Physical Fitness and Age-Related Differences in Cognition and Cortical Thickness in Young Adulthood

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Abstract

The association between physical fitness and age-related differences in cognition and brain structure has been studied fairly extensively during development and aging, yet comparatively less in young adulthood. The current study examined 1195 young adults aged 22 to 36 (54% female; 67% Caucasian) to better understand associations between physical fitness—grip strength and submaximal cardiovascular endurance—and age-related differences in executive function (EF), memory, and average cortical thickness. EF, memory, and cortical thickness were negatively associated with age, and higher endurance was positively associated with EF and memory. Neither physical fitness measure associated with cortical thinning. To follow-up on these analyses, data from monozygotic (n=149 pairs) and dizygotic (n=93 pairs) twins were used to estimate the degree to which heritability versus environment might contribute to the observed associations between cognition and endurance. Environmental effects shared by monozygotic and dizygotic twins alike were estimated to account for roughly 50% of the correlation between endurance and cognition (EF and memory). Heritability and non-shared environmental effects were inconsistent across EF and memory. Overall, these findings suggest an association between cardiovascular endurance and age-related differences in cognition in young adulthood and that these associations may be independent of cortical thinning. Whereas there was consistent evidence for a moderate contribution of the shared environment, there was limited and inconsistent evidence for a role of heritability.

Keywords: heritability; environment; memory; executive function; cortical thickness; physical fitness

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Introduction

Much focus has been placed on understanding associations between aspects of physical fitness—including muscle strength and cardiovascular endurance—and neurocognitive development in childhood and adolescence (Chaddock, Hillman, Buck, & Cohen, 2011; Fedewa & Ahn, 2011). The observed positive association between fitness and various aspects of cognition and markers of brain health has led to the design and implementation of physical activity interventions intended to promote fitness, and in turn, cognitive performance and academic achievement (Donnelly et al., 2016). At the same time, another large field of study has focused on links between physical fitness and cognitive decline and brain atrophy in older age (Barnes, Yaffe, Satariano, & Tager, 2003; Clouston et al., 2013; Falck, Davis, Best, Crockett, & Liu-Ambrose, 2019; Wendell et al., 2014; Zammit et al., 2019). Generally, this research has suggested that higher physical fitness is correlated with higher cognitive functioning and positive markers of brain health, and perhaps, can be protective against age-related cognitive decline and brain atrophy.

The focus on the two ends of the lifespan—childhood development and aging—has been prompted in part by the hypothesis that these are critical periods of neurocognitive change, and therefore might represent sensitive windows during which other external factors, including physical fitness, might exert disproportionate influence on neuro-cognitive differences as compared to the middle portion of the lifespan (Best, 2010; Erickson, Leckie, & Weinstein, 2014). However, there is other evidence that suggests that the association between physical fitness and neuro-cognitive differences might be evident among young and middle-aged adults as well. Zhu and colleagues (2014) observed that higher cardiovascular endurance between the ages of 18 to 30 predicted better memory and attention performance 25 years later in midlife with differences between the 1st and 4th quartiles of endurance ranging from 0.3 to 0.5 standard deviation (SD) units in cognitive outcomes. A recent randomized trial by Stern and colleagues (2019) demonstrated that 6 months of 4 days/week aerobic exercise increased aerobic capacity, increased cortical thickness, and improved executive functioning (EF) in young and middle-aged adults. Interestingly, the effects on EF appeared to be moderated by age, such that the magnitude increased from approximately 0 SD units in young adulthood to 0.23 SD units by age 40. This might suggest that associations between fitness and cognition may vary across young and middle adulthood. A large-scale study by Åberg and colleagues (2009) of over 1 million Swedish men enlisted for military service found that cardiovascular endurance, and not muscle strength, correlated ($r \sim 0.2$) with general and specific aspects of intelligence at age 18.

Caution is warranted when interpreting the current body of research on physical fitness and cognition in young adulthood. Foremost, as pointed out in a recent meta-analysis (Ludyga, Gerber, Puhse, Looser, & Kamijo, 2020), there are very few studies that have investigated this topic in young adults, and the largest previous study on this topic only analyzed young men (Åberg et al., 2009). Second, observational studies have the limitation of unmeasured confounding that might lead to spurious associations between fitness and cognition. This could arise from insufficient adjustment for socioeconomic or other physical health factors that influence fitness and cognition, or an inability to account for genetic factors that could contribute to variation in fitness and in cognition. Third, reverse causation is possible in observation studies, such that the direction of the effects flow from cognition to fitness, rather than vice versa. One longitudinal study observed that the association between midlife fitness and cognition could be explained in large part by childhood cognition and that higher cognition might promote subsequent fitness in midlife through protection against obesity (Belsky et al., 2015). Fourth, the degree to which the phenotypic correlation between fitness and cognition might be attributed to heritability versus environmental effects is largely unknown; a strong heritability effect might imply that the phenotypic correlation is largely driven by genetic variation that affects both fitness and cognition (i.e., genetic confounding), or alternatively, genetic variation affects one phenotype, which consequently affects the other phenotype. As an example, strong heritability of fitness might lead to variation in exercise (i.e., higher fit children might actively seek out exercise activities; Huppertz et al., 2016; Scarr & McCartney, 1983), and in turn, increased engagement in exercise promotes cognition. Finally, not all findings have been consistent, as some observational studies have failed to detect statistically significant associations between physical fitness and cognition in young adults (Ho, Gooderham, & Handy, 2018; Stillman et al., 2018). These null findings could partially be explained by fairly small sample sizes (e.g., 100 participants or less) that limit statistical power to detect modest-sized effects.

