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Cardiorespiratory fitness attenuates the influence of amyloid on cognition

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Abstract

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Objective—To examine cross-sectionally whether higher cardiorespiratory fitness (CRF) might favorably modify amyloid-β (Aβ)-related decrements in cognition in a cohort of late-middle-aged adults at risk for Alzheimer's disease (AD).

Methods—Sixty-nine enrollees in the Wisconsin Registry for Alzheimer's Prevention participated in this study. They completed a comprehensive neuropsychological exam, underwent ^{11}C Pittsburgh Compound B (PiB)-PET imaging, and performed a graded treadmill exercise test to volitional exhaustion. Peak oxygen consumption (VO_2peak) during the exercise test was used as the index of CRF. Forty-five participants also underwent lumbar puncture for collection of cerebrospinal fluid (CSF) samples, from which Aβ42 was immunoassayed. Covariate-adjusted regression analyses were used to test whether the association between Aβ and cognition was modified by CRF.

Results—There were significant VO_2peak*PiB-PET interactions for Immediate Memory (p= .041) and Verbal Learning & Memory (p= .025). There were also significant VO_2peak*CSF Aβ42 interactions for Immediate Memory (p<.001) and Verbal Learning & Memory (p <.001). Specifically, in the context of high Aβ burden—i.e., increased PiB-PET binding or reduced CSF Aβ42—individuals with higher CRF exhibited significantly better cognition compared with individuals with lower CRF.

Conclusion—In a late-middle-aged, at-risk cohort, higher CRF is associated with a diminution of Aβ-related effects on cognition. These findings suggest that exercise might play an important role in the prevention of AD.

Keywords

Alzheimer's disease; Physical fitness; Amyloid; Cerebrospinal fluid; Cognition; Neuroimaging

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia and is neuropathologically marked by extracellular amyloid-β (Aβ) deposits (Hyman et al., 2012; Thal, Rub, Orantes, & Braak, 2002). Furthermore, alterations in *in vivo* measurements of Aβ, such as cerebrospinal fluid (CSF) Aβ42, in cognitively normal (CN) individuals indicates a preclinical stage of AD (Jack et al., 2013; Jack et al., 2010; Sperling et al., 2011). This preclinical stage portends increased risk for prospective cognitive decline and eventual development of AD dementia in initially CN adults (Fagan et al., 2007; Villemagne et al., 2011). Several studies have shown that low CSF Aβ42 levels in CN individuals predict incident cognitive impairment (Gustafson, Skoog, Rosengren, Zetterberg, & Blennow, 2007; Roe et al., 2013; Skoog et al., 2003). Similarly, Resnick and colleagues (2010) found that Aβ deposition, as assessed with ^{11}C Pittsburgh Compound B (PiB)-positron emission tomography (PET), was associated with steeper trajectories of cognitive decline in the years preceding and concurrent to PiB-PET scans in CN older adults. Specifically, these findings were observed in cognitive domains of immediate free recall and executive function. Furthermore, in a study of CN individuals, Morris and colleagues (2009) found an association between the level of Aβ deposition, measured by PiB-PET, and progression to AD dementia.

A growing body of literature suggests that a physically active lifestyle, which conduces to greater cardiorespiratory fitness (CRF), may ameliorate AD-related pathology (Boots et al., 2014; Erickson et al., 2011) and boost cognitive function (Barnes, Yaffe, Satariano, & Tager, 2003; Boots et al., 2014; Lautenschlager et al., 2008; Pizzie et al., 2014; Zhu et al., 2014). Several of these studies (Brown et al., 2013; Head et al., 2012; Liang et al., 2010) have found that individuals who were physically active had significantly lower Aβ deposition compared to inactive individuals. More recently, our group (Okonkwo et al., 2014) assessed whether a physically active lifestyle might favorably alter the adverse influence of age on key biomarkers of AD. By utilizing a comprehensive neuropsychological evaluation and an array of neuroimaging techniques, we found that those who were physically active exhibited an attenuation in age-related changes in Aβ burden, glucose metabolism, hippocampal volume, and Immediate Memory and Visuospatial Ability cognitive test scores (Okonkwo et al., 2014).

Although physical activity has been shown to be associated with both Aβ accumulation and cognition independently, it is yet to be determined whether the deleterious effects of Aβ burden on cognition are modified by CRF. Accordingly, in this study, we investigated whether CRF attenuates Aβ-related alterations in cognition in a cohort of CN late-middle-aged adults.

