The Role of Visual Association Cortex in Associative Memory Formation across Development

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Abstract

■ Associative learning underlies the formation of new episodic memories. Associative memory improves across development, and this age-related improvement is supported by the development of the hippocampus and pFC. Recent work, however, additionally suggests a role for visual association cortex in the formation of associative memories. This study investigated the role of category-preferential visual processing regions in associative memory across development using a paired associate learning task in a sample of 56 youths (age 6–19 years). Participants were asked to bind an emotional face with an object while undergoing fMRI scanning. Outside the scanner, participants completed a memory test. We first investigated age-related changes in neural recruitment and found linear age-related increases in activation in lateral occipital cortex and fusiform gyrus, which are involved in visual processing of objects and faces, respectively. Furthermore, greater activation in these visual processing regions was associated with better subsequent memory for pairs over and above the effect of age and of hippocampal and pFC activation on performance. Recruitment of these visual processing regions mediated the association between age and memory performance, over and above the effects of hippocampal activation. Taken together, these findings extend the existing literature to suggest that greater recruitment of category-preferential visual processing regions during encoding of associative memories is a neural mechanism explaining improved memory across development. ■

INTRODUCTION

Associative memory—the ability to bind together information that was previously unrelated—underlies the formation of episodic memories (Suzuki, 2007). Although associative memory formation and the neural mechanisms that support associative memory have been studied across development (DeMaster, Pathman, Lee, & Ghetti, 2014; DeMaster, Pathman, & Ghetti, 2013; Paz-Alonso, Bunge, Anderson, & Ghetti, 2013; Ghetti, DeMaster, Yonelinas, & Bunge, 2010), scant research has investigated the role of visual association cortex in the development of visual associative memory. Recent evidence shows that recruitment of visual association cortex during encoding is associated with memory performance (Hasinski & Sederberg, 2016; Wendelken, Baym, Gazzaley, & Bunge, 2011; Chai, Ofen, Jacobs, & Gabrieli, 2010; Xue et al., 2010; Grill-Spector, Kushnir, Hendler, & Malach, 2000), suggesting that secondary sensory areas may facilitate memory encoding by maintaining attention to the representation of the to-be-remembered stimulus. This study investigates neurodevelopmental changes in associative memory for faces and objects to determine whether visual processing regions that respond preferentially to particular stimuli (e.g., faces or objects) support developmental and individual differences in associative memory.

Evidence from both animal and human studies documents a central role of the hippocampus in associative memory formation (Ghetti et al., 2010). Behavioral work has found that the ability to form associative memories continues to develop into middle childhood before plateauing to adult-like performance at around the age of 9 or 10 years (Ghetti & Angelini, 2008). This developmental trajectory likely reflects both the development of the pFC and associated control processes (Ofen et al., 2007), as well as structural, functional, and connectivity changes in the hippocampus throughout development, which have each been shown in recent work to be associated with increases in long-term memory performance (DeMaster et al., 2013, 2014; Mabbott, Rovet, Noseworthy, Smith, & Rockel, 2009; Menon, Boyett-Anderson, & Reiss, 2005). Current perspectives acknowledge that the development of the hippocampus and prefrontal and parietal cortices each play a role in the increasing capacity to form associative memories across development (Ghetti & Bunge, 2012).

Work in adults has shown that activation in secondary sensory areas involved in the initial encoding of stimuli is also related to subsequent memory for those stimuli (Hasinski & Sederberg, 2016; Xue et al., 2010; Grill-Spector et al., 2000). Emerging evidence indicates that increased

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activation in category-preferential visual association cortex during encoding may be related to an increased ability to sustain that representation, underlying age-related increases in memory performance (Wendelken et al., 2011; Chai et al., 2010). Activation during initial encoding in the parahippocampal gyrus—a secondary visual scene processing region (Epstein, Harris, Stanley, & Kanwisher, 1999)—increases with age and is positively associated with later memory for complex scenes in children and adults (Chai et al., 2010). In addition, adults exhibit greater activation of the parahippocampal gyrus than children when they are instructed to attend to scenes (Chai et al., 2010), and greater activation of this region is associated with greater working and long-term memory for scenes (Gazzaley, Cooney, McEvoy, Knight, & D'Esposito, 2005). Attentional modulation of this region also increases with age among children (Wendelken et al., 2011). Taken together, this work demonstrates a role of the parahippocampal gyrus in the development of long-term memory encoding and subsequent memory for complex scenes and highlights a potential role of visual processing regions in age-related changes in memory for complex visual information. A recent study from our laboratory found similar results, demonstrating linear age-related increases in recruitment of the fusiform gyrus—a face processing region (Kanwisher, McDermott, & Chun, 1997)—during a task involving working memory for faces and that recruitment of this region was positively associated with working memory performance (Rosen et al., in preparation). Together, these findings suggest that age-related increases in memory of visual information might be related to increased recruitment of visual processing regions during encoding. Indeed, recent theoretical models have highlighted the important role of visual processing regions in increases in both attention and memory performance across development (Amso & Scerif, 2015).

An important interplay between attention, memory, and visual processing regions has been documented in adults. Top–down attention to visual information is associated with activity in visual processing regions even in the absence of visual stimuli or in the presence of competing stimuli (Gazzaley et al., 2005; Ranganath, DeGutis, & D'Esposito, 2004; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999). The presence of distractors at encoding can reduce later memory performance (Ganor-Stern, Seamon, & Carrasco, 1998), whereas greater visual attention to the target stimulus at encoding is associated with improved subsequent memory (Ballesteros, Reales, Garcia, & Carrasco, 2006). Attention to stimulus features enhances activity in category preferential visual processing regions and medial-temporal lobe regions and is ultimately associated with enhanced memory for those features (Uncapher & Rugg, 2009). Moreover, top–down attention to a target presented at a previously suppressed location enhances activity in visual cortex, and this enhancement is associated with better subsequent memory (Markant, Worden, & Amso, 2015). It is clear that visual processing regions play an important role in memory formation in adults. Although the role of medial-temporal lobe and frontoparietal regions have been explored in memory formation across development (Ghetti & Bunge, 2012; Ofen et al., 2007), this study sought to explore the role of category preferential visual processing regions during encoding to support memory formation across development.

Specifically, we investigate the role of visual processing regions in associative memory using a paired associate learning task in which children and adolescents were asked to bind an emotional face with an object. Here, we make several novel contributions to the study of the development of associative memory. Although previous studies have found age-related increases in activation of the parahippocampal cortex during encoding of scenes (Wendelken et al., 2011; Chai et al., 2010), the parahippocampal cortex also has a known role in long-term memory function (Eichenbaum, Yonelinas, & Ranganath, 2007). By using faces and objects, we were able to investigate whether activation in different regions of category-preferential visual association cortex that are not thought to play a general role in memory function—including the fusiform and lateral occipital cortices—increased with age and whether increased activation in these regions was predictive of subsequent memory.

We hypothesized that we would replicate previous findings of changes in hippocampal and prefrontal recruitment with age and positive associations between hippocampal and prefrontal activation during stimulus encoding and subsequent memory. Furthermore, we hypothesized that we would observe age-related increases in recruitment of the fusiform gyrus and the lateral occipital cortex (LOC) due to our use of faces and objects as stimuli and the known role these regions have in processing faces and objects, respectively (Aylward et al., 2005; Grill-Spector et al., 1999, 2000; Kanwisher et al., 1997). Finally, we hypothesized that activation in the fusiform and LOC would be associated with increased subsequent memory performance and would mediate age-related improvements in associative memory.

