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FMRI activity during associative encoding is correlated with cardiorespiratory fitness and source memory performance in older adults



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ABSTRACT

Older adults (OA), relative to young adults (YA), exhibit age-related alterations in functional Magnetic Resonance Imaging (fMRI) activity during associative encoding, which contributes to deficits in source memory. Yet, there are remarkable individual differences in brain health and memory performance among OA. Cardiorespiratory fitness (CRF) is one individual difference factor that may attenuate brain aging, and thereby contribute to enhanced source memory in OA. To examine this possibility, 26 OA and 31 YA completed a treadmill-based exercise test to evaluate CRF (peak VO₂) and fMRI to examine brain activation during a face-name associative encoding task. Our results indicated that in OA, peak VO₂ was positively associated with fMRI activity during associative encoding in multiple regions including bilateral prefrontal cortex, medial frontal cortex, bilateral thalamus and left hippocampus. Next, a conjunction analysis was conducted to assess whether CRF influenced age-related differences in fMRI activation. We classified OA as high or low CRF and compared their activation to YA. High fit OA (HFOA) showed fMRI activation more similar to YA than low fit OA (LFOA) (i.e., reduced age-related differences) in multiple regions including thalamus, posterior and prefrontal cortex. Conversely, in other regions, primarily in prefrontal cortex, HFOA, but not LFOA, demonstrated greater activation than YA (i.e., increased age-related differences). Further, fMRI activity in these brain regions was positively associated with source memory among OA, with a mediation model demonstrating that associative encoding activation in medial frontal cortex indirectly influenced the relationship between peak VO_2 and subsequent source memory performance. These

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results indicate that CRF may contribute to neuroplasticity among OA, reducing age-related differences in some brain regions, consistent with the brain maintenance hypothesis, but accentuating age-differences in other regions, consistent with the brain compensation hypothesis.

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1. Introduction

Aging is associated with deficits in source monitoring (Johnson, DeLeonardis, & Hashtroudi, 1995; Johnson, Hashtroudi, & Lindsay, 1993), which refers to attributing a mental experience to a particular source, such as remembering whether something was real or imagined (Johnson & Raye, 1981; Sugimori, Mitchell, Raye, Greene, & Johnson, 2014) or remembering specific details about an event, such as the color or location of a previously seen item (Hayes, Buchler, Stokes, Kragel, & Cabeza, 2011; Siedlecki, Salthouse, & Berish, 2005). Among older adults (OA), source monitoring deficits are frequently attributed to age-related behavioral impairments in associative encoding (Chalfonte & Johnson, 1996; Glisky & Kong, 2008; Naveh-Benjamin, 2000; Old & Naveh-Benjamin, 2008), which are likely underpinned by agerelated alterations in brain activation in prefrontal, medial temporal, and parietal regions that are frequently observed during associative encoding (Dennis et al., 2008; Leshikar, Gutchess, Hebrank, Sutton, & Park, 2010; Sperling et al., 2003; de Chastelaine, Mattson, Wang, Donley, & Rugg, 2016).

Despite age-related impairments in associative encoding and pervasive alterations in brain activation, there is substantial variability among OA. For instance, some OA show comparable memory performance to young adults (YA) (Glisky, Rubin, & Davidson, 2001) and exhibit intact functional networks during encoding (Duzel, Schutze, Yonelinas, & Heinze, 2011). One individual difference factor that may attenuate age-related changes in memory and brain activation is cardiorespiratory fitness (CRF; Voss, Vivar, Kramer, & van Praag, 2013; Hayes, Hayes, Cadden, & Verfaellie, 2013), which refers to the capacity of one's circulatory and respiratory systems to supply oxygen to skeletal muscle during sustained moderate to vigorous physical activity. Our previous work has shown that among OA, CRF is positively associated with visual episodic memory as well as associative face-name memory (Hayes, Forman, & Verfaellie, 2016). Recent longitudinal studies have revealed that lower CRF was associated with accelerated cognitive decline (Wendell et al., 2014) and that OA with lower CRF had an increased risk for dementia (Defina et al., 2013), suggesting that CRF may also be a marker of neurodegenerative disease.

However, little is known about the functional brain correlates of CRF in the context of associative encoding paradigms. Our previous work has demonstrated that CRF is positively associated with face-name retrieval accuracy (source memory) among OA, and we also observed a positive association between CRF and a composite measure of standardized neuropsychological tests of visual episodic memory (see Hayes et al., 2016 for detailed analysis of CRF and neurocognitive measures in young adults (YA) and OA). However, fMRI data were not reported. Previous aging studies of functional brain correlates of CRF or exercise have examined executive functions (Colcombe et al., 2004; Prakash et al., 2011; Rosano et al., 2010; Voelcker-Rehage, Godde, & Staudinger, 2011), semantic memory (Smith et al., 2011), and motor function (McGregor et al., 2013). In general, these studies show that exercise or higher CRF is associated with greater brain activity, a pattern observed in both frontal and parietal regions (e.g., Colcombe et al., 2004; Prakash et al., 2011; Smith et al., 2011).

