Hippocampal-medial prefrontal event segmentation and integration contribute to episodic memory formation

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Abstract

How do we encode our continuous life experiences for later retrieval? Theories of event segmentation and integration suggest that the hippocampus binds separately represented events into an ordered narrative. Using an open-access functional Magnetic Resonance Imaging (fMRI) movie watching-recall dataset, we quantified neural similarities between separate events during movie watching and related them to subsequent retrieval of events as well as retrieval of sequential order. We demonstrate that distinct *activation patterns* of the hippocampus and medial prefrontal cortex form event memories. By contrast, similar within-region *connectivity patterns* between events facilitate memory formation and are critical for the retention of events in the correct sequential order. We propose that distinct *activation patterns* represent neural segmentation of events while similar *connectivity patterns* act as the 'chunking code' for integration across events. Our results provide novel evidence for the role of hippocampal-medial prefrontal event segmentation and integration in episodic memory formation of real-life experience.

Keywords: subsequent memory effect; hippocampus; medial prefrontal cortex; event segmentation; event integration

Significance

How do our brains encode continuous life experience? Prior work suggests that the hippocampus represents information with dissimilar patterns to separate them, but it remains unclear how events could be both separated and integrated into the sequenced narrative that characterizes episodic memory. We used functional MRI during movie watching to identify complementary patterns of brain activity in the hippocampus and medial prefrontal cortex that perform these dual operations. Successful encoding was dependent on events being represented with dissimilar *activity patterns*, while a similar *connectivity pattern* linked events and preserved the order they were encoded. These findings reveal a network that simultaneously separates and integrates event memories, and highlights the potential of connectivity patterns to examine dynamic memory processes in brains.

MAIN TEXT

Introduction

How we form memories of our life experiences is a fundamental scientific question with broad implications. In the past two decades, human neuroimaging and electrophysiology studies using the subsequent memory effect paradigm have implicated a distinct set of brain regions involved in successful memory formation (1–4). In these subsequent memory studies, increased neural activity of the hippocampus, parahippocampal gyrus, and the prefrontal cortex during memory encoding is associated with successful subsequent retrieval. However, real-world memories are formed based on a continuous stream of information rather than the sequentially presented, isolated items used in most subsequent memory studies (3). Potentially, continuous sensory experience is segmented into distinct events (i.e., event segmentation) (5–7) that are then bound together into a coherent narrative, preserving their sequential relationships (i.e., event integration) (8). To examine episodic memory formation of real-life-like experiences in humans, we analysed brain activity using functional Magnetic Resonance Imaging (fMRI) while participants were watching a movie. Based on subsequent memory recall, we aimed at identifying brain regions and neural representational processes underlying event segmentation and integration during episodic memory formation.

Thanks to recent advances in statistical analysis of ongoing neural activity (9–12), naturalistic stimuli (e.g., movie, spoken narratives, music) have been increasingly used in neuroscience (12–15). This is especially valuable for memory research because naturalistic stimuli can greatly enhance the ecological validity of experimental studies (7, 16–18). Hasson and colleagues first investigated memory formation with cinematographic stimuli and demonstrated that brain activity was more correlated among participants for later remembered than forgotten events (18). While that study uncovered regions that encode continuous experiences, the nature of representations in those regions remained unclear, particularly with regard to how episodes are segmented into separate events and then integrated into a coherent sequence.

Event segmentation theory suggests that continuous experiences need to be segmented into discrete event representations, and thereafter they can be better understood and encoded (6, 19, 20). Two recent studies provided novel perspectives into segmentation theory. Using Multi-Voxel Pattern Analysis (MVPA) and a movie watching-recall dataset, Chen and colleagues showed similar *activation patterns* of the same events across individuals and event-specific reinstatements of *activation patterns* between encoding and retrieval (16). Following this, Baldassano and colleagues demonstrated a nested processing hierarchy of events ('hierarchical memory system', (21)) from coarse segmentation in early sensory regions to fine-grained segmentation in regions of the higher-order default-mode network (e.g., medial prefrontal cortex (mPFC) and posterior medial cortex (PMC)). Importantly, boundaries of long events at the top of the hierarchy matched with event boundaries annotated by human observers and were coupled to increased hippocampal activity (7). These results demonstrated that human brains spontaneously used different *activation patterns* to represent events during continuous movie watching, and how these *activation patterns* reactivated during recall. Also, it may suggest that regions such as mPFC, PMC, and hippocampus encode events at the same level that we consciously perceive boundaries between events. However, it remains unclear how exactly this event segmentation at the neural level relates to subsequent memory recall.

Event segmentation alone is not sufficient for episodic memory formation of continuous real-life experiences. Temporal context theory suggests that it is essential to integrate segmented events into a coherent narrative via time, meaning, or other abstract features (22, 23). Therefore, a non-exhaustive list of questions are: (1) what are the neural underpinnings of event integration during continuous memory formation, (2) does integration occur in the same brain regions as segmentation, and (3) how does integration relate to subsequent memory recall. A promising approach to answer these questions is to examine local *connectivity pattern* (also called *multi-voxel correlation structure*), which may represent a brain signal that integrates events (24). This method was derived from rodent electrophysiology (25–27) and has been used in human fMRI studies (28, 29) to quantify distributed memory representations in neuronal assemblies. Recently, Tambini and Davachi (24) proposed that *activation patterns* are the

representations of specific perceptual inputs (e.g., stimuli), while local *connectivity patterns* reflect particular encoding contexts or states. However, the different mnemonic functions of *activity patterns* and *connectivity patterns* have yet to be compared empirically within a single study. If local *connectivity patterns* represent encoding context, they may facilitate integration across events. Examination of *connectivity patterns* alongside *activation patterns* would help to characterise how the brain simultaneously performs event segmentation and integration.

Recently, a hippocampal neural code (chunking code) that simultaneously tracked subdivisions of a continuous experience (i.e., events) and their sequential relationship was described in rodents' CA1 region (30). This 'chunking code' could be a fundamental neural code by which episodic experience is integrated, but has yet to be revealed in humans. Hippocampal activity was found to increase at the boundaries between two events during continuous experience (5, 7, 31–34), but what these hippocampal signals represent in terms of event segmentation and integration is not clear. Theoretical models proposed that increased hippocampal signal may reflect a rapid shift in mental representations (e.g., temporal and/or contextual information of an event) (35–37). Therefore, it can be regarded as the neural signature of event segmentation. Alternatively, this increase may link to the integration of episodic memories across event boundaries, as suggested by scalp electrocorticography (EEG) studies (38, 39) and the event conjunction framework (8). However, fMRI evidence for the role of hippocampal signals in integration across events is still limited.

The current study aimed to reveal the neural underpinnings of the two processes in question – event segmentation and event integration - during memory formation of naturalistic experiences. To that end, we used an existing dataset (7, 16) where participants watched a movie while being scanned (**Figure 1A**) and afterwards were instructed to freely recall the story of the movie (**Figure 1B**). This design allowed us to associate different neural measures during episodic encoding with subsequent memory retrieval (**Figure 1C-D**). We extracted voxel-wise Blood Oxygenation Level Dependent (BOLD) time courses during movie watching (encoding) from six predefined regions-of-interest (ROI) in the 'hierarchical memory

system' (21) including early auditory and visual areas, posterior medial cortex, medial prefrontal cortex, hippocampus, and posterior parahippocampal gyrus (**Figure 2A**; **Figure S1**). To probe the role of a broader set of regions in event segmentation and integration, we repeated all analyses in each parcel of a neocortical parcellation (40) (**Figure 2B**). We first examined the relationship between ROI-based activity time courses and subsequent memory recall and replicated the classical subsequent memory effects (i.e., greater activation for *remembered* compared to *forgotten* events) in regions including the hippocampus as well as the posterior parahippocampal gyrus (**Figure S2-3**, details in **Supplementary Materials**). To dissociate the two event processes, we used voxel-wise activity (Figure 2C) from each ROI to quantify the similarity between neural representations of events by two different multivariate methods (i.e., *activation* and *connectivity patterns)* (**Figure 2D-E**). We reasoned that if the neural representation (*activation* or *connectivity pattern*) shows a large transition (i.e., negative neural similarity value) between two adjacent events, and if this dissimilarity associates with better subsequent memory for events, then this representation might be involved in event segmentation (**Figure 2E**). By contrast, if the neural representation remains stable (i.e., higher similarity) across two or more neighboring events, and this stability relates to event memory as well as retention of the correct order for those events (order memory), then this representation may underlie event integration (**Figure 2F**).

Results

Subsequent memory performance measured by spoken recall

The dataset (7, 16) is from an experiment in which 17 healthy participants watched a 50-min audio-visual movie (BBC's Sherlock) while undergoing an fMRI scan (**Figure 2A**). Immediately thereafter, participants were instructed to verbally recall the movie in as much detail as possible (**Figure 2B**). No visual or auditory cues were given during the retrieval session.

Similar to the previous experiments probing the subsequent memory effect (1, 2, 4), the central purpose of our analyses was to identify brain regions and their response patterns that predict subsequent recall. To quantitatively analyse memory retrieval performance, the movie was divided into 50 events based on major narrative shifts (e.g., director's cuts). Each participant's spoken recall was transcribed and segmented into events matching those from the movie (**Figure 1B**) (Details in *Methods and Materials*). The current analyses used the same event annotations for the movie and spoken recall as the original studies (7, 16).

