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# The influence of item familiarization on neural discriminability during associative memory encoding and retrieval

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# ABSTRACT

Associative memory requires one to encode and form memory representations not just for individual items, but for the association or link between those items. Past work has suggested that associative memory is facilitated when individual items are familiar rather than simultaneously learning the items and their associative link. The current study employed multivoxel pattern analyses (MVPA) to investigate whether item familiarization prior to associative encoding affects the distinctiveness of neural patterns, and whether that distinctiveness is also present during associative retrieval. Our results suggest that prior exposure to item stimuli impacts the representations of their shared association compared to stimuli that are novel at the time of associative encoding throughout most of the associative memory network. While this distinction was also present at retrieval, the overall extent of the difference was diminished. Overall the results suggest that stimulus familiarity influences the representation of associative pairings during memory encoding and retrieval, and the pair-specific representation is maintained across memory phases irrespective of this distinction.

# 1. Introduction

Associative memory requires the binding of two or more items into a unified representation. Based upon the multiple inputs and increased task demands, associative memory constitutes a more difficult process compared to item memory (Castel & Craik, 2003; Gold, Hopkins, & Squire, 2006; Kilb & Naveh-Benjamin, 2007; Naveh-Benjamin, 2000; Overman & Becker, 2009; Yonelinas, 1997; Yonelinas & Parks, 2007). Over the years, many strategies have been examined to try to reduce associative memory demands. To this end, studies that have used item and associative repetition during encoding have suggested that extended practice with individual stimuli, prior to associative encoding, leads to enhanced associative memory, compared to when item and associative information needs to be simultaneously encoded (Dennis, Turney, Webb, & Overman, 2015; Kilb & Naveh-Benjamin, 2011; Light, Patterson, Chung, & Healy, 2004; Overman & Becker, 2009; Overman & Stephens, 2013). Yet, it is unclear whether this familiarization leads to differential mnemonic representations of associative information across encoding conditions, and whether this associative advantage is specific to encoding or has carry over effects at retrieval as well. The current study will explore these questions using a functional MRI-based pattern classification approach.

The fact that prior exposure to, and familiarity with, stimuli leads to differential processing and behavior is evident from a large number of studies including visual working memory (Blalock, 2015; Hollingworth, 2015; Jackson & Raymond, 2008; Ngiam, Khaw, Holcombe, & Goodbourn, 2019), change detection tasks (Buttle & Raymond, 2003; Curby & Gauthier, 2007; Kochs, Kohler, Merz, & Sterzer, 2017), priming (Buckner & Koutstaal, 1998; Schacter, Wig, & Stevens, 2007; Vuilleumier, Schwartz, Clarke, Husain, & Driver, 2002), and episodic memory (Bird, Davies, Ward, & Burgess, 2011: Robin & Moscovitch, 2014: Wang, Mao, Li, Lu, & Guo, 2016). The benefits of familiarity in associative memory are observed in research showing that exposing people to individual item information prior to associative encoding results in greater associative hit rates relative to when the initial presentation of item information occurs during associative encoding (Dennis et al., 2015; Earles & Kersten, 2008; Kilb & Naveh-Benjamin, 2011; Lee, Kim, & Yi, 2020). Neuroimaging studies have also suggested that differences in preexperimental item familiarity lead to differential neural recruitment during episodic encoding (Dennis et al., 2015; Kremers et al., 2014; MacKenzie, Alexandrou, Hancock, & Donaldson, 2018; Nie et al., 2014; Vannini, Hedden, Sullivan, & Sperling, 2013). For example, repeated

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presentation of item-item pairs has been associated with activation reductions in stimulus processing regions and activation increases in parietal cortices (Kremers et al., 2014; Vannini et al., 2013), as well as dissociable ERP signals within parietal cortex (MacKenzie et al., 2018; Nie et al., 2014).

Additionally, neuroimaging work from our lab investigating the role of item familiarity within associative memory (Dennis et al., 2015), also shows that prior familiarization with items results in reduced BOLD activity across brain regions involved in item-specific processing and item-item binding, including occipitotemporal cortex, prefrontal cortex (PFC) and medial temporal lobe (MTL) regions including the parahippocampal cortex (PHC) and hippocampus (HC). Prior familiarization of items was also accompanied by increased activity in regions supporting integration of information/associative integration, including bilateral parietal cortex and precuneus, and is correlated with associative memory success. Together, this behavioral and neuroimaging evidence indicates that prior experience with individual items can improve associative encoding by reducing the demand on cognitive resources incurred by simultaneously encoding both item and associative information, potentially by facilitating the binding of item representations and reducing the attentional load of encoding novel stimuli (Dennis et al., 2015; Poppenk & Norman, 2012).

Through the use of multivariate analyses, research has also begun to answer questions about how familiarity of stimuli impacts neural representations. A number of studies using multivoxel pattern analyses (MVPA) have shown that familiarity of a stimulus can be distinguished from unfamiliar stimuli, such as for faces (Martin, McLean, O'Neil, & Kohler, 2013; Natu & O'Toole, 2015; Rissman, Greely, & Wagner, 2010), places (Kafkas et al., 2017; Martin et al., 2013), and even general knowledge information (Wang, Brashier, Wing, Marsh, & Cabeza, 2018). For example, Martin et al. (2013) showed that regions within the MTL, specifically perirhinal cortex (PrC) and PHC, could distinguish the perceived familiarity of faces, buildings, and chairs from that of novel objects within each category. By excluding recollection-related memory responses from their analysis the authors demonstrated that this distinction was specific to item familiarity. Similarly, Natu & O'Toole (2015) found that regions along the ventral-temporal pathway exhibited neural discriminability with respect to learned, familiar faces versus novel faces during a memory retrieval test. Taken together, the foregoing results suggest that patterns of neural activity can be discriminated based on the degree of familiarity of one's explicit memory.

