Dissociation of the Perirhinal Cortex and Hippocampus During Discriminative Learning of Similar Objects

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Discriminative learning is a paradigm that has been used in animal studies, in which memory of a stimulus is enhanced when it is presented with a similar stimulus rather than with a different one. Human studies have shown that through discriminative learning of similar objects, both item memory and contextual memories are enhanced. However, the underlying neural mechanisms for it are unclear. The hippocampus and perirhinal cortex (PRC) are two possible regions involved in discriminating similar stimuli and forming distinctive memory representations. In this study, 28 participants (15 males) were scanned using high-resolution fMRI when a picture (e.g., a dog) was paired with the same picture, with a similar picture of the same concept (e.g., another dog), or with a picture of a different concept (e.g., a cat). Then, after intervals of 20 min and 1 week, the participants were asked to perform an old/new recognition task, followed by a contextual judgment. The results showed that during encoding, there was stronger activation in the PRC for the “similar” than for the “same” and “different” conditions and it predicted subsequent item memory for the “similar” condition. The hippocampal activation decreased for the “same” versus the “different” condition and the DG/CA3 activation predicted subsequent contextual memory for the “similar” condition. These results suggested that the PRC and hippocampus are functionally dissociated in encoding simultaneously presented objects and predicting subsequent item and contextual memories after discriminative learning.

Key words: discriminative learning; hippocampus; PRC; subsequent memory

Significance Statement

How the brain separates similar input into nonoverlapping representations and forms distinct memory for them is a fundamental question for the neuroscience of memory. By discriminative learning of similar (vs different) objects, both item and contextual memories are enhanced. This study found functional dissociations between perirhinal cortex (PRC) and hippocampus in discriminating pairs of similar and different objects and in predicting subsequent memory of similar objects in their item and contextual aspects. The results provided clear evidence on the neural mechanisms of discriminative learning and highlighted the importance of the PRC and hippocampus in processing different types of object information when the objects were simultaneously presented.

Introduction

How the brain separates similar input patterns into nonoverlapping representations and forms distinct memory for them is a fundamental question for the neuroscience of memory. The discriminative learning of similar stimuli provides an efficient way to establish distinct representations and enhance memory details in animals (Frankland et al., 1998; McHugh et al., 2007; Wang et al., 2009; Sahay et al., 2011; Niibori et al., 2012) and

humans (Koutstaal et al., 1999; Carvalho and Goldstone, 2014; Zhou et al., 2018). In a human study of discriminative learning, after participants judged whether the two simultaneously presented objects were the same, similar, or different, the objects that were learned in the “similar” condition could be better remembered in both item details and contextual information (Zhou et al., 2018). However, the underlying neural mechanisms for discriminative learning are not yet understood. The hippocampus and perirhinal cortex (PRC) are two possible regions that are involved in discriminative learning. Some animal studies have suggested that the hippocampus is critical for contextual discrimination (Frankland et al., 1998; McHugh et al., 2007; Sahay et al., 2011; Niibori et al., 2012; Czerniawski and Guzowski, 2014), but others have shown that animals with damage to the hippocampus could obtain the ability to discriminate between similar contexts under certain conditions (Good and Honey, 1991; Frankland et al., 1998; McHugh et al., 2007; Wang et al., 2009).

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There have thus far been no human studies that apply the discriminative learning paradigm to directly exploring the role of the hippocampus in memory after discriminative learning. However, studies using a similar paradigm of the mnemonic similarity task (MST) have suggested that the DG/CA3 is responsive to discriminating between the repeated and similar objects, and CA1 is responsive to integrating the repeated and similar objects (for reviews, see Kirwan and Stark, 2007; Yassa and Stark, 2011; Deuker et al., 2014; Horner and Doeller, 2017). Nevertheless, during the MST, the repeated, similar, and new stimuli are presented separately and the hippocampal activation is usually obtained during memory retrieval. It is therefore necessary to adopt the discriminative learning paradigm in humans to investigate to what extent the hippocampus is involved in successful encoding of similar objects when they are simultaneously presented.

Another line of evidences has suggested that the PRC is important for object visual discrimination (for reviews, see Murray and Richmond, 2001; Bussey and Saksida, 2005; Murray et al., 2007; Graham et al., 2010). In these studies, two similar objects are simultaneously presented or one of two similar objects have to be chosen to fit the target object (Bussey et al., 2002; Barense et al., 2005, 2010). The common process for these paradigms is that participants have to discriminate the details of objects and overcome the interference from similar lures. As such, the PRC is responsible for processing and storing representations of complex feature conjunctions. These representations help resolve “feature ambiguity” (Bussey and Saksida, 2005), especially when similar objects are simultaneously presented. However, there have been few studies exploring whether the ability to discriminate similar objects in the PRC predicts subsequent memory performance. In addition, after discriminating between similar objects, both item memory and contextual memory performance were enhanced (Zhou et al., 2018). Whether the two types of memory enhancement are associated with differential activation in the hippocampus and the PRC is unknown.

In this study, we asked participants to discriminate pairs of same, similar, and different objects during scanning and then, after intervals of 20 min and 1 week, they were asked to perform a recognition task to discriminate a repeated and a similar picture, followed by the contextual judgment. High-resolution fMRI (1.6 mm isotropic) was applied and we focused on the analysis within the medial temporal lobe (MTL). In addition, we divided the hippocampus into CA1 and DG/CA3 (Yushkevich et al., 2015; Wisse et al., 2016; Giuliano et al., 2017) and by so doing, could explore the relationship between their activations and discriminative learning.

Materials and Methods

Participants. Twenty-eight right-handed subjects (15 males) with a mean age of 22.57 ± 3.07 years participated in the study. All subjects were native Chinese speakers and gave written informed consent in accordance with procedures and protocols approved by the Review Board of School of Psychological and Cognitive Sciences, Peking University.