We first calculated recall accuracies for each participant. On average, 68.7% (*SD* = 12%, range 48% - 94%) of the 50 events (*Mean* = 34.4 events, *SD* = 6) were retrieved successfully (**Figure 2C**). Among these remembered events, we further defined *in-order* and *out-of-order* events based on whether they were recalled in the correct sequential order. On average, 58.8% (*SD* = 8%, range 40% - 71%) of the remembered events were *in-order* (**Figure 2D**).

Distinct activation pattern-mediated event segmentation is associated with subsequent retrieval success

We quantified neural similarities of event-specific *activation patterns* before and after event boundaries (i.e., two neighbouring events). Specifically, we generated a voxel-wise *activation pattern* per event by averaging over all time points in that event. This time-averaged *activation pattern* of all voxels within an ROI for an event was compared to the pattern of its subsequent event using Pearson's correlation. A negative Pearson's r indicates two separateble activation patterns and thus distinct neural representations for two distinct events. We investigated whether *activation pattern* similarities relate to memory formation by contrasting the pattern similarities of remembered with forgotten events in six ROIs. That is, pattern similarity between two events was compared to subsequent memory for the first of those events. We found that subsequently remembered events were associated with lower *activation pattern* similarities than

subsequently forgotten events in early auditory cortex (t = -3.56, p_{FDR} = 0.007, Cohen's d = 0.92, **Figure 3B**), hippocampus (t = -3.62, p_{FDR} = 0.007, Cohen's d = 0.92, **Figure 3E**), mPFC (t = -2.79, p_{FDR} = 0.01, Cohen's d = 0.80, **Figure 3C**) and posterior parahippocampal gyrus (pPHG) (t = -2.85, p_{FDR} = 0.01, Cohen's d = 0.89, **Figure 3F**). This finding suggests that distinct *activation patterns* for two sequential events are beneficial for the memory of the first event in that sequence. Early visual areas (t = -1.13, p_{FDR} = 0.27, Cohen's d = 0.35, **Figure 3A**) and PMC (t = -1.91, p_{FDR} = 0.08, Cohen's d = 0.65, **Figure 3D**) did not show this marked effect.

So far, within-participant comparisons between remembered and forgotten events revealed that differences in *activation pattern* similarities of several ROIs are related to subsequent memory. Next, we examined whether a similar relationship is evident across participants. Specifically, we investigated the relationship between the *event-specific recall rate* (the percentage of participants that successfully recalled a particular event) and the averaged *activation pattern* similarity for the corresponding event (the first one in the sequence) across all participants. Consistent with our main analyses, this analysis revealed that the recall rate negatively correlated with *activation pattern* similarity in the hippocampus (r = -0.292, p_{raw} = 0.042) and pPHG (r = -0.344, p_{raw} = 0.015), suggesting that events with lower *activation pattern* similarity were more likely to be recalled (**Figure S5**).

Similar connectivity pattern-mediated event integration is correlated with subsequent retrieval success

Next, we investigated the association between *connectivity patterns* – a different multivariate method to characterise neural representations – and subsequent memory retrieval. Within-region multi-voxel c*onnectivity patterns* were calculated by a voxel-by-voxel pairwise correlation matrix resulting from the correlations between time courses of all voxels within a given region. This represents the relative correlation structure between all voxels in a certain region during event processing. We first calculated the

event-specific within-region *connectivity patterns* for two sequential events, and then we quantified the similarity between *connectivity patterns* across event boundaries also using Pearson's r. Contrasting similarities of *connectivity patterns* of subsequently remembered and forgotten events allowed us to examine how transitions in *connectivity patterns* contribute to memory formation. We found higher *connectivity pattern* similarity for subsequently remembered compared to forgotten events in the early auditory area (t = 2.9, p_{FDR} = 0.02, Cohen's d = 0.72, **Figure 4B**), visual areas (t = 3.34, p_{FDR} = 0.01, Cohen's d = 0.74, **Figure 4A**), hippocampus (t = 3.39, p_{FDR} = 0.01, Cohen's d = 0.73, **Figure 4E**), and PMC (t = 2.79, p_{FDR} = 0.02, Cohen's d = 0.47, **Figure 4D**). The same contrast was not significant for mPFC (t = 1.22, p_{FDR} = 0.23, Cohen's d = 0.25, **Figure 4C**) and pPHG (t = 1.36, p_{FDR} = 0.22, Cohen's d = 0.30, **Figure 4F**). A follow-up permutation test examining the specificity of subsequent memory effects (both *activity* and *connectivity patterns*) to actual event boundaries (as opposed to randomly generated pseudo boundaries) can be found in the **Supplementary Materials (Figure S4 and S6)**.

The event-specific correlational analysis demonstrated that the recall rate positively correlated with *connectivity pattern* similarity in the early auditory area (r = 0.327, p_{raw} = 0.022), visual areas (r = 0.35, p_{raw} = 0.014), hippocampus (r = 0.301, p_{raw} = 0.036), PMC (r = 0.341, p_{raw} = 0.017), and pPHG (r = 0.341, p_{raw} = 0.017) (**Figure S7**). These results suggest that events with higher connectivity pattern similarity in these ROIs were more likely to be recalled.

Similar connectivity pattern-mediated event integration preserves sequential order of events in later retrieval

So far we have shown the opposite association between our two multivariate neural pattern measures and subsequent memory performance: distinct *activation patterns*, but similar within-region *connectivity patterns* across events in the early auditory cortex and hippocampus predict retrieval success. This pattern of results suggests that the *connectivity pattern* may represent the 'chunking code' to integrate events into

a continuous sequence. To directly test this 'chunking code' hypothesis, we examined the relationship between *connectivity pattern* similarity and sequential order of subsequent recall. We reasoned that if the *connectivity patterns* remain stable across event boundaries, events should tend to be recalled in the correct sequential order. We compared the mean *connectivity pattern* similarities for *in-order* and *out-of-order* events. Controlling for multiple comparisons, we found that *connectivity pattern* similarity in early visual cortex to be larger for *in-order* compared to *out-of-order* events (t = 3.16, p_{FDR} = 0.03, Cohen's d = 0.47, **Figure 5A**). Similar trends that did not survive correction for multiple comparisons were detected in the hippocampus (t = -2.43, p_{raw} = 0.026, p_{FDR} = 0.08, Cohen's d = 0.53, **Figure 5E**), auditory area (t = -2.08, p_{raw} = 0.053, p_{FDR} = 0.084, Cohen's d = 0.46, **Figure 5B**) and posterior parahippocampal gyrus (t = -2.05, p_{raw} = 0.056, p_{FDR} = 0.084, Cohen's d = 0.36, **Figure 5F**). No such effect was observed in the mPFC (t = -1.35, p_{FDR} = 0.19, Cohen's d = 0.19, **Figure 5C**), and PMC (t = -2.05, p_{FDR} = 0.12, Cohen's d = 0.33, **Figure 5D**).

Hippocampal activation and connectivity patterns change differently with event distance

Among our six ROIs, we found converging evidence for a dissociation of event segmentation and integration in the hippocampus: lower *activation pattern* similarity, but higher *connectivity pattern* similarity was beneficial for memory formation. Building on these findings, we hypothesized that hippocampal *activation patterns* of neighboring events should be less similar than events that occur far apart. By contrast, hippocampal *connectivity patterns* of close events should be more similar than events with a long interval in between. Thus, we calculated the *activation* and *connectivity pattern* similarity between all possible combinations of event pairs ('Event A' and 'Event B') within all 50 events (**Figure 6A** and **6D**). For all pairs of events with the same event distance (e.g., separated by four events), we calculated the mean similarity measure for *activation pattern* and *connectivity pattern* separately. This calculation was repeated for all possible event distances. To ensure reliable estimations of pattern

similarities, we only present the similarities of distances with at least ten event pairs ($d \leq 40$) in the main text. (Complete calculations can be found in **Figure S8**.)

We analysed the hippocampal *activation* and *connectivity patterns* separately. First, our *activation pattern* analysis found that the shorter the event distance, the more distinct the hippocampal *activation patterns* ($r = 0.21$, $p_{raw} = 1.8 \times 10^{-8}$; **Figure 6B** and **S9A**). This positive correlation was largely driven by the negative similarity values between events that occurred close to each other: events separated by a distance of less than four were represented by two distinct (neural similarity significantly lower than 0) hippocampal *activation patterns* ($d = 1$, $t = -5.52$, $p_{FDR} = 0.0006$; $d = 2$, $t = 3.86 \times 10^{-11}$, $p_{FDR} = 1.5 \times 10^{-9}$; $d = 3$, $t = 6.75 \times 10^{-6}$, $p_{FDR} = 0.0001$; $d = 4$, $t = -2.98$, $p_{FDR} = 0.08$). Events with a distance larger than or equal to four did not show markedly distinct *activation patterns* (neural similarity not significantly different from 0) (**Figure 6B**). Furthermore, we found that subsequent memory recall of Event A modulated the relationship between event distance ($d = 1 - 4$) and *activation pattern* similarity (ANOVA with event A × distance interaction: $F(3,48) = 10.1$, $p < 0.001$; **Figure 6C**). That is, hippocampal *activation pattern* similarities increased as the event distance changes from 1 to 4, but only if event A was later recalled ($F_{remembered}(3,48) = 9.54$, $p < 0.001$; $F_{forgotten}(3,48) = 1.35$, $p = 0.268$).

