

Differential activation of the medial temporal lobe during item and associative memory across time

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ABSTRACT

Studies have shown that the hippocampus plays a crucial role in associative memory. One central issue is whether the involvement of the hippocampus in associative memory remains stable or declines with the passage of time. In the majority of studies, memory performance declines with delay, confounding attempts at interpreting differences in hippocampal activation over time. To address this issue, we tried to equate behavioral performance as much as possible across time for memory of items and associations separately. After encoding words and word pairs, participants were tested for item and associative memories at four time intervals: 20-min, 1-day, 1-week, and 1-month. The results revealed that MTL activation differed over time for associative and item memories. For associative memory, the activation of the anterior hippocampus decreased from 20-min to 1-day then remained stable, whereas in the posterior hippocampus, the activation was comparable for different time intervals when old pairs were correctly retrieved. The hippocampal activation also remained stable when recombined pairs were correctly rejected. As this condition controls for familiarity of the individual items, correct performance depends only on associative memory. For item memory, hippocampal activation declined progressively from 20-min to 1-week and remained stable afterwards. By contrast, the activation in the perirhinal/entorhinal cortex increased over time irrespective of item and associative memories. Drawing on Tulving's distinction between recollection and familiarity, we interpret this pattern of results in accordance with Trace Transformation Theory, which states that as memories are transformed with time and experience, the neural structures mediating item and associative memories will vary according to the underlying representations to which the memories have been transformed.

1. Introduction

Episodic memory is a unique memory system by which people can vividly remember past experiences (Tulving, 1985a). How episodic memory changes over time is a topic of considerable interest to memory researchers (Dudai et al., 2015; Moscovitch et al., 2005; Sekeres et al., 2018a; Winocur and Moscovitch, 2011). One central issue is whether the involvement of the hippocampus remains stable or declines over time. Although not the focus of Tulving's work, his insights on changes in recollection and familiarity with time (Tulving, 1985b), and his views on the role of the hippocampus in mental time travel (Tulving et al.,

1988), have had a profound influence on the field, and provided some of the theoretical framework of this paper.

In humans, questions regarding hippocampal involvement in memory over extended time periods of weeks, months or years, have been addressed primarily by studying memory for public and personal events (e.g., Bonnici et al., 2012; Bonnici and Maguire, 2018; Furman et al., 2012; Soderlund et al., 2012; Viard et al., 2007). Less is known about how memory for simple items and associations changes over time. Converging evidence has shown that the hippocampus is crucial in binding unrelated information into relational associations and retrieving them at recognition (Davachi, 2006; Eichenbaum et al., 1994;

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Eichenbaum et al., 2007; Mayes et al., 2007). The hippocampus has also been shown to play a more prominent role in recollection compared with familiarity during memory retrieval (Eichenbaum et al., 2007; Tulving and Markowitsch, 1998; 2002). However, studies comparing remote and recent associative memory over time have yielded inconsistent findings with some showing decreased activation of the hippocampus (e.g., Smith et al., 2010; Takashima et al., 2009; Yamashita et al., 2009) and others showing increased or stable activation (e.g., Bosshardt et al., 2005; Smith et al., 2010). For example, in a study of Takashima et al. (2009), participants learned face-location associations, and were tested 15 min and 24 h later. The results showed that hippocampal activation related to high-confidence retrieval decreased and neocortical activation increased over that interval. Similarly, Yamashita et al. (2009) found that retrieving picture pairs that were learned immediately led to stronger activation in the hippocampus than those were learned eight weeks earlier. By contrast, Bosshardt et al. (2005) found that when participants' memory for word pairs was tested after learning, hippocampal activation increased from 1 day to 1 month for good learners but not for poor learners.

Similar inconsistencies have been reported for item memory. Compared to retrieving recent item memory, retrieving remote item memory leads to decreased (e.g., Ritchey et al., 2015; Takashima et al., 2006) or unchanged (e.g., Ritchey et al., 2015; Stark and Squire, 2000) activation in the hippocampus. Recently, Ritchey et al. (2015) reported a dissociation between anterior and posterior hippocampus for item memory decay, with posterior hippocampus activation declining for recollection-related trials, whereas activation in the anterior hippocampus and cortical regions (including the perirhinal cortex, PRC) remaining stable across the two intervals.

How neural representations of associative memory and item memory vary with time since acquisition has implications for various theories of hippocampal-neocortical interactions and memory consolidation (Moscovitch et al., 2016; Sekeres et al., 2018a). In order to clarify this issue, it is important to control other factors that influence hippocampal activation in addition to memory age. Most studies mimic the natural forgetting process by asking participants to learn stimuli to the same level, and test them at different intervals. When applying the 'natural forgetting' approach, however, recent and remote memories differ not only with respect to the time since they were acquired, but also in memory accuracy across delays. Remote memory performance is usually much lower than recent memory performance, approaching chance in some studies. Thus, it is hard to tell whether a change in hippocampal contribution over time is related to the age or accuracy of the memory.

Another approach for examining the effects of age on associative and item memories, which we call the 'matching' approach, is to match recent and remote memory performance on accuracy as much as possible at all time intervals. By this approach, we directly ask whether successful remote memory relies on the same mechanisms as recent memory. To achieve this goal, stimuli could be presented several times at different time intervals (e.g., Bosshardt et al., 2005; Smith et al., 2010; Stark and Squire, 2000). Taking this 'matching' approach, and applying it retrospectively to autobiographical memory, Bonnici et al. (2012) equated recent and remote autobiographical memories on event details and memory vividness, and found comparable representation in the anterior hippocampus for recent and remote memories, but higher classification accuracies in the posterior hippocampus for remote than recent memories. We wished to apply the same approach to study the role of the hippocampus in retrieving associative information at recent and remote intervals.

In sum, the aim of the current study was to track the fate of successful item and associative memories over a month. Participants studied pairs of words, and their memory for the intact pair, or one of the items in it, was tested at different delays after acquisition (20-min, 1-day, 1-week, and 1-month). To explore brain activation as a function of time, we attempted to equate as much as possible memory performance across time for each memory type. To equate memory performance across

delays, the number of study repetitions varied according to the delay interval - the longer the delay, the greater the number of repetitions. Although it may not be possible to match performance across all intervals, the 'matching' approach allows us to approximate our goal, and determine how activation of different structures varies with time when accuracy is comparable. The correct trials for words and word pairs (Hits and correct rejections (CRs)) were used for fMRI analysis. It should be noted that for associations, Hits referred to the accuracy in recognizing intact pairs, and CRs to the accuracy in rejecting recombined pairs. Although both depend on relational memory, memory for intact pairs may be based in small part on familiarity in that the two items form a unitized representation (Haskins et al., 2008; Quamme et al., 2007). Performance on associative CRs (aCR), however, is based almost entirely on relational memory supported by recollection (Cohn and Moscovitch, 2007; Gallo et al., 2006), since neither item memory (both items are old) nor unitized memory (no such combination appeared at study) can support performance (Cohn and Moscovitch, 2007; Cohn et al., 2008).

Theories on memory consolidation and retention make different predictions on the 'matching' approach. Standard Consolidation Theory (SCT, Squire and Alvarez, 1995; Squire and Bayley, 2007) predicts that repetition and delay should promote greater consolidation, and lead to less hippocampal activation over time. Multiple Trace Theory and Trace Transformation Theory (Moscovitch et al., 2005, 2016; Nadel and Moscovitch, 1997; Sekeres et al., 2018a; Winocur and Moscovitch, 2011) predict that insofar as repetition helps retention across delay, hippocampal activation should be sustained. This prediction applies only to associative memory, particularly performance on aCR, whose relational nature makes it dependent on the hippocampus (Cohn et al., 2009). Recognition memory for items, however, is dependent on both hippocampal and extra-hippocampal structures such as the PRC, depending on whether recognition is based on recollection or familiarity or a combination of the two (Davachi et al., 2003; Eichenbaum et al., 2007). With the passage of time, the recollection is more vulnerable to decay (Sadeh et al., 2014). As memory for items is transformed with time (Moscovitch et al., 2016; Sekeres et al., 2018a, Winocur and Moscovitch, 2011) and comes to rely less on recollection and more on familiarity, the activation of the hippocampus should decrease and that of extra-hippocampal structures increase. As the whole-brain analysis was applied, we also explored to what extent the activation in cortical regions (e.g., prefrontal gyrus) (Moscovitch et al., 2016; Sekeres et al., 2018a; Preston and Eichenbaum, 2013) changed over time, although their activation is not the focus of the current study.