The current analysis aims to expand upon previous work by examining whether such familiarity-based neural distinctiveness is present when the brain in engaged in cognitive operations outside of direct tests of memory retrieval. That is, while differences in prior familiarity are evident in the level of activation observed in BOLD contrasts and are associated with neural distinctiveness during explicit memory retrieval, it remains to be determined (1) whether prior familiarization of items results in distinctions at the level of neural representations between familiarized and novel associative mnemonic information, and (2) whether these differences are present across both encoding and retrieval phases of memory processing. By elucidating whether an item's familiarity affects memory representations across both encoding and retrieval phases of associative memory we can gain a deeper understanding of factors that support successful associative encoding, including those that lead to enhanced memory success.

To test the foregoing questions, the current study aims to evaluate the effect of item familiarity on both encoding and retrieval phases of associative memory using MVPA analyses applied to a previously collected dataset from our lab (Dennis et al., 2015). Extending our previous univariate analyses described above, we employ a multivariate approach to examine whether patterns of neural activity during associative encoding are distinguishable as a function of whether the items included in the associative pair were familiar prior to associative encoding or were novel at the time of associative encoding. We then investigate the relationship between the MVPA classification accuracy of familiarized and unfamiliarized pairs, separately, with overall memory performance (*d'*). Critically, we also sought to determine whether any uniqueness in encoding activation patterns between conditions is also present during associative retrieval. Based on prior univariate results showing both suppression and enhancement of neural activity associated with item familiarization during encoding, we hypothesize that patterns of neural activity for familiarized pairings will be uniquely discriminable from that of unfamiliarized pairings across much of the associative memory network, including regions of the MTL, PFC, occipital, and parietal cortices. We further predict that this discriminability will be related to behavioral memory measures, whereby individuals demonstrating more distinct neural patterns between the two conditions will show greater memory success, reflective of a familiarity benefit. We will openly investigate whether this difference also carries over to retrieval.

# 2. Methods

# 2.1. Participants

Twenty-two participants were recruited from The Pennsylvania State University community. Participants were screened for histories of neurological and psychological disorders, learning disabilities, and drug/substance abuse. Two participants were excluded from the present analyses due to failure to complete the task (one) and failure to follow the task instructions (one). Thus, the present analysis included 20 righthanded participants (12 female) between the ages of 18 and 29 years old (mean age = 23 years, SD = 3.07). Of the 20 participants, 16 identified as White; 2 Hispanic; 1 Asian/Pacific Islander; and 1 Black. All participants provided written informed consent approved by the Institutional Review Board of The Pennsylvania State University. Monetary compensation was given for their participation.

# 2.2. Stimuli

[The stimuli description and task procedures were detailed in our previously published paper reporting univariate results of the study (Dennis et al., 2015). They are reprinted here for completeness.] The stimuli consisted of 220 color photographs of faces (50% male, 50% female) and 220 color photographs of scenes. The face stimuli consisted of both male and females faces, each exhibiting a neutral expression, taken from the following online databases: the Color Facial Recognition Technology (FERET) database (Phillips, Moon, Rizvi, & Rauss, 2000; Phillips, Wechsler, Huang, & Rauss, 1998), the adult face database from Denise Park's lab (Minear & Park, 2004), the AR face database (Martinez & Benavente, 1998), and the FRI Computer Vision Laboratory Face Database (Solina, Peer, Batageli, Juvan, & Kovac, 2003). The scene stimuli consisted of outdoor and indoor scenes collected from an Internet image search. No scene included people or text of any kind. Additionally, with regard to complexity, a requirement for scene choice included a minimum level of complexity such that the scene did not appear to reflect a single object, but was perceived as a 'background setting'. While no formal rating was recorded, this determination was unanimously agreed upon across 3 independent raters. As such, we believe scene stimuli reflect real world "context" conditions while maintaining generally consistent criteria across scenes. Using Adobe Photoshop CS2, version 9.0.2, and Irfanview 4.0 (www.irfanview.com), we edited the face stimuli to a uniform size (320  $\times$  240 pixels) and background (black), and the scene stimuli were standardized to 576 imes432 pixels. During the item familiarization phase (prior to the associative memory task), 90 faces and 90 scenes were presented centrally on the screen one at a time to each participant. Item retrieval was tested following the initial training with a yes/no recognition task including the original 90 faces and scenes and 40 new faces and scenes. Following this, an associative encoding task was completed within the fMRI environment. This task incorporated 195 face-scene pairs (90 pairs of familiarized items from the previous item familiarization phase and 105 pairs of unfamiliarized, novel items)<sup>1</sup>. All pair types were randomly presented against a black background with the face positioned to the left of center and the scene to the right (see Fig. 1). The associative retrieval task consisted of 220 total trials: 130 encoding pairs (60 familiarized and 70 unfamiliarized pairs) were presented as targets (studied face–scene pairings), and the remaining 65 pairs were randomly recombined as related lures (new face–scene pairings: 30 familiarized, 35 unfamiliarized). Additionally, 25 completely novel face–scene combinations were also presented during retrieval, serving as novel lures.