MATERIALS AND METHODS

Participants

Sixty-nine CN late-middle-aged adults from the Wisconsin Registry for Alzheimer's Prevention (WRAP) cohort participated in this study. WRAP is a longitudinal registry composed of more than 1500 late-middle-aged adults who were between the ages of 40 and 65 at study entry (Sager, Hermann, & La Rue, 2005). The 69 subjects included in the analyses underwent PiB-PET imaging, performed a physician-supervised graded exercise test (GXT), and completed a comprehensive neuropsychological evaluation. A subset (n = 45) also underwent lumbar puncture for CSF collection. The University of Wisconsin Institutional Review board approved all study procedures and each subject provided signed informed consent before participation.

Graded exercise testing

GXT was performed using a modified Balke protocol (Balke & Ware, 1959). Comfortable brisk walking speeds were determined prior to testing as a safety precaution and to ensure a valid test. For participants who were capable of walking at 3.5 miles per hour (mph) comfortably, this speed was used throughout the test. For participants who found this walking speed uncomfortable, a slower speed was chosen. Of the 69 participants included in our analyses, 47 walked at a speed slower than 3.5 mph (29 of these 47 walked at a speed between 3.0 mph and 3.5 mph whereas 18 walked at a speed less than 3.0 mph). The grade of the treadmill was increased by 2.5% every two minutes until the participant reached volitional exhaustion or the examiner stopped the test due to safety concerns. Continuous measurements of oxygen uptake (VO_2), carbon dioxide production, minute ventilation, heart rate, and work rate were obtained using a metabolic cart and two-way non-rebreathing valve

(TrueOne® 2400 metabolic cart, Parvomedics, Sandy, UT). The system was calibrated prior to each test using standard gases with known concentrations and with a calibrated three-liter syringe. Peak effort was determined based on the American College of Sports Medicine (ACSM) criteria (ACSM, 2014) which require meeting at least two of the following: (1) respiratory exchange ratio ≥ 1.1, (2) change in VO_2 < 200 ml with an increase in work, (3) rating of perceived exertion of 17 or greater, and (4) achieving at least 90% of age predicted maximal heart rate. All 69 individuals included in this report met peak effort criteria. Peak oxygen consumption (VO_2peak, mL/kg/min) during exercise was used as the index of CRF.

PiB-PET protocol

Details on the acquisition and post-processing of the PiB-PET examinations have been previously described (Johnson et al., 2014; Okonkwo et al., 2014). Briefly, 3-dimensional PiB-PET data were acquired on a Siemens EXACT HR+ scanner (Siemens AG, Erlangen, Germany). Imaging consisted of a 6-minute transmission scan and a 70-minute dynamic scan upon bolus injection. Post-processing was based on an in-house automated pipeline (Floberg et al., 2012). We derived distribution volume ratio (DVR) maps from the PiB images using the Logan method, with a cerebellar gray matter reference (Price et al., 2005).

An anatomical atlas (Tzourio-Mazoyer et al., 2002) was used to extract quantitative DVR data from eight bilateral regions of interest (ROIs) that are sensitive to Aβ accumulation (Rosario et al., 2011). These ROIs were the precuneus, posterior cingulate, orbitofrontal cortex, anterior cingulate, angular gyrus, supramarginal gyrus, middle temporal gyrus, and superior temporal gyrus. The DVR data from the ROIs were combined to form a composite measure of global Aβ load. The time interval between the PET scan and the GXT was 3.10 ± .47 years. GXT was subsequent to the PiB-PET scan for all 69 participants.

CSF assessment

In a subset of individuals (n = 45), lumbar puncture for collection of CSF samples was performed the morning after a 12-hour fast, with a Sprotte 24- or 25-gauge spinal needle at L3/4 or L4/5 using gentle extraction into polypropylene syringes. Each sample consisted of 22 mL of CSF, which was then combined, carefully mixed, and centrifuged at 2000g for 10 minutes. Supernatants were frozen in 0.5 mL aliquots in polypropylene tubes and stored at −80°C. The samples were immunoassayed for Aβ42 using INNOTEST enzyme-linked immunosorbent assays (Fujirebio, Gent, Belgium) by board-certified laboratory technicians who were blind to clinical data and used protocols accredited by the Swedish Board for Accreditation and Conformity Assessment as previously described (Palmqvist et al., 2014). Participants completed the lumbar puncture procedure at the same study visit as the PiB-PET scan.