METHODS

Participants

A sample of 66 youths aged 6–19 years (M = 13.68 years, SD = 3.23 years; 35 male) without MRI contraindications (e.g., orthodontic braces) participated. The sample was recruited in Seattle, WA, between February 2014 and February 2015. Youths were recruited at schools, after-school and prevention programs, medical clinics, and in the general community. The study sample was racially and ethnically diverse (53.5% White, 6.25% Black, 14.55% Hispanic, 2.1% Asian, 23.6% multiracial or other) and varied with regard to parental socioeconomic status

(maximum parental educational attainment: less than high school, 10.5%; high school degree, 19.3%; some college, 10.5%; college degree, 22.8%; graduate degree, 31.6%; no report, 5.3%). The institutional review board at the University of Washington approved all procedures. Participants were compensated, and written informed consent was obtained from legal guardians and youths provided written assent.

Five participants (one 6-year-old girl, two 8-year-old girls, one 9-year-old boy, one 13-year-old boy) were excluded from analyses because of below-chance performance on the memory task. One participant (15-year-old girl) was excluded because of an incidental finding, one participant (9-year-old boy) did not complete the memory task outside the scanner, and two participants (one 8-year-old girl and one 10-year-old girl) did not complete the encoding task in the scanner. Two participants (one 11-year-old girl and one 12-year-old girl) were excluded for excessive motion throughout all runs (>20% repetition times [TRs] with framewise displacement outliers of more than 0.5 mm). One run from two participants (one 8-year-old boy and one 10-year-old boy) was removed from analyses because of excessive motion. The final analytic sample included 56 participants (age: 14.12 ± 0.40, 27 girls).

Twenty-three participants in the final analytic sample had experienced violence at some point in their lives, although violence exposure was not a factor of interest in this analysis. We controlled for violence exposure by including it as a binary covariate of noninterest (i.e., 1 = *exposed*, 0 = *never exposed*) in all models of fMRI data in the present analyses. Results were identical with and without this covariate, but we retain it in all final models. In addition, no interactions were found between age and violence exposure in predicting activation in category-preferential visual processing ROIs ($ps > .7$), suggesting that the inclusion of children with histories of violence did not influence the associations of interest. Finally, violence exposure did not moderate the association between activation and performance in any of our ROIs ($ps > .2$). These findings suggest that the associations reported here did not differ for children with and without exposure to violence.

Encoding Task

Participants completed blocks of a paired associate learning task (face and object) and encoding of single items (face or object) in the scanner (Figure 1A). All stimuli were faces drawn from a standardized stimulus set (Tottenham et al., 2009). Stimuli were neutral, happy, and angry faces. During paired associate learning blocks, participants were instructed that the emotional expression on the face reflected how the person felt about the object presented with them (i.e., happy face meant they liked the object, neutral face meant they did not like or dislike the object, and angry face meant they did not like the object) and were instructed that they should try to remember the pairings of people and objects. Participants were presented with 30 pairs made up of 10 faces

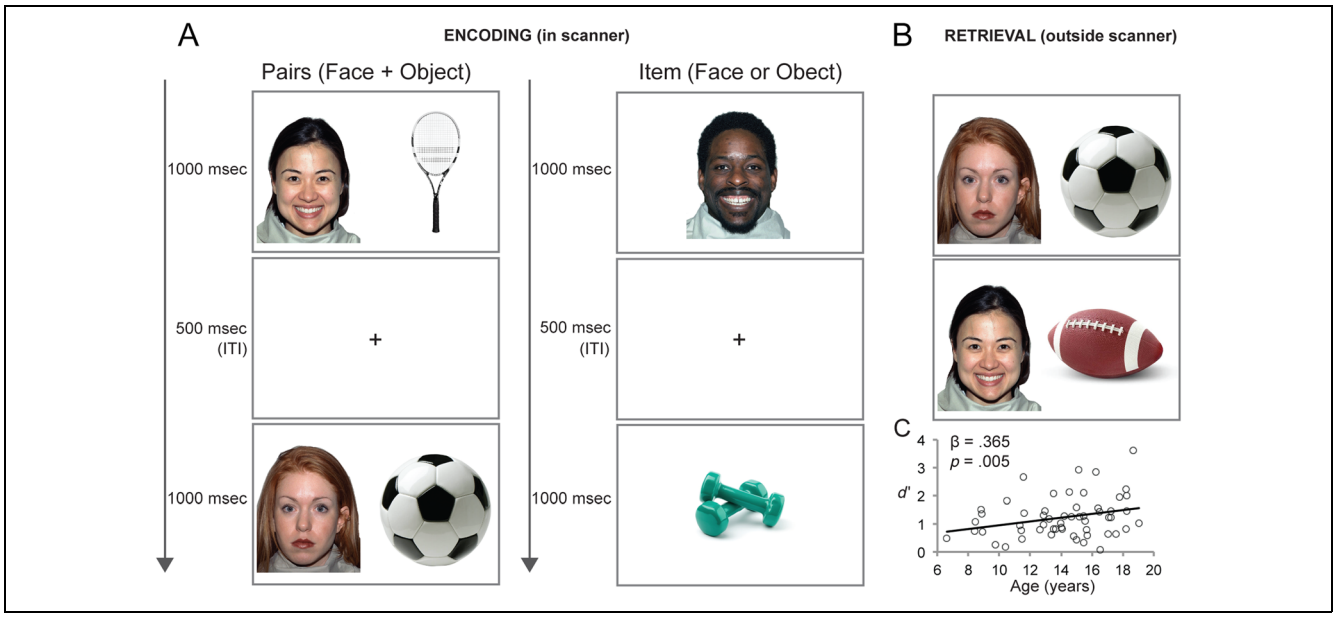

Figure 1. Paired associate learning task. (A) Encoding: Participants were presented with Pairs of faces and objects or Single Items (face or object). (B) Retrieval: During the test phase, participants saw pairings of faces and objects. Face–object pairings fell into several categories: correct pairing (i.e., a face with that particular emotional expression was paired with the object seen during encoding), incorrect item (i.e., the face was presented with the wrong object), novel face (i.e., the face was not seen in the scanner), and incorrect emotion (i.e., the identity of the face was paired with the correct object, but the emotional expression was incorrect). Participants responded whether or not the emotional faces were presented with the correct object. (C) Association between performance (d') and age.

with three emotional expressions per person, each paired with a different object. Each pair was presented six times throughout the session. Object face pairings were randomized and counterbalanced across participants, such that each possible emotional face–object pairing was presented to at least one participant. During item blocks, participants viewed single items (faces alone or objects alone) that had not been presented as part of a pair and were instructed to remember the single items. Stimuli were presented for 1000 msec followed by a 500-msec intertrial interval. Pair and item blocks were interleaved with blocks of fixation. Blocks lasted 24 sec and included 16 trials per block, and the order of presentation was pseudorandomized. Participants completed two runs of the task for a total of 180 trials (90 pairs and 90 item trials, broken up into 45 face alone and 45 object alone trials).

Retrieval Task

Outside the scanner at least 30 min after encoding, participants were presented with a test phase. During this phase, participants saw pairings of faces and objects. Face–object pairings fell into several categories. The first three categories specifically test associative memory: correct pairing (i.e., a face with that particular emotional expression was paired with the object seen during encoding), incorrect item (i.e., the face was presented with the wrong object), and incorrect emotion (i.e., the identity of the face was paired with the correct object, but the emotional expression was incorrect). In addition, the memory test involved a final category of incorrect pairings involving a novel face (i.e., the face was not seen in the scanner). Participants were instructed to indicate whether a face with a particular emotion was presented with the object with which it was previously paired. Memory for single items was not tested.

Image Acquisition and Processing

Before undergoing scanning, children 12 years and younger and any older children exhibiting anxiety about the scan were trained to minimize head movements in a mock scanner. They watched a movie with a head-mounted motion tracker that stopped playing if a movement of over 2 mm occurred. This method has been shown to significantly reduce head motion once children are in the scanner (Raschle et al., 2012). In addition, in the scanner, we used a head-stabilizing pillow to further restrict movement.

