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RESEARCH ARTICLE

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Reminders activate the prefrontal-medial temporal cortex and attenuate forgetting of event memory

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Abstract

Replicas of an aspect of an experienced event can serve as effective reminders, yet little is known about the neural basis of such reminding effects. Here we examined the neural activity underlying the memory-enhancing effect of reminders 1 week after encoding of naturalistic film clip events. We used fMRI to determine differences in network activity associated with recently reactivated memories relative to comparably aged, non-reactivated memories. Reminders were effective in facilitating overall retrieval of memory for film clips, in an all-or-none fashion. Prefrontal cortex and hippocampus were activated during both reminders and retrieval. Peak activation in ventro-lateral prefrontal cortex (vPFC) preceded peak activation in the right hippocampus during the reminders. For film clips that were successfully retrieved after 7 days, pre-retrieval reminders did not enhance the quality of the retrieved memory or the number of details retrieved, nor did they more strongly engage regions of the recollection network than did successful retrieval of a non-reminded film clip. These results suggest that reminders prior to retrieval are an effective means of boosting retrieval of otherwise inaccessible episodic events, and that the inability to recall certain events after a delay of a week largely reflects a retrieval deficit, rather than a storage deficit for this information. The results extend other evidence that vPFC drives activation of the hippocampus to facilitate memory retrieval and scene construction, and show that this facilitation also occurs when reminder cues precede successful retrieval attempts. The time course of vPFC-hippocampal activity during the reminder suggests that reminders may first engage schematic information meditated by vPFC followed by a recollection process mediated by the hippocampus.

KEYWORDS
episodic memory, event memory, fMRI, hippocampus, reactivation, vlPFC, vmPFC

1 | INTRODUCTION

Episodic memory relies heavily on the hippocampus for encoding and retrieval of the detailed elements of the event with precise perceptual and contextual information (Moscovitch, Cabeza, Winocur, & Nadel, 2016). Damage to the medial temporal lobe, specifically the hippocampus, selectively impairs the retrieval of these detailed elements (Gilboa et al., 2006; Rosenbaum et al., 2005; Steinvorth, Levine, & Corkin, 2005; St-Laurent, Moscovitch, Levine, & McAndrews, 2009). In healthy individuals, these detailed elements of the episode are forgotten over time, as the memory becomes more gist-like, retaining primarily the general features of the event

(Conway, 2009; Conway, Cohen, & Stanhope, 1991; Sekeres et al., 2018). Whether forgotten memory details are irretrievably lost in people with intact brains, reflecting a failure to store the details, or are just inaccessible in the absence of appropriate retrieval cues, is usually difficult to ascertain (Hardt, Nader, & Nadel, 2013; Sadeh, Ozubko, Winocur, & Moscovitch, 2014; Tulving & Pearlstone, 1966).

Using wearable cameras to capture everyday events and subsequently presenting photographic scenes to cue those autobiographical events after varying delays enhances memory retrieval both in memory-impaired patients and in healthy adults (Berry et al., 2007; Chow & Rissman, 2017; Hodges, Berry, & Wood, 2011; Rissman, Chow, Reggente, & Wagner, 2016). When presenting healthy young adults with photographs taken from a recorded personal event to reactivate a week-old event memory, St. Jacques, Conway, Lowder, and Cabeza (2011), observed fMRI activity in ventromedial and ventrolateral prefrontal cortex (vmPFC, vlPFC), left hippocampus as well as lateral temporal regions, and midline posterior regions during vivid recollection, or mentally reliving, of the autobiographical event. Similarly, Risman and colleagues (2016) found that recollection in response to memory reactivation with photographs one to three weeks after the experience recruited regions of the recollection network, which includes the hippocampus and parahippocampal cortex, angular gyrus, parietal, and medial frontal regions (Cabeza & St Jacques, 2007; Rugg & Vilberg, 2013). Thus, brief reactivation of complex everyday events can be an effective means of enhancing recall of otherwise inaccessible details, possibly through mental reinstatement of the context (Loveday & Conway, 2011; Smith, Handy, Angello, & Manzano, 2014; Tulving & Thompson, 1973).

Recording autobiographical events at the time of encoding and their subsequent retrieval is a powerful way of assessing memory for complex experiences. One notable limitation to this method, however, is the labor-intensive approach to collecting the variable experiences of each individual, and verifying the accuracy of the recollected event details. The use of standardized film clips of everyday events, or complex movies, is becoming an increasingly popular method for assessing nuanced differences in the qualitative content of retrieved declarative memories, and for assessing neural networks supporting naturalistic episodic memory encoding and retrieval over time (St-Laurent, Moscovitch, Jadd, & McAndrews, 2014; Bird, Keidel, Ing, Horner, & Burgess, 2015, Sekeres et al., 2016; Sekeres, Winocur, & Moscovitch, 2018; Tang et al., 2016; Chen et al., 2017; Oedekoven, Keidel, Berens, & Bird, 2017; Oedekoven, Keidel, Anderson, Nisbet, & Bird, 2019; Bonasia et al., 2018; Kauttonen, Hlushchuk, Jääskeläinen, & Tikka, 2018; see Baraly et al. (2020) for a new standardized database of film events). Advantages to this approach include the ability to standardize the content of the events, to control the timing and duration of exposure to the events, and to verify easily the accuracy of memory for the events. Studies typically use screenshots taken from an encoded film (or novel foil screenshots) to test for recognition memory for the clips (Tang et al., 2016). While this is a useful method for assessing the accuracy of recognition memory, this approach is limited in its ability to identify effortful or self-generated recollection of perceptual details, and the temporal sequence of the unfolding event in the clip.

By objectively assessing the qualitative content of a participant's memory through narrative recollection, it is possible to identify the specific type of retrieved information. Previous approaches using narratives to report recollected details of film events and recollected autobiographical memories found that the perceptual details within both types of events are particularly susceptible to loss in patients with medial-temporal lobe damage (St-Laurent et al., 2014; St-Laurent, Moscovitch, & McAndrews, 2016). Using the same film clip stimuli as the present study, we previously reported that, over the course of 1 week following encoding of the film clips, memory for the perceptual details (called "peripheral details") of the events declines greatly, while memory for the general schematic story content (called "central elements") declines only modestly over time (Sekeres et al., 2016; Sekeres, Winocur, & Moscovitch, 2018). The dramatic decline in recollection of the perceptual/peripheral details was accompanied by a decline in posterior hippocampal activity, but continued activation of anterior hippocampus after 7 days. When the week-old memories for the film clips were recalled with a high degree of vividness, however, robust anterior and posterior hippocampal activity was observed, suggesting that the hippocampus continues to support the retrieval of perceptually detailed memory over time (Barry, Barnes, Clark, & Maguire, 2019; Bonnici et al., 2012; McCormick, Barry, Jafarian, Barnes, & Maguire, 2020; Sekeres, Winocur, & Moscovitch, 2018; Sheldon & Levine, 2018).

Reminders at, or just prior to, retrieval are an effective means of boosting retrieval of otherwise inaccessible episodic details for complex events. For example, replaying brief scenes from the previously viewed movie *Memento* facilitated the retrieval of temporally coherent scene memory for the event (Kauttonen et al., 2018). Behaviorally, we found that after 1 week, brief reminders of film clips with partial screenshot photographs taken from the film clip event (see Figure 1a) boosted retrieval of perceptual/peripheral details, but not retrieval of the central story elements which were generally well retained over time even in the absence of a reminder (Sekeres et al., 2016). This finding of a memory enhancing effect following partial screenshot reactivation suggests that the inability to recall certain elements of an event memory after a delay of a week largely reflects a retrieval deficit, rather than a storage deficit for this information (Dudai, 2004; Hardt, Wang, & Nader, 2009; Loveday & Conway, 2011; Tulving, 1972). Here, we investigated whether brief screenshot reminders of week-old event memories for film clips were sufficient to activate the prefrontal-hippocampal network, and enhance subsequent elaborative retrieval of the events that might not otherwise be accessible in the absence of a pre-retrieval cue.

Several studies seeking to identify how the prefrontal-hippocampal networks dynamically interact to support retrieval have found that vPFC activity often precedes hippocampal activity during episodic memory retrieval, although it remains unclear what each region functionally contributes to the retrieval process (Barry et al., 2019; Fuentemilla, Barnes, Düzel, & Levine, 2014; McCormick

