


# Integration of event experiences to build relational knowledge in the human brain

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We investigated how the human brain integrates experiences of specific events to build general knowledge about typical event structure. We examined an episodic memory area important for temporal relations, anterior-lateral entorhinal cortex, and a semantic memory area important for action concepts, middle temporal gyrus, to understand how and when these areas contribute to these processes. Participants underwent functional magnetic resonance imaging while learning and recalling temporal relations among novel events over two sessions 1 week apart. Across distinct contexts, individual temporal relations among events could either be consistent or inconsistent with each other. Within each context, during the recall phase, we measured associative coding as the difference of multivoxel correlations among related vs unrelated pairs of events. Neural regions that form integrative representations should exhibit stronger associative coding in the consistent than the inconsistent contexts. We found evidence of integrative representations that emerged quickly in anterior-lateral entorhinal cortex (at session 1), and only subsequently in middle temporal gyrus, which showed a significant change across sessions. A complementary pattern of findings was seen with signatures during learning. This suggests that integrative representations are established early in anterior-lateral entorhinal cortex and may be a pathway to the later emergence of semantic knowledge in middle temporal gyrus.

**Key words:** fMRI; semantic memory; learning; medial temporal lobe; middle temporal gyrus; temporal relations; event cognition; relational memory.

## Introduction

We use experiences of specific events to build general knowledge about typical event structure. For example, by integrating across multiple instances of making coffee, throwing a ball, or going to a restaurant, we come to know the typical components of these events and their typical temporal relations. To recognize common event structure across instances, we must integrate information across diverse experiences and contexts: making coffee with different methods or ordering in restaurants that differ in taste and décor. The complementary learning systems (CLS) theory (McClelland et al. 1995; Norman and O'Reilly 2003) proposes that two distinct systems are involved: an episodic system that rapidly encodes recent experiences and a semantic system that learns more gradually. However, exactly when and where integration takes place remains less well understood.

The hippocampus (HC) is a critical part of the episodic system. It rapidly binds together the temporal and spatial aspects of specific experiences (Sutherland and Rudy 1989; Mishkin 1997; Eichenbaum and Cohen 2001; O'Reilly and Rudy 2001; Eichenbaum 2004; Ranganath 2010; Ranganath and Hsieh 2016) but is less critical for longer ago learned information (Hodges and McCarthy 1995; Levy et al. 2004; Maviel et al. 2004; Frankland and Bontempi 2005; Tse et al. 2007; Wang et al. 2009; Winocur et al. 2010; Lesburguères et al. 2011). It also has a role in some aspects of integration: prior work has shown that the ability to link separately presented stimulus pairs that share a common item, e.g. AB and BC, is critically reliant on an intact HC (Bunsey and Eichenbaum 1996; Dusek and Eichenbaum 1997), is correlated

with HC engagement during learning (Shohamy and Wagner 2008; Kuhl et al. 2010; Zeithamova and Preston 2010; Wimmer and Shohamy 2012; Zeithamova et al. 2012; Schlichting and Preston 2016; Tomparly and Davachi 2017; Barron et al. 2020), and can result in integrative representations linking A and C (Collin et al. 2015; Schlichting et al. 2015; Tomparly and Davachi 2017). However, HC is also known to pattern-separate information associated with distinct contexts (Winocur et al. 2010; Dimsdale-Zucker et al. 2018; Pacheco Estefan et al. 2019; Zheng et al. 2021) and its integrative representations are not typically expected to persist in time.

In contrast, semantic knowledge about long-learned, familiar actions and events, such as the categories *throwing* or *making coffee*, particularly relies on areas in lateral posterior temporal cortex surrounding the middle temporal gyrus (MTG; Bedny et al. 2008; Bedny et al. 2011; Bedny et al. 2013; Bottini et al. 2020; Kable et al. 2005; Leshinskaya and Thompson-Schill 2020; Tarhan et al. 2016; Tranel et al. 2003; Wurm and Caramazza 2021). It is not likely that all of the reviewed effects are in the same functional area, but the broader region can be thought of as a mosaic of highly related functions (see Leshinskaya et al. 2020 for a review). However, little work has examined how representations in MTG are learned or updated with experience. Our prior findings have revealed that MTG represents novel temporal relations learned a week prior (Leshinskaya and Thompson-Schill 2020) but we know little about the mechanisms by which it comes to do so, including when integrated representations begin to form. Cognitively, event and action concepts rely on an understanding of shared relational structure (Miller and Johnson-Laird 1976; Gentner 1983;

Pinker 1989; Markman and Gentner 1993; Markman and Stilwell 2001; Rehder and Ross 2001; Jones and Love 2007; Carey 2009), which offers the hypothesis that relation learning mechanisms in the episodic system are critical to their formation. Yet, in between episodic and semantic relational representations is a large empirical gap.

Here, we consider the possibility that this gap is mediated by the contribution of anterior-lateral entorhinal cortex (alEC). Entorhinal cortex (EC) mediates the major efferent and afferent pathways between HC and cortex (Burwell et al. 1995; Suzuki 1996) but is traditionally depicted as a simple conduit. However, these connections are essential for temporal associative learning (Suh et al. 2011; Kitamura et al. 2014) and increasing evidence reveals recurrent processing between EC and HC and its likely role in forming stable and generalizable memory traces across diverse experiences (Behrens et al. 2018; Boccarda et al. 2019; Baram et al. 2021; Gerlei et al. 2021; Park et al. 2021a). A number of considerations suggest that EC is also more likely to hold integrative mnemonic information than HC (Kumaran and McClelland 2012; Kitamura et al. 2014; Koster et al. 2018). However, its role in integrative and semantic learning, particularly across time, remains poorly investigated. Recent work has also suggested that EC is composed of anatomically and functionally distinct sub-regions, posterior-medial (pmEC) and anterior-lateral (alEC) portions, with the latter specialized for temporal and object-related information (Schroder et al. 2015; Tsao et al. 2018; Bellmund et al. 2019; Montchal et al. 2019). These considerations motivate our hypothesis that alEC specifically has an important role in building temporal relational semantic memory, including by integrating across distinctly cued temporal contexts, and such, serving as a gateway to the later emergence of relational semantic representations in MTG.

To test these ideas, we used functional magnetic resonance imaging (fMRI) to measure neural signatures of learning and memory for novel temporal relations across two sessions one week apart. Stimuli were sequences of animated events (Fig. 1). A given sequence was composed of six different animated, dynamic stimuli (“Events”) repeated over 150 trials according to a probabilistic transition structure. Events took place in the context of a continually present background Object (a novel geometrical figure). The dynamic Event stimuli were either movements of the Object (“movement events”) or appearances of other stimuli surrounding the object (“ambient events”). A transition structure specified the probability that any particular Event followed any other, as designated by a specific role (A–F) for each stimulus. In this structure, Event A (a movement event) was reliably followed by Event B (an ambient event). Participants were encouraged to interpret these temporal relations as the Object “causing” the appearance of the Event by virtue of its movement, which our prior work with similar materials has established participants do readily (Leshinskaya and Thompson-Schill 2019). We assessed various aspects of learning and memory for these sequences during fMRI.

During learning, we measured *surprise* as the difference in BOLD signal between predictable and unpredictable Events and *change in surprise* as the difference in surprise between the start and end of the learning phase. This latter was used to index the amount of learning-related change in a given neural area. Subsequently, during recall, we measured relational memory strength for individual Event pairs using *associative coding*, a difference of multivoxel pattern correlations between related pairs (Event A and Event B) vs unrelated pairs (Sakai and Miyashita 1991; Schapiro et al. 2012).

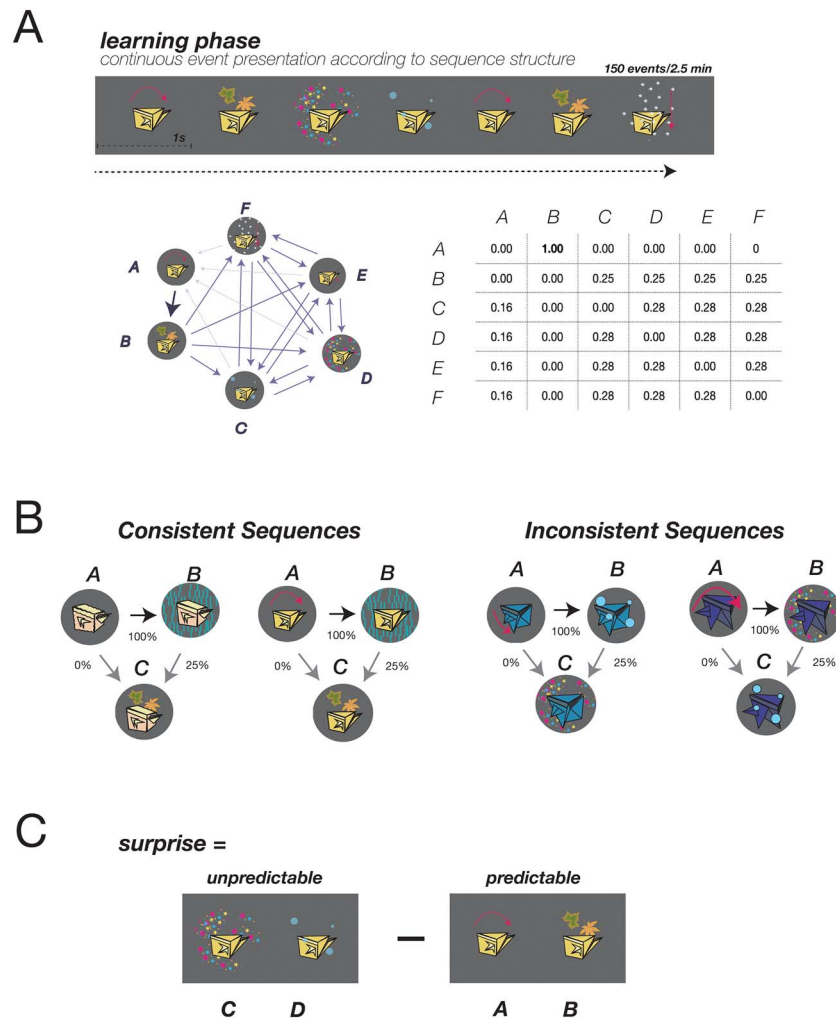
To measure if representations were *integrative*, we compared these measures between different conditions. We assumed that integrative representations would be influenced by cross-context learning history, such that the representation of the current A–B pair would be influenced by the A–B pair learned in the immediately preceding sequence, even though these were shown in different runs and had a distinctive background Object. We thus varied whether the relational structure between consecutively shown sequences was similar or different. In the Consistent condition, the same stimulus served as Event B as in the preceding sequences, so that the Object “caused” the same outcome in each one. In the Inconsistent condition, the stimulus serving as Event B varied between sequences, creating a certain amount of conflict from the relation previously learned. If the representation in a neural area is integrative across contexts, the representation of an A–B pair in a given sequence will be influenced by prior A–B pairs, and will thus be strengthened in Consistent sequences and weakened in the Inconsistent sequences. If representations are not integrative, they will encode the A–B pair of each sequence irrespective of what was learned previously. We were interested in the extent of integration in each ROI at each Session, predicting that these effects would vary between medial temporal and cortical ROIs.