The current study examined the relationship between CRF and fMRI activity during associative encoding among OA. We used an associative encoding task in which participants were asked to learn face-name associations, which is related to the most common cognitive complaint among OA, forgetting proper names (Reese, Cherry, & Norris, 1999). A direct measure of peak VO₂ was obtained during a progressive treadmillbased maximal exercise protocol, which is considered the gold standard for assessment of CRF. The study had three main goals: (1) To examine whether CRF is positively associated with fMRI activity during associative encoding in OA; (2) To assess how CRF in OA impacts age-related differences in fMRI activity; and (3) To evaluate whether brain regions sensitive to CRF are associated with source memory performance among OA.

2. Material and methods

2.1. Participants

The sample included in the reported analyses consists of 26 OA (age 55-74 years; 22 Caucasian, two African-American, one Caucasian-Hawaiian) and 31 YA (age 18-31 years; 23 Caucasian, 6 Asian, 2 African–American). For some analyses, OA were assigned peak VO_2 percentile scores based on ageand gender-specific normative values and median-split into low or high CRF based on the American College of Sports Medicine (ACSM) percentile scores. Relative to published normative data (Heyward & Gibson, 2014), the mean peak VO₂ value of the low fit OA (LFOA) group fell within the poor range whereas the mean peak VO₂ value of the high fit OA (HFOA) group fell within the excellent range (see Table 1 for ACSM percentiles). To ensure recruitment of participants with a wide range of CRF levels, participants were recruited from general participant pools (Boston University community for YA and the Boston University Memory Disorders Research Center at VA Boston, Boston University Alzheimer's Disease

	Young adults (YA)	Older adults (OA)	Low fit older adults (LFOA)	High fit older adults (HFOA)	Age comparisons	Comparisons across the three groups
Number of participants	31 (17 F)	26 (13 F)	13 (6 F)	13 (7 F)		
Age (years)	21.0 (3.1)	63.2 (6.4)	64.5 (7.1)	61.9 (5.7)	OA > YA	LFOA & HFOA > YA
Education (years)	14.4 (1.8)	16.4 (2.6)	15.5 (2.6)	17.2 (2.4)	OA > YA	HFOA & LFOA > YA
WTAR (raw score)	42.7 (4.4)	41.7 (6.2)	38.8 (6.5)	44.5 (4.6)	ns	YA & HFOA > LFOA
MoCA	28.5 (1.5)	27.5 (2.0)	26.6 (2.3)	28.4 (1.0)	YA > OA	YA & HFOA > LFOA
CES-D	6.4 (4.0)	5.8 (4.2)	5.8 (4.1)	5.9 (4.5)	ns	ns
BMI (kg/m²)	23.0 (3.0)	26.2 (4.7)	28.8 (5.1)	23.6 (2.4)	OA > YA	LFOA > YA & HFOA
Peak VO ₂ (ml/kg/min)	38.1 (7.3)	30.0 (8.3)	24.0 (5.9)	35.9 (5.7)	YA > OA	YA & HFOA > LFOA
Peak VO ₂ ACSM percentile	39.7 (25.1)	43.7 (28.2)	19.2 (12.6)	68.1 (14.4)	ns	HFOA > YA > LFOA
Source memory accuracy (percent correct)	81.3 (7.7)	64.6 (8.3)	59.1 (6.3)	70.1 (6.2)	YA > OA	YA > HFOA > LFOA

Table 1 – Characteristics (mean and standard deviation) of young and older adults, as well as high CRF older adults (HCOA; ACSM percentile score > 50) and low CRF older adults (LCOA; ACSM percentile score < 50).

ACSM = American College of Sports Medicine; BMI = body mass index; CES-D = Center for Epidemiological Studies Depression Scale; F = female; HFOA = high fit older adults; LFOA = low fit older adults; MoCA = Montreal Cognitive Assessment; OA = older adults; WTAR = Wechsler Test of Adult Reading; YA = young adults.

Center, the Massachusetts Alzheimer's Disease Research Center, and the Alzheimer's Association TrialMatch for OA) as well as through local libraries, YMCAs, and track (running) meets. Participants completed a comprehensive health screen consisting of approximately 150 questions to rule out major medical (e.g., myocardial infarction, vascular disease), neurological (e.g., Alzheimer's disease, Parkinson's disease, multiple sclerosis), psychiatric (e.g., bipolar disorder, schizophrenia), or substance abuse issues that might affect cognition. Participants included in the study did not have any notable medical or neurological illness or history of head trauma, and did not have hypertension (blood pressure greater than 140/90 mmHg as assessed by the exercise physiologist and cardiologist). Additional exclusion criteria included education less than grade 12, and contraindications to cardiopulmonary exercise testing or Magnetic Resonance Imaging. Participants were screened for depression using a cut-off score of 16 on the Center for Epidemiologic Studies Depression Scale (CES-D) 20-item version. Mental status was assessed using the Montreal Cognitive Assessment (MOCA; http://www.mocatest.org/), and participants with scores \leq 23 were excluded (Luis, Keegan, & Mullan, 2009). Participant characteristics are reported in Table 1.