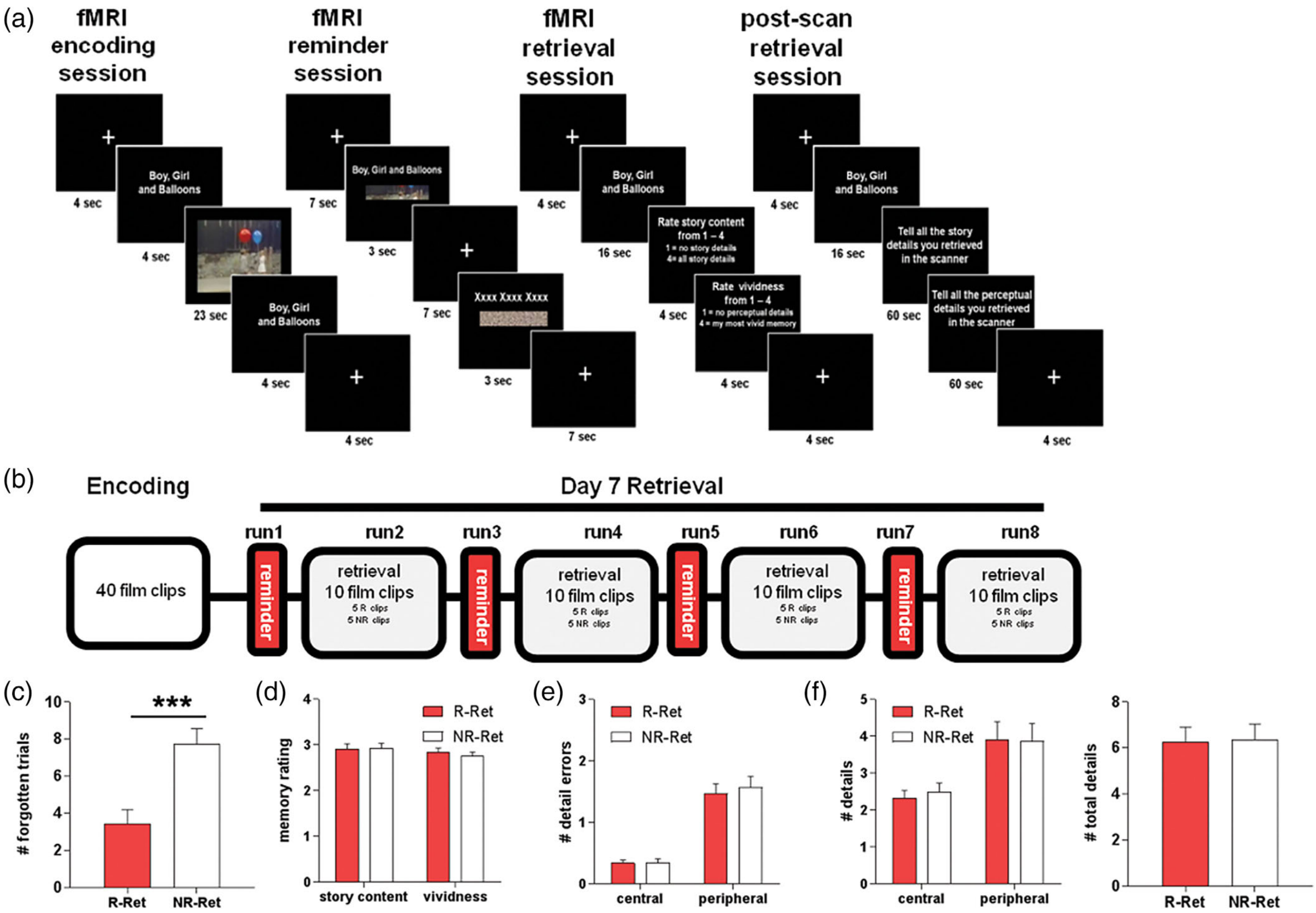

FIGURE 1 Reminders reduce forgetting of film clips after 1 week. (a) Detailed schematic of the study design for the encoding session (left), in-scanner reminder and retrieval sessions (middle), and post-scan retrieval session (right). Encoding session: 40 film clips were shown to participants in a randomized order over 4 runs, with 10 clips presented per run. Reminder session: 7 days following encoding, participants received 5 reminder cues and 5 scrambled control cues for each run. Retrieval session: participants retrieved 10 clips, 5 of which had just been reactivated with a reminder, during each run. (b) Experimental timeline. (c) Mean number of forgotten trials for reminded (R) and non-reminded (NR) clips during the retrieval session. Forgotten trials were classified based on in-scanner memory ratings of 1 (lowest rating) for both story content and perceptual vividness. Reminders were effective in reducing the overall forgetting of the film clips. (d) In-scanner memory ratings of the story content and the vividness of perceptual details for non-reminded clips (NR-Ret, white bars) and reminded clips (R-Ret, pink bars) during the in-scanner retrieval session. There were no differences in memory ratings for either story content or vividness between reminded and non-reminded clips. (e) Mean number of errors per retrieval trial. Errors were subtracted from the total number of retrieved details to produce the corrected number of central and peripheral details (Retrieval Success). (f) Left: mean number of details (central elements and peripheral details) reported per clip during the post-scanner verbal memory retrieval test session for reminded and non-reminded clips. Participants reported more peripheral details than central elements 7 days after encoding. Right: reminded (pink bars) and non-reminded (white bars) clips were recalled with comparable numbers of total detail. Error bars represent the SEM. *** indicates $p < .001$ [Color figure can be viewed at wileyonlinelibrary.com]

et al., 2020). To investigate the temporal pattern of activity supporting cued reminders and retrieval of complex event memory, we asked if viewing a partial screenshot reminder of a previously encoded film clip activates, in a time-dependent manner, memory for the perceptual elements of the event. We examined the neural activity underlying the memory-enhancing effect of reminders 1 week after encoding naturalistic film clip events by determining differences in network activity associated with recently reactivated memories relative to comparably aged, non-reactivated memories. Based on evidence that reactivating a week-old memory enhances subsequent memory retrieval (Sekeres et al., 2016) and engages regions of the recollection network (Rissman et al., 2016; St. Jacques, Conway, et al., 2011; St. Jacques, Kragel, & Rubin, 2011), we hypothesized that (a) the reminder would be sufficient to engage the hippocampus; (b) memory for previously reminded clips would be superior to memory for non-reminded clips; (c) enhanced memory retrieval following a reminder would be supported by enhanced retrieval activity in the hippocampus; and (d) activity in the hippocampus would be preceded by activation of vPFC in response to reminders and during retrieval.

2 | MATERIALS AND METHODS

2.1 | Participants

Twenty-three healthy, right-handed participants (14 female), ranging in age from 19–30 years old (mean age 21.19, *SD* 2.66), were recruited through the participant database at Baycrest Centre. Participants were fluent in English and screened using a detailed health questionnaire to exclude psychiatric and neurological disorders, previous head injuries, or other health problems and/or medications that might affect cognitive function and brain activity, including strokes and cardiovascular disease. All procedures were approved by Baycrest's Research Ethics Board and conducted in accordance with the guidelines set by the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. All participants gave written informed consent, and were reimbursed $100 for their participation in the study. Two participants (1 male, 1 female) were excluded due to incidental findings in their structural MRI, and one participant (female) was excluded due to falling asleep during the encoding scan and excessive movement during the retrieval scan. The remaining 20 participants were included in all imaging analyses. Recording failed during the verbal retrieval session for one participant, so verbal retrieval data are presented for 19 participants.

2.2 | Behavioral methods

2.2.1 | Film clip stimuli

Forty film clips were used to test episodic memory. Clips were 23 s in duration and were taken from foreign films (i.e., non-English language films) with limited dialogue (the same clips were used in previous studies; St-Laurent et al., 2014, 2016; Sekeres et al., 2016; Sekeres et al., 2018; Bonasia et al., 2018). The library of clips is available from the authors upon request. Each clip was analyzed for its content based on four feature categories: visual complexity (color, background complexity, movement, number of frame transitions, number of background characters), story complexity (number of central characters, storyline complexity), sound complexity (speech, music, background noise), and emotional content (funny, surprising, cute, sad, quirky). Three scorers independently rated each clip on each criterion, and assigned a score between 1 (low) and 5 (high), or a yes/no rating. Mean correlations between the three scorers were r = 0.79, r = 0.83, and r = 0.78. Composite scores for each feature category were averaged and transformed to z-scores. Each clip's z-scores were used to divide the 40 clips into four series of 10 clips, balanced across the feature categories. For each participant, half of these clips were randomized to be preceded by a reminder cue, or a scrambled control cue during the reminder session. The order of series tested during the reminder and retrieval sessions was randomized across participants.

2.2.2 | Task

Procedures were based on those developed for a previous study (Sekeres, Winocur, & Moscovitch, 2018). Prior to scanning, participants were read a set of instructions, and then performed a practice session in which they watched two sample clips and performed the memory retrieval task. Participants were told they would be tested on their memory for the clips 1 week later, and instructed not to rehearse the information in the interim. Prior to the memory retrieval session, participants were told that they will be given brief “reminders” for some of the clips studied during the encoding session. Once in the scanner, they were again briefed on the instructions for the task. All experimental stimuli were viewed through a mirror affixed to the head coil, and responses to the memory ratings were recorded using a four-button box taped to the right hand. Experimental stimuli were presented using E-Prime 2 (version 2.0.10.242, E-Studio, Psychology Software Tools Inc., RRID: SCR_009567).

2.2.3 | Encoding session in scanner (Day 1)

During encoding, participants viewed the 40 film clips, presented in randomized order. Each clip was given a unique title (i.e., “Boy, Girl and Balloon”), which appeared centrally on the screen for 4 s immediately before and after the clip played. Clips were centrally presented on a computer screen. Sound was delivered through a rimless Avotech headset. Participants were instructed to pay attention to the title and content of each clip. A fixation cross was presented for 4 s between each clip. Encoding occurred across four runs in the scanner, with 10 clips presented in each run. No response was required during the encoding session. Following encoding, participants were asked if they had previously seen any of the film clip stimuli. No participant reported having previously viewed the clips.

2.2.4 | Reminder session in scanner (Day 8)

Seven days after encoding, participants returned to the scanner. A reminder run preceded each of the four retrieval runs. For each reminder run, half of the clips tested in the following retrieval run were randomly selected to be presented in the reminder condition (5 per run), which consisted of the clip title and a one-inch high horizontal strip taken from a screenshot of the clip (Figure 1a). A Gaussian blur mask was filtered over the screenshot using Image J software (NIH) to partially obscure visual details in the reminder and reduce meaningfulness. Each reminder cue was presented on the computer screen for 3 s, followed by a fixation-cross for a 7 s inter-trial interval. The five reminder trials were presented in a random order, along with five scrambled control cue trials. For each control trial, a one-inch high horizontal strip containing a static snow visual pattern was presented for 3 s using the same procedures used for the reminder trials. No response was required during the reminder or control trials. Within each reminder run, the presentation order of the reminder trials, and the control trials was randomized. The four reminder runs were also presented in a randomized order. Each reminder run was immediately followed by its corresponding retrieval run (see Figure 1a,b for schematics of study design).

