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Research Article

Hippocampal functional connectivity mediates the association between cardiorespiratory fitness and cognitive function in healthy young adults

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Abstract

Objective: Higher cardiorespiratory fitness (CRF) induces neuroprotective effects in the hippocampus, a key brain region for memory and learning. We investigated the association between CRF and functional connectivity (FC) of the hippocampus in healthy young adults. We also examined the association between hippocampal FC and neurocognitive function. Lastly, we tested whether hippocampal FC mediates the association between 2-Min Walk Test (2MWT) and neurocognitive function. **Methods:** 913 young adults (28.7 ± 3.7 years) from the Human Connectome Project were included in the analyses. The 2MWT performance result was used as a proxy for cardiovascular endurance. Fluid and crystalized composite neurocognitive scores were used to assess cognition. Resting-state functional MRI data were processed to measure hippocampal FC. Linear regression was used to examine the association between 2MWT, hippocampal FC, and neurocognitive outcomes after controlling for age, sex, years of education, body mass index, systolic blood pressure, and gait speed. **Results:** Better 2MWT performance was associated with greater FC between the anterior hippocampus and right posterior cingulate and left middle temporal gyrus. No associations between 2MWT and posterior hippocampal FC, whole hippocampal FC, and caudate FC (control region) were observed. Greater anterior hippocampal FC was associated with better crystalized cognition scores. Lastly, greater FC between the anterior hippocampus and right posterior cingulate mediated the association between better 2MWT scores and higher crystalized cognition scores. **Conclusions:** Anterior hippocampal FC may be one underlying neurophysiological mechanism that promotes the association between 2MWT performance and crystalized composite cognitive function in healthy young adults.

Keywords: cardiorespiratory fitness; 2-Minute Walk Test; hippocampus; functional connectivity; anterior hippocampus; posterior hippocampus; neurocognitive function; physical activity; young adults

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Introduction

It has been well-documented that the hippocampus is a crucial brain area for memory and learning (Anand & Dhikav, 2012). The hippocampus is also involved in other aspects of neurocognitive function including executive control, processing speed, fluid intelligence, path integration, and spatial processing (Leal & Yassa, 2015). Hippocampal structure is particularly susceptible to aging (O'Shea et al., 2016) as well as neurodegenerative diseases such as Alzheimer's disease (Mueller et al., 2010), with evidence of declining hippocampal volume and hippocampal-dependent cognitive abilities (Shi et al., 2009). A body of literature suggests that cardiorespiratory fitness (CRF) elicits neuroprotective effects within the hippocampus (Voss et al., 2019), as evidenced by the association between higher CRF and greater hippocampal volume in older adults (Colcombe et al., 2003; Erickson et al., 2009). Higher CRF was also associated with greater cerebral blood volume in the hippocampus in middle-aged adults (Pereira et al., 2007). Furthermore, higher CRF was associated with better microstructure integrity (i.e., lower mean diffusivity) of the hippocampus in older adults (Tian et al., 2014). While the association between CRF and hippocampal structure and function in older adults has been extensively studied, few studies have examined this relationship in young adults. Understanding the association between CRF and hippocampal integrity in early adulthood is critical to the understanding of how CRF-related effects may accumulate over time and yield long-term benefits in later adulthood. Thus, young adulthood is an important timeframe for adopting exercise participation that may promote sustained brain health throughout life.

In addition to volume, blood flow, and microstructure, there is evidence for an association between CRF and hippocampal functional connectivity (FC). Resting-state functional connectivity (FC) analysis reflects the patterns of functional interaction between

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spatially remote brain regions (Damoiseaux et al., 2006) using the coherence of functional MRI (fMRI) blood oxygenation level-dependent (BOLD) signals (Fox et al., 2005). Stillman et al. (2018) cross-sectionally investigated the association between CRF and hippocampal FC in healthy young adults (20–38 years) (Stillman et al., 2018). A whole-brain analysis was used with bilateral anterior and posterior hippocampus, respectively, as seed regions of interest. Results showed that higher CRF ($\dot{V}O_{2max}$) was associated with stronger FC between the bilateral anterior hippocampus and multiple brain regions including the prefrontal and temporal cortical regions (Stillman et al., 2018). However, Stillman et al. (2018) did not demonstrate an association between hippocampal FC and neurocognitive function. The examination of brain-behavior relationships is key to the interpretation of CRF-related associations with hippocampal FC. Moreover, studies using a larger and well-characterized sample could further clarify the association between CRF and hippocampal FC in young adults.

To address this knowledge gap, we investigated the association between CRF and hippocampal FC using the Human Connectome Project Young Adult dataset. The aims of the present study were to (1) investigate the association between CRF and hippocampal FC in young adults, (2) investigate the association between hippocampal FC and neurocognitive function in young adults, and (3) investigate the mediating role of hippocampal FC in the association between CRF and neurocognitive function in young adults. We hypothesized that (1) greater CRF will be associated with stronger hippocampal FC, (2) greater FC between the hippocampus and other brain regions will be associated with better neurocognitive function, and (3) greater hippocampal FC will mediate the association between higher CRF and better neurocognitive function. As a post hoc analysis, we assessed the sex differences in the association between CRF and hippocampal functional connectivity based on the evidence showing sex-related differences in functional connectivity (Ritchie et al., 2018).