The current study attempts to address several of these shortcomings by examining physical fitness and

age-related differences in cognitive performance and cortical thickness in a relatively large cohort of >1,100 young women and men aged 22 to 36, who participated in the Washington University-Minnesota Young Adult Human Connectome Project (YA-HCP) (Van Essen et al., 2013). In assessing cognitive performance, a latent variable approach of multiple indicators of cognition (across the domains of processing speed, attention, EF, and memory) was used in order to reduce the number of cognitive outcomes analyzed. These cognitive measures were chosen because previous research has suggested they are positively associated with physical fitness and exercise training (Ludyga et al., 2020). Physical fitness was assessed by submaximal cardiovascular endurance and grip strength.

Several covariates were included to adjust for socioeconomic differences (income and education) and physical health and performance factors (gait speed, height, and weight) that might confound the association between fitness and cognition. To address the possibility of genetic confounding (i.e., shared genes rather than shared experiences primarily affect physical fitness and cognition), the current study leveraged the fact that the YA-HCP contains pairs of monozygotic and dizygotic twins. Using a bivariate Cholesky decomposition (Grasby, Verweij, Mosing, Zietsch, & Medland, 2017), heritability, the shared environmental, and the non-shared environmental contributions to the phenotypic associations between physical fitness and cognition were estimated. Although this analysis could not resolve the issue of directionality, the estimation of a large heritability component to the fitness-cognition correlation could imply that genetic variation might confound the correlation or might initiate a developmental pathway involving active selection of environments and experiences that results in the observed phenotypic correlation between fitness and cognition (Scarr & McCartney, 1983).

The current study also seeks to better understand the degree to which variation in brain structure might be associated with physical fitness, and thus, might serve as a mechanism by which physical fitness and cognition are associated in young adulthood. As noted previously, Stern and colleagues (2019) observed increases in left frontal cortical thickness following aerobic training. Other studies have also shown that cortical thickness across several regions in the frontal, parietal and temporal lobes of the cortex is associated with aerobic fitness in children (Chaddock-Heyman et al., 2015; Esteban-Cornejo et al., 2019) and in older adults (Williams et al., 2017). Previous research has also linked cortical thickness to cognitive and academic outcomes in youth (Burgaleta, Johnson, Waber, Colom, & Karama, 2014; Chaddock-Heyman et al., 2015; Mackey et al., 2015) and with cognition in older adults (Burzynska et al., 2012), suggesting a relevance to broader functioning. Whether strength is also associated with cortical thickness is largely unknown, with one study in children failing to detect an association (Esteban-Cornejo et al., 2019).

A positive association was hypothesized for both physical fitness measures with cognition and cortical thickness, after adjusting for confounders, but with an expectation of a stronger association with cardiovascular endurance than with grip strength according to a limited number of previous studies (Åberg et al., 2009; Esteban-Cornejo et al., 2019). The expectation was that any latent factors derived from the various cognitive indicators would be associated with fitness given evidence for a fairly broad effect of fitness and exercise training on cognition (Ludyga et al., 2020). Interactions between age, gender and physical fitness were included to test for potential moderating effects of age (Stern et al., 2019), as well as allow for the possibility that the association between fitness and neurocognition might differ for males versus females, perhaps due to biological or environmental differences (Barha, Davis, Falck, Nagamatsu, & Liu-Ambrose, 2017). In line with the results of Stern and colleagues (2019), it was hypothesized that the association between fitness and cognition would increase with age. The nature of the potential moderation by gender was not pre-specified, given some evidence to suggest women might obtain greater cognitive benefits from exercise training to improve physical fitness (Barha et al., 2017), other evidence suggests women might benefit less (Ludyga et al., 2020), and still other evidence suggests no discernible difference between men and women in this respect (Falck et al., 2019).

Additionally, this study was interested in how strong physical fitness was as a predictor compared to age. Although age-related differences in cognition are generally controlled for (either in a design or statistical sense), it is worthwhile to more explicitly analyzing age differences in cognition and cortical thickness in young adulthood. Through analysis of cross-sectional and longitudinal datasets, Salthouse (2009) argued that age-related decline in various aspects of cognition occurs well before the transition to late adulthood, perhaps as early as the mid 20s. Moreover, age-related cortical thinning is observable beginning in at least

adolescence and continues through early adulthood across most of the cortex (Lemaitre et al., 2012; Tamnes et al., 2010).

With respect to secondary behavioral genetic analysis of monozygotic and dizygotic twins, it was hypothesized that the heritability contribution to the correlation between cognition and fitness would be modest, according to a similar analysis undertaken by Åberg and colleagues (2009), who observed that the association between cardiovascular endurance and cognition in young men was primarily attributed to the non-shared environment (~80% of the covariation) and much less to heritability (~15% of the covariation).

Methods

Study Design and Participants

Participant data were provided by the open-access YA-HCP 1200 Subjects Data Release (Van Essen et al., 2013). For our primary analyses, 1195 participants who completed demographic questionnaires (age, gender, ethnicity, education, income), and measures of cognitive testing (flanker task, list sorting, picture sequencing, card sorting, processing speed and word memory), body composition (height and weight) and objective physical fitness (2-min endurance test, gait speed, and grip strength) were analyzed. For structural neuroimaging analyses, 1102 of the aforementioned participants who also had valid Freesurfer-processed 3T structural MRI data were analyzed. For behavioral genetic analyses, 149 monozygotic and 93 dizygotic twin pairs with complete cognitive functioning and objective physical fitness measures were analyzed; these sibling pairs were also included in the primary analyses of the larger dataset. Twin zygosity was verified by genotyping.

