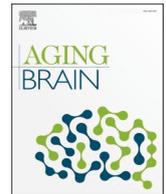




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Neural distinctiveness and discriminability underlying unitization and associative memory in aging

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ABSTRACT

Previous work has suggested unitized pairs behave as a single unit and more critically, are processed neurally different than those of associative memories. The current work examines the neural differences between unitization and non-unitized memory using fMRI and multivoxel analyses. Specifically, we examined the differences across face-occupation pairings as a function of whether the pairing was viewed as a person performing the given job (unitized binding) or a person saying they knew someone who had a particular job (non-unitized binding). The results show that at encoding and retrieval, the angular gyrus can discriminate between unitized and non-unitized target trials. Additionally, during encoding, the medial temporal lobe (hippocampus and perirhinal cortex), frontal parietal regions (angular gyrus and medial frontal gyrus) and visual regions (middle occipital cortex) exhibit distinct neural patterns to recollected unitized and non-unitized targets. Furthermore, the perirhinal cortex and medial frontal gyrus show greater neural similarity within subsequently recollected unitized trials compared to non-unitized trials. We conclude that an encoding based strategy to elicit unitization can produce greater associative memory compared to non-unitized trials in older adults. Additionally, when unitized trials are subsequently recollected in the perirhinal cortex older adults show greater neural similarity within unitized trials compared to non-unitized trials.

1. Introduction

The ability to form and remember correct associations is essential for recollection in episodic memory. Despite this necessity, the ability to successfully recall associations can be a difficult task in older adults (see [54] for meta-analysis). For example, associating names with faces or stores with addresses can be increasingly difficult as a person ages. The associative deficit hypothesis attributes older adults' poor associative memory performance to an age-related difficulty in binding together novel pieces of information [51,53,52]. Unitization has been explored as encoding strategies intended to enhance the binding process and thus support older adults' associative memory [41,75]. The current study seeks to elucidate the neural basis underlying such associative memory strategies in aging individuals. Specifically, we use multivariate pattern classification and neural distinctiveness analyses to investigate whether the advantage afforded by a visual imagery task, used to promote unitization at encoding, supports discriminability and

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distinctiveness in the neural patterns of activation throughout the associative memory network in older adults.

Unitization is an encoding process used to bind arbitrary items together into a meaningful unit [2,5,16,28,59,60,63]. Specifically, the strategy of unitization aims to integrate items in one bound unit which would reduce the involvement of hippocampal-based recollection and increase reliance on perirhinal-based familiarity processing [27], implying unitization may be processed more similarly to a single item [29,32,33,81]. Unitization strategies have also been applied to unrelated pairings [34,48]. For example, asking younger adults to encode face pairs as a “married couple” resulted in better associative memory than two faces encoded as two unrelated individuals [59]. Importantly, this finding has been translated to older adults in which they showed greater associative memory in the unrelated pairs that were unitized compared to non-unitized pairings [34]. Critically, unitization instructions have been shown to improve associative memory in older adults [39,47,56,85] by increasing both recollection and familiarity-based responding (e.g., [47]).

One of several often-utilized strategies for inducing unitization has been visual imagery. By visualizing, for example, a color as a feature of an item, it is more likely that a person will create a unitized image of a single object with integrated characteristics [5,56,59,75,84]. For example, Bastin and colleagues [5] behaviorally, found enhanced associative memory in both older and younger adults using item-color pairings with unitized compared to non-unitized instructions. Using the same paradigm, Zheng and colleagues [84] found that age differences were reduced in the unitization instruction group when considering familiarity-based source recognition judgments. This reduction in age differences in memory is found across a variety of imagery manipulations including words with color, size, and a combination of color and size, thus demonstrating how associative memory performance is better in the unitized compared to the non-unitized condition for younger adults [75]. Similarly, face-word pairings that encouraged unitization via visualization and intra-item binding (e.g., imagine a person was a skier) were better remembered than those that encouraged inter-item binding (e.g., the person had simply interacted with a skier) [56,59]. The current task was also run in a sample of younger adults [64]. The results suggest that, in younger adults, unitized face-job pairings are better recollected compared to non-unitized pairs [64]. While older adults have shown advantages for unitized associations, it has typically been related to their use of familiarity [1,59,84]. It is unknown if older adults will be able to use unitization to tap into similar recollection performance as that seen in young adults. The current work aims to examine how visual imagery, when using unitization-based strategies, can enhance recollection-based associative memory both behaviorally and neurally in older adults. Specifically, we examined face-occupation pairings and asked participants to employ two different visual imagery strategies: one in which the face is imagined *doing* the occupation associated with it to help *unitize* the pairing, and the other in which the face is imagined *speaking* about knowing someone else with that occupation. In line with previous work using this task [56], we predict that the ‘doing’ condition will unite or integrate face-occupation pairings, whereas the ‘speaking’ condition will maintain a separation across the face-occupation pairing.

Neurally, associative memory has been shown to rely on activity in a common set of regions, including the hippocampus (HC), medial frontal gyrus (MFG), and angular gyrus (AG) (for a meta-analysis see [6,73]). Specifically in these regions, associative memories elicit increases in blood-oxygen-level-dependent (BOLD) activation within the HC for recollection-based associative binding across novel items [17,19,61,70,80]. Additionally, BOLD activation has been found in the perirhinal cortex (PrC) when using encoding-based strategies like unitization [31,48,70] during an associative memory task, presumably because item-item associations are encoded and retrieved in a manner more similar to that of an item in memory. Furthermore, when looking at associative memory tasks BOLD activation has been found in the MFG when detecting if incoming information is congruent with its encoded memory state [4]. While previous work has found the foregoing areas to be active during both associative memory and unitization, for the current study it is critical to also look at brain areas associated with imagery and schematic memory, as participants in the current study were instructed to use visual imagery to imagine a person enacting the associated occupation. Thus, the MFG is also involved in the retrieval of schemas and is engaged when people attempt to establish connections across associative items [8,44,74]. Additionally in the AG, BOLD activation was found in schema retrieval which allows for the encoding and consolidation of new information [77]. Wagner and colleagues [77] found multi-voxel representations of different schema components in the AG during retrieval of novel, but related, information. They concluded that the AG recombines encoded schemas into one integrated memory. In other words, the AG may guide the binding of information from encoding to retrieval by condensing encoded information for better retrieval recollection [7,67,77]. If regions like the AG and MFG are active during the unitized condition, it provides evidence of participants’ ability to use the strategy given to them. In addition to this core associative network, occipital regions have been consistently activated in visual memory tasks [22,57]. Specifically, classification accuracy was able to discriminate between visual imagery and stimulus-driven perception in the middle occipital cortex (MOC), showing the MOC is associated to visual imagery [72] and is linked to word-dependent source memory [58]. Park and colleagues [58] found that for multivariate neural activity in the MOC, contextualized words are processed more like pictures, aiding to the imagery operations of memory processing.