Neuropsychological assessment

The participants underwent an extensive battery of neuropsychological tests (Sager et al., 2005), which spanned conventional cognitive domains of memory, attention, executive function, language, and visuospatial ability. A previous factor analytic study (Koscik et al., 2014) of these tests within the larger WRAP cohort found that they map onto six cognitive factors. These cognitive factors and their constituent psychometric tests included Immediate

Memory: Rey Auditory Verbal Learning Test (RAVLT) learning trials 1 and 2 (Schmidt, 1996); Verbal Learning & Memory: RAVLT learning trials 3- 5 and Delayed Recall (Schmidt, 1996); Working Memory: Digit Span and Letter-Number Sequencing subtests of the Wechsler Adult Intelligence Scale, 3rd edition (Wechsler, 1997); Speed & Flexibility: Stroop Color-Word Test, Interference Trial (Trenerry, Crosson, DeBoe, & Leber, 1989) and Trail-Making Test A and B (Reitan, 1958); Visuospatial Ability: Block Design and Matrix Reasoning subtests from the Wechsler Abbreviated Scale of Intelligence (WASI)(Wechsler, 1999) and Judgment of Line Orientation Test (Benton, 1994); and Verbal Ability: Reading subtest of Wide-Range Achievement Test, 3rd edition (Wilkinson, 1993), Vocabulary and Similarities subtest from the WASI (Wechsler, 1999), and the Boston Naming Test (Kaplan, 1983). The Mini Mental State Examination (MMSE) was also administered as a measure of global cognitive function.

For this study, we focused on the cognitive factors related to episodic memory and executive function, due to the known association of these cognitive domains with physical activity and aerobic fitness (Boots et al., 2014; Zhu et al., 2014). The selected factors were Immediate Memory, Verbal Learning & Memory, Working Memory, and Speed & Flexibility. Test scores on the psychometric measures that comprise each cognitive factor were first standardized (N (0, 1)) using means and standard deviations from the entire WRAP sample and then averaged to yield the factor score. The time interval between cognitive testing and the GXT was 1.08 ± .74 years, with GXT being subsequent to the neuropsychological assessment for 62/69 participants. The time interval between cognitive testing and the PET scan/CSF sampling was 2.04 ± .81 years, with neuropsychological assessment being subsequent to the PET scan for 67/69 participants.

Statistical analyses

To investigate whether increased CRF modifies the influence of Aβ burden on cognition, we fitted linear regression models—one for each cognitive domain—that included terms for age, sex, education, body mass index (BMI), beta-blocker usage, time interval between PET scan and GXT, time interval between cognitive testing and GXT, VO_2peak, Aβ burden, and a VO_2peak*Aβ burden interaction. This set of analyses was repeated using the two different Aβ burden variables: PiB-PET DVR measure and CSF Aβ42 level. The VO_2peak*Aβ burden interaction term was the effect of primary interest in all models. Where significant, it would indicate a differential effect of Aβ burden on cognitive performance as a function of CRF. For all analyses conducted, evaluations of assumptions for ordinary least squares were carried out via graphical analyses as described by Tabachnick and Fidell (2007). All analyses were conducted using IBM SPSS, version 21.0. Only findings with $p \leq .05$ (two-tailed) were considered to be significant.

RESULTS

Background characteristics

Table 1 details background characteristics of study participants. The average age at the time of the GXT was 63.54 ± 5.93 years and 68.1% were women. The average years of education

was 16.46 ± 2.12, 47.8% were apolipoprotein E (*APOE*) ε4 allele carriers, and 72.5% had a parental family history of AD. The average VO_2peak was 25.95 ± 5.50 mL/kg/min.

CRF and Aβ-related alterations in cognition

There was a significant VO_2peak*PiB-PET DVR interaction for Immediate Memory (p= .041) and for Verbal Learning & Memory (p= .025) (**Table 2**). To display this graphically we followed standard procedure for generating plots for interactions between two continuous variables, which entails solving the regression equation at specific "anchor points" for each of the continuous variables (Tabachnick & Fidell, 2007). In our case, we solved the equation for ±1 standard deviation away from the mean for both VO_2peak and PiB-PET DVR, representing Low vs. High VO_2peak and Low vs. High Aβ burden respectively. These solutions revealed that among individuals who had Low Aβ burden (and thus were at reduced risk for AD), the Low and High VO_2peak groups did not differ statistically from each other: p= .499 for Immediate Memory and p= .441 for Verbal Learning and Memory. In contrast, among those who had High Aβ burden (and thus at increased risk for AD), the High VO_2peak group performed better on these cognitive domains than the Low VO_2peak group: p= .058 for Immediate Memory and p= .039 for Verbal Learning and Memory (**Figure 1**).

There were also significant VO_2peak*CSF Aβ42 interactions for the domains of Immediate Memory (p< .001) and Verbal Learning & Memory (p< .001) (**Table 3**). To graph these findings, we solved the regression equation at ±1 standard deviations for VO_2peak as described above. For CSF Aβ42, we created a dichotomy (i.e., Low vs. High CSF Aβ42) using the established cut-point for normality (i.e., ≥ 550 ng/L) (Hansson et al., 2006). These solutions revealed that among individuals with High Aβ42 (i.e., at reduced risk for AD), the Low and High VO_2peak groups did not differ statistically from each other: p= .200 for Immediate Memory and p= .188 for Verbal Learning & Memory. Whereas among those with Low CSF Aβ42 (i.e., at increased risk for AD), the High VO_2peak group performed significantly better on these cognitive domains than the Low VO_2peak group: p= .002 for Immediate Memory and p= .014 for Verbal Learning & Memory (**Figure 2**).