Neuropsychological and face-name memory retrieval accuracy (Hayes, Alosco, et al., 2015; Hayes et al., 2016), diffusion tensor imaging data (Hayes, Salat, et al., 2015), and cortical thickness data (Williams et al., 2016) from this sample are reported elsewhere, with minor differences in the number of subjects in the analysis sample dependent on the integrity of the particular data points of interest (e.g., a subject may have completed the DTI scan, but not the fMRI scan). All participants gave written informed consent and received financial compensation. The VA Boston Healthcare System institutional review board approved all experimental procedures.

2.2. Cardiopulmonary exercise testing

Participants completed a cardiopulmonary exercise test under the supervision of an exercise physiologist and a cardiologist at the VA Boston Healthcare system. Graded maximal exercise testing in association with air-gas-exchange was conducted using a 2-min Bruce protocol (Bruce, Kusumi, & Hosmer, 1973) on a motor driven Woodway Barimill treadmill. A lightweight disposable pneumotach device was positioned in the participant's mouth during exercise for gas exchange assessments (MedGraphics Ultima II). Peak oxygen consumption (VO₂) and respiratory exchange ratio (RER) were measured, as well as maximum heart rate, blood pressure, and ECG waveforms. Self-reported ratings of perceived exertion were collected at 1 min intervals using the 20-point Borg Scale. Peak VO₂ was considered valid if at least two of the following criteria were met: (1) RER \geq 1.05, (2) Maximum heart rate equivalent to 85% of the age-predicted maximum (i.e., 220 - age), (3) Ratings of perceived exertion \geq 17, which corresponds to an exertion level of "very hard" (a rating of 20 represents "maximal exertion").

2.3. FMRI task: associative memory encoding

Materials were photographs of adult human faces (18–80 yrs; http://agingmind.utdallas.edu/download-stimuli/face-

database; Minear & Park, 2004). Names were collected from a database that provides popular baby names by year (http://www.socialsecurity.gov/OACT/babynames/) and were randomly selected within each decade to include popular names from the birth years of OA and younger adults (1930–1999). Young and older adult names were randomly assigned to the faces.

The experiment consisted of 5 encoding-retrieval blocks (Fig. 1). The encoding phase of each block consisted of the presentation of 36 novel face-name pairs. Interspersed among these pairs were 4 familiar face-name pairs that were presented three times each. This resulted in the presentation of 48 trials (36 novel and 12 repeated face-name pairs) during each encoding block and a total of 180 novel and 60 repeated face-name trials during the entire experiment. Repeated pairs had been presented to the participants 12 times (in the context of a pre-scanning practice session) prior to the experiment proper. During encoding, participants were instructed to remember each face-name pair and were asked to rate how



Fig. 1 – Example of experimental stimuli used during the associative encoding and source memory task.

well the name fit with the face on a 4-point scale. The purpose of the rating task was to confirm that participants were attending to both the name and face stimuli. After encoding, the participants completed a 20 sec filler task during which they were asked to respond whether a presented number was odd or even. Next, participants completed the retrieval phase. Each retrieval block consisted of 48 trials (36 novel and 12 repeated) in which a target face was presented with two names, the target name and a lure name that had been presented with a different face in the same block. During retrieval, participants were asked to select on each trial the name with which a face had previously been presented and to indicate their confidence in the selected choice (definite or probable).

Stimuli were presented for 3.5 sec with a jittered inter-trial interval ranging between .5 and 6.5 sec during both encoding and retrieval. The stimuli were presented using a PC computer with E-prime (version 2.0.8.74) and MRI-compatible fiber optic goggles. Participant responses were collected with a fourbutton fiber optic response pad placed in the participant's right hand.

2.4. Image acquisition and processing

Participants underwent MRI on a 3.0 Tesla Siemens Trio scanner equipped with a 12-channel head coil and located at the Jamaica Plain campus of the VA Boston Healthcare System. A high-resolution T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (voxel size = 1 mm³, matrix = 256², FOV = 256 mm, flip angle = 7°, TR = 2530 msec, TE = 3.32 msec, TI = 1100 msec) was acquired in the sagittal plane. Next, five whole-brain functional images were acquired parallel to the anterior commissure-posterior commissure plane using an echoplanar imaging sequence sensitive to the blood oxygenation level dependent (BOLD) signal: slice order = interleaved, matrix = 64^2 , FOV = 192, slices = 33, thickness = 3.75 mm, voxel size = $3 \times 3 \times 3.75$ mm, volumes = 282, TR = 2000 msec, TE = 30 msec, flip angle = 90° .