2.2.5 | Retrieval session in scanner (Day 8)

Immediately following a reminder run, participants were tested for their memory of 10 clips, half of which had just been cued during the preceding reminder run, and half that had not been cued. During each retrieval trial, participants were presented with the title of a clip for 16 s, during which they were instructed to visualize the clip in their mind, from beginning to end. Next, they used a keypad to rate their memory retrieval for the clip's story content, on a scale of 1 (no story content) to 4 (all story content). Story content refers to the central plot line of the story ("what happened"), and events central to the progression of the episode (Berntsen, 2002; Sekeres et al., 2016; Sekeres, Moscovitch, et al., 2018; Sekeres, Winocur, & Moscovitch, 2018; St-Laurent et al., 2014, 2016). Next, participants rated the vividness of perceptual details retrieved in a similar way (rating of 1 = no perceptual details, rating of 4 = most vivid memory). Perceptual details referred to visual (colors, lighting, textures, facial features, clothing, positions of objects, background details, weather, lighting conditions, etc.) and auditory details (talking, laughing, background music, street sounds). A fixation cross presented centrally on the screen for 4 s separated the retrieval period for each clip. Following the 10-trial retrieval run, participants then completed the next reminder run for another set of clips.

2.2.6 | Retrieval session outside scanner (Day 8)

Following the final in-scanner retrieval run, participants next performed a post-scan test session. During this session, participants were again cued with the title of the clip they had retrieved in the scanner, and given up to 60 s to report verbally the story content details they recalled while in the scanner (what happened, who did what, what was the situation). Participants were next given up to 60 s to report verbally any perceptual (visual or auditory) details they experienced in their mind's eye while they recalled the clip in the scanner. The presentation order of clips was randomized within each retrieval session. The post-scanning retrieval testing was conducted on a desktop computer using E-Prime 2 in a sound-attenuated room.

2.2.7 | Scoring and analysis of behavioral data

Self-report ratings of story content and vividness of perceptual details were averaged across clips for reminded and non-reminded clips. The recordings of the verbal retrieval responses were manually transcribed, and responses were coded and scored to categorize central elements (indicative of story content) and peripheral details (reflecting perceptual details). Central elements were story details that could not be modified or omitted without changing the plotline of the story (Berntsen, 2002). In order to score central elements consistently, 5–6 central story points were identified for each clip and recorded as a "central narrative" (see Sekeres et al., 2016 for a list of central story points for each clip, and for an example of a coded transcript). A participant was given a score of one for each item of retrieved information that corresponded to a point in the central narrative for a given clip. Peripheral details were considered any additional descriptive information, including perceptual, contextual, and emotional details. One peripheral point was scored for each accurate peripheral story detail reported during the verbal retrieval session.

For each clip, both central elements and peripheral details were coded and tallied across the first recording (participant probed for story content) and second recording (participant probed for perceptual details) by an experimenter (S. P.) blind to the reminder condition. A subset of recordings was scored by a second experimenter (M. J. S.) to confirm an acceptable rate of 90% inter-rater reliability in detail scoring. Each reported detail was classified as either central or peripheral. No additional points were assigned for repeated details, or for unrelated information about the film clips (i.e., opinions or speculations). Errors in central elements and peripheral details were also calculated. Errors were considered to be any recalled details that did not match the information presented in the film clip. For each type of detail (central or peripheral), the total number of errors was subtracted from the total number of correct details for each clip (i.e., Retrieval Success = # correct details − # errors) to determine the corrected memory retrieval success scores used in the final data analyses. For each participant, the corrected central and peripheral details were averaged across all clips for each reminder condition (Reminded-Retrieval, R-Ret; Non-Reminded-Retrieval, NR-Ret). For each reminder condition, central and peripheral details were combined to generate a "total detail score" for each clip.

For all behavioral analyses, we excluded "forgotten" retrieval trials, which were trials given memory retrieval ratings of "1" (indicating low memory for story content and low vividness of perceptual details), and for which there were no central or peripheral details reported during the verbal retrieval session. We also excluded trials in which the participant reported details corresponding to the wrong film clip.

2.2.8 | Experimental design and statistical analysis

Schematics of the experimental timeline and design can be seen in Figure 1a,b. Paired samples t-tests were conducted for reminded versus non-reminded trial ratings, forgotten trial number, detail retrieval, and error measures. Data analysis was performed using SPSS 25 (RRID:SCR_002865). Statistical analyses of brain imaging data are described below.

2.3 | fMRI methods

2.3.1 | Image acquisition and preprocessing

Participants were scanned using a Siemens Trio 3T scanner. Anatomical scans were acquired with a three-dimensional magnetization-prepared rapid acquisition with gradient echo (MP-RAGE) sequence (repetition time (TR) = 2000 ms, echo time (TE) = 2.6 ms, field of view (FOV) = 256 mm, slice thickness = 1 mm, 160 slices. Functional runs were acquired with an echo planar imaging (EPI) sequence, with 139 volumes for each retrieval run (TR = 2.2 s, TE = 27 ms, flip angle = 62°, FOV = 225 mm, 64 × 64 matrix, 36 3.5 mm (skip 0.5 mm) thick axial slices, positioned to image the whole brain. Slices were obtained from an axial oblique orientation, parallel to the Sylvian fissure.

Preprocessing of the image data was performed with Analysis of Functional Neuroimages (AFNI, RRID:SCR_005927, Cox, 1996). This included regressing out physiological artifact using RETROICOR, rigid motion correction, spatial normalization to Montreal Neurological Institute (MNI) space and smoothing with an 8 mm Gaussian filter (the final voxel size was 4 × 4 × 4 mm). We also regressed out signals from white matter, cerebral spinal fluid, and vasculature. As motion has been demonstrated to affect brain-activity measures, even after standard correction procedures (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012), we followed a motion-scrubbing procedure described in Campbell, Grigg, Saverino, Churchill, & Grady, 2013. Briefly, this procedure uses a multivariate technique to identify outliers in both the motion-parameter estimates and fMRI signal itself. Where such outliers co-occurred (never more than 5% of the total volumes), we removed the fMRI volumes and replaced them with values interpolated with cubic splines. This method suppresses spikes, yet maintains a consistent length of the time course across subjects.

2.3.2 | Partial least squares analysis

The image data were analyzed using an event-related approach with partial least squares (PLS; McIntosh, Bookstein, Haxby, & Grady, 1996; McIntosh & Lobaugh, 2004), a multivariate analysis technique that identifies whole-brain patterns of covariance related to the experimental design in a single step. PLS uses singular value decomposition in a data-driven approach to reduce the complexity of the dataset into orthogonal latent variables (LVs) that attempt to explain the maximum amount of covariance between the task conditions and the BOLD signal. In event-related PLS, each brain voxel has a weight, known as a salience, indicating how strongly that voxel contributes to the LV overall. For each analysis, the data were mean-centered within condition, and each event had a temporal window size of 8 time-points (i.e., 16 s) post-stimulus onset. Only events (reminders and retrieval trials) corresponding to clips that were successfully retrieved were analyzed. The significance of each LV as a whole was determined with a permutation test (McIntosh et al., 1996) using 1,000 permutations. The reliability of each voxel's contribution to a particular LV was tested by submitting all saliences to a bootstrap estimation of the standard errors (SEs; Efron, 1981), using 1,000 bootstraps. Peak voxels with a salience/SE ratio ≥ 3.0 ($p < .001$) are considered to be reliable (Sampson, Streissguth, Barr, & Bookstein, 1989).

Clusters containing at least 10 contiguous voxels were extracted, with a local maximum defined as the voxel with a salience/SE ratio higher than any other voxel in a 2 cm cube centered on that voxel (the minimum distance between peaks was 10 mm). The 10 voxel cluster size threshold was used for all clusters throughout the brain (including the vlPFC, vmPFC, and hippocampal regions used for the time course analyses, described below). Coordinates of these locations are reported in MNI standard coordinate space (Mazziotta et al., 2001). Because the extraction of the LVs and the corresponding brain images is done in a single step, no correction for multiple comparisons is required. Finally, to obtain summary measures of each participant's expression of each LV's spatial pattern, we calculated brain scores by multiplying each voxel's salience by the BOLD signal in the voxel, and summing over all brain voxels for each participant in each condition. These brain scores were then mean-centered (using the condition mean for each condition), and confidence intervals (CIs; 95%) for the mean brain scores in each condition were calculated from the bootstrap. Following procedures used elsewhere (Garrett, Kovacevic, McIntosh, & Grady, 2010; Grady et al., 2010; McIntosh, Chau, & Protzner, 2004; Sekeres et al., 2018), conservative estimates of differences in activity between conditions and between groups were determined by a lack of overlap in these bootstrapped CIs. That is, non-overlapping intervals between conditions indicated a significant difference.

2.4 | fMRI task analysis

2.4.1 | Reminder cue analysis

To assess modulations of BOLD activity across the conditions, we first conducted an event-related PLS analysis (in which each clip was defined as an event) that contrasted the mean activity (averaged for each TR across conditions, across runs) for the reminder cues and the mean activity for the scrambled control cues during the reminder runs (Figure 2 and Table 1). Brain scores associated with the significant LV1 are shown in Figure 2b, and the time course of percent BOLD signal change across the reminder and control cue conditions were plotted for regions in the vlPFC (coordinates: 32, 32, −12) and in the right hippocampus (coordinates: 24, −16, −20). Activity in the vlPFC and right hippocampus were identified consistently across the reminder and retrieval conditions and, therefore, were selected as seed regions for time course analyses. The coordinates for these seeds were based on peak activations observed in the PLS analysis. Percent signal change data were extracted for each seed voxel from eight TRs, excluding the first one, which was used to determine the signal change in each succeeding TR. The signal change values for these two seeds were entered into a repeated measures ANOVA with region

