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Different types of associative encoding evoke differential processing in both younger and older adults: Evidence from univariate and multivariate analyses

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ABSTRACT

Age-related deficits in associative processing are well-documented (e.g., Naveh-Benjamin, 2000) and have been assumed to be the result of a general deficit that affects all types of binding. However, recent behavioral research has indicated that the visual configuration of the information that is presented to older adults influences the degree to which this binding deficit is exhibited by older adults (Overman, Dennis et al, 2019; Overman, Dennis, et al., 2018). The purpose of the present study was to further clarify the neural underpinnings of the associative deficit in aging and to examine whether functional activity at encoding differs with respect to the visual configuration and the type of associative being encoded. Using both univariate and multi-voxel pattern analysis, we found differences in both the magnitude of activation and pattern of neural responses associated with the type of association encoded (item-item and item-context). Specifically, our results suggest that, when controlling for stimuli composition, patterns of activation in sensory and frontal regions within the associative encoding network are able to distinguish between different types of associations. With respect to the MTL, multivariate results suggest that only patterns of activation in the PrC in older, but not younger adults, can distinguish between associations types. These findings extend prior work regarding the neural basis of associative memory in young and older adults, and extends the predictions of the binding of item and context model (BIC; Diana, Yonelinas, Ranganath, 2007) to older adults.

Compared to younger adults, older adults exhibit impairments in remembering associations between two discrete pieces of information, such as remembering whether two items were previously seen together (item-item associations; Castel and Craik, 2003; Naveh-Benjamin, 2000; Naveh-Benjamin et al., 2003; Old and Naveh-Benjamin, 2008; Overman and Becker, 2009) or whether an item was previously encountered within a particular context (item-context associations; Chalfonte and Johnson, 1996; Naveh-Benjamin and Craik, 1995; Park et al., 1982; Park et al., 1984). Because age-related impairments in associative memory often exceed those found in item memory (e.g., Bender and Raz, 2012; Naveh-Benjamin, 2000; Ratcliff and McKoon, 2015; Silver et al., 2012), it is suggested that older adults' memory impairment is due to a global deficit in forming associations (i.e., the Associative Deficit Hypothesis; Naveh-Benjamin, 2000).

A critical aspect of the Associative Deficit Hypothesis is that age-related memory decline for both item-item and item-context associations is predicated on a common underlying mechanism, impairing the ability to form and remember any type of association (e.g., S. C. Li, Naveh-Benjamin and Lindenberger, 2005). This has been characterized as a binding deficit and aligns with known age-related dysfunction within the hippocampus, directly contributing to age-related impairments in associative memory (Cohn et al., 2008; Miller et al., 2008; Old and Naveh-Benjamin, 2008). However, neuroimaging studies in young adults have found that item-item and item-context associations can be supported by different underlying mechanisms within the medial temporal lobe (MTL; Diana et al., 2010, 2012). This has been outlined in the binding of item and context (BIC) model of associative memory (Diana et al., 2007), which posits that associative memory-related processing within the MTL may be dependent upon the type of association being formed. Specifically, the BIC model states that, whereas both

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item-context and item-item associations involve the hippocampus, item-item binding, and unitized pairs, can be processed by the perirhinal cortex (PrC). Such flexibility of processing could benefit older adults by allowing them to supplement, or substitute, associative processing typically undertaken by the hippocampus, a region which is known to exhibit considerable age-related structural and functional decline (e.g., Daselaar et al., 2006; Persson et al., 2005; Raz, 2000), with processing from PrC. Despite the foregoing functional dissociation across the MTL that is predicted by the BIC model, it is unknown whether differences in the presentations of associations influences successful associative processing within the MTL and other encoding-related brain regions, and whether such a dissociation extends to older adults.

Because prior studies of item-item and item-context associations have used different types of stimuli for item-item pairs (e.g., object-object) and item-context pairs (e.g., object-scene) the comparison between item-item and item-context association-related processing has been confounded by featural differences in the individual stimuli. Indeed, Huffman & Stark (2017) recently called for careful attention to this very aspect of experimental design in order to avoid confounding "high-level cognitive representations" with "low-level sensory features." It has been demonstrated in animal studies that using the same types of stimuli across two tasks and setting up the design to require a different type of processing results in different neural contributions (Eacott and Gaffan, 2005). Additionally, our past behavioral work has demonstrated that using the same types of stimuli and configuring the manner of presentation as "item-item" and "item-context" results in different performance across the item-item and item-context conditions for older adults (Overman, Dennis, McCormick-Huhn, Steinsiek and Cesar, 2019; Overman, McCormick-Huhn, Dennis, Salerno and Giglio, 2018). However, the age-related neural activity associated with processing different types of associative pairs when the stimulus-specific features are held constant remains unknown. Therefore, in the current study we attempted to disentangle stimulus-specific featural processing from encoding of the type of association by keeping stimulus type (e.g., faces and scenes) constant across both item-item and item-context conditions, while simultaneously manipulating the manner in which the pair information was presented during encoding in order to evoke each type of associative encoding (i.e., item-item and item-context). Our manipulation of the two conditions was based on a review of the long-standing cognitive literature on context processing, item processing, and measures of memory (see Richardson-Klavehn and Bjork, 1988, for one such in-depth review of features of contexts, item, and comparison of multiple tasks used to study various types of memory). It is important to note that the labels "item" and "context" do not stem from intrinsic properties of the information, but reflect different roles that can be played by a given piece of information in a given situation. "Items" typically consist of information that is more focal and "contexts" typically consist of information this is more peripheral (e.g., Murnane et al., 1999) or occurring in the "background" (e.g., Hockley, 2008), which is why scenes are so commonly used as "contexts" and objects or faces are so commonly used as "items." However, there is nothing about a particular piece of information, in the absence of its relationship to other pieces of information, that necessarily constrains it to the category of "item" or "context." For example, a sofa can be an item in the context of a living room or a sofa can be the context in which one or more items, such as a sock or doll, can be found. Characterizing something as an item or a context is dependent on its relationship to the other information that is being presented, and to aspects such as how focal/peripheral or foregrounded/backgrounded the information is. Thus, there exists the opportunity for nearly any stimulus to take on the role of an item or a context, depending on the manipulation of the manner in which it is presented.

With regard to stimulus-specific processing within the MTL, research in younger adults strongly supports a dissociation between perirhinal and parahippocampal cortices in memory studies using single items and single contexts (Awipi and Davachi, 2008; Davachi et al., 2003; Liang et al., 2013; Ranganath, Cohen, Dam, & D'Esposito, 2004). These same studies also identify a role of the hippocampus in binding during associative memory. However, a major confound across these studies has been the type of material used during the experimental task. Typically, items have been defined as words, objects or faces and context as background scene, color, location, or task (e.g., Cansino et al., 2002; Diana et al., 2007; Elfman et al., 2008; Hayes et al., 2007; Park et al., 2014; Ranganath, 2010a; Ranganath et al., 2004; Staresina and Davachi, 2008). Such stimulus confounds make it impossible to determine whether any observed differences in MTL activity during the processing of item-item pairs compared to item-context pairs are related to the features of the individual stimuli, or instead, related to the way that the participant experiences the stimuli and encodes the stimuli together to form the association. In order to avoid confounding the type of association being made (item-item versus item-context) with the type of stimulus (face, object, scene, etc.), it is necessary to use the same stimulus categories in both types of associations. Doing so would then clearly distinguish the neural activity that corresponds to binding together two items or an item and context, versus the neural activity that corresponds to particular stimulus features.

One study has attempted to address this question by examining activity underlying encoding for object-scene associations as a function of whether the objects were naturally integrated into the scene (e.g., a vase sitting on a table) or whether the object and scene were viewed as separated entities (i.e., a vase presented next to the table; Memel and Ryan, 2017). Behaviorally, both young and older adults exhibited an advantage for integrated objects opposed to the separated condition. Findings related to general processing across both encoding conditions showed that the integrated condition led to increased activation in bilateral hippocampus, right parahippocampal cortex (PHC) and right PrC compared to the non-integrated condition in both young and older adults. Thus, findings did not support a functional dissociation within the MTL based on item-item vs. item-context associations. Because their results did not include an analysis of activation related to subsequent memory success, they also did not observe functional differences based on recollection and familiarity, a finding the BIC model would also suggest. Rather, the authors posit that their findings reflect the benefit of visual integration, which they assert is supported by overall enhancements in MTL activity for unified object-scene pairs.

Contrary to this work, recent behavioral work from our group, using a similar approach, examined the effect of age on associative memory for face-scene pairs as a function of whether the pairs were presented as an item-item pair (positioned side-by-side at encoding) or whether the pairs were presented as an item-context pair (positioned with the face in front of the scene at encoding) (Overman et al., 2019). Across three separate experiments, we found that the associative deficit in aging was not uniform and the age difference was greater for face-scene pairs presented as item–context compared to item–item associations[1]. In line with the BIC model, we further suggest that older adults may benefit from processing information as an item-item association due to the possibility of recruiting the relatively intact PrC, rather than relying entirely on the hippocampus, which is more vulnerable to age-related impairment (Knoops, Gerritsen, van der Graaf, Mali and Geerlings, 2012; Raz, 2005; Raz et al., 2010; Rodrigue et al., 2011). The current study aims to expand our behavioral findings to test this theory of differences in MTL recruitment across associations types in both younger and older adults. Evidence for differential recruitment across MTL subregions would both extend the BIC model to aging and provide clarification about the extent to which there is a common underlying associative deficit in binding.

