Interplay of the long axis of the hippocampus and ventromedial prefrontal cortex in schema-related memory retrieval

Running title: hippocampus, vmPFC and schema

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Acknowledgments: The work was supported by a grant from the National Natural Science Foundation of China (31571114, J. Yang)

Abstract

When new information is relevant to prior knowledge or schema, it can be learned and remembered better. Rodent studies have suggested that the hippocampus and ventromedial prefrontal cortex (vmPFC) are important for processing schema-related information. However, there are inconsistent findings from human studies on the involvement of the hippocampus and its interaction with the vmPFC in schema-related memory retrieval. To address these issues, we used a human analog of the rodent spatial schema task to compare brain activity during immediate retrieval of paired associations (PAs) in schema-consistent and schema-inconsistent conditions. The results showed that the anterior hippocampus was more involved in retrieving PAs in the schema-consistent condition than in the schema-inconsistent condition. Connectivity analyses showed that the anterior hippocampus had stronger coupling with the vmPFC when the participants retrieved newly learned PAs successfully in the schema-consistent (vs. schema-inconsistent) condition, whereas the coupling of the posterior hippocampus with the vmPFC showed the opposite. Taken together, the results shed light on how the long axis of the hippocampus and vmPFC interact to serve memory retrieval via different networks that differ by schema condition.

Key words: schema; memory retrieval; anterior hippocampus; posterior hippocampus; vmPFC

Introduction

One important factor influencing memory is whether new information is relevant to prior knowledge (Alba & Hasher, 1983; Bartlett, 1932). When it is relevant, the information can be learned quickly and remembered better. This phenomenon is referred as the congruency effect or schema effect (Gilboa & Marlatte, 2017; van Kesteren, Ruiter, Fernández, & Henson, 2012). The hippocampus and ventromedial prefrontal cortex (vmPFC) have been shown to be intensively involved in enhancing schema-related memory (Gilboa & Marlatte, 2017; Preston & Eichenbaum, 2013; van Kesteren et al., 2012). In a landmark series of rodent studies, Tse et al. (2007) manipulated schema as six consistent flavor-location paired associations (PAs) within an arena. The hippocampus was shown to be critical for acquiring new PAs because lesions to the hippocampus given 3 h after learning new PAs blocked later memory, but lesions given 48 h after the learning had no effect on subsequent memory. In the following studies, researchers further demonstrate that schema-related memory encoding and retrieval depend crucially on the vmPFC and that the vmPFC-hippocampus interaction plays an important role during the retrieval of schema-related information (Tse et al., 2011; Wang, Tse, & Morris, 2012).

However, there are inconsistent findings on the involvement of the hippocampus, vmPFC and their interactions in retrieving schema-related information in human studies. For example, using a human analog of the rodent spatial schema task (Tse et al., 2007, 2011), van Buuren et al. (2014) found that the vmPFC was more strongly activated when the trained PAs were compared to the newly learned PAs, but

its activation did not differ when the newly learned PAs on schema-consistent (schema-C) and schema-inconsistent (schema-IC) grids were compared. No significant schema-related hippocampal activation was found either. Sommer (2016) also used a paradigm analogous to Tse et al.'s (2007), but yielded different results that showed the vmPFC and hippocampus were more activated when the schema-related PAs were compared to the control PAs at immediate recall, while hippocampus activation decreased and vmPFC activation increased as the delay was extended. The interaction between the vmPFC and hippocampus in memory retrieval was absent in either of these studies. Therefore, it is necessary to clarify how the hippocampus and vmPFC were involved in and interacted during memory retrieval with a paradigm of spatial schema-related memory.

For the hippocampus, only a few human studies found its activation due to schema during retrieval but in opposite directions (e.g., increased in Webb, Turney, & Dennis, 2016; decreased in Bonasia et al., 2018). It is noteworthy that the increased hippocampus activation was located in the anterior portion (Talaraich space: y= -13) for schematic versus non-schematic scene recollection trials (Webb et al., 2016), and the decreased hippocampus activation was located in the posterior portion (Talaraich space: y= -40) for recalling congruent versus incongruent events (Bonasia et al., 2018; however, see Sommer, 2016). This pattern raises the possibility that the anterior and posterior hippocampus are differentially involved in schema-related memory retrieval.

The idea that the anterior hippocampus (aHPC) and posterior hippocampus (pHPC) may serve different functions emerged a long time ago (e.g. Nadel, 1968;

Scoville & Milner, 1957). The anterior and posterior parts of the hippocampus have differential anatomical connections to other brain regions along with varied functional characteristics (Eichenbaum, 2017; Poppenk, Evensmoen, Moscovitch, & Nadel, 2013; Preston & Eichenbaum, 2013; Ranganath & Ritchey, 2012; Robin & Moscovitch, 2017; Sheldon & Levine, 2016; Strange, Witter, Lein, & Moser, 2014). The aHPC strongly connects to the anterior temporal lobe and vmPFC, and is associated with representing coarser, more global representations and relations that support the gist of an episode or environment. In contrast, the pHPC strongly connects to posterior neocortical regions and is more associated with detailed, perceptually based memory representations.

With regard to the spatial schema, it is developed in the context of associations between trained PAs (Tse et al., 2007; van Buuren et al., 2014). After establishing the schema, participants could learn and retrieve new PAs more easily with reference to the global or schematic context. Without such a schematic context, participants have to rely on the precise memory of each separate PA. Correspondingly, human fMRI studies have suggested that activation in the aHPC is associated with retrieving positions within a global context (Ekstrom, Copara, Isham, Wang, & Yonelinas, 2011; Morgan, MacEvoy, Aguirre, & Epstein, 2011) and activation in the pHPC often concerns local spatial and detailed features (Hassabis et al., 2009; Howard et al., 2014; Javadi et al., 2017). For example, when new streets were entered during navigation of a simulational city, the aHPC was more associated with a global transition structure across the street network and the pHPC was more associated with local path options (Javadi et al., 2017). Therefore, based on the functional distinction between the aHPC and pHPC along with

previous findings (e.g., Webb et al., 2016; Bonasia et al., 2018), it is reasonable to hypothesize that the aHPC and pHPC play different roles in retrieving schema-related memory, with the anterior part activated more for schema-related and the posterior part more for schema-unrelated retrieval.

The distinction of the aHPC and pHPC may also be related to the hippocampus-vmPFC interactions. Few human studies have reported the interactions during schema-related retrieval, and those that have produced inconsistent results (e.g. Bonasia et al., 2018; Sweegers, Takashima, Fernández, & Talamini, 2014). There are direct vmPFC-ventral hippocampus (human analog aHPC) anatomical reciprocal connections (Catenoix, Magnin, Mauguière, & Ryvlin, 2011; Kier, Staib, Davis, & Bronen, 2004; see reviews in Poppenk et al., 2013; Eichenbaum, 2017), and an indirect vmPFC to the dorsal hippocampus (human analog pHPC) pathway meditated by the nucleus reuniens (Eichenbaum, 2017). During memory retrieval, when participants are presented with a specific contextual cue, the vmPFC has a selective role in determining the specificity of hippocampal activation (Eichenbaum, 2017). Human fMRI studies also provide evidence that the two pathways related to the aHPC and pHPC may play differential roles in schema-related processing. For example, when decision-making required the use of a recently learned rule, stronger coupling between the aHPC and the vmPFC was associated with better performance (Kumaran, Summerfield, Hassabis, & Maguire, 2009). In addition, using a posterior parahippocampal seed, Bonasia et al. (2018) showed that enhanced MTL-vmPFC connectivity was associated with increasing incongruence of film clips during immediate retrieval. Therefore, the anterior and

posterior parts of the hippocampus may be tuned separately with the vmPFC to access different types of schema-related information.