Methods

Participants

The WU-Minn HCP Young Adults 1200 Subject Data Release (https://www.humanconnectome.org/) was used for the present study (Van Essen et al., 2013). Participants with the age range of 22–35 years old were recruited from the Missouri area. Recruitment was administered to reflect the ethnic and racial composition of the United States. A complete list of eligibility criteria was previously reported (Van Essan et al., 2013). Briefly, exclusion criteria included: (1) Significant history of psychiatry disorder, substance abuse, neurological, or cardiovascular disease; (2) Two or more seizures after age 5 or a diagnosis of epilepsy; (3) Any genetic disorder (e.g., cystic fibrosis or sick cell disease); (4) Multiple sclerosis, cerebral palsy, brain tumor or stroke; (5) Moderate or severe claustrophobia. Participants provided written consent at the beginning of their first visit approved by the Institutional Review Board of Washington University. The research was completed in accordance with Helsinki Declaration.

2-Minute Walk Test

We used the 2MWT as a proxy for cardiovascular endurance. The 2MWT was performed as part of the motor domain of the NIH toolbox (Reuben et al., 2013). During the test, participants were instructed to walk as fast as possible for two minutes on a 50-foot course (15.24 m). The raw score was measured in feet and inches as the total distance walked in 2 minutes. Raw scores were then normalized to the entire NIH Toolbox normative sample (≥ 18 years old), regardless of age or any other variable; thus, the scores were normalized to have a mean of 100 with standard deviation of 15, indicating 100 reflects the national average performance and scores of 85 and 115, respectively, reflect performances 1 SD below and above the national average. Higher scores indicate longer walking distance. The 2MWT underwent extensive reliability and validity testing before its implementation into the NIH toolbox, showing good test-retest reliability (ICC > 0.8) and excellent external validity with the 6-minute walk test ($r > 0.96$) (Reuben et al., 2013).

Gait speed measurement

The four-meter gait test, an established and valid measurement of gait speed, was performed. The test was administered as a part of the motor assessment of the NIH toolbox (Reuben et al., 2013) which was adapted from the Short Physical Performance Battery (Guralnik et al., 2000). During the test, participants were instructed to walk 4 meters at their usual pace. Participants completed one practice session before performing two timed 4-meter walking tests; the fastest trial was used for scoring and was expressed as meters per second (m/sec). As there was a significant association between gait speed and 2MWT performance ($r = 0.24$, $p < 0.001$), gait speed was used as a covariate in later analysis to account for variance in cardiovascular endurance that could be attributed to differences in gait speed (Dalgas et al., 2012).

Cognitive performance

On the first day visit, participants completed a neurocognitive test battery using the NIH Toolbox that includes Flanker, Dimensional Change Card Sort, Picture Sequence Memory, List Sorting and Pattern Comparison, Picture Vocabulary, and Reading Recognitions, which took approximately two hours to complete (Gershon et al., 2013). Among the battery that was administered, we used the Fluid Cognition Composite and Crystalized Cognition Composite scores. The Fluid Cognition Composite *Score* was created based on average performance on the Dimensional Change Card Sort Test, Flanker, Picture Sequence Memory, List Sorting, and Pattern Comparison test. The Crystallized Cognition Composite Score consisted of performance on a Picture Vocabulary and Reading Recognition test. Fluid cognition reflects the capacity to process and integrate information, act quickly, and solve novel problems and is less dependent on learning, experience, and education (Stawski et al., 2010). Meanwhile, crystallized cognition is an indicative of the accumulation of learned procedures and knowledge and is more dependent on experience and education (Heaton et al., 2014). Neurocognitive composite scores from the NIH toolbox have demonstrated good test-retest reliability and high discriminant and convergent validity with similar gold-standard composites in healthy young adults (Heaton et al., 2014). Raw neurocognitive composite scores were normalized to the entire NIH Toolbox normative sample (≥ 18 years old) with scores normalized to have a mean of 100 and standard deviation of 15. For example, a score of 100 indicated performance at the national average and a score of 115 or 85, indicating performance 1 SD above or below the national average, respectively. Higher scores indicate higher levels of cognitive functioning.

MRI data acquisition

Whole-brain magnetic resonance imaging (MRI) was conducted using a customized Siemens (Munich, Germany) 3.0 T Skyra MR

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scanner at the Washington University. A 32-channel head coil was used for radio frequency transmission and reception. A high-resolution T1-weighted anatomical image was acquired with gradient echo sequence: field of view = 224 mm, voxel size = 0.7 × 0.7 × 0.7 mm, slice thickness = 0.9 mm, repetition time = 2400 ms, echo time = 2.14 ms, inversion time = 1000 ms, flip angle = 8°, and duration = 7:40 min. Resting-state fMRI data were collected using gradient-echo echo-planar imaging with 2.0 mm isotropic resolution: field of view = 208 × 180 mm, matrix = 104 × 90, slices = 72, repetition time = 720 ms, echo time = 33.1 ms, flip angle = 52°, multi-band factor = 8, 1200 frames. Resting-state fMRI data were acquired in four different runs and each run lasted 14.4 minutes with two runs in one session and two in another session. During the scan, participants were asked to keep their eyes on a bright fixation projected on a dark background. Oblique axial acquisitions alternated between phase encoding in a right-to-left (RL) direction in one run and phase encoding in a left-to-right (LR) direction in the other run within each session (i.e., four different scans for each participant (scan 1: session 1 LR, scan 2: session 1 RL, scan 3: session 2 LR, and scan 4: session 2 RL). The sequence parameter was the same across the four resting-state fMRI scans.