In addition to the localization of neural processing, it is also of

[1] A follow up study also suggested that this finding may be modified not only by the type of association, but also by the configural match with the retrieval presentation (see Overman et al., 2018).

importance to understand how aging affects the neural specificity, or the distinctiveness of different neural patterns, underlying associative memory encoding. If item-item and item-context associations are represented differently within the brain, then patterns of neural activity associated with the encoding of each should be detectable via multivoxel pattern analyses (MVPA), an analytical tool that is sensitive to detecting subtle differences in pattern of neural activation. Furthermore, if neural patterns across item-item and item-context associations, that are composed of the same component parts (e.g., faces and scenes), are found to be distinct from one another, this would be interpreted as evidence that different types of associations are processed differently. Given the manipulation of face-scene pairs we describe above, we would expect significant differences in patterns of activation across the visual cortex, reflecting mere differences in stimuli configuration. However, it is of interest to know whether regions involved in higher-order processing of memory, such as subregions within the MTL (hippocampus, PHC, PrC) and PFC, also distinguish between item-item and item-context associations, and if the neural discriminability of different types of associations differs with age. Evidence for distinct neural patterns associated with different types of associations across the associative encoding network would support the BIC model by showing that successful associative encoding depends on both the formation of a link between two discrete pieces of information, and on the type of link being formed (e.g., item-item or item-context). If, however, the PFC and MTL subregions process associations only with respect to the features of the stimuli pair, then the type of association should have no effect on patterns of activation and therefore we should observe no differences in classification accuracy across these regions in the current study.

With respect to neural specificity in aging, research shows a reduction in the specificity of neural representations during information processing (Carp et al., 2011; Dennis and Cabeza, 2011; Grady, 2008; S. C. Li, Lindenberger and Sikstrom, 2001). Such dedifferentiation has been found across a range of neural regions and tasks, affecting both perception of visual information (Goh et al., 2010; Park et al., 2004; St-Laurent et al., 2014; Voss et al., 2008), as well as the distinctiveness of neural patterns across memory tasks (Dennis and Cabeza, 2008; Koen et al., 2019; Sambataro et al., 2012; St-Laurent et al., 2014; St-Laurent et al., 2011; Zheng et al., 2018). Recent work has also suggested that, compared to younger adults, older adults exhibit less distinct patterns of neural activity during associative encoding, and this reduction in neural specificity, in turn predicts their poorer associative memory (Saverino et al., 2016).

In the current study we aimed to a) extend the BIC model to aging and b) extend prior behavioral findings by identifying the neural correlates supporting specific association types. Specifically, we aimed to identify whether the localization of activation within the MTL differed with respect to the type of association being encoded, when controlling for the characteristics of the stimuli that make up the pair. In addition to investigating differences in the localization of activation across association types, we also aimed to go beyond previous studies by investigating whether pairs of content-equated item-item and item-context stimuli are associated with different patterns of neural representation within the MTL and other memory-related processing regions, as a function of the type of association. To do so we used classifier-based MVPA to quantify the discriminability of neural patterns elicited during encoding of item-item and item-context associations. By manipulating pairs of stimuli (face and scenes) to present them as either item-item or item-context associations at encoding, any differences in the localization and patterns of neural activity between conditions should correspond to the type of association that is being encoded rather than reflecting the processing of the individual stimuli that are components of the pair. Finally, we aimed to investigate whether neural specificity relating to associative encoding within MTL subregions differs between young and older adults.

1. Methods

Participants. 30 right-handed native English-speaking young adults and 30 older adults from the State College community participated in this study. Participants were screened for history of neurological disorders and psychiatric illness, alcoholism, drug abuse, and/or learning disabilities, as well contraindications for MRI. One young and two older adults were excluded from the analysis due to head motion in excess of 4 mm; two young adults exited the scanner due to issues with claustrophobia; one young adult was excluded for failure to comply with task instructions; and one older adult received the incorrect version of the task, leaving data from 26 young participants [19 females; $M_{age} = 20.5$ years, $SD_{age} = 1.95$] and 27 older adults [20 females; $M_{age} = 71.19$ years, SD = 6.19]. All participants provided written informed consent and received financial compensation for their participation. The Pennsylvania State University's Institutional Review Board for the ethical treatment of human participants approved all experimental procedures. Older adults participated in a 1-h cognitive assessment battery prior to participation in the study. The cognitive battery consisted of MMSE, GDS, Letter-Number Sequencing, WAIS-III Vocabulary, Symbol Coding, Symbol Copy, and Digit Span. Results are reported in Table 1.

Stimuli. Stimuli consisted of 170 color photographs of faces and 170 color photographs of scenes paired together. Face stimuli consisted of both male and females faces, each exhibiting a neutral expression, taken from the following online databases: the Color FERET database (Phillips et al., 2000), adult face database from Dr. Denise Park's lab (Minear and Park, 2004), the AR face database (Martinez and Benavente, 1998), and the FRI CVL Face Database (Solina et al., 2003). Scene stimuli consisted of outdoor and indoor scenes collected from an Internet image search. Using Adobe Photoshop CS2 version 9.0.2 and Irfanview 4.0 (http://www.irfanview.com/), we edited face stimuli to a uniform size (320 × 240 pixels) and background (black), and scene stimuli were standardized to 576 × 432 pixels.

During the associative encoding task, 170 face-scene pairs were presented either a) in a manner that characterized them as an item (face) embedded within a context (scene) or b) in a manner that characterized them as two independent items (face and scene side-by-side). To accomplish this the focality of scenes were manipulated across the item-context (IC) and item-item (II) conditions. Specifically, in item-context associations, scenes were presented as contexts by placing them behind the faces (reduced focality of the scene) and in item-item associations, scenes were presented as items by placing them next to faces

Table 1
Participant demographics and behavioral rates.

	Older adults (N = 27)	Younger adults (N = 26)
Participant Demographics	M (SD)	M (SD)
Age	71.1 (6.06)	20.5 (1.95)
Cognitive Assessment Tasks		
MMSE	29.52 (0.98)	–
Digit Symbol Coding	12.43 (2.29)	–
Symbol Copy	102.5 (23.76)	–
Digit Span	12.48 (2.64)	–
Letter Number Sequencing	12.09 (3.11)	–
WAIS- Vocabulary	11.39 (1.68)	–
GDS	0.86 (1.14)	–
Memory Task—Retrieval Rates		
Recollection Rates		
II	0.42 (0.14)	0.54 (0.14)
IC	0.44 (0.14)	0.57 (0.15)
Familiarity Rates		
II	0.44 (0.18)	0.43 (0.14)
IC	0.44 (0.23)	0.50 (0.17)

The table reports the means and standard deviations of participant demographics and proportions of retrieval rates broken down by age group. MMSE, Mini-Mental State Examination; WAIS- Wechsler Adult Intelligence Scale; GDS, Geriatric Depression Scale; II, item-item; IC, item-context.

with a small white gap between the two images (see Fig. 1 for examples of stimuli configurations).

During encoding 17 item-context and 17 item-item associations were presented in a random order in each of 5 encoding blocks. Each retrieval block consisted of 17 congruent (matching the same visual configuration as encoding) and 17 incongruent (opposite visual configuration from encoding) pairings in comparison to those they were presented with at encoding. Within the retrieval condition, 10 of the pairings were lures (5 of which were item-item and 5 of which were item-context) in which the face-scene pair was rearranged from that presented at encoding. A jittered interstimulus interval (2–8s) separated the presentation of each image. Each encoding and retrieval block lasted 4 min and 18 s.

Procedure. Prior to scanning, all participants practiced the procedure through both encoding and retrieval practice blocks. The researcher verbally emphasized that both stimuli in the pair should be attended to. Additionally, the instructions on the screen during practice and during the experiment while in the scanner also emphasized that the participants should choose the rating based on how welcoming the face and scene pairing was *together*. This was intended to facilitate encoding of both the face and the scene, rather than just one or the other. Participants were encouraged to ask questions during this time. The scanning session began with a structural scan (MPRAGE) that took approximately 7 min. During this time, the participants were asked to remain as still as possible. Following the structural scan, participants completed 5 encoding and 5 retrieval blocks (alternating order). Instructions screens were presented prior to each block reiterating the verbal instructions participants received prior to entering the scanner. Presentation of all instruction screens were self-paced, meaning that the participants pressed "1" on the handheld button box to advance to the next screen when they read the instructions and were ready to begin the task. When the instruction slide appeared on the screen, the participant was asked to explain the instructions verbally before proceeding with the experiment in order to verify an accurate understanding of the task.

After advancing past the instruction slides in encoding, the participant was presented with a series of face and scene pairings displayed on the screen in either in an item-item or an item-context configuration. Each pair was presented for 4 s, during which time the participant responded to the question: "How welcoming are the scene and face?" (presented in text below each pair) by utilizing a rating scale from 1 to 4 (1 = not at all; 4 = very) and making a key press on their hand-held button box. This question was deliberately phrased with the scene listed first in order to help ensure that participants paid attention to the scene, even when it was configured behind the face in the item-context condition because we did not want the scene to be incidentally encoded while the face was intentionally encoded. Two versions of the task were created for counter-balancing purposes. Across versions, face and scenes were counter-balanced for their inclusions in either an item-item or an item-context pair. No differences across versions were noted and all analyses are collapsed across versions.