2. Materials and methods

2.1. Participants

Twenty-three healthy, right-handed subjects (10 males) with a mean age of 22.73 ± 1.40 years participated in the study. One participant's data were excluded due to large head motion during scanning. All participants were native Chinese speakers. They were paid and gave written informed consent in accordance with procedures and protocols approved by the department Review Board of Peking University.

2.2. Materials

Two within-subjects factors were included in the study: memory type (associative, item) and time interval (20-min, 1-day, 1-week, 1-month). We first selected 618 Chinese words that were all composed of two Chinese characters. These words composed 309 unrelated pairs (e.g., class - skin), nine of which were used as practice pairs. The remaining 300 word pairs had a medium word frequency (18.04 ± 32.15 per million) and number of word strokes (18.39 ± 4.83). The word pairs were divided into five sets to be used for the four time intervals and new stimuli. The words in the five sets had comparable frequency and number of strokes (both $p > 0.10$). The relatedness of the word pairs and

the imaginability, familiarity, and concreteness of the words were also rated (5 participants). The words in the five sets, and the words on the left or right of the pairs were comparable in these features (all $p > 0.60$). The five sets were counterbalanced by the Latin-square principle so that each set had an equal chance of being used in the four time intervals and in a new set.

For each set, there were 60 pairs. Among them, 20 pairs were used as old pairs in the test phase, 20 pairs as recombined pairs (i.e., one word from the left position of one pair and one word from the right position of a different pair were taken, and then paired together as a recombined pair), and the remaining 20 pairs were used as old words (i.e., one of the two words within a pair were randomly presented). The new words were randomly selected from the new set (120 words in total, 20 words per interval). The stimuli were counterbalanced so that each pair had an equal chance of being used as old and recombined pairs for associative memory, and each word had equal chance of being old and new words for item memory.

2.3. Procedure

The procedure included study and test phases (Fig. 1). During the study phase, both item and associative encoding tasks were performed. When a word pair was presented at the center of the screen for 2 s, the participants first judged the concreteness of the two words from left to right. Then, the word pair was presented again for 4 s, during which the participants performed one of two tasks: constructing sentences or imagining scenes that combined the unrelated words and determined to what extent they succeeded. Because the participants learned the same word pairs several times, the two tasks were used alternately to diminish the effects of repetition suppression (i.e., sentence construction, imagination, sentence construction; or imagination, sentence construction, imagination) (Bosshardt et al., 2005). To prevent the participants from rehearsing the word pairs after the study phase, they were reminded that it was not necessary to intentionally retrieve or forget the stimuli. To ensure that memory performance was above chance, especially for the intervals of 1-week and 1-month, and comparable among different time intervals, the words and word pairs were learned different numbers of times (Yang et al., 2016). Specifically, the materials were learned twice for the 20-min interval, six times in massed presentation for the 1-day

interval, four times over two days for the 1-week interval and nine times over three days for the 1-month interval. The encoding lists were learned in the same room, at the same time of day and with the same experimenters.

During the test phase, the participants were scanned while they were tested for item memory and associative memory over different time intervals (Fig. 1). To test item memory, the old or new words were randomly presented at the center of the screen one at a time for 2 s, and the participants determined whether or not they had seen the words during the study phase. To test associative memory, the old or recombined word pairs were randomly presented for 4 s, and the participants determined whether or not they had seen the words together during the study phase. They were also asked to provide a confidence rating for item memory and associative memory (unsure to very sure on a scale from 1 to 3) to indicate their certainty and the vividness of their memory. For example, in case the participants did not remember any detailed information, they were instructed to indicate the lowest confidence rating of 1. In case they could vividly retrieve any information, e.g., task response for the word or word pair, they were instructed to indicate the highest confidence rating of 3. In this way, the confidence scale reflected vividness of retrieved information for item and associative memories. For the event-related design, the inter-trial interval was an average of 4 s in both tests (range 1–7 s).

The words or word pairs at each time interval were tested in blocks. In each block the participants were told which time interval and which test type would be performed (e.g., 1-day word pairs). Altogether there were eight blocks, with the association block lasting for 282 s and item block lasting for 262 s. The order of the blocks was pseudo-randomized across the participants. They learned 240 word pairs before scanning at four time intervals (60 per interval), and were tested, during scanning, with 160 words (40 per interval, half as old and half as new) and 160 word pairs (40 per interval, half as old and half as recombined). The words for item and associative memories were different and counterbalanced across the participants. To diminish the interference from other stimuli, the item and associative tests for the 20-min interval were performed in the first two blocks, with their orders counterbalanced across the participants. The participants were asked to subtract by 7 from 1000 continuously during the anatomical scan to prevent the rehearsal of the 20-min stimuli. They had a chance to practice before the

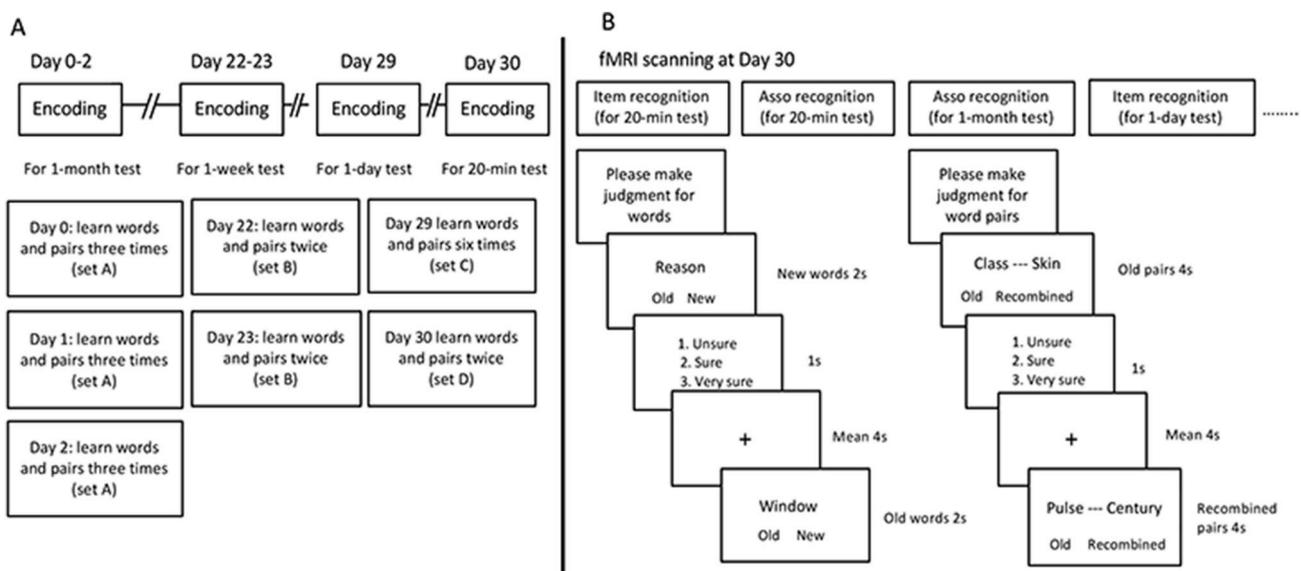


Fig. 1. Timeline of the study and procedure of the test phase during scanning. The participants learned word pairs at different intervals before test (A). To match memory performance at different intervals, different learning times were adopted. Different stimulus sets were used for four intervals. Then they performed the tests of old/new word recognition and old/recombined word pair recognition in the same day (i.e., Day 30) when they were scanned (B). Chinese words are replaced by English words for illustration purpose.

formal study and test phases until they were familiar with the procedure.