Experimental design and materials. Two within-subject factors were included in the study: encoding condition (same, similar, different) and retention interval (20 min, 1 week).

We selected 720 objects (240 triplets) from Hemera Photo Clipart and from the Internet. Each triplet included three similar but slightly different color pictures with the same basic concept/name (e.g., dog, tomato). The three pictures used in the experiment had clear and easy-to-be-extracted concepts and they differed in dimensions such as orientation, color, number, and position. They were the same size (640×480 pixels) and with white backgrounds.

The 720 pictures were selected from an original pool of 1344 pictures (448 triplets) based on the results of their naming performance, ratings of familiarity (1 for most unfamiliar, 5 for most familiar) and similarity (1 for most dissimilar, 5 for most similar) within the triplets. A total of 23 subjects (12 males, mean age of 22.83 ± 2.67 years) who did not participate in the experiments were recruited for the picture naming and rating tasks. During the familiarity rating task, each picture was presented and the participants were asked to name it and rate how familiar they felt the object was. During the similarity rating task, two pictures with the same concept object were presented together and the participants were asked to rate how similar the two pictures were. As one concept object had three similar pictures, three similarity rating scores for every two pictures of a triplet were acquired and averaged as one similarity score for each concept. To control the influence of familiarity and similarity, the stimuli that had low level of familiarity and middle level of similarity were finally selected. The naming accuracy for the final material was 0.91 ± 0.12 , for the familiarity score it was 1.81 ± 0.33 , and for the similarity score it was 2.93 ± 0.51 .

All selected triplets were first randomly assigned to four groups (Groups A–D; 60 triplets per group), with one group used for the “same” condition, one for the “similar” condition, and the other two for the “different” condition. For the “different” condition, two pictures were randomly selected from the two groups. Then, each group was further assigned to two different sets (S1, S2) of retention intervals (30 triplets per set). The three pictures within a triplet were separated into three subsets. For the “same” condition (A1–A1), pictures in one subset were presented during encoding and as old pictures during recognition and those in one of the other two subsets were randomly used as lure pictures (A2 or A3). For the “similar” condition (B1–B2), pictures from two subsets were paired (with the same concept) during encoding. The pictures in one of them were randomly used as old pictures during recognition and the pictures in the third subset were used as lure pictures (B3). For the “different” condition (C1–D1), pictures in one subset in each of the two groups were randomly paired during encoding. The pictures in one of them were used as old pictures during testing and those in the other subset from the same group were used as lure pictures (C2 or D2). The material in groups, sets, and subsets was counterbalanced across the participants so that each picture had the same chance to be used for each condition. There were no significant differences in naming performance, familiarity of pictures, and similarity within triplets across groups, sets, or subsets ($p > 0.60$).

Procedure. The participants learned the 180 object pairs in the scanner and then performed the item and contextual memory tests outside of the scanner at two retention intervals (90 objects per interval, 30 pairs per encoding condition) (Fig. 1A). During the encoding phase, for each trial, the picture pair (same, similar, or different) was presented in the center of the screen for 4 s and the participants were asked to judge whether the two pictures were the same, similar, or different (Fig. 1B). The order of the three buttons was counterbalanced across the participants. All of the pairs were pseudorandomly presented during the encoding phase so that no more than three stimuli that were in the same condition were presented consecutively. For the “similar” and “different” conditions, the position of the old picture (that appeared in the test) was pseudorandomly presented on the left or right of the pair. The intertrial interval was adjusted in the event-related design to an average of 7 s (range: 2–12 s). The 180 trials were randomly divided into four runs, with each run having 45 trials and 462 s (including the first six TRs for magnetic stability).

During the test phase, each picture was presented in the center of the screen for 2 s and the participants judged whether the picture was old or new as accurately and quickly as possible, followed by the confidence rating (from unsure to sure on a scale of 1 to 6) (Fig. 1C). If the picture was judged as old, then the participants had to judge whether the picture appeared in the “same,” “similar,” or “different” condition. Half of the pictures were old and the other half were new but similar pictures (i.e., lures). The old and lure pictures were pseudorandomly presented at each time interval so that no more than three pictures in the same condition were presented consecutively. The press button for the recognition judgment was counterbalanced across the participants.

Figure 1. Experimental procedure. Participants learned the pictures on the same day and then performed memory tasks at two retention intervals (**A**). During the encoding phase in the scanner, participants were asked to judge whether the two pictures were the same, similar, or different (**B**). During each of the test phases, the participants finished a recognition task and a contextual memory task (**C**).

Before each test phase, to avoid rehearsing the stimuli learned in the study phase, the participants were asked to count backward by 7 continuously from 1000 for 10 min. The participants had separate opportunities to practice study and test trials before the formal phase.

MRI acquisition. The MRI data were collected on a Siemens Magnetom Prisma 3 T scanner with a 64-channel head–neck coil. High-resolution functional images were acquired using a prototype simultaneous multislice EPI sequence (TR = 2000 ms, TE = 30 ms, flip angle = 90°, FOV = 198 mm, matrix = 124 × 124, resolution = 1.6 × 1.6 × 1.6 mm³). Anatomical images were acquired using a high-resolution T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (TR = 2530 ms, TE = 2.98 ms, flip angle = 7°, FOV = 256 mm, matrix = 256 × 256, resolution = 1 × 1 × 1 mm³) before functional scanning. High-resolution T2-weighted structural images perpendicular to the

hippocampal long axis were obtained to cover the whole hippocampus and MTL regions (TR = 13150 ms, TE = 82 ms, flip angle = 150°, FOV = 220 mm, matrix = 512 × 512, resolution = 0.43 × 0.43 × 1.5 mm³). The encoding phase was scanned first, followed by the anatomical scans.