Participants were healthy adults within the age range of 22 to 36, who were drawn primarily from families that included twins in Missouri, USA. Families were excluded where individuals within the family had severe neurodevelopmental disorders (e.g., autism), neuropsychiatric disorders (e.g., schizophrenia) or neurological disorders (e.g., Parkinson’s disease). Individuals were also excluded if they had illnesses thought to impact neuroimaging data quality (e.g., high blood pressure or diabetes). Additional details on the participants and study design can be found elsewhere (Van Essen et al., 2013). Extensive details on all the measures included in the HCP study can be found at: <https://wiki.humanconnectome.org>. The original study was approved by the Washington University institutional review board. All participants provided written informed consent. Approval for this secondary analysis was provided by the institutional review board at Simon Fraser University (Title: “Genetic Contributions to Cognition and Physical Functioning in Young Adults: Analysis of the Human Connectome Project Study”; Study no: 2019s0471).

Demographic and Other Covariate Variables

Age in years, gender, race/ethnicity, years of completed education, annual total household income, height, and weight were self-reported. Gait speed (meters per second) was assessed over 4-meters, starting from rest, and was included to account for variance in the endurance measure due to differences in gait.

Cognition and Physical Fitness

Participants completed several instruments from the NIH Toolbox for Assessment of Neurological and Behavioral Function on the first of the two-day assessment schedule (‘NIH toolbox’). The NIH toolbox includes psychometrically-validated measures of cognition and behavior, suitable for use across the human lifespan (Gershon et al., 2013; Reuben et al., 2013; Weintraub et al., 2013). Details on its implementation within the HCP can be found elsewhere (Barch et al., 2013). For the current study objectives, only measures of physical and cognitive functioning were included.

Physical Fitness

Two measures of physical fitness were included. Sub-maximal cardiovascular endurance was assessed by having participants walk as far as possible over a 2-minute period of time, back-and-forth over a 50-ft course. The total distance is recorded. Two trials were completed, with the faster trial used as the outcome of interest. Full force grip strength is measured with both hands using a Jamar Plus Digital dynamometer with the elbow bent to 90 degrees and arm against the trunk. Practice is conducted for each hand. Pounds of force for the dominant hand is used as the outcome of interest. Age-normalized scores were used (Mean = 100, SD = 15). Both fitness measures have shown good test-retest reliability (Intraclass correlation coefficient [ICC] ≥ 0.88) and convergent validity ($r \geq 0.77$) with ‘gold standard’ measures of endurance and grip strength across adulthood (Reuben et al., 2013). Further, although grip strength is a more direct measure of upper body strength, it also strongly correlates with knee extension performance ($r \geq 0.77$), a measure of lower body strength, suggesting grip strength may serve as a proxy body strength more generally (Bohannon, Magasi, Bubela, Wang, & Gershon, 2012).

Cognitive Performance

Five cognitive tests were completed on a computer and followed the standardized protocol for the NIH Toolbox Cognition administration (Weintraub et al., 2013). Scores normalized against the entire NIH Toolbox normative sample were used (rather than age-normalized scores), given that a core interest was to examine interactions between age trends and physical fitness on cognition. These measures cover aspects of attention, processing speed, executive function, and memory, all of which have been positively associated with physical fitness and exercise training (Ludyga et al., 2020). Briefly, the picture sequence memory task is a measure of episodic memory that asks participants to recall a sequence of pictures presented in a story fashion. Correct responses are noted when the participant correctly places two adjacent pictures together. The dimensional change card sort task is a measure of EF/cognitive flexibility that asks participants to categorize pictures along two dimensions (i.e., shape and color). Scoring is based on a combination of accuracy and reaction time. The flanker task measures EF/inhibition by having participants respond to the direction of a central stimulus that is surrounded by flanking stimuli that either point in the same direction (congruent) or in the opposite direction (incongruent). Scoring is based on a combination of accuracy and reaction time. List sorting is a measure of working memory that asks participants to recall a sequence of food or animals presented visually and orally from smallest to largest (1-list condition) or a sequence of food and animals from smallest to largest, starting with the food items and then the animals (2-list condition). Scores are based on the accuracy of the response. Processing speed was assessed by asking participants to respond as quickly as possible to whether two side-by-side pictures are the same or not. One additional cognitive test was included in the current study that was not part of the NIH Toolbox. Verbal episodic memory was assessed with the Penn Word Memory Test Form A (Gur et al., 2010), during which participants are asked to discriminate 20 previously studied words from 20 new words. A total correct score is calculated. Psychometric properties are acceptable across these cognitive measures, with the ICC test-retest reliability ranging from 0.73 (processing speed) to 0.84 (picture sequence memory test) in a sample of adults between the ages of 20 and 85 (Weintraub et al., 2014), and convergent validity ($r > 0.50$) with ‘gold-standard’ measures of cognition within each domain (Carlozzi et al., 2014; Dikmen et al., 2014; Tulskey et al., 2014; Zelazo et al., 2014).

Structural MRI Data Acquisition and Processing

All neuroimaging acquisition and processing was conducted by the HCP research team with no additional processing on the freely-available data. Extensive details on the imaging protocol are found elsewhere, including details of additional scanning paradigms not included in the current study (Van Essen et al., 2013; Van Essen et al., 2012). All participants were scanned on a Siemens 3T customized ‘Connectome Skyra’ at Washington University in St. Louis, using a 32-channel Siemens head coil. Two T1-weighted and two T2-weighted scans were acquired at a spatial resolution of 0.7 mm isotropic voxels over two sessions. Each scan was evaluated by a trained rater for overall quality and only good/excellent scans were submitted to the structural pipelines, which used FreeSurfer 5.1 software and custom steps that combine images from the T1- and T2-weighted scans for more accurate white and pial surfaces (Van Essen et al., 2013). Initial registration to MNI152 space was completed by FSL’s FLIRT tool, followed by nonlinear FNIRT to align subcortical structures. Cortical surface alignment was achieved using a surface-based registration using FreeSurfer, separately for each hemisphere. Gray matter was then parcellated into 68 cortical thicknesses and areas across the two hemispheres. Average cortical thickness was computed across the 68 cortical parcellations, weighted by the area of each parcellation.