For both the PiB-PET and CSF Aβ42 analyses, we removed the VO_2peak*Aβ term from those models wherein it was not significant (i.e., Speed & Flexibility and Working Memory) and refit the model to assess the main effect of VO_2peak and Aβ on those cognitive domains. The only significant finding was an association between VO_2peak and Speed & Flexibility (p= .033), wherein more fit individuals had better scores compared with less fit individuals. We also failed to find a significant association between VO_2peak and Aβ burden —whether measured by PiB-PET or CSF Aβ42—in our sample (p's > .789).

Secondary analyses

Number of parameters in our regression models—Our original models included beta-blocker usage and BMI because beta-blocker usage was negatively correlated with all cognitive outcomes and BMI was similarly negatively associated with VO_2peak. However, because these additional parameters may have resulted in model overfit, we re-analyzed our data after excluding them. These revised models still showed significant VO_2peak*PiB-PET

DVR interactions for Immediate Memory (p= .048) and Verbal Learning & Memory (p= .024), and significant VO_2peak*CSF Aβ42 interactions for Immediate Memory (p <.001) and Verbal Learning & Memory (p= .001), suggesting that our initial findings were not driven by the number of regressors in our models.

Criteria for peak effort—Compared to younger individuals, older adults are usually more reluctant to give maximal effort during a GXT, which may attenuate their recorded VO_2peak (ACSM, 2012). Thus, we employed the ACSM criteria for ascertaining peak effort in order to minimize the likelihood of age-dependent effects in our observed VO_2peak. This was of particular concern since both Aβ burden and cognitive function track closely with age. Even so, to verify that our results were not solely a function of the peak criteria implemented, we refit our models after implementing alternative criteria used in other studies of older adults, i.e., (1) a respiratory exchange ratio ≥ 1.0 and (2) at least 85% of age predicted maximal heart rate (Billinger, Vidoni, Honea, & Burns, 2011). Our results remained essentially the same with the exception that there was no longer a significant VO_2peak*Aβ interaction for the domain of Verbal Learning & Memory.

DISCUSSION

In this cross-sectional study, we found that CRF modifies the effect of Aβ burden on cognition. This effect was observed across the two indices of Aβ accumulation that were examined (i.e., PiB-PET DVR and CSF Aβ42 levels). Specifically, among persons with minimal Aβ burden, performance on measures of Immediate Memory and Verbal Learning & Memory did not vary significantly as a function of CRF. In contrast, among persons with higher Aβ burden, increased CRF was associated with better scores on these domains. To our knowledge, this is the first study to show that CRF might modify the well-established influence that Aβ burden has on cognition.

We noted with great interest that the essence of our findings is in line with prior studies done in AD mouse models (Ke, Huang, Liang, & Hsieh-Li, 2011; Parachikova, Nichol, & Cotman, 2008). One such study (Wang et al., 2013) revealed that voluntary exercise mitigates the deleterious effects of a neurotoxic Aβ form (Aβ25-35) on memory. When injected intracerebroventricularly (ICV), Aβ25-35 induces cognitive impairment in adult mice. However, voluntary wheel running for 12 days was shown to diminish Aβ25-35-generated memory deficits. Similarly, findings from Kim and colleagues (2014) suggest that treadmill exercise alleviates Aβ25-35-induced short-term memory impairment in adult rats. They observed that animals receiving bilateral ICV injection of Aβ25-35 performed significantly worse on a short-term memory test compared to the sham group. Importantly, when a group of the Aβ25-35-injected rats also underwent treadmill exercise, they failed to exhibit this Aβ25-35-associated memory deficit. Our study nicely translates these preclinical findings to humans by showing that, in late-middle-aged adults, increased CRF might diminish Aβ-related cognitive changes.

Further, we add to the growing literature suggesting that CRF in adults is beneficial for cognitive function. One study (Barnes et al., 2003) found preserved cognitive function spanning domains of attention/executive function, verbal memory, and verbal fluency, over

a 6-year period in participants who were determined to have high CRF levels at baseline. Additionally, a large community-based study (Zhu et al., 2014), found that higher CRF, measured by maximal duration during a GXT, was associated with better performance on cognitive measures of episodic memory, cognitive flexibility, and working memory. Similarly, Boots and colleagues (2014) demonstrated an association between a CRF estimate and cognitive function in middle-aged adults enrolled in the WRAP cohort. Specifically, they reported that individuals with higher levels of estimated CRF performed better on domains of Verbal Learning & Memory, Speed & Flexibility, and Visuospatial Ability compared to those with lower CRF levels. Overall, our study extends these earlier investigations by showing that there is an interaction between Aβ load and aerobic fitness on cognitive performance, such that increased aerobic fitness may be particularly beneficial in the context of elevated Aβ accumulation.