### 2.3. Task procedure

Item familiarization was completed outside of the scanner, prior to scanning. During this item-encoding phase, each image was presented for 2500 ms, during which time participants were asked to rate the friendliness of the faces and the pleasantness of the scenes (the faces and scenes were studied in alternating blocks). In order to verify that items were indeed learned, item memory was assessed using a yes/no recognition task in which each image was presented for 2500 ms. Again, face and scene memory were tested in separate blocks. (Pilot testing showed that going through this process only once resulted in 75% accuracy across all participants.)

Associative encoding and retrieval were carried out in the fMRI environment. During both associative encoding and retrieval, participants viewed face-scene images projected onto a screen that was viewed through a mirror mounted on the head coil. The associative encoding consisted of five 4-min runs. Although all of the encoding pairs were novel, familiarized pairs consisted of faces and scenes that had previously been studied by the participants (familiarized items) in the itemencoding phase. Unfamiliarized pairs consisted of faces and scenes that were completely novel to the participants (unfamiliarized items; see Fig. 1). The presentation of each pair type was random across all runs. During encoding, each face-scene combination was presented for 3000 ms, during which time participants were asked to rate on a scale of 1-4 how well the face fit with the scene (i.e., how likely it was that the person would live, work, or vacation in the pictured scene). Presentation of each pair type was randomized across the 5 runs. Participants were also informed that an associative memory test would follow.

During associative retrieval, the targets and recombined lures (created by recombining items of the encoded pairs) from both encoding conditions, as well as novel lures (new pairs composed of faces and scenes never previously presented during any phase) were randomly intermixed and displayed for 4000 ms across 5 runs, during which time participants made memory responses using the Remember-Know-New paradigm (Yonelinas, 2002; Yonelinas, Otten, Shaw, & Rugg, 2005; Yonelinas et al., 2007). The participants were specifically alerted to the inclusion of the three different response types, and they were further instructed to respond "remember" if they could remember specific details about the association and the pairing's presentation from the study phase. In addition, participants were instructed to respond "know" if the exact face-scene pair looked familiar, but their memory was lacking any specific details of its prior presentation/association. Finally, participants were told to respond "new" if they believed that the exact face-scene pair had not been presented together during the encoding session (even if the individual items had been presented during the encoding phase). It was further made clear that a rating of "new" should be made even if participants remembered having seen a particular face or scene before,

but had not seen that specific combination before. Retrieval lasted approximately 25 min and consisted of five 5-min runs.

### 2.4. Image acquisition

Images were collected using a Siemens 3 T scanner and a 12-channel head coil. They were acquired using a T1-weighted sagittal localizer to align the scans to the AC–PC line. High-resolution anatomical MPRAGE images were acquired with a 1650-ms repetition time (TR), 2.03-ms echo time (TE), 240-mm field of view (FOV), 256  $\times$  256 matrix, 160 axial slices, and 1-mm slice thickness for each participant. Echoplanar functional images were acquired using interleaved acquisition and a 2500-ms TR, 25-ms TE, 240-mm FOV, 80  $\times$  80 matrix, and 48 axial slices with a 3.0-mm slice thickness, resulting in 3.0-mm isotropic voxels. The angle of acquisition was set approximately perpendicular to the hippocampus, without sacrificing coverage of the frontal lobes.

## 2.5. Data Preprocessing and model estimation

Preprocessing of the fMRI data was carried out using SPM12 (Statistical Parametric Mapping; Wellcome Trust Centre for Neuroimaging, www.fil.ion.ucl.ac.uk/spm). The time-series data were corrected for differences in slice acquisition times and realigned. Slice time correction and realignment were carried out using the first volume of the first run as the reference slice. The high-resolution structural images were coregistered to the standardized Montreal Neurological Institute (MNI) space, and this was applied to all functional images during normalization in order to transform the individual images to standard MNI space. Data was resampled to 2.0-mm isotropic voxels but were not spatially smoothed. Trial-related activity was modeled using a general linear model (GLM) with a stick function corresponding to the trial onsets, convolved with a canonical hemodynamic response function. Each trial was modeled separately, resulting in individual beta maps for all trials of interest for each subject. An additional 6 nuisance regressors were included in each run corresponding to participant motion. Whole-brain beta parameter maps were generated for each trial at encoding and retrieval separately for each subject. In a given parameter map, the value in each voxel represents the regression coefficient for that trial's regressor in a multiple regression containing all other trials in the run and the motion parameters.