Statistical Analyses

Analyses were conducted using R version 4.0.0 (r-project.org). An a priori power calculation was not conducted given that this is a secondary analysis of an existing dataset. For each analysis the maximum sample size possible was used. The first step was to determine the structure of cognition using structural equation modeling with the package *lavaan* (version 0.6-5) using the full sample of 1195. In light of the clustering of siblings within family, cluster-robust standard errors were used by specifying that individuals with the same maternal ID were clustered together. Full-information maximum likelihood estimation handled missing data on any of the cognitive measures. Two possible structures of cognition were compared: 1) a single cognitive factor in which all six cognitive tests loaded on a common latent variable (**Figure 1a**); and 2) a two-factor model in which list sorting and picture sequencing loaded on a common latent variable (memory) and the flanker and card sorting tasks loaded another latent variable (EF) (**Figure 1b**). Model fit was assessed us-

ing standard measures, including root mean square error of approximation (RMSEA), Bayesian information criterion (BIC), Akaike information criterion (AIC), Tucker-Lewis index (TLI), and comparative fit index (CFI); TLI/CFI values > 0.95 and RMSEA values < 0.05 reflect good model fit (Hu & Bentler, 1999). Models were directly compared using the scaled chi-squared difference test (Satorra & Bentler, 2001).

Figure 1: Simplified Measurement Models for Single Latent Cognitive Factor (A) and Two-Factor Model with Separate Memory and Executive Function Factors (B).

The second step was to calculate factor scores using the beta weights from the best-fitting measurement model (described above) and then regress these factor score(s) and average cortical thickness on a set of covariates (age, gender, ethnicity, income, education, gait speed, height and weight) and the physical fitness measures (grip strength and submaximal endurance). Generalized linear models fit by restricted estimated maximum likelihood were used for these regressions. All two- and three-way interactions of physical fitness with age and gender were included. To allow for nonlinearity in the association of age and physical fitness with the outcome of interest, restricted cubic splines were specified with knots located at the 10th, 50th, and 90th percentile values of the age and physical fitness variables (Harrell, 2019a). A compound symmetry covariance matrix accounted for the clustering of participants by maternal ID. A separate model was constructed for each outcome. Across all models, the Wald statistic was used to evaluate the importance of the variables. This test follows a χ^2 distribution and determines whether setting a given variable's association with the outcome to zero substantially worsens model fit. Importantly, this is not an analysis of individual parameters (e.g., a beta estimate for a given covariate); rather, all parameters involving a covariate (including nonlinear effects and higher-order interactions with other variables) are included in calculating the Wald statistic. Larger χ^2 values suggest greater contribution of that variable to the model. All predictors were retained in the models regardless of the statistical significance of their Wald test; however, interpretation was only done for variables with statistical significance of $p < .01$. As a measure of effect size, explained variance (R^2) was calculated for the total model as well as specifically for age, endurance, and strength. These regression models were constructed using *rms* version 5.1-4 (Harrell, 2019b).

The third step was to estimate the proportion of phenotypic covariance between cognition and physical fitness that can be attributed to shared genes, shared environment, and non-shared environment. These

analyses were limited to the 149 monozygotic and 96 dizygotic genotype-confirmed twin pairs. Using the package **OpenMx** (version 2.13.2), a bivariate Cholesky decomposition twin model was specified (**Figure 2**). A Cholesky decomposition is a structural equation model, in which phenotypic variation in cognition and physical fitness can be attributed to heritability variance (A), shared environmental variance (C), and non-shared environmental variance (E) (Grasby et al., 2017). These sources of variation are estimated by assuming that monozygotic twins share 100% of heritability effects and that dizygotic twins share 50% of heritability effects. The shared environmental effects are assumed to be equivalent for both MZ and DZ twin pairs, and thus, are fixed to 1 for each group. To estimate the heritability and environmental contributions to the correlation between cognition and physical fitness, the observed physical fitness variable is also allowed to load onto the latent heritability and environmental (shared, and non-shared) contributors to cognitive variation (Grasby et al., 2017). The result is the estimation of the variation in cognition and physical fitness, as well as the covariation between cognition and physical fitness. Prior to being entered into the Cholesky decomposition, cognitive and physical fitness variables were regressed on age, age², and sex and their interactions in an ordinary least squares regression model (one model per outcome including all twins together).

Figure 2: Overview of Bivariate Cholesky Decomposition Model.

Next, the assumptions of equality of means and variances across twin order and zygosity were tested using the likelihood ratio test of nested models. A saturated model was fit first, in which all means and variances were allowed to vary freely across twins and zygosity. Next, means and variances were constrained to be equal across twin order, and then, across zygosity. Finally, the ACE model was estimated. To summarize the results of this model, standardize estimates and standard errors for each of the labeled paths in **Figure 2** (e.g., “a11”) are presented, as well as the proportion of variation or of the cross-trait correlation that can be attributed to each of the components (i.e., A, C, or E). (Note. Total variance or covariance is the sum of the A, C, and E components. Covariance can then be converted into a correlation by dividing by the product of the standard deviation of the cognition measure and the standard deviation of the fitness measure).