In our paradigm, such integration also required a certain amount of stimulus generalization. The Object in each sequence, including Consistent sequences, had a different shape and Event A was a different movement of that Object, mimicking how, in real-world concepts, different specific movements or actions lead to the same outcome, such as in *making coffee*. This kind of generalization is an important characteristic of action semantics and, thus, integration across such stimulus differences is a signature of semantic knowledge acquisition.

## Methods

### Overview of paradigm

Participants underwent two sessions of MRI scanning, one week apart, with identical materials. Each run began with a Learning phase (Fig. 1A), in which participants explicitly learned the temporal relations among a set of events. These relations were such that Event A (an object movement) was always followed by Event B (an ambient event), but not by Events C–F, which appeared unpredictably. Learning was immediately followed by a Probe phase (Fig. 2A), where a subset of the same Events (A, B, C, and D) again appeared but no longer according to the learned sequence, but instead such that all transitions were equally likely. Thus, any predictive information was only available in memory. The background Object was always present in the Events pertaining to a given sequence. Each sequence was shown in a separate run and belonged either to the Consistent or Inconsistent condition based on its relational similarity to immediately preceding sequences (Fig. 1B). Across Consistent sequences, the relational structure among the stimuli was similar, such that Event B was always the same stimulus (e.g. leaves falling). Across Inconsistent sequences, a different stimulus served as Event B (exchanging their roles from prior sequences). If the representation of an A–B relation in a given sequence is influenced by prior sequences, and thus integrative, it should be strengthened in the Consistent condition and weakened in the Inconsistent condition. The stimuli and sequences for these conditions were identical in Session 2. We examined the effect of Consistency on neural relational memory strength for individual A–B pairs in each sequence in the Probe phase and the overall amount of learning-related change in the Learning phase, across



**Fig. 1.** Learning phase materials, task, and analysis design. (A). Illustration of the Learning phase, using an example set of stimuli for one sequence. Each sequence was 150 trials long and composed of six visually distinct stimuli, “Events,” labeled A–F. The six Events followed a specific sequence transition structure, depicted below (graph; matrix). A background Object (here, the central geometric shape) was continually present during the Events. Events were either the Object moving (“object-based events”) or the appearance of other stimuli in the background (“ambient events”). The transition structure was such that Event A (the “cause”) was always followed by Event B (the “effect”). Event A was always object-based, creating the impression that the Object “caused” the appearance of Event B. Participants’ task was to identify this A–B relationship. (B) In each run, participants saw a unique sequence with a distinct Object. The transition matrix was always the same, but the way the stimuli were assigned to roles A–F could vary. Among Consistent sequences, the same ambient stimuli served as Events B and C; Event A varied, being a distinct movement of each Object. Among Inconsistent sequences, Events B and C varied (in fact, they were swapped, so that the stimuli exchanged roles). A brief demo of the stimuli is available at <https://osf.io/2kxyv>. (C) During the Learning phase, we measured “Surprise” as a differential response to unpredictable stimuli minus predictable (A–B) stimuli. “Change in surprise” measured how much Surprise strengthened over the course of the learning phase.

Session 1 and Session 2, in several critical ROIs (Fig. 3). These included anatomically defined right-lateralized anterior and posterior HC (aHC, pHC), anterior-lateral and posterior-medial EC (alEC and pmEC), two parts of MTG (Glasser atlas areas TE1m and TE1p; Glasser et al. 2016) and two parts of vmPFC (Glasser atlas areas 9m and p32). Except for vmPFC, ROI definitions were pre-registered, as were analysis methods unless otherwise indicated.

## Participants

Thirty participants were recruited from the University of California, Davis community and provided written informed consent. Procedures were approved by the UC Davis Institutional Review Board. Twenty-four participants (18 female, 6 male; mean age 24 years) were included in analyses: four were excluded for excessive head motion and two did not complete both sessions. This target sample size was pre-registered. All were neurologically healthy, right-handed, and eligible for fMRI.

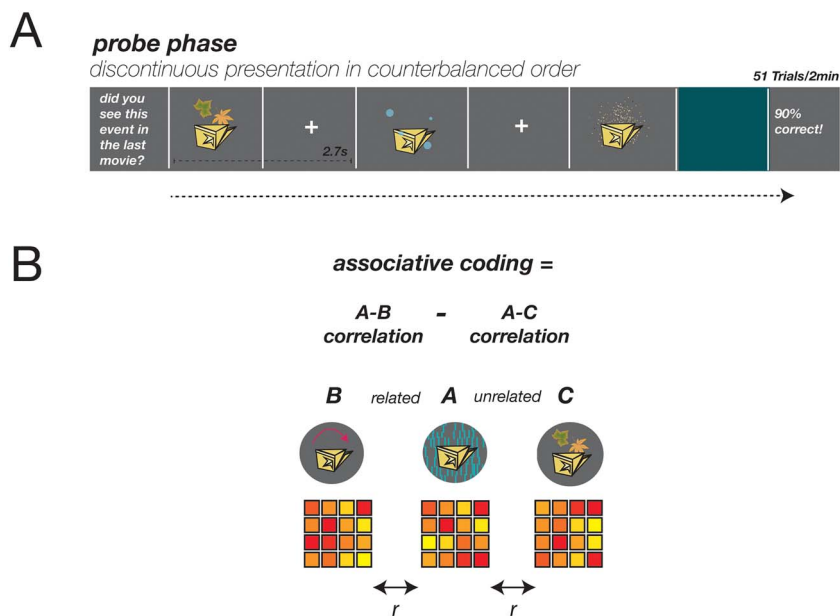
## Preregistration

Methods were pre-registered on the Open Science Framework at <https://osf.io/5xpza/>, DOI:10.17605/OSF.IO/5XPZA. The present report focuses on a subset of the data collected and described in the pre-registration. Deviations and exploratory (additional) analyses are indicated throughout.

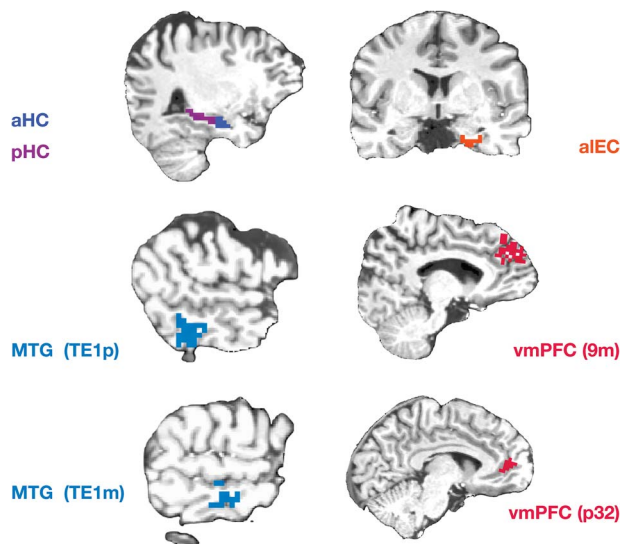
## Stimuli & Procedure

Participants took part in two sessions, 1 week apart, and performed six runs of fMRI scanning in each session (as well as other tasks not reported here). Each run pertained to one of the different sequences and consisted of a Learning phase followed immediately by a Probe phase and lasted 5 minutes.

During the Learning phase (152 s), participants watched a continuous sequence of 150 1-s-long Events that was created from six distinct animated stimuli. The animations included a continually



**Fig. 2.** Illustration of the Probe phase task and analyses. (A) Participants performed a cover task in which they indicated whether each Event was one they had seen in the prior Learning phase. The order of Events did not follow the learned sequence structure but was rather counterbalanced such that each transition was equally likely, allowing us to estimate the neural response to each event independently of the others. (B) During the Probe phase, Associative coding was used as an index of relational memory strength between A and B. The neural response to each individual event (A–D) was estimated at each voxel (depicted for illustration as grids of squares). In a given ROI, the correlation among the voxel response patterns for each pair of events was computed. The difference in correlation between pairs A and B vs A and C and A and D served as the measure of relational memory strength (associative coding).



**Fig. 3.** ROIs: hand-traced aHC, pHC, aIEC, examples in an individual participant. MTG and vmPFC areas were defined using the surface-based Glasser anatomical atlas (Glasser et al. 2016) using areas TE1p, TE1m, 9m, and p32.

present background Object, and the Events could be “ambient” (various items that appeared, moved, and disappeared around the Object, such as bubbles, leaves, or stars) or object-based (a rotation, vibration, or part movement of the Object). There were five distinct object-based events in total and six distinct ambient events in total.