# 2.6. Regions of interest

As mentioned previously, regions of interest (ROIs) were selected a priori to use for classification analyses based on their involvement in associative memory and stimulus-specific processing. Specifically, associative memory regions included the inferior occipital cortex (IOC), prefrontal cortex (PFC), angular gyrus (AG), precuneus (PCU), and the MTL broken down into subregions including the hippocampus (HC), entorhinal cortex (ErC) and perirhinal cortex (PrC) (Kim, 2011; Mitchell & Johnson, 2009; Spaniol et al., 2009). Fusiform gyrus (FG) and parahippocampal cortex (PHC) were chosen for their involvement in the processing of faces and places, respectively (Kanwisher, McDermott, & Chun, 1997; Prince, Dennis, & Cabeza, 2009). The AG, PCU, and HC were defined bilaterally using the AAL pickatlas in SPM12 (Tzourio-Mazoyer et al., 2002). The PFC ROI was additionally defined with respect to subregions critical to associative memory processing as identified in metanalyses of memory (Kim, 2011; Maillet & Rajah, 2014), and included the inferior, medial and middle frontal gyri, identified with AAL Pickatlas and combined to form the single PFC ROI. The entorhinal cortex (ErC) region was taken using the Juelich atlas available in FSL (Amunts et al., 2005). As this atlas is probabilistic, the threshold of the region was set to 50% and then binarized to obtain the final mask of the ErC. The PrC region was derived from a mask taken from Holdstock and colleagues (Holdstock, Hocking, Notley, Devlin, & Price, 2009), with the ErC mask being subtracted from this region to

<sup>&</sup>lt;sup>1</sup> Due to a programming error, associative encoding included 15 additional unfamiliar pairs (three per run), which resulted in five additional unfamiliar lures and ten additional unfamiliar targets at retrieval, as compared to the familiarized condition. By default, the CoSMoMVPA toolbox (see Section 2.7) balances trial numbers prior to analysis, and subsequently removed 3 unfamiliar trials per run at random.

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Fig. 1. Encoding-Retrieval Paradigm. (A) During the item familiarization (training) phase, participants study individual face and scene items and then complete an old-new recognition task for those items. (B). During associative encoding, participants are shown pairs of faces and scenes, with 50% of all pairings being comprised of previously seen stimuli (i.e., familiarized) and 50% comprised of new face-scene pairs. During retrieval, participants are shown face-scene pairings viewed at encoding along with novel recombinations of faces & scenes (Figure adapted from Dennis et al., 2015).

eliminate overlapping voxels. Additionally, because the PHC region included large portions of both the ErC and PrC, voxels from these regions were removed from the PHC to prevent overlapping inclusions. All ROIs were defined bilaterally as we had no *a priori* hypothesis regarding laterality. Each ROI was fit to the dataset using the 3dresample function in AFNI (Cox, 1996). The size of each ROI is reported in Supplementary Table 1.

#### 2.7. Multivoxel pattern analyses

All classification analyses were performed using the CoSMoMVPA toolbox (Oosterhof, Connolly, & Haxby, 2016). Given our primary question of determining if regions in the associative encoding network could discriminate between familiarized and unfamiliarized stimuli, separate classification accuracies were computed in all aforementioned ROIs. Specifically, classification analyses were computed using the beta parameter maps for encoding runs separately using a support vector machine (SVM) classifier with a linear kernel using information from all voxels within each ROI (Mumford, Turner, Ashby, & Poldrack, 2012). The training and testing of the classifier followed a standard leave-onerun-out cross-validation procedure, where four runs of the functional data were used to train the classifier and one run were used to test within either encoding or retrieval. Subject-level results were generated from averaging across validation folds from all possible train-data/test-data permutations. To test whether the classifier was accurately able to discriminate between familiarized and unfamiliarized stimuli presentations above chance (50%), a one-tailed one-sample t-test was conducted for accuracy within each ROI for both encoding and retrieval. All significant findings were further confirmed using permutation testing in order to correct for the occurrence of false positives. Specifically, we ran a follow up test that repeatedly randomized the familiarized/unfamiliarized labels and reran the classification analysis on the permuted data. This was done 1000 times for each significant finding to produce a null distribution that simulates the potential accuracy scores that could be obtained if the encoding manipulation had no effect.

In order to examine how the ability to classify brain patterns relates to memory discriminability, we computed separate regression models for each ROI that reached above chance classifications, using hit rate and d' for remember trials only (see below) as the dependent variables predicted by classification accuracy in that ROI. We chose to examine recollection rates as they reflect the strongest signal associated with memory success. We also chose to examine d' as it is a measure of corrected behavior, representing not only accurate encoding and retention of targets, but also discrimination of memory for associations, controlling for errors related to familiarity of lures (false alarms). We conducted a separate regression for each ROI that exhibited significant classification for both familiarized and unfamiliarized recollection hit rates, as well as familiarized and unfamiliarized d'.

# 3. Results

[The behavioral results were reported in a previously published paper reporting univariate results of the encoding portion of the study (Dennis et al., 2015). They are represented here for completeness.]

# 3.1. Behavioral

<u>Item familiarization task</u>: The average hit rates for faces and scenes in the familiarization phase were 0.77 (SD = 0.11) and 0.91 (SD = 0.09), respectively, suggesting that familiarized faces and scenes were successfully learned prior to associative encoding.