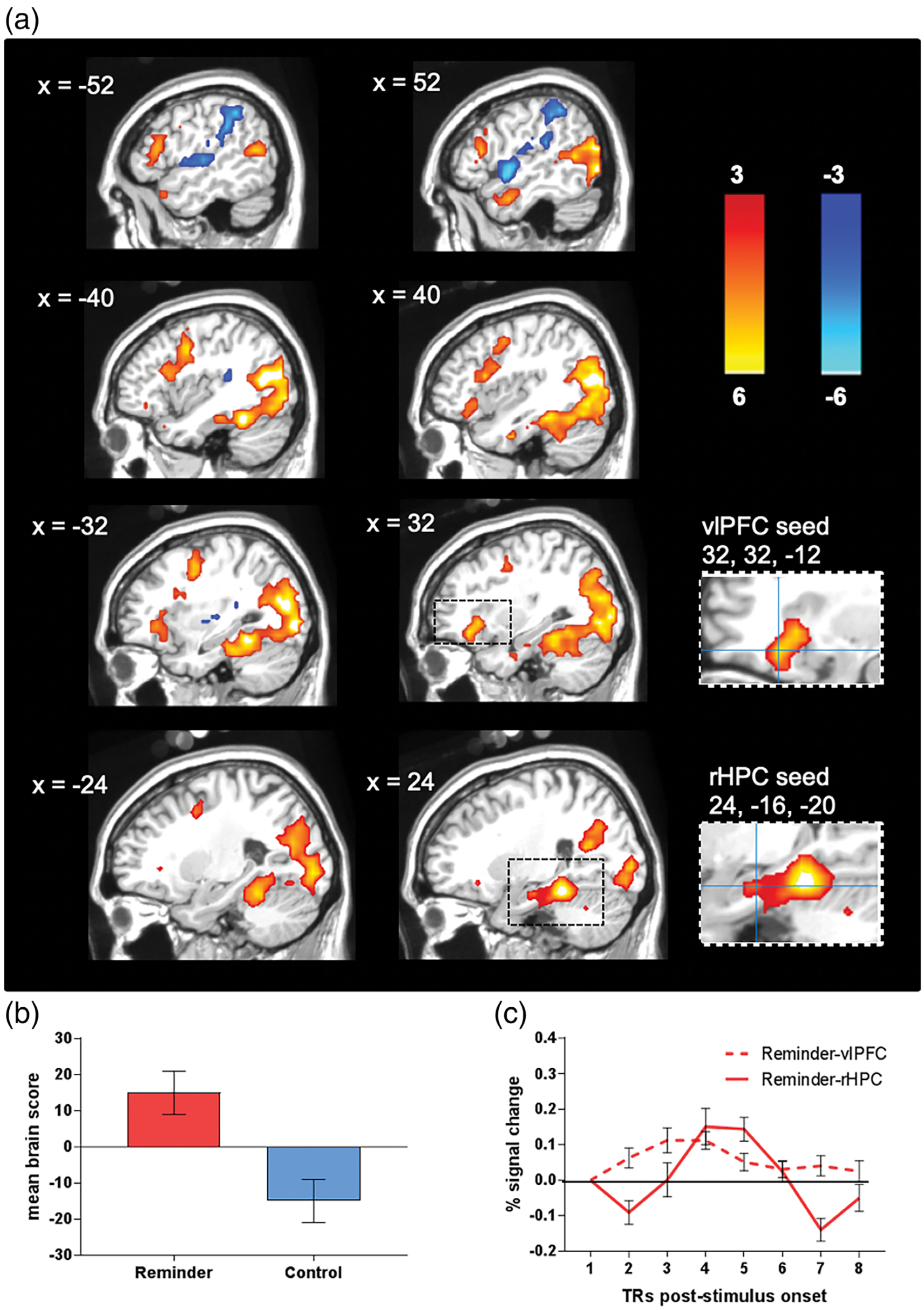

FIGURE 2 Reminders given after 7 days activate the ventrolateral prefrontal cortex followed by hippocampus. Mean-centered, event-related design PLS analyses were conducted to assess modulations in BOLD activity across the brain during the reminder sessions. (a) LV depicting brain activity associated with the reminder cue trials (warm colors) contrasted with scrambled control cue trials (cool colors) during TR 4 of each trial. Note the bilateral vlPFC and right anterior hippocampal activation during the reminder task. vlPFC and rHPC seed regions are shown in insets on the right. (b) Brain scores reflecting the degree to which reminders (positive BSRs) and scrambled control cue (negative BSRs) correlate with the LV shown in 3(a). (c) Mean time course of percent signal change in the vlPFC seed (coordinates: 32, 32, −12; dashed line) and in the rHPC seed (coordinates: 24, −16, −20; solid line) during the reminder trials. Note that the peak of reminder activity in the vlPFC precedes the peak of reminder activity in the rHPC. Error bars are 95% confidence intervals. fMRI results are displayed using Mango (Research Imaging Institute, UTHSCSA, RRID: SCR_009603). PLS, partial least squares; BOLD, blood-oxygen-level dependent; LV, latent variable; BSR, bootstrap ratio; TR, repetition time; vlPFC, ventrolateral prefrontal cortex; rHPC, right hippocampus [Color figure can be viewed at wileyonlinelibrary.com]

and TR as factors to determine if the timing of activity increases differed across these two regions (i.e., a region by TR interaction).

2.4.2 | Retrieval analyses

To determine those regions with increased activity during retrieval, we next conducted an event-related PLS analysis to contrast retrieved clips that had been previously reminded (R-Ret), retrieved clips that had not been reminded (NR-Ret), and a fixation control task during the retrieval session (Figure 3 and Table 2). Brain scores associated with the significant LV1 are shown in Figure 3b, and the time course of percent BOLD signal change across the retrieval conditions was analyzed for seed regions in the vlPFC (seed coordinates: 32, 24, −4), vmPFC (seed coordinates: −4, 56, −16), and the right hippocampus (seed coordinates: 24, −16, −20), identified from this analysis and based on our group's previous findings of a time-dependent increase of activity in these regions during retrieval of the film clip events 1 week after initial encoding (Sekeres et al., 2018). The time course analysis was run as described above for the reminder cue data. We also ran a PLS analysis directly contrasting the reminded and non-reminded retrieval trials (Figure 5 and Table 3). Forgotten

TABLE 1 Coordinates of regions associated with film clip reminders

Hemisphere	BSR	X (mm)	Y (mm)	Z (mm)	Cluster size (voxels)	Area	BA
Reminder > control					71		
Right	5.772	32	32	−12	71	Inferior frontal gyrus[a]	47
Left	4.408	−32	32	−4	37	Inferior frontal gyrus	47
Right	5.371	36	0	44	33	Middle frontal gyrus	6
Left	5.578	−4	20	44	84	Medial frontal gyrus	6
Left	5.949	−36	0	44	212	Precentral gyrus	6
Right	5.525	40	16	16	98	Insula	13
Right	5.315	40	−4	−36	13	Middle temporal gyrus	21
Right	5.076	52	0	−28	46	Middle temporal gyrus	21
Left	4.825	−44	16	−32	28	Temporal pole	38
Right	8.695	44	−76	−4	1846	Inferior occipital gyrus[b]	19
Right	4.064	0	−72	−24	11	Cerebellum	
Left	3.583	0	−56	−44	14	Cerebellum	
Control > reminder							
Left	−4.287	−32	−20	4	12	Insula	13
Right	−5.922	52	0	−4	340	Superior temporal gyrus	22
Right	−4.628	4	−84	20	43	Cuneus	18
Left	−5.460	−52	−44	44	198	Inferior parietal lobule	40

Note: Top: MNI coordinates of the peak activation voxel within each cluster for LV1 for the PLS analysis for the reminder cues contrasted with the scrambled control cues (warm color activations in Figure 2a, positive BSRs). Bottom: MNI coordinates of the peak activation voxel within each cluster for the scrambled control cues contrasted with the reminder cues (cool color activations in Figure 2a, negative BSRs). Clusters reported for TR 4 with a minimum of 10 voxels and BSR > ±3.

Abbreviations: BA, Brodmann area; BSR, bootstrap ratio from the PLS analysis indicating the robust contribution of the reported voxel.

[a]The cluster contains the vlPFC seed.

[b]The cluster contains the rHPC seed in Figure 2c.

trials (assigned in-scanner ratings of 1 s) were excluded from the retrieval analysis due to the limited power resulting from the low number of subsequently forgotten trials that had previously been reactivated with a reminder (mean 3.45 trials per participant, *SE* 0.76, Figure 1c).

3 | RESULTS

3.1 | Behavioral results: Reminders attenuate forgetting of film clips after 1 week

3.1.1 | In-scanner retrieval

Memory for short film clips was tested during fMRI scanning following the reminder session. Significantly fewer film clips were rated as forgotten for reminded clips (R-Ret) compared to non-reminded clips (NR-Ret) ($t_{(19)} = 4.62$, $p < .0001$, Figure 1c). To determine if the successfully retrieved clips that were preceded by a reminder were rated as more vividly recalled during scanning than those without a reminder, we conducted paired-samples *t*-tests between reminded and non-reminded trials using the self-report ratings for story content and ratings of vividness of perceptual detail. No significant differences were found for story content ratings between reminded and non-reminded clips ($t_{(19)} = 0.133$, $p = .896$), or for vividness ratings between reminded and non-reminded clips ($t_{(19)} = -1.197$, $p = .246$, Figure 1d), indicating that the reminders did not enhance subjective reports of remembering in the scanner beyond that associated with remembering the clip in the non-reminded condition.