Scanning was performed on a 3-T Phillips Achieva scanner at the University of Washington Integrated Brain Imaging Center using a 32-channel head coil. T1-weighted multiecho MPRAGE volumes were acquired (TR = 2530 msec, echo time = 1640–7040 μsec, flip angle = 7°, field of view = 256 mm^2, 176 slices, in-plane voxel size = 1 mm^3). BOLD signal during functional runs was acquired using a gradient-echo T2*-weighted EPI sequence. Thirty-two 3-mm-thick slices were acquired parallel to the AC–PC line (TR = 2000 msec, echo time = 30 msec, flip angle = 90°, bandwidth = 2300, echo spacing = 0.5, field of view = 256 × 256, matrix size = 64 × 64). Before each scan, four images were acquired and discarded to allow longitudinal magnetization to reach equilibrium.

fMRI Preprocessing

Preprocessing and statistical analysis of fMRI data were performed in a pipeline using Make, a software development tool that can be used to create neuroimaging workflows that rely on multiple software packages (Askren et al., 2016). A four-dimensional realignment algorithm in Nipy was used to perform simultaneous motion and slice-time correction and has been shown to provide superior image reconstruction to sequential methods (Roche, 2011). Spatial smoothing with a Gaussian kernel (6-mm FWHM) was performed in FSL. Data were inspected for artifacts, and volumes with motion >0.5 mm or >3 *SD* change in signal intensity were excluded from analysis. Six rigid body motion regressors were included in person-level models. Person- and group-level models were estimated in FSL. A component-based anatomical noise correction method (Behzadi, Restom, Liau, & Liu, 2007) was used to reduce noise associated with physiological fluctuations. Following estimation of person-level models, the resulting contrast images were normalized into standard space. Specifically, functional data were registered to each participant's T1 scan and were then normalized to an intermediary pediatric template (NIH Pediatric MRI Data Repository: https://pediatricmri.nih.gov/nihpd/info/index.html), then from the pediatric template to MNI space. Anatomical coregistration of the functional data with each participant's T1-weighted image was performed using surface-based registration in FreeSurfer version 5.3 (Dale, Fischl, & Sereno, 1999), which provides better alignment than other methods in children (Ghosh et al., 2010). Normalization was implemented in Advanced Normalization Tools software, Version 2.1.0 (Avants et al., 2011).

Statistical Analysis

Behavioral Data

Behavioral performance on the paired associate learning task was assessed using discrimination sensitivity (d'), which was calculated using the following formula:

$$d' = z(\text{hit rate}) - z(\text{false alarm rate})$$

where z is the standardized score, as a measure of the sensitivity to remember pairs. The relationship between d' and age was estimated using age as a linear and logarithmic predictor. Primarily analyses focus on d' using

all trials of the memory test. In addition, we perform sensitivity analysis excluding the 15 memory trials that presented a novel face in the face–object pair. This was done to ensure that our results reflect associative memory and not simply recognition memory.

fMRI

fMRI data processing was performed using FEAT (fMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Regressors were created by convolving a boxcar function of phase duration with the standard double-gamma hemodynamic response function for each trial type (Pairs and Items). A general linear model was constructed for each participant. Higher-level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) Stage 1 (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). We constructed a model to investigate age and behavioral associations with brain activity using correctly remembered trials only. To construct the correct trials only model, we used responses from the subsequent memory task outside the scanner to classify trials into correctly remembered and forgotten trials. Individual-level estimates of BOLD activity were submitted to group-level random effects models of Item and correctly remembered Pairs, each compared with Baseline (intertrial interval) and additionally constructed contrasts of correctly remembered Pairs > Item. Forgotten pairs were included in the model as a regressor of noninterest. All analyses included a covariate of noninterest for violence exposure. Cluster-level correction in FSL was performed using methods that are associated with low risk of false-positive findings in recent simulations (see Eklund, Nichols, & Knutsson, 2016, Figure 1). Specifically, we used a threshold of $z > 3.1$, $p < .001$, for our analysis of task-related effects in the entire sample. Results were projected onto the cortical surface for visualization purposes using Connectome Workbench (Washington University, St. Louis, MO; Marcus et al., 2013).

ROI Analysis

Because of the known role of the hippocampus in associative memory and its development (DeMaster & Ghetti, 2013; Ghetti et al., 2010; Eichenbaum et al., 2007), we created ROIs for the left and right hippocampus. ROIs were created by masking the correct Pairs > Items contrast in the entire sample with a mask of the hippocampus from the Harvard–Oxford subcortical atlas in FSL (20% threshold).

Similarly, we investigated the associations between age and activation in pFC due to this region's established contribution to improved memory across development (Ofen et al., 2007). To do so, we created ROIs for the left and right middle frontal gyrus (MFG) for correct trials only by masking the correct Pairs > Items contrast in the entire sample with a mask of the MFG from the Harvard–Oxford cortical atlas in FSL (20% threshold).

Finally, we evaluated our hypothesis that activation of the fusiform gyrus and LOC would increase with age and predict memory performance in an ROI analysis. We conducted this analysis in two ways. First, we created functionally defined regions by masking the correct Pairs > Items contrast in the entire sample with a mask of (a) the left and right temporal-occipital fusiform gyrus and (b) left and right LOC, inferior division (20% threshold) from the Harvard–Oxford cortical atlas in FSL (Figure 2B). Critically, the ROIs for fusiform gyrus, LOC, MFG, and hippocampus were all defined using an identical approach, such that we took the whole-brain contrast of correct Pairs > Items and intersected this with a mask from the Harvard–Oxford Atlas (cortical atlas for all regions except hippocampus, which was defined using the subcortical atlas), using a 20% probability threshold.

Because we did not perform a functional localizer task with faces and objects, we performed additional ROI analyses to ensure that any age-related increases in recruitment seen in this study were indeed in the category-preferential regions of fusiform and LOC. To do so, we took coordinates from a study investigating the development

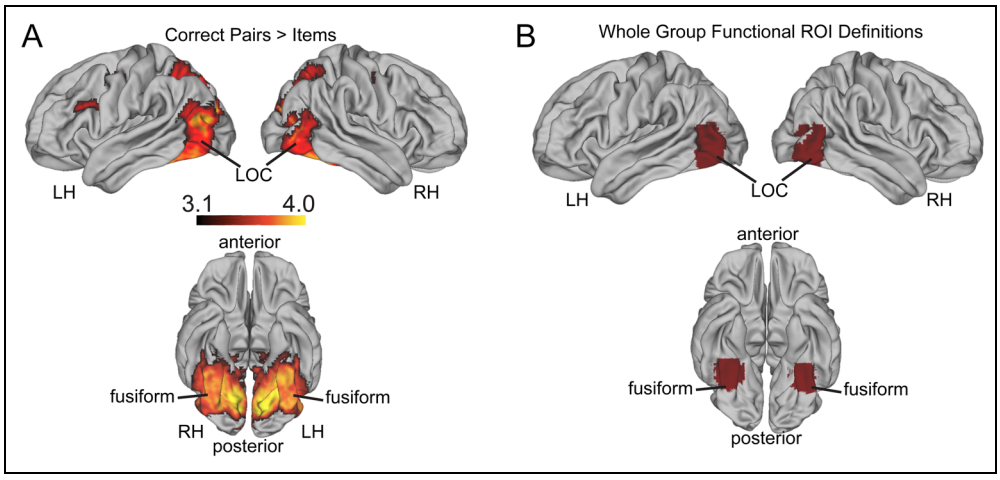

Figure 2. Whole group whole-brain effects of associative learning. See Table 1 for details.

of visual processing regions (Scherf, Behrmann, Humphreys, & Luna, 2007). In this study, children, adolescents, and adults were compared. The mean age for the adolescent group in this sample was approximately 14 years, similar to our study. We thus used the coordinates reported for the adolescent group in response to faces and objects (Scherf et al., 2007). Because the article only reports coordinates for the right fusiform face area (FFA), we created a symmetric left set of coordinates to test our hypotheses bilaterally. Next, we converted the reported Talairach coordinates to MNI coordinates. Then we created ROIs of the FFA (left FFA: $x = -43$, $y = -47$, $z = -20$; right FFA: $x = 40$, $y = -46$, $z = -21$) and LOC (left LOC: $x = -43$, $y = -57$, $z = -2$; right LOC: $x = 41$, $y = -50$, $z = -14$). Finally, we created a sphere with a 5-mm diameter around the MNI coordinates reported for each of these regions.