Our findings were consistent across two Aβ detection platforms (i.e., PiB-PET binding and CSF Aβ42 levels), strengthening their validity. It has been well-established that low CSF Aβ42 highly correlates with increased PiB-PET signal (Degerman Gunnarsson et al., 2010; Fagan et al., 2006; Jagust et al., 2009; Palmqvist et al., 2014; Tolboom et al., 2009). Our findings are consistent with this notion by showing that CRF similarly modifies PiB- and Aβ42-associated changes in cognition. Even so, it is noteworthy that the interactions between CRF and Aβ42 seemed qualitatively stronger than those between CRF and PiB-PET signal. These observations are supported by results from recent work by Landau and colleagues (2013). They found that individuals classified as having abnormal CSF Aβ42 levels but normal PiB-PET Aβ load had more cognitive impairment compared to their peers with normal Aβ42 levels and abnormal PiB-PET Aβ load (Landau et al., 2013). Another study also showed that discordance between these Aβ biomarkers, specifically low CSF Aβ42 but normal amyloid PET binding, is primarily found in the pre-dementia stages of AD, suggesting that CSF Aβ42 may be an earlier indicator of disturbances in Aβ metabolism than amyloid PET (Mattsson et al., 2015). In combination with our study, this suggests that, in some populations, CSF Aβ42 may be more sensitive than PiB-PET for predicting cognitive performance.

It bears mentioning that although we only observed significant VO_2peak*Aβ interactions for Immediate Memory and Verbal Learning & Memory, we did detect a significant main effect of VO_2peak on Speed & Flexibility performance, wherein individuals with greater VO_2peak also had higher scores on this cognitive domain. This facilitation of Speed & Flexibility (which indexes cognitive skills commonly called executive function) by VO_2peak is a consistent finding in the literature including two recent papers from our group (Boots et al., 2014; Okonkwo et al., 2014). In the Okonkwo et. al. (2014) study, we found that whereas physical activity modified the influence of age on cognitive domains of Immediate Memory and Visuospatial Ability, it had a direct (i.e., main) effect on Speed & Flexibility. Taken together, those findings and our present observations suggest that physical activity/fitness might facilitate some cognitive functions (e.g., executive function) by impacting them directly while preserving others (e.g., episodic memory) by attenuating the influence that specific risk factors, such as age and Aβ burden, exert on them. We also note that whereas some studies have reported a direct association between physical activity and Aβ [e.g., Brown et al. (2013); Liang et al., (2010)] the present study and others [e.g., Gidicsin et al.

(2015); Landau et al. (2013); Vemuri et al. (2012)] have failed to uncover such effects. Future studies might yet elucidate the variables (e.g., age of cohort) that account for this heterogeneity in study findings.

Curiously, the plots generated from our VO_2peak*Aβ models appeared to suggest that, among individuals with low Aβ burden, higher CRF was associated with somewhat lower cognitive test scores compared with lower CRF (note though this lower performance was not significantly so, and was always around −0.5 SD of the mean). Such seemingly counterintuitive observations have been made in prior reports. For example, a study by Bugg and Head (2011) found that in younger age, individuals who were less active had *larger* medial temporal lobe volumes compared to those deemed to be more active. In a recent paper (Okonkwo et al., 2014) we also found that, among younger middle-aged adults, inactive persons had *lower* Aβ burden and *higher* scores on some cognitive domains compared with active individuals, whereas the reverse was true among older middle-aged adults. There is clearly a need for additional studies in order to further understand the complex interplay between physical activity/CRF and AD risk factors.

This study was not without limitations, the most significant being the cross-sectional design. Although we have used statistical approaches to estimate the potential for CRF to ameliorate Aβ-related decrements in cognition, a prospective design will be critical in determining whether fitness exerts a causal influence on cognition in people at risk of AD. Additionally, there was, on average, a three-year time interval between the PET/CSF exams and the GXT. Although we attempted to accommodate this asynchrony by including the PET-GXT time interval in all of our models, we cannot exclude the possibility of reverse causality, whereby increased Aβ burden adversely affects CRF levels. Future studies would benefit from collecting Aβ and GXT measurements in closer temporal proximity. Lastly, the demographic make-up of the study sample is not representative of the U.S. population. Therefore, the generalizability of our findings might be somewhat limited.

Overall, this study provides cross-sectional evidence that the deleterious effect of Aβ burden on cognition might be modified by higher CRF among late-middle-aged CN individuals at risk for AD. These findings add to the existing literature suggesting that a physically-fit lifestyle may delay or prevent the onset of symptomatic AD.