3.1.2 | Post-scan retrieval

The qualitative content of the memories was evaluated immediately following the scanning session. To determine if the successfully retrieved clips that were preceded by a reminder were recalled with more detail than those that were successfully retrieved without a reminder, we conducted paired-samples *t*-tests on the number of correctly retrieved central and peripheral details, corrected for errors (Retrieval Success = # correct details – # errors). Comparable numbers of central details were reported for reminded and non-reminder trials ($t_{(18)} = 0.944$, $p = .358$). Similarly, there was no difference in the number of peripheral details reported for reminded and non-reminded trials ($t_{(18)} = 0.189$, $p = .852$; Figure 1f), indicating that the reminders were not effective in facilitating the retrieval of memory details after 7 days beyond those that could be retrieved in response to the title cue alone. Participants did not make significantly more errors during retrieval of reminded trials when compared to the non-reminded trials

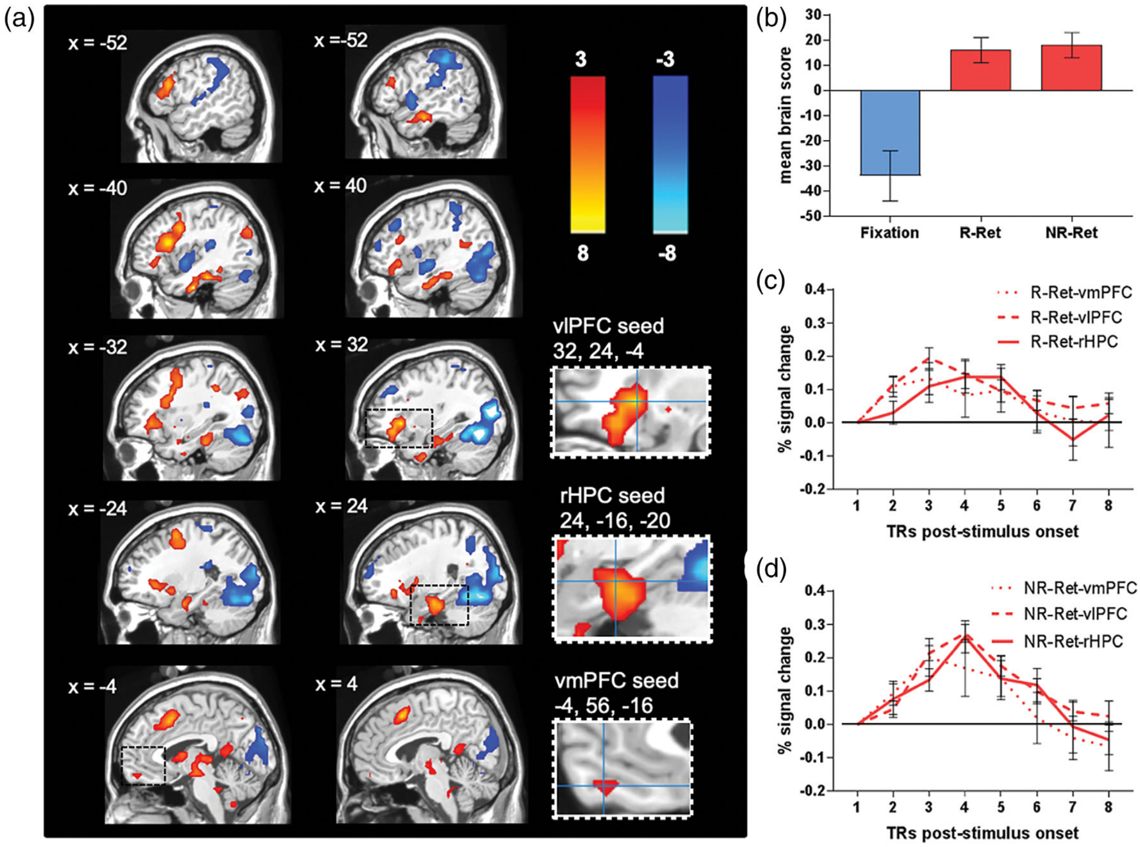

FIGURE 3 Successful retrieval of both reminded and non-reminded clips after 7 days similarly activates prefrontal cortex and hippocampus. Mean-centered, event-related design PLS analyses assessed modulations in BOLD activity across the brain during successful memory retrieval. (a) LV depicting brain activity associated with the retrieval (Ret, warm colors) contrasted with fixation (cool colors) during (TR 4) of each retrieval trial. vlPFC, vmPFC, and rHPC seed regions are shown in insets on the right. (b) Brain scores reflecting the degree to which reminded retrieval (R-Ret), non-reminded retrieval (NR-Ret) (positive BSRs) and fixation (negative BSRs) correlate with the LV shown in 3a. (c) Mean time course of percent signal change in the vmPFC seed (coordinates: −4, 56, −16; dotted line), the vlPFC seed (coordinates: 32, 24, −4; dashed line), and the rHPC seed (coordinates: 24, −16, −20; solid line) during successful retrieval of the previously reminded film clips. (d) Mean time course of percent signal change in the vmPFC seed, vlPFC seed, and rHPC seed during successful retrieval of the previously non-reminded film clips. Error bars are 95% confidence intervals. PLS, partial least squares; BOLD, blood-oxygen-level dependent; LV, latent variable; BSR, bootstrap ratio [Color figure can be viewed at wileyonlinelibrary.com]

for either central detail errors ($t_{(18)}$ = 0.236, p = .816), or peripheral detail errors ($t_{(18)}$ = 0.643, p = .528; Figure 1e).

Together, these results suggest that reminders enhance the overall likelihood of successfully remembering the event. If the event is successfully retrieved after 7 days, reminders do not enhance the subjective feeling of vividness (ratings), nor do reminders enhance the number of retrieved details for the event, or the accuracy of memory for the clips.

3.2 | fMRI results: Analysis of BOLD activity

3.2.1 | Reminders and recollection activate prefrontal cortex and the hippocampus

We first assessed modulations of fMRI BOLD activity across the brain during film clip reminders using PLS, a multivariate approach to assessing co-varying patterns of activity across brain-wide retrieval networks. To identify patterns of activity that characterized each condition, we first contrasted activity during the reminder cues with the scrambled control cue task. The significant increases in activity (p < .001) during reminder trials for TR 4 are shown in warm colors in Figure 2a. Positive brain scores associated with LV1 are shown in Figure 2b (activity associated with the control cue task is shown in cool colors, and negative brain scores in Figure 2b). Reminders of the film clips engaged bilateral parahippocampus, right anterior hippocampus, bilateral retrosplenial cortex, inferior frontal gyrus, and vlPFC (see Table 1 for full list of regions). Repeated measures ANOVA (RMANOVA) using the peak activations within the vlPFC and right hippocampus (rHPC) across the eight TRs revealed no main effect of region ($F_{(1,19)}$ = 3.576, p = .074, η^2 = 0.158), but a significant main effect of TR ($F_{(6,114)}$ = 13.132, p < .001, η^2 = .409), and a region by TR interaction ($F_{(6,114)}$ = 11.236, p < .001, η^2 = 0.372). Post-hoc paired-samples t-tests across the first four TRs of the

TABLE 2 Coordinates of regions associated with successful retrieval of film clips after 7 days

Hemisphere	BSR	*X* (mm)	*Y* (mm)	*Z* (mm)	Cluster size (voxels)	Area	BA
R-retrieval and NR-retrieval > fixation							
Right	8.161	8	16	48	156	Medial frontal gyrus	32
Left	3.684	−4	56	−16	15	Medial frontal gyrus[a]	10
Left	7.342	−40	20	16	346	Middle frontal gyrus	9
Right	4.600	44	28	20	41	Middle frontal gyrus	9
Right	7.803	32	24	−4	176	Insula[b]	13
Right	4.181	44	−52	12	18	Middle temporal gyrus	39
Left	9.258	−40	−12	−36	93	Inferior temporal gyrus	20
Left	7.410	−16	−12	−20	540	Hippocampus[c]	34
Left	4.124	−12	−64	52	13	Precuneus	7
Left	5.131	−32	−44	36	10	Inferior parietal lobule	40
Left	4.905	−8	−52	12	104	Posterior cingulate cortex	29
Left	4.684	−40	−76	32	43	Superior occipital gyrus	19
Left	3.565	−8	−56	−48	10	Cerebellum	
R-retrieval and NR-retrieval < fixation							
Right	−6.010	20	60	16	30	Superior frontal gyrus	10
Left	−3.876	−20	56	16	15	Superior frontal gyrus	10
Right	−5.471	36	32	36	57	Middle frontal gyrus	8
Right	−4.019	40	52	12	12	Middle frontal gyrus	10
Left	−6.554	−60	−32	20	354	Insula	13
Right	−5.967	44	−8	−12	178	Insula	13
Right	−4.577	28	−60	52	30	Superior parietal lobule	7
Right	−9.357	60	−28	24	433	Inferior parietal lobule	40
Right	−12.295	32	−68	−16	1,666	Fusiform gyrus	19

Note: Top: MNI coordinates of the peak activation voxel within each cluster for LV1 for the PLS analysis of retrieval (both R-retrieval and NR-retrieval) contrasted with the fixation control (warm color activations in Figure 3a, positive BSRs). Bottom: MNI coordinates of the peak activation voxel within each cluster for fixation contrasted with retrieval (cool color activations in Figure 3a, negative BSRs). Clusters reported for TR 4 with a minimum of 10 voxels and BSR > ±3.

Abbreviations: BA, Brodmann area; BSR, bootstrap ratio from the PLS analysis indicating the robust contribution of the reported voxel.

[a]The cluster contains the vmPFC seed.

[b]The cluster contains the vlPFC seed.

[c]The cluster contains the rHPC seed in Figure 3c,d. Note that the rHPC seed is located in the large cluster also containing the left hippocampus.

reminder task found that vlPFC activation is significantly higher than rHPC activity during TR 2 ($t_{(19)}$ = −3.576, p = .002), and TR 3 ($t_{(19)}$ = −2.437, p = .025), then the opposite pattern emerges during TR 5 when rHPC activity exceeds vlPFC activity ($t_{(19)}$ = 2.708, p = .014, Figure 2c), although only the effect at TR 2 survives correction for multiple comparisons.

These results suggest that reminders are effective in engaging a set of regions, including the hippocampus, that our prior work has shown is active when memory for film clips is retrieved 1 week after encoding (Sekeres et al., 2018). These results further show that reminders engage vPFC activity prior to activity seen in the hippocampus.