While past work has focused on univariate BOLD differences within this associative network, more recent work is emerging that places an emphasis on understanding memory processing in aging using multivariate analyses. Related to the current work, multivoxel pattern analysis (MVPA) in older adults, has been used to identify unique neural patterns associated with subtle differences in stimulus properties, such as classifying true and false memories [10,11,20], categories like faces and houses [9,36] and recollection- and familiarity-based responding versus responding at chance [37]. Previous work from our own group has found that neural patterns across the encoding network, including those within prefrontal and occipital cortex, can reliably distinguish between different types of associative memory during encoding [21,24]. The fact that such subtle differences in neural processing are detected in older adults speaks to the idea that even for similar sets of information, different encoding instructions can result in uniquely represented associations in the encoding network. That is, neural representation for similar information can differ as a function of how information is processed at encoding.

The examination of neural patterns at a multivariate level also gives insight on the distinctiveness of different memory processes

and how neural representations contribute to and support episodic memory performance [69]. By examining the distinct neural patterns related to specific memory behaviors, such as associative recollection, we can gain further insight into how unique representations during encoding lead to successful memory. Similar representations within an encoding condition indicate that trials within that condition share overlapping representations of information, which is to be expected when representing several related items from the same category [43,69]. However, when information is more distinctly processed in memory, neural patterns will represent this uniqueness, reflected in less overlapping representation within a category of stimuli and instead, more distinct patterns of neural activity. In neuroimaging memory research, different types of associations, such as unitized associations compared to non-unitized associations, rely on different neural processes [46,70]. Knowing how memory is represented and how those representations are related to successful retrieval is important for understanding how we might be able to improve memory processing older adults. It is unknown how older adults' neural activation may differ in their ability to encode and retrieve information when using a unitization-based strategy versus an associative memory strategy compared to younger adults. Specifically, using neural distinctiveness analyses to identify differences in the neural patterns underlying recollection-related activity. Additionally, determining if there are any underlying unitization for associative memories at each memory stage. Our focus is on regions within the core associative memory network.

The current study aims to examine whether a visual imagery encoding strategy, intended to promote unitization, will result in improved recollection-based associative memory in older adults compared to young adults. The current study also aims to determine whether use of such an encoding strategy enhances the distinctiveness of memory representations during both encoding and retrieval. If the condition promoting unitization is effective in enhancing associative memory in aging, as we have seen in previous work implementing a strategy-based unitization manipulation [5,16,23,34,63], then we expect older adults to have greater recollection in the unitized condition than in the associative memory condition and be on par with young adults. Neurally, we expect unitized and non-unitized memory for targets to show neural discriminability within the core network, including the HC, PrC, MFG, AG, and MOC. Further, we predict that the unitized encoding strategy pairs would show greater distinctiveness compared to the non-unitized associative memory pairs when taking into account subsequent recollection of the associative information [43,68,69]. Our approach was undertaken in order to assess how encoding strategies are processed during an associative memory task.

2. Materials and methods

2.1. Subjects

25 older adults were recruited from the Centre County community and 28 younger adults were recruited from The Pennsylvania State University. The older adults received monetary compensation for their participation. Participants were screened for history of psychiatric and neurological illness, head injury, stroke, learning disability, medication that affects cognitive and physiological function, and substance abuse. On the day of the study, all participants provided written informed consent for a protocol approved by The Pennsylvania State University Institutional Review Board. All participants were native English speakers or had learned English before the age of 8, with normal or corrected-to-normal vision and were right-handed. All participants had completed high school. All 25 older adults were included in all analyses ($M_{age} = 70.08$ years, $SD_{age} = 6.77$ years, range = 60–84 years; 14 female, 11 male). Participants identified as white ($n = 23$), more than one race ($n = 1$), or preferred not to answer ($n = 1$), and were all well-educated ($M_{years} = 16.50$, $SD_{years} = 2.65$). All older adults scored above a 27 on the Mini Mental State Examination (MMSE; [25]; $M = 29.22$, $SD = 1.02$) and below a 3 on the Geriatric Depression Scale (GDS; [78]; $M = 0.88$, $SD = 1.17$). All 28 younger adults were included in all analyses ($M_{age} = 22.11$ years, $SD_{age} = 0.57$ years, range = 18–28 years; 24 female, 4 male). Participants identified as white ($n = 15$), as well as Asian/Pacific Islander ($n = 10$), and more than one race ($n = 3$), and were all well-educated ($M_{years} = 15$, $SD_{years} = 0.36$).

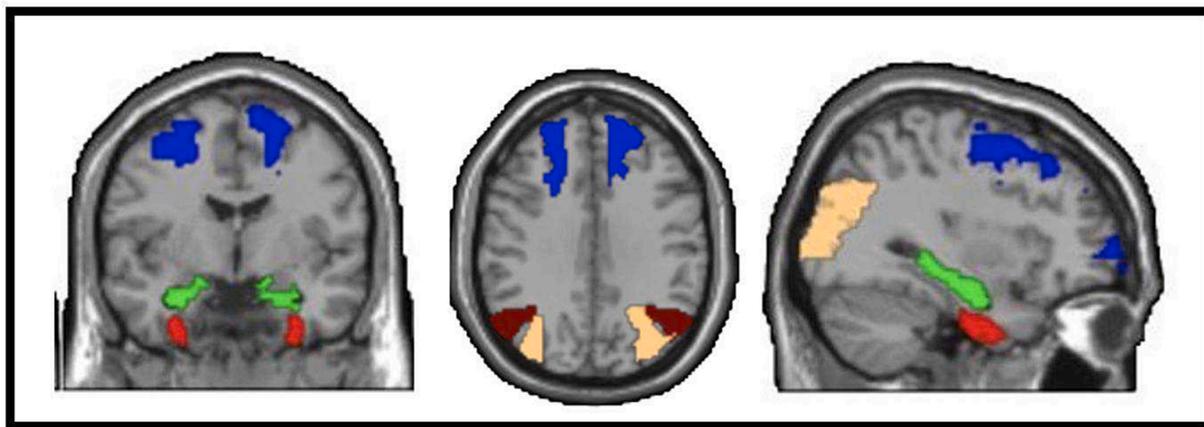


Fig. 1. Regions of interest for multivariate classification. Regions defined from AAL pickatlas. Tan = MOC, Dark Red = AG, Blue = MFG, Green = HC, Light Red = PrC. Slice numbers: $y = -6$; $z = 36$; $x = 32$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.2. Regions of interest (ROIs)

Based upon previous work mentioned above, we restricted our analysis to the angular gyrus (AG), hippocampus (HC), perirhinal cortex (PrC), medial frontal gyrus (MFG), and middle occipital cortex (MOC) [4,7,17,19,31,72]. The ROIs were defined anatomically and created using the human AAL Pickatlas through SPM12 [25] (See Fig. 1).