Stimuli were assigned to the roles of Events A–F such that Event B, C, and D were perfectly counterbalanced across participants. As such, each stimulus served each role the same number of

times across participants. Thus, associative coding analyses controlled for stimulus effects. Events C and D were typically grouped together for analyses given their equivalence in the experiment.

The roles A–F designated a particular statistical role in the sequence. Event B was strongly and uniquely predicted by Event A, whereas the appearance of Events C–F was relatively random. To convey this relational structure, the sequential appearance of Events A–F was governed by a transition matrix that specified the probability of any Event appearing, given the occurrence of any other (Fig. 1A). Participants’ task was to identify the predictable Event B, called “the effect,” which they selected in a four-alternative forced-choice question at the end of the run from alternatives Events C, D, and F. This test ensured that participants had identified Event B during learning on the basis of its predictability. The 150-event-long sequence was generated probabilistically, including a random selection of the first Event in the sequence, then proceeding to select the subsequent events according to the probabilities in the transition matrix.

During the Probe phase (135 s), participants’ task was to indicate, for each Event, if it had appeared in the just-seen sequence or was novel. Events shown included all the events from the Learning phase except Event E (to increase efficiency as it was not of interest to analyses). Additionally, a null trial (a turquoise rectangle) was shown to create an implicit baseline and thus improve the ability to separately estimate the response to each other Event. For the purpose of the task, Lure Events were added by selecting randomly from other sequences (seven trials total). Events no longer followed the predictive structure of the Learning phase; they instead appeared in counterbalanced order, such that each Event followed every other an equal number of times (exactly seven for Events of interest and lures, and eight times for the null event). There were 50 trials in total. The events also appeared discontinuously: the entire background object disappeared and the animated event was replaced with a fixation cross for 1.7 s

for a total ITI of 2.7 s per trial (Fig. 2A). This was designed to discourage participants from continuing to learn about any sequence structure among the events.

The sequences (shown in separate runs) differed in the ways the particular stimuli were assigned each Event Role A–F, although the transition structure was always the same. Sequences 1–3 were Consistent in their relational structure, while Sequences 4–6 were Inconsistent (Fig. 2B). Within Consistency conditions, sequences were shown consecutively but the order of the two conditions was counterbalanced across subjects. Thus, participants either saw 1–3 followed by 4–6, or 4–6 followed by 1–3. In either order, Sequence 1 was never “consistent” with anything prior and was thus considered Inconsistent for purposes of analyses, unless indicated otherwise.

The Consistent sequences each used a distinct object-based stimulus as Event A (e.g. *tilting*, *color changing*, or *rippling*). Event B was always the same stimulus (e.g. *bubbles*), as was Event C (e.g. *leaves*). Event D could vary among the sequences (for the purposes of the cover task) but never conflicted with other Event types. The relational structure among Events was thus kept consistent, in that Events which served the predictable role always stayed the same and those participating in unpredictable roles either continued to do so or were new.

In the Inconsistent sequences, distinct object-based stimuli again served as Event A, exactly as in the Consistent sequences (e.g. were again *tilting*, *color changing*, and *rippling*). However, the stimuli serving the roles of Events B exchanged roles with Events C or D. For example, in Sequence 4, Event B could be stars, whereas Events C and D were *bubbles* and *leaves*. In Sequence 5, Event A would be leaves while Events C and D are stars and bubbles, etc. Thus, the relational structure was conflicting among the Inconsistent sequences.

The sequences were distinguished by a unique Object present in all of that sequence’s events. To encourage integration, the three sequences belonging to the same Consistency condition were assigned similarly-shaped objects, as depicted in Fig. 2. Thus, Sequences 1–3 had three similarly-shaped objects and Sequences 4–6 also had similarly-shaped objects. The specific set of three shapes assigned to each condition were counterbalanced.

Session 2 was identical to Session 1: the same stimuli and sequences were shown to the participants in the same order. This means that the Consistent sequences remained consistent with those shown in Session 1, such that if the shared Event B was *bubbles* in Session 1, it was the same in Session 2. Inconsistent sequences were also repeated. The only difference was that at the very end of Session 2, the scan was followed by an additional set of forced-choice questions regarding all of the Events from all sequences participants had learned about. On each question, participants selected between two snippets of Event pairs (drawn from one of the six sequences): either A–B vs A–C or A–B vs A–D. These were different and harder than prior questions because they included questions about every sequence in a single, inter-mixed question set. This required participants to recall which Event stimuli were related in the context of each Object, which was challenging as many of the Event stimuli were the same. For an analysis of these questions, Sequence 1 was grouped with the Consistent sequences.

## fMRI acquisition

MRI data were acquired using a Siemens Skyra 3 T scanner at UC Davis using a 32-channel coil. Anatomical volumes were acquired with a T1-weighted MPRAGE sequence with  $1 \times 1 \times 1 \text{ mm}^3$  voxel resolution, 256 mm field of view, time to repetition (TR) = 1.90 s, and time to echo (TE) = 3.06 ms. Functional data were acquired

with a multiband echo-planar imaging (EPI) blood oxygen level-dependent (BOLD) sequence using 64 interleaved slices with a multiband acceleration factor of 2,  $3 \times 3 \times 3 \text{ mm}^3$  in-plane voxel resolution,  $64 \times 64 \text{ mm}^2$  matrix size, TR = 1,250 s, TE = 24 ms, and flip angle =  $76^\circ$ . Slices were aligned to  $-36^\circ$  from ACPC to minimize anterior temporal distortion. Static fieldmap estimation were performed by collecting four volumes in the reverse encoding direction as the main scans.

## Analyses

Preprocessing was performed with the fMRIPrep package with standard defaults as well as freesurfer and AFNI packages. Anatomical scans were skull-stripped and white matter was segmented from gray. Functional data were registered to the pre-processed anatomical scans using the function *flirt*, and head-motion and rotation realignment parameters extracted. Signal outliers were identified and a high-pass filter of 128 s was applied. Functional slices were slice-time corrected and corrected for distortion based on fieldmap estimation. Finally, functional data were smoothed with a 4-mm full-width half-maximum Gaussian kernel.

Linear models were used to estimate condition coefficients on fMRI timeseries. Regressors of no-interest included six motion and rotation realignment parameters and their first-order derivatives; voxels flagged as signal outliers during preprocessing were excluded. Regressors of interest were created for each type of Event seen during the Learning phase (A–F) and Probe phase (A, B, C, D, F, and lure trials) separately, with null trials and fixation periods as the implicit baseline. Learning phase data were binned by time in order to examine changes during this phase: trials of each event type were assigned to a bin based on their order of appearance, such that bin 1 for event C included the first three appearances of event C, bin 2 the next three, and so on, for a total of five bins per event type. Because Events A and B were perfectly colinear during the Learning phase, they formed the same regressor, AB.

During the Learning phase, we computed a measure of “surprise” as a contrast between the unpredictable Events (C and D) minus the predictable Event pair AB, at each time bin. The slope of this measure across time bins were used as a measure of learning, as changes in the magnitude of this difference must be attributable to learning-related processes.

During the Probe phase, we measured relational memory strength using a multivariate measure, *associative coding*, which compared voxelwise correlations among pairs of Events. For each individual condition, the t-value of the coefficients from linear modeling for a given event type was extracted in each voxel, reflecting the extent to which that voxel was activated in response to that condition relative to the null trials. For a given region of interest (ROI), this produced a vector of t-values for all of the voxels in that ROI. This vector was then correlated pairwise between specific pairs of conditions, here A & B, A & C, and A & D, and then subtracted. The difference in correlation between A and B minus the other two pairs served as the measure of relational memory strength for the A–B pair. This was done in the same fashion for each sequence, performed separately, and then grouped by condition for analyses as follows: Consistent sequences 2 and 3 composed the Consistent condition while Consistent sequence 1 (the first shown), and Inconsistent sequences 4–6 composed the Inconsistent condition. For behavioral analyses, Events C and D were combined into a single condition (henceforth “C/D”) as they were functionally identical and served the same role in relevant analyses.

## ROI definition

The ROIs reported are shown in Fig. 3. HC was defined using automatic segmentations performed by Freesurfer, then split into anterior and posterior portions by hand using morphological criteria: the head was labeled as anterior and the body and tail were labeled posterior. This split was motivated by prior observations regarding functional differences between anterior and posterior HC in the memory integration literature and others (Poppenk et al. 2013; Preston and Eichenbaum 2013; Schlichting et al. 2015; Schapiro et al. 2017). EC was hand-traced, with aEC and pmEC delineated using tracing criteria guided by previous validation studies (Maass et al. 2015) and the split motivated by functional differences between these subregions (Schroder et al. 2015; Bellmund et al. 2019). Our preregistration indicated that functional differences between aEC and pmEC were expected, with aEC predicted to be relevant here given past work showing its role in temporal relational memory (Bellmund et al. 2019). No evidence of associative coding was seen in pmEC and it was not further considered. For MTG and other cortical areas, we used the Glasser cortical-surface based atlas (Glasser et al. 2016) aligned to individual anatomical surfaces to create individual anatomical ROIs. Prior work on MTG, including ours, does not offer a particular functional or anatomical definition, but we chose the Glasser atlas so as to improve replicability for future work. Our pre-registration indicated two Glasser areas for MTG: right TE1p and TE1m, but we noted in our pre-registration that pilot data indicated TE1p to be of particular importance, which held up in these data as well as no associative coding was observed in TE1m. Our pre-registration also described a functional localizer that did not work and is not reported here. We did not pre-register vmPFC, but chose Glasser ROIs p32 and 9m based on proximity to previously reported results (Schlichting and Preston 2016; Tomparly and Davachi 2017); this was motivated directly by connecting our work to past findings. The focus on the right hemisphere throughout is based on prior work showing the role of right MTG in associative coding for similar stimuli (Leshinskaya and Thompson-Schill 2020). In exploratory analyses, we also examined left-lateralized areas and further address the issue of laterality in the Discussion.