<u>Response time results</u>: During the associative-encoding task, participants' speed in making a "goodness-of-fit" rating (see the Methods section) to familiarized-item pairs (M = 1862.34 ms, SD = 152.84) was significantly faster than their speed to unfamiliarized-item pairs (M = 1925.46 ms, SD = 191.12), t(39) = 4.748, p < 0.001. [Despite this difference in the encoding task, participants viewed all images for the same duration (3000 ms) and thus had a similar amount of time to encode associative memory traces]. A similar pattern was found at retrieval, where for "remember" responses participants were also faster to identify familiarized-item pairs as targets (M = 1679.53 ms, SD = 219.35) than to identify unfamiliarized-item pairs as targets (M = 1809.57 ms, SD = 250.23), t(19) = 3.302, p = 0.004. [Again, total trial duration was held constant across conditions (2500 ms)].

<u>Goodness of fit encoding task</u>: The mean goodness of fit encoding ratings for the familiarized pairs was 2.79 (SD = 0.25) and 2.74 (SD = 0.27) for the unfamiliarized pairs. The difference between conditions was not significant (p = 0.2).

Associative memory task: Associative hits and false alarms were identified as "remember" responses to intact face-scene pairs and recombined pairs, respectively, at retrieval. Table 1 reports means and standard deviations (SD) of memory metrics for all response types. Direct comparisons between familiarized-item pairs and unfamiliarizeditem pairs revealed that participants identified familiarized targets as old at a higher rate than unfamiliarized targets (M = 0.65, SD = 0.19, vs. M = 0.44, SD = 0.22, respectively), t(19) = 8.877, p < 0.001, and showed higher rates of false alarms to unfamiliarized lures (M = 0.19, SD = 0.12) than to familiarized lures (M = 0.15, SD = 0.11), t(19) =-2.218, p = 0.039. Participants also showed higher discriminability (measured by d') for familiarized (M = 2.06, SD = 1.64) than for unfamiliarized (M = 0.82, SD = 0.43) item pairs, t(19) = 3.601, p =0.002. A significant difference was found in "remember" responses between hits and false alarms in both the familiarized, t(19) = 12.27, p < 12.270.001, and unfamiliarized, t(19) = 6.89, p < 0.001, conditions. Finally, participants showed significantly reduced rates of false alarms to entirely novel face-scene lures (M = 0.012, SD = 0.045), relative to both familiarized (M = 0.15, SD = 0.11), t(19) = 5.92, p < 0.001, and unfamiliarized lures (M = 0.19, SD = 0.12), t(19) = 7.15, p < 0.001.

# 3.2. Pattern classification of familiarized/unfamiliarized stimuli

We first compared classification accuracy for familiarized versus unfamiliarized stimuli to chance (50%) in each ROI for both the encoding and retrieval task. With regard to the encoding data, the results showed above chance classification in the majority of regions including FG (*M* = 0.520, *t*(19) = 2.45, *p* < 0.05), PFC (*M* = 0.535, *t*(19) = 3.94, *p* < 0.001), AG (M = 0.533, t(19) = 3.351, p < 0.005), and PCU (M =0.560, *t*(19) = 5.45, *p* < 0.001)<sup>1</sup> (Table 2; Fig. 2a). However, the IOC (*M* = 0.526, t(19) = 1.94, p = 0.07), PHC (M = 0.522, t(19) = 1.75, p = 1.75)0.10), PrC (M = 0.500, t(19) = 0.04, p = 0.97), ErC (M = 0.509, t(19) = 0.101.08, p = 0.29), and HC (M = 0.513, t(19) = 1.12, p = 0.27) were not statistically above chance. To investigate the null finding within the MTL regions at encoding, we performed a follow-up analysis using a searchlight within the region to determine if a subsection (e.g., anterior vs. posterior) showed above chance classification. The searchlight analysis followed the same leave-one-out cross-validation procedure performed previously within each ROI. The classifier was trained within each of the foregoing MTL regions (HC, PHC, PrC, ErC) using 3 runs and tested on the left out run. The searchlight was performed using a sphere with a 2 mm radius given the small size of the regions. We again found no significantly above chance classification in any clusters within any of the MTL regions.

Results for the retrieval data showed above chance classification in

#### Table 1

Behavioral Results for Familiarized and Unfamiliarized Tri	als.

	Familiarized		Unfamiliarized		Novel	
	Mean	SD	Mean	SD	Mean	SD
Hits						
Remember	0.65	0.19	0.44	0.27	-	
Know	0.24	0.16	0.22	0.12	-	
False Alarms						
Remember	0.15	0.11	0.19	0.12	0.01	0.05
Know	0.23	0.11	0.25	0.12	0.08	0.09
d Prime (d')						
	0.81	0.46	0.43	0.23	-	

only three regions, the FG (M = 0.531, t(19) = 2.931, p = 0.009), PHC (M = 0.527, t(19) = 2.94, p = 0.009), and PCU (M = 0.550, t(19) = 4.230, p < 0.001)<sup>2</sup> (see Table 2, Fig. 2b). There were no other regions for which classification accuracy was significantly different from chance (all ps > 0.05; Table 2).

# 3.3. Pattern classification and memory performance

Following the discriminability between familiarized and unfamiliarized stimuli found at encoding, we then asked if classifier accuracy was related to memory performance. Given that memory success also depends on overall discriminability, we also chose to examine *d'* in task performance as it normalizes the difference between the hit rate and false alarm rate, speaking directly to memory discriminability within each experimental condition. We computed regressions using recollection *d'* and hit rate for familiarized and unfamiliarized trial types, separately, predicting classifier accuracies within regions with above chance classification. Classification accuracy did not significantly predict *d'* or hit rate for either condition within any ROI for encoding and retrieval (all *ps* > 0.05).

