THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Psychological Sciences
cite as: *J Gerontol B Psychol Sci Soc Sci*, 2016, Vol. 71, No. 3, 474–482
doi:10.1093/geronb/gbu167
Advance Access publication December 20, 2014

OXFORD

Original Research Report

Cardiorespiratory Fitness Is Associated With Cognitive Performance in Older But Not Younger Adults

Scott M. Hayes,[1,2] Daniel E. Forman,[3,4] and Mieke Verfaellie[1]

[1]Memory Disorders Research Center, VA Boston Healthcare System and Boston University School of Medicine, Massachusetts. [2]Neuroimaging Research for Veterans Center, VA Boston Healthcare System, Massachusetts. [3]Geriatric Research, Education, and Clinical Center, VA Pittsburgh Healthcare System, Pennsylvania. [4]Geriatric Cardiology Section, University of Pittsburgh Medical Center, Pennsylvania.

Correspondence should be addressed to Scott M. Hayes, PhD, Memory Disorders Research Center (151A), VA Boston Healthcare System, 150 South Huntington Avenue, Boston, MA 02130. E-mail: scott.hayes@va.gov.

Received July 29, 2014; Accepted October 21, 2014

Decision Editor: Bob G. Knight, PhD

Abstract

Objectives: Aging is associated with declines in executive function and episodic memory. Cardiorespiratory fitness (CRF) has been associated with enhanced executive function in older adults (OA), but the relationship with episodic memory remains unclear. The purpose of the study was to examine the relationship between CRF and cognition in young and OA and whether CRF mitigates age-related cognitive decline.

Methods: Participants completed exercise testing to evaluate CRF (peak VO_2) and neuropsychological testing to assess cognition.

Results: In OA, peak VO_2 was positively related to executive function, as well as to accuracy on an experimental face–name memory task and visual episodic memory. In young adults (YA), a relationship between peak VO_2 and cognition was not evident. High-fit OA performed as well as YA on executive function measures. On episodic memory measures, YA performed better than high-fit OA, who in turn performed better than low-fit OA.

Conclusions: CRF is positively associated with executive function and episodic memory in OA and attenuates age-related cognitive decline. We provide preliminary support for the age-dependence hypothesis, which posits that cognition and CRF relationships may be most readily observed during lifetime periods of significant neurocognitive development.

Key Words: Cognition—Executive function—Memory—Physical activity—Physical fitness—Successful aging

Background

There is extensive evidence for age-related cognitive decline in executive function, including inhibition, task switching, maintenance, and manipulation of information in one's mind (Goh, An, & Resnick, 2012), as well as in episodic memory (Naveh-Benjamin, 2000). At the same time, there is substantial performance variability among older adults (OA), and individual difference approaches have highlighted the fact that some OA maintain performance in the cognitive domains most often associated with age-related decline (Glisky, Rubin, & Davidson, 2001), in some instances to the same level as young adults (YA).

One individual difference factor that may attenuate age-related cognitive decline is cardiorespiratory fitness (CRF), an indicator of one's ability to perform moderate to vigorous physical activity. CRF has been linked to structural and functional changes in the human brain (Hayes, Hayes, Cadden, & Verfaellie, 2013), and as such, may modulate cognitive performance. Yet, evidence for a contribution of CRF to the preservation of cognition in aging varies across cognitive domains. For example, CRF has been positively associated with

executive function but not with episodic memory in a sample of obese OA (Bugg, Shah, Villareal, & Head, 2012). Others have observed larger effects for executive function relative to episodic memory (Barnes, Yaffe, Satariano, & Tager, 2003).

The lack of a consistent link between CRF and episodic memory is surprising in light of the animal literature, which has consistently shown an association between wheel running and hippocampally mediated, episodic-like, memory tasks (Cotman, Berchtold, & Christie, 2007). For instance, aged mice demonstrated enhanced performance on the Morris water maze as well as increased hippocampal neurogenesis in response to wheel running (van Praag, Shubert, Zhao, & Gage, 2005). In another study, voluntary wheel running in mice with the Apolipoprotein (ApoE) ε4 allele, a genetic risk factor for AD in humans, was associated with increased performance on the radial-arm water maze (Nichol, Deeny, Seif, Camaclang, & Cotman, 2009).

One reason for the discrepancy in animal and human studies may lie in the fact that animal studies have consistently used memory tasks known to be hippocampally mediated, whereas human studies have used a variety of neuropsychological tests assessing recall or recognition, tests that may differentially draw on the hippocampus and surrounding subhippocampal cortices (Aggleton & Brown, 1999) as well as on frontal regions (Johnson, Hashtroudi, & Lindsay, 1993). It is known that the hippocampus is particularly engaged in relational memory tasks that require that different informational elements be bound in memory [e.g., remembering a name that goes with a face; (Giovanello, Verfaellie, & Keane, 2003; Hayes, Buchler, Stokes, Kragel, & Cabeza, 2011)]. Moreover, aging has a greater detrimental impact on relational memory relative to memory for single items [e.g., name alone or face alone; (Old & Naveh-Benjamin, 2008)]. Thus, relational memory tests might be more sensitive to effects of CRF on age-related memory decline.