Each encoding block was followed by a retrieval block. Similar to encoding, each face-scene pair at retrieval was presented for 4 s. During this time participants were asked to respond to the question: "Please identify the pairings that have been presented previously." Displayed below the question were the following choices: 1 = remember, 2 = know, 3 = new. They were asked to respond "remember" if they remembered exact details about the face and scene that were presented together in the previous task. Participants were instructed to make their memory judgements based on the co-occurrence of the face and scene and not to base their judgements on the configuration of the display. A Remember-Know-New design was chosen in order to isolate recollection-related activity, associated with 'remember' responses, from that of familiarity, associated with 'know' responses. This distinction has shown to be critical when assessing memory-related activity particularly within the MTL (Yonelinas, 2002; Yonelinas et al., 2005; Yonelinas et al., 2007). Similar to encoding, all responses were made using the button box. (Only encoding data is analyzed in the current analysis). With respect to retrieval configurations, half of the trials were congruent with respect to their encoding configuration and half incongruent (such that an II trial at encoding was presented as an IC trial at retrieval). While our past research has suggested that this manipulation influences the behavioral metrics reported in the current paper (e.g., Recollection, Familiarity, d'), we feel that a breakdown of behavior as a function of retrieval congruency is best understood in association with the retrieval data itself. This will be the focus of a subsequent analysis/paper and as such we have not broken down any behavioral metrics as a function of retrieval condition.

Image Acquisition. Structural and functional images were acquired using a Siemans 3T scanner equipped with a 12-channel head coil, parallel to the AC-PC plane. Structural images were acquired with a 1650 ms TR, 2.03 ms TE, 256 mm field of view (FOV), 256^2 matrix, 160 axial slices, and 1.0 mm slice thickness for each participant. Echo-planar functional images were acquired using a descending acquisition, 2500 ms TR, 25 ms TE, 240 mm FOV, a 80^2 matrix, 90° flip angle, 42 axial slices with 3.0 mm slice thickness resulting in 3.0 mm isotropic voxels.

Image Processing. For univariate analyses, raw anatomical and

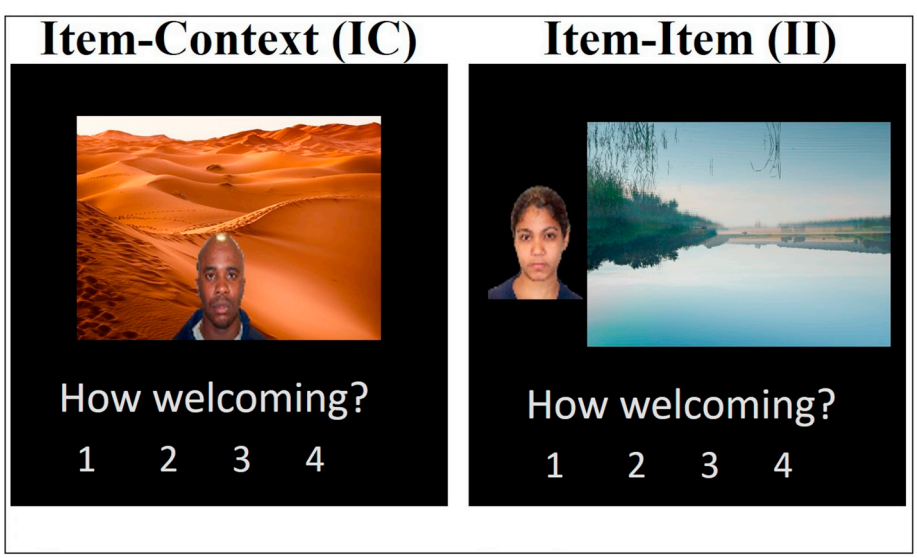

Fig. 1. Item-context and item-item encoding configurations.

functional images were first skull stripped using the Brain Extraction Tool (Smith, 2002) in the FMRIB Software Library (FSL) version 5.0.10 (www.fmrib.ox.ac.uk/fsl). FSL's MCFLIRT function (Jenkinson et al., 2002) was then applied for realignment and motion correction within each functional run. All volumes were aligned to the middle volume of the middle run of encoding. The realigned functional images were then processed by FSL's fMRI Expert Analysis Tool (FEAT; Woolrich et al., 2001), where they were high-passed filtered and spatially smoothed at 6 mm FWHM. These data were then prewhitened to account for temporal autocorrelations within voxels. Lastly, the structural data underwent non-linear transformation into the standardized Montreal Neurological Institute (MNI) space by using the warping function in FSL's FNIRT (Andersson et al., 2010). For multivariate analyses the raw data underwent the exact same steps as above, absent smoothing.

1.1. Behavioral analyses

Using the Remember-Know-New responses and the calculations for independence Remember/Know (IRK) procedure (Yonelinas and Jacoby, 1995), we calculated a Recollection score for each condition based on the rate of Remember responses to targets for both the II and IC conditions. Familiarity was calculated as K/(1-R) where K is the proportion of Know responses and R the proportion of Remember responses. For each participant, the R and F estimates for lure pairs were subtracted from the corresponding parameters for target pairs, in order to adjust for false alarm rates (Yonelinas and Jacoby, 1995). Memory discrimination (d') was calculated for each condition by calculating z(total Hit rate) - z (total False Alarm rate) (Green and Swets, 1966; Macmillan and Creelman, 2005).

1.2. fMRI analyses

Univariate analyses. At the first level, trial-related activity was modeled in SPM12 using the general linear model (GLM) with a stick function corresponding to trial onset convolved with a canonical hemodynamic response function. A second-level random effects GLM was created and one sample *t*-tests were conducted to investigate contrasts of interest. The current analyses focused on 4 trial types of interest: 1) II Recollection, which were defined as subsequently 'Remembered' II pairs; 2) IC Recollection, which were defined as subsequently 'Remembered' IC pairs 3) II Other, which were defined as II pairs that were responded to with either a 'Know' or 'New' response at retrieval; and 4) IC Other, which were defined as IC pairs that were responded to with either a 'Know' or 'New' response at retrieval. [Unfortunately, low trial counts in the Know responses precluded us from modeling, and examining, Familiarity within each condition. Thus, in line with previous studies encountering this same issue (Dennis et al., 2008; Dennis et al., 2015; Geib et al., 2017; Prince et al., 2005; Schon et al., 2004; Sperling et al., 2003), the decision was made to isolate Recollection-related activity across conditions and combine Know and New responses to create an 'Other' regressor for contrasting Recollection in obtaining subsequent memory effects.] All encoding trials that were subsequently recombined at retrieval to form lures, along with no response trials, were coded together as a regressor of no interest, as were movement parameters.

The first goal of the paper was to elucidate the neural mechanisms supporting associative recollection success in each age group, irrespective of association type. To do so, II and IC Recollection were compared to II and IC Other conditions, respectively to obtain subsequent memory effects within each condition. Next, differences across successful associative recollection were identified by directly contrasting II Recollection with IC Recollection in each age group. To ensure that Recollection differences were founded within subsequent memory effects, Recollection effects were implicitly masked with subsequent memory contrasts. Finally, age differences in each contrast of interest were assessed. Based on our *a priori* hypotheses regarding the role of MTL subregions with relation to memory success across item-item and item-context associations, we investigated all subsequent memory and multivariate effects within the bilateral hippocampus, bilateral PHC, and bilateral PrC. The hippocampus and PHC were derived from the aal pickatlas (Lancaster et al., 2000) and bilateral PrC was derived from a mask taken from Holdstock and colleagues (Holdstock et al., 2009). For all univariate contrasts, we employed Monte Carlo simulations as implemented by 3dClustSim in AFNI version 16.0 (Cox and Hyde, 1997), to determine activation that was corrected for multiple comparisons at $p < .05$, using an uncorrected p threshold ($p < .005$). An additional simulation was run to determine a correction specific to the MTL (using all subregions).

Multivariate pattern analysis. In order to estimate neural activity associated with individual trials, an additional GLM was estimated in SPM12 defining one regressor for each trial at encoding (170 in total). An additional 6 nuisance regressors were included in each run corresponding to motion. Whole-brain beta parameter maps were generated for each trial at encoding, 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. These beta parameter maps were next concatenated across runs and submitted to the CoSMoMVPA toolbox (Oosterhof et al., 2016) for pattern classification analyses. Given our interest in determining which regions in the associative encoding network discriminated between II and IC presentation, separate classification accuracies were computed in regions previously identified as supporting associative memory in both young and older adults. These regions include the aforementioned MTL subregions (hippocampus, PHC, PrC), the PFC and regions of visual cortex. Specifically, regions that comprised the PFC and visual ROIs were first identified from meta-analyses of subsequent memory, including inferior, medial and middle frontal gyri (Kim, 2011; Maillet and Rajah, 2014). These regions were then identified in aal pickatlas and combined to form the single PFC ROI. Visual cortex regions included inferior occipital cortex (i.e., early visual cortex), and middle occipital cortex (i.e., late visual cortex). All ROIs were defined bilaterally and examined for their responsiveness to II and IC associations, as we had no *a priori* hypothesis regarding laterality.