Second, our *connectivity pattern* analysis found that the shorter the event distance, the more similar the hippocampal *connectivity patterns* ($r = -0.439$, $p_{raw} = 1.8 \times 10^{-33}$; **Figure 6E** and **S9B**). At the same time, across all event distances, the *connectivity pattern* similarities were consistently higher than zero (from $d = 1$, $t = 31.86$, $p_{FDR} = 2.29 \times 10^{-14}$ to $d = 40$, $t = 18.16$, $p_{FDR} = 4.4 \times 10^{-12}$; $p_{FDR} < 0.05$ for all d). Furthermore, we found a significant interaction between event A recall and distance ($F(19, 304) = 2.37$, $p = 0.001$), and a significant main effect of event A ($F(1, 16) = 7.53$, $p = 0.014$). That is, if event A was recalled later, its hippocampal connectivity pattern was more similar to any other event in the sequence, compared to when event A was not successfully recalled (**Figure 6F**). This suggests that if *connectivity patterns* between pairs of events are more similar, for both short and long distances, then events are more likely to be successfully encoded.

Subregions of the prefrontal cortex perform event segmentation and integration

Our ROI-level analyses found that (1) distinct hippocampal *activation patterns* were associated with better event memory; (2) similar hippocampal *connectivity patterns* were beneficial for event memory; (3) although not surviving multiple comparison correction, similar hippocampal *connectivity patterns* tended to preserve the sequential order of events (**Figure 7A**). To investigate whether these relationships are present in other brain regions beyond our six ROIs, we ran a parcel-based searchlight version of our pattern similarity analysis to identify overlapping event segmentation and integration computations across neorcortical parcels. In sum, we investigated three potential relationships between neural pattern similarity and subsequent retrieval separately. First, we identified brain parcels whose lower *activation pattern* similarities across events were associated with retrieval success (**Figure S10A**). Next, we mapped the association between higher *connectivity pattern* similarities and retrieval success on each parcel (**Figure S10B**). Then, we identified the parcels, which demonstrated a positive association between *connectivity pattern* similarities and order memory (**Figure S10C**).

To identify brain parcels that may support all three neural computations, similar to the hippocampus, we overlapped spatial patterns for these three effects (all $p_{FDR} < 0.05$). This revealed a set of brain regions including relatively large clusters (at least 50 voxels) in the mPFC, right inferior frontal gyrus (IFG), anterior/middle cingulate cortex and supplementary motor area (SMA), left inferior temporal gyrus (ITG) and left insular (**Figure 7B**). These results suggest that this network of cortical regions may use the same neural processes to perform event segmentation and integration as the hippocampus during continuous memory encoding.

Discussion

To successfully form memories of our life experiences, we need to segregate continuous experience into events (5, 7), and integrate those events across their boundaries into a coherent narrative (41). Here we

show that distinct hippocampal *activation patterns*, but similar hippocampal *connectivity patterns* across event boundaries, facilitate these two vital episodic memory functions. We propose that distinct *activation patterns* reflect event segmentation while similar *connectivity patterns* represent a 'chunking code' that integrates separately represented events into a narrative. Supporting this role of *connectivity patterns* for event integration, we found that similar hippocampal *connectivity patterns* were crucial for the correct sequential order of subsequent retrieval. Our whole-brain analysis demonstrates that similar neurocomputations were performed by a network of cortical regions, in particular for the mPFC. Overall, these results suggest that both hippocampal and medial prefrontal event segmentation and integration support memory formation of continuous experience.

Using multivoxel pattern analysis, we found that distinct local *activation patterns* across event boundaries in the early auditory area, mPFC, posterior parahippocampal gyrus, and hippocampus, were associated with better subsequent memory, indexed by more negative similarities of activation patterns between two adjacent events. The ability to segment continuous experience has been linked to successful memory encoding in a behavioural experiment (42) and compelling evidence suggested that the hippocampus is activated around event boundaries (5, 31–34). This hippocampal activity has been proposed to be associated with a hippocampal segmentation process, but how the hippocampus represents two separate events, and whether the corresponding neural representations are relevant for memory remained unclear. Our findings suggest that the hippocampus and other brain regions (e.g., mPFC) segment events by representing them with two distinct patterns of activity. This is consistent with the role of the hippocampus in pattern separation: when similar experiences need to be discriminated and encoded, the underlying hippocampal neural representations tend to be dissimilar (43, 44). This has typically been studied to show how the brain separates perceptually similar stimuli (i.e., images), but our findings indicate that a similar separation occurs at the level of events and this determines subsequent memory. The episodic memory system may use 'orthogonalized' neural representations to encode two events for the purpose of event segmentation. Further, we show these 'orthogonalized' neural representations are

potentially event-distance dependent: the hippocampus only generates consecutive dissimilar patterns when events occur relatively close in time. Taken together, this suggests the existence of a brain network (mainly hippcampus and mPFC) for the continuous segmentation of ongoing experience, and the degree of neural separation is relevant for memory formation.

Complementing this, we found that more similar within-region *connectivity patterns* of several regions across event boundaries, including again the early auditory area and hippocampus, were associated with better subsequent recall. Compared to local *activation patterns* (9, 10), within-region *connectivity patterns* are a less used multivariate approach. Recently, Tambini and Davachi proposed that both *activation* and *connectivity patterns* could be used to capture neural states during memory encoding and reactivation, but *connectivity patterns* tend to encode contexts or states instead of particular perceptual inputs (24). Our results support this notion, whereby *activation patterns* were more event-specific, while *connectivity patterns* were more associated with the temporal context of events. Therefore, the *connectivity pattern* acts as the 'chunking code' to integrate segmented and separately represented events into a coherent narrative. Previous evidence from invasive recordings of hippocampal neurons in rats (45) and patients with pharmacologically intractable epilepsy (46) suggested that the temporal context of events is hippocampally encoded. Specifically, Paz and colleagues found that neuronal activity in the hippocampus became more correlated across viewing repetitions of short movie clips, which suggests coding of the temporal context within events (46). Our *connectivity pattern* measure suggests that the hippocampus also codes temporal context across successive events, integrating them into a narrative.

In addition, we found that close event pairs tend to have more similar *connectivity patterns*, and that *connectivity pattern* similarities are lower for forgotten compared to remembered events. This holds for event pairs with both short and long distances, suggesting the relevance of similar *connectivity patterns* for memory formation across the entire narrative. Multi-voxel *connectivity pattern* analysis, as a less used multivariate neural measure, may be applied as an alternative approach to study how temporal sequences are neurally represented. Evidence suggests that neural activity in the hippocampal-entorhinal region,

measured in both rats and humans, represents the temporal sequence of experience (17, 47–52). Adding to this evidence, our findings suggest that a stable *connectivity pattern* across events appears to be a marker of this temporal sequence coding. Future studies are needed to further investigate the precise mnemonic functions of different neural measures (e.g., *activity pattern*, within-region *connectivity pattern*, and system-level interaction between regions) during memory formation (24).

Our ROI analysis highlights the two functions of the hippocampus in the separate representation of segmented events and the binding function that linked events into a narrative, and parcel-based searchlight analysis identified the role of subregions of the prefrontal cortex (e.g., mPFC, IFG), insular, and inferior temporal gyrus in event segmentation and integration during memory formation. The role of the mPFC in event integration is particularly thought-provoking. The mPFC is generally implicated in encoding and retrieval of episodic memories (53, 54). Among its variety of functions in learning and memory (55), the online integration of events we observed here is consistent with its function in the facilitation of associative inference (56–60), accumulation of knowledge (61, 62), and integration of new and prior knowledge (63–65). We propose that the general mnemonic function of mPFC is to establish links between separate elements across time and space. Taken together, we found that the hippocampus-mPFC circuit performs event segmentation and integration during memory formation of continuous experience. These findings demonstrate the contribution of two complementary event processing mechanisms and underlying neural representations in episodic memory formation. The hierarchical network model of event segmentation proposes that higher-order regions receive event representations from lower-order perceptual regions, and then transfer these representations to the hippocampus for storage (7, 21). Our study suggested that event integration is another key cognitive process involved in event memory by showing how distinct event representations are integrated by similar *connectivity patterns* of hippocampus and mPFC.

Our study, together with previous studies also combining human fMRI with naturalistic stimuli (7, 16, 18), demonstrates the potential of this approach to advance our understanding of the human memory system, in

particular for the formation of real-life memories. Similar paradigms and analyses can be easily adapted in clinical (e.g., memory and affective disorders) and developmental neuroimaging studies (e.g., children and older adults) to reveal changes related to disease or (mal)development. For example, fMRI-based event segmentation and integration measures could be used to probe how these processes are impaired in Alzheimer's disease and mild cognitive impairment, how they develop from childhood to adulthood and diminish in normal ageing. In addition, *connectivity patterns* have the potential to inform our understanding of other cognitive operations that require integration of information, such as inferential reasoning (59). However, due to the low temporal resolution of fMRI, the directionality of information flow between the neocortical regions of the 'hierarchical memory system' (21) and the hippocampus remains unclear. Future application of deep-source magnetoencephalography (MEG) (e.g., Backus, Schoffelen, Szebényi, Hanslmayr, & Doeller, 2016) or intracranial electroencephalography (iEEG) (e.g., Jafarpour, Griffin, Lin, & Knight, 2019) with naturalistic memory paradigms may bridge this gap.