T1 structural image processing and hippocampal volume assessment

T1-weighted anatomical volumes were processed as a part of the HCP preprocessing pipeline using FreeSurfer's (version 5.3.0) automated processing stream (recon-all) for cortical parcellation and subcortical segmentation based on tissue-specific intensities and atlas probabilities (Fischl, 2012). The hippocampal volume was examined to test whether the association between cardiovascular endurance and hippocampal FC was independent of the association between cardiovascular endurance and hippocampal volume. Volumes of the bilateral hippocampi were calculated based on FreeSurfer's anatomical segmentation algorithm (recon-all) (Fischl, 2012). For the linear regression analysis in which we examined the association between 2MWT performance and bilateral hippocampal volume, we included total intracranial volume estimated by FreeSurfer as a covariate to account for sex-related differences in total intracranial volume (Raz et al., 2005; Won et al., 2019).

Functional magnetic resonance imaging data preprocessing

Examination of raw fMRI data was then administered before we discarded five volumes from the beginning of each time series to minimize magnetization disequilibrium (Cox, 1996) using AFNI's 3dTcat function. The motion-corrected functional volumes were then co-registered to FreeSurfer-rendered anatomical images using AFNI's align_epi_anat function and were visually inspected for proper alignment. Next, we used AFNI's single subject processing program (afni_proc.py) for the remaining analyses. Functional data were despiked (3dDespike) and slice-timing wascorrected to the beginning of the TR (3dTshift). Functional volume was registered based on a 6-parameter rigid-body affine transformation calculated using the volume with the minimum outlier fraction as the registration base. The anatomical image and anatomical segmentations (FreeSurfer-processed gray matter, white matter, and ventricular segmentations) were warped to the standard space (AFNI's MNI152_T1_2009c template) using non-linear transformation (3dQwarp), with interpolation to 2.0 mm^3 isotropic voxels. Volumes exceeding 0.2 mm (~0.2° rotation) of uncorrected motion or exceeding 0.05 of outlier fraction threshold were

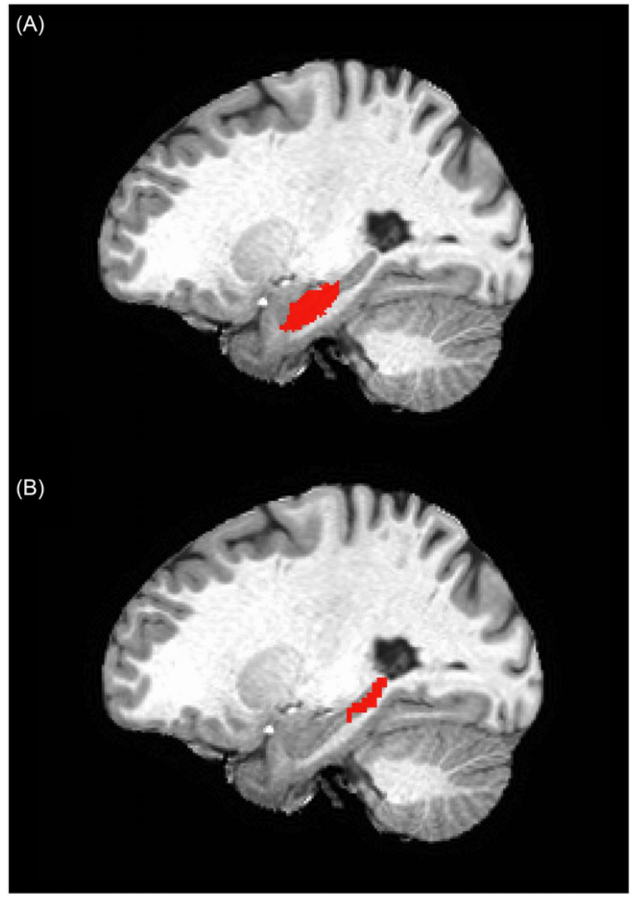

Figure 1. Location of the anterior (Panel A) and posterior (Panel B) seed regions. The seed masks are exhibited on a representative subject's structural image. The whole hippocampal mask was split into anterior and posterior parts based on the center of gravity of the region. The bilateral anterior and posterior hippocampi masks were then combined using AFNI's 3dcalc function, respectively, and were used as primary seeds of interest.

censored from the time series and the resulting time series data were bandpass filtered to retain frequencies between 0.01 and 0.1 Hz using AFNI's 3dDeconvolve function, which was used in subsequent connectivity analyses. Participants were excluded if their maximum framewise displacement (i.e., motion between successive TRs) was greater than 1.0 mm, which was calculated by motion estimates (AFNI's 3dvolreg).

Functional connectivity analysis

We administered a seed-based correlation analysis using the bilateral anterior and posterior hippocampi as *priori* seed regions of interest, based on the previous studies showing preferential effects induced by exercise training on the anterior part of the hippocampus relative to posterior regions (Erickson et al., 2011; Stillman et al., 2018). Left and right hippocampal masks were extracted from each participant's Freesurfer-processed anatomical segmentation that was warped to the standard MNI space (Fischl, 2012). Each of the left and right hippocampal masks was then split into anterior and posterior parts based on the center of gravity of the region (Fig. 1). Using AFNI's 3dcalc function, we then combined the left anterior and right anterior hippocampi as well as left posterior and right posterior hippocampi to create bilateral anterior hippocampi and bilateral posterior hippocampi masks.