For all ROIs, we investigated both linear and logarithmic associations between age and activation, given prior work suggesting that activation in hippocampus during memory encoding changes during late childhood and is adult-like by age 14, the mean age in our sample (Ghetti et al., 2010). Separately, we used activation in these regions to predict performance on the memory task. All analyses controlled for violence exposure, and a false discovery rate (FDR) correction for multiple comparisons (Benjamini & Hochberg, 1995) was applied to all analyses.

Finally, to determine whether activation in category-preferential visual processing regions significantly predicted memory performance over and above the known contributions of the hippocampus, we determined whether activation in the fusiform and LOC continued to predict subsequent memory after controlling for activation in the hippocampus.

Exploratory Whole-brain Analyses

Our primary approach to investigate study hypotheses relied on ROIs of the fusiform gyrus and LOC (i.e., regions where we had a priori hypotheses) as well as hippocampus and MFG (i.e., areas previously shown to be associated with age-related changes in associative memory). However, we additionally present a whole-brain analysis of age-related effects and associations of behavioral performance (i.e., d') with neural activation to determine whether other regions were involved in age-related increases in associative memory. In these analyses, we used a cluster-level correction threshold of $z > 2.3$, $p < .01$, given an absence of any age-related effects or associations with behavioral performance at the more stringent threshold. We believe that the absence of such effects reflects a lack of statistical power, not a true lack of age-related changes in neural recruitment for associative learning, which has been observed in many other studies using cluster-level correction levels similar to what we use here (DeMaster et al., 2013; Wendelken et al., 2011; Chai et al., 2010). The threshold we use for examining age- and behavior-related effects in the whole brain is not associated with substantial elevation in risk of false positives and also minimizes risk of false negatives in recent simulations (Eklund et al., 2016).

Mediation Analyses

Finally, we examined whether age-related increases in memory performance were explained by neural recruitment during encoding in regions where we observed age-related effects and associations with memory performance. We used a standard test of statistical mediation that allows multiple mediators to be examined simultaneously and estimates the significance of indirect effects using a bootstrapping approach that provides confidence intervals for the indirect effect (Hayes, 2013). Given extensive prior evidence on the role of the hippocampus in age-related increases in associative memory, we first examined the left and right hippocampus as mediators. Next, we examined whether the visual processing ROIs here (i.e., left and right LOC and fusiform cortex) mediated the association between age and memory performance. Finally, we examined whether visual processing regions significantly mediated the association between age and performance when controlling for hippocampal activation. Confidence intervals that do not include 0 are considered evidence for statistically significant indirect (i.e., mediated) effects. All mediation analyses controlled for violence exposure.

RESULTS

Behavioral Results

d' across the whole sample was 1.23 ± 0.96. We investigated the association of age with d' examining linear and logarithmic functions of age in regression analysis. We used Akaike's information criteria to determine that a linear predictor of age was the best fit for d', both unadjusted ($\beta = .285$, $p = .033$) and after controlling for exposure to violence ($\beta = .365$, $p = .005$; Figure 1C).

Neural Responses to Encoding of Pairs Compared with Single Items

To examine task-related BOLD activation, we performed whole-brain general linear model analyses in the entire sample for encoding of correctly remembered pairs compared with single items. This contrast revealed widespread activation in frontoparietal cortex including left MFG/inferior frontal sulcus, bilateral intraparietal sulcus (IPS), and bilateral activation in the dorsal ACC, as well as activation in striate and extrastriate cortex including lateral occipital and ventral temporal cortex including fusiform gyrus, superior temporal gyrus, bilateral hippocampus, and inferior temporal cortex (Figure 2A; Table 1).

Table 1. Whole Group Results: Significant Areas of Activation in the Task Contrasts

Anatomical Region	*x*	*y*	*z*	*Voxels*	*z-Max*	*p*
Correct Pairs > Items						
Bilateral calcarine sulcus	−6	−84	4	23360	9.71	<.0001
IPS						
Lingual gyrus						
Precuneus cortex						
LOC						
Fusiform gyrus						
Cuneal cortex						
Cerebellum						
Occipital pole						
Inferior temporal gyrus						
Superior parietal lobule						
Posterior cingulate gyrus						
Posterior parahippocampal gyrus						
Thalamus						
Hippocampus						
Left MFG	−38	−4	46	323	5.62	<.0001
Precentral gyrus						
Inferior frontal gyrus						
Left MFG	−38	6	28	288	4.50	<.0001
Right precentral gyrus	40	−2	44	108	4.47	<.0001
Bilateral medial superior frontal gyrus	−2	10	54	120	4.47	<.0001
Supplementary motor area						
Bilateral precuneus	0	−54	58	112	5.12	<.0001

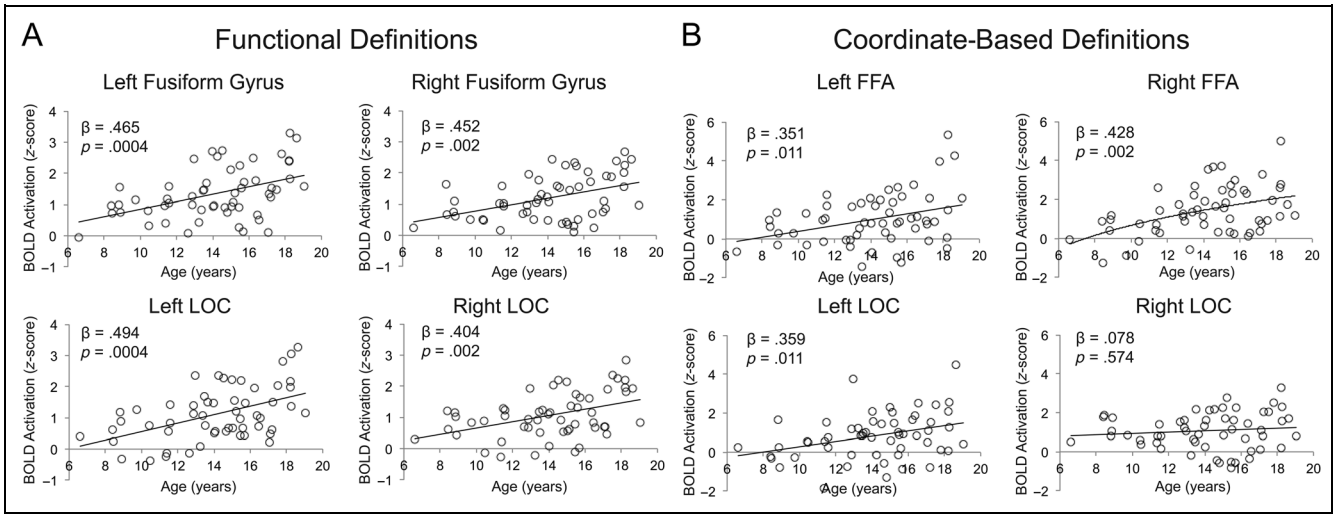

Figure 3. Age-related effects in category-preferential visual processing regions during associative encoding for (A) functional ROI definitions and (B) coordinate-based ROI definitions.