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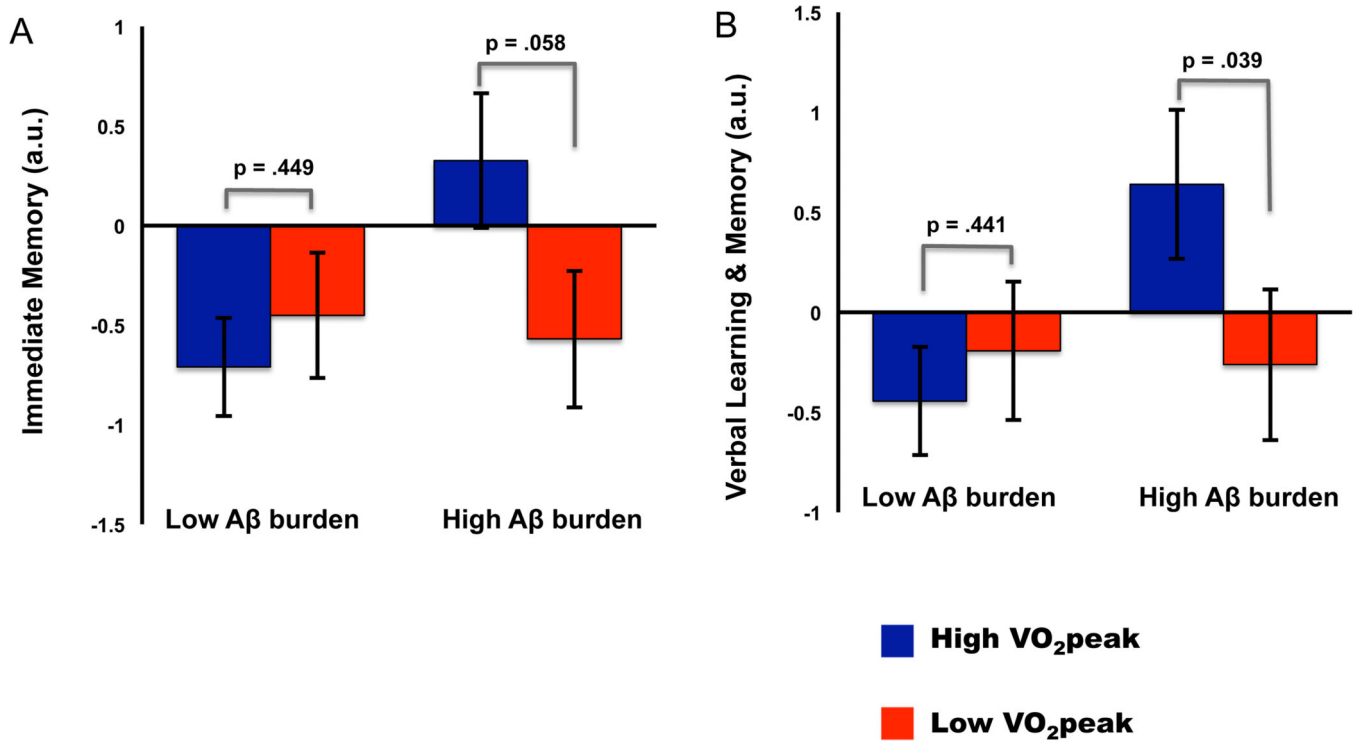

Figure 1. CRF modifies Aβ-related alterations in cognition detected by PiB-PET

CRF=cardiorespiratory fitness; Aβ=β-amyloid; PiB=^{11}C Pittsburgh Compound B; PET=positron emission tomography; a.u.=arbitrary units; DVR=distribution volume ratio; VO_2peak=peak oxygen consumption during graded exercise test (GXT). Panels display adjusted means and standard errors from analyses that modeled Immediate Memory (A) and Verbal Learning & Memory (B) as a function of age, sex, education, body mass index, beta-blocker usage, time interval between the PET scan and GXT, time interval between cognitive testing and GXT, VO_2peak, PiB-PET DVR, and a VO_2peak*PiB-PET DVR. The VO_2peak*PiB-PET DVR interaction term was the effect of primary interest in all models. Although VO_2peak and PiB-PET DVR were included in the analyses as continuous variables, for the purposes of graphing the study findings we chose two anchor points (i.e., ±1 standard deviation away from the mean) to represent Low vs. High VO_2peak, and Low vs. High Aβ burden.