In summary, the objective of the study was to investigate to what extent different parts of the hippocampus were involved in and interacted with the vmPFC in retrieving spatial schema-related information. Participants learned four grids (two schema-C grids, two schema-IC grids) of 20 object-location trained PAs for the first three training days. On day 4, the participants learned 12 new PAs together with eight trained PAs on each grid once. They were tested immediately on day 4 in the scanner and day 5 outside. For the schema-C grids, the objects and locations of the trained PAs on each grid were combined consistently across day 1-day 4. For the schema-IC grids, the combinations changed across day 1-day 4. Based on the distinctive functions and different interactions with the vmPFC, we hypothesized that the anterior and posterior parts of the hippocampus contribute differently to retrieving the PAs in the schema-C and schema-IC conditions, which could be shown via their activations as well as their functional couplings with the vmPFC.

Materials and methods

Participants

A total of 44 participants (25 female; mean age = 21.20 years, SD = 2.38) were recruited from the Peking University community and were paid for their participation. Among the participants, 25 (14 female; mean age = 21.48 years, SD = 2.50) were recruited in the fMRI group. As the initial behavioral analyses revealed two patterns of

results, to further explore behavioral patterns, an additional group of behavioral-only participants (19 participants, 11 female; mean age = 20.83 years, SD = 2.23) was recruited. In the fMRI group, two participants were excluded from the analyses due to falling asleep during scanning. Another four participants were excluded because they had a small number of trials (< 5) for fMRI analyses and poor memory performance (< 20%). Therefore, 19 participants in the fMRI group (11 female; mean age = 21 years, SD = 1.89) were included in the final behavioral and fMRI analyses. All participants were native Chinese speakers and gave written informed consent in accordance with procedures and protocols approved by the department Review Board of Peking University.

Materials

The object-location PAs were used as materials in this study. They were located on either the schema-C or schema-IC grids.

First, 128 black and white line drawings of everyday objects were selected based on a series of rating scores for 384 converted grayscale pictures from a bank of standardized stimuli (Brodeur et al., 2010) and ecological alternatives to Snodgrass and Vanderwart (Moreno-Martínez & Montoro, 2012). In a separate study, another group of 16 participants (7 female; mean age = 24.43 years, SD = 2.93) were asked to name the objects and rate the pictures for their familiarity, visual complexity, and object agreement (Brodeur et al., 2010; Moreno-Martínez & Montoro, 2012). The naming accuracy for each object was calculated as the percentage of the participants who

correctly named the object. All rating scores (i.e., familiarity, visual complexity, and object agreement) ranged from 1 to 7 from lowest to highest. The final 128 pictures were easy to name (mean naming accuracy 96% ± 7%), had high levels of familiarity (5.61 ± 0.79) and object agreement (6.05 ± 0.39), and had a moderate level of visual complexity (3.56 ± 0.95).

As four grids were employed for the schema-C and schema-IC conditions, the pictures were divided into four object-sets, with 32 pictures for each grid. The four object-sets (i.e., O-Set A1, O-Set A2, O-Set B1, and O-Set B1) were comparable in terms of naming, familiarity, visual complexity, and object agreement (all $F < 1$, all $p > 0.8$). The O-Sets A1 and A2 were paired and assigned to one of the schema conditions (i.e., schema-C and schema-IC), and O-Sets B1 and B2 were paired and assigned to the other schema condition. The assignment was counterbalanced across the participants. In addition, for each object set, 20 objects were randomly selected and used for the trained PAs during the training session, and the remaining 12 objects were used for the new PAs during the new learning session.

Second, the locations used in this study were on four 8×8 grids, which only differed in the colors used for their borderlines (i.e., red, yellow, blue, and green). Two grids were employed for each schema condition. Assignment of the grids (color) to the schema-C and schema-IC conditions was counterbalanced over the participants. Then four location-sets (i.e., L-Set X1, L-Set X2, L-Set Y1, and L-Set Y2) of 32 locations were created so that L-Sets X1 and X2 were paired and assigned to one of the two schema conditions and L-Sets Y1 and Y2 were paired and assigned to the other schema

condition. The assignment was counterbalanced across the participants. The locations of each pair of location-sets were selected in such a way that the 64 locations of a grid were pseudo-randomly assigned into two sets of 32 locations, and the locations of each set were distributed equally on four quadrants of the grid.

Third, two object-sets and two location-sets were randomly paired for each participant. The 32 objects of a specific object-set were pseudo-randomly assigned to the 32 locations of its corresponding location-set, so that the locations of the 20 objects for the trained PAs and the 12 objects for the new PAs were divided equally over the quadrants of the grids. Therefore, there were two schema-C grids and two schema-IC grids, and each grid consisted of 32 PAs. On each grid, 20 PAs were learned as the trained PAs during the training session, and the remaining 12 PAs were learned as the new PAs in the new learning session. In addition, eight PAs (two on each quadrant) of the 20 trained PAs were pseudo-randomly selected to be used as schema cues in the new learning session. Thus, in the new learning session (day 4, day 5), 12 new PAs and 8 trained PAs on each grid were learned and tested (i.e., 24 new PAs and 16 trained PAs per schema condition).

The difference between the schema-C grids and schema-IC grids was with respect to the consistency of the trained PAs across the training days. On a schema-C grid, the 20 trained PAs remained unchanged and were consistent from day 1 to day 3. On a schema-IC grid, the objects and their possible locations of the 20 trained PAs were fixed, but the combinations between them changed across the training days (see a detailed example in Fig. 1), although they were consistent within the same day.

Therefore, before the new learning session on day 4, the trained PAs on the schema-C grid had been overlearned in the training session and a stable spatial associative schema of object-location PAs could have been established. However, the combinations of the trained PAs on the schema-IC grid were completely new and no such stable schema had been established.

Figure 1 about here

Procedure

There were two sessions in this experiment: a training session and a new learning session (Fig. 2A). The training session was performed during the first three days. In this session, the participants were trained to learn four grids of 20 object-location PAs. The new learning session was performed on days 4 and 5. During this session, the participants learned 12 new PAs, together with eight PAs that were learned in the training session within each 8×8 grid, followed by the immediate and delayed (day 5) object-cue recall tests. Only on day 4, the participants performed the tasks in the fMRI scanner.

Figure 2 about here

The training session lasted three days. For the first two days, there were three learning-test cycles, and the PAs in each grid were learned and tested once per cycle (Fig. 2B). At the start of each cycle, one of the grids with its 20 object-location PAs

was presented on the screen for 90 s, during which the participants were asked to remember these PAs. Next, the PAs were recalled with feedback. Each of the 20 objects was presented as a cue on the center of the screen for 1 s, and then a blank 8 × 8 grid was presented for 3 s. The participants were asked to select the corresponding location for the object by moving the cursor and pressing the left button of the mouse. The feedback of the correct object-location PA was presented for 2 s after the blank grid, regardless of whether the response was correct or incorrect. After the 20 trials, the participants began to learn the next grid with the same procedure. Two grids for the same schema condition were always trained successively, and their order was counterbalanced across the participants and days.

On the third day, there were still three cycles. After a similar training cycle, to obtain a final training performance, two grids for one of the schema conditions were trained again successively, followed by a 5-min odd/even digit task and retrieval task without feedback (see a description of the tasks in the new learning session). Then, the remaining two grids for the other schema condition were trained and tested with the same procedure. The presentation order of the 20 object cues for each grid was random and different across cycles and days. The order of the schema conditions was counterbalanced across the cycles, days, and participants.