Statistical analysis. The corrected recognition (Hit-FA), hit rate, and false alarm (FA) rate were analyzed using a repeated-measures ANOVA with encoding condition and retention interval as within-subjects factors. The accuracy of contextual memory was calculated as the number of correct trials for the contextual task out of the correct trials for item recognition and analyzed by ANOVA. One participant did not follow the instructions for the contextual judgment, so only 27 subjects' data were analyzed for the contextual memory effect. Partial eta squared (η^2) was calculated to estimate the effect size of each analysis. *Post hoc* pairwise comparisons were Bonferroni corrected ($p < 0.05$, two-tailed).

The AFNI software program was used to preprocess the imaging data and for the statistical analysis (Cox, 1996) (RRID:SCR_005927). The analyses included voxelwise and ROI approaches. For the voxelwise approach, the EPI volumes were registered, smoothed with a 3D FWHM of 3 mm, and scaled to a voxelwise mean of 100. Then, the individual subject analysis (3dDeconvolve) was performed, in which a time window of 7 TRs (14 s) was determined to capture the BOLD response of each stimulus with a presumed hemodynamic response function. The trials were labeled as Hit-context, Hit-item, and Miss according to each participant's behavioral performance in item recognition and contextual memory tests. Altogether, 18 regressors of interest (two retention intervals by three types of trials) and six regressors of noninterest motion parameters were applied, and the estimated β weights indicated the BOLD response amplitude for each condition. They were then warped into the standard space of the Talairach and Tournoux (1988) atlas for the group voxelwise analysis.

The group analysis focused on the predetermined subregions of the MTL. There were four types of ANOVA. First, to determine the difference between the experimental conditions during encoding, the voxelwise mixed-effects ANOVA was performed with the encoding condition (same, similar, different) as a fixed-effects factor and subject as a random-effects factor. Second, to determine whether the encoding activation predicted the subsequent item memory effect (i.e., difference in memory, item-Dm), we defined the item-Dm effect as the difference between subsequently remembered (i.e., Hit) and subsequently forgotten (i.e., Miss) items during the item recognition. Then the voxelwise mixed-effects ANOVA was performed with the encoding condition (same, similar, different) and retention interval as fixed-effects factors and subject as a random-effects factor. Third, to determine whether the encoding activation predicted subsequent contextual memory, we defined the context-Dm effect as the difference between subsequently context correct (i.e., Hit-context) and subsequent context incorrect (i.e., Hit-item) during the contextual judgment task. As the number of trials for the context correct was few at the 1 week interval, to ensure sufficient number of trials to enter into the analysis, each type of item was combined across retention intervals. The voxelwise mixed-effects ANOVA was performed with the encoding condition (same, similar, different) as a fixed-effects factor and the subject as a random-effects factor.

Fourth, in addition to the item-Dm effect for the subsequent correct memory (remembered vs forgotten), we investigated whether the encoding activity predicted subsequent memory for the similar pictures, i.e., lure/similar trials where they were called “old” (i.e., FA trials) than those where they were called “new” [i.e., correct rejection (CR) trials]. The lure-Dm effect was defined as the difference between the FA and CR items during the item recognition. The preprocessing and statistical steps were the same as those for analyzing the item-Dm effect except that the trials were labeled as FA item and CR item according to each participant's behavioral performance. Altogether, 12 regressors of interest (two retention intervals by three types of trials) and six regressors of noninterest motion parameters were applied.

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 (Eklund et al., 2016; Cox et al., 2017). Based on the correction for multiple comparisons, the minimum cluster size for the corrected p of 0.05 (two-tailed) was determined in cortical regions (volume = 532 mm³) (~130 clusters) and the MTL subregions (small-volume correction or SVC with volume = 205 mm³) (~50 clusters).

For the ROI analysis, the preprocessing steps were the same as that for the voxelwise analysis, except for two aspects: (1) the smoothing was not applied in the original individual space to maintain the high spatial resolution and precise anatomical localization against the physical proximity of the MTL subregions and (2) the individual images were not transformed to Talairach space. We focused on the subregions of the MTL, including the subfields of the hippocampus (i.e., CA1, DG/CA3), PRC, and parahippocampal cortex (PHC). Beta weights from each subregion of the MTL were extracted from each participant's original individual space, averaged across all voxels in the same subregion, and

Figure 2. Segmentation of the hippocampal subfields (CA1 in blue and DG/CA3 in orange) in T1 and T2 images for one participant. The original T2-weighted structural images are shown with (A) or without (B) the CA1 and DG/CA3 illustrated. The ROIs were created from ASHS program based on T2 image and resampled based on T1 image with (C) or without (D) the CA1 and DG/CA3 illustrated. The top-left index for each row represents the approximate distance of each slice from the anterior commissure ($y = 0$ in Talairach coordinates).

evaluated with mixed-effects ANOVAs. The four ANOVAs were the same as those with the voxelwise approach to examine the activation in the MTL subregions during encoding and three types of Dm effects. The Dm effects were first analyzed to determine whether they were significantly above chance level, and then the subregions that had above-chance activations and significant effects were reported ($p < 0.05$, two tailed).

The MTL ROIs were obtained separately for the hippocampus and parahippocampal regions. For the hippocampus, the four subfields (i.e., CA1, CA2, DG, and CA3) in each hemisphere were obtained by an automatic segmentation software (“Automatic Segmentation of Hippocampal Subfield” or ASHS) (Yushkevich et al., 2015; Giuliano et al., 2017) upon T2 images for each participant (Fig. 2). The hippocampal tail and the subiculum were also segmented but were not included for further analysis. Segmentation was realized through algorithms using pretraining datasets with manually tagged masks (Wisse et al., 2016). After the automated segmentations, each subfield was visually checked and manually corrected following the protocol described by Wisse et al. (2012) to exclude false segmentations. The hippocampal ROIs were then transformed to T1 individual images (Fig. 2), visually rechecked, and resampled to the EPI resolution using nearest-neighbor interpolation for the ROI analysis. As the EPI resolution (1.6 mm isotropic) in the current study is not high enough to separate apart the four regions precisely, the CA2 and CA1 regions were combined (2203 ± 231 mm³) and the DG was collapsed with the CA3 (1145 ± 143 mm³).