This study examined the relationship between CRF and cognition in OA using a direct measure of peak VO_2 obtained during a treadmill-based maximal exercise protocol. In addition to standardized neuropsychological tasks of executive function and episodic memory, we used a relational memory task in which participants were asked to learn face–name associations. This task is known to rely on hippocampal function and relates closely to the most common cognitive complaint among OA, forgetting proper names (Reese, Cherry, & Norris, 1999). We predicted that performance on tests of executive function as well as episodic memory, and in particular the relational face–name memory task, would be associated with CRF in OA. YA were also tested to examine (a) whether CRF can fully mitigate age-associated cognitive decline and (b) whether the predicted association between CRF and cognition is specific to OA.

Method

Participants

Thirty-four YA (age 18–31 years) and 33 OA (age 55–82 years) participated in the study. Five OA were excluded from data analysis (four due to incidental findings on the MRI and one due to failure to meet criteria for valid peak VO_2) as well as one YA (statistical outlier based on high peak VO_2 value). The final sample included in the analyses consisted of 33 YA (24 Caucasian, seven Asian, two African-American) and 28 OA (26 Caucasian, two African-American). Four OA reported a diagnosis of hypertension, one of whom also reported diabetes.

To ensure recruitment of participants with a wide range of CRF levels, participants were recruited from general participant pools (Boston University for YA and the Boston University Memory Disorders Research Center at VA Boston, Boston University Alzheimer's Disease Center, the Massachusetts Alzheimer's Disease Research Center, and the Alzheimer's Association Trial for OA) as well as through local track meets. Exclusion criteria were current alcohol or substance dependence, current DSM-IV Axis I disorders, history of serious mental illness (e.g., schizophrenia), serious health issue (e.g., heart attack), serious neurological condition (e.g., stroke), or education less than grade 12. Further, all participants were screened for contraindications to cardiopulmonary exercise testing and Magnetic Resonance Imaging (data not reported here) prior to study participation. Mental status was assessed using the Montreal Cognitive Assessment (MOCA; http://www.mocatest.org/), and participants with scores ≤23 were excluded. Participants were also screened for depression using a cut-off score of 16 on the Center for Epidemiologic Studies Depression Scale (CES-D) 20-item version. All participants gave written informed consent and received financial compensation. The VA Boston Healthcare System institutional review board approved all experimental procedures.

Participant characteristics are presented in Table 1. For each group, peak VO_2 values are presented both in absolute terms (ml/kg/min) and as percentile scores relative to age- and gender-specific normative values established by the American College of Sports Medicine (2010; see Table 1). The mean, min, and maximum percentile scores presented in Table 1 highlight the wide range of aerobic capacity within each age group, as well as the distinct levels of aerobic capacity within the OA sample. There were no differences in YA and OA on measures of mental status (MOCA), premorbid intellectual function (WTAR), or depression (CES-D). The difference in years of education between YA and OA was significant, $t(59) = 3.42$, $p = .001$. Given that the YA were Boston University undergraduates in the process of earning a bachelor's degree (education = 16 years), a premorbid estimate of intellectual function (WTAR), rather than years of education, is likely a more valid indicator of intellectual abilities of the two groups. Therefore, WTAR scores, rather than education, were entered into the regression models. YA, compared to OA, had a lower mean body mass index (BMI), $t(59) = 2.58$, $p < .05$.

A subset of participants, 30 YA and 23 OA, completed the face–name memory task, and these groups also differed

Table 1. Characteristics of Young and Older Adults, as well as Subgroups of Older Adults Based on Median Split of Peak VO_2 (Mean and Standard Deviation)

	YA	OA	LFOA	HFOA
Number of participants	33 (18 F)	28 (16 F)	14 (8 F)	14 (8 F)
Age (years)	21.0 (3.1)	64.1 (7.2)	64.9 (8.4)	63.3 (5.9)
Education (years)	14.5 (1.7)	16.3 (2.5)	15.6 (2.6)	17.1 (2.5)
WTAR	42.9 (4.3)	43.0 (5.6)	40.6 (5.5)	45.4 (4.7)
CES-D	6.2 (4.0)	5.6 (4.2)	5.8 (3.8)	5.4 (4.6)
MOCA	28.6 (1.5)	27.8 (1.9)	27.1 (2.3)	28.4 (0.9)
BMI	23.1 (2.9)	25.7 (4.8)	27.8 (5.8)	23.6 (2.3)
Peak VO_2 (ml/kg/min)	38.5 (11.6)	30.0 (8.5)	23.9 (6.4)	36.0 (5.4)
Peak VO_2 ACSM percentile score, min–max percentile score	40.9 (25.9) 10–90	45.5 (29.9) 10–90	20.0 (14.7) 10–50	71.1 (13.9) 50–90

Notes. ACSM = American College of Sports Medicine; BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression Scale; *F* = number of females; 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.

in years of education and BMI *t*'s (59) > 3.0, $p < .05$. No differences were observed in WTAR, CES-D, or MOCA scores.

Cardiopulmonary Exercise Testing

Graded maximal exercise testing in association with air–gas exchange was conducted using a 2-min Bruce protocol on a motor driven Woodway Barimill treadmill. Peak volume of oxygen consumption (VO_2, ml/kg/min) and respiratory exchange ratio were measured. Self-reported ratings of perceived exertion were collected at 1-min intervals using the 20-item Borg Scale. Peak VO_2 was considered valid if at least two of the following criteria were met: (a) respiratory exchange ratio ≥ 1.0, (b) maximum heart rate equivalent to 85% of their age-predicted maximum (220 – age), (c) ratings of perceived exertion ≥ 17, which corresponds to an exertion level of "very hard" (a rating of 20 represents "maximal exertion").