Two sets of sensitivity analyses were conducted. First, the HCP dataset also contains 119 non-twin full siblings that are within 5 years in age; these non-twin sibling pairs were included in a more complex, ACTwE model (i.e., an ACE model with an additional ‘Tw’ component), which distinguishes the shared environment shared by siblings generally from a twin-specific shared environment. Second, the entire set

of analyses were re-conducted using age-adjusted NIH Cognition Toolbox scores, rather than non-adjusted scores. The complete analysis script and output has been included as Supplement A. Separate analysis scripts and output are provided for the two sensitivity analyses (Supplements B and C, respectively). All data used for the current study can be freely obtained by qualified registered researchers **here** and the supplemental material can be found **here**.

Results

Sample Characteristics and the Structure of Cognition

Demographic, cognitive, and physical fitness data on the full sample are summarized in *Table 1*. Our initial comparison of two measurement models of cognition suggested that a two-factor model, with flanker, processing speed and card sorting performance loading on a latent variable (interpreted as attention, speed and EF) and word memory, list sorting and picture sequence loading on a separate, correlated factor (interpreted as working and episodic memory) provided superior fit to a unitary cognitive factor, χ^2 (df = 1) = 127.6, $p < .0001$. Indeed, the two-factor model was consistently superior to the unitary factor model according to all fit statistics (see top portion of **Figure 3**). The standardized path estimates for the two-factor model are shown in the bottom portion of **Figure 3**; loading onto the latent factors were similar across the observed variables with the exception of the Penn Word Memory Test, which had a smaller standardized loading and which may be attributed to it being a non-NIH toolbox measure.

Table 1. Descriptive information on total sample

	Overall
n	1195
Gender = M (%)	545 (45.6)
Race_5cat (%)	
Asian or Pacific Islands	68 (5.7)
Black/African American	189 (15.8)
Hispanic/Latino	105 (8.8)
Non-Hispanic, White	805 (67.4)
Other	28 (2.3)
Age_in_Yrs (mean (SD))	28.86 (3.69)
Height (mean (SD))	67.49 (3.95)
Weight (mean (SD))	176.38 (43.35)
SSAGA_Income (%)	
1	90 (7.5)
2	102 (8.5)
3	153 (12.8)
4	136 (11.4)
5	126 (10.5)
6	249 (20.8)
7	154 (12.9)
8	185 (15.5)
SSAGA_Educ (%)	
11	44 (3.7)
12	175 (14.6)
13	78 (6.5)
14	152 (12.7)
15	75 (6.3)
16	487 (40.8)
17	184 (15.4)
Endurance_AgeAdj (mean (SD))	107.12 (14.17)
Strength_AgeAdj (mean (SD))	103.87 (20.33)
GaitSpeed_Comp (mean (SD))	1.32 (0.20)

Associations Among Cognition, Cortical Thickness and Physical Fitness

Bivariate correlations among age, cognition, cortical thickness and the two fitness measures are shown in *Table 2*. Age had modest negative correlations with EF, memory, and cortical thickness, whereas endurance

Figure 3: Overview of Model Fit Statistics and Comparison for Single-Factor and Two-Factor Models (Top Portion) and Standardized Solution for Two-Factor Model (Bottom Portion).

had modest positive correlations with EF and memory. Strength had even smaller correlations with the two cognitive factors. Cortical thickness had correlations very close to zero with the measures of cognition and physical fitness. Endurance and grip strength were modestly positively correlated.

Table 2. Bivariate Pearson Correlations Among Age, Cognition, Cortical Thickness and Physical Fitness

	Age	EF	MEM	CortThick	Endurance	Strength
Age	1	-0.18	-0.11	-0.18	0.01	-0.03
EF		1	0.59	0.02	0.26	0.12
MEM			1	0.03	0.22	-0.03
CortThick				1	0.04	0.04
Endurance					1	0.3
Strength						1

Figure 4 summarizes the regression models for EF (panel A) and memory (panel B). The total R^2 values were 16.2% and 20.9%, respectively. The predictors are arranged in order of their contribution of the overall χ^2 for the model, from smallest (top) to largest (bottom). Age was the strongest contributor in both cognitive outcomes, followed by endurance. The Wald tests clearly rejected the null hypotheses that age and endurance had no association with EF and memory (see panels A and B for test statistics). The R^2 associated with age (including its non-linear effects) was 5.3% for EF and 3.7% for memory; for endurance, the R^2 was 2.6% and 1.7%, respectively. With the exception of education, other covariates—including grip strength and gender—had weaker contributions, with associated Wald test p values > 0.05 . The R^2 associated with strength was 1.8% for EF and 1.2% for memory.

To visualize the association between age and cognition, predicted values across age derived from the regression models are summarized in panels A and B. These values are adjusted for all the predictors shown in the summary of the Wald tests. Ninety-five percent confidence intervals are shaded in gray. EF decreased linearly with age (panel C), whereas memory differences appeared to be somewhat stronger at older ages in our age span (panel D). To visualize the association between endurance and cognition across the age range, age-related differences in EF and memory are plotted at different levels of endurance. Values at the 25th, 50th, and 75th percentile were chosen to reflect low, average, and high endurance. Better endurance was associated with higher EF performance across the studied age span, perhaps especially at early and latter segments (panel E), and endurance was associated with higher memory performance, especially in the latter part of young adulthood (panel F).

Figure 4: Summary of Wald Test Chi-squared Statistics for Executive Function (A) and Memory (B), Age-Related Differences In Executive Function (C) and Memory (D), and Associations Between Submaximal Cardiovascular Endurance with Executive Function (E) and Memory (F).