We were interested in whether the neural patterns associated with the II and IC conditions are distinguishable within the foregoing brain regions, and how age might affect the neural discriminability of these trial types. As such, classification analyses were computed for encoding runs using a support vector machine classifier with a linear kernel using all voxels within an ROI (Mumford et al., 2012). Training and testing followed a standard leave-one-run-out cross-validation procedure with four runs used as training data and one run as testing data. 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 II and IC encoding presentations and chance (50%), a one-tailed one-sample *t*-test was conducted for accuracy within each ROI for each trial type, for each age group. 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 IC/II 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. Additionally, for regions showing above-chance classification in either age group, we computed follow-up comparisons between age groups by submitting classification accuracy to an ANCOVA that included age group as the only predictor of interest. To ensure that any effects identified were not driven by differences in overall univariate activity across age groups or trial types, we included covariates for average univariate encoding activity in a given ROI for II and IC trials, in each ANCOVA.

In order to examine how the ability to classify brain patterns relates to memory discriminability, we computed separate multiple regression

models for each ROI, using d' as the dependent variable. We chose d' as our measure of behavior as it represents not only accurate encoding and retention of targets, but also discrimination in memory for associations, controlling for errors related to familiarity of lures (false alarms). We conducted a separate regression for each ROI for both II d' and IC d'. Each regression analysis included the following predictors of interest: (1) classification accuracy for the given ROI, (2) age group as a categorical predictor, and (3) an age X classification accuracy interaction effect. We also included the above-described univariate activity as nuisance regressors.

2. Results

2.1. Behavioral results

Participants' welcomingness ratings to face-scene pairs in the encoding task were averaged within each encoding condition. Both age groups provided similar ratings in the IC condition (young: $M = 2.30$, $SD = 0.37$; older: $M = 2.46$, $SD = 0.41$) and in the II condition (young: $M = 2.37$, $SD = 0.41$; older: $M = 2.45$, $SD = 0.37$). A 2 (age group) X 2 (encoding condition) repeated-measures ANOVA on mean welcomingness ratings found no effect of age group, $F(1,51) = 1.36$, $p = .25$, no effect of encoding condition, $F(1,51) = 1.56$, $p = .22$, and no interaction, $F(1,51) = 2.75$, $p = .10$. Response times (RT) for welcomingness ratings were also analyzed by finding each participant's median RT within each encoding condition, then using those values to compute mean RT across participants within each age group. A 2 (age group) X 2 (encoding condition) repeated-measures ANOVA on mean RT found significant effects of age group, $F(1,51) = 6.48$, $p = .014$, $\eta^2_p = .11$, $MS = 2.50$, and encoding condition, $F(1,51) = 36.68$, $p < .001$, $\eta^2_p = .44$, $MS = 0.437$. Both age groups exhibited longer response times in the II condition (young: $M = 2.21$s, $SD = 0.48$s; older: $M = 2.50$s, $SD = 0.44$s) than in the IC condition (young: $M = 2.06$s, $SD = 0.44$s; older: $M = 2.39$s, $SD = 0.42$s). No interaction was found, $F(1,51) = 1.10$, $p = .30$.

Subsequent memory was analyzed with respect to *d'* (Green and Swets, 1966; Macmillan and Creelman, 2005) as well as R and F parameters. For *d'*, a 2 (age group) x (encoding condition) repeated measures ANOVA found a main effect of age group, such that young adults ($M = 2.09$, $SD = 0.47$) had greater discrimination of target versus lure pairs than older adults ($M = 1.71$, $SD = 0.43$), $F(1,51) = 9.24$, $p = .004$, $\eta^2_p = 0.15$, $MS = 3.75$. The main effect of condition was also significant, such that target versus lure discrimination was greater for IC pairs ($M = 1.97$, $SD = 0.55$) than for II pairs ($M = 1.82$, $SD = 0.51$), $F(1,51) = 6.88$, $p = .011$, $\eta^2_p = 0.12$, $MS = 0.60$. There was no significant interaction, $F(1,51) = 1.18$, $p = .28$. Means of *d'* are displayed in Fig. 2.

Recollection and familiarity estimates were computed according to the IRK procedure (Yonelinas and Jacoby, 1995) for both target and lure pairs. For each participant, the R and F estimates for lure pairs were subtracted from the corresponding parameters for target pairs, in order to adjust for false alarm rates. For Recollection, a 2 (age group) x (encoding condition) repeated measures ANOVA found a main effect of age group, such that young adults ($M = 0.56$, $SD = 0.13$) had greater recollection than older adults ($M = 0.43$, $SD = 0.13$), $F(1,51) = 11.61$, $p = .001$, $\eta^2_p = 0.19$, $MS = 0.42$. Numerically, Recollection was greater overall in the IC condition ($M = 0.51$, $SD = 0.16$) than the II condition ($M = 0.48$, $SD = 0.15$), but the effect of condition was not statistically significant, $F(1,51) = 3.78$, $p = .057$. There was no significant interaction, $F(1,51) = 0.17$, $p = .69$. For Familiarity, a 2 (age group) x (encoding condition) repeated measures ANOVA found that age group was not significant, $F(1,51) = 0.30$, $p = .59$, nor was the effect of condition, $F(1,51) = 1.86$, $p = .18$. Numerically, there was a slightly larger age difference in Familiarity for the IC condition (young adults: $M = 0.50$, $SD = 0.17$; older adults: $M = 0.44$, $SD = 0.23$) than in the II condition (young adults: $M = 0.43$, $SD = 0.14$; older adults: $M = 0.44$, $SD = 0.18$), however the interaction was not statistically significant, $F(1,51) = 1.79$, $p = .19$.

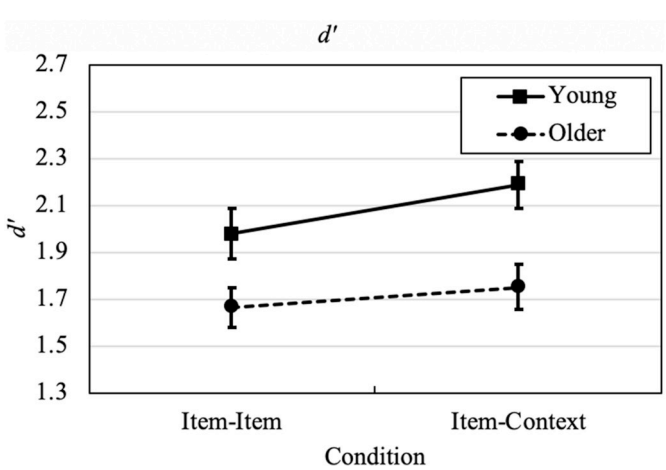

Fig. 2. d' broken down by age and condition.

2.2. Univariate fMRI

Successful associative encoding exhibited neural activity within the typical associative memory network including bilateral occipital cortex, bilateral superior parietal cortex, bilateral medial and superior PFC, and bilateral MTL in both young and older adults (see Fig. 3a and b). Compared to older adults, younger adults exhibited greater overall successful encoding activity across a majority of the foregoing regions. For a complete list of activations in each age group as well as age differences, please see Table 2 and 3 and Supplemental Fig. 1.

Successful encoding in the II compared to the IC condition showed significantly greater activity within inferior, middle and superior occipital cortex in both age groups, as well as right posterior PHC in young adults (see Fig. 3c) and portions of parietal cortex in OAs. Only small portions of early visual cortex (BA 17/18) exhibited greater activation for successful IC compared to II encoding in both age groups. With regard to age differences, young adults showed increased activity in left inferior occipital cortex for II compared to IC associations, as well as bilateral cuneus for IC compared to II associations. For a complete list of activations in each age group as well as age differences, please see Table 4.

2.3. MVPA

We first compared classification accuracy for II versus IC associations to theoretical chance (0.5) in each ROI, for each age group. Results showed above chance classification in both age groups in inferior occipital cortex (young: $M_{accuracy} = 0.65$; $t(25) = 15.64$, $p < .001$; old: $M_{accuracy} = 0.61$; $t(27) = 9.01$, $p < .001$), middle occipital cortex (young: $M_{accuracy} = 0.77$; $t(25) = 17.50$, $p < .001$; old: $M_{accuracy} = 0.73$; $t(27) = 13.25$, $p < .001$), and prefrontal cortex (young: $M_{accuracy} = 0.54$; $t(25) = 3.96$, $p < .001$; old: $M_{accuracy} = 0.52$; $t(27) = 2.67$, $p < .001$). Older adults exhibited above-chance classification accuracy in the parahippocampal cortex ($M_{accuracy} = 0.52$; $t(27) = 2.69$, $p < .01$) and perirhinal cortex ($M_{accuracy} = 0.51$; $t(27) = 2.13$, $p < .05$)[2]. Classification failed to reach above-chance performance for young adults in the parahippocampal cortex ($M_{accuracy} = 0.50$; $t(25) = 0.52$, $p = .61$) and the

[2] Noted above, we ran a follow up permutation test to confirm this and all significant classification results. In the PrC, of the 1000 samples in this null distribution, 31 were higher than the accuracy we obtained in the unpermuted analysis, resulting in a p value of .031. This result provides convergent support for the original analysis. Similar convergent evidence from permutation testing was found for all other MVPA results (all ps < .05).