## Searchlight analysis

Freesurfer software was used to generate inflated cortical surfaces for each participant (Dale 1999; Fischl et al. 1999; Fischl et al. 2004), which were aligned into a common space and to functional data using AFNI (maplcosohedron) and algorithms implemented in the Surfing toolbox (Oosterhof et al. 2014, 2011). Surfing software was also used to define searchlight neighborhoods (curved cylinders that conform to individual surface topography) of 27 voxels in size. Analyses were then performed in each neighborhood, treated equivalently to an ROI, and results plotted on the cortical surface maps at the center coordinate of each neighborhood.

Multiple comparison correction was performed using permutations over maximal cluster sizes, which tests the probability of obtaining a cluster of a given size by chance alone. Clusters are defined as contiguous activations above a given individual activation threshold (here,  $P < 0.001$ ). Permutations are created by creating null maps, data that are not expected to reflect real effects, by exchanging condition labels at the linear modeling stage. However, null maps retain smoothness. Ten null maps were created for each participant, then sampled randomly for group analyses, which were performed as usual. At each of 1,000 iterations, a group test is performed and the largest observed cluster size is recorded, creating a null distribution of maximal cluster

sizes under the assumption of no meaningful data. Observed clusters can then be evaluated for probability using this distribution.

## Results

### Behavior during the probe phase

During the Probe phase, participants identified whether Events were part of the just-seen sequence or not with high accuracy both in Session 1, Consistent  $M = 99.1\%$ , Inconsistent  $99.0\%$ , and Session 2, Consistent  $M = 99.1\%$ , Inconsistent  $M = 99.7\%$ , indicating high vigilance on the cover task. Analyses reported in the Supplement established that accuracy and reaction time (RT) data were not confounded with the fMRI analyses.

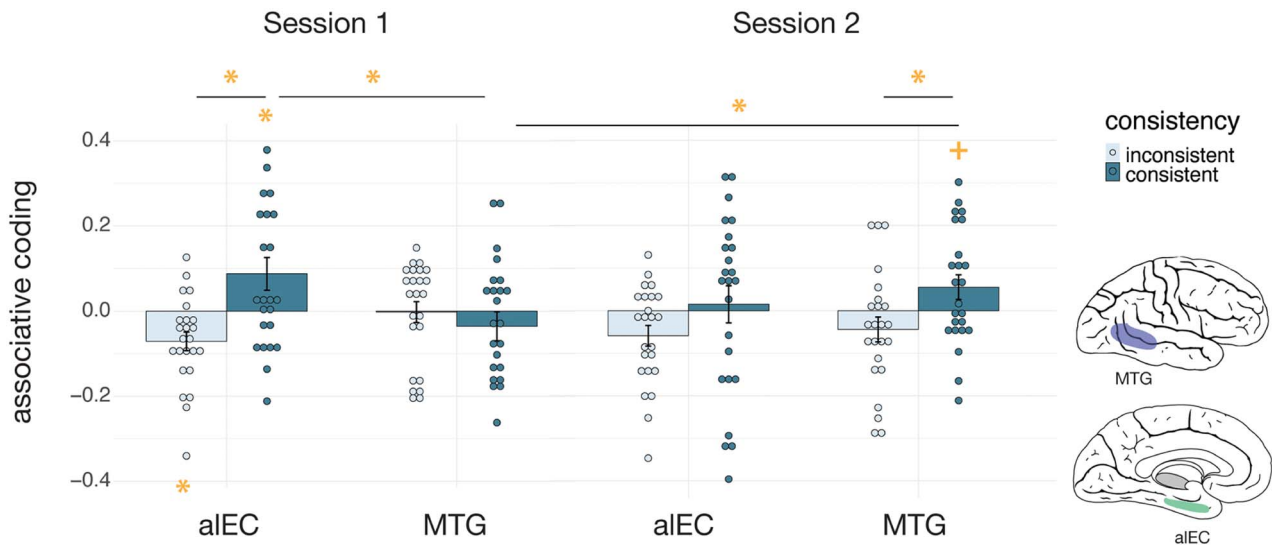
During the Probe phase, the order of Events was counterbalanced such that all Event transitions were equally likely, but it could be expected that cover task RTs would be facilitated for transitions that had been more likely during learning. We thus examined whether RTs to Event B differed as a function of whether it was preceded by the predictive Event A or by unpredictable Events C or D. A Consistency by Transition Type ANOVA in Session 1 revealed a main effect of Transition Type,  $F(1,23) = 5.948$ ,  $MSE = 0.0252$ ,  $P = 0.023$ , indicating that, counter-intuitively, RTs to Event B were slower when preceded by predictive than unpredictable events. Simple effects revealed that this effect was significant within the Inconsistent condition,  $t(23) = 2.29$ ,  $P = 0.031$ , but not in the Consistent one ( $P > 0.20$ ). No effects were seen in Session 2. The full pattern of results is shown in Figure S1. Overall, this shows reverse behavioral facilitation in the Inconsistent condition in Session 1, with unpredictable Events C/D facilitating RTs to Event B relative to its predictor, Event A, perhaps reflecting the conflict created in this condition.

### Associative coding during the probe phase

We measured relational memory strength for each individual A–B pair using associative coding: a previously reported effect in which events related in memory exhibit a more correlated neural response than unrelated events (Sakai and Miyashita 1991; Schapiro et al. 2012). During the Probe phase of each run, we obtained an independent measure of the neural response to each Event Type (A, B, C, and D), producing for each one a vector of voxel responses in each ROI. Within each run, we correlated the vector of voxel responses to Event A with that of Event B, subtracting from this the average correlation of Event A and Event C and of Event A and Event D (Fig. 2B). This correlation difference served as our dependent measure, associative coding, separately for each learned sequence/run. Associative coding greater than 0 indicated evidence of relational memory. To investigate whether representations were integrative, we tested whether the magnitude of associative coding varied by Consistency condition. Effects of Session were used to understand how relational memory strength varied as a function of exposure and time, and interactions between Consistency and Session to understand the influence of exposure and time on the extent of integrative coding.

### Anterior-lateral entorhinal cortex

Associative coding in each condition in aEC is shown in Fig. 4. If aEC memory representations are integrative, associative coding should be stronger in the Consistent condition than the Inconsistent condition. A Session by Consistency ANOVA revealed that associative coding in aEC was higher in the Consistent than Inconsistent sequences,  $F(23,1) = 8.999$ ,  $MSE = 0.323$ ,  $P = 0.006$ , with



**Fig. 4.** Associative coding for individual A–B pairs in aIEC and MTG (TE1p) as a function of Consistency and Session. In Session 1, aIEC exhibited associative differentiation in the Inconsistent condition but positive associative coding in the Consistent condition, with a significant difference between these; no effects were seen in Session 2 but there were no interactions with Session. MTG showed significantly less associative coding than aIEC in Session 1. In the Consistent condition, associative coding increased in Session 2 vs Session 1 in MTG, yielding a Consistency effect in Session 2. A three-way interaction indicated that these ROIs exhibited effects of Consistency of different magnitudes in Session 1, but not in Session 2. Error bars indicate standard error of the mean (SEM), asterisks denote effects significant at  $P < 0.05$ , crosses indicate marginally significant effects.

no effect of Session. We further examined effects within Session. There was an effect of Consistency in Session 1,  $M = 0.158$ ,  $t(23) = 3.214$ ,  $P = 0.004$ , such that Consistent sequences exhibited significant associative coding,  $M = 0.088$ ,  $t(23) = 2.349$ ,  $P = 0.028$ , while Inconsistent sequences exhibited significant differentiation, that is, negative associative coding,  $M = -0.071$ ,  $t(23) = -3.306$ ,  $P = 0.003$ . Differentiation indicates that Events A and B were less correlated than Events A and C or D. Within Session 2, however, there was no effect of Consistency. Consistent sequences did not show associative coding or differentiation, although there was significant differentiation in Inconsistent sequences,  $M = -0.059$ ,  $t(23) = -2.463$ ,  $P = 0.022$ . We saw no evidence of associative coding in any condition (all  $P > 0.30$ ) or any differences in pmEC (all  $P > 0.40$ ).

While surprising, differentiation, in which associated stimuli are pulled apart in their neural patterns, is a commonly reported phenomenon (Barron et al. 2017; Ritvo et al. 2019; Brunec et al. 2020; Wammes et al. 2021) and may especially arise in the Inconsistent condition because relations were conflicting with prior sequences. This neural effect also aligns with the RT findings reported above, which showed inhibition of A–B transitions relative to C/D–B transitions, although there was no significant correlation across participants for these behavioral and neural measures (the amount of associative coding for Inconsistent sequences in Session 1,  $r = 0.33$ ,  $P = 0.11$ , and Session 2,  $r = -0.19$ ,  $P > 0.30$ ).

Overall, aIEC exhibited associative coding that was highly sensitive to relational consistency in Session 1, such that it was strongly positive in the Consistent condition and negative in the Inconsistent condition, indicating integrative representations. These effects were absent in Session 2 but there was also no significant decline.