Figure 5 presents the findings for age, physical fitness, and average cortical thickness. The total R^2 for the model was 11.8%. Age was the strongest contributor to variance in cortical thickness, with the evidence strongly rejecting the null hypothesis of no association, χ^2 (df = 20) = 72.3, $p < .0001$, and with an associated R^2 of 6.4%. Endurance and grip strength were much smaller contributors to cortical thickness variance, with evidence indistinguishable from no association (see panel A for details). As shown in panel B, average cortical thickness was linearly and negatively associated with age. In a set of models including the full study sample, cortical thickness was added as an additional predictor to the models shown in **Figure 4** panels A and B. This determined whether cortical thickness predicted cognitive variance and further, whether inclusion of cortical thickness as an additional predictor attenuated the effects of physical fitness. As shown in detail in Section 12 of Supplement A, inclusion of cortical thickness had no discernable impact on the results shown in **Figure 4**; this was somewhat anticipated in light of the near-zero correlations involving cortical thickness previously discussed in *Table 2*.

Additional analyses of each of the 68 brain parcels that comprise overall cortical thickness provided very little evidence that either endurance or strength had selective associations with specific cortical regions (see Supplement D). The smallest nominal P values were observed for left and right superior temporal lobes ($p = 0.002$ and 0.005 , respectively); however, a false discovery rate correction (Benjamini & Hochberg, 1995)

Figure 5: Summary of Wald Chi-squared Statistics for Cortical Thickness (A) and Age-Related Differences in Cortical Thickness (B).

to account for the 68 separate outcomes renders these estimates statistically non-significant.

Bivariate Behavioral Genetic Analysis of Monozygotic and Dizygotic Twins

Based on the results from the larger sample, bivariate behavioral genetic models were estimated between EF and endurance, and between memory and endurance. *Table 3* presents the bivariate cross-twin, cross-trait, and cross-twin/cross-trait correlations among monozygotic and dizygotic twins using cognitive and endurance scores adjusted for age and sex. The decomposition of variance and co-variance was done formally in the bivariate Cholesky decomposition twin models described below; however, these correlations provide an initial glimpse of what those models reveal. Most prominently, these correlations show that cross-twin intraclass correlations were uniformly higher in MZ twins compared to DZ twins, suggesting at least some role of heritability in variation in these measures. In contrast, the larger cross-trait and cross-twin/cross-trait correlations in DZ as compared to MZ twins is surprising and might be attributed to sampling error; it also suggests a limited role of heritability in the phenotypic covariation. Cross-twin/cross-trait correlations for the EF-endurance association were nearly as large as the cross-trait correlations for this same association, which would imply that the shared environment largely contributes to the EF-endurance association. In contrast, the weaker cross-twin/cross-trait correlation relative to cross-trait correlation for the memory-endurance association suggests a stronger non-shared environmental contribution with respect to memory-endurance.

Table 3. Cross-Twin, Cross-Trait, and Cross-Twin/Cross-Trait Pearson Correlations

Correlation	MZ	DZ
EF cross-twin	0.45	0.073
Memory cross-twin	0.61	0.39
Endurance cross-twin	0.48	0.41
EF-endurance cross-trait	0.13	0.26
Memory-endurance cross-trait	0.14	0.28
EF-endurance ct/ct	0.14	0.21
Memory-endurance ct/ct	0.072	0.18

Standardized estimates and standard errors for the labelled paths shown in **Figure 2** are provided in *Table 4*. The largest standardized estimates (i.e., >0.60) were associated with the heritability (a11) of cognition (both EF and memory) and non-shared environmental (e11, e22) components of cognition and endurance. The standard errors for these estimates were small relative to the size of the estimate, suggesting good precision in these estimates. The heritability estimate for endurance was moderate (a22 ~ 0.45) and with a somewhat larger standard error (~ 0.20), implying moderate uncertainty in the estimate. The shared environmental estimates (c11, c22) were modest (<0.30) and had large standard errors, thus suggesting large uncertainty with very small to very large associations being compatible with the current data. With respect to cross-loadings, the shared environmental cross-loading (c21) for EF on endurance was fairly large and precisely estimated ($b = 0.51$, $SE = 0.17$); the same cross-loading for memory was somewhat smaller with a relatively large standard error ($b = 0.32$, $SE = 0.44$). All other cross-loadings were small (i.e., <0.20) and had large standard errors relative to the size of the estimate.

Table 4. Standardized Estimates (and Standard Errors) from Bivariate Cholesky Decomposition Models

name	Estimate	Std.Error	Model	Cognition
a11	0.62	0.079	ACE	EF
a21	0.15	0.17	ACE	EF
a22	0.45	0.2	ACE	EF
c11	0.17	0.17	ACE	EF
c21	0.51	0.17	ACE	EF
c22	3.9e-07	0.68	ACE	EF
e11	0.77	0.042	ACE	EF
e21	0.0032	0.056	ACE	EF
e22	0.72	0.041	ACE	EF
a11	0.72	0.13	ACE	Memory
a21	0.043	0.19	ACE	Memory
a22	0.48	0.21	ACE	Memory
c11	0.32	0.27	ACE	Memory
c21	0.32	0.44	ACE	Memory
c22	0.39	0.39	ACE	Memory
e11	0.62	0.036	ACE	Memory
e21	0.11	0.058	ACE	Memory
e22	0.71	0.04	ACE	Memory