In sum, we show that the hippocampus and mPFC may perform a dual function during naturalistic memory formation. Both regions segment events by representing them with distinct *activation patterns*, while also integrating those events by retaining similar *connectivity patterns* across events, enabling the representation of a coherent narrative. The ability to measure segmentation- and integration-related neural operations using fMRI opens new opportunities to investigate the mechanisms of memory encoding for real-life experience.

Methods

1. Participants and procedure

1.1 Participants

Twenty-two healthy young adults (10 female, age range 18-26, mean age 20.8 years) participated in the experiment. All participants were native English speakers and naïve to the BBC crime drama *Sherlock.* Data were discarded from participants with excessive motion (> 1 voxel; n = 2), low recall duration (< 10 min; n = 2), or sleeping during the experiment (n = 1). This leaves 17 participants in total for our analyses. Due to a technical problem, one participant (s5) is missing data for the last 75 s (part of event 49 and all of event 50) and the affected two events were excluded in the analyses.

1.2 Procedure

All our analyses are based on the Sherlock Movie Dataset (7, 16); see *Data availability* below) acquired and pre-processed at Princeton Neuroscience Institute. No similar analysis or results (excluding behavioural results of recall accuracy) have been reported in previous studies using this dataset.

Participants were informed that they would watch a movie and would later be required to recall its content. They were then presented with a 48-min segment of the first episode of the *Sherlock* series (encoding phase), split into two parts of approximately equal length (23 min and 25 min) and presented in two consecutive blocks. A 30 s introductory cartoon clip was prepended before each block. Immediately after the movie presentation, participants were instructed to verbally describe the movie in as much detail as they could and for as long as they wished (recall phase). They were asked to recall the episode in the correct sequential order but were permitted to return to earlier points in the narrative if they remembered further content. Audio was simultaneously recorded by a customized MR-compatible recording system throughout the recall phase.

2. Behavioural data analysis

2.1 Event annotations of the movie and verbal speech recording

The movie was segmented into 48 events by an independent observer, following major shifts in the narrative (e.g., director's cuts). Including the two introductory cartoon clips, 50 scenes were analysed in total. The timestamps for both the onset and offset of identified scenes were recorded and aligned across all participants. Both the onset and offset are referred to as the boundaries of the respective event. This is a widely used method for event segmentation and has been validated by a data-driven approach (Baldassano et al., 2017). The length of the scenes ranges from 11 to 180s (Mean ± SD: 57.5 ± 41.7 s). Each subject's verbal speech was transcribed, segmented and matched to the events that were recalled from the movie.

2.2 Event and order memory

For each participant, we first asked whether events were successfully recalled or not, as in the classical subsequent memory paradigm (1, 2, 4). An event was labelled as 'remembered' if any part of the event was described during the recall. 'Forgotten' events are the ones that were not mentioned throughout the recall phase.

Secondly, *out-of-order* events were identified as a measure of sequential memory. Among all remembered events, an event was labelled as *out-of-order* if it was not described immediately after its preceding event in the original movie. For example, if *event 3* is described immediately after *event 1* without mentioning *event 2*, then *event 3* is an *out-of-order* event. By contrast, if a participant described *event 4, 5, 6* sequentially during the recall phase, since *event 5, 6* correctly followed their preceding event, *event 5, 6* were counted as *in-order* events. The first event verbally described in the recall phase was always labelled as 'not available' in the order memory analysis since it is not preceded by any event. It was possible that a single scene was mentioned multiple times (in different parts) during the recall, in which case the position of its first recall was used in the analyses.

3. fMRI data analysis

3.1 fMRI data acquisition and pre-processing

fMRI data were acquired using a T2*-weighted EPI sequence on a 3T Siemens Skyra scanner (20-channel head coil; TR 1,500 ms; TE 28 ms; flip angle 64, spatial resolution 3*3*4 mm^3). Only data from the encoding phase were analysed and reported in the current study.

A standard pre-processing pipeline was followed using FSL (68), which includes slice timing correction, motion correction, linear detrending, high-pass filtering (140 s cutoff), co-registration and affine transformation into 3 mm MNI standard space (16). The time series were shifted 3 TRs (4.5 s) to account for the Haemodynamic response function (HRF). Data were z-scored across time at every voxel and a 6 mm smoothing kernel was applied.

All subsequent analyses were performed on the pre-processed voxel-wise BOLD signal, in units of functional volume (TR = 1.5 s). Custom MatLab (R2018b, The Mathworks, Natick, MA) and Python (version 3.6) scripts were used for both Region of Interest and parcellation-based searchlight analysis.

3.2 Region of interest (ROI) selection

The six ROIs used in this study were independently defined by Chen and colleagues, in correspondence to the timescale hierarchy of the event segmentation model (7, 21). Early visual and early auditory cortex were functionally defined based on inter-subject correlation during an audio-visual movie and an audio narrative, respectively (69, 70). ROIs for medial prefrontal cortex (mPFC) and posterior medial cortex (PMC) were taken from the functional atlas derived from resting-state default mode network (https://findlab.stanford.edu/functional_ROIs.html) from FIND lab at Stanford University (71). The hippocampus and posterior parahippocampal gyrus were anatomically defined from the probabilistic Harvard-Oxford Subcortical Structural Atlas (72). Chen and colleagues manually adjust the threshold of around 50% to ensure better anatomical coverage during the visual check.

3.3 Whole-brain parcellation

Alongside the ROI-based analysis, we performed a parcel-based searchlight analysis on the basis of 1000 functionally parcellated cerebral regions

(https://github.com/ThomasYeoLab/CBIG/tree/master/stable_projects/brain_parcellation/Schaefer2018_LocalGlobal). The parcellation was based on a gradient-weighted Markov Random Field (gwMRF) model, which integrated local gradient and global similarity approaches (Schaefer et al., 2018). Using both task and resting-state fMRI acquired from 1489 participants, parcels with functional and connectional homogeneity within cerebral cortex were generated (hippocampus and subcortical regions were not included). In this fashion, each of these biologically meaningful and non-overlapping parcels can be treated in the same way as an independent region similar to an ROI in the following analyses.

3.4 fMRI-based neural responses to event boundaries

3.4.1 Univariate response

BOLD signals were first averaged for each TR across all voxels in an ROI. Then the time series were z-scored and segmented based on the event annotations mentioned above. The shortest event was 7 volumes (10.5 s), therefore we averaged 6 volumes at the beginning and end of all events in order to assess the change in activity between them.

3.4.2 Activation patterns

Voxel-wise BOLD time series from separate events were first extracted based on the onset and offset timestamps derived from the movie. Multivariate patterns of brain activation were generated for each event by averaging across all volumes within this event. To assess the similarity between two neighboring events, the *activation pattern* for each event of interest was correlated with its following event. The resulting Pearson's correlation coefficient depicted the extent to which similar representational activity patterns were elicited by neighboring scenes. Lower similarity between two events represented a greater change in neural patterns across the event boundary.

3.4.3 Connectivity patterns

Intra-regional *connectivity pattern* analyses were conducted based on a method originally used in rodent electrophysiology studies to quantify the reactivation of sparsely distributed neuron assemblies (25, 27), and recently used in human fMRI (24, 28, 29). For each event within each brain region, Pearson's correlations were performed on the extracted m*n (volumes*voxels) BOLD-fMRI time series, between each of the n voxel time series. This yielded an n-by-n pairwise correlation matrix (containing p values indicating the significance of the Pearson's correlations), representing the within-region connectivity structure for each scene. For two neighboring events, the Pearson's correlation coefficient of their correlation matrices was calculated to quantify the similarity for *connectivity patterns*. Lower similarity between two *connectivity patterns* represented a greater change in the intra-region connectivity patterns across the event boundary.

3.5 Relationship between neural responses during encoding and subsequent memory

3.5.1 Remembered and forgotten events comparisons

We first compared our neural pattern similarities (i.e., *activation pattern* similarity and *connectivity pattern* similarity) at the single-subject level explained above for each brain region (ROI or brain parcel). The similarity indices (Pearson's r between two matrices) for both *activation* and *connectivity patterns* were averaged for the two types of event pairs (*remembered* and *forgotten*) for each participant. If the first event of the pair was retrieved during the recall phase, the event pair was labelled as *remembered*. *Remembered* and *forgotten* event pairs were then compared in two separate *t*-tests for *activity* and *connectivity pattern* transitions (indexed by pattern similarity).

We further examined the relationship between *connectivity pattern* transitions and order memory (i.e., temporal order of event recall). More specifically, *connectivity patterns* were averaged for another two types of event pairs (i.e., *In-order* or *Out-of-order*) for each participant. If the second event of the pair was recalled in an incorrect sequential order (e.g., *event 4* was recalled immediately after *event 6*), the event

pair was labelled as *Out-of-order*. *Connectivity pattern* transitions for *In-order* and *Out-of-order* event pairs were then compared with *t*-tests.

3.5.2 Event-specific correlational analysis

Thus far we have examined the association between memory and neural pattern similarity in a within-participant fashion. We then examined whether the likelihood of an event being remembered correlated with neural responses across participants. The recall rate for an event was the proportion of participants that remembered it. At the same time, pattern similarity of both *activation* and *connectivity patterns* was calculated and averaged across all participants, generating the neural transition indices across participants. Recall rates for all 50 events and their corresponding pattern transition measures were then correlated, providing a further indication of how subsequent memory related to pattern transitions across boundaries.