Finally, we sought to determine if there was a bias in classification accuracy driven by any particular subsequent memory response. For this, we separated the classification accuracies for each trial based upon their behavioral response (remember/know/new) for each encoding condition (familiarized/unfamiliarized) and submitted accuracies to a one-way ANOVA using behavioral response as the grouping variable. This was done separately for familiarized and unfamiliarized trials within encoding and retrieval tasks. The results showed no effect of response in any region for either encoding or retrieval classification accuracies (all ps > 0.05).

#### 4. Discussion

The overarching goal of this study was to investigate the influence of item familiarity on neural representations of associative encoding and retrieval. Our analyses identified two critical findings. First, results showed that patterns of neural activity supporting the encoding of familiarized and unfamiliarized item pairs can be reliably differentiated across higher order processing regions within the associative memory network during encoding, yet not within regions in the MTL. Second, only the fusiform gyrus and precuneus continued to demonstrate this distinctiveness during associative retrieval. Building on previous univariate results from this dataset (Dennis et al., 2015), these results suggest that item processing, prior to associative encoding, can influence associative encoding in a unique manner that is also detectable in some regions of the brain at retrieval; however, this discriminability may not be fully carried over to retrieval, suggesting the advantage of item familiarization in associative memory has its greatest benefit to encoding. The results have implications for our understanding of familiarity in memory and principles that guide associative memory processing.

Earlier work has shown that prior familiarity with items can affect performance in cognitive tasks such as working memory, change detection, and episodic memory (e.g., Buttle & Raymond, 2003; Ngiam et al., 2019; Wang et al., 2016). Within the field of associative memory, prior item familiarity has led to increased associative hit rates when the associative pair includes familiar items in novel arrangements compared to the use of novel item pairs (Giovanello, Keane, & Verfaellie, 2006; Kilb & Naveh-Benjamin, 2011; Light et al., 2004), and differences in the extent of neural activation during associative encoding based on item history (Dennis et al., 2015). The current analysis expands on this prior work by showing that patterns of neural activity underlying associative

<sup>&</sup>lt;sup>2</sup> Noted above, we ran a follow up permutation test to confirm all significant classification results. The results provided convergent support for all reported analyses.

#### Table 2

Classification Results for Encoding and Retrieval Tasks.

	Encoding				Retrieval			
ROI	Mean	df	t	р	Mean	df	t	р
Prefrontal Cortex	0.54	19	3.94	<0.001	0.50	19	0.25	0.809
Inferior Occipital Cortex	0.53	19	1.94	0.068	0.52	19	1.55	0.138
Fusiform Gyrus	0.52	19	2.45	0.024	0.53	19	2.93	0.009
Angular Gyrus	0.53	19	3.32	0.003	0.50	19	-0.38	0.710
Precuneus	0.56	19	4.45	< 0.001	0.55	19	4.23	< 0.001
Parahippocampal Cortex	0.52	19	1.75	0.096	0.53	19	2.94	0.009
Hippocampus	0.51	19	1.12	0.27	0.51	19	1.53	0.143
Entorhinal Cortex	0.51	19	1.08	0.293	0.50	19	0.19	0.854
Perirhinal Cortex	0.50	19	0.04	0.972	0.48	19	-1.08	0.294

Note: Bold indicates significance at noted p value.



**Fig. 2.** Classification Results Between Familiarized-Unfamiliarized Trials for Encoding & Retrieval. Classifier accuracy for (a) encoding and (b) retrieval. Anatomical locations for each region of interest can be seen in the middle. Error bars represent SEM. PFC = prefrontal cortex; AG = angular gyrus; PCU = precuneus; FG = fusiform gyrus; IOC = inferior occipital cortex; PHC = parahippocampal cortex; PrC = perirhinal cortex; ErC = entorhinal cortex; HC = hippocampus. \*p < 0.05.

encoding are discriminable throughout higher-order processing regions within the associative encoding network, based on whether the items were familiar or novel to the participant prior to associative encoding. Specifically, the PFC and regions in parietal cortex (AG & PCU) exhibited distinct patterns of neural activity based solely on whether the individual items presented within a pairing were studied prior to associative encoding.

Prior work has linked both parietal and frontal cortices to processing of familiarity. For example, the precuneus has been shown to be responsive to stimulus reactivity (Brodt et al., 2016; Engelmann et al., 2012) and exhibits increased activity when processing familiar information (Dorfel, Werner, Schaefer, von Kummer, & Karl, 2009; Lundstrom, Ingvar, & Petersson, 2005; Yonelinas et al., 2005), including face familiarity (Cloutier, Kelley, & Heatherton, 2011; Gobbini & Haxby, 2006; Lee, Leung, Lee, Raine, & Chan, 2013; Maddock, Garrett, & Buonocore, 2001). With respect to reactivation of previously studied information, experience-related changes within parietal cortex have been detected in as short as one hour (Brodt et al., 2018) and shown to occur after a single stimulus presentation (Brodt et al., 2016). These changes are also predictive of memory for the familiar information. Additionally, areas of angular gyrus and the prefrontal cortex have been linked to judgments and decisions involving familiar images (Kafkas & Montaldi, 2014; Petrides, Alivisatos, & Frey, 2002). The current results build upon this work by showing that these same brain regions are sensitive to the familiarity of items during associative encoding, even when familiar items are presented in configurations different than their original presentation (e.g., pairing with a second stimuli, change in their location on the screen, etc.). Moreover, familiarity-based distinction in lateral parietal cortex and the precuneus at the level of neural representation are consistent with our previous univariate findings showing these parietal areas demonstrate activation differences based on item history (Dennis, et al., 2015). The current results also expand upon this early finding by showing that familiarity-based differences in neural discriminability within the precuneus extend to retrieval as well. This is of note given the fact that, at retrieval, all elements of the associative pair and the pair configuration itself is familiar (having been presented at encoding). As such, retrieval-based neural discriminability between conditions suggests that prior item familiarity has an extended influence on stimulus processing within the precuneus beyond the items' initial reactivity.