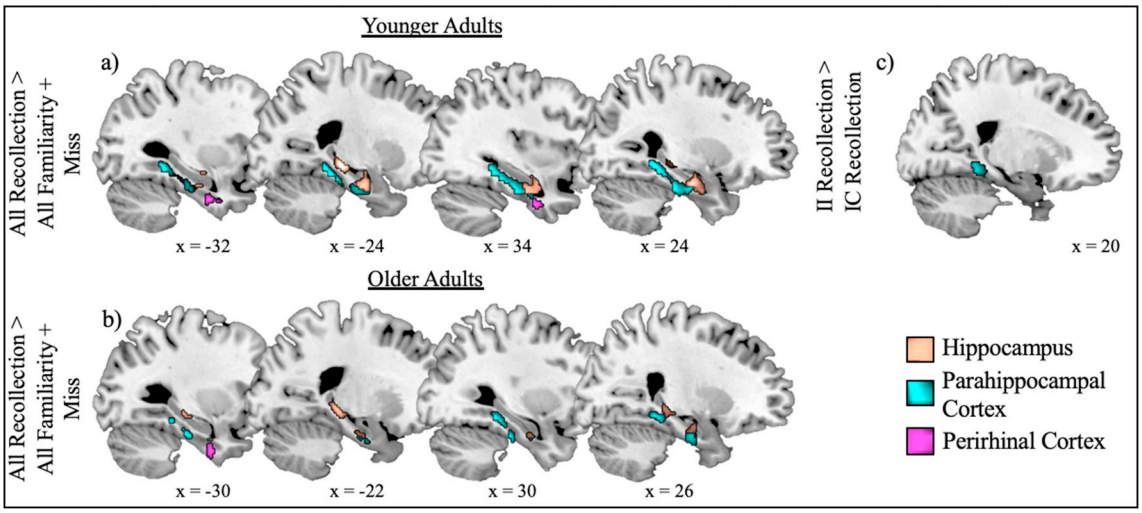

Fig. 3. Recollection success activity in subregions of the medical temporal lobe. Overall recollection success in younger adults (a) and older adults (b) across the hippocampus, parahippocampal cortex, and perirhinal cortex. Panel c) presents right posterior parahippocampal activation that was greater for II Recollection compared to IC Recollection in younger adults. No medical temporal lobe region showed greater activity for IC Recollection, or differences in aging.

perirhinal cortex ($M_{accuracy} = 0.49$; $t(25) = -1.23$, $p = .23$), and in both age groups in the hippocampus (young: $M_{accuracy} = 0.51$; $t(25) = 1.08$, $p = .29$; old: $M_{accuracy} = 0.51$; $t(27) = 0.74$, $p = .47$). See Fig. 4.

We then tested whether there were reliable age differences in classification within each region that showed above-chance classification performance within our *a priori* ROIs. After controlling for univariate differences, older adult classification was significantly greater than that of younger adults in the perirhinal cortex ($F(5,47) = 4.25$, $p < .05$), whereas differences between younger and older adults' classification larger, but no longer statistically significant in the inferior occipital cortex ($F(5,47) = 3.83$, $p = .06$) and middle occipital cortex ($F(5,47) = 3.61$, $p = .06$). See Fig. 4.

Relationship between pattern classification accuracy and memory discriminability. Classification accuracy did not significantly predict d' within any ROI (all $ps > .05$).

3. Discussion

The focus of the current investigation was to examine behavioral and neural differences related to how different types of associations are successfully encoded into long term memory when the featural aspects of the individual stimuli are not confounded. To do so, we used a paradigm we developed in previous work (Overman et al., 2018, 2019) that allowed us to manipulate the configuration of face-scene associations such that they would be viewed as either item-item or item-context associations. While we did not statistically replicate past behavioral differences across groups with respect to differential memory success across association type and age, we did identify differences in both magnitude of activation and pattern of neural responses associated with the type of association encoded, as well as age differences therein. Specifically, our results suggest that, when controlling for stimulus content, patterns of activation in sensory and frontal regions within the associative encoding network are distinguishable between different types of associations. Results also suggest an age-related decrease in neural discrimination in occipital cortex. With respect to the MTL, results suggest that only patterns of activation in the PrC in older, but not younger adults, can distinguish between associations types. The results contribute to our understanding of successful associative encoding across the adult lifespan and speak to how differences in association types are differently processed within the associative network. Results are discussed in greater detail below.

3.1. Behavioral findings

Consistent with many prior studies (e.g., Naveh-Benjamin, 2000) young and older adults differed in associative memory performance such that young adults were better able to discriminate target versus lure pairs, and had higher levels of recollection, based on analysis of remember and know responses (e.g., Kilb and Naveh-Benjamin, 2011; Koen and Yonelinas, 2014; Schoemaker et al., 2017). Overall performance was better in the Item-Context condition than in the Item-Item condition, which is consistent with young adult performance found in a similar prior study (Overman et al., 2019). However, in that study the effect of condition differed between age groups such that there was a greater age difference in the Item-Context condition than in Item-Item condition. Although no age × condition interaction was found in the present study, the qualitative pattern of the current results does not contradict the prior findings (see Fig. 2). The difference in statistical findings for the behavioral results across studies could be attributable to methodological differences between studies. For example, the present study used a Remember/Know/New retrieval task, which has been shown to result in better performance in older adults than an Old/New task (Naveh-Benjamin and Kilb, 2012). Additionally, the present task was structured in a manner that was intended to encourage successful encoding, with multiple encoding-retrieval blocks rather than one large encoding block and one large retrieval block as in the previous study. As a result, the absolute level of performance for both young and older adults was substantially higher in the present results than in the previous study, which could have altered the relative age differences across conditions. An additional consideration is that due to fMRI screening procedures and the types of participants willing to volunteer for MRI studies, the older adults in the present study may have been higher-performing than older adults in the purely behavioral study (selection bias and volunteer bias (Ganguli et al., 2015);).

3.2. Recollection success

Replicating a large prior literature, we found successful associative recollection to be mediated by neural activity across bilateral occipital cortex, middle frontal gyrus, superior medial frontal gyrus and MTL, including hippocampus, PHC, and PrC in both younger and older adults (see Supplemental Figure A). Consistent with previous aging research, younger compared to older adults showed greater recruitment, throughout occipital cortex including both early and late visual regions, extending throughout fusiform and PHC. Greater recruitment and

Table 2
Recollection Success activity.

	T&T coordinates						
	BA	H	x	y	z	k	*t*
Recollection>Other (young)							
Occipital Lobe	R	19/18/17/39/31	31	−47	−9	31627	15.08
	L	19/18/17/39/32	−26	−47	−9		11.71
*Middle/Inferior Frontal Gyrus	L	44/45/46	−38	7	25		8.17
*Middle/Inferior Frontal Gyrus	R	44/45/46	42	8	28		11.82
*Superior Medial Frontal Gyrus	M	6/32	4	16	42		7.26
*Orbitofrontal Cortex	M	11	−2	25	−21		6.58
*Premotor Cortex	L	6	−33	−34	36		4.50
*MTL (PHC/HC)	L	35/36/30	−28	−44	−2		10.02
	R	35/36/30	29	−42	−2		10.89
*Fusiform Gyrus	L	37	−34	−57	−11		10.93
	R	37	38	−60	−7		14.88
*Middle Occipital Gyrus	L	19	−32	−78	24		10.75
	R	19	39	−71	28		9.00
*Superior Parietal Cortex	L	7	−22	−60	44		11.75
	R	7	23	−60	43		8.77
*Inferior Parietal Gyrus	L	7/40	−28	−61	44		6.62
	R	7/40	29	−56	47		8.74
Inferior Frontal Gyrus	R	11/47	29	25	−11	396	6.33
*Inferior Frontal Gyrus	L	11/47	−35	25	−13		5.68
	R	47	30	21	1	124	6.25
Superior Medial Frontal Gyrus	M	6/32	−8	50	41	168	4.82
Caudate	R	–	25	1	0	367	5.95
*Caudate	L	–	−23	3	1		5.75
Cerebellum	M	–	0	−53	−29	132	6.25
MTL Subregions							
PrC	R	28/35	31	−11	−25	27	5.44
	L	28/35	−33	−9	−26	34	5.71
Anterior hippocampus	R	–	23	−29	0	81	9.61
	L	–	−21	−29	−1	84	8.68
Posterior hippocampus	R	–	23	−14	−15	206	7.99
	L	–	−19	−14	−15	135	4.81
Posterior PHC	R	37/36	29	−42	−2	532	10.89
	L	37/36	−28	−44	−2	309	10.02
Recollection>Other (old)							
Early & Late Occipital Cortex	R	19/18/17/39/31	29	−35	−16	22122	8.43
	L	19/18/17/39/31	−32	−41	−15		7.07
*Fusiform Gyrus	R	37	37	−70	−7		8.35
	L	37	−33	−72	−7		7.98
*Middle Occipital Gyrus	R	19	41	−79	24		7.96
	L	19	−32	−82	23		5.86
*Superior Parietal Cortex	L	7	−22	−62	44		3.51
	R	7	27	−60	42		4.20
*Caudate	L	–	−12	1	4		3.74
Inferior Frontal Gyrus	R	45/46	48	22	23	463	5.00
	L	45/46	−48	20	18	412	4.60
Inferior Frontal Gyrus	R	44	42	1	23	476	5.11
	L	44	−48	0	22	513	4.16
Caudate	R	–	15	3	1	196	4.87
Inferior Frontal Gyrus	L	47	−41	25	−15	145	4.53
Retrosplenial Cortex	R	18	16	−51	9	312	4.51
MTL Subregions							
Posterior HC	L	–	−23	−31	−1	98	6.42
	R	–	19	−31	0	49	5.16
Anterior HC	L	–	−21	−14	−17	13	3.34
	R	–	19	−10	−13	43	3.77
Posterior PHC	L	36/37	−26	−39	−8	14	3.44
	R	36/37	25	−39	−6	101	5.11
Anterior PHC	L	35	−27	−10	−20	40	3.21
	R	35	23	−12	−18	92	4.83
	L	35	−30	−27	−17	22	4.01
PrC	L	28	−31	−9	−28	42	3.61