2.3. Stimuli & Procedure

The current design and stimuli were modified from Overman & Stephens [56] and previously reported in Ricupero and colleagues [64] where only the young adult sample was analyzed. The experimental stimuli consisted of 144 black and white photographs of faces (see [13] for standardization details) and 144 single-word occupations (ex: pianist; welder), with a majority of the occupations taken from Yovel & Paller [82] and additional occupations added as needed. During encoding, participants were shown an image of a face and either a name tag stating “Hello, I’m [occupation]” (‘doing’ condition) or a speech bubble stating “I know [occupation]” (‘speaking’ condition). Participants were asked to imagine the face-occupation association and remember the pairings using one of two strategies designed to either promote unitization (‘doing’) or simply to create an association (‘speaking’). Specifically, in the ‘doing’ condition participants were asked to imagine the pictured individual performing actions related to the occupation. In the ‘speaking’ condition participants were asked to imagine the pictured individual knowing someone else with the given occupation. During practice, participants were asked to repeat the instructions back and explain what they should be imagining during the two strategy tasks. Participants were prompted by an instruction screen as to which strategy they should employ, with both encoding strategies used in each run. Participants were also asked to indicate, using a four-point button box, how easy or how difficult it was to use the given strategy for each unique face and job pairing (response options included: very difficult, somewhat difficult, somewhat easy, very easy). Finally, the background screen color randomly alternated between either yellow or blue, with each appearing 50% of the time (analyses related to this color manipulation were not included in the current set of analyses).

During encoding trials, participants received a prompt for a duration of 2.5 s indicating which of the strategies to use (i.e., speaking). Participants then viewed 9 trials followed by a prompt to use the other strategy (i.e., doing) and then viewed 9 trials. This process repeated itself twice per run. Eleven participants completed this version of task before it was changed to alternate between instructions after 18 trials ($N = 14$), and prompt lasting 5 s. There were no repetitions of strategy in each run (i.e., participants saw one doing and one speaking strategy block per run). This change was made in response to feedback from older adults. There were no significant differences in any result between versions. During retrieval trials, participants were presented with both target pairs and recombined lure pairs on a white background. Most face-job pairs were recombined within the same condition.¹ Participants responded during retrieval using a standard Remember-Know-New paradigm [79]. They responded ‘Remember’ if they remembered specific details about the face-occupation pair, ‘Know’ if they believed they had seen the pairs together previously, but could not remember specific details of the pair, and ‘New’ if they believed the pair was not presented together previously. Each retrieval run included 36 trials, 24 targets and 12 recombined lures. The order of runs included two encoding runs, followed by two retrieval runs, repeated twice (for a total of four encoding and four retrieval runs). All encoding and retrieval trials were presented for 5 s. Participants were provided with practice prior to beginning the task to facilitate learning the two encoding strategies. Participants were given a total of 8 trials at encoding in which they a prompt indicating they should use one of the strategies, then viewed 4 trials, and then were presented with a prompt to use the other strategy and viewed another 4 trials. Following encoding practice, they also had 8 trials of retrieval practice with 6 of those trials being targets. (See Fig. 2).

2.5. Image acquisition

Structural and functional images were acquired using a Siemens 3-T scanner equipped with a 20-channel head coil, parallel to the AC-PC plane. Structural images were acquired with a 2300-msec repetition time, a 2.28-msec echo time, a 256-mm field of view, 192 axial slices, and a 1.0-mm slice thickness for each participant. Echoplanar functional images were acquired using a descending acquisition, a 2500-msec repetition time, a 33-msec echo time, a 192-mm field of view, a 80° flip angle, and 64 axial slices with a 2.0-mm slice thickness resulting in 2.0-mm isotropic voxels.

2.6. Anatomical data processing

A total of 1T1-weighted (T1w) images were found within the input BIDS dataset. The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection [76], distributed with ANTs 2.2.0 ([3], RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a Nipype implementation of the ants-BrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast (FSL 5.0.9, RRID:SCR_002823, [83]). Brain surfaces were reconstructed using recon-all (FreeSurfer 6.0.1, RRID:SCR_001847, [14]), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the

¹ Due to an error in programming, a subset of lures were recombined between (rather than within) condition. All between condition lures were removed from behavioral and imaging analyses.

