2007; Blumenfeld et al., 2011) to support integration of perceptual
444 features. In our paradigm, participants were asked to generate a story linking the associations
445 together, and so early IFG activity may help to generate meaningful semantic associations
446 necessary to support feature binding (Gabrieli et al., 1998). Interestingly, and in contrast to prior
447 literature, we did not find a similar relationship between hippocampal onset activity and later
448 encoding success. Instead, we observed a shift whereby left hippocampal activity at event *offset*
449 significantly predicted the number of features recalled. Collectively, these findings suggest that
450 both hippocampus and left IFG contribute to the integration of event components (Staresina and
451 Davachi, 2006; Zeithamova and Preston, 2010) but reveal that their memory signals are
452 temporally dissociable. As such, while left IFG may control organizational strategies,
453 hippocampus may act upon this organizational structure to bind an item with its context.

454 Previous research supports this distinction, showing that IFG generates associations whereas
455 hippocampus is sensitive to an existing relational structure (Addis and McAndrews, 2006), with
456 the former tracking subsequent memory confidence and the latter the number of details
457 remembered (Qin et al., 2011). Another interesting contrast suggests that IFG may actively
458 control encoding processes while hippocampal signals are driven by inherent memorability of a
459 scene's perceptual features (Bainbridge et al., 2017). Furthermore, intracranial EEG work has
460 demonstrated that memory-related activity in IFG precedes that in hippocampus (Long and
461 Kahana, 2015), thus providing convincing evidence for their distinct functional and temporal
462 roles in integration during memory encoding.

463 The absence of hippocampal correlates of subsequent memory at the onset of an event
464 is particularly interesting in light of inconsistency in the literature. Although hippocampal
465 encoding effects have often been reported (Spaniol et al., 2009; Kim, 2011), many individual
466 studies have not found them (Sommer et al., 2005; Haskins et al., 2008; Cooper et al., 2017;
467 Tibon et al., 2019). Although variability in hippocampal encoding effects might be attributed to
468 differences in memory strength and trial selection (Henson, 2005), the current results suggest
469 an additional possible explanation-- namely, that such inconsistencies might be related to the
470 duration of encoding event used in fMRI analyses. Most event-related fMRI tasks use short
471 trials, often 2-3 seconds, and analyze activity locked to an event onset, meaning that memory
472 correlates at different times will be virtually indistinguishable. Meanwhile, studies using longer,
473 naturalistic events have consistently shown increased hippocampal activity at the end of an
474 event (Ben-Yakov et al., 2014; Ben-Yakov and Henson, 2018), which correlates with later
475 memory reinstatement both neurally and behaviorally (DuBrow and Davachi, 2016; Baldassano
476 et al., 2017). Here, like our whole brain results, this offset response is mostly selective to the
477 hippocampus. The hippocampal offset signal is thought to reflect a binding operation based on
478 event discontinuities, linking together all the features that just co-occurred within the same
479 spatial-temporal context before transitioning to a new environment (Staresina and Davachi,

2009). Evidence that earlier visuo-perceptual activity predicts a hippocampal event boundary response within continuous experience (Baldassano et al., 2017) provides support for this proposal and complements the temporal shift from sensory memory correlates to hippocampal memory effects observed here.

To our knowledge, this is the first study to explicitly test the hypothesis that hippocampal activity at event onset reflects binding per se; previous studies have not separately tested memory for distinct kinds of episodic features. Our paradigm allowed us to tease apart which features and conjunctions influenced this signal most, where left hippocampal activity was enhanced selectively on trials were spatial information was successfully remembered *and* integrated with color or sound features, or both. This neural finding corroborates previous explanations of the hippocampal event offset effect (Cohen et al., 2015; Ben-Yakov and Henson, 2018) as well as theoretical accounts that hippocampus binds information within a contextual framework (Davachi, 2006; Ranganath, 2010; Eichenbaum, 2017). Moreover, it aligns with our previous behavioral analysis of this dataset showing that dependencies in recall are centered around memory for the object's spatial context, such that color and sound features were more likely to be bound to the object's scene location than each other (Cooper and Ritchey, 2019). Evidence of an offset-type hippocampal encoding signal is also present in other event-related tasks: When learning overlapping associations across trials, hippocampal activity predicts subsequent memory after being exposed to component event associations (Horner et al., 2015) and binds previously studied associations based on shared context (Zeithamova and Preston, 2010; Zeithamova et al., 2012), suggesting a prominent function is the integration of previously encoded event features.

When interpreting the results of this study, it is important to consider some limitations of the current experimental approach. First, although our events were longer than those in most event-related encoding studies, 6 seconds is still relatively short and as such, we were unable to map out the full time course of memory-related signals over a longer period. This partially

506 reflects the fact that, even though participants were encouraged to generate a story to encode
507 the events, the features were static rather than evolving over time. Although this design enabled
508 us to measure memory for distinct event features, future studies would benefit from using
509 temporally dynamic videos while controlling event features that can be objectively tested later
510 on. Second, our findings of spatial primacy, in terms of sensory signals and later hippocampal
511 binding, might not necessarily demonstrate that space is always the dominant contextual
512 framework. Rather, the object's background scene may have been particularly salient in our
513 task, meaning that attention and binding was centered around this feature. Future work could
514 therefore manipulate both the content of an event and the relative salience of those features to
515 explore how these factors modulate onset and offset binding effects in IFG and hippocampus.
516 In summary, we demonstrated that feature-specific neural representations are
517 dissociable and support encoding early in an event. Integration of these features into a coherent
518 episode as an event unfolds is likely supported by complementary lateral frontal and
519 hippocampal signals, with early left IFG operations providing a meaningful structure, and later
520 hippocampal operations integrating these associations within a unified spatial-temporal
521 framework. This multifaceted process thus promotes subsequent episodic retrieval, helping us
522 to mentally reconstruct the rich detail of our environment and predict the future.
523

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