Received: 25 January 2023 | Revised: 25 September 2023 | Accepted: 26 September 2023

DOI: 10.1111/psyp.14469

PSYCHOPHYSIOLOGY SPR WILEY

ORIGINAL ARTICLE

Data-driven MRI analysis reveals fitness-related functional change in default mode network and cognition following an exercise intervention

Katherine M. Lloyd[1] | **Timothy P. Morris**[1] | **Sheeba Anteraper**[2] | **Michelle Voss**[3] | **Alfonso Nieto-Castanon**[4] | **Susan Whitfield-Gabrieli**[1] | **Jason Fanning**[5] | **Neha Gothe**[6] | **Elizabeth A. Salerno**[7] | **Kirk I. Erickson**[8,9,10] | **Charles H. Hillman**[1,11] | **Edward McAuley**[6] | **Arthur F. Kramer**[1,6]

[1]Northeastern University, Boston, Massachusetts, USA
[2]Carle Illinois Advanced Imaging Center, Urbana, Illinois, USA
[3]University of Iowa, Iowa City, Iowa, USA
[4]Boston University, Boston, Massachusetts, USA
[5]Wake Forest University, Winston-Salem, North Carolina, USA
[6]University of Illinois, Urbana, Illinois, USA
[7]Washington University in St. Louis, St. Louis, Missouri, USA
[8]University of Pittsburgh, Pittsburgh, Pennsylvania, USA
[9]PROFITH "PROmoting FITness and Health Through Physical Activity" Research Group, University of Granada, Granada, Spain
[10]AdventHealth Research Institute, Neuroscience Institute, Orlando, Florida, USA
[11]Department of Physical Therapy, Movement, and Rehabilitation Sciences, Northeastern University, Boston, Massachusetts, USA

Correspondence
Katherine M. Lloyd, Department of Psychology, Northeastern University, 675 ISEC, 805 Columbus Ave, Boston, MA 02120, USA.
Email: mcdonald.kath@northeastern.edu

Funding information
Center for Nutrition, Learning, and Memory at University of Illinois, Grant/Award Number: C4712; National Institute on Aging, Grant/Award Number: R37 AG025667

Abstract

Previous research has indicated that cardiorespiratory fitness (CRF) is structurally and functionally neuroprotective in older adults. However, questions remain regarding the mechanistic role of CRF on cognitive and brain health. The purposes of this study were to investigate if higher pre-intervention CRF was associated with greater change in functional brain connectivity during an exercise intervention and to determine if the magnitude of change in connectivity was related to better post-intervention cognitive performance. The sample included low-active older adults ($n = 139$) who completed a 6-month exercise intervention and underwent neuropsychological testing, functional neuroimaging, and CRF testing before and after the intervention. A data-driven multi-voxel pattern analysis was performed on resting-state MRI scans to determine changes in whole-brain patterns of connectivity from pre- to post-intervention as a function of pre-intervention CRF. Results revealed a positive correlation between pre-intervention CRF and changes in functional connectivity in the precentral gyrus. Using the precentral

---

https://doi.org/10.1111/psyp.14469

gyrus as a seed, analyses indicated that CRF-related connectivity changes within the precentral gyrus were derived from increased correlation strength within clusters located in the Dorsal Attention Network (DAN) and increased anti-correlation strength within clusters located in the Default Mode Network (DMN). Exploratory analysis demonstrated that connectivity change between the precentral gyrus seed and DMN clusters were associated with improved post-intervention performance on perceptual speed tasks. These findings suggest that in a sample of low-active and mostly lower-fit older adults, even subtle individual differences in CRF may influence the relationship between functional connectivity and aspects of cognition following a 6-month exercise intervention.

KEYWORDS

cardiorespiratory fitness, cognition, default mode network, individual differences

1 | INTRODUCTION

As global populations age, effective methods for maintaining, enhancing, and predicting cognitive and brain health during the later stages of the lifespan are needed. Normal aging can include memory loss, slowed processing speed, and decreased executive function (Anderson & Craik, 2017; Deary et al., 2009). However, regular physical activity (PA) is considered to be neuroprotective as circulatory and respiratory systems adapt and build endurance over time, which might have downstream effects on brain health outcomes. The amount of adaptation is dependent upon an individual's basal cardiorespiratory fitness (CRF) level, as well as the type, intensity, duration, and frequency of their exercise exposure (Wilmore & Costill, 1994). Some individuals are susceptible to significant improvements in CRF through exercise intervention, while others who experience the same intervention exposure demonstrate less meaningful changes (Bouchard et al., 1997). The reason for these individual differences is likely related to the complex genetic, behavioral, and environmental factors that account for the physiological effects of exercise on CRF which may account for as much as half of the variance in individual differences in CRF changes and sensitivity to training (Bouchard et al., 2011). Unfortunately, these individual differences are often overlooked in studies that investigate associations between CRF or exercise interventions with brain structure and function.