The standardized estimates above can be used to quantify the memory and endurance variances and covariances. Further, these can be parsed into A, C, E components (ACE model). For example, cognitive variace is defined as below:

$$Var_{cog} = Var_{Cog_A} + Var_{Cog_C} + Var_{Cog_E}$$

For cognition, each of the variance components is the square of the respective standardized loading For example,

$$Var_{Cog_A} = a_{11}^2$$

For endurance, each of the variance components is the sum of the respective squared cross-loading and the squared endurance-specific standardized loading For example,

$$Var_{Endu_A} = a_{21}^2 + a_{22}^2$$

The component-specific covariance between cognition and endurance is the product of the respective standardized cognition loading and the respective cross-loading. For example,

$$Cov_A = a_{11} \times a_{21}$$

The converted proportions are shown in **Figure 6**. In line with the description of the standardized estimates, panel A shows that cognitive variance could largely be attributed to heritability (A) and non-shared environment (E) sources. Endurance variance was largely attributed to non-shared environment, with the remaining variance roughly equally apportioned to heritability (A) and shared environment (C). Correlations between cognition and endurance were modest at 0.17 for EF and 0.20 for memory (panel B) and roughly $\frac{1}{2}$ the correlation was attributed to shared environment.

Figure 6: Proportion of Variance (panel A) and Correlation (panel B) Attributable to Heritability (“A”), Shared Environment (“C”), or Non-shared Environment (“E”).

Additional Analyses

The inclusion of non-twin full siblings in a more complex ACTwE model suggests that variation in endurance attributed to the shared environment can be attributed roughly to twin-specific shared environmental and more general sibling shared environmental effects. Similarly, the covariation between EF and endurance previously attributed to the shared environment was equally split between twin-specific and sibling-general effects. For covariation between memory and endurance, sibling-general effects appeared to contribute more to the shared environment effects than did twin-specific effects. See Supplement B for complete results, including section 6 for a visual comparison of the ACE and ACTwE models.

Re-analysis of the data using age-adjusted NIH Cognition Toolbox scores shows a very similar pattern of results as described above. Specifically, the two-factor measurement model remained the best fit to the cognitive data, cardiovascular endurance explained more variation in cognition than did grip strength, and the results of the behavioral genetic analyses mirrored those described above. See Supplement C for complete details.

Discussion

The current study found that among a set of socio-economic, demographic, and physical-related variables, age and cardiovascular endurance had the strongest statistical associations with EF and memory. Both aspects of cognition decreased across young adulthood from age 22 to 36 years, but individuals with higher cardiovascular endurance tended to have higher cognitive performance. Because the current study involved a reasonably large sample size and the analysis of endurance and strength, along with several factors that could confound the fitness-cognition association (including basic gait speed and body composition), the current study addresses many of the weaknesses of previous studies that have been smaller and with fewer potential confounds included.

Age, Fitness, Cognition and Cortical Thickness

In comparison to cardiovascular endurance, grip strength had a much smaller and statistically non-significant contribution to cognitive performance, a finding that aligns with a previous analysis of a large cohort of young men (Åberg et al., 2009). The association between endurance and cognition had clear statistical significance, due to the large sample size, but the associations were modest in size, with unique explained variance estimated at 2-3%. This effect was only somewhat larger for EF than with memory. This finding aligns with the conclusions of Ludyga and colleagues (2020), who observed broad, though modest, effects of exercise training on cognition in a meta-analysis of studies including health participants across the lifespan.

Age had the strongest association with cortical thickness, with the results showing a fairly constant rate of cortical thinning across the studied age span. Similarly, a previous study estimated a linear association between age and cortical thinning beginning at age 20 and continuing into late adulthood (Lemaitre et al., 2012), and another study observed a roughly linear rate of cortical thinning from late childhood into early adulthood (Gennatas et al., 2017). The analyses did not reliably detect an association between either measure of physical fitness—grip strength or cardiovascular endurance—with cortical thinning, in contrast to previous studies in children (Chaddock-Heyman et al., 2015; Esteban-Cornejo et al., 2019) and older adults (Williams et al., 2017). The lack of association between cardiovascular endurance and cortical thickness implies that cortical thickness may not mediate the association between cardiovascular endurance and memory and EF in this sample of young adults. This absence of evidence for mediation was further bolstered by (1) the lack of an association between cortical thickness and either measure of cognition and (2) the fact that inclusion of cortical thickness in multivariate models did not attenuate the association of endurance with EF or memory. Further, other aspects of brain structure not studied herein may link physical fitness to cognition in this age range. Indeed, a recent analysis of a subset of the YA-HCP found that white matter structural integrity, as measured by diffusion tensor imaging-based fractional anisotropy, mediates the association between cardiovascular endurance and various measures of cognition (Opel et al., 2019). Another possible outcome for future research is gray matter area, which has been found to be genetically and phenotypically distinct from gray matter thickness (Winkler et al., 2010). Finally, brain function, e.g., as measured by resting-state or task-based functional MRI, is a plausible mediator of fitness-cognition associations (Kronman et al., 2019).

Contrary to expectations, age did not moderate associations with cognition or cortical thickness, suggesting that despite the observed age differences in these outcomes, there was not sufficient evidence to suggest that associations with fitness varied from the early 20s to the mid 30s. The difference to the findings of Stern and colleagues (2019), which motivated this hypothesis, could be explained in part by the much wider age range studied by Stern that extended through middle adulthood. Gender did not moderate these associations either, which is relevant to the ongoing discussion in the literature as to whether women or men gain greater cognitive benefits from exercise training (Barha et al., 2017; Ludyga et al., 2020). Gender and biological sex effects might vary by age, with normal lifespan developmental changes in sex hormone levels being a factor that interplays with these associations (Barha et al., 2017). Therefore, what is observed in young adulthood may not apply at other points in the lifespan.