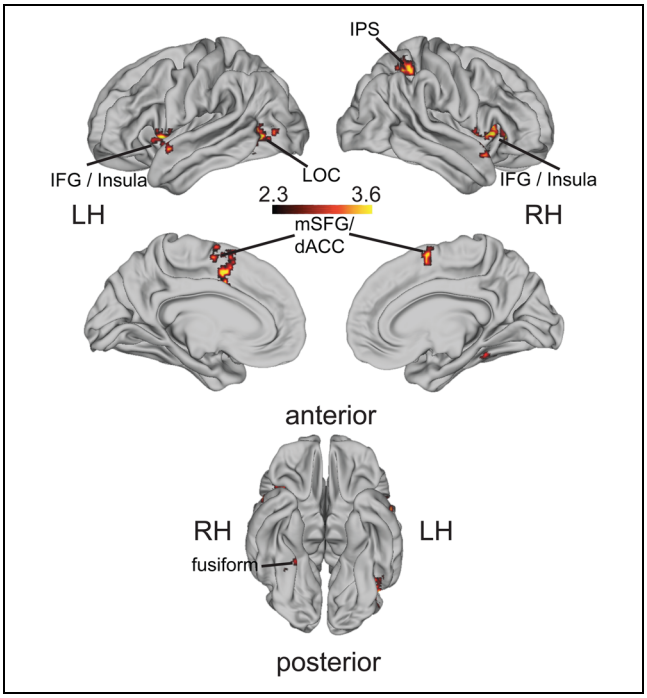

Figure 4. Whole-brain age-related changes in recruitment during associative memory encoding.

Age-related Effects

First, we sought to replicate previous studies showing age-related increases in recruitment of the hippocampus and MFG during memory encoding. After correction for multiple comparisons, the association between age and activation in the left and right hippocampus was marginally significant ($\beta = .255$, $p = .078$; $\beta = .233$, $p = .078$). There were no significant associations between age and activation in the left or right MFG ($\beta = .139$, $p = .323$; $\beta = .177$, $p = .323$). For all regions, the linear model showed stronger age-related associations with activation than the logarithmic model.

Next, we tested the hypothesis that activation in the fusiform gyrus and LOC increases with age. We created ROIs of these regions using two approaches, as described in the Methods section. First, we created a functional mask based on activation in the entire sample for correct Pairs > Items. This analysis revealed strong positive linear associations between age and activation in the left ($\beta = .465$, $p = .0004$) and right fusiform gyrus ($\beta = .452$, $p = .002$) and in the left ($\beta = .494$, $p = .0004$) and right LOC ($\beta = .404$, $p = .002$, Figure 3A). Second, we used coordinates for the FFA and LOC from an independent developmental study. Using the coordinates from Scherf et al. (2007) to define the FFA in our sample, we found a positive linear association between age and activation in the left FFA ($\beta = .351$, $p = .011$) and a positive logarithmic association in the right FFA ($\beta = .428$, $p = .002$). Using the coordinates from Scherf et al. (2007) to define the LOC, we found a positive linear association between activation in the left LOC ($\beta = .359$, $p = .011$). There was no significant association between age and activation in the right LOC ($\beta = .078$, $p = .574$; Figure 3B). All p values are FDR-corrected.

Table 2. Whole-brain Linear Age Analysis

Anatomical Region	*x*	*y*	*z*	*Voxels*	*z-Max*	*p*
Associations between Age and Activation						
Right frontal operculum	48	14	−8	439	4.75	<.0001
Anterior insula						
Inferior frontal gyrus						
Right occipital fusiform gyrus	20	−62	18	350	3.71	<.0001
Temporal fusiform gyrus						
Cerebellum						
Left frontal orbital cortex	−38	16	−18	219	3.46	.0002
Anterior insula inferior frontal gyrus						
Bilateral supplemental motor cortex	0	8	64	204	3.35	.0005
Medial superior frontal gyrus						
Dorsal anterior cingulate						
Left LOC	−48	−66	4	161	3.58	.003
Right anterior IPS	28	−46	50	155	2.36	.004
Superior parietal lobule						

As an added check that we are not simply observing global age-related increases in activation during encoding, we performed ROI analyses in a control region. We chose the precentral gyrus, as this region is not associated with memory encoding or retrieval, and we did not anticipate any age-related increases in activation. Indeed, ROI analyses reveal no significant age-related increases in activation during encoding of Pairs > Items ($\beta = .180, p = .20$; $\beta = .153, p = .26$, uncorrected) in the left and right precentral gyrus, respectively.

Finally, we performed a whole-brain analysis to determine whether any additional brain areas increased activation with age. This analysis revealed significant age-related increases in activation in the left LOC, a small cluster in the right fusiform, bilateral dorsal anterior cingulate/medial superior frontal gyrus, bilateral inferior frontal gyrus/anterior insula, and right anterior IPS (Figure 4; Table 2).

Brain–Behavior Associations

We next examined associations between brain activation and associative memory. First, we sought to replicate prior work demonstrating that hippocampus and MFG activation during encoding predict subsequent memory. Consistent with previous results, there was a significant association between activation in the left and right hippocampus and subsequent memory performance (i.e., d'; $\beta = .416, p = .006$ and $\beta = .399, p = .006$, respectively). In addition, there was significant association between activation in the left MFG and subsequent memory performance ($\beta = .345, p = .009$), but not the right MFG ($\beta = .152, p = .277$). All p values are FDR-corrected.

The positive associations between the left and right hippocampal activation and performance and the left MFG and performance remained significant over and above the effect of age (Table 3).

We next tested the hypothesis that increases in recruitment of fusiform gyrus and LOC would be associated with greater subsequent memory performance. First, using the functional ROI definition, we found significant associations between activation in both the right and left fusiform gyrus (left: $\beta = .548, p = .0002$; right: $\beta = .464, p = .0002$), as well as the left and right LOC (left: $\beta = .501, p = .0002$: right: $\beta = .396, p = .003$; Figure 5A) and d' on the memory test outside the scanner. Using coordinates from an independent study of FFA and LOC development, we found the same pattern of results. Specifically, we observed positive associations between activation in the right and left FFA (left: $\beta = .331, p = .011$; right: $\beta = .370, p = .005$), as well as in the left and right LOC (left: $\beta = .436, p = .002$; right: $\beta = .267, p = .042$; Figure 5B) and memory performance. All p values are FDR-corrected. The positive associations of activation in functionally defined fusiform and LOC with subsequent memory remained significant after adjusting for age. Results remained significant for the coordinate-defined

Table 3. Brain–Behavior–Age for Correct Pairs > Items

ROI	*Hemi*	*R*	*Predictor*	*β*	*p*-value
Functional ROI Definitions					
Fusiform	LH	.629			.0001
			Age	.138	.269
			Activation	.487	.0004
Fusiform	RH	.570			.0001
			Age	.192	.269
			Activation	.381	.005
LOC	LH	.590			.0001
			Age	.153	.269
			Activation	.429	.004
LOC	RH	.529			.001
			Age	.244	.269
			Activation	.299	.026
Coordinate-based ROI Definitions					
Fusiform	LH	.507			.001
			Age	.282	.064
			Activation	.237	.069
Fusiform	RH	.513			.002
			Age	.255	.064
			Activation	.264	.069
LOC	LH	.564			.0004
			Age	.237	.064
			Activation	.355	.002
LOC	RH	.514			.001
			Age	.346	.028
			Activation	.241	.069
MFG and Hippocampal ROIs					
Hippocampus	LH	.555			.0001
			Age	.277	028
			Activation	.342	.017
Hippocampus	RH	.328			.0001
			Age	.288	.028
			Activation	.328	.017
MFG	LH	.545			.0001
			Age	.323	.020
			Activation	.302	.017
MFG	RH	.463			.005
			Age	.350	.020
			Activation	.085	.524

All p-values are FDR-corrected.