### Hippocampus

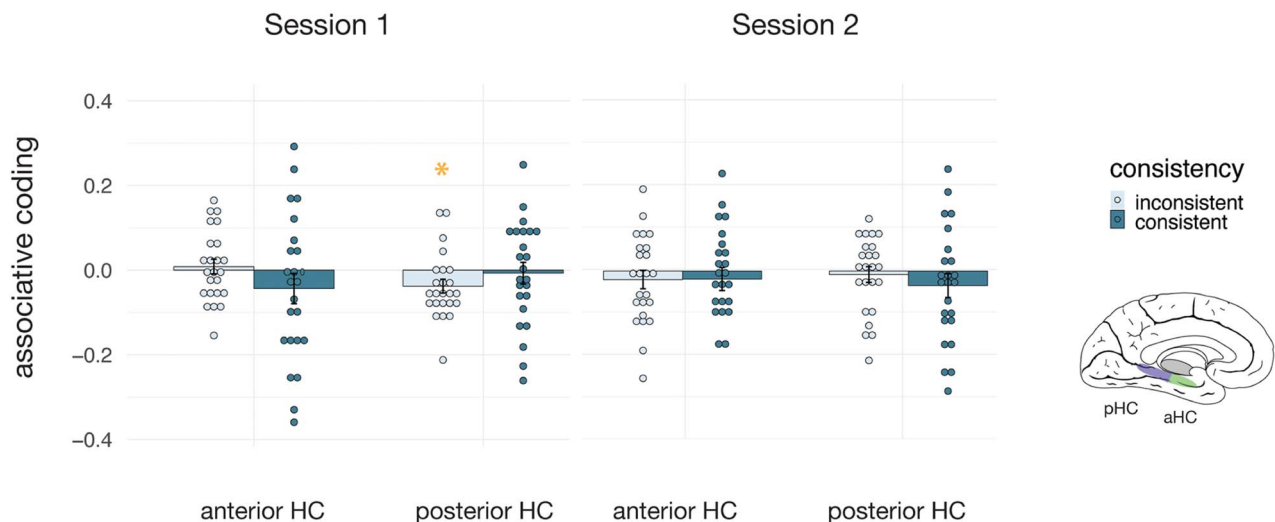
In aHC, we saw no significant associative coding in any condition (Fig. 5). A 2 Session (1 vs 2) by Consistency (Consistent vs Inconsistent) ANOVA did not reveal any effects. There were also no effects of Consistency within Session 1 or Session 2, all  $P > 0.20$ .

In pHC, a Session by Consistency ANOVA likewise did not reveal any effects and there were no effects of Consistency within Session 1 or Session 2. Associative coding was negative in the Inconsistent condition in Session 1,  $M = -0.038$ ,  $t(23) = -2.359$ ,  $P = 0.027$ , like in aIEC and in alignment with the reported RT findings but also did not correlate with them across individual participants. In summary, there was little evidence of positive associative coding in HC, and no reliable influence of Session or Consistency, indicating little participation of HC in the Probe phase.

Although HC and EC are anatomically interconnected, effects in aIEC and pHC appeared divergent. To test this directly, we compared associative coding in aIEC and pHC using an ROI by Session by Consistency ANOVA. This revealed a marginal main effect of Consistency,  $F(23,1) = 4.250$ ,  $MSE = 0.167$ ,  $P = 0.05$  and an ROI by Consistency interaction,  $F(23,1) = 8.998$ ,  $MSE = 0.156$ ,  $P = 0.006$ , indicating that aIEC was more sensitive to Consistency than pHC. This was significant within Session 1,  $F(32,1) = 6.25$ ,  $P = 0.02$ , and within Session 2,  $F(23,1) = 4.69$ ,  $P = 0.041$ . When aIEC was compared with aHC, there was similarly an ROI by Consistency interaction,  $F(23,1) = 13.99$ ,  $P = 0.001$ , which specifically held in Session 1  $F(23,1) = 13.11$ ,  $P = 0.001$  but not in Session 2,  $P > 0.10$ . This reveals overall that integrative coding was generally higher in aIEC than HC.

### Middle temporal gyrus

In MTG, using the TE1p ROI, a Consistency by Session ANOVA showed a Consistency by Session interaction,  $F(23,1) = 6.589$ ,  $MSE = 0.106$ ,  $P = 0.017$  (Fig. 4). Within Session 1, there was no evidence of associative coding in any condition, nor any Consistency effects, indicating little participation of this area. In Session 2, however, associative coding was significantly higher for Consistent than Inconsistent sequences,  $t(23) = 2.99$ ,  $P = 0.007$ . Associative coding in Session 2 was marginal for Consistent sequences,  $M = 0.055$ ,  $t(23) = 1.970$ ,  $P = 0.061$ , but not significant in the Inconsistent ones,  $M = -0.044$ ,  $P > .13$ . Correspondingly, there was stronger associative coding in Session 2 than Session 1 within Consistent sequences,  $t(23) = -2.491$ ,  $P = 0.020$ , but not within



**Fig. 5.** Associative coding for individual A–B pairs in aHC and pHC in Session 1 and Session 2 as a function of Consistency. In Session 1, pHC exhibited negative associative coding (“differentiation”) such that related Events (A–B) exhibited less correlated responses relative to unrelated Events (A–C and A–D). No area exhibited positive associative coding. Error bars indicate SEM and asterisks denote effects significant at  $P < 0.05$ .

Inconsistent ones,  $P > 0.25$ , explaining the Consistency by Session interaction. This indicates that MTG showed highly integrative representations, but only in Session 2, with a significant increase from Session 1.

We did not see any effects in TE1m, an ROI we had pre-registered but had noted was less likely to show effects based on a prior pilot sample. In Session 1, there was no associative coding in either condition ( $P > .20$ ) and no condition difference ( $P = 0.17$ ), and similarly so in Session 2 (all  $P > 0.38$ ), and no effects of Session ( $P > 0.65$ ). This suggests our effects are relatively anatomically specific to the more posterior ROI, which is also in line with many of the findings on action and event knowledge in posterior aspects of MTG (Leshinskaya et al. 2020). Effects were also specific to the right hemisphere, which we had pre-registered as the focus due to the right-lateralization of prior findings (Leshinskaya and Thompson-Schill 2020).

The MTG (TE1p) effect appears qualitatively different from that of aLEC. We thus tested whether MTG showed a quantitatively different pattern of effects than aLEC using an ROI by Session by Consistency ANOVA over associative coding in the two ROIs. This revealed a main effect of Consistency,  $F(23,1) = 7.388$ ,  $MSE = 0.266$ ,  $P = 0.012$ , an ROI by Consistency interaction,  $F(23,1) = 5.709$ ,  $MSE = 0.083$ ,  $P = 0.026$ , and a three-way interaction between ROI, Session, and Consistency  $F(23,1) = 6.59$ ,  $MSE = 0.141$ ,  $P = 0.017$ . Within Session 1, there was an ROI by Consistency interaction,  $F(23,1) = 14.39$ ,  $MSE = 0.220$ ,  $P < 0.001$ , whereas in Session 2, there was a main effect of Consistency,  $F(23,1) = 7.439$ ,  $MSE = 0.180$ ,  $P = 0.012$ , and no interactions. This reveals that both ROIs were sensitive to Consistency in Session 2, but in Session 1, aLEC was more sensitive than MTG. Follow-up t-test showed that associative coding was stronger in aLEC than MTG among Consistent objects in Session 1,  $t(23) = 2.488$ ,  $P = 0.0206$ , and that the Consistency effect in Session 1 was stronger in aLEC than MTG,  $t(23) = 3.794$ ,  $P < 0.001$ . Overall, this reveals that MTG showed an effect of consistency primarily in Session 2, whereas aLEC did so at both timepoints, and the three-way interaction demonstrated that these patterns of effects were reliably different between the ROIs.

### vmPFC

Because of the relevance of vmPFC to theories of memory integration (Schlichting and Preston 2015), we performed similar

analyses in two anatomically defined vmPFC ROIs (Glasser areas p32 and 9 m). In 9 m, a Session by Consistency ANOVA revealed no effects (all  $P > 0.10$ ); within-Session effects were also unreliable ( $P > 0.07$ ). In p32, there were no effects overall or within Session (all  $P > 0.14$ ). Associative coding was not significantly positive or negative in any condition. Thus, there was little evidence of associative coding in vmPFC in the Probe phase.

Prior work on vmPFC, however, has often reported mean activation differences, notably more activation during “congruent” or consistent information (Tse et al. 2011; van Kesteren et al. 2013), rather than effects on the strength of mnemonic information encoding as examined above. In post-hoc analyses that better correspond to these prior approaches, we examined mean activation during the Probe phase as a function of Consistency. In Session 1, we saw marginally more activation in the Inconsistent than Consistent condition, in 9 m  $t(23) = -2.059$ ,  $P = 0.051$ , and significantly in p32,  $t(23) = -2.208$ ,  $P = 0.038$ . This is opposite in direction to prior reports. No mean activation effects were observed in HC, aLEC or MTG (post-hoc analyses).

### Searchlights

To identify any additional areas that might show Consistency or Session effects on associative coding, we used whole-brain searchlights. We did not find any clusters passing the significance threshold, but sub-threshold maps reveal that the strongest areas to show a Consistency by Session interaction were in the vicinity of our MTG ROI and precentral sulcus (Fig. S2, Supplementary data). This suggests that our MTG findings are relatively anatomically specific. Further searchlight results are shown in the Supplementary Data.

### Learning phase

During the Learning phase at the start of each run (Fig. 1A), participants were either initially exposed (Session 1) or re-exposed (Session 2) to predictive information by watching each intact sequence (the memory of which we examined during the Probe phase.) The Learning phase fMRI data provided an opportunity to examine how the roles of our ROIs in memory compare to their roles in learning. To measure learning-related signals, we used a measure of “surprise” (Fig. 1C) as the differential activation to unpredictable vs predictable events. During this phase, Event



B always followed A, and thus could be anticipated, whereas Events C and D could not be anticipated. (Events A and B had to be modeled as one regressor, as they were perfectly temporally correlated). This differential response could be in either direction, where a positive value would reflect a stronger response to unpredictable information and a negative value would reflect a stronger response to familiar information, perhaps due to recollective processes. Either response is expected to scale as participants increasingly learn to identify the predictive pairs. We thus computed “change in surprise” as the difference in surprise between the start and end of each learning phase to measure the amount of learning-related change in each ROI. This was then compared to 0 to measure if learning-related change was reliable (positive or negative), and then compared between Sessions and Consistency conditions. If change in surprise is stronger in the Consistent than Inconsistent condition, then an area exhibited more learning-related change in situations where information could be built up from the preceding sequences than when it conflicted, suggesting that learning was facilitated by Consistency and was thus integrative. Although these measures were pre-registered, we had not pre-registered the comparisons between Consistency conditions or Sessions for surprise, so these analyses are exploratory and motivated by comparing them to effects observed in the Probe phase.