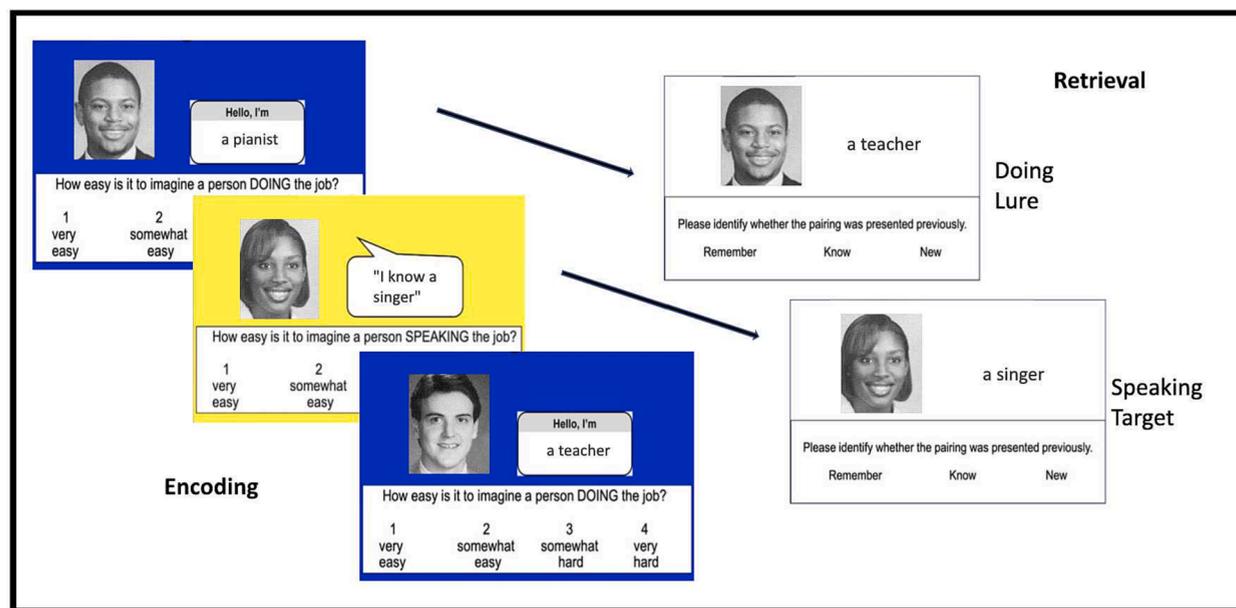


Fig. 2. Based on Overman and Stephens [56], Example stimuli for the unitized and associative memory conditions. Face and job pairings were presented on one of two background colors (yellow or blue). Both the encoding conditions contained blue and yellow trials. At retrieval, the pairings were presented on a white background color. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

cortical gray-matter of Mindboggle (RRID:SCR_002438, [40]). Volume-based spatial normalization to one standard space (MNI152NLin2009cAsym) was performed through nonlinear registration with antsRegistration (ANTs 2.2.0), using brain-extracted versions of both T1w reference and the T1w template. The following template was selected for spatial normalization: ICBM 152 Nonlinear Asymmetrical template version 2009c [[26], RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym].

2.7. Functional data preprocessing

For each of the 8 BOLD runs found per subject (across all tasks and sessions), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using mcflirt (FSL 5.0.9, [35]). BOLD runs were slice-time corrected using 3dTshift from AFNI 20160207 [12], RRID:SCR_005927). Susceptibility distortion correction (SDC) was omitted. The BOLD reference was then co-registered to the T1w reference using bbregister (FreeSurfer) which implements boundary-based registration [30]. Co-registration was configured with six degrees of freedom. The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying the transforms to correct for head-motion. These resampled BOLD time-series will be referred to as preprocessed BOLD in original space, or just preprocessed BOLD. The BOLD time-series were resampled into standard space, generating a preprocessed BOLD run in MNI152NLin2009cAsym space. First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. Several confounding time-series were calculated based on the preprocessed BOLD: framewise displacement (FD), DVARS and three region-wise global signals. FD was computed using two formulations following Power (absolute sum of relative motions, [62]) and Jenkinson (relative root mean square displacement between affines, [35]). FD and DVARS are calculated for each functional run, both using their implementations in Nipype (following the definitions by [62]). The three global signals are extracted within the CSF, the WM, and the whole-brain masks. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each [66]. Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardized DVARS were annotated as motion outliers. All resamplings can be performed with a single interpolation step by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using antsApplyTransforms (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels [45]. Non-gridded (surface) resamplings were performed using mri_vol2surf (FreeSurfer).

2.8. Multivariate pattern analyses

All analyses were conducted in normalized, MNI space. The anatomical masks were drawn from the AAL pick atlas and were co-

registered to a subject's brain in MNI space. All trials were modeled within each individual trial GLMs. To estimate neural activity associated with individual trials, separate GLMs on unsmoothed data were estimated in SPM12 defining one regressor for each trial at encoding and retrieval (172 total for each phase). An additional 6 nuisance regressors were included in each run corresponding to motion. Whole-brain parameter maps were generated for each trial for encoding and retrieval for each participant. In any given parameter map, the value in each voxel represents the regression coefficient for that trial's regressor in multiple regression containing all other trials in the run and the motion parameters. These beta parameter maps were concatenated across runs and submitted to CoSMoMVPA toolbox [55] for pattern classification [50], and representational similarity/distinctiveness [32,33] analyses.

Neural pattern classification

Given our interest in determining how unitization and non-unitized associative memory strategies are discriminated in each region in the associative memory network, classification analyses were conducted to determine if a classifier was able to discriminate between unitization or non-unitized memory target trials in our selected ROIs. Separate classification accuracies were computed between the foregoing trial types at both encoding and retrieval using a support vector machine (SVM) classifier with a linear kernel using all voxels within each ROI [50]. Training and testing were performed following an n-fold cross-validation wherein the data was split across the 4 runs. The classifier was trained on 3 runs and tested on the 4th, repeating across different folds. Group-level results were generated from averaging across validation folds from all possible train-data/test-data permutations from the individual participant level. Finally, we tested whether a classifier was significantly able to discriminate neural patterns above chance between the two target types using a one-tailed one-sample *t*-test for classification accuracy within each ROI. All *t*-tests were corrected for multiple comparisons using Benjamini-Hochberg corrections and any significance was confirmed with permutation testing (using 10,000 Monte-Carlo simulations). Following *t*-tests, ANOVAs were run with age as a between factor and the mean univariate activity of the unitized trials and mean univariate activity of the non-unitized condition as within factors. The MVPA was conducted only on target trials, absent of behavior. Classification in the current study begets the idea of pattern distinctiveness compared to chance. The current classification analysis was run to determine how discriminable target trials were from one another. In order to determine how behavior was affected by these trial types, we next conducted pattern distinctiveness analyses accounting for that behavior.

Neural pattern distinctiveness

Neural distinctiveness metrics examine how distinct neural patterns are from one another in different conditions in order to determine if brain regions are able to discriminate between different conditions or stimuli [32,33,42,46]. Pattern distinctiveness analyses were conducted in the current study to examine the representation of stimuli associated with unitization and non-unitized memory on subsequently recollected targets. Thus, trials will be unequal between conditions and participants. Recollected targets are encoded trials that are subsequently responded to with the subjective response of 'Remember' during retrieval, indicating a detailed memory for that pair. For the current analyses, the similarity of activation patterns across different trials of the same category was calculated (within-category correlation, a measure of reliability; [68]) in each participant for participants subsequently recollected trials (e.g., correlation between all beta parameter maps for unitized subsequently recollected trials correlated individually to all beta parameter maps for all other unitized subsequently recollected trials at encoding) and a between-category similarity score for each participant's subsequently recollected trials (e.g., one beta parameter map for a unitized subsequently recollected trial correlated individually to all beta parameter maps for non-unitized subsequently recollected trials, done for all unitized trials individually and then averaged) [32,33]. As described in Simmonite and Polk [68], increased within-category similarity indicates greater reliability and consistency of neural patterns within a given condition. Next, an overall distinctiveness score was calculated by taking the mean of the