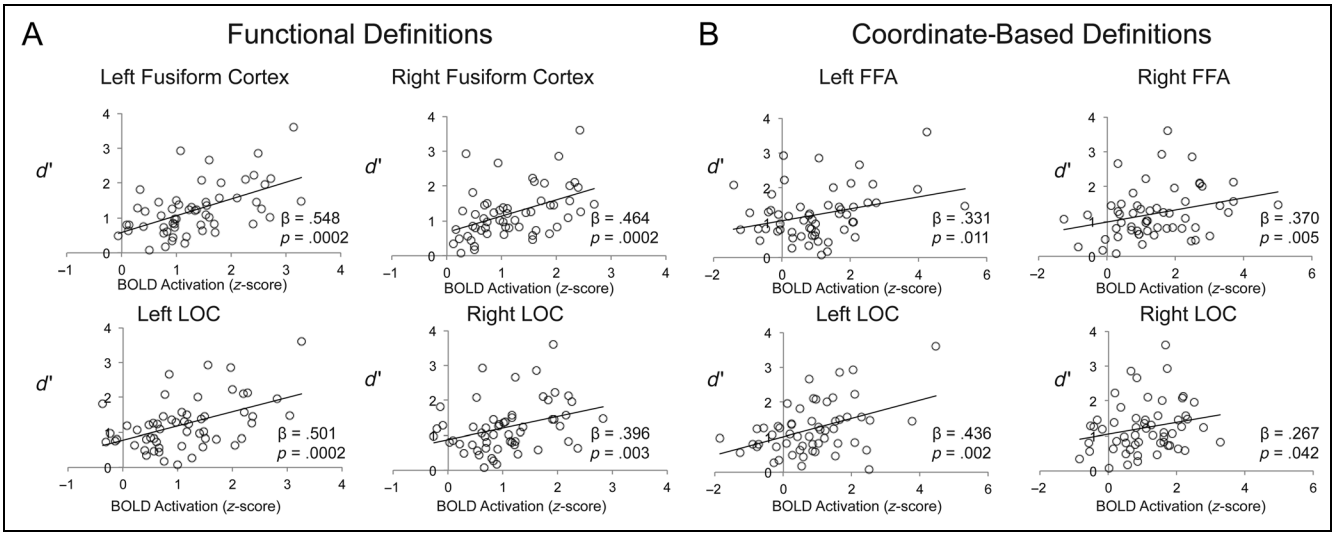

Figure 5. Brain–behavior associations. Associations between activation in category-preferential visual processing regions during associative encoding and subsequent memory performance for (A) functional ROI definitions and (B) coordinate-based ROI definitions.

left LOC and were at trend level for the coordinate-defined FFA and the right LOC. See Table 3 for details.

To determine whether the category-preferential visual processing regions make a unique contribution to memory performance, we performed linear regression for activation in these functionally defined regions predicting d' while controlling for activation in the ipsilateral hippocampus and MFG separately. Activation in all four regions was significantly associated with d' over and above the effect of activation in the MFG, and activation in the left and right fusiform and left LOC, but not right LOC, was significantly associated with d' over and above the effect of activation in the hippocampus. See Table 4 for details.

As a sensitivity analysis to ensure that our effects were not driven solely by recognition memory rather than associative memory, we reran all analysis after removing the 15 memory trials where the face and object were novel. All brain–behavior associations remain intact.

Finally, to determine whether other brain regions similarly track with performance, we performed a whole-brain analysis using mean-centered d' as a predictor. Results revealed linear associations between performance and activation in bilateral LOC, left fusiform, bilateral dorsal anterior cingulate/medial superior frontal gyrus, bilateral occipital cortex, and right MFG (Figure 6; Table 5).

Neural Mechanisms of Age-related Increases in Associative Memory

Finally, we evaluated whether activation in regions that demonstrated both age-related effects and associations with associative memory (i.e., LOC, fusiform gyrus, and hippocampus) significantly mediated the association between age and memory performance. First, we examined the hippocampus and MFG, regions previously shown to be involved in age-related improvements in memory, and found that activation in the left and right hippocampus mediated the association between age and memory performance (95% CI [0.002, 0.237]; Figure 7A). Second, we examined a model using only category-preferential visual processing regions (left and right LOC, left and right fusiform gyrus) and found that, jointly, activation in these regions significantly mediated the association between age and performance (95% CI [0.105, 0.519]; Figure 7B). Finally, to determine whether activation in visual processing regions make a unique contribution to age-related increases in memory performance, we conducted a final analysis examining the right and left LOC and fusiform controlling for hippocampal recruitment and found that visual processing regions significantly mediated the association of age and performance even after adjustment for hippocampal activation (95% CI [0.028, 0.417]; Figure 7C).

DISCUSSION

This study sought to investigate the age-related contributions of visual association cortex to increased associative memory ability across development. By using faces and objects, we were able to probe whether category-preferential visual processing regions, including the fusiform gyrus and LOC, showed age-related changes in recruitment during encoding and whether activation in these regions was associated with greater subsequent associative memory. Here, we provide evidence that, from childhood to late adolescence, recruitment of visual processing regions increases linearly with age during associative encoding and that activation within these regions is associated with increased subsequent memory. Furthermore, activation in these visual processing regions mediated the association between age and memory performance, over and above a separate mediating effect of hippocampal activation, suggesting that recruitment of these regions during memory

Table 4. Brain–Behavior Controlling for MFG and Hippocampus

ROI	*Hemi*	*R*	*Predictor*	*β*	*p*-value
Controlling for Hippocampal Activation					
Fusiform	LH	.625			.0001
			Hippocampus	.127	.422
			Fusiform	.478	.004
Fusiform	RH	.552			.0001
			Hippocampus	.132	.422
			Fusiform	.381	.023
LOC	LH	.605			.0001
			Hippocampus	.222	.204
			LOC	.403	.004
LOC	RH	.521			.001
			Hippocampus	.249	.204
			LOC	.264	.072
Controlling for MFG Activation					
Fusiform	LH	.619			.0001
			MFG	.063	.634
			Fusiform	.514	.0002
Fusiform	RH	.545			.0001
			MFG	.034	.807
			Fusiform	.456	.0002
LOC	LH	.593			.0001
			MFG	.159	.807
			LOC	.433	.001
LOC	RH	.483			.003
			MFG	.033	.807
			LOC	.387	.004

All *p*-values are FDR-corrected.

encoding is a neural mechanism explaining age-related changes in memory. These findings add to the growing body of literature that implicates visual processing regions in increased age-related associative memory performance (Wendelken et al., 2011; Chai et al., 2010).

Across the whole sample, encoding of correctly remembered pairs compared with single items was associated with recruitment of left MFG, bilateral IPS, LOC, occipital cortex, and ventral temporal cortex, including fusiform gyrus. These findings are similar to prior work on associative memory in adults and children (Ghetti & Bunge, 2012). Using age as a continuous predictor in ROI analyses, we found linear increases in recruitment of bilateral fusiform gyrus and bilateral LOC during encoding of faces and objects. Not only did we see these associations in functionally defined ROIs, but we also found similar results in the left and right fusiform gyrus and in the left LOC when we used ROIs defined by an independent developmental study of these regions in youths (Scherf et al., 2007). The present findings suggest that age-related changes in recruitment during encoding occur in regions involved in the category-preferential visual processing of the stimuli themselves. These results are consistent with studies that have observed increased activation in parahippocampal cortex during initial associative memory encoding in adults versus children (Wendelken et al., 2011; Chai et al., 2010). We extend these prior findings by demonstrating increases in both the fusiform and LOC with from childhood to adolescence during associative memory encoding of faces and objects.