### Anterior-lateral entorhinal cortex

Overall surprise in aLEC was negative but not significantly different from zero (Session 1:  $M = -0.028$ ,  $P > 0.40$ ; Session 2,  $M = -0.048$ ,  $P > 0.15$ ). However, there was significant change in surprise, indicating that a stronger response to predictable than unpredictable events increased with learning. Session 1, Consistent sequences showed significant negative change in surprise,  $M = -0.061$ ,  $t(23) = -3.01$ ,  $P = 0.006$ , but Inconsistent sequences showed no change,  $M = 0.037$ ,  $P > 0.10$  (Fig. 6). A Session by Consistency ANOVA on change in surprise revealed a Consistency by Session interaction,  $F(23,1) = 12.100$ ,  $MSE = 0.154$ ,  $P = 0.002$ , revealing a Consistency effect within Session 1,  $t(23) = -3.215$ ,  $P = 0.004$ , but not in Session 2. Session comparisons revealed that Consistent sequences showed more change in surprise in Session 1 than Session 2,  $t(23) = -2.256$ ,  $P = 0.034$ , whereas Inconsistent sequences showed more change in surprise in Session 2 than in Session 1,  $t(23) = 2.240$ ,  $P = 0.035$ , explaining the interaction. Change in surprise was not significant in Session 2 in either condition,  $P > 0.10$ . Thus, change in surprise in aLEC was sensitive to Consistency and Session, with stronger (more negative) effects of Consistency in Session 1 than in Session 2. This indicates integrative representations that were updated more in Session 1 than in Session 2.

### Hippocampus

Surprise in aHC was also overall negative (Session 1,  $M = -0.907$ ,  $t(23) = -3.40$ ,  $P = 0.003$ , Session 2,  $M = -0.914$ ,  $t(23) = -2.53$ ), as was change in surprise: there was significant negative change in surprise in Session 1 in Consistent sequences,  $M = -0.057$ ,  $t(23) = -2.535$ ,  $P = 0.019$ , and marginally so in Inconsistent sequences,  $M = -0.040$ ,  $t(23) = -2.01$ ,  $P = 0.056$ , but no change in surprise in Session 2,  $P > 0.20$ . A Session by Consistency ANOVA did not reveal any effects of Consistency or Session on change in surprise magnitude (Fig. 7). Thus, although aHC showed some learning-related changes in Session 1, these did not vary by Session or Consistency. The observation of negative surprise in aHC is consistent with the observation that unpredictability per se does not largely drive HC responses and that instead, recollective

processes engaged during predictive trial pairs might dominate the responses here (Kumaran and Maguire 2007). However, there was no evidence of change or condition differences. In pHC, there was no significant change in surprise and no effects in a Session by Consistency ANOVA.

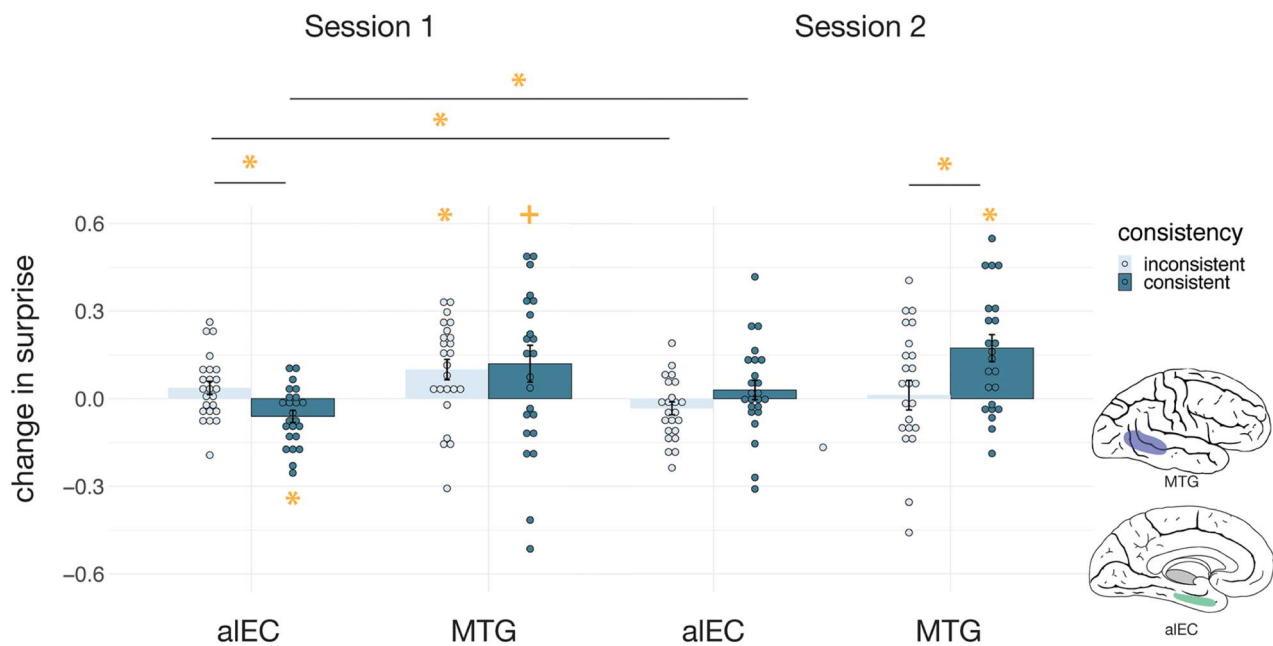
The above set of results suggest that aLEC might be more sensitive to Consistency than aHC. We tested this directly using a three-way ANOVA over change in surprise, with factors ROI, Session, and Consistency. This revealed a three-way interaction,  $F(23,1) = 4.434$ ,  $MSE = 0.049$ ,  $P = 0.046$ , and a two-way interaction between Session and Consistency,  $F(23,1) = 6.685$ ,  $MSE = 0.112$ ,  $P = 0.017$ . Simple effects revealed that across both ROIs, the effect of Consistency was overall larger (more negative) in Session 1 vs Session 2,  $t(23) = -2.586$ ,  $P = 0.017$ . Moreover, the Consistency effect changed more between Session 1 and Session 2 in aLEC than aHC,  $t(23) = -2.106$ ,  $P = 0.046$ . However, there were not greater Consistency effects overall in aLEC than aHC. This suggests these areas were not differentially sensitive to Consistency overall, but that aLEC exhibited more Session differences. This is consistent with the idea that integrative learning in aLEC declined by Session 2.

### Middle temporal gyrus

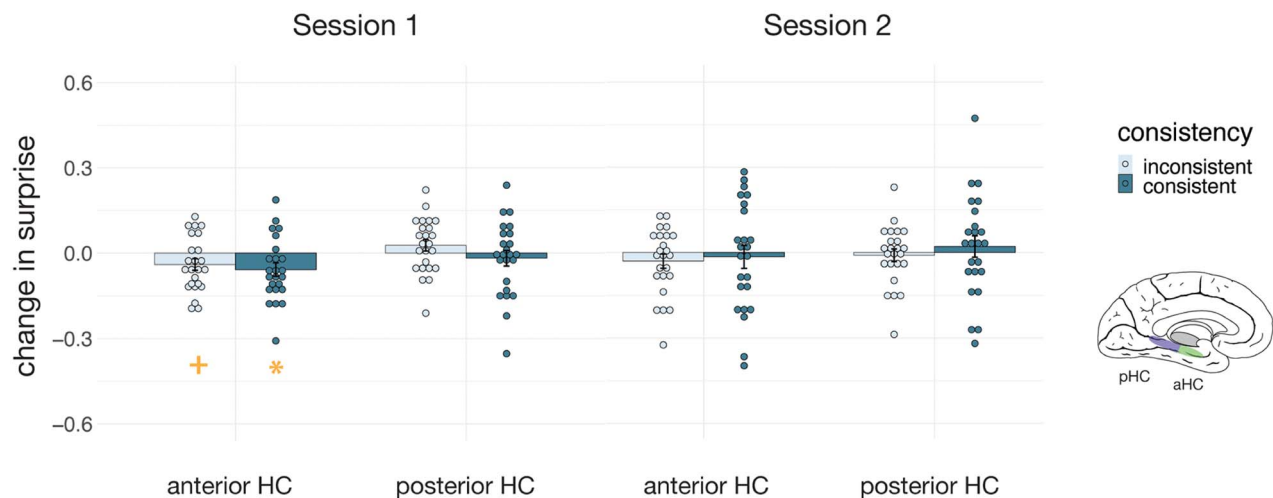
Unlike aLEC and aHC, MTG exhibited positive change in surprise, i.e. more activation in response to unpredictable than predictable increasing with learning (Fig. 6). Overall surprise was positive but not different from zero (Session 1,  $M = 0.080$ ,  $P > 0.17$ ; Session 2,  $M = 0.046$ ,  $P > 0.40$ ). However, surprise changed significantly over exposure. In Session 1, Consistent sequences showed marginally positive change in surprise,  $M = 0.112$ ,  $t(23) = 1.945$ ,  $P = 0.064$ , and Inconsistent ones were significantly positive,  $M = 0.100$ ,  $t(23) = 2.900$ ,  $P = 0.008$ . In Session 2, the change in surprise was significantly positive within Consistent sequences,  $M = 0.174$ ,  $t(23) = 3.847$ ,  $P < 0.001$ , but not within Inconsistent ones,  $M = 0.013$ ,  $P > 0.80$ . A Session by Consistency ANOVA on change in surprise revealed only a marginal main effect of Consistency,  $F(23,1) = 3.887$ ,  $MSE = 0.197$ ,  $P = 0.061$  and no interactions. Within Session 1, there was no effect of Consistency,  $P > 0.70$ , but there was in Session 2,  $t(23) = 2.511$ ,  $P = 0.020$ . Overall, MTG exhibited learning-related change activity throughout both Sessions with only some evidence of Consistency differences.