We next contrasted reminded and non-reminded retrieval trials with the fixation control trials. The significant increases in activity (p < .001) during retrieval trials are shown for TR 4 in warm colors in Figure 3a, and positive brain scores associated with LV1 are shown in Figure 3b. Successful retrieval of the film clips activated regions of the recollection network including the right hippocampus, bilateral parahippocampus, left precuneus, right angular gyrus, bilateral vlPFC, and vmPFC (See Table 2 for full list of regions). RMANOVA of the time course of activity across the eight TRs within the three ROIs (vmPFC, vlPFC, rHPC) for reminded and non-reminded retrieval trials found no main effect of region (reminded retrieval: $F_{(2,38)}$ = 0.356, p = .703, η^2 = 0.018; non-reminded retrieval: $F_{(2,38)}$ = 0.453, p = .639, η^2 = 0.023), but did find evidence for a main effect of TR (reminded retrieval: $F_{(6,114)}$ = 9.808, p < .001, η^2 = 0.340; non-reminded retrieval: $F_{(6,114)}$ = 17.452, p < .001, η^2 = 0.479). No evidence of a region by TR interaction emerged (reminded retrieval: $F_{(12,228)}$ = 1.246, p = .252, η^2 = 0.062; non-reminded retrieval: $F_{(12,228)}$ = 1.257, p = .246, η^2 = 0.062). Unlike what is observed during the reminder cues, the prefrontal cortical regions do not precede hippocampal activity during effortful retrieval.

TABLE 3 Coordinates of regions associated with successful retrieval of reminded and non-reminded film clips after 7 days

Hemisphere	BSR	*X* (mm)	*Y* (mm)	*Z* (mm)	Cluster size (voxels)	Area	BA
R-retrieval > NR-retrieval							
Right	4.242	28	12	44	14	Middle frontal gyrus	6
Left	4.325	−32	60	12	25	Middle frontal gyrus	10
Right	4.690	36	36	36	31	Middle frontal gyrus	8
Left	4.106	−56	4	4	11	Precentral gyrus	44
Right	4.278	52	8	0	11	Insula	13
Right	5.834	16	−64	48	153	Precuneus	7
Left	5.561	−4	−28	24	50	Posterior cingulate cortex	23
Left	4.547	−44	−56	44	59	Angular gyrus	39
Right	5.940	44	−60	52	223	Superior parietal lobule	7
Left	3.947	−52	−52	28	13	Supra marginal gyrus	40
R-retrieval < NR-retrieval							
Left	−5.093	−60	4	−16	17	Middle temporal gyrus	21
Right	−4.596	56	−8	−16	11	Superior temporal gyrus	21
Left	−5.039	−12	−52	12	88	Posterior cingulate cortex	30

Note: Top: MNI coordinates of the peak activation voxel within each cluster for LV1 for the PLS analysis of reminded retrieval (R-retrieval) contrasted with the non-reminded retrieval (NR-retrieval) (warm color activations in Figure 5a, positive BSRs). Bottom: MNI coordinates of the peak activation voxel within each cluster for NR-Ret contrasted with R-Ret (cool color activations in Figure 5a, negative BSRs). Clusters reported for TR 4 with a minimum of 10 voxels and BSR > ±3.

Abbreviations: BA, Brodmann area; BSR, bootstrap ratio from the PLS analysis indicating the robust contribution of the reported voxel.

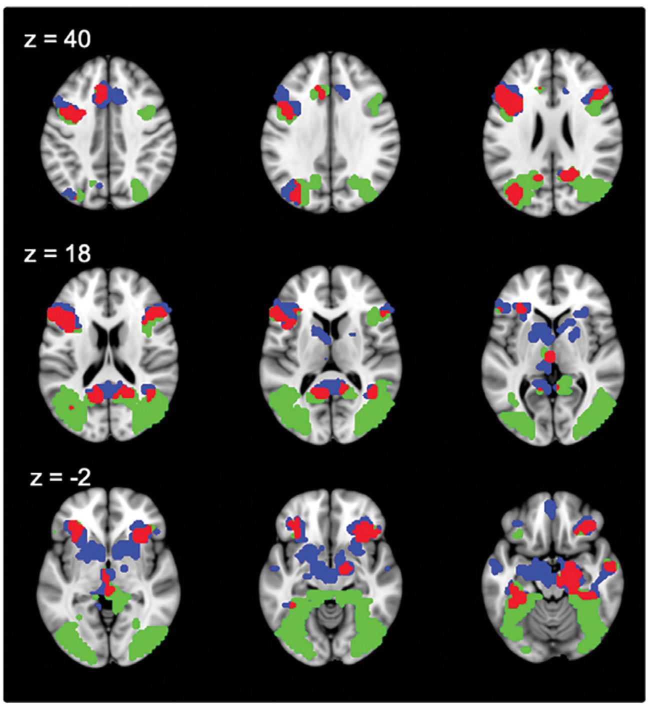

FIGURE 4 Reminders recruit regions of the retrieval network. Overlap (red) of reminders versus scrambled control stimuli (green = warm regions from Figure 2a), and both retrieval conditions (R-Ret and NR-Ret) versus fixation control (blue = warm regions from Figure 3a) shows that reminders activate most of the regions activated by successful retrieval [Color figure can be viewed at wileyonlinelibrary.com]

For successfully recalled clips, an overlapping pattern of BOLD activity (red regions in Figure 4) was observed in prefrontal cortex, hippocampus, and parietal cortex during both reminders (green regions in Figure 4) and retrieval trials (blue regions in Figure 4), suggesting that the pattern of neural activity observed during the reminder reflects a recollective process. Consistent with our first hypothesis, hippocampal activity is engaged during the reminder. This "refresher" is likely what boosts the ability to later successfully retrieve the clip. Note that reminders also recruit visual areas including large bilateral clusters in the occipital lobes (green regions in Figure 4), despite the small amount of visual detail presented in the reminder stimuli.

To test the prediction that reminders would enhance subsequent retrieval activity in the hippocampus, we next directly contrasted retrieval activity for previously reminded film clips (R-Ret) with retrieval of non-reminded clips (NR-Ret). The significant increases in activity ($p < .001$) during reminded retrieval trials are shown in warm colors, and increases in activity during non-reminded retrieval are shown in cool colors in Figure 5a. Brain scores associated with LV1 are shown in Figure 5b. No difference in hippocampal activity was evident between reminded and non-reminded retrieval. However, retrieval of reminded clips activated bilateral clusters in the precuneus, cingulate gyrus, insular cortex, and dorsolateral prefrontal cortex. During successful retrieval of non-reminded clips, greater activity was evident in retrosplenial cortex, and the superior and middle temporal gyrus (See Table 3 for full list of regions).

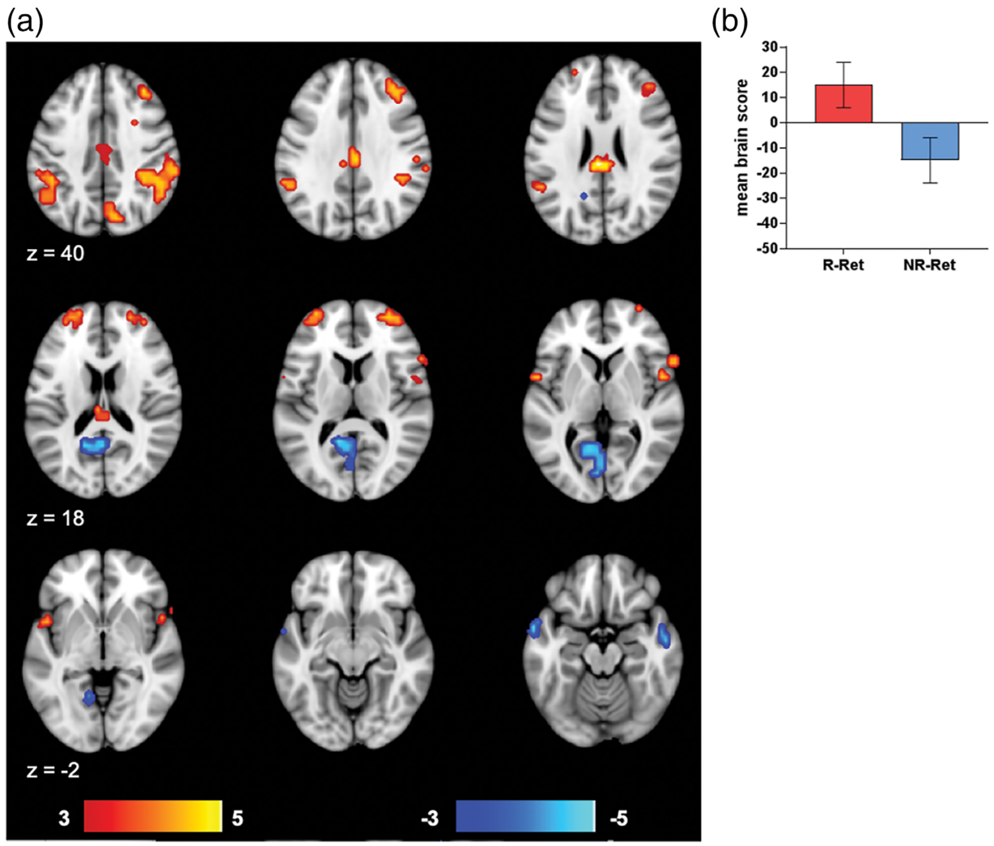

FIGURE 5 Successful retrieval of reminded and non-reminded film clips after 7 days does not differentially activate the prefrontal cortex-hippocampal network. Mean-centered, event-related design PLS analyses assessed modulations in BOLD activity across the brain during successful memory retrieval of reminded and non-reminded film clips. (a) LV depicting brain activity associated with retrieval of previously reminded clips (R-Ret, warm colors) contrasted with retrieval of non-reminded clips (NR-Ret, cool colors) during TR 4 of each retrieval trial. (b) Brain scores reflecting the degree to which reminded retrieval (positive BSRs) and non-reminded retrieval (negative BSRs) correlate with the LV shown in in 5a. Note that no difference in either prefrontal cortical activity or hippocampal activity is observed between retrieval of previously reminded and previously non-reminded film clips. Error bars are 95% confidence intervals. PLS, partial least squares; BOLD, blood-oxygen-level dependent; LV, latent variable; BSR, bootstrap ratio [Color figure can be viewed at wileyonlinelibrary.com]