3.6 Relationship between hippocampal pattern similarity and event distance

The above analyses focused on neural pattern similarities between two neighboring events. Here, we examined the hippocampal pattern similarities between events with variable distances. Event distance was defined as the number of event boundaries between two events (the event distance between event 1 and event 3 is 2). For each event, we first calculated its *activation* and *connectivity pattern*. Then, we calculated the *activation* and *connectivity pattern* similarity between all possible combinations of event A-B pairs ('Event A' is the event which appeared earlier in the temporal sequence and 'Event B' is the one presented later) within all 50 events. Finally, for each participant and each event distance, two mean similarities for activation and connectivity pattern were calculated separately. Note that the number of available pairs decreases as the distance increases (e.g., events 1-50 are the only event pair with a distance of 49). To ensure a well-powered analysis for every event distance, we only compared event pairs with a distance less than or equal to 40, meaning at least 10 event pairs contributed to the event distance calculation. Analysis of all distances ($d \leq 49$) can be found in the **Supplementary Materials**.

First, one-sample *t*-tests were performed separately on each distance to test the difference between zero and the distance-specific activation and connectivity pattern similarities. All resulting *p* values were corrected for False Discovery Rate (FDR) based on the number of distances included (from $d_{min} = 1$ to $d_{max} = 40$). Next, we used linear regression to examine the relationship between pattern similarity and event distance. In addition, to investigate how the subsequent memory of the preceding event (event A) modulates the relationship between event distance and pattern similarity, we ran a two-way ANOVA (memory * event distance) using the memory performance (remembered or forgotten) of the preceding event and event distance (range from 1 to 40) as two independent variables.

4. Statistical analysis

For hypothesis tests involved in the fMRI data analyses, the significance level was set to $p = 0.05$ (two-tailed). Except for the permutation test for simulated event boundaries (see **Supplementary Materials**), *p* values were based on the parametric testing. To account for the multiple comparisons problem that comes with multiple ROIs or parcels, all reported *p* values in the main text were FDR-corrected (p_{FDR}) (73) unless otherwise stated (p_{raw}). Specifically, this means correction was made for six tests in ROI analyses, and 1000 tests for the whole-brain analyses. All significant *p* values were reported together with the effect sizes (Cohen's d or partial η^2). The custom modified version of DABEST (https://github.com/ACCLAB/DABEST-python) was used to plot individual data points alongside bootstrapping-based resampled distributions of the mean difference between conditions (74).

5. Data and code availability

ROI data are available at http://datasets.datalad.org/?dir = /workshops/mind-2017/sherlock. Whole-brain neuroimaging data are available at https://dataspace.princeton.edu/jspui/handle/88435/dsp01nz8062179. Custom code used in this study will be publicly available via the Open Science Framework (OSF) (Link: https://osf.io/p68cv/?view_only=483703873dae4cfd8b36e9d6df6b8c92) upon publication. Further requests for scripts should be directed to the corresponding author.

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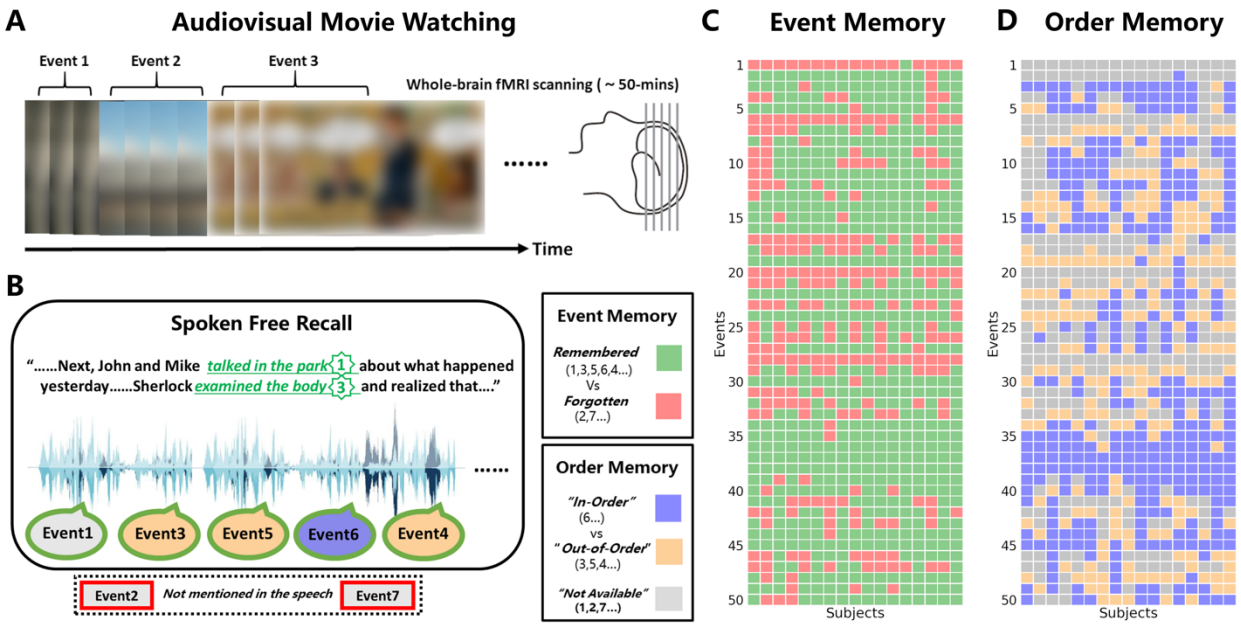

Figure 1. Experimental procedure and behavioural performance. (A) Each participant watched a 50-min audiovisual movie, BBC's Sherlock (season 1, episode 1), while brain activity was recorded with fMRI. The movie was divided into 50 events based on major narrative shifts. Blurred images are shown here due to copyright reasons. However, the movie was shown in high resolution during the experiment. **(B)** Immediately after movie-watching, participants verbally recalled the movie content in as much detail as possible without any visual or auditory cues. Speech was recorded using a microphone and then transcribed. Critically, speech was also segmented into events and matched with the events segmented from the movie. All events mentioned in the speech were labelled as *remembered* while missing events were labelled as *forgotten*. In addition, among those remembered events, the ones that were recalled in the correct sequential order were labelled as *in-order* events (e.g., *event 6* was recalled after *event 5*). *Out-of-order* events were those that were recalled in an incorrect sequential order (e.g., *event 4* was recalled after *event 6*). We labelled the first recalled event and all *forgotten* events as *not available* because no sequential information can be accessed. **(C)** Illustration of all *remembered* and *forgotten* events during movie-watching in all participants**. (D)** Illustration of all *in-order* and *out-of-order* events during movie watching in all participants. Each row of the heatmap is a different event, and each column represents a participant.