FMRI data processing was carried out using FEAT (fMRI Expert Analysis Tool) Version 6.0, part of FSL 5.0.8 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The following prestatistics processing was applied; motion correction using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002); slicetiming correction using Fourier-space time-series phaseshifting; non-brain removal using BET (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 6.0 mm; grandmean intensity normalization of the entire 4D dataset by a single multiplicative factor; and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 45.0 sec). In a two-step registration process, each functional image was co-registered to the participant's samesession T1-weighted structural image using FMRIB Linear Image Registration Tool (FLIRT). Between-subject registration was accomplished by alignment of functional images to the Montreal Neurological Institute (MNI) 152 standard space template and further refined using the FMRIB Nonlinear Image Registration Tool (FNIRT; Jenkinson et al., 2002). Images were visually inspected to confirm proper registration to MNI space.

2.5. Statistical approach

2.5.1. Behavioral data

T-tests were used to compare YA and OA demographic variables, and one-way analysis of variances (ANOVAs) were used to compare characteristics of YA, low fit older adults (LFOA), and high fit older adults (HFOA). To examine the nature of the relationship between face-name retrieval accuracy (collapsed across 'definitely old' and 'positively old' responses) and CRF among OA, a two-step hierarchical regression model was implemented. In Step 1, age, sex, and WTAR-scores were entered as predictors of face-name retrieval accuracy. In Step 2, peak VO₂ was entered into the model to assess the contribution of CRF to face name retrieval accuracy (collapsed across high and low confidence responses). The alpha level for all tests was set at p < .05.

2.5.2. FMRI data

Time-series statistical analysis utilized FMRIB's Improved Linear Model (FILM) with local autocorrelation correction. Trial onset times were convolved with a single gamma hemodynamic response function and explanatory variables (i.e., encoding Novel and Repeated trials) were modeled. Trials in which the participant failed to respond were included in the model as a condition of no interest, as were trials from the filler and retrieval phase. Our analysis focused exclusively on fMRI activity during novel associative encoding, i.e., encoding all Novel trials (regardless of subsequent memory performance) > all Repeated trials. Subject level analysis was carried out using a fixed effects model, by forcing the random effects variance to zero in FLAME (FMRIB's Local Analysis of Mixed Effects; Beckmann, Jenkinson, & Smith, 2003; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). Group-level analysis was carried out using FLAME stage 1. The resulting statistical images for all reported whole brain analyses were thresholded using clusters determined by Z > 1.96 and a (corrected) cluster significance threshold of p = .05. To examine the association between associative encoding and CRF among OA, we used a single group (OA) model contrasting encoding Novel versus Repeated trials and entering demeaned peak VO₂ as a variable of interest and included demeaned age, sex, and estimated IQ as covariates of no interest. To examine age-related differences during associative encoding, a twogroup model (OA < YA and OA > YA) controlling for sex and estimated IQ was implemented.

Conjunction analyses using the age-difference maps (OA < YA; OA > YA) and the whole-brain map that identified brain regions sensitive to CRF during associative encoding were also conducted. We used an inclusive masking approach, which functions as a logical AND operator. Thus, these maps identified voxels that independently showed both an ageeffect (Z > 1.96 and a corrected cluster significance threshold of p = .05) AND an association with CRF among OA (Z > 1.96and a corrected cluster significance threshold of p = .05; Nichols, Brett, Andersson, Wager, & Poline, 2005). We extracted individual subject mean z-stat values for the associative encoding contrast for these regions, and set a minimum cluster size of 10 contiguous voxels to maintain sensitivity of these effects in smaller subcortical structures, such as the thalamus. We stratified the OA group into those with high CRF (50th percentile or greater peak VO₂) and those with low CRF (lower than 50th percentile peak VO₂) based on normative data from the ACSM (Pescatello & American College of Sports Medicine, 2014). To compare fMRI activity in the clusters resulting from the conjunction analysis for each of these subgroups with that in YA, we used a repeated measures ANCOVA with group (YA, HFOA, and LFOA) as a betweensubjects factor and brain region as a within-subjects factor while controlling for sex and estimated IQ.

Next, we assessed whether activation in brain regions that were associated with CRF in OA and exhibited age-related differences in activation during associative encoding was related to memory performance. We ran a linear regression model on the OA group in which source memory accuracy was regressed onto associative encoding activation with age, sex, and estimated IQ as covariates. Multiple-testing corrected significance (*p*-corrected, adjusting for analysis of multiple ROIs) was determined using Monte-Carlo null simulation with 10,000 replicates and alpha level of .05.

Finally, given our previous report that CRF was positively associated with memory performance in the current sample of OA (Hayes et al., 2016), we aimed to examine the role of encoding-related brain activation in this association. Using the PROCESS macro for SPSS (Preacher & Hayes, 2008) we tested a mediation model, with CRF (peak VO₂) entered as the independent variable, associative encoding activity as the mediator, and source accuracy (percent correct) as the dependent (or outcome) variable while controlling for age, sex, and estimated IQ. A regression-based path analysis was performed estimating direct and indirect effects. Bootstrapping was used to estimate the sampling distribution (n = 10,000) and 95% confidence intervals for the indirect effects. Age, sex, and estimated IQ were included as covariates.