Neurocognitive Testing

All participants completed neurocognitive testing prior to completion of cardiopulmonary exercise testing. Premorbid intellectual abilities were assessed with the Wechsler Test of Adult Reading (WTAR).

Executive function

The following standardized tests of executive function were administered: Trail Making and Verbal Fluency from the Delis Kaplan Executive Function System (D-KEFS), Mental Arithmetic and Digit Span (backwards) from the Wechsler Adult Intelligence Scale Third Edition (WAIS-III), and the computerized version of the Wisconsin Card Sorting Test (WCST).

Episodic memory

A face–name memory task (Figure 1) for 180 face–name pairs was administered (5 lists, each comprised 36 trials). During encoding, participants were instructed to remember each face–name pair and were asked to rate on a four-point scale how well the name fit with the face. During retrieval for each list, they 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). Between each encoding and retrieval block, participants completed a 20-s filler task. Presentation duration for each encoding and retrieval trial was 3.5 s, with an intertrial interval varying between 0.5 and 6.5 s. The task was administered while participants underwent functional MRI (data not reported here). Overall accuracy for novel face–name trials was used as the dependent measure.

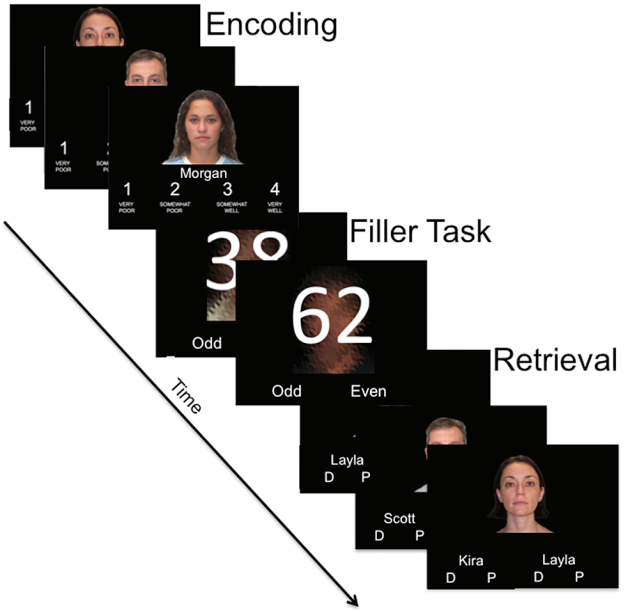

Figure 1. Example of experimental stimuli used during the face–name relational memory task.

Standardized tests of visual memory consisted of the Brief Visuospatial Memory Test Revised (BVMT-R) and the Faces subtests from the Wechsler Memory Scale Third

Edition (WMS-III). Verbal Memory was assessed using the California Verbal Learning Test Edition II (CVLT-II) and the Logical Memory subtest from the WMS-III.

Statistical Approach

All neurocognitive scores were expressed as z-scores based on the mean and standard deviation from the YA sample. For data reduction purposes, z-scores on standardized neuropsychological tests within a given cognitive domain were averaged to generate composite measures of executive function, visual memory, and verbal memory. Dependent variables included in the composite scores are listed in Table 2.

The alpha level for all tests was set at $p < .05$. To examine the nature of the relationship between cognition and CRF, separate four-step hierarchical regression models were implemented for the executive function composite score, face–name retrieval accuracy, visual memory composite score, and verbal memory composite score. In Step 1 of each model, WTAR-scores, CES-D scores, and gender were entered as predictors for the dependent variable of interest. In Step 2, age group was entered into the model to assess performance differences between YA and OA. In Step 3, peak VO_2 was entered into the model to examine the contribution of CRF to cognitive function. Finally, in Step 4, the age group × peak VO_2 interaction was entered into the model. Significant age group × peak VO_2 interactions were followed up with regression models to examine whether peak VO_2 predicts cognitive performance in YA or OA. Because Step 1 of the regression models was not significant for any of the dependent variables, all F's < 1.59, all p's > .20, more parsimonious models were subsequently re-run with three steps and results are reported below.

Finally, to directly assess the degree to which CRF attenuates age-related cognitive decline, OA were assigned peak VO_2 percentile scores based on age- and gender-specific normative values (American College of Sports Medicine, 2010), and median-split into low-fit OA and high-fit OA based on the ACSM percentile scores (see Table 1 for ACSM mean, minimum, and maximum percentile scores within each group). Relative to published normative data (Heyward & Gibson, 2014), the mean peak VO_2 value of the low-fit OA group fell within the poor range whereas the mean peak VO_2 value of the high-fit OA group fell within the excellent range, further highlighting the distinct levels of aerobic capacity within the OA sample. One-way analysis of variance (ANOVAs) were performed to compare cognitive performance among YA, high-fit OA, and low-fit OA, with significant F-values followed-up with least significant difference tests.

Results

The composite scores for executive function and visual memory were significantly lower in OA than in YA, t's (59) > 3.29, p's < .005, and a trend was observed for verbal memory, t (59) = 1.86, p = .068 (Table 2). Face–name memory retrieval was also significantly lower in OA relative to YA, t (31.7) = 4.62, $p < .001$. Raw scores on each test comprising the respective composite measures are listed for YA, OA, and OA median-split by CRF in Table 2.