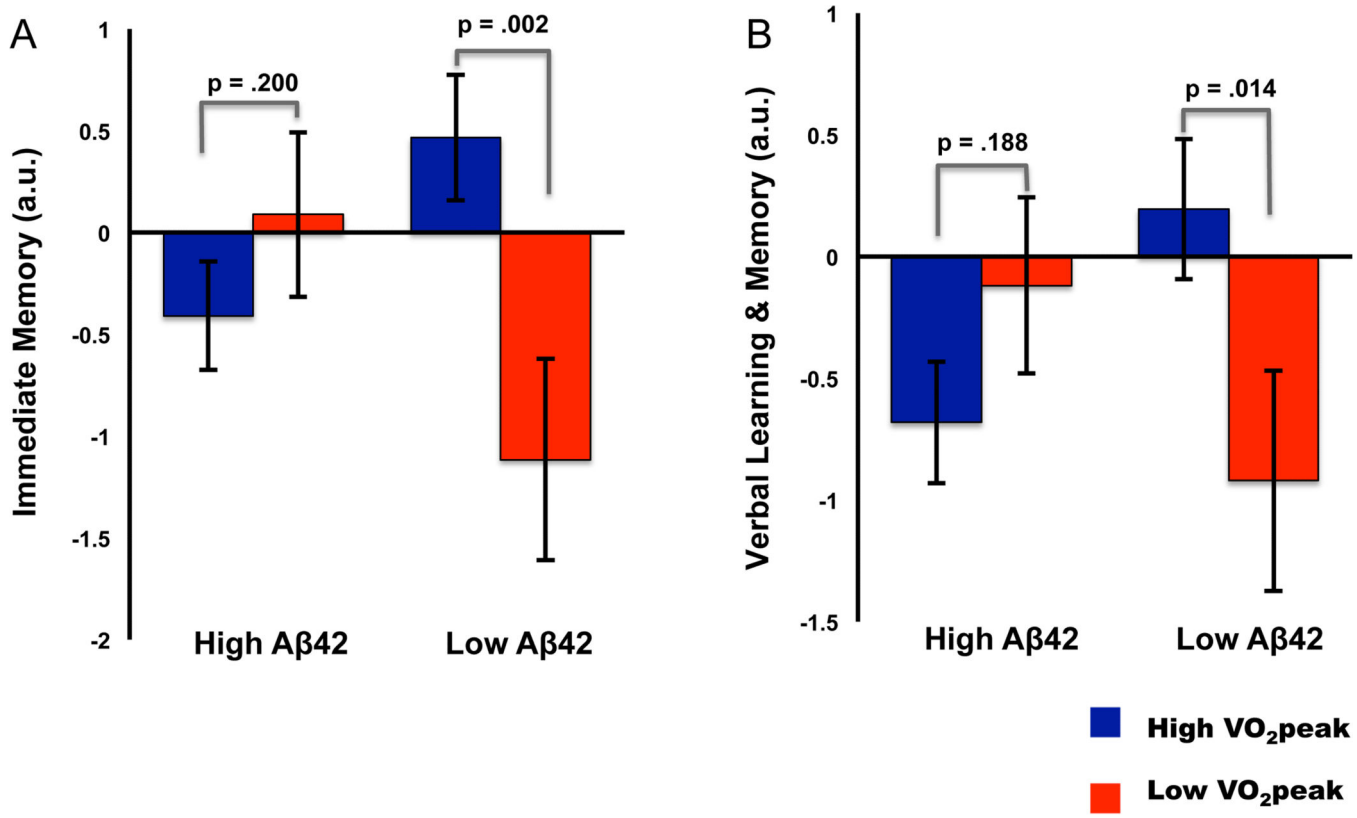

Figure 2. CRF modifies Aβ-related alterations in cognition detected by CSF Aβ42

CRF= cardiorespiratory fitness; Aβ=β-amyloid; CSF=cerebrospinal fluid; a.u.=arbitrary units; VO_2peak = peak oxygen consumption during graded exercise test (GXT).

Panels display adjusted means and standard errors from analyses that modeled Immediate Memory (A) and Verbal Learning & Memory (B) as a function of age, sex, education, body mass index, beta-blocker usage, time interval between the CSF sampling and GXT, time interval between cognitive testing and GXT, VO_2peak, CSF Aβ42, and a VO_2peak*CSF Aβ42 interaction. The VO_2peak*CSF Aβ42 interaction term was the effect of primary interest in all models.

Although VO_2peak and CSF Aβ42 were included in the analyses as continuous variables, for the purposes of graphing the study findings we chose two anchor points (i.e., ±1 standard deviation away from the mean) to represent Low vs. High VO_2peak, and dichotomized CSF Aβ42 (i.e., Low vs. High CSF Aβ42) using the established cut-point for normality (i.e.; ≥ 550 ng/L).