The new learning session consisted of three tasks for each condition (schema-C, schema-IC): a learning task, an immediate test, and a delayed test. For the learning task, the participants learned 12 new PAs together with eight trained PAs within each grid. The learning procedure was the same as that in the training session, except that

the participants learned and cued the 20 PAs with feedback only once. The 20 object cues on each grid were also randomly presented. The order of the schema conditions was counterbalanced across the participants.

During the immediate test, for each trial, an object cue was randomly presented on the center of the screen for 1 s, and then the participants moved the cursor and pressed the left button of the mouse to select the correct location within a response period of 3 s. After the selection, the grid turned grey, and the feedback was no longer presented. Each immediate test consisted of 40 trials for each schema condition (on two grids), i.e., 20 trials (8 trained PAs and 12 new PAs) for each grid. The immediate test followed the learning task for the same condition. In addition, to reduce interference between the two grids, the PAs for the first encoding grid were tested in the first 20 trials, and the PAs for the second encoding grid were tested thereafter. The order of the object cues was pseudo-randomly presented so that no more than three cues for each PA type were presented consecutively.

The delayed test task was performed on day 5. The 20 PAs of each grid that were learned on day 4 were tested again using the same procedure but in a different random order.

In addition, before the first learning task and after the learning task for each schema condition, a 5-min resting state scan was carried out separately, during which the participants performed an odd/even digit task (the odd/even task before the first learning task was omitted in the behavioral group). As the learning task and the immediate test were both event-related, in the fMRI scanner, the inter-trial interval was

4-8 s (fixation cross, mean of 6 s; fixed 1 s in the behavioral group). In addition to the three resting state runs, for each schema condition, there were two runs (342 s each) for the learning task and one run (412 s) for the immediate test task. Finally, a 10-min structural MRI scan was administered. The total scanning time was approximately 70 min.

As an adapted version, the grid setup and procedure were similar to those of van Buuren et al. (2014), though with two main differences. First, to make the schema formation and manipulation simpler, black and white line drawings were selected as object pictures and fewer PAs (n = 20) were assigned on each grid. Second, to avoid the repetitive reactivation of the memory trace (van Kesteren et al., 2012), the participants encoded the new PAs only once (rather than three times) on day 4 and then were scanned during the immediate retrieval.

fMRI data acquisition

A 3T Siemens Prisma MRI scanner with a 20-channel head coil in the MRI Center at Peking University was used to acquire MRI images. In the structural MRI scan, T1-weighted high-resolution MRI volumes were obtained using a 3-dimensional magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence (FOV = 256 × 256 mm; matrix = 256 × 256; slice thickness = 1 mm, TE/ TR = 2.98/2530 ms, flip angle = 7°). High-resolution functional MRI image were obtained using a simultaneous multiband EPI sequence (FOV = 224× 224 mm; matrix = 112 × 112, resolution = 2 ×2 × 2 mm, TE/ TR = 30/2000 ms, flip angle = 90°). Visual stimuli were

presented using MATLAB 2014b (MathWorks, Natick, MA, USA) and elements of the Psycholotoolbox3 (Brainard & Vision, 1997; Kleiner et al., 2007), back-projected to a screen, and viewed with a mirror mounted on the head coil. Responses were collected with an MRI-compatible mouse.

fMRI Analyses

The AFNI software package (Cox, 1996) was applied for the fMRI analyses. The EPI volumes were registered, smoothed with a 3D FWHM of 6 mm, and scaled to a voxel-wise mean of 100. They were then warped into the Talairach and Tournoux, (1988) atlas before individual subject analysis (3dDeconvolve). With 3dDeconvolve, option [–polort 3] was selected, which is roughly equivalent to a high-pass filter with a cutoff of 1/ (run duration) Hz. Estimates of brain activity related to each event for each participant were constructed via a general linear model. Stimulus-evoked BOLD responses to each event were modeled using AFNI's GAM response function adjusted for a 4-s stimulus duration. In this study, only the fMRI results of the immediate test were reported (Fig. 2A). As there were very few incorrect trials of trained PAs (mean of 1.63 ± 1.77) in the schema-C condition for each participant, all incorrect trials of the trained PAs were modeled as a variable of no-interest. The other six events were included as variables of interest: correct trials of the trained PAs (schema-C, schema-IC), correct trials of the newly learned PAs (schema-C, schema-IC), and incorrect trials of the newly learned PAs (schema-C, schema-IC). In addition, six-parameter motion estimates were entered as nuisance variables.

Group-level effects were then identified using two whole-brain repeated measures ANOVAs. First, to explore the interaction of the schema and PA type, an ANOVA was performed with schema (schema-C, schema-IC) and PA type (trained, newly learned) as within-subject factors and the subject as a random factor. Only correct trials were included during the first analysis. Second, to investigate how the established schemas affected the brain activity of newly acquired information, the other ANOVA was conducted with schema (schema-C, schema-IC) and memory (correct, incorrect) as within-subject factors and the subject as a random factor. Only trials of newly learned PAs were included in the second analysis.

To identify the connectivity between the long axis of the hippocampus and vmPFC during schema-related memory retrieval, a generalized form of context-dependent psychophysiological interactions (PPI) (McLaren, Ries, Xu, & Johnson, 2012) was used. The vmPFC seed regions with a radius of 5 mm were chosen based on peak activation of the interaction effect from the first ANOVA and the main effect of memory from the second ANOVA. For each seed, all regressors were convolved with the canonical HRF using the AFNI's GAM response function adjusted for a 4-s stimulus duration. The general linear model was estimated for each participant separately using AFNI's 3dDeconvolve function. Again, the incorrect trials of the trained PAs and six-parameter motion estimates were modeled as nuisance variables, and six events were included as PPI factors of interest: correct trials of the trained PAs, correct trials of the newly learned PAs, and incorrect trials of the newly learned PAs in the schema-C and schema-IC conditions. Thereafter, the same whole-brain repeated measures ANOVAs

(i.e. schema × PA type for correct trials and schema × memory for newly learned PAs) were conducted. In addition, to verify the PPI results with a more independent seed selection and exclude a potential circular issue, we carried out PPI analyses with the seeds from activation peaks of the vmPFC in two previous studies of schema-related retrieval (Brod, Lindenberger, Werkle-Bergner, & Shing, 2015; van Kesteren, Rijpkema, Ruiter, & Fernandez, 2010) (Fig. S1-S3).

To better localize the hippocampus and vmPFC, we defined the masks with anatomical regions of interest (ROIs). Bilateral hippocampus anatomical masks were created using AFNI's FS_Desai_PM atlas, which was originally parcellated by FreeSurfer (Fischl & Dale, 2000). Hippocampal activity was considered anterior when y was > −21 in Talairach space and posterior otherwise (Poppenk et al., 2013). The vmPFC anatomical mask was defined using the Mackey vmPFC Atlas (Mackey & Petrides, 2014). As we focused mainly on the potential activity in the ROIs, following the previous schema-related literatures (e.g., van Buuren et al., 2014; Sommer, 2016), the small-volume correction (SVC) for multiple comparisons was done in each ROI separately with a family-wise error (FWE) rate $p < 0.05$ after a voxel-wise threshold of $p < 0.05$ (two-tailed). The Monte Carlo simulation for the correction was conducted by the most recent versions of the AFNI programs, 3dFWHMx and 3dClustSim. These new versions incorporate a mixed autocorrelation function (ACF) that better models non-Gaussian noise structure (Cox, Chen, Glen, Reynolds, & Taylor, 2017; Eklund, Nichols, & Knutsson, 2016). The isotropic voxel sizewas 2 × 2 × 2 mm^3 in our study. Based on each ROI mask and the ACF parameters in each ROI, the simulation with

10,000 runs yielded minimum cluster extents of 39 voxels for the left hippocampus, 41 voxels for the right hippocampus, and 139 voxels for the vmPFC. As we had no specific hypothesis outside the ROIs, for the whole-brain analysis, the simulation determined a voxel-wise threshold of $p < 0.001$ (two-tailed) in combination with a minimum cluster extent of 75 voxels to maintain an FWE rate of $p < 0.05$ in a whole-brain mask (Chen, Taylor, & Cox, 2017; Flandin & Friston, 2017). The figures in the text displayed the brain activation inside the ROIs, and the activations outside the ROIs were illustrated in Table 2-3.