The parahippocampal subregions were manually drawn in the individual T1 original space for each participant (Insausti et al., 1998; Pruessner et al., 2000, 2002; Kivisaari et al., 2013; Frankó et al., 2014), including the PRC, entorhinal cortex (EC), and PHC (Fig. 3). The PRC stretches along the anterior–posterior axis from 2 mm anterior to the first coronal slice in which gray matter occurs in the limen insulae to 3 mm posterior to the most posterior coronal slice containing the apex of the intralimbic gyrus. The medial and lateral border of the PRC relies on the number of gyri of Schwalbe and the depth of the collateral sulcus (for a detailed description, see Insausti et al., 1998 and Kivisaari et al., 2013). The anterior border of the EC is indicated by 2 mm posterior to the most anterior slice containing white matter in the limen insulae and the posterior border of the EC is defined as 1 mm posterior to the most posterior slice in which the apex of the intralimbic gyrus occurs. The medial border of the EC is defined as the shoulder of the superomedial bank of the parahippocampal gyrus and the lateral border of the EC resides next to the PRC

Figure 3. Segmentation of parahippocampal subfields (PRC, EC, and PHC) in T1 images for one participant. The original T1-weighted structural images are shown with (A, C) or without (B, D) the ROIs illustrated. The ROIs were manually drawn in the individual T1 original space. The bottom-left index for each row represents the approximate distance of each slice from the anterior commissure ($y = 0$ in Talairach coordinates).

(Insausti et al., 1998; Kivisaari et al., 2013). The PHC starts anteriorly at the coronal slice after the posterior border of the PRC and ends posteriorly when the pulvinar disappears (Kivisaari et al., 2013). The medial border of the PHC is equivalent to the medial border of the parahippocampal gyrus and the lateral border depends on the depth of the colateral sulcus similarly to the one of the PRC as aforementioned. The parahippocampal ROIs were finally resampled to the EPI resolution for the ROI analysis.

The drawn subregions of the MTL were used for the ROI analysis in their original individual space. In addition, the subregions were separately averaged across the participants and combined as the MTL mask. The MTL mask was only used to constrain the MTL subregions in the results of voxelwise analysis (as shown in Figs. 5A, 6A, 7A, and 8A) and to calculate the SVC on a group level. Note that due to lower spatial resolution of the EPI sequence and smoothing application, the MTL subregions, including the subfields of the hippocampus, could not be well differentiated in the voxelwise analysis. The precise activation of the MTL subregions (i.e., CA1, DG/CA3, PRC, PHC) was shown in the ROI analysis.

Results

Behavioral results

During the encoding phase, the participants judged the pairs of objects with high accuracy (0.98 ± 0.02). There were significant effects of the encoding condition for the accuracy ($F_{(2,54)} = 5.55$, $p = 0.007$, $\eta^2 = 0.18$) and reaction times (RTs) ($F_{(2,54)} = 30.78$, $p < 0.001$, $\eta^2 = 0.53$). The “different” pairs were judged more accurately (0.99 ± 0.01 , P 's < 0.03) and quickly (1.20 ± 0.19 s, $p < 0.001$) than the other two conditions; the “same” (0.98 ± 0.02 , 1.56 ± 0.35 s) had comparable accuracy ($p = 1.0$) but slower RTs ($p = 0.06$) than the “similar” (0.98 ± 0.02 , 1.44 ± 0.26 s) condition.

For the corrected recognition, there was a significant effect of encoding condition ($F_{(2,54)} = 23.23$, $p < 0.001$, $\eta^2 = 0.46$). Further analysis showed that memory performance was the highest for the “same” condition, followed by the “similar” condition, and finally the lowest for the “different” condition ($p < 0.01$) (Fig. 4A). In addition, memory accuracy decreased over time ($F_{(1,54)} = 58.99$, $p < 0.001$, $\eta^2 = 0.69$). The interaction between encoding condition and retention interval was not significant ($F_{(2,54)} = 1.322$, $p = 0.28$, $\eta^2 = 0.05$). The results suggested that after discriminative learning of the “same” and “similar” pairs, the participants had better discrimination of detailed information of the objects, and this effect remained for 1 week. This

memory enhancement was consistent with a previous finding (Zhou et al., 2018).

The Hit rate was higher for the “same” and “similar” condition than the “different” condition ($p < 0.01$), but the Hit rate in the “same” and “similar” conditions did not differ ($F_{(2,54)} = 41.92$, $p < 0.001$, $\eta^2 = 0.61$) (Fig. 4B). The Hit rate decreased over time ($F_{(1,54)} = 19.86$, $p < 0.001$, $\eta^2 = 0.42$) and the interaction between condition and retention interval was not significant ($F_{(2,54)} = 2.26$, $p = 0.11$, $\eta^2 = 0.08$). For the FA rate, there was a significant effect of encoding condition ($F_{(2,54)} = 17.89$, $p < 0.001$, $\eta^2 = 0.39$), as the FA rate was higher for the “similar” condition than for the other two conditions ($p < 0.01$), but comparable for the “same” and “different” condition ($p = 1.0$). The effects of retention interval and the interaction were not significant ($p > 0.05$) (Fig. 4D). As both Hit and FA rates were higher for the “similar” than for the “different” condition, the results suggest that presenting two similar objects lead to more generalized representation of the object (Reagh and Yassa, 2014) and, at the same time, the detailed representation was strengthened, as shown by stronger memory performance in corrected recognition.