Results

3.1. Participant characteristics

Groups were matched in sex, χ^2 (1) = .13, p = .72, and there were no group differences in estimates of pre-morbid intellectual functioning on the Wechsler Test of Adult Reading (WTAR), t (55) = .77, p = .44, or self-reported depression symptoms (CES-D), t (55) = .56, p = .58. OA completed a greater number of years of formal education, t (55) = 3.31, p < .01. The difference in education was expected, given that the majority of YA were completing their bachelor's degree; therefore, we elected to control for pre-morbid intellectual function (WTAR scores) rather than education for the primary analyses of interest. OA scored lower on a test of mental status, the MOCA, t (55) = 2.19, p < .05, and had a higher body mass index (BMI), t (55) = 3.10, p < .01 relative to YA. Note that it would not be appropriate to control for BMI (weight in kg/height in m²) in our primary analyses, as the primary variable of interest, peak VO₂ (ml/kg/min), already corrects for body weight. As expected, peak VO₂ (ml/kg/min) was significantly lower in OA relative to YA, t (55) = 3.92, p < .01. However, there was no significant difference in the American College of Sports Medicine (ACSM) mean peak VO2 percentile scores for YA and OA, t (55) = .56, p = .58, indicating that both groups were equivalently fit relative to their age and sex-based peers (Pescatello & American College of Sports Medicine, 2014). Furthermore, ACSM percentile scores for both age groups ranged from the 10th to 90th percentiles, indicating representative samples in terms of CRF levels based on peak VO2. In addition to age group comparisons (YA vs OA) on demographic variables, we also conducted one-way ANOVA with follow-up least significant difference comparisons between YA and OA classified as high or low fit. Significant effects are summarized in Table 1 with Supplementary Materials providing more detailed statistical results.

3.2. Relationship between source memory and CRF

The results of the hierarchical regression of face-name memory in OA revealed that age, sex, and estimated IQ (Step 1) accounted for 26.6% of the variance in face-name memory accuracy, which approached significance, model F (3,25) = 2.64, p = .07. Adding peak VO₂ (Step 2) to the model accounted for an additional 23.8% of the variance with F change = 10.11, which was significant, p = .005, and the overall model became significant, F (4,21) = 5.35, p < .005, accounting for 50.5% of the variance. To assess whether CRF alone could account for the majority of variance in face-name memory accuracy among OA, we reversed the steps of the previous model, i.e., peak VO₂ was entered in Step 1 and age, sex and estimated IQ were entered in Step 2. Indeed, peak VO2 alone (Step 1) accounted for 43.7% of the variance, and the model was significant, F (1,25) = 18.64, p < .001. Adding age, sex, and estimated IQ in Step 2 accounted for an additional 6.8% of the variance, but it did not improve the model, F-change < 1, p = .43, model F (4,25) = 5.35. The positive association between peak VO₂ and source memory accuracy among OA is shown in Fig. 2.



Fig. 2 – Scatterplot, best fit line, regression equation, and R^2 value (peak VO₂ predicting face-name memory accuracy) showing the relationship between peak VO₂ and source memory accuracy among older adults.

Results of a one-way ANOVA comparing face-name memory accuracy among YA, HFOA, and LFOA was significant, F (2,56) = 47.01, p < .0001. Follow-up least significant difference pairwise comparisons indicated that YA had greater accuracy than both low and HFOA (p's < .0001) and that HFOA had greater face-name accuracy than their lower CRF peers (p < .0001). This pattern of results (YA > HFOA > low CRF OA) was not altered when face-name memory was assessed with an ANCOVA with sex and estimated IQ included in the model as covariates. Related analyses examining age differences in cognitive performance and the association between CRF and face-name memory retrieval, visual episodic memory, and executive function have been previously reported in this sample (Hayes et al., 2016).

3.3. Relationship between associative encoding activity and CRF in OA

Among OA, multiple brain regions showed a positive relationship between associative encoding activity and CRF (peak VO₂; see Fig. 3; Table 2) while controlling for age, sex, and estimated IQ. Importantly, these associations were observed in regions known to be important for learning and memory, including bilateral inferior frontal gyrus, left hippocampus, bilateral thalamus, and fusiform gyrus. No brain regions showed a negative association between CRF and associative encoding.

3.4. How does CRF impact age-related differences in associative encoding activity?

First, we identified regions showing age-related decreases (OA < YA) and age-related increases (OA > YA) during associative encoding, controlling for sex and estimated IQ (see Fig. 4A; Supplementary Table 1). Reduced activation in OA relative to YA was observed in the medial temporal lobe and thalamic regions, as well as in visual processing regions, left inferior frontal and medial frontal gyrus. Increased

activation in OA relative to YA was observed primarily in cortical areas, encompassing regions of the temporal, parietal, and frontal lobes.