In an exploratory whole-brain analysis, we also found support for age-related increases in recruitment of visual association cortex. This analysis revealed linear increases in the left LOC and right fusiform gyrus. In addition, the bilateral anterior insula/inferior frontal gyrus, bilateral medial superior frontal gyrus, and right anterior IPS also showed linear increases in recruitment across age. These findings suggest that age-related increases in recruitment during encoding occur both in regions involved in working memory and attention, such as the IPS, as well as regions involved in category-preferential visual processing of the stimuli themselves. These results are consistent

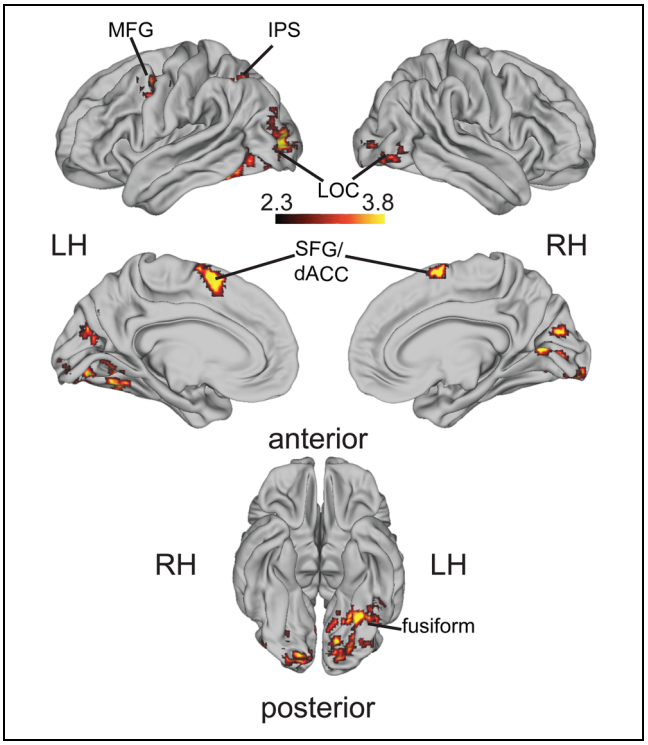

Figure 6. Whole-brain associations between performance (*d′*) and neural recruitment during associative memory encoding.

Table 5. Whole-brain Brain–Behavior Associations

Anatomical Region	*x*	*y*	*z*	*Voxels*	*z-Max*	*p*
Associations between Activation and Performance						
Left occipital fusiform gyrus	−28	−72	4	962	4.3	<.0001
Temporal occipital fusiform cortex						
LOC						
Right occipital fusiform gyrus	26	−72	0	501	4.14	<.0001
Lingual gyrus						
Calcarine sulcus						
LOC						
Left supplemental motor cortex	−4	8	60	292	4.77	<.0001
Medial superior frontal gyrus, Superior frontal gyrus						
Left IPS	−22	70	52	213	4.03	<.0001
Superior parietal lobule						
Left MFG	−40	−6	36	177	3.76	.0002
Left cerebellum	−22	−46	−42	152	2.29	.0005
Right anterior superior temporal gyrus	62	2	0	523	4.74	<.0001
Planum polare						
Planum temporale						
Anterior paracingulate cortex						
Right supplemental motor cortex, medial PFC, dorsal anterior cingulate	12	52	12	521	4.08	<.0001
Left supramarginal gyrus	−58	−30	48	496	4.29	<.0001

with studies that have implicated increased recruitment of frontal and parietal regions supporting improved long-term memory performance across development (Ofen et al., 2007) as well as those that have found greater recruitment in visual association cortex for adults than children during encoding of scenes (Wendelken et al., 2011; Chai et al., 2010).

Behaviorally, we observed linear increases in performance across our sample. Recent work has found that the ability to bind different types of information follows different developmental trajectories (Lee, Wendelken, Bunge, & Ghetti, 2016). For instance, while the binding of item-space information reaches adult-like performance by age 10, item–item binding has a much slower trajectory. Although this study did not use item–item pairings, our findings indicate that the ability to bind face–item pairings may also follow a more protracted development, where performance continues to improve through late adolescence. The neural findings in this study are also consistent with the behavioral findings given that the majority of our age–activation associations followed a linear pattern.

Greater activation during encoding of face–object pairs in category-preferential visual processing regions—bilateral fusiform gyrus and LOC—was associated with better performance on the associative memory test outside the scanner. This was true using functional definitions of these regions as well as using coordinates reported in an independent article that investigated the development of these regions in samples that spanned a similar age as ours (Scherf et al., 2007). These brain–behavior associations remained significant over and above the effect of age in bilateral fusiform gyrus and left LOC using functional definitions, in the right fusiform and bilateral LOC using coordinate definitions, and in bilateral LOC and left fusiform gyrus in our exploratory whole-brain analysis. In addition, ROI analyses revealed that activation in the hippocampus and left MFG during encoding was associated with better memory performance, and whole-brain analysis revealed significant performance-related recruitment of the left MFG, bilateral medial superior frontal gyrus, and left anterior IPS. These findings are consistent with previous studies that have implicated the hippocampus, MFG, and IPS in memory performance across development (Ghetti & Bunge, 2012; Ofen et al., 2007). Importantly, we found that activation in category-preferential visual processing regions made a unique contribution to memory performance, illustrated by the findings that greater activation in fusiform and LOC was associated with greater memory performance

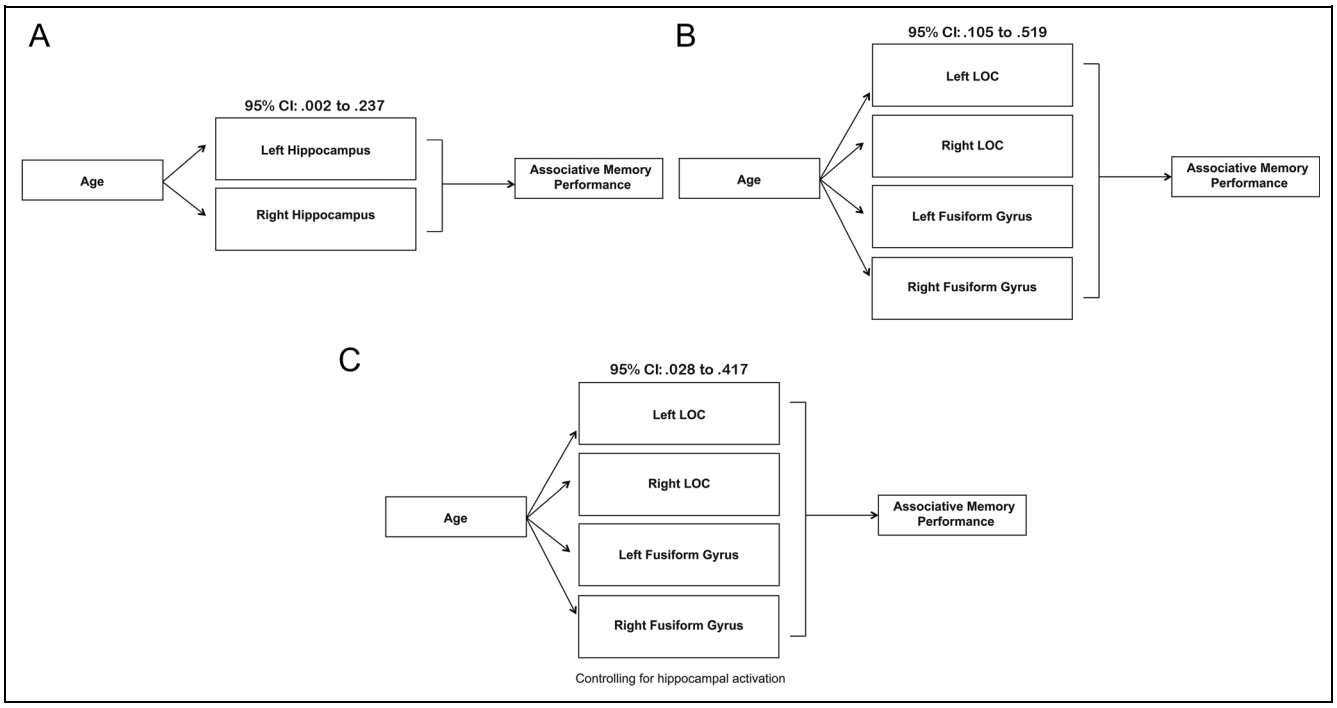

Figure 7. Mediation analyses. Analyses explore investigated recruitment of (A) hippocampus, (B) category preferential visual processing regions, and (C) category preferential visual processing regions controlling for hippocampal recruitment as mechanisms explaining the association between age and memory performance. Confidence intervals that do not include 0 are considered evidence for statistically significant indirect (i.e., mediated) effects.

controlling for activation in the hippocampus and MFG. Together, these findings provide support for the idea that, in addition to the hippocampus and pFC, greater activation in category-preferential visual association cortex during initial associative memory encoding is predictive of individual differences in memory performance.