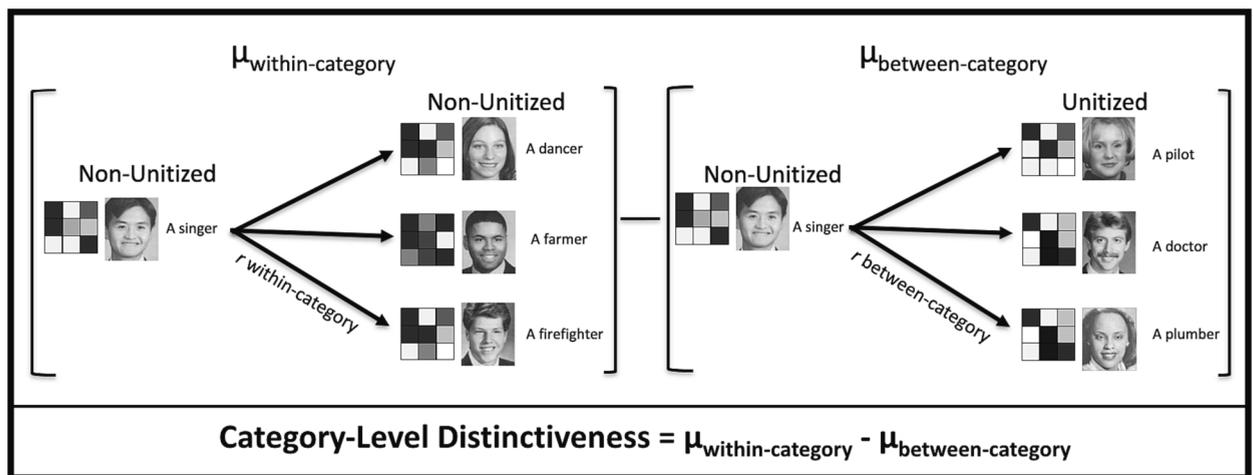


Fig. 3. Based on Haxby et al. [32,33], calculation of neural distinctiveness. Calculations were repeated twice; once for encoding trials and once for retrieval trials. Distinctiveness was calculated by taking the within-condition similarity correlations for all trials within a condition subtracted by the between-condition similarity correlation for all trials between the condition.

unitized-within and non-unitized-within similarities scores and subtracting the between similarity score. This value was then compared to 0 using one-sample t-tests, for each ROI, to determine if distinctiveness differed from chance. To further examine whether the discrete distinctiveness was driven by within-category differences, the within-category similarity for the unitized and non-unitized conditions were compared using a mixed factorial ANOVA in each ROI. This process was repeated for both encoding and retrieval trials separately. (See Fig. 3 for an example).

3. Results

Behavioral results

Overall hit rates across conditions were relatively high, (YA: unitized $M = 0.83$ $SD = 0.08$ and non-unitized $M = 0.74$, $SD = 0.10$; OA: $M = 0.79$ $SD = 0.11$ and non-unitized $M = 0.68$, $SD = 0.15$), as were correct rejection rates (YA: unitized $M = 0.59$, $SD = 0.21$ and non-unitized $M = 0.56$, $SD = 0.13$; OA: unitized $M = 0.54$, $SD = 0.21$ and non-unitized $M = 0.52$, $SD = 0.16$). A series of ANOVAs were run between older and younger adults and the unitized and non-unitized memory trials for recollected hits, familiarity hits, and correct rejections (CR), with version of the task included as a covariate.

With respect to recollected hit rates, there was a main effect of condition, $F(1,49) = 88.12$, $p < .001$, $ges = 0.108$, such that the unitized memory trials had greater recollected hits ($M = 0.56$ $SD = 0.17$) compared to the non-unitized memory trials ($M = 0.45$ $SD = 0.16$). The main effect of age $F(1,49) = 2.08$, $p = .16$, version $F(1,49) = 0.31$, $p = .58$, the interaction between version and condition $F(1,49) = 0.04$, $p = .84$, the interaction between version and age $F(1,49) = 0.23$, $p = .64$, the interaction between condition and age $F(1,49) = 1.99$, $p = .17$, the interaction between version, age $F(1,49) = 0.18$, $p = .68$, were not significant.

With respect to familiarity hits, we found no main effects between unitized (YA: $M = 0.24$ $SD = 0.10$; OA: $M = 0.25$ $SD = 0.16$) and non-unitized (YA: $M = 0.25$ $SD = 0.10$; OA: $M = 0.27$ $SD = 0.13$) memory trials with version as a covariate, condition $F(1,49) = 1.99$, $p = .17$, version $F(1,49) = 0.26$, $p = .61$, age $F(1,49) = 0.11$, $p = .74$, or an interaction between version and condition $F(1,49) = 0.29$, $p = .59$, the interaction between version and age $F(1,49) = 0.01$, $p = .94$, the interaction between condition and age $F(1,49) = 0.00$, $p = .99$, the interaction between version, age $F(1,49) = 2.29$, $p = .14$.

Similarly, for CR, we found no main effects for condition $F(1,49) = 0.64$, $p = .43$, $ges = 0.003$, version $F(1,49) = 1.61$, $p = .21$, age $F(1,49) = 1.61$, $p = .21$, or an interaction between version and condition $F(1,49) = 0.35$, $p = .56$, the interaction between version and age $F(1,49) = 0.65$, $p = .43$, the interaction between condition and age $F(1,49) = 0.03$, $p = .87$, the interaction between version, age $F(1,49) = 0.06$, $p = .80$.

Classification results

To examine whether classifiers were able to significantly discriminate between our two target conditions, two multivoxel pattern analyses were run. The first classification analysis attempted to classify all unitized and non-unitized memory trial targets at encoding, and the second to classify all unitized and non-unitized memory trial targets at retrieval. Comparing classification of unitized and non-unitized memory trial targets at encoding against chance (50%), collapsed across age, showed that in the AG, the classifier accuracy was significantly above chance (AG: $M_{accuracy} = 0.535$, $t(52) = 3.14$, $p < .001$, $CI[0.50, 0.52]$, $d = 0.176$). To confirm significance, permutation testing was conducted, using 10,000 Monte-Carlo simulations performed within the AG. In doing so, the AG maintained significance, $p = .002$. Furthermore, in addition to identifying regions showing signals for unitized targets that were discriminable from those of non-unitized targets, we also tested whether there were univariate activation and age differences in the AG. In the AG, the region showing above-chance classification performance, we computed an ANCOVA with classification accuracy, including mean univariate BOLD activation of unitized targets versus baseline, non-unitized targets versus baseline, and age as nuisance covariates. The three covariates did not show a significant difference for target classification (p 's > 0.8). No other ROIs were significant at

Table 1

Means and standard deviations of each ROI for classification analyses during encoding and retrieval for younger and older adults.