Table 1

Characteristics of study participants*

Variable	Value
Female, %	68.1
Age at GXT visit, mean (SD) [range], y	63.54 (5.93) [49.53-74.23]
Education, mean (SD) [range], y	16.46 (2.12) [12-22]
APOE4 positive, %	47.8
Family history positive, %	72.5
Caucasian, %	94.2
MMSE Score, mean (SD) [range]	29.38 (1.16) [24-30]
VO_2peak, mean (SD) [range], ml/kg/min	25.95 (5.50) [11.64-38.43]
Taking a beta-blocker at GXT visit, %	5.8
Systolic blood pressure at GXT visit, mean (SD) [range], mmHg	123.68 (13.89) [94-160]
Diastolic blood pressure at GXT visit, mean (SD) [range], mmHg	71.32 (10.19) [44-90]
BMI at GXT, , mean (SD) [range], kg/m^2	27.70 (5.40) [17.65-48.03]
Interval between PET scan and GXT, mean (SD) [range], y	3.10 (.47) [2.23-4.10]
Interval between cognitive testing and GXT, mean (SD) [range], y	1.08 (.74) [0-3.79]

APOE4=the varepsilon 4 allele of the apolipoprotein E gene; MMSE=Mini-Mental State Examination; VO_2peak=peak oxygen consumption during graded exercise test (GXT); BMI=body mass index; PET=positron emission tomography.

Table 2

CRF favorably alters Aβ-related changes in cognition detected by PiB-PET

Cognitive domain	VO_2peak*PiB-PET DVR[§]			VO_2peak (Low Aβ burden)[†]		VO_2peak (High Aβ burden)[‡]	
	β (SE)	p	Partial η^2	β (SE)	p	β (SE)	p
Immediate Memory	**.523 (.25)**	**.041**	.07	−.251 (.37)	.499	.901 (.47)	.058
Verbal Learning & Memory	**.526 (.23)**	**.025**	.08	−.261 (.34)	.441	**.897 (.42)**	**.039**
Speed & Flexibility	.214 (.19)	.274	.02	-	-	-	-
Working Memory	−.047 (.29)	.875	<.01	-	-	-	-

CRF=cardiorespiratory fitness; Aβ=β-amyloid; PiB=^{11}C Pittsburgh Compound B; PET=positron emission tomography; DVR=distribution volume ratio; VO_2peak=peak oxygen consumption during graded exercise test (GXT); β=regression estimate; SE=standard error; η^2=eta squared.

Variables included in the model were age, sex, education, body mass index, beta-blocker usage, time interval between PET scan and GXT, time interval between cognitive testing and GXT, VO_2peak, PiB-PET DVR, and a VO_2peak*PiB-PET DVR interaction; with the VO_2peak*PiB-PET DVR interaction term being the effect of primary interest.

[§]The regression estimates and associated p values are for the VO_2peak*PiB-PET DVR interaction term in each cognitive measure's model. This term assessed whether VO_2peak modifies the effect of amyloid burden on the examined cognitive domain.

[†]The regression estimates and associated p values are for the simple main effect for the influence of VO_2peak on cognition *within the Low Aβ burden group.*

[‡]The regression estimates and associated p values are for the simple main effect for the influence of VO_2peak on cognition *within the High Aβ burden group.*

Table 3

CRF favorably alters Aβ-related changes in cognition detected by CSF Aβ42

Cognitive domain	VO_2peak*CSF Aβ42[§]			VO_2peak $_{(High Aβ42)}$[†]		VO_2peak $_{(Low Aβ42)}$[‡]	
	β (SE)	**p**	**Partial η^2**	**β (SE)**	**p**	**β (SE)**	**p**
Immediate Memory	**−.128 (.03)**	**<.001**	.38	−.498 (.38)	.200	**1.580 (.48)**	**.002**
Verbal Learning & Memory	**−.102 (.03)**	**<.001**	.31	−.482 (.36)	.188	**1.169 (.45)**	**.014**
Speed & Flexibility	−.047 (.03)	.072	.09	-	-	-	-
Working Memory	−.029 (.04)	.435	.02	-	-	-	-

CRF=cardiorespiratory fitness; Aβ=β-amyloid; CSF=cerebrospinal fluid; VO_2peak=peak oxygen consumption during graded exercise test (GXT); β=regression estimate; SE=standard error; η^2=eta squared.

Variables included in the model were age, sex, education, body mass index, beta-blocker usage, time interval between the CSF sampling and GXT, time interval between cognitive testing and GXT, VO_2peak, CSF Aβ42, and a VO_2peak*CSF Aβ42 interaction; with the VO_2peak*CSF Aβ42 interaction term being the effect of primary interest.

[§]The regression estimates and associated p values are for the VO_2peak*CSF Aβ42 interaction term in each cognitive measure's model. This term assessed whether VO_2peak modifies the effect of amyloid burden on the examined cognitive domain.

[†]The regression estimates and associated p values are for the simple main effect for the influence of VO_2peak on cognition *within the High Aβ42 group*.

[‡]The regression estimates and associated p values are for the simple main effect for the influence of VO_2peak on cognition *within the Low Aβ42 group*.