To quantify differences between MTG and aLEC, a three-way ROI by Session by Consistency ANOVA revealed a main effect of ROI,  $F(23,1) = 13.890$ ,  $MSE = 0.559$ ,  $P = 0.001$ , an interaction between ROI and Consistency,  $F(23,1) = 6.066$ ,  $MSE = 0.140$ ,  $P = 0.022$ , and an interaction between Session and Consistency,  $F(23,1) = 8.642$ ,  $MSE = 0.272$ ,  $P = 0.007$ . Within Session 1, there was a main effect of ROI,  $F(23,1) = 7.82$ ,  $MSE = 0.354$ ,  $P = 0.01$ , reflecting that change in surprise was positive in MTG and negative in aLEC. There was also a trend toward an ROI by Consistency interaction,  $F(23,1) = 3.73$ ,  $MSE = 0.0829$ ,  $P = 0.066$ , in the direction of potentially stronger Consistency effect in aLEC than MTG. In Session 2, there was a main effect of ROI,  $F(23,1) = 10.08$ ,  $MSE = 0.2138$ ,  $P = 0.004$ , again reflecting positive vs negative change in surprise in the two ROIs. Unlike in Session 1, there was a main effect of Consistency,  $F(23,1) = 6.00$ ,  $MSE = 0.301$ ,  $P = 0.022$ , reflecting the fact that both ROIs exhibited Consistency effects in Session 2. Follow-up t-tests revealed that Consistency effects were stronger in Session 2 than Session 1 overall,  $t(23) = -2.940$ ,  $P = 0.007$ . In summary, MTG showed positive change in surprise while aLEC showed negative change, and the ROIs did not differ in the strength of their Consistency effects.

vmPFC In vmPFC (9 m and p32), p32 showed negative overall surprise in Session 1,  $M = -0.182$ ,  $t(23) = -2.500$ ,  $P = 0.020$  and marginal negative change in surprise in Consistent sequences in



**Fig. 6.** Change in Surprise during the Learning phase in aIEC and MTG (TE1p) as a function of Session and Consistency. In Session 1, aIEC showed increasingly negative surprise in the Consistent condition, significantly more than the inconsistent condition, which showed no change. This interacted with Session, such that this difference was weaker and absent in Session 2. MTG showed significant change in surprise in the inconsistent condition in Session 1 with no Consistency difference. A Consistency effect emerged in Session 2, where only the Consistent conditions exhibited significant change. Error bars indicate SEM, asterisks denote effects significant at  $P < 0.05$ , and crosses indicate marginal effects.



**Fig. 7.** Change in Surprise during the Learning phase in aHC and pHC as a function of Session and Consistency. Only aHC showed any significant change in surprise, with increasingly negative surprise from the start to the end of the Learning phase in Session 1 in the Consistent condition, but no effect of Consistency or Session and no interactions. Error bars indicate the SEM, asterisks denote effects significant at  $P < 0.05$ , and crosses indicate marginal effects.

Session 1,  $M = -0.096$ ,  $t(23) = -2.005$ ,  $P = 0.057$ , as well as marginal change in surprise overall in Session 2,  $M = -0.0785$ ,  $t(23) = -2.038$ ,  $P = 0.053$ . Surprise and change in surprise were not significant otherwise ( $P > 0.10$ ) and there were no effects of Consistency or Session ( $P > 0.10$ ). Thus, some parts of vmPFC showed learning-related change in this task but we did not observe any influence by Consistency.

To summarize, learning-related changes during sequence exposure revealed effects of Consistency and Session most prominently in aIEC, which exhibited learning-related changes more strongly in the Consistent than Inconsistent condition in Session 1, but not so in Session 2, mirroring the memory effects in the Probe phase. MTG exhibited learning-related changes

through both Sessions. This aligns with the idea that aIEC was not substantially affected by the presentation of learning materials after Session 1, whereas MTG was, corresponding with its slower updating of memory representations (which became stronger in Session 2). Learning-related changes were minimal in HC and in vmPFC, also in line with Probe phase findings.

### Inter-region correlations

The findings from the Learning and Probe phases overall suggest that both aIEC and MTG played significant roles in learning and memory, but with different time courses, such that aIEC showed a rapid formation of memory representations and a later decline in learning, whereas MTG representations were slower to update and

showed continued learning-related change. Our pre-registration included the hypotheses that there would be a functional relationship between aLEC in Session 1 and MTG in Session 2, which we tested by examining cross-session correlations of individual participants' memory strength (associative coding) and learning related change (change in surprise). We saw that change in surprise was negatively correlated between aLEC at Session 1 and MTG at Session 2,  $r = -0.565$ ,  $t(22) = -3.209$ ,  $P = 0.004$ , showing that more negative change in surprise in aLEC in Session 1 predicted less negative change in surprise in MTG in Session 2. There were no correlations in associative coding ( $P > 0.70$ ). This suggests some functional relationship between these areas across time, but this did not appear to hold for memory measures, indicating mixed evidence for this hypothesis.

### Post-scan recall

Forced-choice questions at the end of Session 2 required participants to recall each of the predictive relations they had learned from all sequences tested in a single block. Questions asked participants to selected between two Event pairs: A followed by B vs A followed by C, in the context of the background object cueing the sequence it belonged to. We found that for pairs from Inconsistent sequences, participants were not overall above chance (50%),  $M = 46\%$ ,  $P > 0.35$ , but they were significantly above chance for pairs from Consistent sequences,  $M = 56\%$ ,  $t(23) = 2.106$ ,  $P = 0.046$ , with no significant difference between conditions. As emphasized in the Methods, these questions were especially difficult because they required participants to recall which relational structure went with which Object, as event stimuli were highly overlapping across sequences.

In a post-hoc exploratory analysis, we tested which neural signatures might have predicted participants' ability to retrieve these event associations from their context cues (the Object shapes) using correlations between individual participants' accuracy on this test and their neural measures (associative coding and change in surprise) in our ROIs. We found a correlation with associative coding in aHC in Session 1,  $r = 0.467$ ,  $t(22) = 2.476$ ,  $P = 0.021$  and with change in surprise in pHc in Session 2,  $r = -0.444$ ,  $t(22) = -2.323$ ,  $P = 0.029$ . In vmPFC, we saw correlations in Session 1 in p32,  $r = 0.435$ ,  $t(22) = 2.2632$ ,  $P = 0.034$  and marginally so in 9 m,  $r = 0.389$ ,  $t(22) = 1.983$ ,  $P = 0.060$ ; effects held across Sessions, 9 m,  $r = 0.486$ ,  $t(22) = 2.607$ ,  $P = 0.016$ , and p32,  $r = 0.425$ ,  $t(22) = 2.204$ ,  $P = 0.038$ , but not in Session 2 alone. These correlations tentatively suggest that HC and vmPFC did have functional relevance to context-cued relational memory in our task, but should be interpreted with caution given their post-hoc nature. No correlations were seen with either learning or memory measures in MTG or aLEC.

### Discussion

Using fMRI, we observed that aLEC and MTG play complementary roles in the acquisition of relational knowledge. Signatures of relational memory and of integrative coding were seen immediately after learning in aLEC and were followed after more exposure and time by similar effects in MTG, revealing different time courses for similar functions in these areas. Congruently, the amount of learning-related change declined with time/exposure in aLEC but persisted in MTG. These findings offer the new insight that aLEC and MTG have important complementary roles in building new, integrative representations of event relations, shedding light on the neural pathways that build semantic memory from experience. This serves to bridge a major gap between episodic encoding,

memory integration, and the formation of semantic memory, and aligns with the idea of different specializations within these systems.

### Implications for theories of neural organization of episodic and semantic memory

CLS theory has long proposed that experiences are first encoded in an episodic memory system in MTL (HC and EC) but eventually come to rely on cortical sites elsewhere. Yet prior work has rarely tracked memory representations both in MTL and in specific semantic areas, many of which have content specializations, nor investigated when in the course of learning integrated memory representations emerge in semantic sites. We reasoned that, with exposure and time, signatures of new relational knowledge should emerge in semantic sites specialized for the content of what is learned—here, temporal relation knowledge in MTG, selected on the basis of prior patient and imaging evidence on its role in action and event concepts (discussed further below). We also predicted that aLEC might serve as an intermediate stage between episodic and semantic memory for temporal relations. Our findings support these ideas by showing signatures of integrative coding in MTG that increased with time and exposure following rapidly formed integrative memory in aLEC. The participation of these particular areas aligns with their specializations in temporal episodic memory and action and event semantics, respectively.

Our findings suggest that aLEC has a special role: its learning is both rapid and integrative. In the first session, aLEC already showed evidence of relational memory representations and these representations were integrative (revealed as an effect of Consistency). These effects were significantly stronger than in HC. Relational memory strength and consistency effects are likely related: by virtue of integrating across contexts, aLEC could build stronger representations in the Consistent condition than it could if it did not integrate. In Session 2, we saw no significant decline in relational memory strength, suggesting aLEC's role in memory may persist across a week's delay. In contrast, learning-related changes were stronger in Session 1 than Session 2, suggesting less updating during the second exposure, consistent with rapidly formed but then stable memory representations.

MTG showed evidence of relational memory and integrative coding subsequently to aLEC, after more exposure and a week's delay, with a significant increase from Session 1 to Session 2. Learning-related changes were seen in both sessions, in line with continual learning throughout exposure. We thus supported the hypothesis that, following sufficient exposure and time, new, integrated relational knowledge increases its reliance on this specific semantic site. That said, we cannot distinguish, in this study, whether Session effects were due specifically to additional exposure, reflecting a slower learning rate in MTG, or due to time-dependent reorganization processes such as consolidation.