Differences between neural activity for Recollection > Other (Familiarity + Miss); BA: Brodmann's area; H: hemisphere (L: left; R: right; M: medial); x, y, z represent peak Talairach coordinates; k, cluster extent; t: statistical t value; *selected subpeaks from larger cluster. MTL; medial temporal lobe. PHC; parahippocampal cortex. HC; hippocampus. PrC; perirhinal cortex.

Table 3
Comparative neural activity for Recollection>Other across age groups.

	T&T coordinates						
	BA	H	x	y	z	k	*t*
Young>Old							
Fusiform/IOC/MOC	19/37	R	38	−31	−20	3856	5.95
*Retrosplenial Cortex	23	R	22	−53	11		4.64
Retrosplenial Cortex	23	L	−15	−51	11	222	6.18
Fusiform/IOC/MOC	19/37	L	−26	−44	−4	2477	5.75
Middle/Inferior Frontal Gyrus	44/45/46	R	39	12	28	168	4.48
Superior Parietal Cortex	7	R	23	−65	50	286	4.21
MTL Subregions							
Posterior PHC/HC	36	L	−26	−44	−2	65	5.70
	36	R	29	−42	−2	229	5.55

Comparative neural activity for Recollection > Other (Familiarity + Miss) across age groups; BA: Brodmann's area; H: hemisphere (L: left; R: right; M: medial); x, y, z represent peak Talairach coordinates; k, cluster extent; t: statistical t value; *selected subpeaks from larger cluster. IOC, inferior occipital cortex; MOC, middle occipital cortex; MTL; medial temporal lobe. PHC; parahippocampal cortex. HC; hippocampus.

encoding processing within occipital regions has also been linked to enhanced memory for item-specific details needed for recollection-based memory (Dennis et al., 2012; Gutchess et al., 2005; Slotnick and Schacter, 2004; Yonelinas et al., 2001). This interpretation is supported by the behavioral results showing higher memory discrimination (d') in young compared to older adults in the current study as well as a greater contribution of recollection (R) to memory performance in young compared to older adults. There were no regions within the general retrieval network in which older adults exhibited great activity compared to young adults.

With respect to the role of the MTL in associative encoding, activity was greater for subsequent recollection compared to subsequent familiarity and forgetting, irrespective of encoding condition, across all MTL subregions, including bilateral hippocampus, PHC and PrC in both younger and older adults (seeTable 2 for breakdown of MTL clusters; see Fig. 3 for MTL activity). Thus, results indicate that, irrespective of association type, the MTL remains an important brain region for forming recollection-based associations across the adult lifespan. In particular, robust activation throughout the bilateral hippocampus speaks strongly to the role of this region in the successful formation of meaningful links between discrete pieces of information, a process referred to as associative binding (Staresina and Davachi, 2008; Yonelinas, 2002; Yonelinas et al., 2005). The fact that the hippocampus is involved in the successful formation of both item-item and item-context associations that lead to subsequent recollection of that association further points to a role of the hippocampus in forming strong associative links irrespective of how associations may be presented during encoding (Diana et al., 2007). Similarly, involvement of the PHC and PrC across II and IC associations suggests that MTL subregions also contribute to

Table 4
Differences in Recollection between association trial types (II and IC).

	T&T coordinates						
	BA	H	x	y	z	k	*t*
II>IC (Young)							
Inferior/Medial/ Superior Occipital Cortex	18/19/ 39	R	12	−78	0	1550	11.07
	18/19/ 31	L	−5	−83	2	750	8.54
MTL Subregions							
Posterior PHC	35/36	R	17	−42	−4	74	7.11
II>IC (Old)							
Inferior/Medial/ Superior Occipital Cortex	17/18/ 19/31/ 39	L	−7	−85	4	13795	11.95
	17/18/ 19/31/ 39	R	12	−72	−2		11.04
Agular Gyrus	39	L	−51	−53	20	228	4.51
*Precuenus	31	M	0	−55	44		4.03
IC>II (Young)							
Cuneus^	17/18	L	−16	−96	2	451	6.70
	17/18	R	18	−98	11	487	5.86
IC>II (Old)							
Cuneus	17/18	R	18	−99	11	278	5.70
	17/18	L	−24	−99	13	329	5.47

Differences in Recollection activity between association trial types (II, item-item; IC, item-context); BA: Brodmann's area; H: hemisphere (L: left; R: right; M: medial); x, y, z represent peak Talairach coordinates; k, cluster extent; t: statistical t value; *selected subpeaks from larger cluster. ^Regions showing age-related decreases in activation including right inferior occipital cortex for II > IC association (x = 10, y = −77, z = 11; k = 315; t = 4.93) and both left (x = −18, y = −89, z = 1; k = 208, t = 4.45) and right (x = 22, y = −93, z = 8; k = 221; t = 4.13) cuneus for IC > II association.

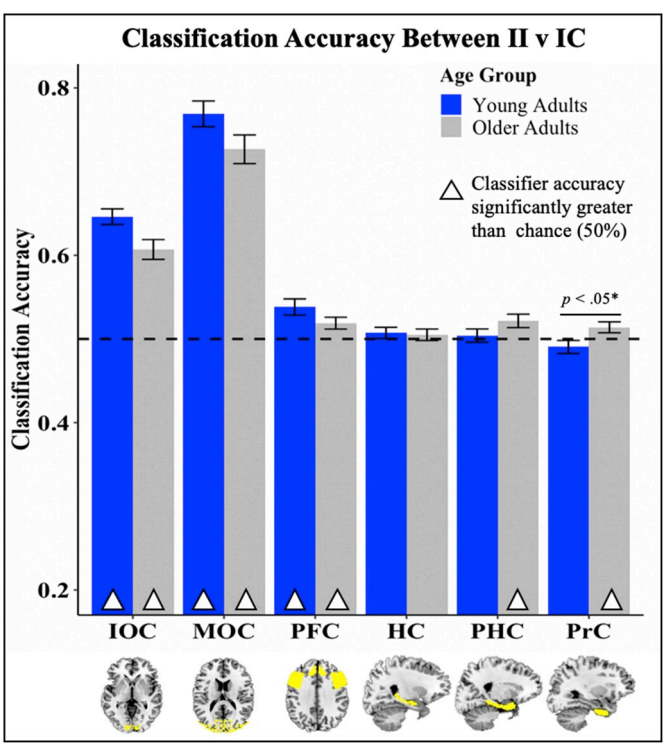

Fig. 4. Multivoxel classification accuracy for item-item (II) and item-context (IC) trials across younger and older adults. * = significance after controlling for univariate activation. PrC = perirhinal cortex; IOC = inferior occipital cortex; MOC = middle occipital cortex; PFC = prefontal cortex; HC = hippocampus; PHC = parahippocampal cortex; PrC = perirhinal cortex.

recollection-based associative binding irrespective of the association type. Finally, results support the needed involvement of all three MTL subregions in successful associative encoding across the adult lifespan.

In addition to common MTL activity across both age groups, younger adults exhibited greater recollection success activity in right posterior PHC compared to that observed in older adults. Direct comparisons between Recollection success across conditions also showed this region to be recruited to a greater extend for II Recollection compared to IC Recollection in younger adults. No MTL region showed greater activity in older compared to younger adults at a corrected threshold. These results are also consistent with a large prior literature that finds age-related decreases in PHC recruitment during associative memory encoding (Angel et al., 2013; Dennis et al., 2008; Gutchess et al., 2005). Often when such age-related reductions in MTL recruitment are observed in the literature they are accompanied by age-related decreases in memory success, as was the case in the current study. That is, both recollection rates and discrimination of old versus new pairs was poorer among older adults in the current study. This pattern of behavioral differences may suggest that the observed age-related reduction in the PHC activation on successful associative encoding trials may, alongside their reduction in occipital activation noted above, reflect an impairment in encoding and binding of item details during encoding that is necessary to discriminate target from lure face-scene pairs. This interpretation is consistent with a wealth of aging research that has linked age-related decreases in MTL activity with decreases in memory success and specifically, recollection-related processing (Angel et al., 2013; Dennis et al., 2008; Gutchess et al., 2005; Mitchell et al., 2006).