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Table 1. Demographics data of the participants

		Total Sample ($n = 913$)
		Mean ± SD
Demographics		
	Age (years)	28.7 ± 3.7
	Female (n,%)	493 (53.9%)
	Education (years)	14.9 ± 1.7
	Body Mass Index (kg/m^2)	26.3 ± 5.1
	Systolic Blood Pressure (mmHg)	123.0 ± 13.7
	Gait Speed (m/s)	1.3 ± 0.1
	2-Minute Walk Test	110.3 ± 11.8
Cognitive Function		
	Fluid Composite Score	115.6 ± 11.6
	Crystalized Composite Score	118.0 ± 9.8
	Early Composite Score	117.6 ± 10.7
	Total Composite Score	122.5 ± 14.5

SD = standard deviation.
2-Minute Walk Test and Cognitive composite scores were normalized across all participants in the study to have a mean of 100 with standard deviation of 15, indicating 100 reflects the national average performance and scores of 85 and 115, respectively, reflect performances 1 SD below and above the national average. Higher scores indicate longer walk distance and higher levels of cognitive function.

These bilateral anterior and posterior hippocampal masks were used as primary seeds of interest. We also evaluated the association between 2MWT and the bilateral whole hippocampus FC using undivided (i.e., whole) hippocampal masks. Bilateral caudate masks (Supplementary Figure 1) were also extracted from the anatomical segmentation, combined to create bilateral caudate mask using the 3dcalc function. Bilateral caudate FC was used as a control seed region to test the specificity of the association between 2MWT and hippocampal FC. The caudate was selected as a control region for the following reasons. First is to check the possibility of replicating the results from Stillman et al. (2018) in which the caudate was used as a control region. Second, the caudate volume significantly mediated the association between cardiovascular endurance and task-switching performance (Verstynen et al., 2012), suggesting the potential mediating role of the caudate FC on the association between cardiovascular endurance and cognition.

Next, from each seed region, the average signal time series were extracted and cross-correlated with all voxels in the brain to isolate a brain FC map for each participant. Finally, correlation coefficients using a Fisher's r-to-z transformation were standardized for group-level analysis. Since four separate resting-state scan data were acquired for each participant, four different correlation coefficients were created for each participant. Thus, we used AFNI's 3dMean function to compute the average across the four correlation coefficients per participant and this averaged correlation coefficient was used for the subsequent analyses.

Gray matter voxel-wise group analysis

Using FreeSurfer-defined gray matter, white matter, and ventricle segmentations, a gray matter mask was created for group-level analysis. The final group mask was an intersection of individual subject masks, such that only those voxels defined as gray matter for all subjects were included. White matter and ventricle segmentations were subtracted from this whole-brain anatomical mask to reduce nuisance physiological artifacts (i.e., signals from ventricles and white matter and the analysis was restricted to voxels within gray matter regions. To assess the association between the 2MWT and hippocampal FC, subject-level z-scored correlation maps were submitted to an AFNI's group-analysis program performing traditional ANOVA- and ANCOVA-style computations (3dMVM). 2MWT performance was entered into the 3dMVM script as a predictor, with covariates including age, sex, years of education, body mass index (BMI), systolic blood pressure (SBP), and gait speed. Family-wise error rate was controlled using AFNI's cluster-size threshold computation program (3dClustSim), with an uncorrected voxel-wise threshold of $p < 0.001$. Defining a FWER-corrected alpha value of 0.05 resulted in a cluster-size threshold of $k \geq 130$ voxels (1040 mm^3).

Statistical analysis

We used the Shaprio-Wilk test to determine normality of demographic information (i.e., age, education, and BMI), 2MWT performance, neurocognitive function performance, SBP, and gait speed. First, we investigated the association between 2MWT performance and neurocognitive function. Linear regression models were used for this analysis and 2MWT performance was added as an independent variable and neurocognitive composite scores including fluid and crystalize scores were, respectively, included as dependent variables. Covariates included age, sex, years of education, BMI, SBP, and gait speed. Next, we investigated the association between hippocampal FC and neurocognitive function. To assess this, average z-scored connectivity within the 2MWT-related hippocampal FC was extracted from subject-level correlation maps. In the linear regression model, hippocampal FC was set as an independent variable and neurocognitive composite scores were, respectively, included as dependent variables after controlling for age, sex, years of education, BMI, SBP, and gait speed. To examine the interaction between sex and 2MWT on hippocampal FC, we extracted the z-score values for the significant clusters for the association between 2MWT and hippocampal FC. Then we used the regression model with the interaction term between 2MWT and sex as an independent variable and hippocampal FC as a dependent variable after adjusting for age, sex, years of education, BMI, SBP, gait speed, and 2MWT score.

Mediation analysis was conducted for the third aim of the study which is to examine whether hippocampal FC mediates (or partially mediates) the association between 2MWT and neurocognitive function. Based on the significant associations that meet the assumption of mediation from the prior linear regression analyses, we conducted a bootstrapped mediation analysis to determine the association between 2MWT (IV; independent variable) and neurocognitive function (DV; dependent variable), indirectly through hippocampal FC (M; mediator). The mediation analysis package within SPSS (v. 26.0, IBM, Armonk, NY) was used for mediation analyses (Hayes, 2013). We used the 95% confidence interval obtained from 5000 bootstrap resamples to explore the indirect mediation effect of hippocampal FC on the association between 2MWT and cognitive function (Preacher & Hayes, 2008). All statistical analyses were performed using SPSS (v. 26.0, IBM, Armonk, NY).