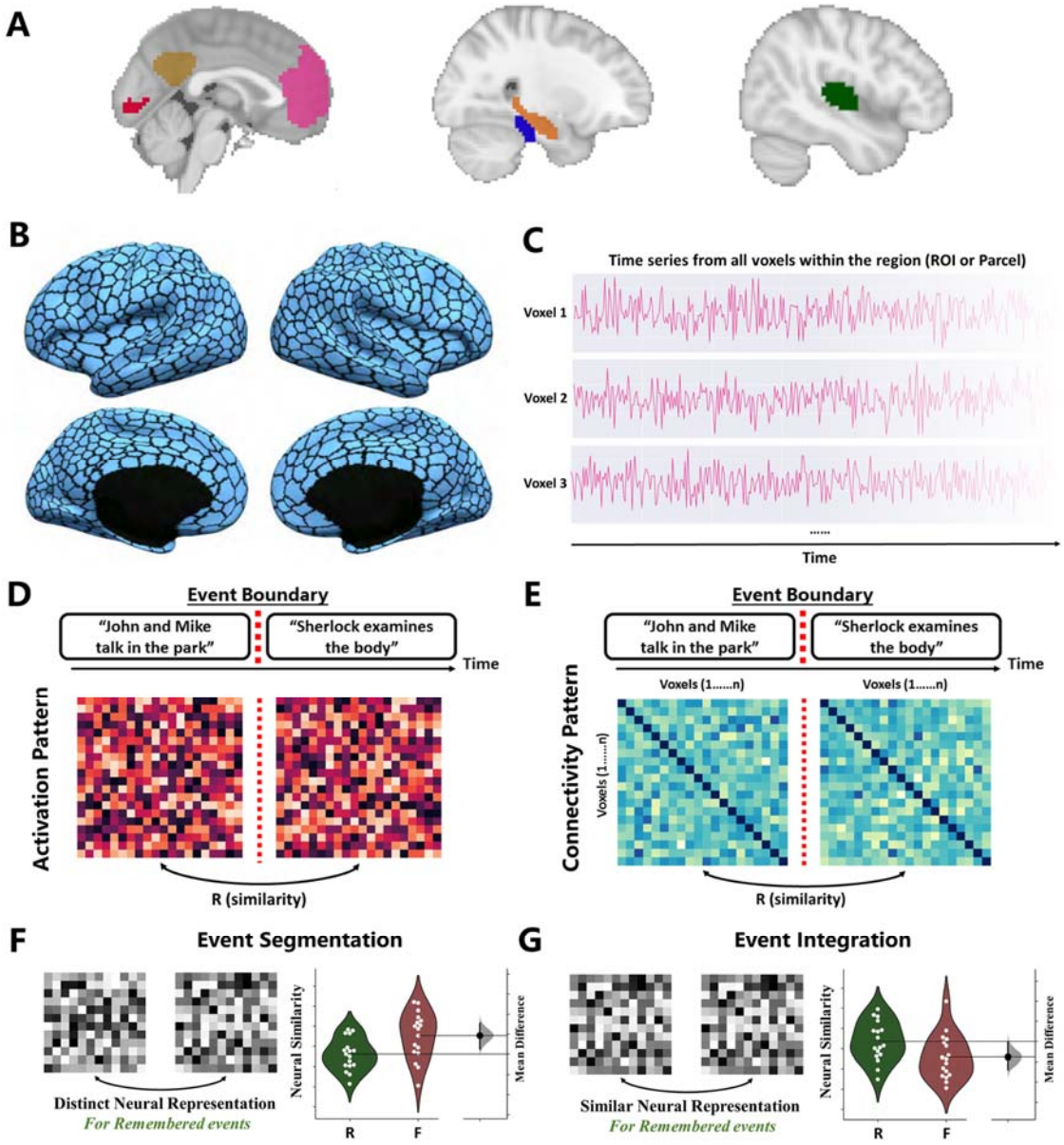

Figure 2. Neural similarities between separate events and their link with subsequent memory recall. (A) Six predefined regions-of-interest (ROIs): early auditory (green) and visual area (red), posterior medial cortex (brown), medial prefrontal cortex (pink), hippocampus (blue), and posterior parahippocampal gyrus (orange). See also **Supplementary Figure 1**. **(B)** Neocortical parcellation (1000 parcels) used in searchlight analysis. **(C)** For each region (ROI or parcel), voxel-wise signal during movie watching was extracted and then segmented into 50 events based on the event annotations. **(D)** We first generated event-specific *activation patterns* by averaging over all time points in that event. Then *activation pattern* similarity was calculated by Pearson's correlation between *activation patterns* of two sequential events. If a region encodes two events separately, we expect two distinct neural representations and therefore a negative correlation (i.e., lower than zero). **(E)** Event-specific within-region *connectivity patterns* were represented by voxel-by-voxel pairwise correlation matrices. *Connectivity pattern* similarity across event boundaries was also calculated using Pearson's r between two sequential events. Stable neural representations across two events should yield a positive correlation (i.e., higher than zero) in the corresponding region. **(F)** fMRI evidence for event segmentation. For a certain multivariate neural measure, if it can be found that two distinct neural representations are used to encode the adjacent events while the neural patterns for remembered *('R')* events are more dissimilar compared to forgotten *('F')* events, this measure is likely to be associated with event segmentation. **(G)** fMRI evidence for event integration. If the multivariate neural measure remains stable across the boundary of two neighboring events and remembered *('R')* events have higher neural similarity compared to forgotten *('F')* events, this measure may relate to event integration.

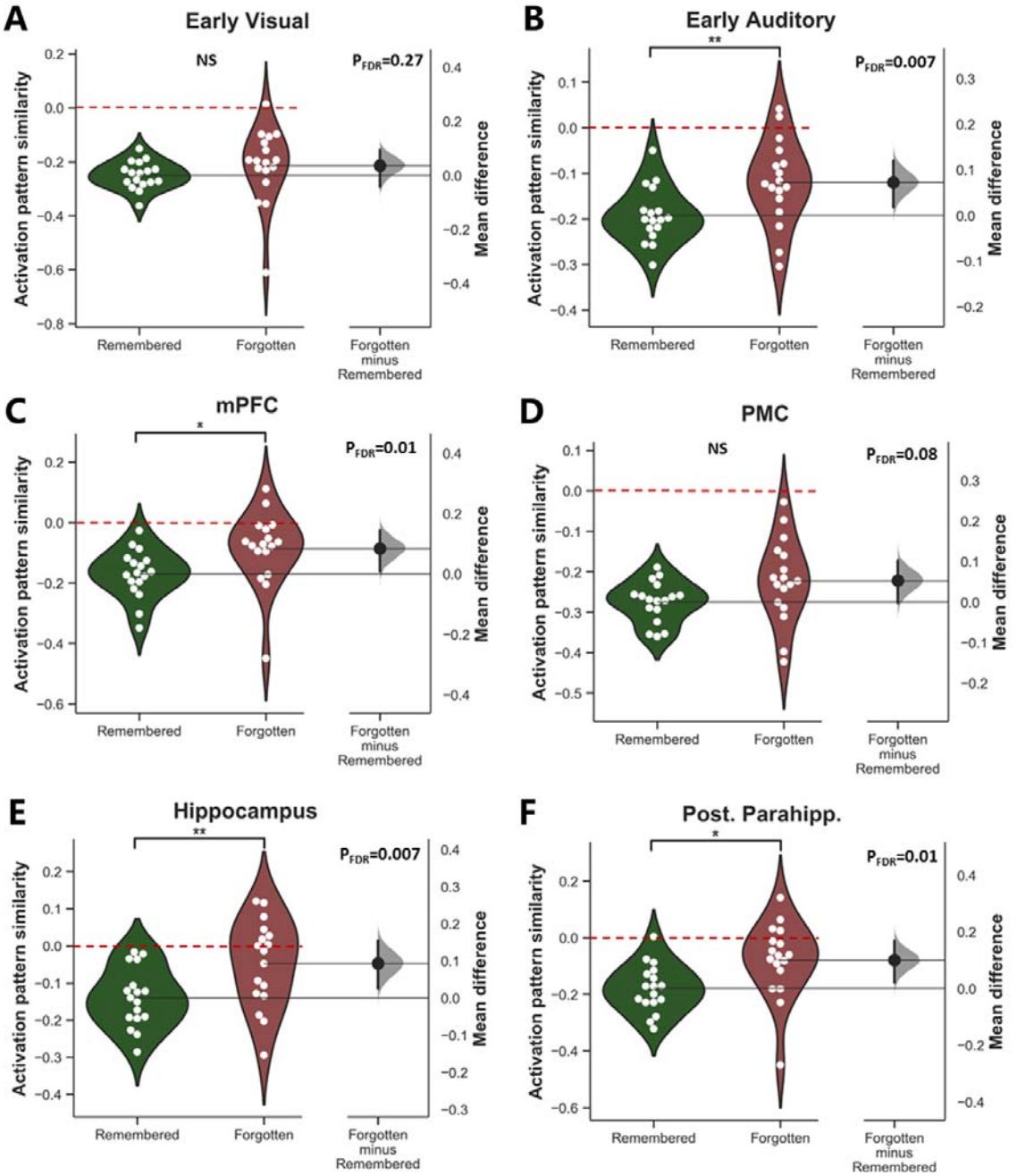

Figure 3. Association between activation pattern similarities of six ROIs and subsequent memory recall. We compared *activation pattern* similarities of sequential event pairs based on subsequent memory performance of the first event (*Remembered* vs. *Forgotten*) across six ROIs. For panel A-F, *activation pattern* similarities for *Remembered* events are displayed on the left (*green*), while similarities for *Forgotten* events are displayed on the right *(red)*. For each comparison, a separate axis displays the *mean difference*. The curve (gray) indicates the resampled distribution of the *mean difference* generated via bootstrapping. The solid vertical line attached to the curve represents the *mean difference* as a 95% bootstrap confidence interval. We found significantly lower *activation pattern* similarity for *Remembered* vs. *Forgotten* event pairs in the early auditory area (t = -3.56, p_{FDR} = 0.007, Cohen's d = 0.92; panel **B**), mPFC (t = -2.79, p_{FDR} = 0.01, Cohen's d = 0.80; panel **C**), hippocampus (t = -3.62, p_{FDR} = 0.007, Cohen's d = 0.92; panel **E**), and pPHG (t = -2.85, p_{FDR} = 0.01, Cohen's d = 0.89; panel **F**). No significant differences were found in early visual areas (t = -1.13, p_{FDR} = 0.27, Cohen's d = 0.35; panel **A**) and PMC (t = -1.91, p_{FDR} = 0.08, Cohen's d = 0.65; panel **D**). NS=Not significant; * p_{FDR}<0.05; ** p_{FDR}<0.01.