Although the behavioral results indicated the presence of the schema effect, there were still a few participants who had better memories under the schema-IC (vs. schema-C) condition. To confirm that our findings reflected the schema-related retrieval, we performed additional analyses with only the participants who had schema effect of the newly learned PAs (schema-C ≥ schema-IC on day 4, n = 13). The results showed similar patterns of those with all the 19 participants (Fig. S5-6, see details in Supplementary Material).

Results

Behavioral results

Consistent with rodent and human studies (Tse et al., 2007, 2011; van Buuren et al., 2014), only the trials in which participants chose the exact correct locations were considered as correct trials. In both the training and new learning sessions, memory accuracy was calculated as the proportion of correct trials for each condition (i.e., the

number of correct trials out of the total number of trials) (Table 1).

For the training session, memory accuracy was calculated separately for each schema condition (schema-C, schema-IC) and each learning cycle (1, 2, 3) for each day (1, 2, 3). With this, a 2 × 3 × 3 repeated-measures ANOVA was conducted. The results showed that the accuracy increased over days (F (1.81, 67.01) = 215.34, $p < 0.001$, η^2 = 0.85) and cycles (F (1.59, 58.65) = 378.63, $p < 0.001$, η^2 = 0.91) (Fig. 3A). The accuracy was also higher for the schema-C condition than the schema-IC condition (0.70 ± 0.09 vs. 0.61 ± 0.12; F (1, 37) = 143.45, $p < 0.001$, η^2 = 0.80) (i.e., schema effect). There was also a significant interaction of schema × cycle × day (F (2.83, 104.77) = 11.54, $p < 0.001$, η^2 = 0.24). Further analyses showed that the schema effect was not significant for day 1 (p = 0.43), but increased over days (interaction schema × day: F (1.57, 57.99) = 54.23, $p < 0.001$, η^2 = 0.59). For the final retrieval task of the third day, the memory performance was significantly better for the schema-C condition than for the schema-IC condition (0.94 ± 0.06 vs. 0.81 ± 0.14; t (37) = 8.41, $p < 0.001$) (Fig. 3A), indicating a successful manipulation of the spatial associative schema.

Figure 3 about here

For the immediate and delayed test in the new learning session, a 2 × 2 × 2 repeated-measures ANOVA was conducted, with schema (schema-C, schema-IC), PA type (trained, newly learned) and retention interval (day 4, day 5) as within-subject factors. The result showed that the main effects were significant for schema (schema-C > schema-IC (0.68 ± 0.12 vs. 0.39 ± 0.16, F (1, 37) = 156.73, $p < 0.001$, η^2=0.81),

PA type (0.62 ± 0.12 vs. 0.45 ± 0.15, trained > newly learned, F (1, 37) = 146.61, p < 0.001, η^2 = 0.80), and retention interval (0.62 ± 0.15 vs. 0.45 ± 0.11, day 5 > day 4, F (1, 18) = 143.91, p < 0.001, η^2 = 0.80). There was a significant interaction of schema × PA type (F (1, 37) = 98.999, p < 0.001, η^2 = 0.73) and a significant interaction of schema × retention interval (F (1, 37) = 36.19, p < 0.001, η^2 = 0.41). Further analyses showed that the schema effect was greater for the trained (0.86 ± 0.17 vs. 0.37 ± 0.21) than the newly learned PAs (0.50 ± 0.19 vs. 0.40 ± 0.22), and greater for day 5 (0.62 ± 0.27 vs. 0.28 ± 0.16) than day 4 (0.74 ± 0.23 vs. 0.50 ± 0.21), and all schema effects were significant (all p < 0.005). There was no significant three-way interaction (F (1, 37) = 0.51, p = 0.48, η^2 = 0.01). Figure 3B and 3C illustrate the accuracy distribution in each condition. For each PA type, the schema effect was significant on each day (all p < 0.001), except for a marginal significance on day 4 for the newly learned PAs (0.57 ± 0.17 vs. 0.51 ± 0.21, p = 0.059). The results confirmed a reliable schema effect by the paradigm, and suggest that the schema effect is modulated by PA type and retention interval, which are consistent with previous findings (e.g., Hennies, Lambon Ralph, Kempkes, Cousins, & Lewis, 2016; van Buuren et al., 2014).

To be clearer with respect to the behavioral results of the fMRI group, we performed the ANOVAs for the fMRI group separately. The results for both the training session and new learning session were similar to those in the whole sample. In the training session, there was a significant interaction of schema × cycle × day (F (3.13, 56.29) = 4.02, p = 0.011, η^2 = 0.18). For the final retrieval task of the third day, memory performance was significantly better for the schema-C condition than for the schema-

IC condition (0.94 ± 0.06 vs. 0.82 ± 0.12; $t_{(18)} = 6.404$, $p < 0.001$). In the new learning session, memory was better for the schema-C than schema-IC condition on both day 4 and day 5 for the trained PAs (p's < 0.001). For the newly learned PAs, memory for the schema-C condition was numerically higher than that for the schema-IC condition on day 4 (0.56 ± 0.16 vs. 0.49 ± 0.18, $p = 0.13$) and day 5 (0.38 ± 0.18 vs. 0.30 ± 0.17, $p = 0.13$), but the differences were not significant.

As the behavioral data of both behavioral and fMRI groups were included, we further added group as a factor in the ANOVA for the new learning session. There was no significant group effect (0.55 ± 0.15 vs. 0.53 ± 0.10; F (1, 36) = 0.24, $p = 0.63$, $\eta^2 = 0.01$) or interactions between group and each condition (all $p > 0.10$).

fMRI Results

Activity and connectivity in retrieving schema-related trained and newly learned PAs

To explore the interaction between schema and PA type in brain regions, especially in the hippocampus and vmPFC, an ANOVA with schema (schema-C, schema-IC) and PA type (trained, newly learned) as factors was performed for the correct trials. In the predefined ROIs using the SVC, for the main effect of schema, the activations in the bilateral aHPC were stronger for the schema-C than schema-IC condition (left: 101 voxels; peak: -29, -7, -16; $t_{(18)} = 4.47$, $p < 10^{-4}$; right: 147 voxels; peak: 25, -7, -18; $t_{(18)} = 3.94$, $p < 0.001$; Fig. 4A). For the main effect of PA type, a cluster surrounding the right pHPC was stronger for the newly learned PAs than for

trained PAs (52 voxels; peak: 31 -27 -14; $t_{(18)} = -3.67$, $p < 0.002$), but this cluster was mostly in the parahippocampal cortex. The results also revealed a significant schema × PA type interaction in the vmPFC (peak: 5, 35, -4; $t_{(18)} = 4.22$, $p < 0.001$; Fig. 4B). Further analysis showed that schema-related vmPFC activation was shown for the trained PAs but not for the newly learned PAs (Fig. 4C). This suggests that the schema-related activation in the vmPFC is modulated by PA type. For the whole-brain analysis, the main effect of PA type was also found in some cortical regions, including the middle frontal gyrus, precuneus and angular gyrus (Table 2, Fig. S4), which showed stronger activations for the newly learned PAs than trained PAs. Note that because of a priori focus on the HPC and vmPFC， a threshold ($p < 0.05$, SVC-corrected) was used in our study to detect the effects in these regions, which might not have been evident with a whole-brain analytical approach.