ROI	Encoding		Retrieval	
	Mean	Standard Deviation	Mean	Standard Deviation
YA				
AG	0.540	0.073	0.528	0.064
HC	0.503	0.071	0.527	0.056
MFG	0.511	0.093	0.508	0.070
MOC	0.507	0.082	0.505	0.062
PrC	0.516	0.076	0.512	0.067
OA				
AG	0.533	0.091	0.517	0.053
HC	0.490	0.091	0.493	0.064
MFG	0.514	0.076	0.513	0.044
MOC	0.515	0.084	0.508	0.069
PrC	0.519	0.086	0.506	0.058

encoding (HC: $t(52) = -0.30, p = .62$; MFG: $t(52) = 1.07, p = .14$; MOC: $t(52) = 0.94, p = .18$; PrC: $t(52) = 1.57, p = .06$).

At retrieval, comparing classification of unitized and non-unitized memory trial targets at encoding against chance (50%), collapsed across age, showed that in the AG, the classifier accuracy was significantly above chance (AG: $M_{\text{accuracy}} = 0.523, t(52) = 2.83, p < .01, CI[0.50, 0.52], d = 0.196$). To confirm significance, permutation testing was conducted, using 10,000 Monte-Carlo simulations performed within the AG. In doing so, the AG maintained significance, $p = .003$. Furthermore, in addition to identifying regions showing signals for unitized targets that were discriminable from those of non-unitized targets, we also tested whether there were univariate activation and age differences in the AG. In the AG, the region showing above-chance classification performance, we computed an ANCOVA with classification accuracy, including mean univariate BOLD activation of unitized targets versus baseline, non-unitized targets versus baseline, and age as nuisance covariates. The three covariates did not show a significant difference for target classification (p 's > 0.8). No other regions of interest showed significant classification of unitized and non-unitized memory against chance (HC: $t(52) = 1.31, p = .10$; MFG: $t(52) = 1.32, p = .10$; MOC: $t(52) = 0.71, p = .24$; PrC: $t(52) = 1.04, p = .15$). See [Table 1](#) for all means and standard deviations.

Encoding distinctiveness

In order to examine neural discriminability related to successful memory at encoding, a neural distinctiveness calculation [32,33] was conducted for unitized and non-unitized memory subsequently recollected targets (within-category similarity minus between-category similarity) for each encoding condition. At encoding, overall distinctiveness of recollected targets, collapsed across condition and age, was significantly greater than 0 within all ROIs [AG: $t(52) = 7.70, p < .001$; HC: $t(52) = 6.07, p < .001$; MFG: $t(52) = 10.56, p < .001$; MOC: $t(52) = 9.03, p < .001$; PrC: $t(52) = 8.12, p < .001$]. The within-condition similarity scores associated with both conditions were then compared in a mixed ANOVA to determine if one condition showed higher similarity in a given region compared to the other condition.

A mixed factorial ANOVA was conducted to compare the main effects of age (old versus young) and condition (unitized versus non-unitized) on the within-condition similarity within each ROI that was greater than 0. In the HC, we found no main effects of age $F(1,51) = 0.05, p = .83$, condition $F(1,51) = 1.07, p = .31$, nor an interaction $F(1,51) = 0.75, p = .39$. In the AG there was a main effect of age $F(1,51) = 5.13, p = .03, \eta^2 = 0.071$ such that younger adults had greater within-condition similarity ($M = 0.15, SD = 0.07$) than older adults ($M = 0.11, SD = 0.08$). There was no main effect of condition $F(1,51) = 0.19, p = .66$, nor an interaction $F(1,51) = 0.43, p = .52$. Similarly, in the MOC there was a main effect of age $F(1,51) = 6.37, p = .02, \eta^2 = 0.101$ such that younger adults had greater within-condition similarity ($M = 0.39, SD = 0.16$) than older adults ($M = 0.29, SD = 0.16$). There was no main effect of condition $F(1,51) = 2.09, p = .15$, nor an interaction $F(1,51) = 3.74, p = .06$. In the PrC there was no main effect of age $F(1,51) = 3.68, p = .06$ or condition $F(1,51) = 3.42, p = .07$ but there was an interaction $F(1,51) = 5.68, p = .02, \eta^2 = 0.016$. Follow up t -test revealed that there was a significant difference only in older adults between the unitized ($M = 0.13, SD = 0.07$) and non-unitized ($M = 0.10, SD = 0.05$) condition $t(24) = 2.72, p = .01, d = 0.465$. Additionally, there was a significant difference only within the non-unitized condition such that younger adults had greater within-condition similarity ($M = 0.14, SD = 0.06$) than older adults ($M = 0.10, SD = 0.05$) $t(50.44) = -3.20, p < .001, d = .869$. Finally, in the MFG, there was a significant main effect of age $F(1,51) = 5.30, p = .03, \eta^2 = 0.074$, condition