We next performed a conjunction analysis that identified regions that showed significant decreases in activation in OA relative to YA during associative encoding AND significant positive associations with CRF among OA (Fig. 4B; Table 3). This analysis revealed clusters in left inferior frontal and medial frontal gyrus, thalamus, and fusiform gyrus/cerebellum. Using subject data extracted from these group conjunction maps, we conducted a repeated measures ANCOVA with group (YA, HFOA, and LFOA) as a between subjects factor and brain region (nine regions: Table 3, OA < YA) as a within subjects factor while controlling for sex and estimated IQ. The analysis revealed a main effect of group, F(2,52) = 10.4, p < .0001, with follow-up least significant differences pairwise comparisons indicating a step-wise pattern in which YA showed a trend for greater activation than the HFOA (p = .06), who in turn had greater activation than the LFOA (p = .04).

Using the same conjunction analysis approach, we also identified regions that showed significant age-related increases (OA > YA) in associative encoding activity AND significant positive associations with CRF among OA. The resulting conjunction map revealing clusters restricted to the frontal lobes (Fig. 4C; Table 3). A repeated measures ANCOVA revealed a main effect of group, F(2,52) = 13.00, p < .0001 and reflected the fact that HFOA showed significantly greater activation than their low CRF peers (p < .01), as well as YA (p < .0001). There was no difference in activation between LFOA and YA, p = .11.

3.5. Linking CRF, associative encoding activity, and source memory performance

We examined whether activation in any of the brain regions that were sensitive to CRF and also showed age-related differences in fMRI activation was associated with source memory performance among OA. Table 3 lists the partial correlation coefficients between associative encoding activation and source memory accuracy (controlling for age, sex, and estimated IQ) for each region. Associative encoding activity in the left inferior frontal gyrus, medial frontal gyrus, left thalamus and brain stem were significantly associated with source memory performance in OA. The medial frontal gyrus (corrected p = .002) and brainstem (corrected p = .01) survived corrections for multiple comparisons. Using the brain region that showed the strongest association with source memory (medial frontal gyrus, MNI coordinates -8 16 54), we next tested whether fMRI activity mediated the relationship between peak VO₂ and associative memory performance. Path models examining these associations are displayed in Fig. 5. The effects of peak VO₂ on fMRI activity in medial prefrontal cortex was significant (p = .0004), as was the effect from medial prefrontal cortex activity to memory performance (p = .02), adjusting for age, sex, and estimated IQ. The direct effect of VO₂ on memory performance was not significant (p = .19). A bias-corrected bootstrap confidence interval for the indirect effect of peak VO2 on memory performance via medial frontal cortex activity did not encompass zero



Fig. 3 – Brain regions in older adults showing a positive association between peak VO₂ (ml/kg/min) and associative encoding activity. White numbers at top of axial images represent MNI value in z (axial) plane. Scatterplots (and best fit line) from several regions are also displayed. FMRI activity z-residual (y-axis) represents fMRI signal after regressing age, sex, and estimated IQ. L = left; R = right.

(ab = .004, 95% CI [.0004, .0092], indicating that the mediation model was significant.

4. Discussion

To our knowledge, this is the first study to examine the neural correlates of CRF during an associative encoding task in OA. Moreover, this is one of the first fitness - fMRI studies to

include both young and OA, allowing one to compare brain activation in high and low fit OA to younger adults. We found that CRF was positively associated with fMRI activity in multiple brain regions, including bilateral prefrontal cortex, hippocampus and thalamus. Age-related decreases in fMRI activation in the thalamus, fusiform gyrus/cerebellum, left orbitofrontal cortex and medial frontal cortex were less prominent among HFOA. At the same time, age-related increases in activation in frontal regions, including lateral and

Table 2 – Brain regions showing a positive association between peak VO₂ and associative encoding activity in older adults.

Brain region	Hemi	Cluster extent (voxels)	Х	Y	Ζ	Mean z-value	
Inferior frontal gyrus	R	1610	58	18	24	2.41	
Inferior frontal gyrus	L	1330	-40	40	-14	2.43	
Fusiform/cerebellum	R	967	24	-44	-34	2.29	
Thalamus/hippocampus	В	907	-6	-24	-4	2.29	
Medial frontal gyrus	В	856	-10	14	60	2.49	
Medial frontal gyrus	В	852	0	60	18	2.52	
Mid cingulate gyrus	В	688	16	81	53	2.30	
Superior frontal gyrus	R	24	10	48	46	2.14	
Middle frontal gyrus	L	21	-24	14	56	2.15	
Brainstem	R	17	16	-30	-32	2.11	
Lateral occipital	R	13	56	-66	-24	2.30	
Inferior frontal gyrus	L	10	-60	16	0	2.17	
XYZ coordinates reflect the peak z-value within each cluster re-							

ported in MNI space. B = bilateral; Hemi = hemisphere; L = left;R = right.

medial prefrontal cortex, were more prominent among HFOA. Finally, activation in many of these regions was positively associated with source memory performance, and activation in medial frontal gyrus indirectly influenced the relationship between CRF and source memory performance.