Results

Participants

Among a total of 1206 participants who completed the study protocol, 93 individuals were excluded due to uncollected MRI data, 164 participants were excluded due to missing ≥1 resting-state fMRI scan, and 36 participants were excluded due to MRI data preprocessing errors. Therefore, 913 participants' data

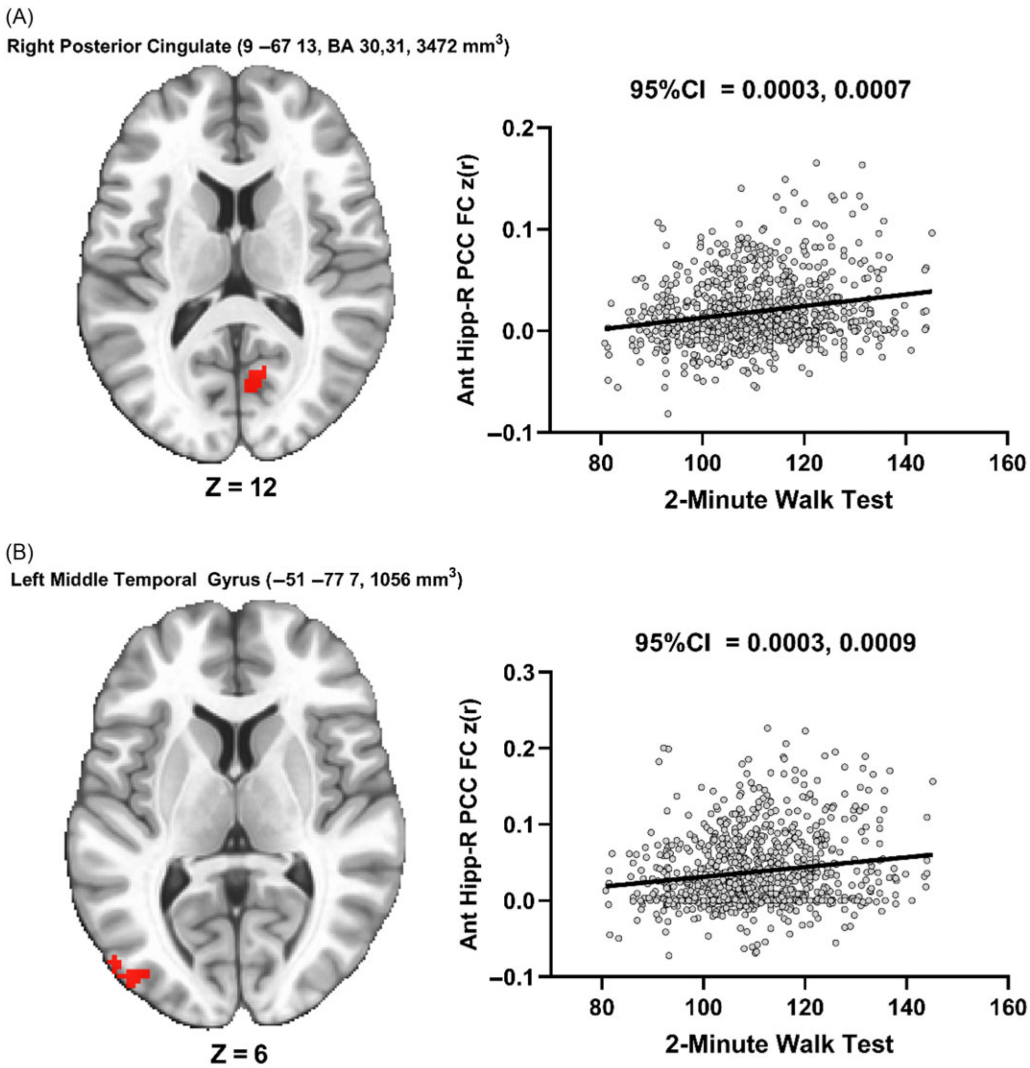

Figure 2. Association between greater 2-Minute Walk Test score and greater functional connectivity between the anterior hippocampal seed and (A) right posterior cingulate and (B) left middle temporal gyrus. 95% confidence interval indicates the association between the 2 Minute Walk Test Score and hippocampal functional connectivity across participants. CI = confidence interval, Ant Hipp = anterior hippocampus, R PCC = right posterior cingulate, FC = functional connectivity.

were included in the current study. Overall, the participants had an average age of 28.7 years, 14.9 years of education, BMI of 26.3 kg/m^2, and SBP of 123 mm Hg (Table 1).

Associations between 2-min walk test and hippocampal functional connectivity

Better 2MWT performance was associated with stronger FC between the anterior hippocampus and brain regions including the right posterior cingulate (MNI 9 -67 13 [LPI], BA 30 and 31, 3472 mm^3 (Fig. 2; Panel A)) and left middle temporal gyrus (MNI -51 -77 7 [LPI], 1056 mm^3 (Fig. 2; Panel B)). We did not find significant associations between 2MWT and posterior and whole hippocampal FC. There were also no significant associations between 2MWT and bilateral caudate FC. Our post hoc analysis of the interaction between sex and 2MWT on hippocampal FC suggests no significant association between sex × 2MWT on the FC between anterior hippocampus and right posterior cingulate ($p = 0.781$) as well as the FC between anterior hippocampus and left middle temporal gyrus ($p = 0.883$).

Associations between 2-min walk test and hippocampal volume

We did not find a significant association between 2MWT performance and bilateral hippocampal volume (t (905) = 1.233, $p = 0.218$, $\beta = 0.036$) after controlling for age, sex, years of education, BMI, SBP, gait speed, and total intracranial volume.

Associations between 2-min walk test and cognitive composite scores

We found that 2MWT performance explained 13.1% of variance in fluid composite (F (7,906) = 18.896, $R^2 = 0.131$, $p < 0.001$) and 29.5% of variance in crystalized composite (F (7,906) = 52.935, $R^2 = 0.295$, $p < 0.001$) scores. Specifically, there were significant positive independent standardized effects (β) of 2MWT on fluid composite (t (906) = 5.201, $p < 0.001$, $\beta = 0.194$) and crystalized composite scores (t (906) = 4.430, $p < 0.001$, $\beta = 0.148$).