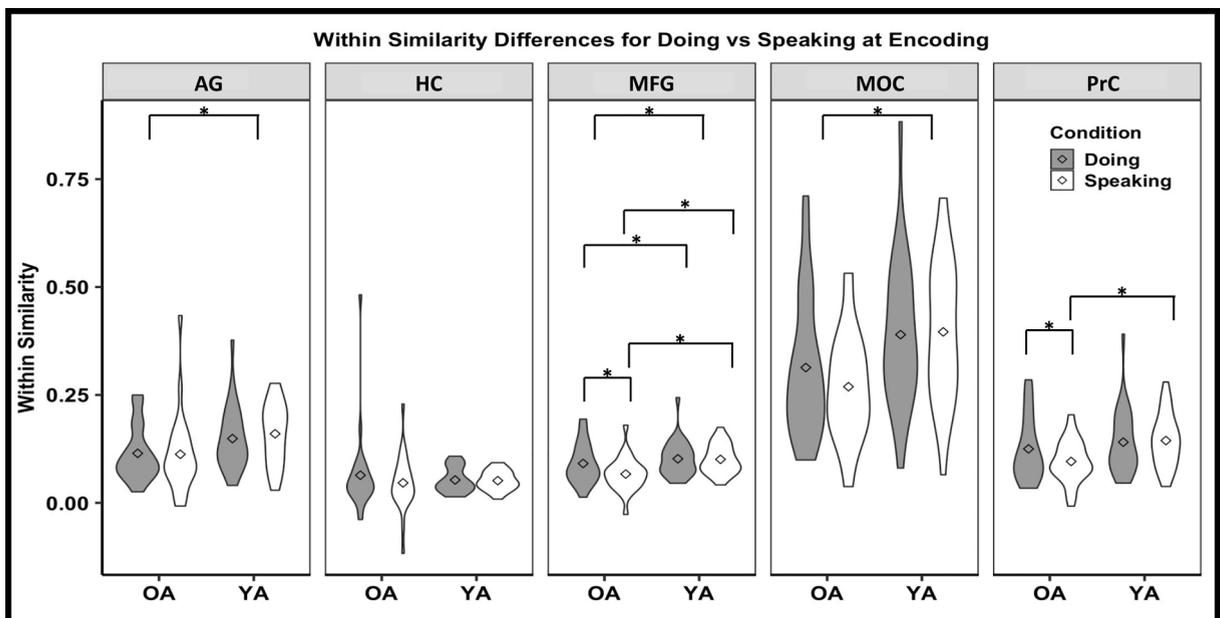


Fig. 4. Within-similarity between the two encoding conditions in the AG, HC, MFG, MOC, and PrC between younger and older adults. Neural within-similarity scores significantly different between doing versus speaking conditions indicated with *; p 's < 0.05 .

$F(1,51) = 5.98, p = .02, ges = 0.026$, and an interaction $F(1,51) = 4.75, p = .03, ges = 0.021$. In the above analysis, younger adults had greater within-condition similarity ($M = 0.10, SD = 0.04$) than older adults ($M = 0.08, SD = 0.04$) and the unitized condition had greater within-condition similarity ($M = 0.10, SD = 0.04$) than the non-unitized condition ($M = 0.08, SD = 0.04$). Interestingly, when looking at the interaction of age and condition follow up t-tests revealed that only within older adults they had greater within-condition similarity in the unitized condition ($M = 0.09, SD = 0.05$) compared to the non-unitized condition ($M = 0.07, SD = 0.04$) $t(24) = 2.73, p = .01, d = 0.567$. Additionally, similar to that of the PrC, there was a significant difference only within the non-unitized condition such that younger adults had greater within-condition similarity ($M = 0.10, SD = 0.03$) than older adults ($M = 0.07, SD = 0.04$) $t(47.10) = -3.35, p < .001, d = 0.931$. (See Fig. 4).

Retrieval distinctiveness

In order to examine neural discriminability between two successful retrieval conditions, a neural distinctiveness calculation was conducted for unitized and non-unitized memory recollected targets (within category similarity minus between category similarity). At retrieval, overall distinctiveness of subsequently recollected targets, collapsed across condition, was not significantly greater than 0 within any ROIs [AG: $t(52) = -0.48, p = .68$; HC: $t(52) = 0.52, p = .30$; MFG: $t(52) = 0.51, p = .31$; MOC: $t(52) = -0.48, p = .68$; PrC: $t(52) = 1.01, p = .16$]. Since no region of interest was significantly distinct above 0, these conditions were not compared to determine if one condition showed higher similarity in a given region compared to the other condition.

4. Discussion

The goal of the current study was to examine the underlying neural mechanisms of unitization, induced through the manipulation of encoding instructions that employed visual imagery. During encoding, participants were given two strategies, one of which promoted unitization of face-occupation pairs through intra-item binding and visualization, while the other, non-unitized encoding strategy, used visualization to promote inter-item binding. Specifically, in the unitized encoding strategy, participants saw a face-occupation pairing and were prompted to imagine the person they were viewing as doing the occupation. This condition attempted to elicit unitization since participants were supposed to imagine the face and occupation as a cohesive item, and thus would always remember the shown pairing. In contrast, in the non-unitized encoding strategy participants saw a face-occupation pairing and were prompted to imagine the person they were viewing as knowing someone with the occupation. In this condition, participants are using a typical associative memory paradigm. In alignment with previous work using this paradigm with younger adults [64], and older adults [56], as well as similar studies in older adults, (e.g., [5,16,23,59,63]) we found that the unitized condition resulted in greater recollected hits than the non-unitized condition in our sample of older and younger adults with no age differences. Results support the idea that a visual encoding unitization binding leads to enhanced associative memory and highlights the ability of older adults to take advantage of such a strategy.

We hypothesized that across both memory phases, information processed within the unitized encoding condition would show greater neural discriminability and neural distinctiveness than information in the non-unitized encoding condition [43,68,69]. However, only within the AG at both memory phases (encoding and retrieval), did MVPA exhibit greater than chance classification between the two conditions. This is consistent with prior work in which AG activation is associated with the presence of schemas during encoding and posited to aid participants to consolidate new information [7,67,77], including contributing to the encoding of a schema into a bound memory [77]. In the current study, classification within the AG may have reflected the difference in processes used to encode and later retrieve an integrated schema of person and their occupation as opposed to the mere association amongst a face and an occupation of a separate individual. This differs from previous aging work in our lab [21] in which it was found that neural patterns across the encoding network can reliably distinguish between two different types of visual associations. One difference across results may be that the current study used similar configurations for both conditions even though the visual associations created by the encoding instructions differed. Specifically, our prior study found that when encoding face-scene associations, regions within prefrontal and occipital cortex, as well as the perirhinal cortex, reliably discriminated between item-item and item-context presentations in older adults. While both the current and prior study controlled for the content of information across associative encoding conditions, our previous study included a greater configural difference across conditions, whereas a similar visual layout was used across encoding conditions in the current study (see Fig. 1). Taken together, the results suggest that encoding processing differences alone may not be enough to promote distinct neural patterns during associative memory in aging within medial temporal regions including the hippocampus and perirhinal cortex. Rather, it may be that in order to represent information uniquely across different encoding and retrieval conditions, there must be both configural differences and differences in visual encoding between conditions. This aligns with computational modeling work that has suggested a primary age difference in associative memory may be a decrease in the uniqueness of encoded features that enable accurate discrimination of old versus new information [71]. Interestingly, no age differences were found within the AG at either memory phase. Further work should continue to explore how encoding strategy and configural differences across encoding conditions supports such neural discriminability.

Similar to the concept of neural discriminability across encoding conditions, the investigation of neural distinctiveness, related to behavioral outcomes [32,33], allows us to investigate whether neural patterns of successfully recollected unitized and non-unitized memories are presented uniquely both within and across study conditions. In the current study, subsequently recollected targets from both conditions exhibited above-chance distinctiveness across all regions of interest (HC, PrC, MFG, AG, and MOC) collapsed across age, indicating that neural patterns associated with these associative pairs are distinct from one another within each condition, during encoding. The fact that recollected trials were only distinct from one another at encoding, and not retrieval, suggests that older

and younger adults utilize encoding based strategies and schemas to later benefit their recollection for face-occupation pairings. While we predicted that trials in the unitized condition would be more distinct, leading to better memory, than that of the non-unitized condition, our results indicate that differences in distinctiveness were driven by greater neural pattern similarity within the unitized condition.