Heritability, the Environment and Phenotypic Associations Between Endurance and Cognition

The inclusion of genotype-confirmed monozygotic and dizygotic twins allowed for important secondary analyses to estimate heritability and environmental contributors to variance in cardiovascular endurance and

cognition, as well as estimate the degree to which the observed phenotypic association might be driven by shared genetic versus environmental factors that influence fitness and cognition. In many aspects, the results of these analyses align with the estimates reported by Åberg and colleagues in their analysis of young Swedish males enlisted for military service (2009). In both studies, heritability and non-shared environmental factors were estimated to have moderate contributions to cognitive variance, with smaller contributions from the shared environment (i.e., prenatal and postnatal experiences and environments shared by twins). Previous studies have specifically investigated the heritability of EF and have estimated stronger heritability effects in youth (Engelhardt, Briley, Mann, Harden, & Tucker-Drob, 2015) and young adults (Friedman et al., 2008) in comparison to the current study; however, common with the current results, these previous studies also found limited shared environmental effects on EF variance.

With regard to cardiovascular endurance, the current estimate of the heritability effect was somewhat lower than that of previous studies (Åberg et al., 2009; Miyamoto-Mikami et al., 2018), whereas estimates of the shared and of the non-shared environment—which encompasses previous experiences not shared within the sibling pair, differences in the testing experience, and measurement error (Grasby et al., 2017)—were higher comparison to previous research.

Across EF and memory, roughly $\frac{1}{2}$ of the cognition-endurance correlation was attributed to the shared environmental component. In contrast, heritability and non-shared environmental effects varied across EF and memory, and there was large degree of imprecision in the estimates of the cross-paths between cognition and endurance. Thus, the current findings provide scarce evidence for a clear heritability effect, but instead, suggest environmental effects (especially those common to twins) might contribute at least modestly to the endurance-cognition correlation. These shared environmental effects encompass a multitude of possibilities, from shared prenatal exposures to all the postnatal socioeconomic contexts and experiences that impact twin siblings reared together. It would be worthwhile for future research to attempt to pinpoint more precisely the source of shared environmental effects, as has been done in other areas of research (e.g., Briley, Harden, & Tucker-Drob, 2014).

These findings stand somewhat in contrast Åberg and colleagues estimated modest heritability and shared environment contributions to the phenotypic correlation between cardiovascular endurance and cognition (estimates between 5%-15%) in a larger sample containing over 3,000 DZ and 1,000 MZ twin pairs. Åberg and colleagues estimated a large role of the non-shared environment in explain cognition-endurance covariance (roughly 80%). One possibility for the discrepancy between the current study and Åberg and colleagues (2009) is that the tools used to measure endurance and cognition differ in important ways. Whereas Åberg and colleagues relied on broad measures of intelligence and content knowledge (e.g., performance on mathematical and physics problems), the current study had access to more precise measures of cognitive processes and therefore could better differentiate variation more closely aligned with EF and with memory. In contrast, Åberg and colleagues used a more precise measure of endurance using a cycle ergometry test that incorporated measures of power output and heart rate. Another key difference is the inclusion of males and females in the current study versus only males in the study by Åberg and colleagues.

Limitations and Strengths

There are several noteworthy limitations to the current study. Foremost, the cross-sectional design of the study cannot determine whether there is a temporal association between physical fitness and cognition (i.e., changes in physical fitness precede changes in cognition), much less whether these associations reflect causal effects. Important is that although the physical fitness measures are objective, have established psychometric properties, and were chosen following a rigorous selection process (Reuben et al., 2013), there are more precise measures of cardiovascular endurance, including the maximal cycling ergometer test implemented in previous studies (Åberg et al., 2009). Also related to measurement, the initial SEM to characterize the structure of cognition could not estimate cognition more finely—e.g., the subdomains of EF (Engelhardt et al., 2015; Friedman & Miyake, 2017)—to examine whether more specific aspects of EF and of memory are related to physical fitness differently. Finally, the sample size available for the twin analyses was fairly small, and interpretation of the decomposition of the cognition-endurance covariation should be done cautiously, as the precision of many of the estimates from the ACE model was limited. These effects should also be considered in the context that overall phenotypic correlations between fitness and endurance were modest ($r \leq 0.20$).

Strengths of the current study include the use of structural equation modelling of multiple cognitive indicators. This approach has several advantages, including a comparison of different measurement models of cognition in young adulthood (unitary versus separate EF and memory factors) and the minimization of the number of outcomes included in the primary analyses. Additional strengths include the fairly large sample size available for the primary analyses, the high-quality imaging data collected as part of the YA-HCP, and the inclusion of confirmed monozygotic and dizygotic twins to investigate potential heritability and environmental contributions to (co)variation in cognition and physical fitness.

Conclusions

Along with a small number of previous studies, the current study brings attention to age-related differences in cognition and the association between physical fitness and cognitive health in young adulthood. Across young adulthood, higher levels of endurance, but not grip strength, were associated with better cognitive performance, independent of a number of confounding variables. This association appears to be broad, though modest in size, and encompasses aspects of attention, processing speed, executive function, and memory. These results further suggest that the effects were independent of cortical thickness, which suggests that other aspects of brain structure or perhaps brain function might link better endurance to better cognition. Finally, the results point to a moderate degree of heritability in endurance and cognition, but also to a limited role of heritability in the endurance-cognition correlation. Instead, a larger, more precisely estimated, role of the environment was observed, which suggests that the endurance-cognition correlation might be primarily attributed to experiences and environments that impact both endurance and cognition.

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