For the accuracy of contextual memory, it was significantly higher than chance level (0.33) for the “similar” conditions at two retention intervals ($p < 0.01$), but only higher than chance level for the “same” and “different” conditions at 20 min interval ($p < 0.01$). There was a significant effect of encoding condition ($F_{(2,52)} = 13.36$, $p < 0.001$, $\eta^2 = 0.33$), as the contextual memory was best for the “similar” condition ($p < 0.001$) and comparable for the “same” and “different” conditions ($p = 0.75$) (Fig. 4C). In addition, the contextual memory decreased significantly over time ($F_{(2,52)} = 189.00$, $p < 0.001$, $\eta^2 = 0.88$). The interaction between encoding condition and interval was not significant ($F_{(2,52)} = 2.20$, $p = 0.31$, $\eta^2 = 0.05$). The results suggest that discriminative learning of similar objects enhanced the contextual memory and remained for 1 week.

Hippocampus and PRC were dissociated when encoding different types of object pairs

We first looked at the MTL activation during encoding of different types of object pairs. The voxelwise analysis showed a significant effect of encoding condition in the hippocampus, PRC and PHC. When the “same” and “different” conditions were compared, the bilateral hippocampus (left: $-24, -18, -10$, $t_{(27)} = 4.03$, $p < 0.001$; right: $21, -20, -15$, $t_{(27)} = 3.80$, $p < 0.005$; $32, -17, -10$, $t_{(27)} = 2.94$, $p < 0.01$) and the left PHC ($-29, -33, -16$, $t_{(27)} = 5.12$, $p < 0.001$) showed significantly stronger activation for the “different” condition (Fig. 5A, left). When the “similar” and “different” conditions were compared, the activations of the right PRC ($27, -6, -26$, $t_{(27)} = 4.21$, $p < 0.001$) (Fig. 5A, middle) and right PRC/occipitotemporal cortex ($37, -10, -20$, $t_{(27)} = 3.57$, $p < 0.001$) were significantly stronger for the “similar” condition. When the “similar” and “same” condition were compared, the right PRC ($30, -2, -34$, $t_{(27)} = 3.55$, $p = 0.002$), PHC (left: $-29, -35, -18$, $t_{(27)} = 4.01$, $p < 0.001$; right: $27, -33, -18$, $t_{(27)} = 3.93$, $p < 0.001$) and left PRC/occipitotemporal cortex ($-35, -13, -18$, $t_{(27)} = 4.52$, $p < 0.001$) showed significant stronger activation for the “similar” condition (Fig. 5A, right).

The ROI analysis demonstrated similar findings (Fig. 4B). For the right CA1 ($F_{(2,54)} = 4.51$, $p = 0.01$, $\eta^2 = 0.13$) and right DG/CA3 ($F_{(2,54)} = 3.58$, $p = 0.04$, $\eta^2 = 0.12$), the ANOVA showed a significant effect of encoding condition. Further analysis showed the signal changes were stronger for the “different” condition than the “same” conditions ($p < 0.05$). The left CA1

Figure 4. Behavioral results. The Hit-FA rate (**A**) and Hit (**B**) rate were higher for the “similar” and “same” conditions than for the “different” condition in the recognition task. The contextual memory was higher for the “similar” condition than the other two conditions (**C**). The FA rate was also higher for the “similar” condition than the other two conditions (**D**). Error bars indicate SEM. Asterisks represent significant differences between the two conditions ($p < 0.05$).

Encoding

Figure 5. MTL activation when different types of object pairs were encoded. For both voxelwise analysis (**A**) and ROI analysis (**B**), the left PRC elicited stronger activation for discriminating similar (vs different or same) pictures, whereas the activation in the bilateral hippocampus was strongest for discriminating two different (vs same) pictures. The left PHC also showed significant activation when the two different pictures were presented. The left brain is on the left coronal side. The warm colors in the brain represent stronger activation for the former condition in each contrast, and the cold colors represent the opposite. Error bars indicate SEM. Asterisks represent significant differences between the two conditions ($p < 0.05$); “A” represents marginal significant differences ($p < 0.10$).

Item-Dm effect

Figure 6. MTL activation for the item-Dm effect by voxelwise analysis (**A**) and ROI analysis (**B**, **C**). The PHC and PRC showed a significant effect of encoding condition and the interaction (**A**, **B**). Their activations were mainly shown at the 1-week interval (**A**, right, **C**). The left brain is on the left coronal side. The warm colors in the brain represent stronger activation for the former condition in each contrast, and the cold colors represent the opposite. Error bars indicate SEM. Asterisks below the x-axis represent significant activation above chance level and those above the bars represent a significant difference between the two conditions ($p < 0.05$).

and left DG/CA3 showed similar trends for the effect of encoding condition (F 's < 2 , $p \geq 0.15$), with stronger activation for the “different” than the “same” conditions ($p = 0.11$ for the left CA1 and $p = 0.03$ for the left DG/CA3).

For the left PRC, there was a significant effect of encoding condition ($F_{(2,54)} = 5.68$, $p = 0.006$, $\eta^2 = 0.17$). Further analysis showed that the signal change was stronger for the “similar” than the other two conditions ($p < 0.05$) (Fig. 5B). For the left PHC, the ANOVA showed a significant effect of encoding ($F_{(2,54)} = 4.09$, $p = 0.02$, $\eta^2 = 0.13$). Further analysis showed that the signal change was weaker for the “same” than the other two conditions ($p < 0.05$) (Fig. 5B). The right PRC showed a trend for the effect of encoding condition ($F_{(2,54)} = 1.88$, $p = 0.16$, $\eta^2 = 0.07$), with stronger activation for the “similar” condition than the other two ($p = 0.07$) (Fig. 5B). The right PHC ($F_{(2,54)} = 3.73$, $p = 0.10$, $\eta^2 = 0.08$) showed stronger activation for the “similar” condition than the “same” condition ($p = 0.05$).