Table 2. Neurocognitive Performance (z-Scores and Raw Test Scores; Mean and Standard Deviation) by Age Group and Subgroups of Older Adults Based on Median Split of Peak VO_2

	YA	OA	LFOA	HFOA
Executive function z-score	0.00 (0.62)	−0.66 (0.82)	−0.98 (0.88)	−0.23 (0.54)
DKEFS trails 4 (s)	54.4 (12.5)	78.2 (25.0)	87.0 (29.6)	69.3 (15.7)
WCST % preservative responses	9.7 (3.7)	10.2 (6.5)	9.0 (3.7)	11.4 (8.4)
Digit span backwards	5.6 (1.4)	5.3 (1.6)	4.9 (1.8)	5.7 (1.3)
Mental arithmetic	16.4 (2.2)	15.5 (3.6)	13.3 (3.6)	17.8 (1.9)
Phonological fluency (FAS)	45.5 (11.5)	47.3 (11.9)	42.4 (12.5)	52.1 (9.4)
Face–name memory z-score	0.00 (1.02)	−2.02 (1.88)	−2.58 (2.22)	−1.40 (1.24)
Accuracy (%)	81.2 (7.9)	65.7 (14.5)	61.3 (17.2)	70.5 (9.6)
Visual memory z-score	0.00 (0.60)	−1.91 (1.40)	−2.63 (1.21)	−1.19 (1.20)
BVMT total recall	30.6 (3.5)	21.1 (6.0)	18.4 (6.2)	23.8 (4.7)
BVMT delayed recall	11.2 (0.7)	8.8 (2.4)	7.6 (2.3)	10.0 (1.8)
Faces I (WMS-III)	40.3 (3.2)	37.6 (4.4)	36.4 (4.1)	38.7 (4.6)
Faces II (WMS-III)	40.5 (3.1)	37.7 (4.9)	37.2 (4.4)	38.2 (5.5)
Verbal memory z-score	0.00 (0.82)	−0.44 (1.0)	−0.71 (1.08)	−0.16 (0.90)
CVLT total recall (Trials 1–5)	56.0 (7.8)	53.1 (7.6)	51.4 (8.3)	54.8 (6.6)
CVLT long delay free recall	12.9 (2.7)	11.8 (3.0)	11.0 (3.6)	12.7 (2.1)
Logical memory I recall	51.6 (6.6)	48.7 (9.6)	46.5 (9.2)	50.9 (9.8)
Logical memory II recall	34.2 (5.3)	31.5 (7.2)	30.1 (7.6)	32.8 (6.7)

Notes. BVMT = Brief Visuospatial Memory Test; CVLT = California Verbal Learning Test; DKEFS = Delis-Kaplan Executive Function System; HFOA = high-fit older adults; LFOA = low-fit older adults; OA = older adults; WMS = Wechsler Memory Scale; YA = younger adults.

Examination of Peak VO_2 and Cognition by Age Group

Executive function

Age group (Step 1) accounted for 15.5% of the variance (Table 3). Adding peak VO_2 (Step 2) to the model accounted for an additional 7.8% of the variance. Including the age group × peak VO_2 interaction (Step 3) to the model did not account for additional significant variance. Nonetheless, we implemented follow-up regressions, given that aerobic fitness was shown to have the largest impact on executive function in OA in a landmark meta-analysis (Colcombe & Kramer, 2003). Peak VO_2 did not predict the executive function score in YA, R^2 = .027, F (1, 32) < 1, but did in OA, R^2 = .174, model F (1, 27) = 5.48, p < .05 (Figure 2A).

Episodic memory

For face–name memory (Table 3), age group (Step 1) accounted for 32.7% of the variance. Adding peak VO_2 (Step 2) to the model accounted for an additional 5.2% of the variance, and adding the age group x peak VO_2 interaction (Step 3) term to the model accounted for an additional 4.7% of the variance. Follow-up analyses indicated that peak VO_2 did not predict face–name memory in YA, F(1, 29) < 1, but did predict face–name memory in OA, R^2 = .205, F(1, 22) = 5.40, p < .05 (Figure 2B).

For the composite measure of visual memory (Table 3), age group (Step 1) accounted for 46.5% of the variance. Adding peak VO_2 (Step 2) accounted for an additional 7.1% of the variance. Finally, inclusion of the age group × peak VO_2 interaction term (Step 3) accounted for an additional 7.6% of the variance. Follow-up analyses revealed that peak VO_2 did not predict visual memory performance in YA, F < 1. In contrast, peak VO_2 predicted visual memory performance in the OA, R^2 = .335, model F(1, 27) = 13.09, p < .005 (Figure 2C).

There was a trend for age group to account for significant variance in the composite measure of verbal memory, R^2 = .055, F = 3.45, p = .07. Inclusion of peak VO_2 and the interaction term did not account for additional variance, F changes < 1.

Examination of Cognitive Performance of High- and Low-Fit OA Relative to YA

OA were divided into high and low-fit groups based on a median split of peak VO_2 percentile values (based on ACSM

Table 3. Results of Hierarchical Regression Examining Variables That Impact Cognitive Performance