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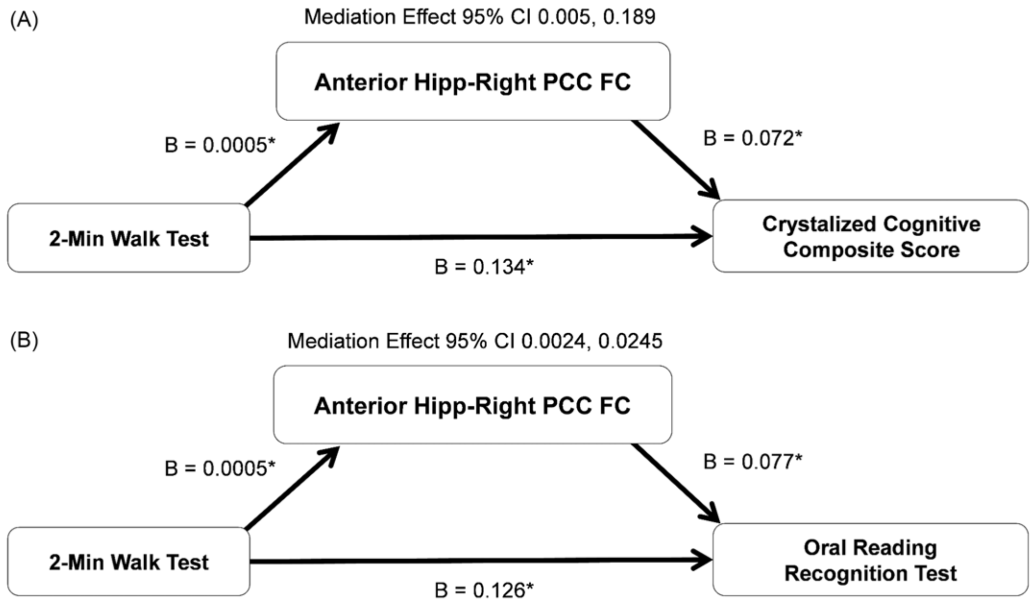

Figure 3. Partial mediating effects of the functional connectivity between the anterior hippocampus and right posterior cingulate in the association between 2-Minute Walk Test performance and crystalized cognitive composite score. Anterior Hipp = anterior hippocampus, R PCC = right posterior cingulated, FC = functional connectivity.

Associations between hippocampal functional connectivity and cognitive composite scores

After controlling for age, sex, education, gait speed, BMI, and SBP, greater FC between the anterior hippocampus and right posterior cingulate was associated with better crystalized composite score (t (906) = 2.482, $p = 0.013$, $\beta = 0.072$). However, there was no statistically significant association between anterior hippocampus connectivity with right posterior cingulate and the fluid composite score (t (906) = 1.738, $p = 0.083$, $\beta = 0.056$). In addition, there were no significant associations between the anterior hippocampus and left middle temporal gyrus FC and the crystalized composite score (t (906) = 1.629, $p = 0.104$, $\beta = 0.048$) or the fluid composite score (t (906) = 0.692, $p = 0.489$, $\beta = 0.023$).

To clarify the association between the anterior hippocampal FC and crystalized composite score, we further examined the association between the anterior hippocampal FC and subdomain neurocognitive scores comprising the crystalized composite score including the picture vocabulary test (sample mean±SD: 117.19 ± 10.71) and oral reading recognition test (sample mean ±SD: 117.03 ± 9.5). Our post hoc analyses suggested that better oral reading recognition test performance was associated with greater FC between the anterior hippocampus and right posterior cingulate (t (899) = 2.588, $p = 0.009$, $\beta = 0.077$). We also found that better oral reading recognition test performance was associated with greater FC between the anterior hippocampus and left middle temporal gyrus (t (899) = 2.805, $p = 0.005$, $\beta = 0.083$). Conversely, there were no significant associations between picture vocabulary test performance and FC between the anterior hippocampus and right posterior cingulate (t (899) = 1.387, $p = 0.166$, $\beta = 0.041$), as well as FC between the anterior hippocampus and left middle temporal gyrus (t (899) = −0.094, $p = 0.925$, $\beta = -0.003$).

Mediation analysis

The presence of significant associations between 2MWT (IV; independent variable) and anterior hippocampi to right posterior cingulate FC (M; mediator), and crystalized cognitive composite scores (DV; dependent variable) suggest that this pathway met the assumption for a mediation analysis. Results of the mediation analysis while controlling for age, sex, years of education, BMI, SBP, and gait speed, revealed a mediating role of the anterior hippocampal FC (Indirect effect 95% CI 0.0005, 0.0189). The direct effect of 2MWT performance on the crystalized composite score was still significant ($\beta = 0.114$, $p < 0.001$) when controlling for anterior hippocampal FC, suggesting a partial mediation effect (Fig. 3; Panel A). Based on the post hoc analysis, results for the association between hippocampal FC and subscores of crystalized cognition, we also tested the mediating role of the FC between the anterior hippocampus and right posterior cingulate on the association between 2MWT and oral reading recognition test performance. Consistent with the crystalized composite score results, our results showed that greater FC between the anterior hippocampus and right posterior cingulate partially mediated the association between better 2MWT performance and better oral reading recognition test performance (Indirect effect 95% CI 0.0024, 0.0245) (Fig. 3; Panel B).