Prior work in adults has implicated category-preferential visual processing regions in subsequent memory for different categories of stimuli. For instance, an early article establishing the role of LOC in visual processing of objects found that greater activation of this region during encoding of objects was associated with greater subsequent memory (Grill-Spector et al., 2000). Since that time, multiple studies have also shown that activation in these category-preferential regions is linked to individual differences in long-term memory performance (Hasinski & Sederberg, 2016; Kim, 2011; Bernstein, Beig, Siegenthaler, & Grady, 2002). Similarly, recent work in children and adults found that increased activation of the parahippocampal cortex for the encoding of complex visual scenes was associated with greater subsequent memory for those scenes (Chai et al., 2010). These findings could provide further support for the role of visual processing regions in increased long-term memory performance across development, although the parahippocampal cortex also has a known role in long-term memory encoding (Eichenbaum et al., 2007). Therefore, the increased recruitment could have been due to memory-related processes rather than the visual processing role of the parahippocampal cortex for scenes. Our study was designed to specifically probe visual processing regions not thought to be directly involved in long-term memory encoding to disentangle these competing interpretations of prior developmental work in this area. Specifically, we used faces and objects to investigate the role of the fusiform gyrus and LOC in associative memory formation across development. In doing so, this study provides evidence that increased recruitment of visual association cortex across development during stimulus encoding supports subsequent memory for those stimuli.

Our findings add to the growing body of literature that suggests that age-related increases in activation of visual processing regions during stimulus encoding contribute to age-related increases in long-term memory (Wendelken et al., 2011; Chai et al., 2010). We extend these findings by demonstrating that recruitment of visual processing regions is a neural mechanism underlying age-related improvements in associative memory, over and above hippocampal contributions. One interpretation of this pattern is that it reflects improvements in visual attention across development that facilitate associative memory by maintaining attention to the stimuli that are being encoded (Rosen et al., in preparation; Wendelken et al., 2011; Chai et al., 2010). Certainly, the importance of top–down attention in enhancing the processing of visual information in visual association cortex and the relation of this enhanced processing to better memory is well established in adults (Markant et al., 2015; Uncapher & Rugg, 2009; Gazzaley et al., 2005). The findings of this study are consistent with the idea that increased attention and sustained activation in visual processing regions during the initial encoding of

a stimulus contributes to the developmental changes in memory performance. Recent theoretical models propose a critical role for the ventral visual stream and category-preferential visual processing regions in the development of attention and memory (Amso & Scerif, 2015), and our results are broadly consistent with these ideas. Importantly, this model also proposes that not only enhanced feed-forward visual processing but also top–down attention contribute to enhanced attention and memory performance across development.

Work from several laboratories has found that although the fusiform gyrus shows selectivity for face processing by age 6, this selectivity increases developmentally and does not reach maturity until adolescence (Golarai, Liberman, Yoon, & Grill-Spector, 2009; Golarai et al., 2007; Scherf et al., 2007; Aylward et al., 2005; for a review, see Cohen Kadosh & Johnson, 2007). Therefore, an alternative interpretation of our findings is that the age-related increases in recruitment of the fusiform and related increases in memory are explained by enhanced perceptual processing of faces with age (Cohen Kadosh & Johnson, 2007) and not increases in top–down attention. Indeed previous studies have found that increases in the size of the selective face-processing region of the fusiform gyrus are associated with enhanced face perception (Golarai et al., 2007). If face perception improves developmentally, it is possible that this enhanced perceptual processing facilitates better encoding, maintenance, or retrieval. In contrast to the fusiform gyrus, however, the LOC is thought to reach adult-like maturity by 5–8 years and does not show age-related changes in size or location beyond this age (Grill-Spector, Golarai, & Gabrieli, 2008; Golarai et al., 2007; Scherf et al., 2007). Although a recent study finds more fine-grained object recognition (e.g., size and view invariance) takes longer to develop in LOC (Nishimura, Scherf, Zachariou, Tarr, & Behrmann, 2015), the present study did not require this level of object recognition.

Given that we show age-related increases in recruitment of LOC, a region believed to have reached maturity in even the youngest children we are testing, this suggests that increased age-related activation in visual association cortex is not fully explained by protracted development of category-preferential visual processing regions like the fusiform gyrus. Another possibility is that age-related increases in recruitment of the fusiform gyrus and LOC are occurring for different reasons. Age-related increases in recruitment of the fusiform gyrus could be due to the protracted development of face selectivity of this region, whereas age-related increases in activation in the LOC could be due to the enhanced attentional processing of the to-be-remembered stimulus. Although this study is not able to definitively disentangle these three possible interpretations, it does provide evidence for an important role of visual association cortex in developmental improvements in associative memory. Although we are also not able to disentangle whether the results from this study are due to enhanced bottom–up visual processing or top–down improvements in attention and encoding, it is important to highlight that visual attention and memory encoding systems are composed of feed-forward and feed-back loops. It is likely that both of these processes are being honed across development, as proposed by a recent theoretical model (Amso & Scerif, 2015).

This study is limited in that we could not investigate differences in activation for remembered versus forgotten pairs as is often done in subsequent memory tasks (DeMaster & Ghetti, 2013; Ghetti et al., 2010) due to the blocked design, relatively high accuracy, and lack of jitter between accurate trials. Instead, we sorted the data into correctly remembered pairs and compared activation in those trials to encoding of single objects. This approach allowed us to investigate brain activation associated with the binding in memory of two items compared with encoding of single items and has been used previously in developmental studies (Sheridan, How, Araujo, Schamberg, & Nelson, 2013). Although age-related changes emerged in visual processing regions, the associations between age and activation during encoding in the hippocampus were only marginally significant and were absent in MFG. Many studies have implicated the hippocampus and MFG in age-related increases in associative memory encoding (DeMaster & Ghetti, 2013; Ghetti & Bunge, 2012; Ghetti et al., 2010; Ofen et al., 2007), and we do not take our lack of results as a contradiction to these prior findings. Rather, it is possible that the age-related changes in hippocampus and MFG recruitment emerge more prominently when looking at remembered vs. forgotten information.

This study provides additional support for recent work that implicates category-preferential visual regions in age-related increases in memory performance (Rosen et al., in preparation; Wendelken et al., 2011; Chai et al., 2010). Using faces and objects in an associative learning paradigm, we show that recruitment of the fusiform gyrus and LOC during stimulus encoding increased linearly with age and that greater recruitment in these visual processing regions was associated with better associative memory performance. Critically, we further demonstrate that activation in category-preferential visual association cortex during encoding is a neural mechanism explaining age-related improvements in associative memory, over and above the effects of hippocampus recruitment. These findings add to our understanding of the neural mechanisms that support increased associative memory performance across development.

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