		B	*SE*	Standardized beta	*t* value	R^2	ΔR^2	$F\,\Delta$	Model *F*
Executive function									
Model 1	(Constant)	1.58E–09	0.124		0.00	0.155	0.155	10.84**	10.84**
	Age group	−0.604	0.184	−0.394	−3.29**				
Model 2	(Constant)	−1.053	0.449		−2.34*	0.233	0.078	5.91*	8.82**
	Age group	−0.37	0.201	−0.241	−1.84				
	peak VO_2	0.027	0.011	0.319	2.43*				
Model 3	(Constant)	−0.518	0.633		−0.82	0.252	0.019	1.43	6.40**
	Age group	−1.29	0.797	−0.841	−1.62				
	peak VO_2	0.013	0.016	0.157	0.83				
	peak VO_2 × age	0.027	0.022	0.558	1.19				
Face–name memory									
Model 1	(Constant)	−0.01	0.265		−0.04	0.327	0.327	24.79**	24.79**
	Age group	−2.005	0.403	−0.572	−4.98**				
Model 2	(Constant)	−2.076	1.037		−2.00*	0.380	0.052	4.23*	15.30**
	Age group	−1.594	0.439	−0.455	−3.63**				
	peak VO_2	0.054	0.026	0.257	2.06*				
Model 3	(Constant)	−0.012	1.441		−0.01	0.427	0.047	4.01*	12.15**
	Age group	−5.141	1.821	−1.466	−2.82*				
	peak VO_2	6.18E–05	0.037	0	0.00				
	peak VO_2 × age	0.102	0.051	0.948	2.00*				
Visual memory									
Model 1	(Constant)	−7.58E–10	0.181		0.00	0.465	0.465	51.30**	51.30**
	Age group	−1.912	0.267	−0.682	−7.16**				
Model 2	(Constant)	−1.84	0.639		−2.88*	0.537	0.071	8.94**	33.57**
	Age group	−1.502	0.286	−0.536	−5.25**				
	peak VO_2	0.048	0.016	0.305	2.99**				
Model 3	(Constant)	0.125	0.834		0.15	0.612	0.076	11.10**	29.98**
	Age group	−4.884	1.049	−1.742	−4.66**				
	peak VO_2	−0.003	0.021	−0.021	−0.15				
	peak VO_2 × age	0.098	0.029	1.122	3.33**				

Note. *p < .05; **p < .01.

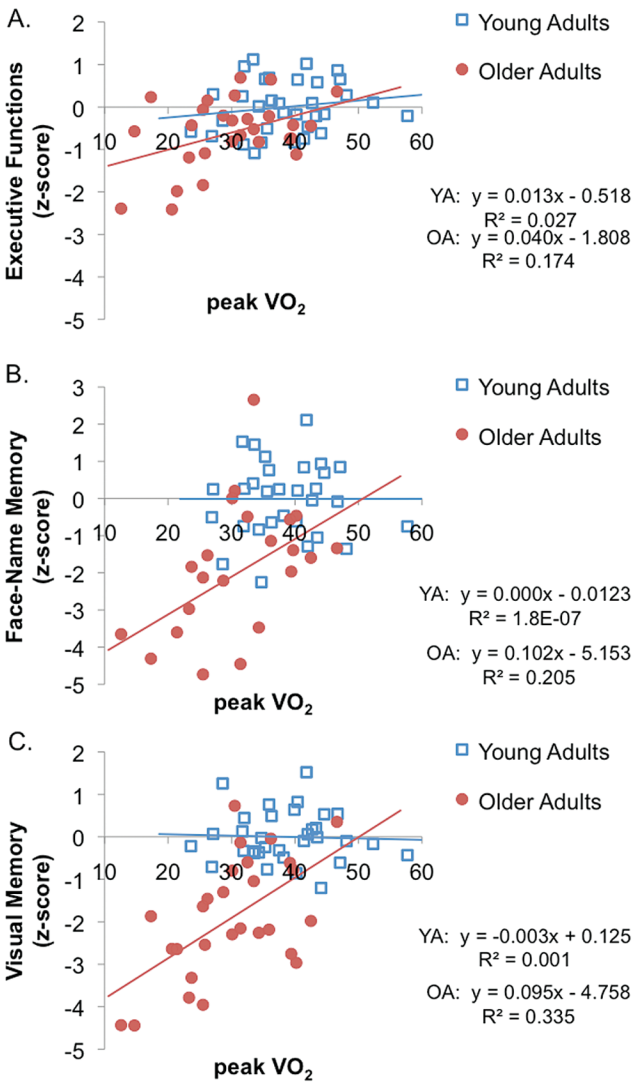

Figure 2. Scatter plot, best-fit line, regression equation and R^2 value (peak VO_2 predicting cognitive score) for YA and OA showing the relationship between peak VO_2 (ml/kg/min) and cognitive performance. (A) The executive function composite score. (B) Retrieval performance on the face–name relational memory task. (C) The visual memory composite score. OA = older adults; YA = younger adults.

norms) and one way ANOVAs were implemented to compare the cognitive performance of high-fit OA, low-fit OA, and YA. Importantly, there was no difference in peak VO_2 and BMI between YA and high-fit OA (p's > .25; Table 1). Verbal memory was not evaluated due to the lack of association with peak VO_2 in our previous analyses.