Discussion

The present study examined the association between cardiovascular endurance, hippocampal FC, and neurocognitive function in healthy young adults. Consistent with our hypothesis, higher cardiovascular endurance (i.e., greater 2MWT distance) was associated with greater anterior hippocampal FC. Furthermore, 2MWT-related greater anterior hippocampal FC was associated with better oral reading recognition performance. Conversely, there were no significant associations between 2MWT and posterior hippocampal FC, whole hippocampal FC, and hippocampal volume. Furthermore, the lack of significant associations between 2MWT and caudate FC suggests that hippocampal FC may be particularly associated with cardiovascular endurance. Finally, anterior hippocampal FC partially mediated the association between higher cardiovascular endurance and better-crystalized cognition composite score.

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The finding of the association between higher CRF and greater anterior hippocampal FC is consistent with the report by Stillman and colleagues (2019) of an association between higher $\dot{V}O_{2max}$ and greater anterior hippocampal FC (Stillman et al., 2018). Importantly, higher FC between the anterior hippocampus and left middle temporal gyrus in relation to CRF was observed in both studies. Additionally, increases in FC between the anterior hippocampus and right posterior cingulate were found in response to 12 weeks of aerobic exercise training in older adults with mild cognitive impairment (MCI) (Won et al., 2021), which also supports the present finding of the association between the 2MWT and higher FC between the anterior hippocampus and right posterior cingulate. Of note, the posterior cingulate is a key region of the default mode network (Buckner et al., 2008) and both the hippocampus and default mode network are particularly sensitive to the neuroprotective effects induced by CRF (Voss et al., 2019), which corroborates our finding. Our finding is also in line with previous cross-sectional studies showing a stronger relationship between CRF and anterior hippocampus compared to posterior hippocampus (Chaddock-Heyman et al., 2015; Erickson et al., 2009; Killgore et al., 2013). Importantly, the present study extends our understanding of the association between cardiovascular endurance and anterior portion of the hippocampus by utilizing a large and well-characterized sample of healthy young adults ($n = 913$). In addition, the lack of a significant interaction between sex and 2MWT on anterior hippocampal FC suggests that the associations between cardiovascular endurance and hippocampal FC are similar in young males and females.

We did not find any significant associations between 2MWT and posterior hippocampal FC. Previous studies have reported an association between higher $\dot{V}O_{2max}$ and greater posterior hippocampal FC in young adults (Stillman et al., 2018) and an exercise training-related increase in posterior hippocampal FC among older adults with MCI (Won et al., 2021). The conflicting results may be derived from the measurement of fitness (2MWT vs maximal exercise test/aerobic exercise training) and sample size ($\geq$ 900 vs $\leq$ 50). Interestingly, we did not find any significant associations between 2MWT and connectivity when the fMRI BOLD signals from whole hippocampus were utilized, further suggesting that the association between 2MWT and hippocampal connectivity may be specific to the anterior portion of the hippocampus. We also did not observe the association between 2MWT and hippocampal volume or caudate FC, which further strengthens the specific association between 2MWT and anterior hippocampal FC. Our results of specific association between 2MWT and anterior hippocampal FC are in line with a previous finding showing that hippocampal FC was dominant in the anterior hippocampus in relation to CRF among young adults (ages 17–30) (Stillman et al., 2018). Also, our results are consistent with previous exercise studies suggesting the effects of ET on the anterior hippocampal volume (Erickson et al., 2011). Importantly, Erickson et al. (2011) found that exercise-induced increases in brain-derived neurotrophic factor were selectively associated with the changes in anterior hippocampal volume resulting from aerobic exercise, which may explain the specific association between 2MWT and anterior hippocampal FC found in the present study.

Regarding the association between hippocampal FC and neurocognitive function, the present study is consistent with several intervention findings. For example, increased hippocampal FC corresponded to improvements in Wechsler Memory Scale-Chinese Version performance after a 12-week Tai Chi Chuan and Badunjin training in older adults (Tao et al., 2016). We have previously reported that increased anterior hippocampal FC after a 12-week walking exercise training intervention occurred in concert with enhanced logical memory performance in older adults with MCI (Won et al., 2021). In young adults, there has been one report of an association between higher $\dot{V}O_{2max}$ and greater hippocampal FC (Stillman et al., 2018), but the association between hippocampal FC and neurocognitive function remained unexplored. Addressing this gap in knowledge and extending previous findings in older adults, the present study confirms an association between greater anterior hippocampal FC and better-crystalized cognition in young adults. Further, our post hoc analysis suggests the association between hippocampal FC and crystalized cognition was specific to the oral reading recognition task.

Crystalized cognition refers to the ability to utilize previously acquired skills and knowledge (Horn, 1967). In the present study, the crystalized cognition score was composed of performance on the oral reading recognition task (i.e., reading and pronouncing words as accurately as possible) and the picture vocabulary test (i.e., matching auditorily presented words to pictures) from the NIH Cognitive Test Battery Toolbox (Gershon et al., 2013). Indeed, the oral reading recognition task is centered on assessing language ability; therefore, the test is not designed to directly measure hippocampus-dependent function such as learning and memory. Nevertheless, performance on the oral reading recognition task requires recalling stored knowledge regarding vocabulary cues, which indirectly demands involvement of hippocampal networks (Hoscheidt et al., 2010). Moreover, it has been reported that the hippocampus engages in recognition (Brown & Aggleton, 2001) and contributes to language processing (Piai et al., 2016). Also, the posterior cingulate is part of the large-scale network related to language (Wylie & Regner, 2014). Collectively, this evidence corroborates the association between oral reading recognition test performance and FC between anterior hippocampus and posterior cingulate found in the present study.