Our results show a positive relationship between CRF and brain activation during associative encoding in OA in bilateral prefrontal cortex (including left inferior frontal gyrus), medial frontal cortex, thalamus, and hippocampus, regions frequently activated during associative encoding, as well as the fusiform gyrus, which is known to play a role in face processing (Kanwisher, McDermott, & Chun, 1997; McCarthy, Puce, Gore, & Allison, 1997) and episodic encoding of visual stimuli (Kim, 2011). These results are consistent with findings in other cognitive domains, such as semantic memory (Smith et al., 2011), executive function (Colcombe et al., 2004; Prakash et al., 2011; Rosano et al., 2010), and motor function (McGregor et al., 2013), where similar positive relationships have been observed (but see (Voelcker-Rehage et al., 2011). Our findings further extend the literature by demonstrating this relationship in the context of associative encoding, which is critical for subsequent source memory (Mitchell & Johnson, 2009), and that this effect was evident in frontal brain regions involved in the strategic aspects of encoding as well as core memory regions involved in binding of informational elements. Interestingly, there does seem to be some consistency across studies in that significant findings are observed in lateral and medial prefrontal cortex. Whether these frontal lobe findings are attributable to shared component processes across cognitive tasks or due to the frontal lobes being particularly sensitive to CRF are unknown. Future work comparing CRF with fMRI activation during tasks that exert differential demands on frontal regions, within subject, may clarify this issue (e.g., Cabeza et al., 2004; Nyberg et al., 2003).

Further insight into the significance of the association between CRF and activation during associative encoding in OA comes from a comparison with activation patterns observed in YA. Aging is associated with both decreases and increases in fMRI activation (Dennis & Cabeza, 2012; Hayes & Cabeza, 2008; Reuter-Lorenz & Park, 2014), and the results of our conjunction analyses revealed that higher CRF was associated with reduced age differences in some regions and increased age differences in other regions. For brain regions in which OA showed reduced activation relative to YA, including left inferior frontal gyrus, medial frontal gyrus, bilateral thalamus, and fusiform gyrus, we observed a step-wise pattern, with the greatest activation in YA, followed by HFOA and then LFOA, indicating that higher fitness in OA reduced age-related differences. These findings suggest that CRF supports successful brain maintenance in aging, in that it promotes the preservation of neural function seen in YA (Nyberg, Lovden, Riklund, Lindenberger, & Backman, 2012). CRF could potentially support maintenance of a youthful brain through a variety of mechanisms, such as angiogenesis, neurogenesis, and promotion of nerve growth factors (Cotman, Berchtold, & Christie, 2007; Voss et al., 2013).

In contrast, the pattern of reduced age differences in HFOA was not evident in brain regions where OA tended to show greater activation than YA. In these regions, high CRF was associated with increased age differences in fMRI activation, as HFOA showed greater activation than YA and LFOA, who did not differ from each other. Notably, regions showing this pattern were all localized to prefrontal cortex, which has been implicated previously in neural compensation (Cabeza, Anderson, Locantore, & McIntosh, 2002; Dennis & Cabeza, 2012). Specifically in the context of memory encoding, increases in frontal cortex have been observed in association with age-related decreases in medial temporal lobe activation, thought to reflect neural compensation (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; Gutchess et al., 2005). In a similar vein, enhanced encoding activation in HFOA may reflect compensatory activation that supports the strategic encoding of novel associations.

Consistent with the notion that CRF exerts beneficial influences on brain function, activation during associative encoding in regions that were sensitive to CRF and showed age-related changes was positively correlated with source memory accuracy. This pattern was evident in a number of regions, including left inferior frontal gyrus and other lateral prefrontal cortex regions (Blumenfeld & Ranganath, 2007), but was strongest in medial frontal gyrus, which also plays a role in successful memory encoding (Spaniol et al., 2009). We formally tested the notion that CRF influences source memory via fMRI activation in this region with a mediation model, and found evidence that activity in medial frontal gyrus supports an indirect relationship between CRF and source memory performance. Previous work has shown that fMRI activation in anterior cingulate/supplementary motor cortex mediates the relationship between CRF and executive function (dual task performance (Wong et al., 2015). The peak coordinates of the cluster reported by Wong et al. (2015) are approximately 20 mm posterior to the cluster observed in the current study, but visual inspection of the figures suggest the clusters are in fact more proximate, which may reflect shared cognitive processes between the two tasks. Nevertheless, the current study further extends the literature by reporting a significant mediation model in the context of associative encoding



Fig. 4 – A. Brain regions showing age-related differences (older adults < young adults; older adults > young adults) in associative encoding activity, controlling for sex and estimated IQ. B. Results of conjunction analysis showing regions in which age-related decreases in associative encoding activity (older adults < young adults) AND a positive association with CRF in older adults was observed. C. Results of conjunction analysis showing regions in which age-related increases in associative encoding activity (older adults > young adults) AND a positive association with CRF in older adults was observed. Bar graphs represent the mean z-residual (controlling for sex and estimated IQ) and error bars represent the 95% confidence interval for regions. Fus = fusiform; IFG = inferior frontal gyrus; L = left; Med FG = medial frontal gyrus; MFG = middle frontal gyrus; OA = older adults; R = right; SFG = superior frontal gyrus; Thal = thalamus; YA = younger adults. Note: superscripts by brain labels correspond to those regions listed in Table 3.