2.4. MRI acquisition

MR data were collected on a Siemens Trio 3 T scanner. Functional data were acquired using a gradient echo, echo-planar imaging (EPI) sequence. Anatomical data were acquired using a high-resolution MP-RAGE sequence (TR = 920 ms, TE = 9.2 ms, flip angle = 37°, FOV = 22 cm, matrix = 256*256, resolution = 1*1*1.3 mm³) before functional scanning. The parameters used for the EPI sequence was TR = 2s, TE = 30 ms, flip angle = 90°, FOV = 22 cm, matrix = 64*64, slice = 33, resolution = 3*3*3 mm³. To better observe the signals in the MTL regions, oblique slices that were perpendicular to the long axis of the hippocampus were adopted (an orientation angle between 30 and 40°).

2.5. Image analysis

The AFNI software program was used to pre-process imaging data and for statistical analysis (Cox, 1996). The EPI volumes were registered, smoothed with a 3D FWHM of 6 mm, and standardized to a mean of 100. Because we obtained the EPI volumes along the hippocampus axis, there was a large orientation angle to warp into the standard stereotaxic space. To diminish the error during the orientation process, the functional volumes were warped into the standard space of the Talairach and Tournoux (1988) atlas before statistical analysis using 3d deconvolve for individual analysis. In 3ddeconvolve, a time window of 7 TRs (14 s) was selected to model the hemodynamic response of each stimulus (general linear model, GLM). Altogether, 32 regressors of interest (4 time intervals, 2 memory types, and 4 stimulus types of Hit, Miss, Correct rejection (CR) and False alarm (FA)) and 6 regressors of non-interest motion parameters were applied, and the β weights of the impulse response function (IRF) were used to estimate the amplitude for each condition (vs. fixation).

To determine the difference between experimental conditions, a voxel-wise mixed-effects ANOVA was performed on the beta weights of Hit and CR trials from the individual analysis, with participants as random factors and memory type (item, associative) and time interval (20-min, 1-day, 1-week, 1-month) as fixed factors. Because the behavioral performance, despite our efforts, was not matched between item and associative memories (especially in Hit-FA), the effect of memory type was not reported in this paper. Instead, the time effect and the interaction of time interval by memory type, and time comparisons within the hippocampus and parahippocampal regions were reported for item memory and associative memory separately. In addition, the participants learned the stimuli repeatedly, the trials of FA and Miss were too few to permit reliable analysis, therefore, only the Hit and CR trials were analyzed. The few trials of FA and Miss also indicated that the Hit trials reflected true memories in item and associative memories. The stable aCR rate ensured that the comparisons across time for the Hit trials reflect the difference with respect to the time in successful retrieval of the old associative information.

In addition, we analyzed the CR trials only for associative memory using the voxel-wise analysis. In each of these trials, the two words were both old, but they were recombined to form a new pair. As rejecting these recombined pairs requires true associative memory (Castel and Craik, 2003; Cohn et al., 2008; Cohn and Moscovitch, 2007), the time comparisons enable us to determine the extent of involvement of the hippocampus and related MTL structures in retaining and retrieving associations over time. Because CR for items (iCR) do not have any clear predictions associated with them and do not bear on the hypotheses we were testing, and the behavioral performance was not matched across time, as aCRs were, we did not report them. We also analyzed the fMRI data of high confidence (rating of 2–3) Hit and aCR trials, and the results were similar to those of all trials. To get more trials to analyze and have greater power, we reported the results of all Hit trials for item and associative memories and aCR trials in this paper.

To identify activated voxels within the MTL that survived small volume correction (SVC), the subregions were manually drawn for each participant following instructions (e.g., Franko et al., 2014; Insausti et al., 1998; Pruessner et al., 2002), including the hippocampus, perirhinal/entorhinal cortex (PRC/EC), and PHC. In brief, the MPRAGE coronal plane was used to segment the subregions of the MTL. The anterior border of the hippocampus was usually found in the most rostral of the lateral ventricle, and the end of the hippocampus was defined as the disappearance of the ovoid grey matter medially to the lateral ventricle. We followed the definition of $y = -20$ in Talairach space to differentiate the anterior and posterior hippocampus (Poppenk et al., 2013). The anterior border of the PRC was defined as the most anterior slice in which the collateral sulcus was visible, and its most posterior slice was defined as the 3 mm after the gyrus intralimbicus disappeared. The PRC was replaced caudally by the anterior of the PHC. The posterior extent of the PHC was defined as the anterior limit of the parieto-occipital fissure. The segmentation of the MTL was co-registered to standard space and averaged across the participants. The masks were defined as 90% overlap for each MTL subregion. Brain activation was reported at the level of $p < 0.05$ for the MTL regions. For the regions outside of the MTL, the simulation determined a voxel-wise threshold of $p < 0.001$ (two-tailed) (Chen et al., 2017). The Monte Carlo simulation for the correction was done by the most recent versions of 3dFWHMx and 3dClustSim. These new versions incorporate a mixed autocorrelation function (ACF) that better models non-Gaussian noise structure (Cox et al., 2017; Eklund et al., 2016). Based on the correction for multiple comparisons, the minimum cluster size for the corrected $p < 0.05$ (two-tailed) was determined in cortical regions (volume = 405 mm³) (~15 clusters) and the MTL subregions (SVC with volume = 594 mm³) (~22 clusters).

3. Results

3.1. Behavioral results

Scores for the Hit rate, CR rate and corrected recognition (Hit-FA) were analyzed by repeated-measures ANOVA separately, with time interval and memory type as within-subjects factors. The d' and response bias (β value) were also analyzed (Supplementary Material). The Hit rate was 0.89 ± 0.05 on average, and above 84% in each condition and comparable at most time intervals (Fig. 2a). There were, however, a significant time effect ($F(3,63) = 11.12$, $p < 0.001$) and a significant interaction between time interval and memory type ($F(3,63) = 2.89$, $p = 0.04$). Simple effect analysis showed that the Hit rates were comparable across time intervals ($ps > 0.20$) except that accuracy at 20-min was lower than that at 1-day interval for both associative and item memories. The lower accuracy at 20-min is likely due to interference after the study list, as the participants immediately had to undergo preparation for the fMRI phase before the memory was well consolidated. The analysis of the Hit rate with high confidence (i.e., 'sure' and 'very sure' ratings) yielded similar results. The participants presented 'sure' and 'very sure' ratings for the correct responses in over 82% for each condition (item 0.86 ± 0.10 and associative 0.85 ± 0.11) (Fig. 2b). In addition, although the number of 'sure' and 'very sure' responses decreased over time, $F(3,63) = 8.09$, $p = 0.001$, the difference was only marginally significant between 20-min and 1-week for item memory ($p = 0.06$), and no significant time comparison was found for associative memory ($p's > 0.10$). There were no significant effects of memory type and their interaction for the number of sure and very sure responses ($p's > 0.05$). This result suggests that the participants' confidence is high for the retrieved information.