Although knowing if the two memory conditions are distinct from each other in specific ROIs can be useful, looking at the similarity within a condition can also provide insight into the quality of the neural representations within a given condition, that is, if participants do show greater within-similarity scores within a specific condition, it can indicate that trials within that condition are more related in their neural representations to one another. When directly comparing pattern similarity of the unitized condition to that of the non-unitized condition with respect to age, the reliability of neural activity of younger and older adults differed in the AG and MOC. For both ROIs the younger adults exhibited greater reliability (greater within-condition similarity of trials) than older adults. This suggests that younger adults exhibit more stability of within condition neural representations than older adults, a finding that is consistent with a wealth of literature showing greater dedifferentiation in aging [21,18,65].

Additionally, an age by condition interaction was found in both the PrC and MFG. A closer examination of these interactions revealed three findings. First, across both ROIs, older adults exhibited reduced similarity and reliability across trials in the non-unitized associative condition, compared to younger adults. Secondly, older adults exhibited greater within-condition similarity across trials in the unitized condition compared to the non-unitized trials. Together, this pattern of results is indicative of an age-related deficit in associative processing during non-unitized associative encoding. Given the focus on subsequent recollection-related trials in the forgoing analysis, the results suggest that greater reliability related to within-category activation may likely underscore less detailed-based memory traces for non-unitized associations in older adults. This may, in turn, speak to the age deficit typically observed in associative memory tasks [51,53]. Finally, there was no age difference when comparing neural pattern similarity of the unitized condition in either ROI. This suggests that, when engaged in unitized encoding, the reliability of neural patterns in the PrC and MFG do not differ with age. This is particularly interesting given the fact that older adults exhibit behavioral benefits from unitized encoding instructions and do not exhibit an age deficit in behavior related to unitized encoding (see [1,5,34,48,85]) for similar behavioral benefits to unitization in aging). This suggests that this behavioral benefit may be due to age-invariant processing within the MFG and PrC related to unitized encoding.

The MFG has been shown to aid in the detection of congruent information from encoding to retrieval as well as to aid in supporting the retrieval of schemas [44,74]. Since neural patterns in the MFG associated with the unitized condition were more similar to other recollected trials in the same condition, it further supports the idea that the MFG contributes to the encoding of integrated schemas, such as imagining a relationship between a person and their occupation. Since the unitization condition in the current study asked older adults to use schemas to bind the face-occupation pairing, the additional detail associated with the schemas may have led to greater recollection in the unitized condition compared to the non-unitized condition. Additionally, previous work has indicated that the PrC plays a critical role in item memory encoding and subsequent retrieval [38,70]. With respect to unitization, the PrC has also been identified in several studies examining the benefits of unitization, whereby PrC activity is found for unitized trials [48,49]. It has been suggested in prior research that if an item-item pair is truly unitized, memory formation will be utilized not by the HC but the PrC [28,23,22]. Greater similarity of neural patterns in the PrC across age groups following unitized encoding, suggests that the benefit of item-related processing in this region may support unitized-based recollection of item-item pairs.

In this study, unitization was designed to be implemented as a top-down mechanism, aiding in the binding of two unrelated items (face-occupation pairing) into a single representation using stored schemas associated with occupation actions. Invoking occupation schemas, combined with generating mental imagery of the actions associated with the occupation, allowed participants to draw on pre-existing information during associative encoding, in a manner similar to that used in previous work [5,48]. Bastin and colleagues [5] asked participants to form visual associations and found that older adults had an increased associative memory compared to the non-unitized strategy. In a similar manner, Memel and Ryan [48] used a visual integration task to bind objects and contexts, in which they placed objects within a logical scene in order to promote schema-related unitization during encoding. This presentation resulted in better associative recollection and increased activation in the prefrontal cortex within their older participants. They concluded visual integrated unitization may be mediated by recollective based encoding processes for older adults [48]. The current works shows how older adults were able use an unitization strategy during an associative memory paradigm and elicit PrC activation when comparing pattern similarity of subsequently recollected encoding trials.

5. Limitations/future directions

While the current findings extend our knowledge of the role of schemas during encoding for older adults when compared to young adults, there were some limitations to the study. Specifically, we cannot be certain that the unitized condition is truly being bound as a single unit, only that behavioral differences across encoding conditions suggest stronger memory for the unitization-based strategy. The unitized condition can only be concluded as being different from the non-unitized associative condition, in a manner that is beneficial to older adults' memory performance. Future work should aim to identify whether these differences in encoding strategies are due to unitization of unrelated information into a singular bound unit. Additionally, further research is needed to determine if a visualization unitization strategy is the most effective strategy to achieve unitized binding. In addition, the benefit of unitization has often been associated with greater use of familiarity, particularly in older adults [91,23]. However, recent work in the realm of neuroimaging has also indicated that recollection may also be important to mediating the effect of unitization on memory [48]. In the current task, familiarity-based hit counts were very low and thus we chose to focus solely on recollection-based hits. Future work should aim to investigate and disentangle the role of familiarity and recollection in unitization in terms of neural distinctiveness.

6. Conclusions

Overall, the results show that older adults are able to benefit from associative encoding instructions that emphasize unitized binding and visualization, exhibiting greater recollection of targets in the unitized compared to non-unitized condition. Contrary to our predictions regarding neural discriminability, only the AG was able to discriminate between unitized and non-unitized targets during encoding and retrieval, suggesting that more contextual differences may be required for older adults to recruit other associative memory regions [21]. In contrast, we found that neural patterns related to unitized and non-unitized associations were distinct from one another within the core associative network and visual imagery regions. Specifically, when comparing the similarity of unitized versus non-unitized trials in older adults, the MFG and PrC exhibited greater reliability at encoding within neural representations of later recollected unitized pairs compared to non-unitized pairs. Given the lack of age differences between younger and older adults across the two visual imagery encoding conditions, and more importantly between younger and older adults within the unitized condition, results indicate how unitization instructions benefit older adults neurally as well as behaviorally. Overall, the results suggest that unitization may help older adults bind new information together into single units when using visual imagery strategies during encoding, which may be in part due to the ability of visual imagery regions to distinguish between types of associative information.

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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