Given the role of the ventral visual cortex in priming (e.g., Schacter et al., 2007; Vuilleumier et al., 2002), and the role of fusiform and PHC

in face and scene processing respectively (Elbich & Scherf, 2017; Epstein, Graham, & Downing, 2003; Epstein & Kanwisher, 1998; Kanwisher et al., 1997), we had anticipated that ventral visual regions would exhibit sensitivity to item familiarity within the associative memory task. Interestingly, the only region in the ventral-visual cortex to exhibit above chance discriminability at both encoding and retrieval was the fusiform gyrus. The fusiform has long been associated with face processing (Kanwisher et al., 1997) and has been shown to discriminate between familiar and unfamiliar faces (Eger, Schweinberger, Dolan, & Henson, 2005; Rossion, Schiltz, & Crommelinck, 2003; Rossion, Schiltz, Robaye, Pirenne, & Crommelinck, 2001; Weibert & Andrews, 2015). While the current results support this large prior work regarding sensitivity to familiar faces, the inferior occipital cortex and PHC did not exhibit above chance discrimination between familiarity conditions at encoding. One explanation for this is that, for faces, early visual cortices are implicated in lower-level processing of images such as categorization of sex (Joyce, Schyns, Gosselin, Cottrell, & Rossion, 2006) or viewpoint differences (Axelrod & Yovel, 2012). Conversely, higher-order processes such as familiarity judgements have been shown to reside elsewhere such as the FG. For example, when comparing the classification values to simple pixel differences between different types of familiarized faces, Goesaert and Op de Beeck (2013) found that, while early visual cortex appeared to discriminate between face familiarity, classification accuracy was positively correlated with the pixel differences of the images which were presented, suggesting the distinction was driven by lowlevel image characteristics and not familiarity itself. Additionally, while models of face processing propose early visual cortices as an input to the face processing system, they do not assign a specific aspect or role for these areas beyond being the gatekeeper for visual information (Duchaine & Yovel, 2015). Thus, the absence of familiarity effects within early visual cortex may simply be attributed to the similarity in stimulus attributes across conditions; attributes that are only discriminable within higher level processing regions (e.g., fusiform gyrus).

Based upon the foregoing logic we would expect that PHC, which has been shown to be specialized for processing scenes, (e.g., Aguirre, Detre, Alsop, & D'Esposito, 1996; Epstein & Kanwisher, 1998; Henderson & Choi, 2015; Staresina, Duncan, & Davachi, 2011) would also exhibit familiarity-based discriminability. Noted in our results, the PHC did exhibit significant discriminability at retrieval and approached significance at encoding, thus largely supporting the foregoing division between lower-level processing regions and more specialized regions within ventral visual cortex. While the current results regarding visual cortices are specific to the face and scene stimuli used in the current study, future research should continue to explore how familiarity affects the representation of different stimuli types within memory paradigms and how this may contribute to memory performance.

While it is regarded in the memory literature that associative encoding depends, in part, on the type of information being bound (e.g., items vs. contexts) (e.g., Diana, Yonelinas, & Ranganath, 2007; Ranganath, 2010), it is generally assumed that associative information involving the same general category of stimuli (e.g., faces and scenes) is encoded and processed in a similar manner. In contrast to this view, the current results demonstrate that the brain represents associations differently at encoding depending on even a brief history with the individual stimuli that comprise the association. Moreover, that difference in neural distinctiveness is maintained, to a certain degree, across memory phases (see above). The fact that the foregoing regions can discriminate between trials as a function of item familiarity suggests that associative encoding processes are not driven solely by the type of stimuli being encoded (e.g., a face vs. word), as has been suggested by past work (e.g., Prince et al., 2009; Ranganath, DeGutis, & D'Esposito, 2004; Summerfield et al., 2006), but also by prior experience with individual information that is undergoing associative binding. Together, with our previous univariate findings, the current results extend our understanding of the effect of familiarity on memory processing by showing that associative memory representations can be altered by prior

knowledge.