Therefore, the results suggested that the PRC is more involved in discriminating similar (vs same/different) pictures, whereas the hippocampus is more involved in discriminating two different (vs same) pictures.

PRC and PHC predicted the item-Dm effect for the “same” and “similar” conditions

When the Hit–Miss was calculated as the item-Dm effect, the voxelwise analysis showed a significant effect of encoding condition in the right PHC (35 , -36 , -7 , $F_{(1,27)} = 9.54$, $p < 0.001$) (Fig. 6A, left). There was a significant interaction between encod-

ing condition and retention interval in the right PRC (26 , -6 , -26 , $F_{(2,54)} = 6.39$, $p = 0.005$) and the right PHC (22 , -38 , -7 , $F_{(2,54)} = 7.67$, $p < 0.01$) (Fig. 6A, middle). Further analysis showed that at 1 week (Fig. 5A, right), there was stronger activation in the right PRC (28 , -7 , -26 , $t_{(27)} = 3.22$, $p < 0.01$) and PHC/fusiform gyrus (left: -30 , -38 , -5 , $t_{(27)} = 3.12$, $p < 0.01$; right: 31 , -36 , -5 , $t_{(27)} = 3.59$, $p < 0.001$) for the “similar” (vs “different”) condition (Fig. 6A, right). There was also stronger activation in the right PRC (28 , -2 , -36 , $t_{(27)} = 3.89$, $p < 0.001$) and left PHC (-18 , -28 , -12 , $t_{(27)} = 4.22$, $p < 0.001$) for the “same” (vs “different”) condition (Fig. 6A, right). The hippocampus did not show significant main effects or the interaction for the item-Dm effect.

The ROI analysis demonstrated similar patterns for the item-Dm effect. First, the Dm effects (i.e., values of Hit–Miss) were significantly higher than chance level (0) for the “same” and “similar” conditions ($p < 0.05$) but not for the “different” condition at each retention interval ($p > 0.30$) in the bilateral PRC and PHC (Fig. 6B). Second, the right PRC and bilateral PHC showed different item-Dm effect among conditions. For the right PRC, there was a marginally significant interaction between encoding condition and time interval ($F_{(2,54)} = 2.82$, $p = 0.07$, $\eta^2 = 0.10$). Further analysis showed that at 1 week, the signal change was stronger for the “same” and “similar” conditions versus “different” condition ($p < 0.05$). For the PHC, there were significant interactions between condition and time interval (left, $F_{(2,54)} = 3.75$, $p = 0.03$, $\eta^2 = 0.12$; right: $F_{(2,54)} = 4.40$, $p = 0.02$, $\eta^2 =$

Figure 7. MTL activation for the lure-Dm effect by voxelwise analysis (**A**) and ROI analysis (**B**). The PHC showed significant effect of encoding condition (**A**, left). Their activations predicted subsequent lure memory for the “similar” than the “different” (**A**, right, **B**) condition. The left brain is on the left coronal side. The warm colors in the brain represent stronger activation for the former condition in each contrast and the cold colors represent the opposite. Error bars indicate SEM. “^” symbols below the x-axis represent marginal significant activation above chance level ($p < 0.10$). Asterisks above the bars represent significant differences between the two conditions ($p < 0.05$) and “^” symbols here represent marginal significant differences ($p < 0.10$).

0.15). Further analysis showed that the signal changes were stronger for the “same” and “similar” conditions versus “different” condition at 1 week ($p < 0.05$) (Fig. 6C). The results of both voxelwise and ROI analyses suggested that the right PRC and PHC are involved in predicting subsequent item memory at 1 week of “same” and “similar” objects.

PHC predicted the lure-Dm effect for the “similar” condition

When the FA-CR was calculated as the lure-Dm effect, for the voxelwise analysis, there was a significant effect of encoding condition in the bilateral PHC (left: $-32, -28, -16$, $F_{(2,54)} = 7.99$, $p < 0.001$; right: $32, -37, -10$, $F_{(2,54)} = 9.02$, $p < 0.001$. Both uncorrected) (Fig. 7A, left). Simple comparisons showed that the activation in the right PHC ($29, -23, -20$, $t_{(27)} = 3.31$, $p < 0.005$; $32, -37, -12$, $t_{(27)} = 4.13$, $p < 0.001$) was stronger for the “similar” than the “different” condition (Fig. 7A, right).

For the ROI analysis, the results showed that the activation in the left PHC ($p = 0.07$) and right PRC ($p = 0.06$) was higher than chance level (0) for the “similar” condition (Fig. 7B). The activation in other ROIs was at chance level for each condition ($p > 0.20$). The ANOVA results showed a main effect of encoding condition in the left PHC ($F_{(2,54)} = 4.46$, $p = 0.03$, $\eta^2 = 0.14$). Further analysis showed that its activation was higher for the “similar” condition than the other two conditions ($p < 0.05$). The activation of the right PRC showed a nonsignificant encoding effect ($F_{(2,54)} = 1.66$, $p = 0.20$, $\eta^2 = 0.06$), although its activation was stronger for the “similar” than the “different” condition ($p = 0.08$). The activation of the right PHC showed a marginal significant encoding effect ($F_{(2,54)} = 2.77$, $p = 0.07$, $\eta^2 = 0.09$), with stronger activation for the “similar” than the “different” condition ($p = 0.02$). There were no significant interactions between condition and interval for each ROI (F 's < 1 , $p >$

0.40). The results suggest that the PHC may be involved in predicting generalized item memory in the “similar” condition. The PRC was involved in item-Dm effect but was statistically weaker in the lure-Dm effect, which indicated that it is more important for establishing specific memory representation for the pictures in the “similar” condition. We should also note that, because all of the lure pictures were not seen by the participants during encoding, the lure-Dm effect is a little different from the typical Dm effect. It is necessary to explore the neural basis of the lure pictures being called “old” during memory retrieval.