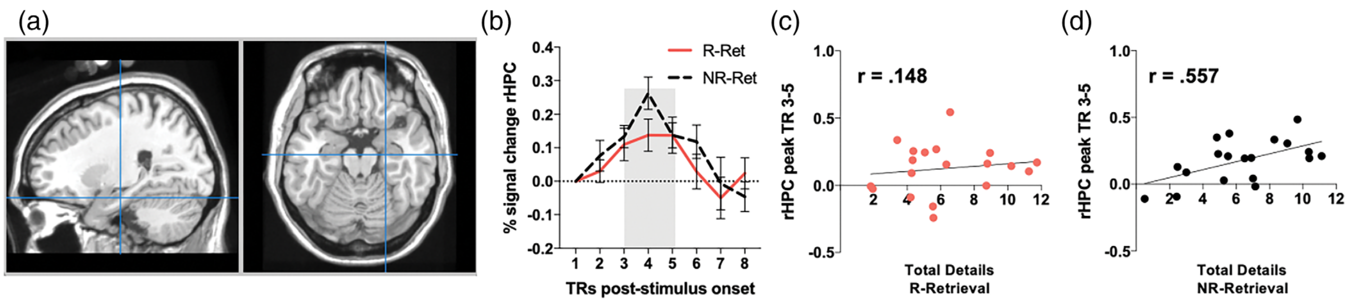

FIGURE 6 Right hippocampal activity correlates with the number of recalled details during retrieval of non-reminded clips. Correlation of the percent signal change in the (a) right hippocampus (rHPC) seed (coordinates: 24, −16, −20) during TRs 3–5 of the retrieval session (b), and the total number of correctly recalled details during retrieval of the previously reminded (c), and non-reminded (d) film clips. Note the significant correlation observed for the non-reminded trials, suggesting that in the absence of prior cuing, the hippocampus must be strongly engaged to support accurate detailed memory retrieval [Color figure can be viewed at wileyonlinelibrary.com]

We next correlated retrieval success with mean activity in the right anterior hippocampal seed region (24, −16, −20) commonly activated across TRs 3–5 of the reminder and retrieval sessions. TRs 3–5 were chosen because this was the point of highest activation in the rHPC for both reminded and non-reminded retrieval (Figure 6b). Peak brain scores in the rHPC seed during TRs 3–5 correlated strongly with the number of retrieved details for NR-Retrieval (r = 0.557, p = .013, Figure 6d), but this relation was not observed for R-Retrieval trials

(r = 0.148, p = .540, Figure 6c). These results suggest that, in the absence of cuing prior to retrieval, the hippocampus must be more strongly engaged to support successful retrieval of the complex naturalistic film clip event.

4 | DISCUSSION

The present results show that a brief reminder (title plus partial degraded screenshot) enhanced the number, but not the quality, of retrieved, week-old memories for complex film clip events compared to memories that were retrieved without the reminder. The behavioral findings suggest that the reminder helps enhance the likelihood of successful memory retrieval, but does not enhance the content of the memory. The reminder engaged the recollection network which included the hippocampus and vPFC, with vPFC activation preceding peak activity in the right anterior hippocampus. These findings suggest that the reminder's memory-enhancing effect was mediated by priming prefrontal cortical nodes of the recollection network that are typically engaged during schematic memory retrieval or general event/scene construction, followed by elaborative episodic memory retrieval mediated by the hippocampus (Addis, Knapp, Roberts, & Schacter, 2012; Barry et al., 2019; Holland, Addis, & Kensinger, 2011). Many of the same regions were activated during retrieval itself but there was no difference in hippocampal activation for memories whose retrieval was preceded by a reminder compared to those that were recalled in the absence of a reminder, consistent with our observation that the quality of the memories did not differ from one another. We discuss the behavioral and neuroimaging findings in turn and relate them to one another.

4.1 | Behavioral results

Contextual cues are known to be effective in enhancing the retrieval of detailed autobiographical event memories in both healthy individuals (Robin & Moscovitch, 2014) and in amnesic patients (Miles, Fischer-Mogensen, Nielsen, Hermansen, & Berntsen, 2013). In the present study, the cues used for the reminder condition were masked segments of screenshots, taken from the film clips and obscuring approximately 80% of the shot. A horizontal strip was selected to ensure that no coherent information about the scene was available. Despite being degraded, our screenshot proved to be an effective reminder, consistent with reports from previous studies that even obscured screenshots serve as good reminders (Tang et al., 2016).

In accord with our second hypothesis, reactivating a week-old memory with a brief reminder cue enhances the overall likelihood of successfully retrieving the memory for that event. Because the same title is presented during the retrieval phase in both the reminder and non-reminder conditions, we infer that the memory advantage in the reminder condition is due to the presence of the screenshot. Though there were fewer successfully retrieved memories after 7 days for non-reminded, relative to reminded, clips, if the memory for the event was successfully retrieved, no difference was observed in the number of retrieved details or in the subjective memory retrieval ratings. If we accept that complex coherent events are forgotten in an "all-or-none" manner (Joensen, Gaskell, & Horner, 2019), our results suggest that the primary function of the reminder was to facilitate access to stored events that might not have been retrieved otherwise. Having helped in accessing the memory, the reminder does not influence the memory's details or its subjective quality. These results fit with findings of Tulving and Pearlstone's (1966) distinction between availability and accessibility. When participants were asked to recall words freely from a previously learned word list, words that were not initially retrieved subsequently became accessible for retrieval when presented with a category retrieval cue. Their findings indicate that the initial failure to retrieve the memory was due to a lack of accessibility, and not to a storage deficit, or a lack of availability. When applied to our findings, pre-retrieval reminders serve to enhance the accessibility of the memory for the film clip. It remains possible that the unsuccessfully retrieved clips remain available in memory storage, but are inaccessible in the absence of a reminder cue.

The lack of enhanced memory for details following a reminder was unexpected given our previous findings using this paradigm, in which we tested the time-dependent loss of memory details over the course of 7 days. We previously reported that both central story elements and perceptual/peripheral details were forgotten over time, with peripheral details being most prone to forgetting. When tested behaviorally, reminders were effective in partially restoring the peripheral detail for the 7 days old memories, but had no enhancing effect on the retrieval of central story details. These earlier findings demonstrated that episodic memory is susceptible to forgetting over time, but that cuing can lead to the partial recovery of faded detailed memory (Sekeres et al., 2016; Sekeres et al., 2018). In our 2016 study, it is notable that passive reminders after 7 days were not as effective in preventing forgetting as a full effortful retrieval performed immediately after encoding. These observations are consistent with the mnemonic-enhancing testing effect, in which repeated "test" or active retrieval session lead to superior retention of information over time relative to a re-study, or reminder, session (Karpicke & Roediger, 2008; Oedekoven et al., 2017; Roediger & Karpicke, 2006; Rowland, 2014).

Our previous behavioral study, however, differed from the present one in several important ways, which may account for the lack of a retrieval-enhancing effect for perceptual/peripheral details observed after 7 days in the present study. In our previous study, participants performed retrieval sessions for subsets of clips immediately following encoding, 3 days, and 7 days following encoding, and received reminders for the clips tested after the 3 day and 7 day delays. A facilitation effect for peripheral details was observed after 7 days, but both reminded and non-reminded clips were recalled with comparable levels of detail after only 3 days (Sekeres et al., 2016). It may be that the multiple retrieval sessions conferred a practice effect which may serve as episodic specificity induction (Fisher & Geiselman, 1992; Madore, Gaesser, & Schacter, 2014; Thakral, Madore, Devitt, & Schacter, 2019), so that participants knew what was expected when reminded and tested during the 7 days trial, allowing them to focus on retrieval itself, and devote less cognitive effort to remembering the task procedures. That no reminder-enhancing effect was observed after 3 days, when participants first performed the reminder-retrieval session, but emerged after 7 days, when participants had experience performing the reminder-retrieval session, suggests that this practice effect may have contributed to more nuanced memory performance observed in our earlier study. Additionally, in the present study, the reminder and retrieval sessions were first conducted in the fMRI scanner, followed by verbal report of the retrieved memories after the scanning session. It is possible that the context-shift and the delay between the initial in-scanner reminder and retrieval, and subsequent re-retrieval outside the scanner may have influenced the qualitative content of the verbally reported memory for the clips.

4.2 | Neuroimaging results

Presentation of the reminder cue, which intentionally contained no coherent scene information, activated vlPFC followed by peak activation of the right anterior hippocampus. While the contribution of these regions remains speculative, the vPFC's early activation in response to the visual stimulus and title likely reflects their interaction with one another in the construction of either a mental scene or schematic event (Barry et al., 2019; Gilboa & Marlatte, 2017; Bonasia et al., 2018; McCormick, Ciaramelli, De Luca, & Maguire, 2018; van Kesteren et al., 2013). This output then biases the subsequent activation of the anterior hippocampus and elaboration of coarsely detailed memory for the event (Poppenk, Evensmoen, Moscovitch, & Nadel, 2013; Poppenk & Moscovitch, 2011).

Further support for this interpretation comes from studies using dynamic causal modelling to identify regional network contributions to the temporal dynamics of autobiographical episodic memory construction and elaboration. St. Jacques, Conway, et al. (2011) and St. Jacques, Kragel, & Rubin (2011) found that the medial prefrontal cortex is strongly engaged during both early memory construction and the subsequent elaboration phase, whereas the medial temporal lobe comes online more strongly during the elaboration phase. A comparable pattern of results was obtained by McCormick et al. (2020) using MEG that affords greater temporal resolution than fMRI. In their study on retrieval of autobiographical memories acquired between 1 month to 5 years ago, vmPFC activation reached a peak at about 125 ms after initiation of retrieval, which preceded that of the hippocampus by 65 ms, for all but the most recent memories. Notwithstanding the lower temporal resolution of fMRI's hemodynamic response function (HRF), we found that vPFC activation preceded hippocampal activation even for memories that were less than a month old. During the reminder, large bilateral clusters of activation were also observed in the posterior occipital regions involved in visual processing. Activity in posterior occipital cortex has been implicated in integration of visual perceptual information during memory recollection, and functional connectivity between hippocampus and visual processing regions has been observed during the elaboration phase of autobiographical memory (McCormick, St-Laurent, Ty, Valiante, & McAndrews, 2015). This finding fits with the time course of late hippocampal activity during the reminder, and suggests that the later stage of the reminder involves perceptual replay of visual information during the elaboration phase (St. Jacques, Conway, et al., 2011; St. Jacques, Kragel, & Rubin, 2011).