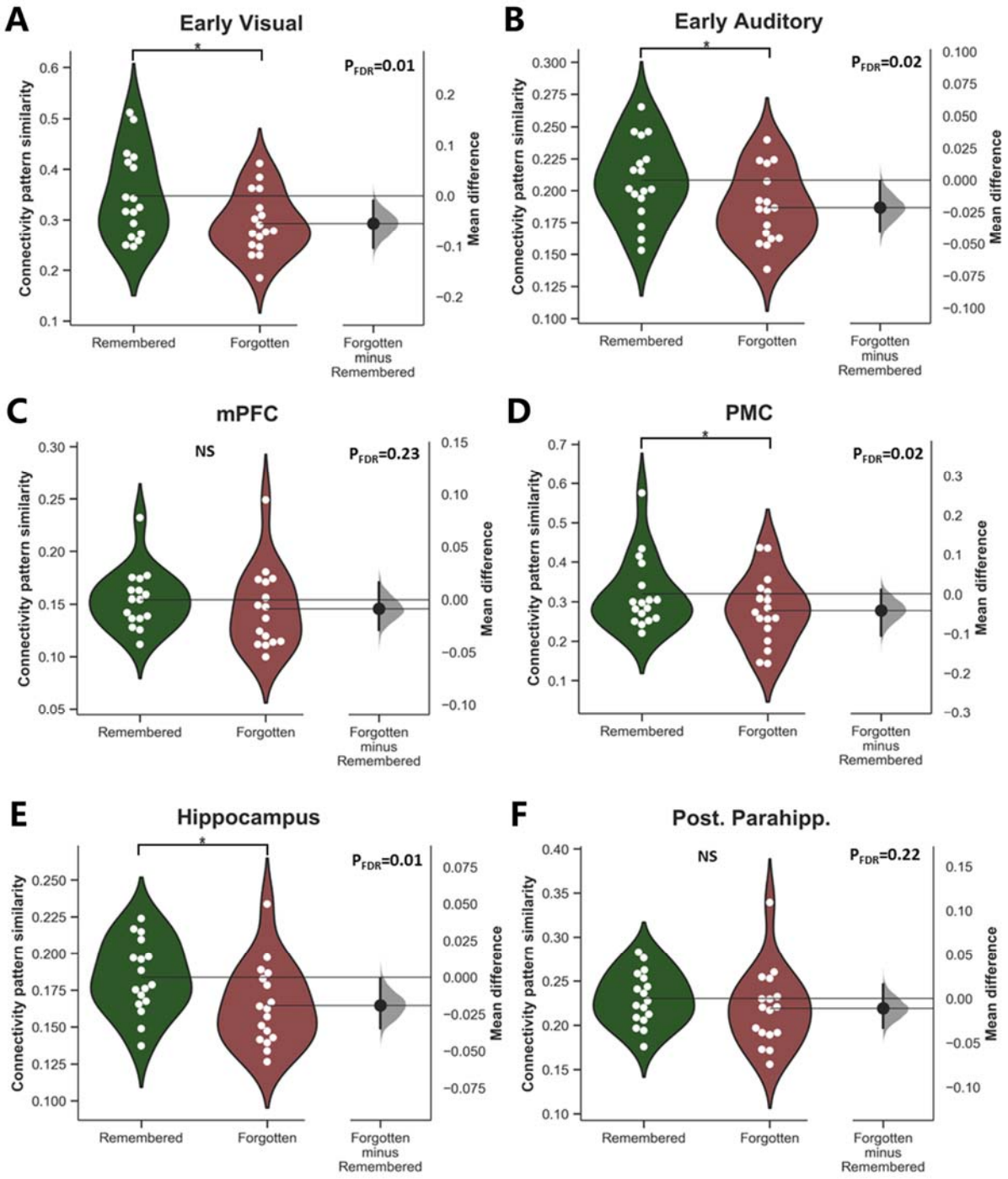

Figure 4. Association between connectivity pattern similarities of six ROIs and subsequent memory recall. We compared connectivity pattern similarities of sequential event pairs based on subsequent memory performance of the first event (*Remembered* vs. *Forgotten*) across six ROIs. For panel A-F, connectivity pattern similarities for *Remembered* events are displayed on the left (*green*), while similarities for *Forgotten* events are displayed on the right *(red).* For each comparison, a separate axis displays the *mean difference*. The curve (*gray*) indicates the resampled distribution of the *mean difference* generated via bootstrapping. The solid vertical line attached to the curve represents the *mean difference* as a 95% bootstrap confidence interval. We found significantly higher connectivity pattern similarity for *Remembered (green)* vs. *Forgotten (red)* event pairs in the early auditory area (t = 2.9, p_{FDR} = 0.02, Cohen's d = 0.72, panel **B**), visual areas (t = 3.34, p_{FDR} = 0.01, Cohen's d = 0.74, panel **A**), hippocampus (t = 3.39, p_{FDR} = 0.01, Cohen's d = 0.73, panel **E**), and PMC (t = 2.79, p_{FDR} = 0.02, Cohen's d = 0.47, panel **D**). No significant differences were found in mPFC (t = 1.22, p_{FDR} = 0.23, Cohen's d = 0.25, panel **C**) and pPHG (t = 1.36, p_{FDR} = 0.22, Cohen's d = 0.30, panel **F**). NS=Not significant; * p_{FDR}<0.05.

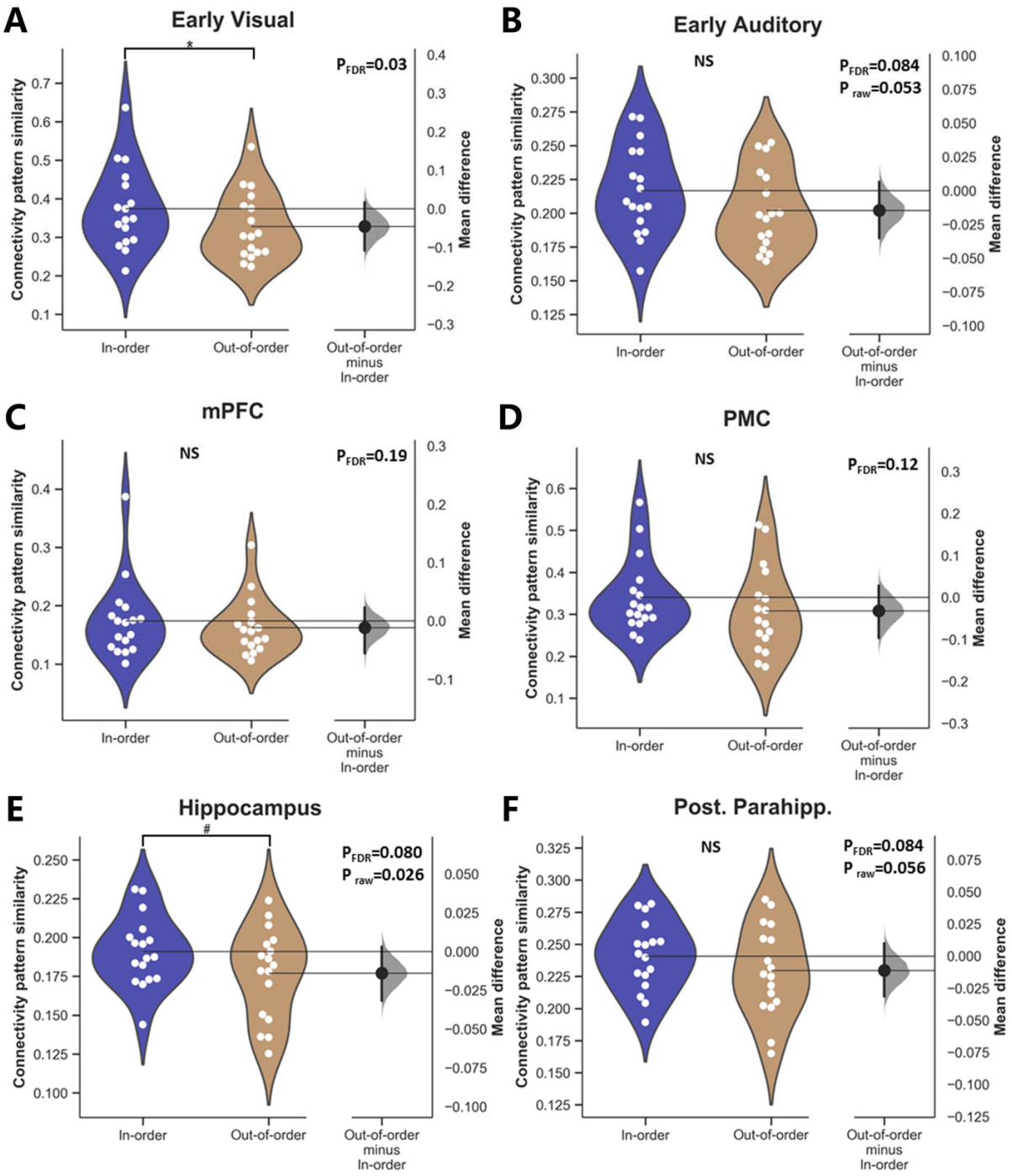

Figure 5. Association between connectivity pattern similarities of six ROIs and sequential order of memory recall. We compared connectivity pattern similarities of sequential event pairs (*In-order* vs. *Out-of-order*) based on sequential memory performance of the first event across six ROIs. For panel A-F, connectivity pattern similarities for *In-order* events are displayed on the left (*BLUE*), while similarities for *Out-of-order* events are displayed on the right *(BROWN)*. Early visual areas (t = 3.16, p_{FDR} = 0.03, Cohen's d = 0.47, panel **A**) demonstrated higher connectivity pattern similarity for the *In-order* events compared to *Out-of-order* events. A similar trend was also detected in the hippocampus (t = -2.43, p_{raw} = 0.026, Cohen's d = 0.53, panel **E**), but it did not survive FDR correction (p_{FDR} = 0.08). We also found modest, non-significant trends in the early auditory area (t = -2.08, p_{raw} = 0.053, p_{FDR} = 0.084, Cohen's d = 0.46, panel **B**) and posterior parahippocampal gyrus (t = -2.05, p_{raw} = 0.056, p_{FDR} = 0.084, Cohen's d = 0.36, panel **F**). No similar effects were detected in mPFC (t = -1.35, p_{FDR} = 0.19, Cohen's d = 0.19, panel **C**), and PMC (t = -2.05, p_{FDR} = 0.12, Cohen's d = 0.33, panel **D**). NS=Not significant; * p_{FDR}<0.05; # p_{raw}<0.05.