Unexpectedly, classification differences were not observed within any MTL region during encoding, including the hippocampus, PrC, ERC and PHC. The MTL, and in particular the hippocampus, may be considered the most critical region for associative memory given its unparalleled role in item-item binding (e.g., Ranganath, 2010; Sperling et al., 2003; Staresina & Davachi, 2008, 2009). The presence of neural discriminability in other regions within the associative memory network, yet absence within MTL regions suggests that the benefit of familiarity to encoding processes likely occurs in stimulus perception and higher order processing and not in associative binding itself. This dissociation between MTL regions and other cortical regions supports previous literature showing that cortical regions aid in encoding, storage and processing of familiar information, such as that related to schemas and established knowledge (Brod, Lindenberger, Werkle-Bergner, & Shing, 2015; Gilboa & Marlatte, 2017; van Kesteren, Rijpkema, Ruiter, Morris, & Fernandez, 2014), whereas the MTL, and specifically the hippocampus is responsible for making new connections, as is required in associative binding of discrete pieces of information (e.g., Ranganath, 2010; Sperling et al., 2003; Staresina & Davachi, 2008, 2009). In the current design, while items themselves were familiar prior to encoding, the bound association created between item pairs was novel for both familiar and unfamiliar trial types. Thus, processing of already familiarized information may be facilitated by neocortical patterns, as evidenced by differential discriminability in cortical encoding-related regions as a function of item history. Interestingly, cortical subregions of the MTL, including the PrC and ERC also did not exhibit an effect of familiarity in their ability to discriminate between associative pairs at either encoding or retrieval. This is noteworthy given the role these regions have been shown to play in familiarity processing during both phases of memory processing (e.g., Haskins, Yonelinas, Quamme, & Ranganath, 2008; Henson, Cansino, Herron, Robb, & Rugg, 2003; Watson, Wilding, & Graham, 2012). Additionally, the lack of hippocampal discriminability differs from studies demonstrating that the hippocampus is able to discriminate between old and new items in a memory recognition test (Chadwick, Hassabis, Weiskopf, & Maguire, 2010; Jeye, MacEvoy, Karanian, & Slotnick, 2018; Ryan, Cox, Hayes, & Nadel, 2008; Zeithamova, Dominick, & Preston, 2012). The absence of a familiarity effect on discriminability within these regions may again lie in the fact that, while the items themselves were familiar, the association was novel in both conditions, thus requiring binding in a similar manner throughout MTL regions. The results further support the idea that itemitem binding within the same class of stimuli (e.g., faces and scenes) engages similar associative binding processes, irrespective of the past history of the items being bound.

Overall, the results have significant implications for how we think about associative memory and strategies for improving associative memory. Specifically, they suggest that interventions and processes that are aimed at enhancing associative memory through item-level processing may have a significant impact during associative binding at encoding, and may also carry over to retrieval even though all items are familiar to the individual. Further work will be needed to investigate under what conditions encoding-related interventions would change the representation of associative information such that they would induce unique and discriminable patterns of activation across all memory phases.

# 5. Limitations and future directions

One potential limitation of the current work is the smaller sample size. While we were sufficiently powered for the multivariate analyses, our sample size may not have included the power and variance needed in order to be able to detect brain-behavior correlations. In addition, high resolution hippocampal imaging would be useful in further interrogating differences in neural representations in this small region. Third, while the current study defined prior familiarity as previous exposure and memory for item information, it did not take into account the strength of familiarity. Future work investigating whether there are conditions under which stronger familiarity of information, such as using famous or personally relevant faces and places, contributes to greater neural discriminability across all memory phases should also be undertaken, or whether familiarity influences the representation of associative pairings across a longer time frame such as hours or days, or with repeated exposure (e.g., learning paradigms). This could also be undertaken using famous or personally relevant materials or with the use of confidence-based memory assessments during the familiarization phase of the study. Related, future work could examine the role of memory strength in the effect of familiarity by examining just high confident (e.g., recollection) associative memories. Finally, as a better understanding of laterality of brain regions within associative memory arises, future work may also examine discriminability differences in laterality.

# 6. Conclusion

The goal of this study was to examine the discriminability of associative pairs consisting of familiarized and unfamiliarized items during both associative encoding and retrieval. Our results suggest that neural pattern discriminability is present throughout higher order processing regions within the associative memory network during associative encoding when familiar items are presented in novel configurations. However, this discriminability is largely reduced at retrieval. Critically, the hippocampus, a key region supporting item-item associative binding does not show an effect of familiarity on neural representations during encoding. While we did not find correlations between discriminability and associative hit rates, we did find that overall individuals performed better in the familiarized condition, lending support to the conclusion that familiarization of items prior to associative encoding influences mnemonic representations of information in a manner that allows for enhanced processing of that information in subsequent cognitive tasks.

By demonstrating that neural patterns at encoding and subsequent memory performance are both influenced by prior experience, we can consider the implications of this with respect to basic memory constructs and memory interventions. Moreover, the fact that these differences based on prior history are retained to some extent at retrieval suggests that item familiarity influences associative memory at all phases of memory. Taken together the results suggest there is an advantage to familiarization that is not simply related to differences in effort of processing (as the general face/scene stimuli is consistent across conditions), but in how the information is perceived and represented at the neural level. Overall, the results demonstrate the ability of item familiarity to influence not only associative encoding processes, but also associative retrieval. This finding has implications for how we understand associative memory and approach interventions for improving associative memory in memory-impaired populations.

#### CRediT authorship contribution statement

Daniel B. Elbich: Conceptualization, Formal analysis, Methodology. Christina E. Webb: Conceptualization. Nancy A. Dennis: Supervision, Conceptualization, Methodology.

#### **Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bandc.2021.105760.

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