We also found that reminders activated the anterior hippocampus, a region reported to come online early to support autobiographical memory construction (Addis, Wong, & Schacter, 2007; McCormick et al., 2015), though this effect has been observed in the left, not right hippocampus. In contrast to our studies, those studies only used a verbal title to cue the memory, whereas we used an additional non-verbal reminder on some trials which may have biased performance towards the right hippocampus. While these approaches differ from the current study in that autobiographical event memories involve self-referential processing which is not captured in standardized film clip events, a similar process likely occurs during the early construction, and subsequent elaboration of the reminder for the film clip events, and a common temporal dynamic appears to occur in the prefrontal cortex, followed by the hippocampus for both types of event memories.

This same vPFC-hippocampal temporal pattern of activity was not observed when participants were asked to explicitly retrieve the clips. During the subsequent retrieval trials, successful retrieval of reminded and non-reminded film clips events was supported by vlPFC, vmPFC, and anterior hippocampal activity, with a similar time course of activity for all three seed regions. The high degree of overlapping regions of activity during reminders and successful retrieval suggest that neural activity observed during the reminder reflects a recollective process, and are also consistent with findings of coherent PFC-hippocampal theta synchrony seen during episodic memory retrieval (Fuentemilla et al., 2014). These findings are consistent with those obtained by McCormick et al. (2020) who, using only the title as a cue, also found no difference in onset of activation between PFC and hippocampus for events less than a month old.

A caveat to note is that there can be HRF differences across regions that may or may not be specifically related to cognitive processes (Taylor, Kim, & Ress, 2018), and one should be generally cautious about interpreting regional time course differences in fMRI data. We have attempted to mitigate this problem in the present study by using PLS's multivariate approach which assesses co-varying patterns of activity across brain-wide retrieval networks. PLS does not assume a particular shape to the HRF, so the results are not biased by assuming a similar shape to the HRF across regions. Despite the sluggish HRF, our finding on the time course of prefrontal cortex preceding the hippocampus during reminder processing was motivated by, and is consistent with, these previous studies investigating how prefrontal-hippocampal networks dynamically interact to support retrieval (Barry et al., 2019; Fuentemilla et al., 2014; McCormick et al., 2020; St. Jacques, Conway, et al., 2011; St. Jacques, Kragel, & Rubin, 2011).

In previous work using the same procedures, retrieval of the film clips, in the absence of a reminder, resulted in a decline in posterior hippocampal activity but continued activation of the anterior hippocampus, and increased recruitment of the vmPFC, vlPFC, and dlPFC, as retrieval of the perceptual/peripheral elements of the clips declined after 7 days (Sekeres et al., 2018). In line with observations that such perceptual details are most prone to forgetting over time, whereas the general features, or gist, of an event memory are maintained (Conway, 2009; Sekeres, Winocur, & Moscovitch, 2018), only a modest decline in the number of retrieved central story elements occurred over the course of 1 week following encoding (Sekeres et al., 2018). These findings are consistent with the interpretation that the time-dependent schematization of an event memory is accompanied by a decline in fine-grained detail retrieval mediated by the posterior hippocampus, maintenance of coarser grained representations in anterior hippocampus (Poppenk & Moscovitch, 2011; Poppenk et al., 2013; Yonelinas et al, 2019), and increased recruitment of vmPFC and vlPFC (Sommer, 2017).

The current study did not have an immediate retrieval condition and, therefore, we are unable to determine if a differential process of schematization and reorganization of the retrieval network occurred for the reminded and non-reminded film clip memories. The similar activity time course of the anterior hippocampus during successful retrieval in the reminded and non-reminded conditions, and the similarity in the quality of the memory ratings and number of retrieved details for both reminded and non-reminded film clips after 7 days, suggest that any transformation in the quality of the week-old memories is comparable, regardless of reminder condition.

We did not find support for the hypothesis that the boost in memory following a reminder is mediated by enhanced activity in the hippocampus at the time of retrieval. While strong activation of the core prefrontal cortical-hippocampal retrieval network was observed during the reminders, this priming of the retrieval network did not differentially activate these areas during subsequent elaborative retrieval when compared to equally aged but non-reminded retrieval trials. Instead, retrieval of previously reminded clips engaged posterior regions of the recollection network including the precuneus, angular gyrus, and posterior cingulate cortex, whereas additional middle and superior temporal cortex and posterior cingulate cortex were recruited during retrieval of non-reminded film clip events. A possible interpretation of these regional differences is that reminder-enhanced retrieval activates regions implicated in imagery (precuneus) (Fletcher et al., 1995; Hebscher, Meltzer, & Gilboa, 2019) and in bottom-up retrieval (angular gyrus) (Burianová, Ciaramelli, Grady, & Moscovitch, 2013; Cabeza, Ciaramelli, & Moscovitch, 2012; Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Ciaramelli, Grady, Levine, Ween, & Moscovitch, 2010); Spreng and Grady (2010), whereas retrieval of non-reminded clips activates areas more implicated in semantic processing (middle and superior temporal cortex) (Martin, 2016; Ralph, Jefferies, Patterson, & Rogers, 2017). Consistent with these finding, reactivation of complex film event memories through repeated retrieval over the course of 1 week has been shown to elicit cortical reinstatement of activity in posterior regions of the recollection network, including precuneus, and posterior hippocampus during each retrieval session (Oedekoven et al., 2017).

While it is possible that the lack of a difference in hippocampal activity between reminded and non-reminded retrieval conditions reflects low power due to a limited number of successfully retrieved trials after 7 days for non-reminded film clips, it is more likely that successful retrieval of a week-old memory engages similar retrieval mechanisms in the prefrontal cortical-hippocampal network, irrespective of a previous reminder. What the reminder appears to do is to increase the overall likelihood of activating this prefrontal cortical-hippocampal network and allowing access to the memory trace for a given film clip event memory. Successful retrieval of non-reminded film clips may be a more effortful process, as indicated by a strong positive correlation the number of recalled details, and hippocampal activity during successful retrieval of non-reminded clips. This brain-behavior correlation should be interpreted cautiously, however, due to the small sample size which limits inferences one can make about individual differences. It is also possible that the film clip title accompanying the partial screenshot cue may have independently served as a schematic reminder. Although we did not specifically test the retrieval-enhancing effectiveness of a title reminder alone, if it were the case that the title was sufficient to cue a schematic retrieval of the film clip event, then the early time course of the NR-retrieval trials (when only the title of a previously viewed clip was presented) would resemble the temporal pattern of the reminder trial. The fact that the non-reminded retrieval trials do not show the temporal pattern of the reminder trials argues against the title alone being sufficient to engage the memory schema. An alternative possibility is that fMRI does not afford us the temporal resolution to distinguish between the onsets of vPFC and hippocampus when the title is presented alone, and when it is presented with the reminder. With the reminder, the vPFC is engaged noticeably earlier than with the title alone, rapidly engaging the schema functions of vPFC, and allowing the temporal difference between vPFC and hippocampal activation to be detected.

These findings are consistent with earlier models of PFC-hippocampal activations during retrieval which posited that frontal cortex guided memory search to enable hippocampally-mediated recovery of memory. (Moscovitch, 1989, 1992; Burgess & Shallice, 1996; Moscovitch & Winocur, 2002; Gilboa, Winocur, et al., 2006; Gilboa, Alain, et al., 2006), Examining retrieval data from confabulation patients with vmPFC lesions, Moscovitch and Melo (1997) noted that the most prominent deficit in retrieving old autobiographical and historical memories to verbal cues was failure to recover any memory at all, indicative of the crucial role that vmPFC played in initiating retrieval and guiding search (see also Schnider, 2013; Gilboa & Moscovitch, 2017; Gilboa & Marlatte, 2017; see also work on frontal involvement in "retrieval mode", Tulving, 1983; Lepage, Ghaffar, Nyberg, & Tulving, 2000; Tarder-Stoll, Jayakumar, Dimsdale-Zucker, Günseli, & Aly, 2020). The data from the current study, and from that of McCormick et al. (2020) suggest that the temporal sequence of PFC-hippocampal activations can vary by the age of the memory and by reminders, but the underlying factors that influence it have yet to be determined.

In summary, our findings on the temporal pattern of activity in the prefrontal cortical-hippocampal network supporting complex event memory reactivation and retrieval are consistent with previous findings and theories, and identify reminders as effective methods for boosting event memory in an all-or-none manner. Further studies using schematic versus perceptually detailed reminders should examine the differential temporal contributions of the vPFC-hippocampal networks during reactivation of complex event memories to determine if the prefrontal cortex similarly leads the hippocampus for equally aged, but perpetually rich, reactivated memories.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

AUTHOR CONTRIBUTIONS

Conceptualization: Melanie J. Sekeres, Morris Moscovitch, Gordon Winocur, Cheryl L. Grady; Methodology: Melanie J. Sekeres, Morris Moscovitch, Gordon Winocur, Cheryl L. Grady; Investigation: Melanie J. Sekeres, Sara Pishdadian, Dan Nichol; Writing—Original Draft: Melanie J. Sekeres, Cheryl L. Grady; Writing—Review Editing: Melanie J. Sekeres, Morris Moscovitch, Gordon Winocur, Sara Pishdadian, Dan Nichol, Cheryl L. Grady; Funding Acquisition: Morris Moscovitch, Gordon Winocur, Cheryl L. Grady; Supervision: Morris Moscovitch, Gordon Winocur, Cheryl L. Grady.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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