DG/CA3 predicted the context-Dm effect for the “similar” condition

For the context-Dm effect, the voxelwise ANOVA showed a significant effect of encoding condition in the hippocampus (left: $-24, -17, -12$, $F_{(2,52)} = 10.20$, $p < 0.001$; right: $32, -21, -10$, $F_{(2,52)} = 4.80$, $p = 0.01$, uncorrected) (Fig. 8A, left). Further analysis showed that its activation was stronger for the “similar” condition than the “different” (left: $-30, -20, -12$, $t_{(26)} = 3.52$, $p < 0.001$; right: $32, -18, -13$, $t_{(26)} = 3.05$, $p = 0.005$) and “same” (left: $-22, -15, -13$, $t_{(26)} = 3.69$, $p < 0.001$) ones (Fig. 8A, right). It suggested that the hippocampal activation could predict subsequent stronger contextual memory in the “similar” condition.

The ROI analysis demonstrated similar patterns and further identified the role of the DG/CA3 in predicting the context-Dm effect for the “similar” condition. First, in the left and right DG/CA3, the context-Dm effects (i.e., context correct – context incorrect) were significantly higher than chance level (0) for the “similar” condition ($p < 0.05$), but not for the “same” and “different” conditions ($p > 0.40$) (Fig. 8B). The context-Dm effects were higher than chance level in the left PRC ($p = 0.05$) and right

Figure 8. MTL activation for the contextual-Dm effect by voxelwise analysis (**A**) and ROI analysis (**B**). The bilateral hippocampus showed stronger activation for the “similar” than for the other two conditions. The activation in the bilateral DG/CA3 was significantly above chance for the “similar” condition. The left brain is on the left coronal side. The warm colors in the brain represent stronger activation for the former condition in each contrast, and the cold colors represent the opposite. Error bars indicate SEM. Asterisks below the x-axis represent significant activation above chance level. Asterisks above the bars represent significant differences between the two conditions ($p < 0.05$), and “^” symbols here represent marginal significant differences ($p < 0.10$).

PHC ($p = 0.06$) for the “different” condition. No other MTL subregions showed significant context-Dm effects ($p > 0.10$).

Second, there were significant effects of encoding condition in the bilateral DG/CA3 (left: $F_{(2,52)} = 5.03$, $p = 0.01$, $\eta^2 = 0.16$; right: $F_{(2,52)} = 4.02$, $p = 0.03$, $\eta^2 = 0.13$). Further analysis showed that the context-Dm effect was stronger for the “similar” than the “same” ($p = 0.02$ in the left and $p = 0.09$ in the right) and “different” ($p < 0.05$) conditions in the bilateral DG/CA3 (Fig. 8B). There were no significant condition differences for the context-Dm effect in the bilateral PRC and PHC ($p > 0.40$). It suggested that the DG/CA3 activation predicts subsequent contextual memory after discriminative learning of similar objects.

Discussion

The novelty of the study was that the PRC and the hippocampus were functionally dissociated in discriminative learning of “similar” and “different” objects and in predicting subsequent item and contextual memories of similar objects. During encoding, the PRC was activated when the two similar pictures were compared and its activation predicted subsequent memory for the pictures in the “same” and “similar” conditions. In contrast, the hippocampus was activated when the two different objects were discriminated, and the activation of DG/CA3 predicted subsequent contextual memory for the “similar” condition. These results suggested that the PRC and hippocampus differentially contribute to representations of item and contextual memories during discriminative learning.

PRC and PHC in discriminative learning and predicting subsequent item memory

During encoding, the PRC was more involved in discriminating between two similar objects. The PRC is the final region in the ventral visual system. It receives projections from the lateral EC and then connects to the hippocampus. Converging evidence from lesion (Barense et al., 2005; Buckley and Gaffan, 2006; Lee et al., 2006) and neuroimaging (Lee et al., 2006; Barense et al., 2010; Clarke and Tyler, 2014; McLelland et al., 2014) studies has suggested that the PRC is important for visual object discrimination when objects are simultaneously presented (for reviews, see Murray and Richmond, 2001; Bussey and Saksida, 2005; Murray et al., 2007; Graham et al., 2010). In the service of object discrimination, the PRC resolves the interference between similar objects and associates different views of objects and their various nonvisual attributes (e.g., smell, texture), thereby binding the various attributes of an object into a unified representation.

The activation of the PRC was also related to subsequent item memory of the “same” and “similar” (vs “different”) objects. The PRC could thus be regarded as a region implicated in pattern separation (Burke et al., 2010; Yassa and Stark, 2011; Leal and Yassa, 2018; Miranda and Bekinschtein, 2018) of two similar objects when they are simultaneously presented. Pattern separation refers to the ability to discriminate among similar experiences, thus they are stored in a distinct, nonoverlapping representations (Yassa and Stark, 2011). During discriminative learning, the two

similar objects could be well distinguished and remembered at later time. In this case, this paradigm reflects pattern separation and the PRC is important for distinctive and accurate memory of the objects.

Likewise, the activation of the PHC predicted subsequent item memory of objects in the “same” and “similar” conditions (LaRocque et al., 2013). As the PHC is more associated with processing spatial–contextual information for the objects (Staresina et al., 2011; Mormann et al., 2017), the results suggested that discriminating both detailed and spatial features of similar objects is important for their subsequent memory. In addition, the PHC activation predicted that a lure object was recognized as an old object for the “similar” condition. This explained the behavioral results that the FA rate was higher for the “similar” condition than the other two conditions and was consistent with the view that presenting similar objects induces generalized representation for the objects (Reagh and Yassa, 2014).