The physiological brain mechanisms that underlie the relationship between CRF and cognition in older adulthood remain somewhat elusive, but there are several hypotheses. One hypothesis is that higher CRF allows for better oxygen transport and metabolism, which enables better neurotransmitter function and helps reduce neuroinflammation (Davenport et al., 2012). Another hypothesis suggests that higher CRF may aid in down-regulation of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) or up-regulation of the excitatory neurotransmitter glutamate, and contribute to changes in cortical excitability and neuroplasticity, which has been observed in the motor cortex using transcranial magnetic stimulation following exercise (Mellow et al., 2020). Or, it could depend on distinct differences in brain morphology, which is sensitive to higher CRF (Colcombe et al., 2003; Erickson et al., 2009; Gordon et al., 2008; Szabo et al., 2011) and has been shown to mediate aspects of cognition (Erickson et al., 2009; Weinstein et al., 2012). Lastly, higher CRF may have aerobic benefits such as lowering high blood pressure and damage in vessels and capillaries in and around the brain that supply energy for neuronal processing (Gauthier et al., 2015; Tarumi et al., 2013). Resting-state functional connectivity captured via functional magnetic resonance imaging (fMRI) is a useful neurophysiological tool for investigating aerobic and neuronal relationships, as it measures local fluctuations of blood oxygenation as a direct consequence of neurotransmitter action and neuronal signaling (Matthews & Jezzard, 2004).

Resting-state functional connectivity is thought to represent core brain processes and is correlated with age-related decline in brain function (Andrews-Hanna, 2012; Dennis & Thompson, 2014; Tomasi & Volkow, 2012). CRF has a direct impact on the very networks most sensitive to age-related decline (Voss et al., 2016). One hypothesis for this is that higher CRF might prime neural networks for greater exercise-based plasticity, since higher CRF has previously been associated with higher levels of nerve growth factors, synaptogenesis, and angiogenesis (Voss et al., 2013). Most prominently in the literature, age-related changes in functional connectivity have been observed in the Default Mode Network (DMN) at rest, a network that reflects the the brain's intrinsic activity (Damoiseaux et al., 2008; Hafkemeijer et al., 2012; Tomasi

& Volkow, 2012), Specifically, the DMN has shown a reduction in density and strength as a result of normal and pathological aging (Hafkemeijer et al., 2012). Importantly, functional connectivity in the DMN has been shown to mediate the relationship between CRF and performance on the Wisconsin Card Sorting Task, a measure of executive function (Voss et al., 2010), further proving the importance of CRF on connectivity and cognition in older adulthood.

The current study was a secondary analysis of data from the Fit and Active Seniors Trial (https://clinicaltrials.gov/ct2/show/NCT01472744) to investigate whether individual differences in baseline CRF would change the intervention's effect on fMRI and cognitive outcomes. We use a data-driven approach to analyze the entire voxel-to-voxel human connectome to determine whether individual differences in pre-intervention CRF were related to change in functional connectivity patterns following an exercise intervention. Compared to ROI-to-ROI or seed-to-voxel analysis, MVPA is a unbiased data-driven approach to test for individual differences in the voxel-to-voxel patterns of functional connectivity (Nieto-Castanon, 2022). We hypothesized that higher pre-intervention CRF, as a result of the multitude of brain benefits documented by exercise and fitness in animal and human literature (Voss et al., 2013), would be associated with greater changes in resting-state functional connectivity in the DMN following an exercise intervention, which, in turn, would be related to better performance on cognitive tasks post-intervention.

It is important to know if some participants are going to benefit more from an exercise intervention based on baseline characteristics such as CRF. In addition, by understanding how individual differences in CRF are related to functional connectivity and cognition, we can potentially identify a threshold or range of CRF that is needed to maximize and maintain cognitive performance through plasticity nurtured by lifestyle, as well as predict which individuals would be most likely to receive cognitive benefits from an exercise intervention. Ultimately, such an understanding could promote health behaviors and interventions, particularly engagement in physical activities that sustain improvements in CRF to best increase the chance of protection against age-related cognitive decline.