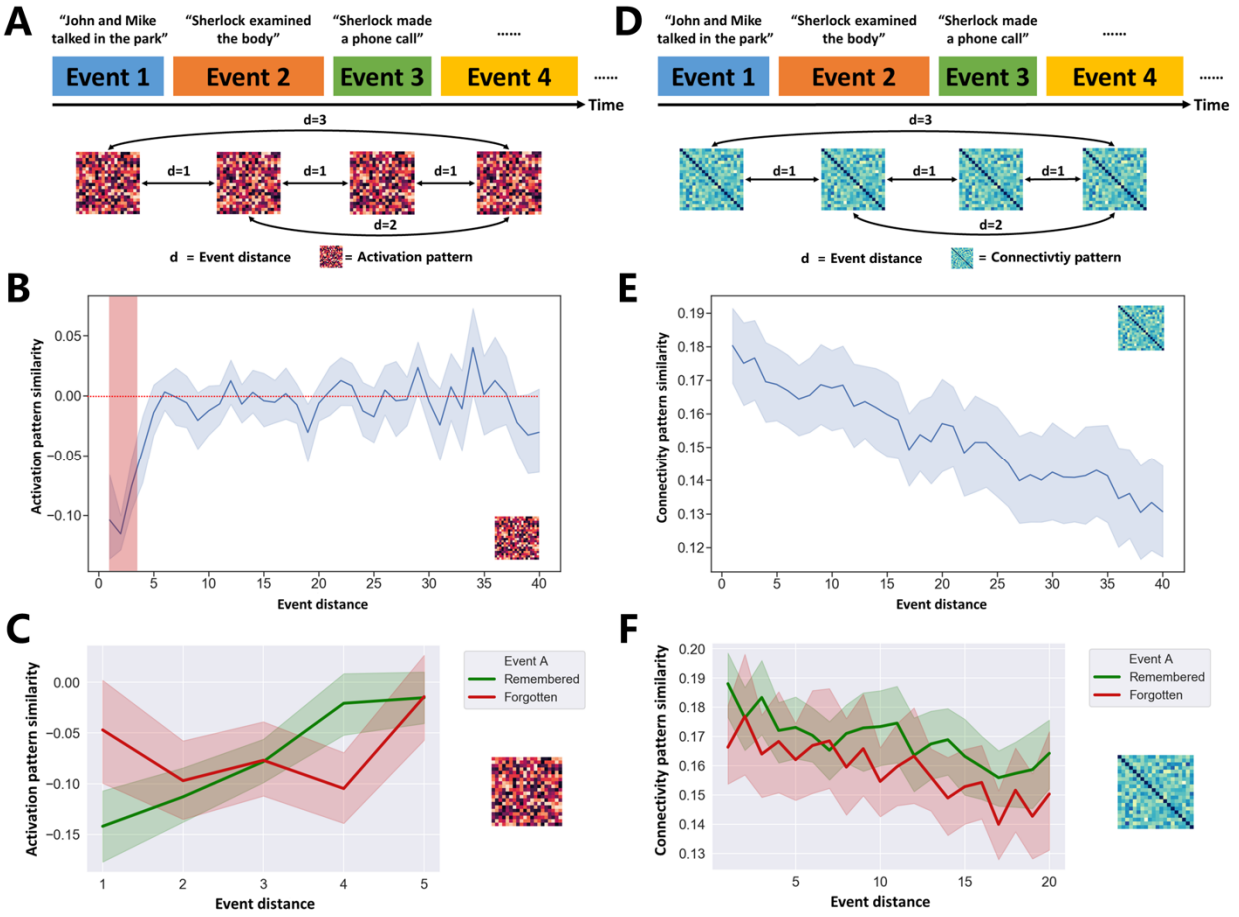

Figure 6. Hippocampal pattern similarity changes with event distance. (A) Hippocampal *activation patterns* were generated for all 50 events. We calculated *activation pattern* similarities between sequential events (event distance = 1) and all possible combinations of non-sequential event pairs (event distance > 1). **(B)** Hippocampal *activation patterns* between pairs of events were significantly dissimilar for events separated by a distance of less than 4 (red shadow). **(C)** Memory performance modulated the distance-*activation pattern* similarity relationship. If the first event (*Event A*) of the pair was successfully encoded, *activation pattern* similarities of the event pair increased with event distance (green line). **(D)** Hippocampal *connectivity patterns* were generated for all possible combinations of event pairs. **(E)** Event pairs with shorter event distance had more similar hippocampus *connectivity patterns*. At the same time, similarities of hippocampus *connectivity patterns* are higher than 0 regardless of event distance. **(F)** Memory performance modulated distance-*connectivity pattern* similarity relationship. If the first event (*Event A*) of the event pair was successfully encoded, *connectivity pattern* similarities of the event pair are enhanced regardless of their event distance. For panel B-F, error bands (i.e., light shadow around the solid line) represent the 95% confidence interval of the mean.

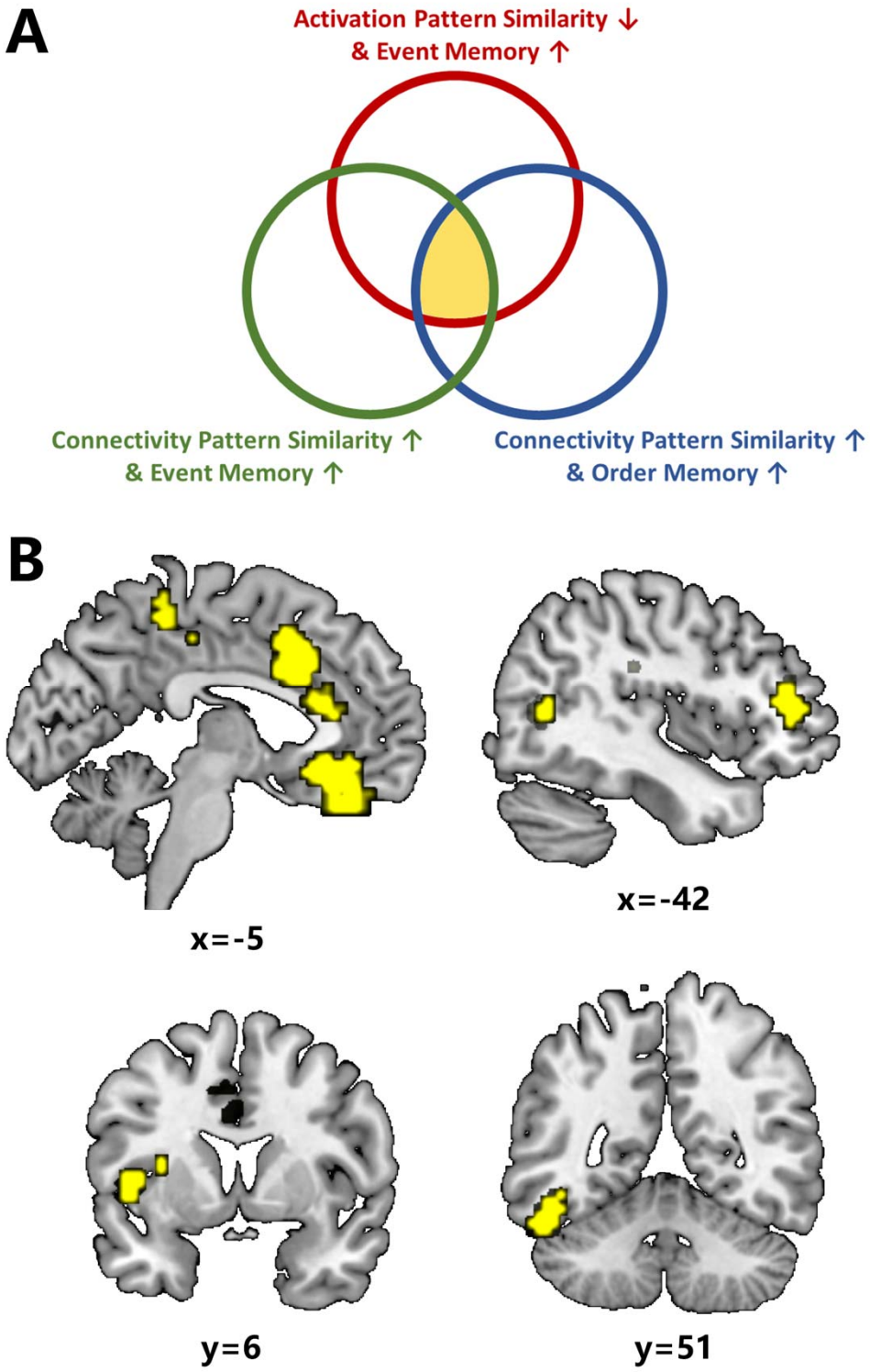

Figure 7. Identifying overlapping event segmentation and integration computations across the neocortex. (A) We identified three relationships between neural pattern similarity and subsequent memory in the hippocampus. **(B)** Similar to the hippocampus, overlapping event segmentation and integration computations were found in a network of brain regions including the medial prefrontal cortex (mPFC), right inferior frontal gyrus (IFG), anterior/middle cingulate cortex and supplementary motor area (SMA), left inferior temporal gyrus (ITG), and left insular ($p_{FDR} < 0.05$ across 1000 parcels, cluster size >= 50).