Figure 4 about here

The PPI analysis was then conducted to examine the connectivity between the vmPFC and other brain regions, specifically in the hippocampus ROIs. The vmPFC seed region was centered at the activation peak (5, 35, -4) based on the schema × PA type interaction effect. Using the SVC, the results revealed a main effect of PA type, which showed that the vmPFC had stronger connectivity with the right pHPC (73 voxels; peak: 31, -31, -6; $t_{(18)} = -4.63$, $p < 0.001$; Fig. 5A left) for retrieving the newly learned PAs than trained PAs. However, a significant schema × PA type interaction was found in the vmPFC-pHPC coupling (left: 78 voxels; peak: -9, -37, 4, $t_{(18)} = 3.67$;

right: 67 voxels; peak: 15, -37, 2; $t_{(18)} = 3.36$, all $p < 0.005$; Fig. 5A right), which showed stronger vmPFC-pHPC connectivity in the schema-IC than in the schema-C condition for the newly learned PAs, but not for the trained PAs (Fig. 5A bottom, for illustration).

Figure 5 about here

In addition, using the independent seed (-4, 30, 15) from Brod et al. (2015), the ANOVA of schema× PA type was conducted (see details in Supplementary Material). Similar to our results, the vmPFC-pHPC connectivity exhibited a main effect of PA type (newly learned > trained) and significant interaction of schema × PA type (Fig. S1). There was also a main effect of schema (schema C > schema-IC) for the vmPFC-aHPC connectivity (Fig. S1). This was consistent with the activation result that showed a main effect of schema in the aHPC, and nicely supplemented the main results of PPI analysis.

Activity and connectivity in successfully retrieving schema-related newly learned PAs

To explore whether the established schema influenced the newly learned PAs in brain activation, especially in the hippocampus and vmPFC, a voxel-wise ANOVA was performed, with schema (schema-C, schema-IC) and memory (correct, incorrect) as within-subject factors. For the main effect of memory, the whole-brain analysis showed that successful memory retrieval (correct vs. incorrect) was associated with

increased activations in various cortical regions (Table 3, Fig. S4). In the predefined ROIs using the SVC, the bilateral hippocampus (left: -27, -23, -6; $t_{(18)} = 5.58$; right: 19, -7, -8; $t_{(18)} = 6.17$, all $p < 10^{-4}$) and bilateral vmPFC (peak: left: -7, 35 -2, $t_{(18)} = 5.74$; right: 9, 31, -2; $t_{(18)} = 6.23$, all $p < 10^{-4}$) showed stronger activation when the PAs were successfully recalled (Fig. 6A). We did not find significant schema-related vmPFC activation in retrieving the newly learned PAs.

Figure 6 about here

For the schema × memory interactions, in the predefined ROIs using the SVC, the right aHPC (59 voxels; peak: 31, -17, -12; $t_{(18)} = 3.45$, $p < 0.005$; Fig. 6B) showed stronger activation for the schema-C condition than the schema-IC condition when the object-location PAs were successfully retrieved (correct vs. incorrect). Further analysis showed that the effect of schema (schema-C > schema-IC) was significant in the right aHPC when only correct trials were compared (98 voxels; peak: 25, -7, -16; $t_{(18)} = 3.63$, $p < 0.002$; Fig. 6C). Therefore, the results suggest that the aHPC is involved in successful schema-related memory retrieval. Note that the results of this part were consistent with those from the first ANOVA, which indicated significant schema-related activation in the aHPC for all correct trials.

Next, a PPI analysis was conducted to explore how the schema influenced the interactions between the vmPFC and hippocampus. The vmPFC seeds were selected from the main effect of memory centered at the two activation peaks (left: -7, 35 -2; right: 9, 31, -2). In the predefined ROIs using the SVC, for the left seed region, a schema

× memory interaction was found in the aHPC, which showed that successful retrieval of PAs in the schema-C (vs. schema-IC) condition was associated with stronger connectivity between the vmPFC and aHPC (48 voxels; peak: -15, -13, -20; $t_{(18)} = 3.53$, $p < 0.005$; Fig. 5B, left). For the right seed region, a schema × memory interaction was found in the pHPC, which showed that successful retrieval of PAs in the schema-IC (vs. schema-C) condition was associated with stronger connectivity between the vmPFC and pHPC (63 voxels; peak: 21, -27, -8; $t_{(18)} = -3.01$, $p < 0.007$; Fig. 5B, right). The result with respect to vmPFC-pHPC connectivity was consistent with that of the ANOVA with the schema × PA type. This suggests that schema-related successful memory retrieval is associated with stronger connectivity between the vmPFC and aHPC, whereas schema-unrelated successful memory retrieval is associated with stronger connectivity between the vmPFC and pHPC.

When the independent seed (-4, 30, 15; Brod et al., 2015) was employed, similar to our results, the ANOVA revealed interactions of schema × memory in the aHPC and pHPC, although the latter did not survive the SVC correction (Fig. S1). In addition, using both seeds (Brod et al., 2015; van Kesteren et al., 2010), vmPFC-aHPC connectivity (Figs. S1-S2) was found for the main effect of schema (schema C > schema-IC).

Discussion

The objective of this study was to explore how the long-axis of the hippocampus and vmPFC were involved and interacted in retrieving schema-related information.

There were three main findings. First, the aHPC was activated more strongly for successful memory retrieval in the schema-C condition than in the schema-IC condition for both trained and newly learned PAs. Second, the vmPFC-aHPC connectivity increased and vmPFC-pHPC connectivity decreased when the newly learned PAs were retrieved successfully in the schema-C (vs. schema-IC) condition. Third, the vmPFC showed a significant interaction between schema and PA type, as schema-related vmPFC activation was shown for the trained PAs, but not for the newly learned PAs. These results suggest that the aHPC is involved in retrieving schema-related information. More importantly, the long axis of the hippocampus and vmPFC interact to serve memory retrieval via different networks differing by schema condition.

Hippocampus in schema-related memory retrieval

A novel finding of our study was that the aHPC was involved in successfully retrieving schema-related trained and newly learned PAs. This pattern was manifested in both ANOVAs, one with the main effect of schema for the correct trials and the other with the interaction between schema and memory for newly learned trials. This was also consistent with our behavioral results showing a significant schema effect for both trained and newly learned PAs.