Conversely, we did not find significant associations between the anterior hippocampus FC and fluid neurocognitive function. A previous study found an association between smaller bilateral hippocampal volume and worse fluid neurocognitive function, while no significant associations were found between hippocampal volume and crystalized neurocognitive function in adults aged 43–85 years (O'Shea et al., 2016). However, we have also recently reported in this same sample that 2MWT performance was associated with lower cortical and subcortical neurite density, including within the hippocampus and cingulate cortex (Callow et al., 2022). Furthermore, this lower cortical and subcortical neurite density was associated with better crystalized neurocognitive function. Taken together with the current study, these findings suggest that cardiovascular endurance may lead to better-crystallized cognition through the pruning of synapses and dendrites and the development of more efficient network connectivity. Some of the discrepancy between previous findings and the present study might be due to the different modalities of MRI measures (volumetric and microstructural assessment vs resting-state fMRI FC), and the mean age of the participants (71.6 years vs 28.7 years). In addition, the association between anterior hippocampus and right posterior cingulate FC and fluid composite score approached statistical significance ($p = 0.083$), partially supporting previous work that showed a positive association between hippocampal volume and fluid neurocognitive function (O'Shea et al., 2016). Given these inconsistencies in findings, more evidence is needed in regard to the association between hippocampal structure and function and composite cognitive function scores derived from the NIH Toolbox Cognitive Test Battery.

Potential mechanisms

Although the present study was not designed to fully elucidate the underlying mechanisms, there are several speculative neurophysiological mechanisms underpinning the associations between cardiovascular endurance and hippocampal FC. In rodents, for example, both voluntary and forced running are associated with increased neurogenesis within the dentate gyrus of the hippocampus in both males and females (Vivar & van Praag, 2017), which may contribute to the maintenance of synaptic density (Voss et al., 2019). Exercise is also associated with enhanced hippocampal mitochondrial function leading to synaptogenesis and dendritic complexity (Steib et al., 2014). In humans, it has been suggested that exercise-related increases in hippocampal volume may occur with increased resting metabolic state or vascular density (Kleemeyer et al., 2016), and we have previously shown that higher cardiovascular endurance is related to more efficient cortical and hippocampal neurite density in healthy young adults (Callow et al., 2022). Collectively, these exercise or CRF-related adaptations at the cellular, molecular, metabolic, and vascular level may facilitate construction of a stronger neural scaffolding (Reuter-Lorenz & Park, 2014) and in turn, stronger functional network of the hippocampus and associated improvements in neurocognitive function. The precise mechanism underpinning the preferential relationship between anterior hippocampus and CRF remains inconclusive. It has been reported that the anterior region of the hippocampus shows greater evidence of neuroplasticity in response to various manipulations. For example, the anterior hippocampus is more influenced by environmental and biological processes (e.g., stress and depression) (Carmichael et al., 2012; De Flores et al., 2015). Also, neurogenesis within the anterior hippocampus is more sensitive to pharmacological agents (Tanti & Belzung, 2013). Therefore, the anterior hippocampus might be more sensitive to structural and functional changes associated with exercise and cardiovascular endurance. Animal studies are needed to better understand how and why exercise may have a greater impact on the anterior part of the hippocampus.

Strengths and limitations

There are three major strengths of the present study. First, the present study used a large and well-characterized sample of young and healthy individuals ($n = 913$). The large sample size is particularly advantageous given that several previous studies in young adults observed null effects likely due to a lack of statistical power (Déry et al., 2013; Hayes et al., 2015, 2016; Herting & Nagel, 2012). Moreover, a recent study suggests that with thousands of participants, replication rates were improved and effect size inflation decreased, highlighting the importance of using large sample sizes (Marek et al., 2022). Second, the present study employed a comprehensive neurocognitive battery that robustly tested a wide range of neurocognitive domains using the NIH toolbox. Third, we utilized the HCP's high-quality resting-state fMRI data. Nevertheless, the cross-sectional design limits the interpretation of the directionality of the associations. Longitudinal and interventional findings will be necessary to clarify the association between CRF and hippocampal FC in young adults. Second, 2MWT was used as a proxy for cardiovascular endurance. 2MWT results demonstrated good test-retest reliability (ICC > 0.8) and excellent external validity with the 6-min walk test ($r > 0.96$), which demonstrated significant associations between brain volume and cognitive function (Makizako et al., 2013). Additionally, to overcome the limitation of using 2MWT, we administered robust statistical adjustments by controlling for demographic (age, sex, and years of education) and other variables that may confound health and 2MWT performance (SBP, BMI, and gait speed) in the regression model assessing the associations between 2MWT, hippocampal FC, and neurocognitive function. Despite these adjustments, 2MWT performance, while clearly associated with fitness, does not perfectly reflect a gold-standard measure of CRF. Thus, future investigations should use direct measures of CRF when plausible (e.g., measure oxygen consumption during a maximal or sub-maximal graded exercise test).

Conclusions

The present study extends the existing literature regarding the association between 2MWT performance and hippocampal function, with evidence of a mediating role of anterior hippocampal FC on the positive association between cardiovascular endurance and crystalized neurocognitive function in healthy young adults. We did not find any significant associations between 2MWT performance and hippocampal volume, suggesting that the association between cardiovascular endurance and cognition may be specific to neural connectivity of the hippocampal network in healthy young adults. Also, there were no significant associations between 2MWT performance and caudate FC, further supporting a degree of specificity for the association between cardiovascular endurance and hippocampal connectivity. Future studies should employ longitudinal cross-sectional designs across the lifespan to better elucidate the long-term impacts of the interactions between cardiovascular endurance, hippocampal connectivity, and neurocognitive function.

Supplementary material. For supplementary material accompanying this paper visit https://doi.org/10.1017/S1355617723000498

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