The composite measure of executive function differed across groups, $F(2, 60) = 10.56$, $p < .001$. Follow-up tests revealed that high-fit OA performed as well as YA, and both groups had higher scores than low-fit OA, p's < .005 (Figure 3). Face–name memory also differed as a function of group, $F(2, 52) = 15.11$, $p < .001$. Follow-up tests showed that YA performed better than high-fit OA, $p < .05$, who in turn performed better than low-fit OA, $p = .052$. Visual memory performance followed the same pattern,

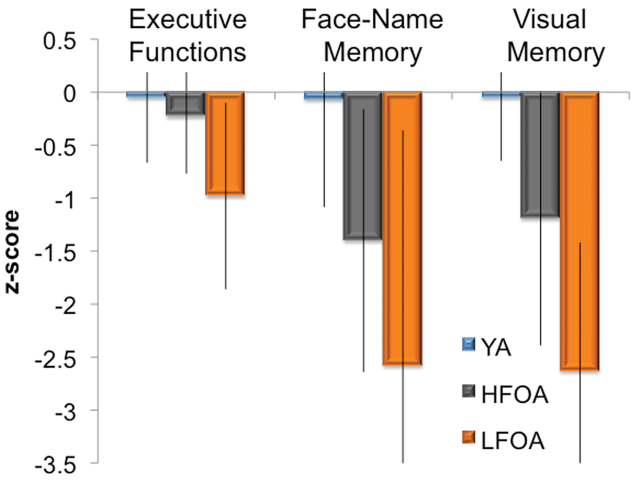

Figure 3. Z-scores of young adults (YA), high-fit older adults (HFOA), and low-fit older adults (LFOA) on executive function tasks, face–name memory task, and visual memory tasks. Mean z-scores of YA are 0.00 but are graphed at –0.05 in order to visualize the bars. Error bars represent *SD*.

$F(2, 60) = 41.09$, $p < .001$: YA performed significantly better than high-fit OA, who in turn performed better than low-fit OA (Figure 3), p's < .001. These findings were replicated when the four OA with hypertension (two of whom were classified as high fit and two as low fit) were excluded from the analyses, with the exception of the face–name memory task, which did not reach significance likely due to the reduced sample size.

Discussion

This study yielded three main findings. First, CRF in OA was positively associated with performance on executive function tasks, an experimental face–name memory task, and standardized tests of visual memory. Second, while peak VO_2 accounted for a significant amount of performance-related variance in OA, no relationship between CRF and cognitive performance was observed in YA. Finally, a median split of OA based on peak VO_2 revealed that high-fit OA performed as well as YA on tests of executive function, suggesting that CRF can eliminate age-related differences in executive function. The same was not true for episodic memory, as YA scored higher than high-fit OA on the face–name memory task and standard neuropsychological measures of visual memory. Nevertheless, high-fit OA performed significantly better than low-fit OA on the face–name memory task and visual memory. These findings are discussed below.

CRF Positively Linked to Cognition in OA But Not YA

Using a direct assessment of peak VO_2, we found that CRF was associated with a composite measure of executive function in OA. These results extend and strengthen the extant

literature, which has often linked CRF and executive function using indirect fitness assessments (Eggermont, Milberg, Lipsitz, Scherder, & Leveille, 2009) or a single test of executive function (Hillman et al., 2006). The use of a composite measure generated from multiple indicators of executive function provides evidence that the relationship between CRF and executive function is not limited to particular tasks, but rather reflects an association with core processes shared across executive function tasks (see Table 2 where high-fit OA outperform low-fit OA on a variety of executive function tasks). The positive association between CRF and executive function is likely underpinned by the positive impact of CRF on frontoparietal regions that mediate task performance, as multiple imaging studies have linked CRF to positive functional and structural changes in frontoparietal regions in OA (Hayes et al., 2013).

More importantly, our findings demonstrate that the effect of CRF is not limited to executive function, but also extends to episodic memory (Wendell et al., 2014). Consistent with our prediction, we observed an effect of CRF on a hippocampally mediated face–name memory task in OA. The current results are consistent with animal findings showing a relationship between physical activity and hippocampally mediated memory tasks. Further, they shed new light on human studies that have demonstrated an association between physical activity and medial temporal lobe integrity (but not episodic memory) by demonstrating the importance of selecting memory tasks that are optimally sensitive to hippocampal function to identify cognitive correlates of CRF.

Our findings further indicate that an association can also be obtained with standard neuropsychological tests of episodic memory. The significant association between CRF and episodic memory observed in the current study highlights the importance of using an optimal measure of CRF. This is a critical difference between the current study and other studies that have used questionnaires or estimates of peak VO_2, which are less precise, and failed to observe a significant relationship with episodic memory (Newson & Kemps, 2006, 2008).

In YA, CRF was not associated with performance in any of the cognitive domains examined. There is limited evidence regarding the relationship between fitness and cognition in YA, and the few published studies vary widely in sample size and cognitive measures (Aberg et al., 2009; Baym et al., 2014). Relative to the aging literature, the dearth of evidence supporting a relationship between CRF and cognition in YA may be attributable to the fact that cognitive abilities are typically at their peak in young adulthood, and therefore, the influence of CRF on cognition may be more limited during this time period.

Our finding that CRF was associated with cognitive performance in OA, but not YA, is consistent with the age-dependence hypothesis (Hotting & Roder, 2013). According to the age-dependence hypothesis, CRF impacts cognitive and brain function during childhood, exerts minimal influence during young adulthood when indicators of neural structure and function are typically at their lifetime peak, but may again positively impact brain structure and function in OA as cognitive decline begins in later adulthood. Supporting this hypothesis are findings of a positive relationship between peak VO_2 and visual memory in pre-adolescent children (Chaddock et al., 2010), as well as data from the current study linking peak VO_2 and face–name memory in OA, but not YA. The lack of a relationship between CRF and verbal memory observed in the current study is also consistent with the age-dependence hypothesis, in that one would not predict a relationship with CRF until significant age-related cognitive decline occurred. Additional studies examining CRF–cognition relationships across the life span are needed to further evaluate the age-dependence hypothesis.