Rodent studies have shown that the hippocampus is critical for acquisition and consolidation of memory of new PAs related to spatial schema (Tse et al., 2007, 2011). The aHPC has been suggested to be more involved in global or gist-like processing (e.g., Poppenk et al., 2013; Robin & Moscovitch, 2017), and our results provided

supports for the role of the aHPC in schema-related memory retrieval. Consistent with our results, Webb et al. (2016) investigated subsequent memory effects for objects that were encoded either in congruent or incongruent scenes and found increased aHPC activation for schema-related recollection. Human fMRI studies have also suggested that activation in the aHPC is associated with constructing mental representations of scenes (Dalton, Zeidman, McCormick, & Maguire, 2018; Zeidman & Maguire, 2016). Taken together, the results support our hypothesis that the schematic context can be used to facilitate retrieving schema-related information, and the anterior hippocampus is involved in this process. On the other hand, we should note that the spatial global context is only one aspect of schematic information, as the anterior hippocampus is also associated with other schema-based processing, such as non-spatial memory integration (e.g., Schlichting, Mumford, & Preston, 2015; Schlichting, Zeithamova, & Preston, 2014). Therefore, the schema-related hippocampal activation in memory retrieval may reflect global and gist-based information, and the spatial or contextual paradigm is an effective example of assimilating new knowledge with the help of schematic information.

In a similar previous study, van Buuren et al. (2014) did not observe schema-related hippocampal involvement. One possibility is that participants learned new PAs three times in their study, which resulted in increased activation in the hippocampus for the schema-IC condition, leading to comparable hippocampal activation between conditions. Studies have shown that hippocampal activation increases via repetitive learning (Zhan, Guo, Chen, & Yang, 2018; for a review, see Kim, 2017). As proposed

by van Kesteren et al. (2012), schema-incongruent associations could be a part of schema if they were reactivated repeatedly. Therefore, repetitive reactivation may diminish the difference in the hippocampus between schema-C and schema-IC conditions.

Another possibility is that different retention intervals influence the involvement of the hippocampus in schema-related memory retrieval. Unlike our study, in which the recall task was scanned immediately after the learning session, in the study of van Buuren et al. (2014), the recall task was scanned 24 h after encoding. Rodent studies have shown that the memory of schema-related new PAs depends on the hippocampus in a short delay (Tse et al., 2007, 2011). A human study also suggests that sleep is associated with increased disengagement of the hippocampus across 24 h for schema-related memories (Hennies et al., 2016).

The short retention interval could also explain why we did not find the expected stronger pHPC activation for the schema-IC condition when the newly learned PAs were retrieved. The pHPC often relates to local spatial details, for example the precise position of individual landmarks (Doeller, King, & Burgess, 2008; Hirshhorn, Grady, Rosenbaum, Winocur, & Moscovitch, 2012). In a short delay, retrieval of schema-related and schema-unrelated memory may have equal access to the precise information, which leads to comparable pHPC activation. Yet, over time, the pHPC activation is reduced more quickly for the schema-related information (Sommer, 2016). Our behavioral results showed that the schema effect was more obvious after a one-day interval. Decreased pHPC activity was also observed after a delay of seven days for

schema-incongruent films (Bonasia et al., 2018). How brain activation changes in accordance with behavioral changes needs further investigations by including both short and long delays.

Interactions between the vmPFC and hippocampus in schema-related memory retrieval

The distinction between the aHPC and pHPC was also manifested in functional connectivity with the vmPFC. The results showed a double dissociation of vmPFC-aHPC and vmPFC-pHPC connectivity in retrieving schema-related and schema-unrelated memories for the newly learned PAs. The results of the independent seeds also showed a significant connectivity between vmPFC and aHPC for the schema-C versus schema-IC conditions. Previous studies have suggested that the direct vmPFC-to-aHPC pathway and the indirect vmPFC-to-pHPC pathway may serve different retrievals of context-appropriate memory representations, with the former used for more global information and the latter more detailed information separately (e.g., Eichenbaum, 2017; Robin & Moscovitch, 2017). To the best of our knowledge, this is the first time that this dissociation has been shown in a single study of schema. The vmPFC-HPC interaction has been investigated in schema-related encoding (e.g., Bein, Reggev, & Maril, 2014; Bonasia et al., 2018; Liu, Grady, & Moscovitch, 2017; Sommer, 2016; van Kesteren, Fernandez, Norris, & Hermans, 2010; van Kesteren, Rijpkema, Ruiter, Morris, & Fernández, 2014) and retrieval (Sweegers et al., 2014; Bonasia et al., 2018). The dissociation obtained in our study reconciled previously inconsistent

findings on the vmPFC-hippocampus connectivity by differentiating the functions of the aHPC and pHPC in schema-related memory retrieval.

Theories have emphasized the role of the vmPFC over the hippocampus to resolve the conflict between existing schemas and newly learned information (Preston & Eichenbaum. 2013) or to form a congruency-dependent trace for new information (van Kesteren et al., 2012). A model also suggests that the anterior hippocampal signals carrying the contextual information are sent directly to the vmPFC, which then engages the appropriate rule and applies it to engage the context-appropriate representations in the pHPC (Komorowski et al., 2013; Preston & Eichenbaum, 2013). Therefore, in the current study, it could be that the aHPC detects the contextual information of the schema (Eichenbaum, 2017) and the vmPFC serves a general-purpose control function of biasing information processing (Gilboa & Marlatte, 2017). In contrast, the vmPFC connects to the pHPC to be responsible for retrieving fine-grained information. As the PAs in the schema-IC condition are less supported by established schematic knowledge, vmPFC-pHPC connectivity was stronger for the schema-IC condition than for the schema-C condition in retrieving the newly learned PAs. In addition, greater vmPFC-pHPC connectivity was found for the newly learned PAs than for the trained PAs, which suggests that the newly learned PAs require more support from this connectivity for detailed spatial information.

An updated version of the Trace Transformation Theory (TTT) suggests that both the memory details and gist mediated by the pHPC and aHPC, respectively, and schemas mediated by mPFC can all co-exist and interact dynamically (Sekeres,

Winocur, & Moscovitch, 2018b). The memory from detail-rich representations to gist-like or schematic representations is accompanied by corresponding neural representations along the long axis of the hippocampus (Robin & Moscovitch, 2017; Sekeres et al., 2018). In sum, our results confirm the important role of hippocampal-neocortical interactions in the dynamics of schematic memory representation (Wang & Morris, 2010) and provide empirical evidence for the recent TTT (Sekeres et al., 2018).

vmPFC in schema-related memory retrieval

The results showed an interaction between schema and PA type, in which the schema-related vmPFC activation was shown for correctly retrieving the trained PAs but not for the newly learned PAs. The schema-related vmPFC activation was also absent when all the newly learned PAs were analyzed in the ANOVA of schema × memory. This pattern was consistent with that in the study of van Buuren et al. (2014) and suggests that different from hippocampal activation, schema-related vmPFC activation is modulated by PA type.

Our behavioral results showed that the schema effect was also modulated by PA type, as the schema effect was stronger for the trained than newly learned PAs. Compared to the newly learned PAs, the trained PAs were repetitively learned over three days to establish stable schematic representations, especially in the schema-C condition. Thus, the interaction between schema and PA type indicated that schema-related activation in the vmPFC may be modulated by the memory age (Bonnici et al.,

2012; Bontempi, Laurent-Demir, & Jaffard, 1999; A. Takashima et al., 2009) and/or repetition learning of PAs and objects. As the memory age of the newly learned PAs was relatively young, the absence of schema-related vmPFC activation for the newly learned PAs may suggest that a stable schema could not be established or available in retrieval over a short time. Only after sufficient consolidation could the well-established schematic information be represented in the vmPFC.