For the CR rate, the results showed a significant interaction between time interval and memory type, $F(3,63) = 30.78$, $p < 0.001$, with a marginally significant time effect, $F(3,63) = 2.71$, $p = 0.07$. Further analysis showed that the CR rate remained stable for associative memory across time intervals ($p's > 0.20$), but decreased from 20-min to 1-day

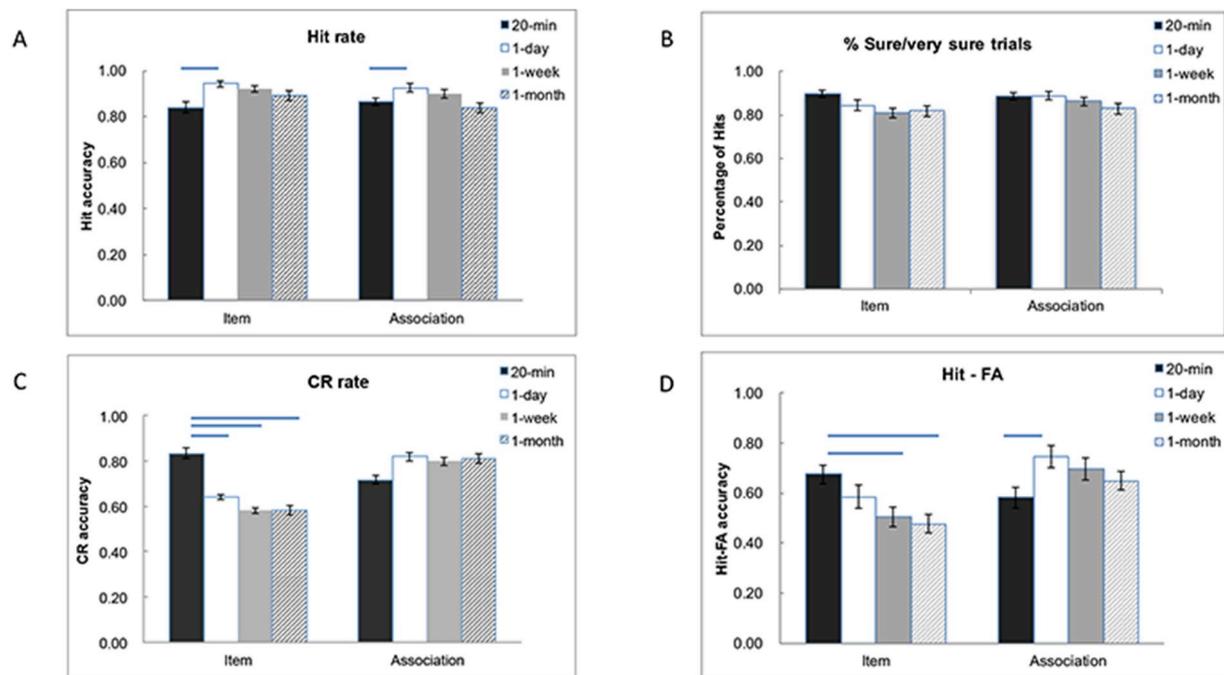


Fig. 2. Behavioral results. A: The results of Hit rate in each condition. The Hit rates were comparable across time intervals except that the accuracy was lower at 20-min than that at 1-day for both item and associative memories. B: The number of trials in sure and very sure ratings were matched across time intervals for associative memory. C: The results of CR rate in each condition. The CRs were comparable across time intervals for associative memory, whereas decreased from 20-min to 1-day for item memory. D: The results of corrected recognition. The accuracy was comparable across time intervals except for 20-min vs. 1-day for associative memory, and 20-min vs. 1-week and 20-min vs. 1-month for item memory. The lines stand for the significant difference ($p < 0.05$) between its beginning and its end (e.g., 20-min vs. 1-day in Fig. 2a). Error bars represent the standard error of the mean (SEM).

for item memory ($p = 0.001$) (Fig. 2c).

For the corrected recognition (Hits minus FA), performance was above chance level (as 0), p 's < 0.01 , in all conditions and remained high even at the 1-month interval. There was a significant interaction between time interval and memory type, $F(3,63) = 13.92$, $p < 0.001$, and a significant main effect of time interval, $F(3,63) = 2.85$, $p = 0.04$. When different time intervals were compared for each memory type, we only found a significant lower performance at 20-min than at 1-day ($p = 0.01$) for associative memory. For item memory, there were significant differences between 20-min and 1-week ($p = 0.04$), and between 20-min and 1-month ($p = 0.01$), but the differences between other time intervals were not significant (p 's > 0.16) (Fig. 2d). The analysis of the corrected recognition with high confidence provided similar results, with additional significant difference between 1-day and 1-month for both associative and item memories (p 's < 0.01).

The behavioral results suggested that for associative memory, the Hit rate, aCR rate, corrected recognition and confidence rating are comparable across time for the most part. So the expected decrease in associative memory caused by time was mitigated. Although not perfect, the data allow for comparisons of participants' brain activation during retrieval of associative memory, with limited behavioral confounds. For item memory, as predicted, performance was high and comparable across delays for the Hit rate, but the iCR rate and corrected recognition were not equated. We, therefore, reported the fMRI data for associative memory and item memory separately.

3.2. fMRI results

3.2.1. Time effect for the Hit trials

The voxel-wise analysis for the Hit trials showed a significant interaction between time interval and memory type in the left posterior hippocampus ($-25, -35, 1$, $F(3,63) = 5.91$, $p < 0.005$, 30 voxels) (Fig. 3a). There was also a significant time effect in the right hippocampus ($38, -23, -4$, $F(3,63) = 6.84$, $p < 0.001$, 29 voxels) (Fig. 3c).

The results suggested that the hippocampus is involved in retrieving associative and item memories, but its activation may change for different types of memory and time intervals.

As four intervals were included in the study, to explore how the hippocampus activations changed over time for each memory type, we extracted signal changes within the two clusters for each participant and performed repeated measure ANOVAs. For the cluster in the left posterior hippocampus, its activation remained stable from 20-min to 1-month for associative memory, with no time comparisons significant (p 's > 0.30) (Fig. 3b). For item memory, the hippocampal activation declined from 20-min to 1-week ($p = 0.01$), and remained stable from 1-week to 1-month ($p = 0.80$). For the cluster in the right hippocampus, its activation declined from 20-min to 1-day ($p = 0.02$), then remained stable from 1-day to 1-month (p 's > 0.20) for associative memory. For item memory, the hippocampal activation declined from 20-min to 1-day ($p = 0.15$), 1-day to 1-week ($p = 0.03$), and 20-min to 1-month ($p = 0.01$) (Fig. 3d).

In addition to the hippocampus, the voxel-wise analysis showed a significant time effect in the left PRC/EC ($-20, -5, -34$, $F(3,63) = 4.80$, $p < 0.001$, 40 voxels) (Fig. 3e). To identify the time change in the left PRC/EC, we extracted signal changes within the cluster for each participant and performed a repeated measure ANOVA. Different from that in the hippocampus, the activation in the left PRC/EC increased over time, with significant difference between 20-min and 1-month for both item and associative memories (p 's < 0.01) (Fig. 3f). Its activation also significantly increased from 20-min to 1-day for item memory ($p = 0.01$).

To explore whether the hippocampus and PRC/EC were differentially involved in retrieving item and associative memories, we performed two ANOVAs with region (hippocampus, PRC/EC), memory type and time interval as factors. The left and right hippocampus were compared separately with the PRC/EC. For the ANOVA including the left posterior hippocampus, there was a significant interaction between region and time interval ($F(3,63) = 4.13$, $p = 0.01$). Further analysis