Differential processing across association types. With respect to our main investigation, both univariate and multivariate analyses detected differences in the magnitude of activation and patterns of neural responses underlying the type of association encoded (see Fig. 4). While both univariate and multivariate differences were identified in the occipital cortex and MTL, multivariate differences alone were identified in the PFC. Additionally, activation within both occipital regions and the MTL exhibited age-related differences both with respect to overall recruitment (i.e., univariate differences) and classifier accuracy. The results suggest that these regions are not only sensitive to the type of information being encoded, but also that there are age-related differences in this process.

As expected, both univariate and multivariate methods were able to detect differences in processing within visual cortex as a function of II and IC associations. Specifically, in both age groups, large portions of occipital cortex, including bilateral midline and lateral occipital cortex, extending into fusiform gyrus exhibited greater BOLD activation for successful encoding of II compared to IC associations. Given the configural differences across association types (despite the content-equated nature of the stimuli used across both association types), this is not surprising. The extent of this activation may simply reflect the larger visual field accompanying II compared to IC displays, as well as the need to process both face and scene as two distinct items across a larger visual field. In line with this evidence, greater activation in fusiform gyrus has been correlated with the number of fixations made during encoding (Liu et al., 2017). While eye movements were not recorded in the scanner, it may be reasonable to assume that more eye movements were required in the II condition. Alternatively, IC trials exhibited greater occipital activation in more posterior occipital cortex, primarily in bilateral cuneus. The finding that the cuneus is more active for integrated information (i.e., IC associations) is in line with previous work showing that global scene information contained in low spatial frequencies differentially activates the cuneus (Ramanoël et al., 2015). It is also consistent with prior work suggested that the cuneus is more active when dissimilar physical features are overlaid within a single percept (Kauffmann et al., 2014). While the two interpretations are not mutually exclusive, additional research is needed to elucidate the exact reason for these visual differences. Finally, while differential recruitment with respect to association type was observed in both age groups, we also identified an

age-related reduction in occipital activation for both II and IC associations. Discussed in more detail below, we posit that such age differences reflect age-related dedifferentiation of the specificity of neural activity with regard to different types of associations.

The multivariate classification analysis also denoted distinct patterns of neural activation evoked by II and IC associations within the occipital cortex in both young and older adults. Specifically, results showed that, despite the same stimuli (face and scenes) present within each association type, both the inferior and medial occipital cortices exhibited above chance classification with respect to II and IC presentations in both age groups. In contrast to the hippocampal findings (discussed below), results suggest that, it is not the content of the stimuli, but rather the configuration of the stimuli that is critical to the representation of information in occipital cortex. This is not altogether surprising giving that the occipital cortex is sensitive to both the physical and categorical properties of visual stimuli (Gibson, 1969; Kanwisher et al., 1997; Kapadia et al., 2000). With respect to associative encoding, the classification results suggest that the initial representations for II and IC trials, which are processed first by sensory regions, prior to being relayed to higher-order regions for memory processing, are unique with respect to the type of association and spatial configuration in which they are presented. While this may reflect pure sensory processing differences, as opposed to encoding-related differences, it is critical to note that encoding is based upon sensory processing. Thus, the two interpretations are not mutually exclusive.

It should be noted that while both age groups exhibited highly significant classification in occipital cortex, older adults did exhibit lower, but not statistically significant ($ps = 0.06$), levels of classification compared to younger adults, once we controlled for univariate analyses in both inferior and middle occipital ROIs. Past research has linked reduced neural distinctiveness and dedifferentiation in occipital cortices with poorer cognitive outcomes in older adults (Bowman et al., 2019; Carp et al., 2011; Koen et al., 2019; Park et al., 2004; Saverino et al., 2016; St-Laurent et al., 2014). The current set of results adds to this literature identifying older adults' ability to establish distinct neural patterns of activation within portions of occipital cortex, with respect to differences in configural displays. Results also suggest that age-related differences in neural distinctiveness may not be as large as previously reported once baseline measures of neural activation are taken into consideration. However, this relative decrease in the specificity of neural patterns within the occipital cortex may contribute to age differences in downstream processing as older adults attempt to transform these representations into long term memory traces.

The idea that less distinctive processing in older adults leads to poorer memory is supported by a wealth of both neuroimaging (e.g., Bowman et al., 2019; Koen et al., 2019; Saverino et al., 2016; St-Laurent et al., 2014; Voss et al., 2008; Zheng et al., 2018) and behavioral work (Benjamin, 2016; Benjamin et al., 2012; S. C. Li et al., 2005; Stephens and Overman, 2018). For example, Saverino et al. (2016) showed that neural distinctiveness at encoding supports associative memory and that age-related reductions in this selectivity of neural recruitment correlated with age-related memory deficits. Similarly, Stephens and Overman (2018) showed that age differences in associative memory were described well by a computational model in which older adults were assumed to store less diagnostic information in memory, either through reduced accuracy of encoding or reduced distinctiveness of memory features. While our analyses did not find an age difference in the relationship between classification accuracy and d' in any ROI, it may be that reductions in the specificity of encoding representations have an effect on subsequent retrieval-related processing, which leads to behavioral outcomes. Future research is needed to investigate this as well as the nature of the differences in neural patterns detected by the classifier.

In contrast to occipital regions, *w*hen taking into account subsequent memory activity, neither age group exhibited univariate differences within the PFC as a function of associative type. Yet, both groups exhibited significant classification of II and IC trials within the PFC, indicating that the uniqueness of neural activation patterns observed in the occipital cortex is carried forward to the PFC. Noted in the methods, we examined classification within PFC regions shown to support associative memory success in both age groups (Kim, 2011; Maillet and Rajah, 2014). Unlike the visual cortex which processes and represents the basic physical configurations of the associative display, as well as the content of information being encoded, the PFC is tasked with more strategic operations with respect to forming successful memory traces (Fletcher et al., 1998; Rajah & D'Esposito, 2005; Shing et al., 2010). With respect to associative memory, the PFC has been posited to reflect the organization of information for encoding and binding processing undertaken by the MTL (McIntosh et al., 1997; Shing et al., 2010; Zeithamova and Preston, 2010). The current results add to this literature, showing that such higher order processing with the PFC is undertaken through unique patterns of neural activation reflecting the specific type of association to be encoded. Taken together with the occipital findings, results further suggest that, prior to binding within the hippocampus, associative information is processed and represented within the encoding network as a function of the type of association being encoded. Specifically, results suggest that neural specificity with respect to item-item and item-context information may be an inherent part of the encoding network (at least prior to binding within the hippocampus).

With respect to processing with the MTL, we identified differential processing within all MTL regions in both age groups with respect to the type of association being encoded. Interestingly, the only MTL subregion to exhibit univariate differences in activation between encoding conditions at a corrected threshold was right posterior PHC, which exhibited greater activity for II compared to IC recollection in younger adults (see Fig. 3c). The location and direction of this activity was not predicted by our *a priori* hypotheses based on the BIC model. The BIC model would suggest that II associations would be mediated by the hippocampus, with possible extra support provided by the PrC because the links are inter-item. Posterior PHC is most often associated with spatial processing and context processing in memory studies (Duzel et al., 2003; Hayes et al., 2004; Ryan et al., 2010). Increased activity in this region for II compared to IC recollection suggests that the scene stimuli used as one of the 'items' may have been processed in a more contextual manner than as an item; whereas again, IC associations were perceived as more integrated. Future studies using a similar configural design, with different stimuli are needed to further examine these possibilities.

We posited that, based on its role in supporting item memory and item-item encoding, that the PrC would contribute to encoding success for II, but not IC pairs. While II encoding activity was found in anterior hippocampus and PrC, the level of activation did not differ from that observed in the IC condition. One possibility for this lack of difference in PrC may stem from the fact that IC trials were unitized to a certain degree, such that they were viewed as a single item. Within the context of associative memory, unitization is a process by which two items are viewed as a single unit (Graf and Schacter, 1989; Tulving and Patterson, 1968; Winograd and Rivers-Bulkeley, 1977). Studies of visual associative memory have attempted to unitize items by presenting the items in a manner than suggests their integrated function (e.g., presenting a can opener over top of a can; Tibon et al., 2014) or placing them in a contiguous (opposed to separated) configuration (Kan et al., 2011). Past research has also sought to induce unitization through verbal instructions (Parks and Yonelinas, 2015). Additionally, the BIC model predicts that PrC is involved in unitization in addition to its possible role in supporting item-item associations (Diana et al., 2007). While not our intention, the current IC configuration may have induced unitization by presented the face and scene in an integrated manner. Given that verbal instructions required a welcomeness judgement be made across both the face and scene stimuli in both the II and IC conditions, the physical layout of the stimuli in the IC condition could have useful to participants in assessing this judgement. While this was not our intended behavioral approach, any differences within MTL subregions would still speak to

encoding differences based upon processing as opposed to stimulus characteristics alone.