Attenuation of Age-Related Cognitive Decline by CRF

The current results support the notion that CRF contributes to successful cognitive aging (Depp, Vahia, & Jeste, 2010). When OA were median split based on peak VO_2 values, age-related performance differences on executive function tasks were eliminated in high-fit OA. On the face–name memory and the visual memory tasks, high-fit OA did not reach the same level of performance as YA, yet they performed better than low-fit OA, demonstrating again that CRF positively impacted episodic memory performance in OA.

CRF likely impacts cognitive function via multiple neurobiological mechanisms. Aerobic exercise and CRF have been linked to enhanced structural volume of the hippocampus and prefrontal cortex, increased gray matter density in frontal and parietal regions, enhanced white matter microstructure, reductions in white matter hyperintensities, enhanced functional connectivity within neural networks that underpin episodic memory and executive function, increased cerebral perfusion, and enhanced cerebral blood volume and hippocampal neurogenesis (Hayes et al., 2013). Animal studies have linked wheel-running to enhanced neurogenesis, synaptogenesis, and angiogenesis (formation of new neurons, synapses, and blood vessels, respectively), as well as growth factors that support these processes (e.g., brain-derived neurotrophic factor), often attenuating age-related reductions (Cotman et al., 2007).

Thus, there is a complex neurobiological cascade that underpins associations between CRF and cognition. The multilevel impact of CRF on the brain, ranging from the molecular level to the systems level, fosters substantial enthusiasm that enhanced CRF may attenuate age-related cognitive decline. Indeed, one of the advantages of exercise training to enhance CRF is that cognitive gains are unlikely to be task-specific, as neural changes that occur via enhanced CRF should impact multiple cognitive tasks mediated by the altered brain regions. Whereas a primary challenge for cognitive training

studies is to demonstrate that enhanced performance subsequent to training generalizes to other stimuli and tasks, exercise interventions, by the very nature of the fitness-induced neurobiological changes impacting cognition, are unlikely to suffer from challenges related to stimulus or task-specificity.

Our findings that CRF may mitigate age-related cognitive decline is appealing for a variety of reasons, including that aerobic activities to enhance CRF (walking, jogging, etc.) are inexpensive, accessible, and could potentially improve quality of life by delaying cognitive decline and prolonging independent function. Although the current study focused on CRF, recent reports have indicated that resistance training may positively impact cognitive performance and brain function, and suggest that different types of exercise training may impact different cognitive functions and distinct brain regions (Hotting & Roder, 2013). Additional research is needed to clarify the impact of specific exercise programs (e.g., strength, aerobic, or combined training) or dose of exercise (frequency, intensity, and duration) on a range of cognitive functions.

Limitations

The current study was cross-sectional, and other cohort factors such as genetics, diet, or blood pressure could have influenced the results. The current study reports associations between CRF and cognition, and does not necessarily represent a causal relationship between CRF and cognition. In regards to our hypothesis about relational memory being particularly sensitive to CRF, it would have been interesting to include an experimental item recognition task (e.g., names alone or faces alone) to more directly compare relational versus item memory to further strengthen our conclusions. In this study, cardiopulmonary exercise testing occurred prior to neurocognitive testing, as the focus of this study was on the relationship between CRF and cognition. Additional research is needed to evaluate whether acute effects of physical activity impact age-related differences in cognition.

Funding

This work was supported by the Department of Veterans Affairs, Rehabilitation Research & Development Service (Career Development Award #e7822w awarded to S.M.H.) and Clinical Science Research & Development Service (M.V.). Assistance with participant recruitment was provided by the Massachusetts Alzheimer's Disease Research Center (P50-AG005134) and Boston University Alzheimer's Disease Center (P30-AG13846).

Acknowledgments

The authors wish to thank Kelly Allsup, Kenneth Manning, Margaret Cadden, Huiting Liu, Kristina Peterson, and Rebecca Lysiak for assistance with data collection. The contents of this article do not represent the views of the U.S. Department of Veterans Affairs or the U.S. Government.

References

Aberg, M. A. I., Pedersen, N. L., Torén, K., Svartengren, M., Bäckstrand, B., & Johnsson, T. (2009). Cardiovascular fitness is associated with cognition in young adulthood. *Proceedings of the National Academy of Sciences of the United States of America*, **106**, 20906–20911. doi:10.1073/pnas.0905307106

Aggleton, J. P., & Brown, M. W. (1999). Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *The Behavioral and Brain Sciences*, **22**, 425–89. doi:10.1017/S0140525X99002034

American College of Sports Medicine. (2010). *ACSM's guidelines for exercise testing and prescription*. In W. R. Thompson, N. F. Gordon, & L. S. Pescatello (Eds.), (8th ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Barnes, D. E., Yaffe, K., Satariano, W. A., & Tager, I. B. (2003). A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. *Journal of the American Geriatrics Society*, **51**, 459–465. doi:10.1046/j.1532-5415.2003.51153.x

Baym, C. L., Khan, N. A., Pence, A., Raine, L. B., Hillman, C. H., & Cohen, N. J. (2014). Aerobic fitness predicts relational memory but not item memory performance in healthy young adults. *Journal of Cognitive Neuroscience*, 26, 2645–2652. doi:10.1162/jocn_a_00667

Bugg, J. M., Shah, K., Villareal, D. T., & Head, D. (2012). Cognitive and neural correlates of aerobic fitness in obese older adults. *Experimental Aging Research*, **38**, 131–145. doi:10.1080/0361073X.2012.659995