The joint participation of aLEC and MTG in these processes suggests that these areas both contribute to event knowledge acquisition. The role of aLEC in forming temporal relational memory from experience (Schröder et al. 2015; Tsao et al. 2018; Bellmund et al. 2019; Montchal et al. 2019) may be part of a functional processing pathway together with MTG, which stores event-related knowledge that is updated with this experience. Investigating this idea was motivated by the longstanding observation that relational structure is a core property of event and action concepts (Garvey and Caramazza 1974; Miller and Johnson-Laird 1976; Gentner 1983; Pinker 1989; Carey 2009; Bedny and Caramazza 2011; Leshinskaya et al. 2020; Wurm and Caramazza 2021). We thus suggest that aLEC and MTG

together form a potentially specialized system for building event knowledge.

It remains unclear whether the representations in aEC and MTG emerged independently or interactively. Our findings were mixed: individual participant differences in relational memory strength in aEC in Session 1 did not significantly predict those in MTG in Session 2, but we did see that the amount of Session 1 learning-related change in aEC inversely predicted those in Session 2 in MTG, which might suggest some dependency between these areas such as a shift in relative reliance. The question of cortico-MTL independence in learning remains an area of research. The classic view that MTL “teaches” cortex (McClelland et al. 1995; Dudai et al. 2015) is challenged by recent findings showing that new information can be cortically represented/updated in parallel with HC in some cases (Tse et al. 2011; McClelland 2013; Hebscher et al. 2019). It thus remains an important question for future research to understand whether and in what cases new semantic knowledge in MTG forms independently of aEC and in what ways they might interact.

In contrast to findings from associative inference paradigms (Schlichting and Preston 2015; Morton et al. 2017), we did not find evidence of integrative representations in HC during memory or learning. However, we also only saw weak evidence of relational memory or learning-related change in this area. We suspect that the cross-context stimulus diversity led HC to separate the A–B pairs across contexts, rather than integrate them, and that this led to weaker A–B representations overall. In prior work that reported integrative memory representations in HC (Collin et al. 2015; Schlichting et al. 2015; Tompary and Davachi 2017), participants learned stimulus pairs A–B and B–C, where B was an identical stimulus. HC played a role in integrating these pairs to infer a transitive relation between A and C. Our paradigm involved stimulus differences in distinctly cued contexts. A–B pairs differed in the shape of the object and in the movement stimulus serving as A. HC is known to elicit diverse responses to similar events when they are associated with unique contextual details (Winocur et al. 2010; Dimsdale-Zucker et al. 2018; Pacheco Estefan et al. 2019; Zheng et al. 2021). We thus suspect that HC did not integrate individual A–B pairs across these contexts, leading to weak A–B pairs in both conditions and the absence of an integration signature. This idea motivated an exploratory analysis in which we correlated individual differences in memory strength in HC with the ability to recall and distinguish all of the A–B pairs at the end of the study based on each context cue. We found tentative, post-hoc evidence for this idea. Another important caveat, however, is that the lower spatial resolution of our functional data precluded a more detailed examination of HC subfields, among which CA1 is known to be more integrative than others (Schlichting et al. 2014; Schapiro et al. 2017). Future work using high resolution imaging could potentially better resolve conflicting findings regarding integrative coding in HC.

vmPFC is also an area commonly targeted in studies of memory integration across neurophysiology (Takehara et al. 2003; Takashima et al. 2006; Lesburguères et al. 2011; Tse et al. 2011; Richards et al. 2014; Kitamura et al. 2017; Graves et al. 2022) and fMRI (Schlichting et al. 2015; Tompary and Davachi 2017; Barron et al. 2020; Park et al. 2020). Again in contrast to prior work, we did not find significant evidence for integrative representations in vmPFC. We saw instead that overall activation was higher in the Inconsistent than the Consistent condition, possibly in line with findings that mPFC is critical for incorporating conflicting information into existing knowledge structures (Richards et al. 2014) and with the view that vmPFC supports the process of integration

more than serving as a memory site for the integrated content per se (Takashima et al. 2006; Preston and Eichenbaum 2013; van Kesteren et al. 2013; Hardt and Nadel 2017). Nonetheless, it is also possible that vmPFC supports integrated memory representations for specific kinds of content, but not for temporal relations among events, stimuli which were designed to engage MTG.

### Relationship to prior work on MTG

We focused on right-lateralized MTG following our prior work showing relational memory in this area with similar stimuli (Leshinskaya and Thompson-Schill 2020) as well as the many findings connecting this anatomical region to semantic memory for actions, tools, and events (Leshinskaya et al. 2020; Wurm and Caramazza 2021). For visual stimuli, MTG responses are often bilateral (Damasio et al. 2001; Bedny et al. 2008; Tarhan and Konkle 2020) and include signatures of action categories generalizing across actors (Kable and Chatterjee 2006; Hafri et al. 2017), effectors (Vannuscorps et al. 2019), or physical manners of execution (Wurm and Lingnau 2015; Moritz et al. 2017) and event memory (Chen et al. 2017). Although these effects surround a similar anatomical site, they are best considered a mosaic of various specializations. These include retrieval of action properties of objects (Martin et al. 1995; Damasio et al. 2001; Kable et al. 2002; Phillips et al. 2002; Tranel et al. 2003) and, on the left side, selectivity for verbs over nouns and sensitivity to grammatical structure (Bedny et al. 2008; Bedny and Caramazza 2011; Peelen et al. 2012; Hernandez et al. 2014) as well as selectivity to tools and hands (Martin et al. 1996; Chao and Martin 1999; Beauchamp et al. 2002; Damasio et al. 2004; Martin 2007; Bracci et al. 2011; Bracci and Peelen 2013). Our prior work has also shown that temporal relational information is explicitly reflected in tool-selective parts of MTG (Leshinskaya et al. 2021). The present findings are within anatomical range of these prior results, but it is not possible to establish if they pertain to the same functional area without a within-study comparison. Using an anatomical atlas, like the Glasser atlas used here, to define these ROIs may improve our ability to relate findings across studies.

### Relationship to prior work on EC

Our work is in line with increasing evidence demonstrating the role of EC in integrative relational memory. Relational memory in general has long been attributed to HC (Eichenbaum and Cohen 2001; O'Reilly and Rudy 2001) with EC implicated alongside it by virtue of EC's role as the major source of afferent and efferent connections between HC and neocortex (Burwell et al. 1995; Suzuki 1996). Yet recent evidence characterizes EC as more than just a relay, and rather as playing an active, integrative role in information processing (Kumaran and McClelland 2012; Kitamura et al. 2014; Koster et al. 2018; Gerlei et al. 2021) and serving as an early bio-marker of Alzheimer's disease (Khan et al. 2014; Holbrook et al. 2020). EC-HC recurrent connections are themselves essential for temporal associative learning (Suh et al. 2011; Kitamura et al. 2014) and it is these recurrent connections that may allow EC, more than HC, to form integrative relational memory (Kumaran and McClelland 2012). Related findings characterize EC as forming relational knowledge that spans diverse experiences. In navigation studies, grid cells in pmEC have more stable, persistent patterns of firing across diverse environments than HC place cells, allowing pmEC to encode common spatial structures across contexts with diverse sensory details (Behrens et al. 2018). EC representations in humans support inferential shortcuts across separately learned but transitively connected information among social stimuli (Park et al. 2020; Park et al. 2021b).

Our findings that aEC integrates predictive information across contexts with diverse sensory detail to build integrative knowledge aligns with this emerging understanding of the general properties of EC function.

Our findings also help characterize the distinct specializations within MTL and within EC. Associative coding, the measure used here in which temporally-associated stimuli elicit correlated neural responses, is a classic result in the neurophysiology of EC and surrounding MTL areas (Miyashita 1993; Higuchi and Miyashita 1996; Messinger et al. 2001; Naya et al. 2001, 2003), with convergent findings in human fMRI (Schapiro et al. 2012; Garvert et al. 2017). The specific contributions of MTL sub-areas have not been well established, but recent evidence has shown notable specializations. In rodents, pmEC encodes information about spatial context, whereas aEC encodes information about temporal context (Tsao et al. 2018). Human fMRI data show that aEC activity correlates with the precision of temporal memory (Montchal et al. 2019) and that memory representations in aEC reflect temporal proximity whereas those in pmEC reflect spatial proximity (Bellmund et al. 2019). Our findings of associative coding for temporal relations in aEC align with this emerging picture.

## Conclusion

The present study sheds light on the neural pathways that build knowledge of temporal relations from experiences of events. We showed that new temporal relation information is rapidly represented and integrated in aEC, prior to similar signatures becoming detectable in MTG with additional exposure and a week's delay. This suggests that new experiences lead to integrated memory representations first in an intermediary stage in aEC and then in a specific semantic site—here, a region previously established as important for action and event concepts. These results shed light on specific sites within episodic and semantic memory systems for building temporal relational knowledge and their time- and exposure- dependent changes. We anticipate these findings to advance neural and theoretical models of memory updating and interaction among episodic and semantic memory systems.

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## Author contributions

Conceptualization and Methodology, A.L. and C.R.; Software, A.L. and M.N.; Formal Analysis, A.L. and M.N.; Investigation, A.L. and M.N.; Resources, A.L. and C.R.; Data Curation, A.L. and M.N.; Writing—Original Draft, A.L.; Writing—Review and Editing, A. L. and C.R.; Visualization, A.L.; Supervision, C.R. and A.L.; Project Administration, A.L.; Funding Acquisition, A.L. and C.R.

## Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

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## Data and code availability

Code for experiments and analysis, as well as processed MRI and behavioral data, is available at the OSF repository at <https://osf.io/5xpza/>, DOI:10.17605/OSF.IO/5XPZA. Raw data are available on request.

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