Brain region	Hemi	Cluster extent (voxels)	Х	Y	Ζ	Source accuracy pr
Older adults < young adults						
Inferior frontal gyrus	L	291	-40	38	-14	.44*
Thalamus/brainstem	L	272	-12	-18	6	.37
Cingulate gyrus	В	197	10	24	32	.38
Fusiform/cerebellum ^d	R	174	42	-54	-26	.40
Medial frontal gyrus ^c	В	148	-8	16	54	.68***
Anterior thalamus ^a	L	36	-6	-6	-4	.43*
Brainstem	R	21	6	-28	-14	.60**
Inferior frontal gyrus ^b	L	15	-48	36	6	.44*
White matter adjacent to hippocampus	L	10	-16	-14	-10	.37
Older adults > young adults						
Middle/superior frontal gyrus	R	86	16	36	34	.31
Middle/superior frontal gyrus ^e	L	56	-22	24	38	.44*
Inferior frontal gyrus	R	23	46	18	10	.30
Medial frontal gyrus ^f	R	15	6	44	40	.48*

Table 3 – Results of conjunction analyses, i.e., brain regions showing both a positive association between peak VO_2 and associative encoding activity in older adults AND an age difference (older adults < young adults or older adults > young adults) in associative encoding activation, as well as the partial correlation coefficients (pr) between associative encoding activation and source memory accuracy.

*p < .05; **p < .01; ***p < .001; XYZ coordinates reflect the peak z-value within each cluster in MNI space; B = bilateral; Hemi = hemisphere; L = left; pr = partial correlation coefficient; R = right; Note: superscripts a-f adjacent to the brain regions correspond to those regions displayed in Fig. 3B and C.



Fig. 5 — Mediation model including standardized regression coefficients for the relationship between CRF and source memory accuracy through the indirect effect of medial frontal gyrus activity, controlling for age, sex, and estimated IQ.

activity in medial frontal gyrus supporting an indirect relationship between CRF and source memory performance.

The observed positive association between CRF and fMRI activation among OA is consistent with our previous studies of CRF and brain structure in aging. That is, among this sample of OA, we have previously reported positive associations between CRF and white matter microstructure (Hayes, Salat, et al., 2015) and cortical thickness (Williams et al., 2016). Moreover, these studies have shown that HFOA exhibit structural metrics more similar to YA than the LFOA. For instance, in some white matter tracts, there was no difference in white matter microstructure in YA and HFOA, with reduced white matter integrity observed only in the LFOA.

Other regions showed a stepwise pattern of white matter integrity, i.e., YA > HFOA > LFOA, which was a prominent pattern observed with our cortical thickness data.

The observed associations with CRF and the aging brain likely underpin the relationship between CRF and memory performance among OA. We have previously reported a positive association between CRF and memory among this older adult sample (Hayes et al., 2016), and the current study demonstrates that CRF alone can account for the majority of variance in face-name memory performance among OA. Further, the current study demonstrates that encoding activity in medial frontal gyrus indirectly supports the relationship between CRF and source memory performance. Future longitudinal studies with larger samples may be able to elucidate which neural metrics (cortical thickness, white matter microstructure, fMRI activation, etc.) are most sensitive to CRF and clarify the potential neuroprotective effects of CRF on the aging brain.

An attractive aspect of the current study is that CRF can be improved though moderate to vigorous physical activity, such as dancing, walking, or swimming. The possibility that such activity can mitigate age-related changes in brain structure (Tian et al., 2015; Hayes, Salat, et al., 2015) and function (Burzynska et al., 2015), as well as cognition (Hayes, Alosco, et al., 2015; Prakash, Voss, Erickson, & Kramer, 2015; Smith et al., 2010), has understandably garnered substantial enthusiasm. Our results provide further support for this notion, with some caveats. The current study reports associations between CRF and fMRI activation, and does not necessarily represent a causal relationship. Also, because the study was crosssectional, it is possible that other cohort factors such as genetics, diet, or other cardiovascular factors may have influenced the results. Finally, the sample had limited ethnic and racial diversity. Nevertheless, our results support the notion that CRF may serve as a neural enrichment factor in aging, as it was positively associated with brain activation during associative encoding, which in turn contributed to enhanced subsequent source memory performance. Future work that assesses CRF, the brain, and cognition over time in healthy individuals, as well as those with cardiovascular risk factors (Hayes, Alosco, & Forman, 2014) and impaired cardiopulmonary function (Alosco et al., 2015; Alosco & Hayes, 2015) will provide greater understanding to the extent that modifiable individual difference factors contribute to brain maintenance.

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Supplementary data

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