Chaddock, L., Erickson, K. I., Prakash, R. S., Kim, J. S., Voss, M. W., & Vanpatter, M. (2010). A neuroimaging investigation of the association between aerobic fitness, hippocampal volume, and memory performance in preadolescent children. *Brain Research* **1358**, 172–183. doi:10.1016/j.brainres.2010.08.049

Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychological Science*, **14**, 125–130. doi:10.1111/1467–9280.t01-1-01430

Cotman, C. W., Berchtold, N. C., & Christie, L. A. (2007). Exercise builds brain health: Key roles of growth factor cascades and inflammation. *Trends in Neurosciences*, **30**, 464–472. doi:10.1016/j.tins.2007.06.011

Depp, C., Vahia, I. V., & Jeste, D. (2010). Successful aging: Focus on cognitive and emotional health. *Annual Review of Clinical Psychology*, **6**, 527–550. doi:10.1146/annurev.clinpsy.121208.131449

Eggermont, L. H., Milberg, W. P., Lipsitz, L. A., Scherder, E. J., & Leveille, S. G. (2009). Physical activity and executive function in aging: The MOBILIZE Boston Study. *Journal of the American Geriatrics Society*, **57**, 1750–1756. doi:10.1111/j.1532-5415.2009.02441.x

Giovanello, K. S., Verfaellie, M., & Keane, M. M. (2003). Disproportionate deficit in associative recognition relative to item recognition in global amnesia. *Cognitive, Affective & Behavioral Neuroscience*, **3**, 186–194. doi: 10.3758/CABN.3.3.186

Glisky, E. L., Rubin, S. R., & Davidson, P. S.R. (2001). Source memory in older adults: An encoding or retrieval problem? *Journal*

of Experimental Psychology. Learning, Memory, and Cognition, **27**, 1131–1146. doi:10.1037//0278-7393.27.5.1131

Goh, J. O., An, Y., & Resnick, S. M. (2012). Differential trajectories of age-related changes in components of executive and memory processes. *Psychology and Aging*, **27**, 707–719. doi:10.1037/a0026715

Hayes, S. M., Buchler, N., Stokes, J., Kragel, J., & Cabeza, R. (2011). Neural correlates of confidence during item recognition and source memory retrieval: Evidence for both dual-process and strength memory theories. *Journal of Cognitive Neuroscience*, **23**, 3959–3971. doi:10.1162/jocn_a_00086

Hayes, S. M., Hayes, J. P., Cadden, M., & Verfaellie, M. (2013). A review of cardiorespiratory fitness-related neuroplasticity in the aging brain. *Frontiers in Aging Neuroscience*, **5**, 31. doi:10.3389/fnagi.2013.00031

Heyward, V. H., & Gibson, A. L. (2014). *Advanced fitness assessment and exercise prescription* (7th ed.). Champaign, IL: Human Kinetics.

Hillman, C. H., Motl, R. W., Pontifex, M. B., Posthuma, D., Stubbe, J. H., & Boomsma, D. I. (2006). Physical activity and cognitive function in a cross-section of younger and older community-dwelling individuals. *Health Psychology* **25**, 678–687. doi:10.1037/0278-6133.25.6.678

Hotting, K., & Roder, B. (2013). Beneficial effects of physical exercise on neuroplasticity and cognition. *Neuroscience & Biobehavioral Reviews*, **37**, 2243–2257. doi:10.1016/j.neubiorev.2013.04.005

Johnson, M. K., Hashtroudi, S., & Lindsay, D. S. (1993). Source monitoring. *Psychological Bulletin*, **114**, 3–28. doi:10.1037/0033-2909.114.1.3

Naveh-Benjamin, M. (2000). Adult age differences in memory performance: tests of an associative deficit hypothesis. *Journal of Experimental Psychology: Learning, Memory and Cognition*, **26**, 1170–1187. doi:10.1037/0278-7393.26.5.1170

Newson, R. S., & Kemps, E. B. (2006). Cardiorespiratory fitness as a predictor of successful cognitive ageing. *Journal of Clinical and Experimental Neuropsychology*, **28**, 949–967. doi:10.1080/13803390591004356

Newson, R. S., & Kemps, E. B. (2008). Relationship between fitness and cognitive performance in younger and older adults. *Psychology & Health*, **23**, 369–386. doi:10.1080/08870440701421545

Nichol, K., Deeny, S. P., Seif, J., Camaclang, K., & Cotman, C. W. (2009). Exercise improves cognition and hippocampal plasticity in APOE epsilon4 mice. *Alzheimer's & Dementia*, **5**, 287–294. doi:10.1016/j.jalz.2009.02.006

Old, S. R., & Naveh-Benjamin, M. (2008). Memory for people and their actions: Further evidence for an age-related associative deficit. *Psychology and Aging*, **23**, 467–472. doi:10.1037/0882-7974.23.1.104

Reese, C. M., Cherry, K. E., & Norris, L. E. (1999). Practical memory concerns of older adults. *Journal of Clinical Geropsychology*, **5**, 231–244. doi:10.1023/A:1022984622951

van Praag, H., Shubert, T., Zhao, C. M., & Gage, F. H. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. *Journal of Neuroscience*, **25**, 8680–8685. doi:10.1523/JNEUROSCI.1731-05.2005

Wendell, C. R., Gunstad, J., Waldstein, S. R., Wright, J. G., Ferrucci, L., & Zonderman, A. B. (2014). Cardiorespiratory fitness and accelerated cognitive decline with aging. *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences*, **69**, 455–462. doi:10.1093/gerona/glt144