The item-Dm effects on the PRC and PHC were significant at 1 week interval. It is unclear why the item-Dm effect was not shown at 20 min in the MTL regions, although the behavioral performance was also higher for the “similar” and “same” conditions than for the “different” condition at 20 min. One possible reason is that at 20 min, regions other than the MTL (Wais et al., 2018) may be responsible or interact with the MTL for the distinctive representations because it takes time to resist from similar interference, especially with short delays (Sadeh et al., 2014). Further studies are needed to address this issue by determining to what extent other regions such as the parietal cortex (Lee et al., 2018) and prefrontal cortex are involved in discriminative learning and subsequent memory retrieval.

Hippocampus in discriminative learning and predicting subsequent contextual memory

During discriminative learning, the hippocampus showed stronger activation for the “different” than for the “same” condition. This suggested that the hippocampus is responsive to distinguishing two objects from different categories. Similarly, in a study by LaRocque et al. (2013), when single objects were presented in different runs, the PRC and PHC showed a higher similarity for within-category objects, whereas the hippocampus showed a higher similarity for cross-category objects.

Our behavioral results showed that discriminating two objects in the “similar” condition enhanced subsequent contextual memory and the fMRI results showed that the activation of the DG/CA3 predicted this enhancement. The hippocampus is critical for encoding and retrieving information related to contextual sources and relationships between stimuli (Davachi, 2006; Eichenbaum et al., 2007; Mayes et al., 2007; Squire et al., 2007). During discriminative learning, although not explicitly, the relations between the objects and their contextual information were established by the involvement of the hippocampus after the two similar objects were simultaneously presented. In particular, recent studies have shown that the DG/CA3 is more responsive to vividly retrieving contextual memory than other subregions of the hippocampus (e.g., CA1) (Chadwick et al., 2014; Dimsdale-Zucker et al., 2018).

There was no significant difference in the hippocampus during encoding in the “similar” and “same” conditions. The hippocampal activation could not predict item memory for the “similar” condition either. Some studies showed that the hippocampus is reactivated when a similar stimulus is presented (Schlichting and Preston, 2014; Horner et al., 2015; van den Honert et al., 2016) and its activation is stronger when similar (vs

repeated) pictures are recognized (Kirwan and Stark, 2007; Bakker et al., 2008). Nevertheless, we consider that our findings on the hippocampus are not contradictory to the previous ones. First, in those previous studies, stimuli were presented separately (Kirwan and Stark, 2007; Bakker et al., 2008; Lacy et al., 2011; Berron et al., 2016), whereas in our study, the two objects were presented simultaneously. When the stimuli are presented separately, the hippocampus may be critical for reactivating previous similar representation to compare between them (Schlichting and Preston, 2014; Horner et al., 2015; van den Honert et al., 2016; Chanales et al., 2017) and minimizing interference between similar stimuli (Chadwick et al., 2014; Berron et al., 2016). However, this step of overcoming representational gaps between episodic elements (e.g., two objects, temporal or spatial features) may not be necessary when the two objects are presented as a pair. In this case, the elaborative processing mediated by the PRC is dominant to overcome the interferences and establish a distinctive representation for the objects.

Second, our study investigated the encoding process, whereas the previous studies mainly focused on the retrieval process, such as recognition (Kirwan and Stark, 2007; Bakker et al., 2008; Lacy et al., 2011; Reagh et al., 2014; Berron et al., 2016; Dimsdale-Zucker et al., 2018). It is possible that the hippocampus is differentially involved in encoding and retrieval processes for discriminating similar objects. Animal studies have shown that hippocampal lesions before learning do not cause significant impairments in contextual discriminative, but hippocampal lesions after learning lead to limited recent memory impairments (Frankland et al., 1998; McHugh et al., 2007; Wang et al., 2009).

Division of labor in the MTL during discriminative learning

Our results provide clear evidence on the neural mechanisms of discriminative learning and highlight the importance of the PRC and hippocampus in successfully processing different types of objects when they were simultaneously presented. The functional dissociation between the PRC and hippocampus has been demonstrated in previous studies when memories of an object and its context (Davachi et al., 2003; Ranganath et al., 2004; Montaldi et al., 2006), intra-item and item-context associations (Staresina and Davachi, 2009), and within-domain and across-domain associations (Mayes et al., 2007) are tested. Through discriminative learning of similar objects, the PRC is not only more involved in processing similar (vs different) pairs (Bussey and Saksida, 2005; Graham et al., 2010), but is also more involved in successful encoding of objects in the “similar” condition when they are presented simultaneously. In contrast, the hippocampus is more involved in successful encoding of contextual information of the objects in the “similar” condition. Their dissociation in discriminative learning of similar objects provided further evidence that the two MTL subregions may mediate different underlying processes. The PRC contributes to episodic memory as a stimulus-based representation, whereas the hippocampus supports associative memory from different information (Brown and Aggleton, 2001; Davachi, 2006; Eichenbaum et al., 2007; Mayes et al., 2007).

Conclusions

Using high-resolution fMRI and focusing on the MTL, we found dissociations of the PRC and hippocampus in predicting subsequent item and contextual memories of “similar” objects. The activations of the PRC were stronger for the “similar” than “different” condition during encoding, and its activation predicted the subsequent item memory in the “similar” condition. How-

ever, the DG/CA3 activation predicted the subsequent contextual memory. These results suggested that through discriminative learning, a unitized representation could be formed by the PRC, causing the details to be remembered better. However, the hippocampus is still involved in establishing the relationship between the item and its contextual information.

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