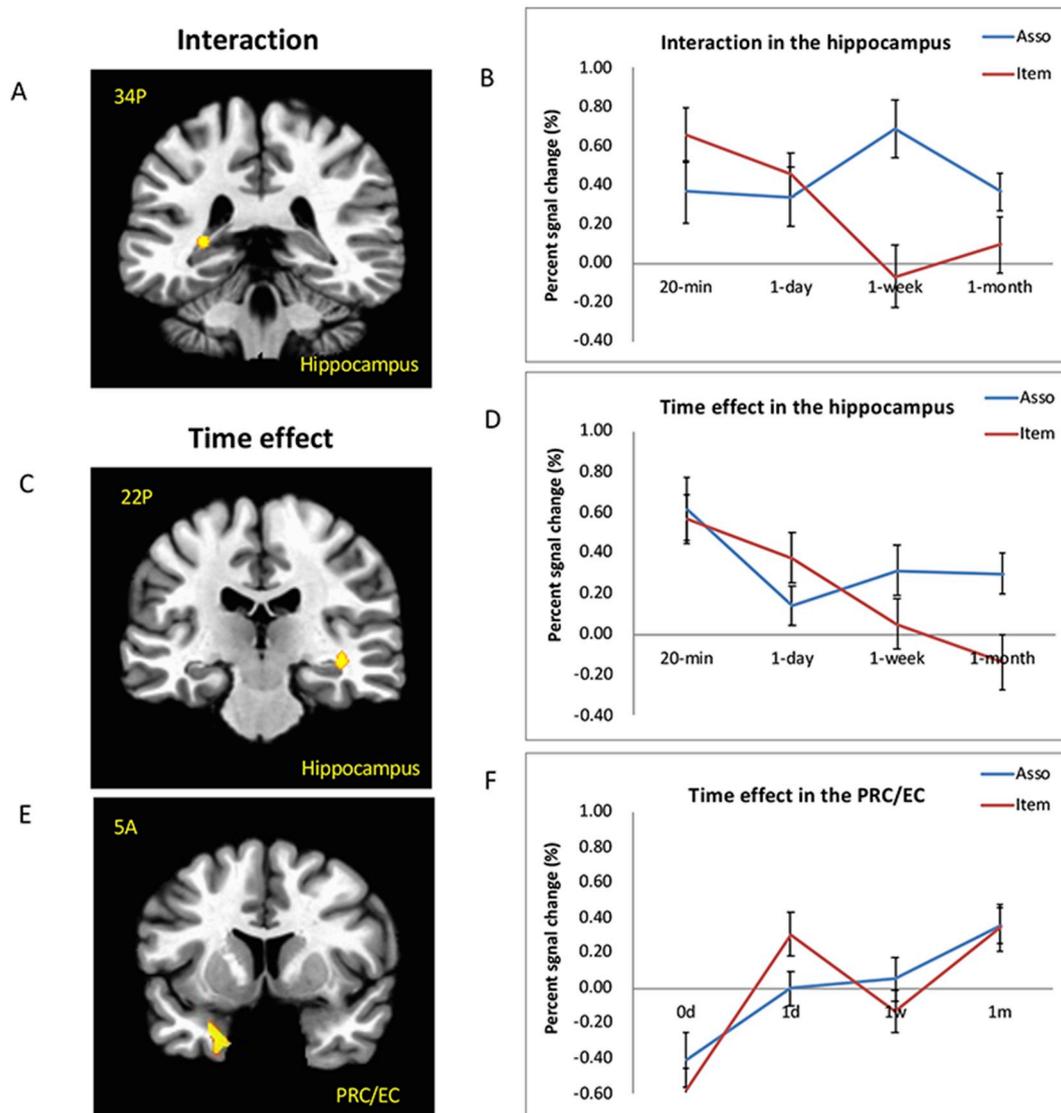


Fig. 3. Time effect and interaction for the Hit trials by voxel-wise analysis. There was a significant interaction between time interval and memory type in the left posterior hippocampus (A). The graph in B illustrates the signal changes in the interaction cluster. There was a main effect of time interval in the right hippocampus (C) and left PRC/EC (E). The graphs in D and F illustrate the signal changes for the time effect. The left side of the images represents the left brain. The warm color represents significant effects. Error bars represent the standard error of the mean (SEM). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

showed that the hippocampal activation remained stable (p 's > 0.20), whereas that of the PRC/EC increased ($p = 0.009$) from 20-min to 1-month. For the ANOVA including the right hippocampus, there was a significant interaction between region and time interval ($F(3,63) = 6.18$, $p = 0.001$). Further analysis showed that the hippocampal activation decreased ($p = 0.03$), whereas that of the PRC/EC increased ($p = 0.009$) from 20-min to 1-month.

The left and right hippocampus showed different change patterns for associative memory, so we performed a repeated measure ANOVA with region (left posterior, right hippocampus) and time interval as factors. The results showed a significant interaction between region and time interval ($F(3,63) = 4.97$, $p = 0.004$). Further analysis showed that the time comparisons were not significant for the left posterior hippocampus (p 's > 0.30); whereas for the right hippocampus, the activation decreased from 20-min to 1-day ($p = 0.02$) then remained stable (p 's > 0.20). It suggested that the left posterior and right hippocampus have different change pattern over time for associative memory.

Further simple comparisons by voxel-wise analysis within the hippocampus and parahippocampal regions shown in Fig. 4 confirmed the

above results. For associative memory, the bilateral anterior hippocampus showed decreased activation from 20-min to 1-day (left: 20, -11, -12, $t(21) = 4.04$, $p < 0.001$; right: 31, -10, -18, $t(21) = 4.01$, $p < 0.001$), but remained stable from 1-day to 1-month (Fig. 4a). For the parahippocampal regions, the left PHC showed decreased activation from 20-min to 1-day (26, -25, -19, $t(21) = -5.05$, $p < 0.001$), but increased activation from 1-day to 1-week (20, -26, -19, $t(21) = -3.35$, $p < 0.005$) and 1-day to 1-month (26, -26, -19, $t(21) = -3.91$, $p < 0.001$). The left PRC/EC showed increased activation from 20-min to 1-month (-23, 2, -34, $t(21) = -3.23$, $p < 0.005$) (Fig. 4a). The results indicated that for associative memory, the activation in the hippocampus and PHC decreased between immediate test and 1 day, then the activation in the hippocampus remained stable and that in the parahippocampal regions increased afterwards.

For item memory, unlike that for associative memory, the activation of the left hippocampus decreased from 20-min to 1-day (-23, -35, -4, $t(21) = 3.69$, $p < 0.001$; -20, -20, -16, $t(21) = 2.85$, $p < 0.01$), 20-min to 1-month (-29, -26, -10, $t(21) = 3.08$, $p < 0.005$) and 1-day to 1-week (-32, -26, -4, $t(21) = 3.63$, $p < 0.002$), but remained stable

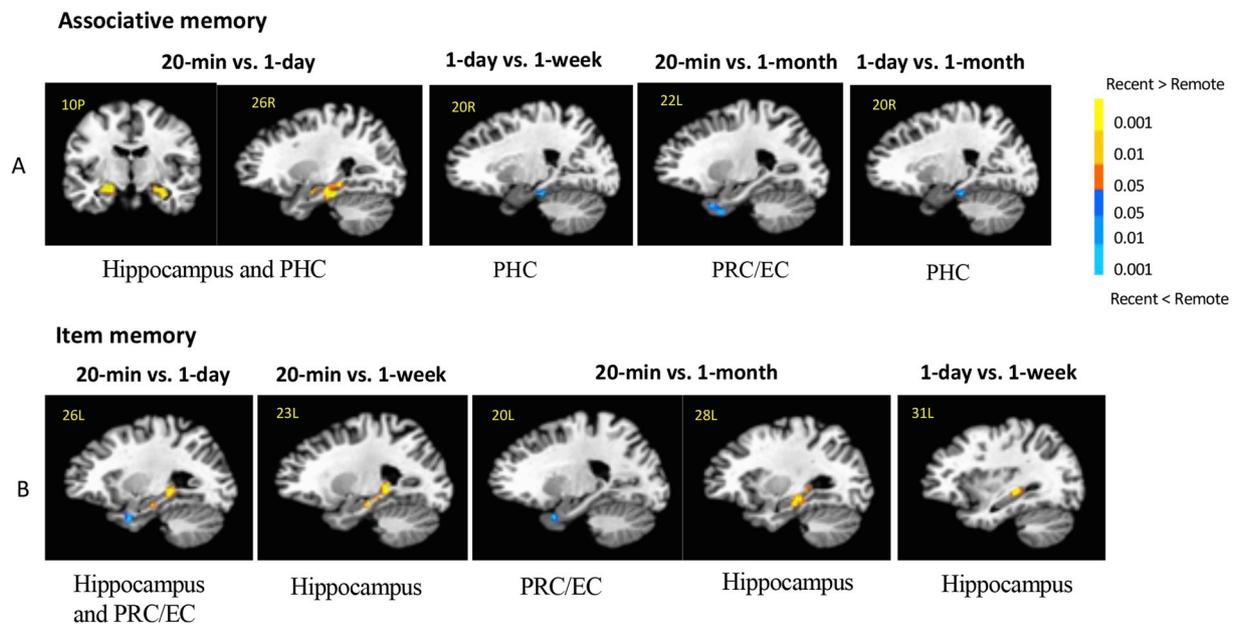


Fig. 4. Time comparisons for the Hit trials by voxel-wise analysis. For associative memory (A), the activation in the bilateral anterior hippocampus and the PHC decreased from 20-min to 1-day, then remained stable afterwards in the hippocampus, and increased in the PHC. The activation in the PRC/EC increased from 20-min to 1-month. For item memory (B), the activation in the hippocampus decreased from 20-min to 1-day, 1-day to 1-week and 20-min to 1-month. The activation in the PRC/EC increased from 20-min to 1-day, and from 20-min to 1-month. The left side of the images represents the left brain. The warm color represents stronger activation for more recent time interval than more remote. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