Although rodent studies have suggested a critical role of the vmPFC in schema-related memory (Tse et al., 2011; Wang et al., 2012), in human studies, its activation increased due to schema in some studies (Brod et al., 2015; Sommer, 2016; van Kesteren, Rijpkema, et al., 2010; Wagner et al., 2015), but did not change in other studies (e.g., Bonasia et al., 2018; van Buuren et al., 2014; Webb et al., 2016). The vmPFC is involved in evaluating and monitoring memory (Gilboa & Moscovitch, 2017), guiding memory retrieval by using relevant contexts to resolve conflicting information (Preston & Eichenbaum, 2013), and replacing the role of the hippocampus as memory ages (Nieuwenhuis & Takashima, 2011). Hence, when schema-related unrelated memories are retrieved and compared, if the comparison includes various cognitive processes, there would be inconsistent findings for the vmPFC. One advantage to including both the trained and the newly learned PAs (van Buuren et al., 2014) was that we could distinguish between the factors influencing schema-related vmPFC activation. We should also be cautious as the concept of schema has been defined in the literatures in different ways (see the review of Ghosh & Gilboa, 2014). Correspondingly, the inconsistent findings of the vmPFC are shown in studies either when schema are

induced experimentally (Brod et al., 2015; Wagner et al., 2015) or defined by a pre-existing knowledge system (Bonasia et al., 2018; van Kesteren, Rijpkema, et al., 2010; Webb et al., 2016) during memory retrieval. Hence, further studies with more careful schema-related designs are needed to clarify the role of the vmPFC in schema-related effects.

Limitations and future directions

Our study has several limitations that may suggest future directions. First, our study was limited by statistical power and individual differences. The average number of trials for each condition was not large and individual performance varied. This was mainly because the total number of trials was limited (i.e., 16 for trained PAs and 24 for newly learned PAs per schema condition). In addition, not all the participants had a schema effect for the newly learned memories. In the fMRI group, the schema effect did not reach significance for the newly learned PAs, mainly because certain participants had opposite memory performance. However, when only the data of the participants who exhibited the schema effect were analyzed, the neural pattern was similar and appeared to be more apparent. With the total sample size of 19 and large individual difference, we did not have sufficient power to explore the brain-behavior correlation. Future research with more participants and trials could examine what neural underpinnings are related to these individual differences.

Second, our study only investigated brain activation and connectivity when memory was retrieved right after learning. Studies have shown that the schema effect

is more pronounced after sleep (Hennies et al., 2016; Lewis & Durrant, 2011) or even longer intervals (Sommer, 2016). Our behavioral results also showed that the schema effect was modulated by retention interval, with a greater schema effect after a one-day interval. Further studies are necessary to investigate how the hippocampus and vmPFC activations, as well as their interactions, change over time by including both recent and remote delays (Sekeres et al., 2018).

(Christian & Thompson, 2003; D. A. McCormick & Thompson, 1984)
(Eichenbaum, Sauvage, Fortin, Komorowski, & Lipton, 2012; Eichenbaum, Yonelinas, & Ranganath, 2007; Knierim, Neunuebel, & Deshmukh, 2014; Squire, 1992)
(Milner, 2005, 1959)
(Squire, Chace, & Slater, 1975)
(Frankland & Bontempi, 2005)
(Bontempi et al., 1999; Markowitsch, 1995; Atsuko Takashima et al., 2006)
(Frankland & Bontempi, 2005; Insel & Takehara-Nishiuchi, 2013; Maviel, Durkin, Menzaghi, & Bontempi, 2004)
(Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006; Nadel & Peterson, 2013)
(Hassabis et al., 2009)
(X. Liu et al., 2012; Ramirez, Tonegawa, & Liu, 2014)
(Frankland & Bontempi, 2005; S.-H. Wang, de Oliveira Alvares, & Nader, 2009)
(Nadel, 1968; Scoville & Milner, 1957)
(Restivo, Vetere, Bontempi, & Ammassari-Teule, 2009)(Takehara-Nishiuchi & McNaughton, 2008; Wierzynski, 2009)
(Bechara, Damasio, & Damasio, 2000)(Barron, Garvert, & Behrens, 2015; Kable & Glimcher, 2007; Knutson, Fong, Bennett, Adams, & Hommer, 2003)
(S M Daselaar, Prince, & Cabeza, 2004; Sander M Daselaar et al., 2009; Huijbers et al., 2012; Maillet & Rajah, 2013; Vannini, Hedden, Sullivan, & Sperling, 2013)
(Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; B Bellana, Liu, Diamond, Grady, & Moscovitch, 2017; Buddhika Bellana, Liu, Anderson, Moscovitch, & Grady, 2016; Bonnici, Richter, Yazar, & Simons, 2016; Rugg & Vilberg, 2013; Spreng & Grady, 2010; Yazar, Bergström, & Simons, 2017)(Vilberg & Rugg, 2008)
(Hebb & Hebb, 1949)(Diana, Yonelinas, & Ranganath, 2007)
(Xue, 2019) (Tonegawa, Morrissey, & Kitamura, 2018)(Sekeres, Winocur, & Moscovitch, 2018a)(G. E. Müller & Pilzecker, 1900)(McClelland, McNaughton, & O'Reilly, 1995; Moscovitch, 2014; Squire & Alvarez, 1995)
(Wiltgen & Tanaka, 2013; Winocur & Moscovitch, 2011) (C. McCormick, St-Laurent, Ty, Valiante, & McAndrews, 2013)(Piaget & Cook, 1953)(Head & Holmes, 1911)(Chase & Simon, 1973; Chiesi, Spilich, & Voss, 1979; Mandler & Johnson, 1977; Steffensen & Colker, 1982)(Wagner et al., 2015b) (Hockley, Bancroft, & Bryant, 2012;

Reder, Liu, Keinath, & Popov, 2016)(Dewitt, Knight, Hicks, & Ball, 2012)(Oren et al., 2017)(Greve, Cooper, Tibon, & Henson, 2019; Tibon, Cooper, & Greve, 2017; van der Linden, Berkers, Morris, & Fernández, 2017)(Bowman & Zeithamova, 2018; Vogel, Kluen, Fernández, & Schwabe, 2018)(Popov & Reder, 2019)(Shen, Popov, Delahay, & Reder, 2018)(Bowman & Zeithamova, 2018)(Jackson & Raymond, 2008; Lupyan, Rakison, & McClelland, 2007; Schwartz & Yovel, 2016)(Antony, Ferreira, Norman, & Wimber, 2017; Skotko et al., 2004)(Euston, Tatsuno, & McNaughton, 2007; Maingret, Girardeau, Todorova, Goutierre, & Zugaro, 2016; Peyrache, Khamassi, Benchenane, Wiener, & Battaglia, 2009)(Schlichting et al., 2014; Tambini & Davachi, 2013; Tambini, Ketz, & Davachi, 2010; Tompary, Duncan, & Davachi, 2015)(Gregory, 2014)(Davachi, 2006; Murdock, 1997; Yonelinas, 2002; Yonelinas, Aly, Wang, & Koen, 2010)(Ning, Li, & Yang, 2018; W.-C. Wang, Brashier, Wing, Marsh, & Cabeza, 2018)(Lewis & Durrant, 2011)(Schlichting et al., 2015)(Chen et al., 2019)(Kriegeskorte, Mur, & Bandettini, 2008)(Dimsdale-zucker & Ranganath, 2018)(Fischl & Dale, 2000; Kaplan, Horner, Bandettini, Doeller, & Burgess, 2014; N. C. J. Müller & Buuren, 2019)(Di, Wolfer, Kühn, Zhang, & Biswal, 2019; Rissman, Gazzaley, & D'Esposito, 2004)(Fernández & Morris, 2018; Hebscher, Wing, Ryan, & Gilboa, 2019)(Coutanche & Thompson-Schill, 2014, 2015)(Cowansage et al., 2014; Sharon, Litsyn, & Alrod, 2011)(Ozubko, Moscovitch, & Winocur, 2017)

Conclusion

We used a human analog of the rodent spatial schema task and fMRI to compare brain activity during retrieval of schema-related and schema-unrelated spatial associations. The results showed that the anterior hippocampus was more involved in successful retrieval of schema-related memory. Furthermore, there was a dissociation between vmPFC-aHPC connectivity and vmPFC-pHPC connectivity when the participants retrieved schema-related and schema-unrelated PAs. These findings offer novel insights into how the hippocampus and vmPFC interact in schema-related memory retrieval. In addition, episodic memory is increasingly being viewed as subject to lifelong transformations that are reflected in the neural substrates that mediate it (Moscovitch, Cabeza, Winocur, & Nadel, 2016). Our study may contribute a better

understanding of how complex episodic memory is organized, especially in terms of the interaction between the hippocampal long axis and vmPFC.