Additionally, MVPA did not detect trial type differences within any subregion with the MTL in younger adults. Thus, despite the fact that the younger adults exhibited greater activation in the right posterior PHC for II associations, the underlying pattern of neural activity between II and IC associations did not significantly differ from one another in this region. This finding suggests that the nature of the PHC involvement, as well as that of the PrC and the hippocampus, was similar across association types. Like our univariate findings, this differs from our *a priori* hypotheses suggesting that II and IC associations would elicit unique neural patterns and recruitment in MTL subregions based on the differential nature of processing items opposed to contexts. This was especially interesting with respect to the hippocampus. With regard to associative memory, the role of the hippocampus is posited to support the *binding* of discrete pieces of information (Eichenbaum et al., 1992; Eichenbaum et al., 2007; Ranganath, 2010a, 2010b). That is, while PrC and PHC are posited to represent item and context information, respectively, the hippocampus encodes representations of the relationships between discrete pieces of information. The current results suggest that, for information of a specific type (e.g., faces and scenes), this linked representation in the hippocampus at encoding does not differ as a function of how the association is presented at encoding (II v IC). Rather, the current results suggest that associative memory representations within MTL subregions in young adults are not sensitive to the type of association being formed, when stimuli content is held constant. This finding expands our knowledge of associative processing in the MTL because we are one of the few studies to de-confound stimulus type from association type. In doing so, our results suggest that differences in MTL activity observed in most previous research that was attributed to association type, may in fact have been due to differences in the types of stimuli used.

With regard to the role of the MTL is associative memory in older adults, a somewhat different pattern of results emerges. While older adults failed to exhibit differences in univariate activity within any MTL subregion across II and IC recollection, they did small, but significant classification of II and IC associations in bilateral PHC and PrC. The absence of univariate activation differences in older adults suggests that, despite differences in the configural layout amongst associative trials types, older adults do not differentially recruit MTL subregions for the successful encoding of different types of associative pairs. This finding is inconsistent with recent work from Memel and Ryan (2017) which found that both young and older adults exhibited differences across MTL subregions when encoding associative pairs that were either separated in space (similar to our II condition) or combined in a single image (similar to our IC condition). Two critical differences across study designs could account for these inconsistent results. First, the prior study did not have the power to assess successful memory and thus focused its analysis on encoding of all items, irrespective of success. Thus, the current work extends this prior study by examining results specific to the successful encoding of associative pairs under different configural presentation. Second, the prior study used an ANOVA approach to identifying differences in the MTL. As such, the subregion differences they reported were identified by examining condition-related differences while collapsing across both age groups. Using this approach with our data, we too would come to similar conclusions. That is, when we include all subjects in a second level analysis examining II and IC differences, we find that the MTL differences identified above in our younger adults is found when collapsing across young and older adults. However, we argue that investigating data in the manner undertaken in the current study, allows for a more accurate assessment of trial type differences *within* each age group, which was our main question of interest.

Despite the absence of univariate differences in MTL subregions in older adults, unique patterns of activation within both PrC and PHC for II and IC associations suggest that older adults maintain different representations across association types within some MTL subregions. Critical to this finding, the individual elements of the stimuli were not different across association types (faces, scenes), only was the manner of configural presentation during encoding. While the PrC has been linked to item processing (Davachi, 2006; Haskins et al., 2008) and the PHC to contextual processing (Epstein, 2008; Hayes et al., 2007), the current results further this literature by suggesting that identical stimuli elements can be distinguished by these MTL subregions based upon the manner of association within older adults. Based on the BIC model, we predicted that these differences would be found across both age groups. However, noted above, neither PHC or PrC classification was observed in younger adults. The absence of classification differences in the younger adults, combined with the findings in older adults, may suggest that the need for cortical MTL regions to utilize discrete representations for II and IC associations may only emerge as a function of aging. Potentially as item and context information is less distinct elsewhere in the encoding network. To this point, not only did older adults exhibit above chance classification within the PrC, but this was the only region to exhibit a significant age interaction after controlling for univariate activation. The fact that patterns of neural activity across association types are more unique in older adults may suggest a greater reliance of older adults to utilize item and contextual processing in the PrC when forming associations of different types. While the effect is relatively small, this finding is consistent with our *a priori* hypothesis suggesting that, based on relative preservation of the PrC in older adults (Daselaar et al., 2006; Raz, 2005), they may be in a position to utilize PrC when encoding II, opposed to IC, associations. Again, given the size of the classification effect in the PrC, additional work is needed to replicate this finding, as well as identify what type of differences the PHC and PrC are exhibiting. Finally, despite classification differences observed in the PHC and PrC in older adults, the multi-voxel pattern analyses did not detect significant differences between II and IC associations in the hippocampus proper. Thus, like younger adults, the results suggest that the bound representation created by the hippocampus are similar for same domain information, irrespective of prior input and the type of association being encoded.

3.3. Limitations and future directions

By controlling for stimulus characteristics, we were able to investigate neural differences in associative memory based solely on the type of association being formed. As one of the first studies to use this approach of understanding the role of MTL subregions with respect to association type, replication is needed to confirm all results with additional studies and larger sample sizes. Additionally, it would be advantageous to examine this question using a variety of different stimuli, beyond those in the current study, in order to clarify the extent to which regions of the MTL are more sensitive to stimulus characteristics or to the type of associative processing that is being encoded. Furthermore, it would be helpful to investigate whether other visual configurations or experimental manipulations can induce pairs to be processed as item-item vs. item-context. Given the sensitivity of the PrC to association type in older adults, it would be of interest to see if this uniqueness of representation is maintained at retrieval and is supportive of memory accuracy. It is also of interest to clarify the role of unitization in memory success, especially with regard to PrC's involvement in unitization (e.g., Haskins et al., 2008). Future work that builds on the current results could explore that nature of representations underlying II and IC configurations (e.g., representational similarity analysis). This would be useful in determining what differences in neural representations are identified by the classifier. While RT can be a confound in MVPA analyses (Todd et al., 2013), with regard to differences in RTs between II and IC trials, we note that, in the current study, this metric captures differences in making a welcoming decision (the incidental encoding task), but is unlikely to reflect total processing time or total eye movements (Liu et al., 2017). Eye movements may be a metric to consider in future studies, as they

have been shown to correlate with hippocampal activity in young adults, with this relationship attenuated in aging (Liu et al., 2017; Liu et al., 2018).

4. Conclusions

The current study allowed for the investigation of behavioral and neural differences in associative memory based on the type of association, in the absence of any confound with regard to stimulus characteristics. Critically, both younger and older adults exhibited differences in both the magnitude of activation and pattern of neural responses related to the type of association. Most notably, large portions of occipital cortex, expanding into temporal and parietal cortices were more active for II compared to IC associations; alternately, the cuneus was found to be more active for item-context compared to item-item associations. Beyond overall differences in the magnitude of activation in the occipital cortex, results from our MVPA analysis in young adults showed that ROIs in both occipital cortex and PFC, but not the MTL, exhibited unique patterns of activation for II and IC associations. Taken together, we interpret this pattern of results as indicating that, prior to binding within the hippocampus, the encoding network maintains unique representations of associations as a function of the manner by which the information is encoded (II v IC). However, the hippocampus and MTL operate in a domain-general manner with respect to binding information into long-term memory. These results both expand the BIC model with respect to associative encoding and question its assumptions regarding specialization within cortical MTL regions. Specifically, the BIC model predicts that the MTL encodes information with respect to the type of association being encoded, particularly with regard to the function of the PHC and PrC. That is, BIC posits that despite hippocampal involvement across all types of associations, the PHG will be involved in the encoding of context and PrC can be utilized to support item-item associations (Diana et al., 2007; Ranganath, 2010a). The absence of either univariate or multivariate differences within the hippocampus speaks to the universal role of this region with respect to its contributions to associative binding of all association types. That is, our results support a domain general view of the hippocampus with respect to its role in creating bound representations during encoding. Irrespective of the uniqueness of item-item and item-context representations within occipital and PFC, the hippocampus exhibited no distinction between the two types of associations. Despite overall greater activation in posterior PHC for item-item compared to item-context associations (a result not predicted by our *a priori* hypothesis or the BIC model), the absence of representational differences between trial types in the PHC suggests that while greater effort may be required by the PHC to encode item-item associations, a similar process across association types is undertaken by this MTL region.

A similar conclusion can be made in older adults with respect to the encoding network and the role of the hippocampus in associative binding. However, older adults did exhibit above chance classification of II and IC associations in the PHC and PrC, and significantly greater classification accuracy in the PrC compared to younger adults. We posited that, based on the BIC model, older adults may be able to take advantage of the PrC to aid in item-item binding, producing a different activation pattern within PrC for item-item and item-context binding. While our results do not address this point directly, they do suggest that older adults maintain unique representations within the PrC with respect to the type of association being encoding. Further research is needed to elucidate how this finding relates to behavior and whether it is also maintained during retrieval of item-item and item-context associations.

CRediT authorship contribution statement

Nancy A. Dennis: Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Amy A. Overman:** Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing - original draft, Writing - review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Courtney R. Gerver:** Software, Validation, Formal analysis, Investigation, Data curation, Visualization. **Kayla E. McGraw:** Formal analysis, Investigation, Visualization. **M. Andrew Rowley:** Formal analysis, Investigation, Visualization. **Joanna M. Salerno:** Formal analysis, Investigation, Visualization.

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Appendix A. Supplementary data

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