from 1-week to 1-month (Fig. 4b). Consistent with that for associative memory, the left PRC/EC showed increased activation from 20-min to 1-day ($-20, 2, -31, t(21) = -3.86, p < 0.001$) and 20-min to 1-month ($-19, 7, -25, t(21) = -3.74, p < 0.005$). The results suggested that for item memory, the activation in the hippocampus decreases and as

activation in the PRC/EC, it increases over time.

With regard to other cortical regions, the middle frontal gyrus ($-32, -14, 63, F(3,63) = 8.03, p < 0.001$; $-20, 8, 51, F(3,63) = 8.03, p < 0.001$) and precuneus ($20, -53, 51, F(3,63) = 7.92, p < 0.001$) showed significantly decreased activation over time. The activations in

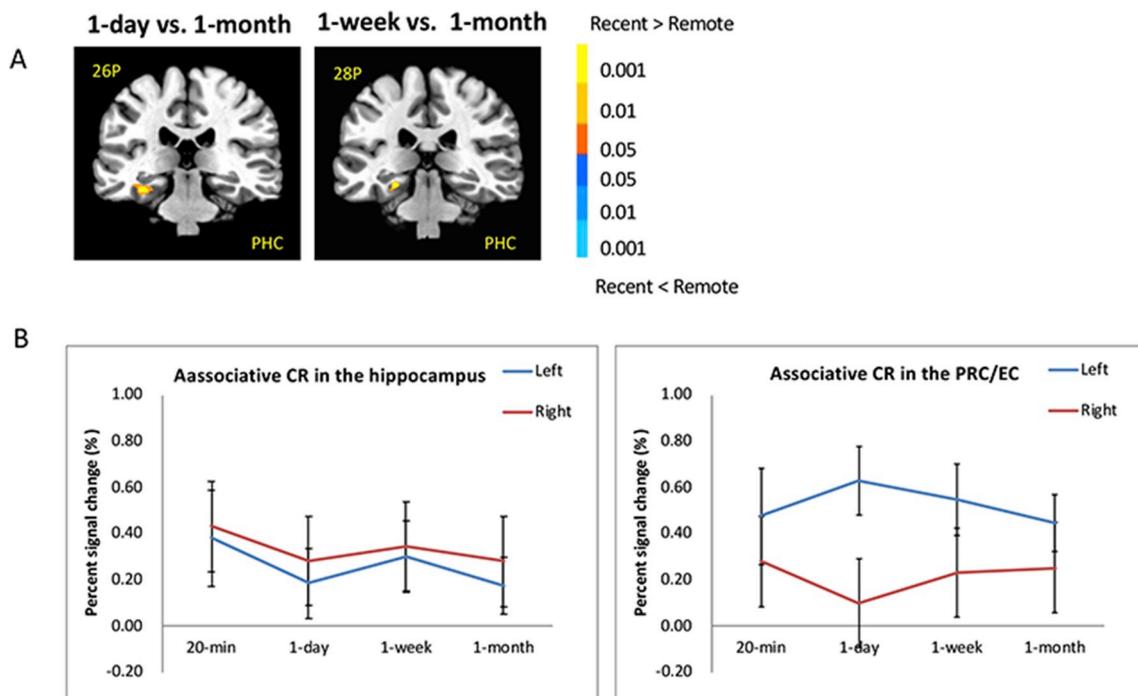


Fig. 5. Time effect for associative CR trials in the MTL. A: Results from voxel-wise analysis. The left PHC showed decreased activation from 1-day to 1-month. No significant hippocampal activation was found in time comparisons of aCRs. B: The time change in the bilateral hippocampus and PRC/EC with the ROIs defined anatomically. The activation remained stable over time. The left side of the images represents the left brain. The warm color represents stronger activation for more recent time interval than more remote. Error bars represent the standard error of the mean (SEM). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

the orbitofrontal cortex ($-23, 20, -10, F(3,63) = 6.05, p < 0.001$) (e.g., Gais et al., 2007; Takashima et al., 2006, 2009) and striatum ($-20, 8, -4, F(3,63) = 7.21, p < 0.001$) increased over time significantly, although they did not survive the correction. No cortical regions showed significant interaction between memory type and time interval.

3.2.2. Time effect for the aCR trials

We performed the voxel-wise analysis for aCR trials. The results did not reveal a significant effect of time interval, nor significant activations in the hippocampus for time comparisons, although the hippocampal activation for aCR ($>$ fixation) was significant. The only difference in the MTL by voxel-wise analysis was that the left PHC activation decreased from 1-day to 1-month ($-31, -24, -16, t(21) = -3.11, p < 0.005$) and 1-week to 1-month ($-24, -27, -12, t(21) = -3.76, p < 0.002$) (Fig. 5a). We, therefore, defined the hippocampal anatomy as ROIs and performed the ANOVA analysis. The results showed non-significant effects of time interval in the bilateral hippocampus (left: $F(3,63) = 0.68, p = 0.57$; right: $F(3,63) = 0.43, p = 0.73$) (Fig. 5b). Similarly, the PRC/EC ROIs extracted from the anatomical mask revealed non-significant effects of time interval (left: $F(3,63) = 1.06, p = 0.37$; right: $F(3,63) = 0.76, p = 0.52$) (Fig. 5b). The results suggest that retention and retrieval of associations uncontaminated by item memory are stable in the hippocampus from 20-min to 1-month.

4. Discussion

The objective of this study was to track, for the first time in the same study, the neural representations for item and associative memories from 20 min to one month while equating, as much as possible, performance for each type of memory across time. In particular, we were interested in whether the involvement of the hippocampus in item and associative memories changed over time when differences in performance were minimized across time intervals. As well, we examined other MTL structures, such as the PRC/EC, PHC, and PFC to document their involvement in these processes.

With respect to behaviour, we could not eliminate differences in memory performance across intervals in all conditions, as we had hoped, but they were minimal for associative memory and somewhat larger for item memory. Importantly, aCR, the purest measure of associative memory, was stable across all intervals. With respect to fMRI, there were two main findings. For associative memory, the activation of the left posterior hippocampus remained stable, although that of the right anterior part decreased from 20-min to 1-day when old pairs were correctly recognized. The hippocampal activation also remained stable when recombined pairs were correctly rejected.

For item memory, activation in the hippocampus decreased progressively from 20-min to 1-week and remained relatively stable afterwards. By comparison, in some extra-hippocampal regions, such as PRC/EC, there was a concomitant increase in activation. We discuss these findings and their interpretation in more detail below.