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Table 1. Memory performance in the behavioral and fMRI groups

		Trained PAs		Newly learned PAs	
		Schema-C	Schema-IC	Schema-C	Schema-IC
Behavioral group					
Day 4	Mean (SD)	0.92 (0.16)	0.51 (0.22)	0.59 (0.19)	0.53 (0.23)
Day 5	Mean (SD)	0.74 (0.21)	0.30 (0.15)	0.49 (0.19)	0.30 (0.19)
fMRI group					
Day 4	Mean (SD)	0.90 (0.11)	0.45 (0.17)	0.56 (0.16)	0.49 (0.18)
Day 5	Mean (SD)	0.88 (0.13)	0.24 (0.12)	0.38 (0.18)	0.30 (0.17)

Table 2. Activation in the ANOVA of schema × PA type at $p < 0.001$ (two-tailed, FWE-corrected)

Brain region	x	y	z	Voxels	T
Schema: schema-C vs. schema-IC					
N.A.					
PA type: trained vs. newly learned					
L precuneus	-29	-71	40	139	-5.88
R inferior parietal lobule	41	-41	40	121	-6.39
L middle frontal gyrus	-35	19	28	110	-7.75
L middle occipital gyrus	-33	-81	16	107	-5.38
L angular gyrus	-29	-57	32	79	-4.66
Interaction					
N.A.					

Table 3. Activation in the ANOVA of schema × memory during retrieval of newly learned PAs at $p < 0.001$ (two-tailed, FWE-corrected)

Brain region	x	y	z	Voxels	T
Memory: correct vs. incorrect					
R middle temporal gyrus	61	-39	0	1218	9.42
L precuneus	-11	-55	32	858	8.44
R middle frontal gyrus	11	57	-4	504	7.09
L angular gyrus	-49	-69	28	472	6.17
L middle temporal gyrus	-61	-33	4	335	6.12
R precuneus	13	-45	62	251	6.05
R lentiform Nucleus	25	1	-16	222	7.29
R inferior parietal lobule	45	-57	42	164	6.42
L middle occipital gyrus	-41	-75	2	135	5.83

R cerebellar	43	-57	-38	135	6.00
R middle occipital gyrus	27	-83	20	133	6.58
R postcentral gyrus	41	-31	48	126	5.76
L fusiform gyrus	-31	-57	-10	117	6.18
R middle temporal gyrus	59	3	-16	108	5.60
R temporal pole	57	5	-2	104	5.86
R inferior parietal lobule	55	-27	30	93	4.43
R insula	43	-9	18	87	9.26
L cerebellar	-27	-63	-34	76	4.92
Schema: schema-C vs. schema-IC					
N.A.					
Interaction					F
R middle frontal gyrus	39	11	32	75	43.67

Figure legends

Figure 1. Example of PAs in the schema-IC condition on each day. An object set and a location set were randomly assigned to the schema-IC condition to form a grid. The objects and their possible locations of the trained PAs were fixed from day1 to day4, but their combinations (i.e., PAs) changed across days. The 8 trained PAs and 12 new PAs were learned on day4. They were then tested immediately on day 4 in the scanner and day 5 outside. The grey squares represent the 20 trained locations on day4, and they are only for illustration purposes and not presented in the experiment.

Figure 2. Experimental procedure. (A) Overview of the procedure. (B) After a grid was presented for 90 s (left), 20 trials for the grid were presented randomly. For each trial (right), an object cue was presented for 1 s, and the participants were asked to recall the

corresponding location in 3 s. The feedback was presented during the training and new learning tasks, but not in the tests.

Figure 3. Behavioral results with both behavioral and fMRI groups were included. (A) Memory performance for each cycle (C1, C2, C3) and each day (Day 1, Day 2, Day 3) in the training session. Error bars represent standard error of the mean (SEM). During the training session, memory performance was better for the schema-C than the schema-IC condition. The final test also showed a significant schema effect, indicating a successful manipulation of the schema. (B) Memory performance of the trained PAs. The schema effect of the trained PAs was significant on each day. (C) Memory performance of the newly learned PAs. The schema effect of the newly learned PAs was significant on day5, and it showed marginal significance on day 4. The box plots in (B) and (C) display the distribution of data based on the five-number summary: minimum, first quartile, median, third quartile, and maximum (from the bottom up).

Figure 4. Activations in the vmPFC and hippocampus ROIs for the ANOVA of schema × PA type on correct trials. (A) The anterior hippocampus showed a main effect of schema (schema C > schema-IC). (B) The vmPFC showed a schema × PA type interaction, and the schema-related activation in the vmPFC was shown for the trained PAs but not for the newly learned PAs (C). The brain maps only illustrate the activations in the predefined ROIs ($p < 0.05$, two-tailed, SVC-corrected). Color bars represent *p*-values, with the warm colors representing increased activation and the cold

colors decreased activation within each contrast. The left is on the left side for each coronal brain slice. Bar graphs are purely for visualization purposes. Error bars represent the standard error of the mean (SEM).

Figure 5. Results of the vmPFC-hippocampus connectivity. (A) ANOVA of schema × PA type. The vmPFC-pHPC connectivity was stronger for the newly learned PAs than the trained PAs (left). The significant interaction of schema × PA type (right) indicated that the stronger vmPFC-pHPC connectivity in the schema-IC (vs. schema-C) condition was only shown for the newly learned PAs. (B) ANOVA of schema × memory for the newly learned PAs. The vmPFC had stronger connectivity with the aHPC (left) for successfully retrieving PAs in the schema-C (vs. schema-IC) condition, whereas it had stronger connectivity with the pHPC (right) for successfully retrieving PAs in the schema-IC (vs. schema-C) condition. The brain maps only illustrate the activations in the hippocampus ROIs ($p < 0.05$, two-tailed, SVC-corrected). The seed regions are depicted as red circles. Color bars represent *p*-values, with the warm colors representing increased connectivity and the cold colors decreased connectivity in each contrast. The left is on the left side for each coronal brain slice. Bar graphs are purely for visualization purposes. Error bars represent the standard error of the mean (SEM).

Figure 6. Activations in the vmPFC and hippocampus ROIs for the ANOVA of schema × memory in retrieving newly learned PAs. (A) Main effect of memory (correct vs. incorrect) within the vmPFC and hippocampus. (B) The right anterior hippocampus

showed a significant schema × memory interaction, and the schema-related activation in the anterior hippocampus was shown for the correct trials (C). The brain maps only illustrate the activations in the predefined ROIs ($p < 0.05$, two-tailed, SVC-corrected). Color bars represent *p*-values, with the warm colors representing increased activation and the cold colors decreased activation within each contrast. The left is on the left side for each coronal brain slice. Bar graphs are purely for visualization purposes. Error bars represent the standard error of the mean (SEM).