4.1. Behavioral matching

Testing four different time intervals allowed us to obtain a comprehensive picture of the effects of time on memory. The advantage of the ‘matching’ approach applied in this study was that the age of memory is not confounded with memory performance and vividness. By using different learning times and repetitions, differences in memory performance were minimized across time intervals (see also Bosshardt et al., 2005; Smith et al., 2010; Takashima et al., 2009), especially for associative memory. Crucially there were no significant differences across time for the aCR rate, the purest measure of associative memory, and percentage of high confidence trials. For other measures of associative memory, the behavioral results showed that the parameters of Hit rate and corrected recognition changed over time to some extent, but were comparable for the most part. The only significant difference was that

the Hit rate and corrected recognition were lower at the 20-min, than at the 1-day interval. The poor performance at 20-min likely was due to the greater interference participants experienced from instructions before scanning that were presented immediately after acquisition in this condition. Overall, the expected decrease in associative memory caused by time was mitigated, and for aCR did not materialize at all, indicating that the matching approach for associative memory was largely successful.

Item memory was not as stable as associative memory with differences evident across some intervals. Here, too, however, though significant, the differences were small. The percentage of high confidence trials were generally equated, with the Hit rate being significantly lower only for the 20-min compared to the 1-day interval. The item CR rate and corrected recognition decreased significantly over time. Nevertheless, note that for the corrected recognition, the performance was equated from 20-min to 1-day, and from 1-day to 1-week. Therefore, we focus our analysis on comparisons between time intervals during which item memory was equated.

4.2. Associative memory and hippocampus from 20-min to 1-month

The fMRI results of Hit trials showed that the hippocampus was equally involved in retention and retrieval of both recent and remote associative memories. This pattern appeared when matched time intervals were compared, e.g., when 20-min was compared to 1-month and when 1-day was compared to 1-week. There was no significant difference in bilateral hippocampal activity, whether in the anterior or posterior part. As participants retrieved the relations between the words during associative recognition, the comparable Hit trials reflected detailed information is remembered at various intervals.

The results of aCR analysis were especially noteworthy as they confirmed that hippocampal activation remained stable across time. As stated by Cohn et al. (2009), recollection contributes to associative recognition in two ways: it can enhance Hit rates (i.e., recall-to-accept) and reduce FA rates to rearranged pairs by opposing a sense of item familiarity (i.e., recall-to-reject). aCR is the ‘process purest’ measure of associative memory (Cohn and Moscovitch, 2007), which allows recollection to override familiarity-based false recognition via a recall-to-reject process (Yonelinas et al., 1995; Gallo et al., 2006; Cohn et al., 2008). Converging evidence suggests that the hippocampus is involved in aCRs (e.g., Bowman and Dennis, 2016; Cohn et al., 2009; Viskontas et al., 2016). For example, Cohn et al. (2009) conducted a study on patients with unilateral temporal lobectomy, and found that they were impaired on aCR (i.e., higher FA for rearranged pairs) during associative recognition tasks. Compared to recall-to-accept (i.e., Hits), the ability of recall-to-reject (i.e. aCRs) in associative memory tasks in older adults are disproportionately impaired (e.g., Castel and Craik, 2003; Cohn et al., 2008; Healy et al., 2005). In addition, when the activity of single MTL neurons was recorded while participants learned and recognized associations between faces and scenes, cells in the hippocampus responded during both Hit and aCR trials (Viskontas et al., 2016). Our results on aCR further suggest that the hippocampus is involved in successfully rejecting rearranged pairs and stabilizing the relational component of associative memory across time.

According to the SCT (Squire and Alvarez, 1995; Squire and Bayley, 2007), both the passage of time and greater opportunities for consolidation with multiple learning trials should lead to decreased hippocampal activation between 20-min and 1-month. Though some minimal decrease was noted using other measures that may have confounded item with associative memory, in the crucial aCR measure no such diminution was observed. Our results are consistent with those on autobiographical memory (AM) where comparable hippocampal activation was reported for recent and remote events equated for memory performance and a host of other factors, such as details and vividness (e.g., Bonnici et al., 2012; Bonnici and Maguire, 2018; Gilboa et al., 2004; Soderlund et al., 2012). Together, the findings suggest that the

decreased hippocampal activation reported in other studies of associative memory may be related to changes in the strength or quality of the memory, as proposed by MTT/TTT (e.g., Takashima et al., 2009; Yamashita et al., 2009). When, however, memory performance (especially the aCR) and confidence are controlled, as they were in our study, the hippocampus is critical for successful retrieval of associative memory that depends on recollection regardless of memory age (Winocur and Moscovitch, 2011).

The results also showed a significant interaction between anterior/posterior hippocampus and time interval. The stable activation across time was most evident in the posterior hippocampus, as the anterior hippocampus showed a decreased activation from 20-min to 1-day, then remained stable afterwards in the voxel-wise results. Note that the division we used to distinguish anterior from posterior hippocampus ($y = -20$) (Poppenk et al., 2013) is close to the division used by others (e.g., Bonnici et al., 2012; Poppenk and Moscovitch, 2011), in which the uncus apex serves as the dividing line ($y = -23$). The results showed that the time effect in the hippocampus was located in the anterior part ($y = -23$), whereas the interaction between time and memory type in the hippocampus was located in the posterior ($y = -35$). In addition, simple comparisons in the voxel-wise analysis revealed significant declines in the bilateral anterior hippocampus ($y = -10$) from 20-min to 1-day, but no significant changes for the bilateral posterior hippocampus for associative memory. It confirmed that the anterior and posterior hippocampus had distinct functional involvement in associative memory with the passage of time.

The difference between the anterior and posterior hippocampus had already been reported by investigators of AM, leading them to conclude that different regions along the long axis of the hippocampus may play distinct roles in memory consolidation (Bonnici et al., 2012; Bonnici and Maguire, 2018; Gilboa et al., 2004; Harand et al., 2012; Moscovitch et al., 2016; Robin and Moscovitch, 2017). In particular, the anterior hippocampus is more implicated in recent memory than remote memory, whereas the opposite is the case for the posterior hippocampus. Our findings on associative memory are generally consistent with those reported for AM (e.g., Bonnici et al., 2012; Gilboa et al., 2004). For recently presented targets, when interference from other information is minimal, even coarse, schematic differences, represented in anterior hippocampus, may be sufficient to distinguish targets from lures. With time, the possibility of encountering interfering stimuli increases substantially, thereby requiring finer and finer representations, mediated by posterior hippocampus, to distinguish targets from lures. Even though a rapid decline in the hippocampus occurs between immediate test and 1 day (e.g., Takashima et al., 2009), its activation seems pretty stable for associative memory after 1 day, as manifested in the current study. It is important to note that hippocampal activation associated with aCR remains stable across time as well. Taken together with the aCR data, our results suggest that for all intents and purposes, hippocampal contribution to associative memory that depends on recollection remains stable if memory performance is equated at all intervals.

4.3. Item memory and hippocampus from 20-min to 1-month

For item memory, hippocampal activation decreased progressively from 20-min to 1-week. Although the corrected recognition was equivalent between 20-min and 1-day, we still found a decrease in activation of the hippocampus. The decrease in the hippocampus also occurred when 1-day was compared to 1-week, and both the Hit and Hit-FA were equivalent in the two time intervals, and no clear distinction in anterior and posterior parts of the hippocampus. These findings are consistent with the results of previous studies using the natural forgetting approach (e.g., Smith and Squire, 2009; Takashima et al., 2006). For example, Takashima et al. (2006) observed reduced activity in the hippocampus when memory regarding pictures was tested after 20-min, 1-day, 1-month and 3-month intervals. If item memory depends on both recollection and familiarity as many, beginning with Tulving (1985b),

have supposed, then a possible interpretation of the decline in hippocampal activation is that it is related to the decline in the recollection component of item memory, and its greater reliance on familiarity. This interpretation is supported by other studies showing that the decline in hippocampal activation for item memory at different delays is indeed related to recollection-related trials (e.g., Harand et al., 2012; Ritchey et al., 2015; Suchan et al., 2008; Viskontas et al., 2009). Consistent with our interpretation is that as recollection declines, item memory comes to rely more on familiarity and that the PRC/RC activation increased from 20-min to 1-month.

As we noted, retrieving memory for single items has been shown to depend on both recollection and familiarity (Brown and Aggleton, 2001; Eichenbaum et al., 2007; Petrican et al., 2010; Ranganath et al., 2004; Tulving, 1985b; Yonelinas et al., 2005; Yonelinas, 2013), with the former mediated by the hippocampus and the latter by extra-hippocampal structures such as PRC/EC. Although we did not test for recollection and familiarity in our study, we assume that similar processes are operating to account for the decline in hippocampal activation associated with item memory: As the recollection component of item memory declines, so does hippocampal activation (Ritchey et al., 2015). In contrast, the familiarity component increases, which leads to increased activation in the PRC/EC. Thus, according to MTT/TTT, the diminished hippocampal activity with time for item memory may due to item memory being transformed with repetition and as retention interval increases (Winocur and Moscovitch, 2011), becoming less dependent on recollective component mediated by the hippocampus and more on familiarity mediated by the PRC/EC.

4.4. Changes in activation in extra-hippocampal and cortical regions across time

We've already noted that there is increased activation in the left PRC/EC for item memory which we attributed to greater reliance on familiarity. We found a similar increase for associative memory. Although largely dependent on recollection process, some associative memories may be unitized and, consequently, more familiarity-based, leading to more involvement of the PRC/EC with time (Quamme et al., 2007; Haskins et al., 2008; Staresina and Davachi, 2006). By contrast, the lateral prefrontal cortex and precuneus have been shown to be mainly involved in recollection process (e.g., Daselaar et al., 2006), and their activation decreased over time in our study. The orbitofrontal and medial prefrontal cortex have been associated with schematic representations (Gilboa and Marlatte, 2017; Ritchey et al., 2015; Takashima et al., 2006, 2009; van Kesteren et al., 2012). Consistent with this idea, orbitofrontal activation increased over time, as has been observed in other studies even when remote memories are highly detailed and are also associated with hippocampal activation (Bonasia et al., 2018; Sekeres et al., 2018a).

The activation in extra-hippocampal and cortical regions helps us understand how remote associative memory is represented. The results showed that the associative memory performance at 20-min and 1-month was comparable. The lack of behavioral differences in accuracy does not necessarily mean that the memory representation remains unchanged over time. The associations between the two words may transform as a more integrated format, and the memory representation may be more schematic, as supported by the increased activation in the PRC/EC and cortical regions. On the other hand, as the participants could correctly distinguish between the old and recombined word pairs, it is reasonable to assume that some associative memory representations have been retained. The confidence rating was also comparable among intervals for associative memory. Previous studies have also shown that remote autobiographical memory has comparable level of the richness and the amount of details (e.g., Bonnici et al., 2012; Gilboa et al., 2004). This pattern of results is consistent with the TTT model which posits that both gist-based and specific-based memory representation could co-exist as memory is consolidated (Moscovitch et al., 2016; Sekeres et al.,

2018a).

4.5. Limitations and future directions

We are mindful that equating performance does not mean that the underlying processes and the brain structures mediating them are equivalent. Here we consider some of the factors that need to be taken into consideration in interpreting not only our results, but those of other studies examining brain activation across time and experience.

First, we used different numbers of learning trials for different time intervals to match behavioral performance across time intervals. There is evidence that multiple learning trials lead to changes in cortical (Wagner et al., 2000; Xue et al., 2011; but see LaRocque et al., 2013) and MTL regions (Zhan et al., 2018). For example, Zhan et al. (2018) showed that the hippocampal activation increased after repetitive learning during memory retrieval. The time change in our study, however, did not simply reflect repetition, as the hippocampal activation generally remained stable over time (Nadel et al., 2007), and even decreased from 20-min to 1-day when more learning times were manipulated. On the other hand, although overall changes in activation may not be associated with repeated learning trials, the pattern of activation in the hippocampus and neocortex may differ, with greater pattern similarity in neocortex (Xue et al., 2011), and greater dissimilarity in the hippocampus (LaRocque et al., 2013), predicting subsequent memory. How these effects influence memory at long delay intervals awaits experimental tests.

Second, when comparing memory between time intervals, it is difficult to exclude every possibility that differs between them except age of memory. For example, reactivation and reconsolidation may play a role. As learning trials are repeated, participants may use the confidence scale differently in judging their memory for items than for associations, and the connectivity between the hippocampus and other structures may vary with repetition (Vilberg and Davachi, 2013). In addition, the 20-min items were always tested first to diminish interference from the stimuli from other intervals, but it is likely the order influences item memory at different intervals. A random or counter-balanced design may diminish these confounds. Therefore, on the one hand, we demonstrated that the matching approach provided a different way from the natural forgetting approach to investigate how item and associative memories are consolidated in the brain over time; on the other hand, we are mindful that matching approach has its own potential limitations. Our basic conclusion is that what matters are the underlying representations and the brain structures that mediate them; equating performance eliminates one important confounding variable.

Though we should exercise caution in our conclusions, we are encouraged that findings similar to ours were obtained in a variety of studies using different methodologies. These sets of findings, particularly with regard to associative memory, are also consistent with recent reports on memory consolidation as measured by activity of collections of single units in rodents. Tonegawa et al. (2015) found that the pattern of activation across this collection of units, which they interpreted as the engram (see also Josselyn et al., 2015), is maintained over time, though level of activation may be diminished. This level can be restored naturally by external cues or reminders (Winocur et al., 2009; Sekeres et al., 2018a), or artificially by optogenetic stimulation of the targeted neurons. A possible interpretation of our findings is that repetition of associations had the same effect, leading to maintained activation across the collection of neurons that mediate associative memories. By this interpretation, repetition affects item memory differently, possibly because single items are not good enough reminders to revive the contextual information that may be encoded along with the item.

4.6. Conclusions

The findings observed in this study have implications in clarifying how memory is maintained in the brain over time. For associative

memory, participants have to maintain relational information between items, even when the information is remote, an effect that is observed most clearly in aCR of recombined pairs. This finding also speaks to the involvement of the hippocampus in retrieving episodes of AM, no matter how long ago they occurred (Nadel and Moscovitch, 1997; Sekeres et al., 2018b; Winocur and Moscovitch, 2011). As it is with retention of associative memory, the hippocampus is implicated in retrieving AM memories for remote events as long as they are perceptually detailed and vivid thereby drawing on recollective processes at retrieval (Gilboa et al., 2004; St-Laurent et al., 2014, 2016).

Consistent with the MTT and TTT, as long as context-specificity is retained, the memory will continue to be dependent on the hippocampus (Winocur and Moscovitch, 2011; Sekeres et al., 2018b) and other regions sensitive to detailed recollection, such as the lateral pre-frontal cortex and precuneus. In contrast to associative memory, we found that for item memory hippocampal activation declined over time. We interpreted this finding as resulting from loss of context specificity, as reflected in a decline in recollection reported for item memory in other studies (Harand et al., 2012; Ritchey et al., 2015; Suchan et al., 2008; Viskontas et al., 2009). In short, as item memory is transformed from a context-dependent to a more familiarity-based memory, hippocampal activation is diminished, as it is when memories are transformed from perceptually-detailed to gist-like or schematic representations of events (Moscovitch et al., 2016; Sekeres et al., 2018a; Winocur and Moscovitch, 2011). Concomitantly, there is an increase in activation of the PRC/EC which is sensitive to item memory, and the orbitofrontal/vmPFC which is sensitive to schematic representations.

Our study takes its place in a very long line of studies that draw heavily on Tulving (1985b) distinction between recollection and familiarity in memory representation. Indeed, Experiment 2 in that paper documents the transformation of item memory over time in which recollection declined over seven days. Moreover, Tulving attempted to link recollection to neural structures that were damaged in amnesic patient KC (Tulving et al., 1988; for a survey of KC's role in cognitive neuroscience of memory, see Rosenbaum et al., 2005 and in this issue). It is a tribute to Tulving, and a mark of his profound influence, that the ideas he proposed over 30 years ago still have great currency as indicated not only by our paper, but by the many others in this issue.

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Appendix A. Supplementary data

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