2 | METHOD

2.1 | Participants

One thousand one hundred nineteen low-active, healthy older adults were screened for eligibility from the greater East-Central Illinois region under the Fit & Active Seniors Trial. Two hundred forty-seven participants met the following criteria: (1) between the ages of 60 and 79 years old; (2) able to complete a VO_2 max test without cardiac abnormality; (3) obtained physician's consent to participate in a graded maximal exercise test without exacerbating pre-existing conditions; (4) scored >21 on the Telephone Interview of Cognitive Status questionnaire (de Jager et al., 2003); (5) scored <10 on the Geriatric Depression Scale (Yesavage, 1988); (6) had normal or corrected-to-normal vision and no diagnosis of colorblindness; (7) had no presence of medical implants, devices, or metallic bodies that could interfere with the MRI; (8) no past history of brain surgeries that involved removing tissue; (9) no past history of stroke or transient ischemic attack; (10) right-handed; (11) fluent in English; (12) low-active, defined as participating in no more than 2 days/week of 30+ min of moderate PA over the previous 6 months; and (13) planned to remain in the local area for the duration of their 6-month participation, and eligible to be randomized into the trial. Participants who successfully met the inclusion criteria were asked to sign informed consent and medical record release forms. Participants had to further pass a mock MRI experience and the Mini-Mental State Examination (score ≥ 23). Those who were claustrophobic or did not meet baseline cognitive requirements were excluded from further participation. For the current analysis, 95 participants were further excluded because they attended less than 50% of the intervention sessions or withdrew from the study, and 13 additional participants were excluded for having poor-quality MRI data (as defined as having >40 invalid scans; Van Dijk et al., 2010; i.e., outliers identified by the "ART" Toolbox described below). In total, 139 participants (71.9% female) were included in this analysis. All participants provided informed consent and the University of Illinois Institutional Review Board approved all procedures included in the study. Further testing included assessments that compared the physical, psychological, and mental status in adults before and after exercise interventions, and participants received $10/h ($20/h for MRI and CRF testing) as remuneration for their participation.

2.2 | Procedure

All participants completed a physician-supervised graded maximal exercise, a cognitive neuropsychological evaluation, and MRI and fMRI protocols before and after a 6-month exercise program. After baseline testing, participants were randomized into one of four exercise programs using a computerized data management system. Randomization ensured that each participant had an equal chance of being in any of the four intervention groups. All groups attended 1-h exercise sessions three times a week for 6 months and were supervised by trained research staff, which consisted of exercise specialists, dance instructors, and undergraduate volunteers. Across all four groups, the intervention was designed to be progressive in nature such that the intensity increased within and across months. Following each session, participants were asked to fill out a log that tracked adherence, perceived exertion, and enjoyment levels. The walking groups also reported heart rates and steps at the end of each session. Group descriptions are below:

1. The walking group ($n=28$) participated in brisk walking at a target intensity of 50%–60% of maximal heart rate based on the graded maximal exercise test for the first 6 weeks, then 60%–75% thereafter. Heart rate and perceived exertion were collected frequently throughout the intervention to ensure that the intensity was maintained. All sessions were conducted at the University of Illinois campus on an indoor track.
2. The walking + nutritional supplement group ($n=31$) engaged in the same criteria as the walking group, described above. However, they also consumed a daily milk-based nutritional supplement drink by Abbott Nutrition that contained beta-alanine, which has antioxidant and anti-inflammatory additives thought to promote lean muscle mass (Zoeller et al., 2007).
3. The dancing group ($n=40$) learned choreographed dance routines over the 6-month intervention. The dance routines were designed to be cognitively challenging and socially engaging. Each routine required partnered dancing, with the expectation that each participant learn both the leading and following roles, regardless of their own gender. Different genres of music were played, including ballroom, square-dancing, contra, line-dancing, folk, etc.
4. The stretching and toning group ($n=40$) engaged in 10–12 flexibility and balance activities per session using exercise bands that targeted improvements in strength and balance of all major muscle groups. Repetitions and sets increased within each month, and exercises progressed within and across months. This intervention was designed to be the active control group.

2.2.1 | Cardiorespiratory fitness testing

Maximal oxygen consumption (i.e., VO_2 max) was measured in milliliters of oxygen per minute adjusted for total body mass expressed in kilograms (mL/kg/min). The protocol involved exercising at a self-selected brisk walking pace with increasing grade increments of 2%–3% every 2 min (Balke & Ware, 1959). Oxygen uptake was measured by expired air samples taken every 30-s until peak VO_2 the maximum value during the treadmill test, was captured. Test termination was determined by symptom limitation, voluntary exhaustion, and/or attainment of a VO_2 max. A histogram illustrating frequency distribution of pre-intervention CRF is included in Materials S1. Additional functional fitness measures, self-reported PA, and associations with VO_2 peak are also included in Materials S1.

2.2.2 | Neuropsychological testing

Neuropsychological testing lasted 2 h before and after the 6-month exercise intervention. Assessments were performed using both computerized and paper-and-pencil tests and consisted of tasks from the Virginia Cognitive Aging Project (Salthouse & Ferrer-Caja, 2003) and the Spatial Working Memory task (Erickson et al., 2011) battery. A brief description of each test in the battery, the measure used for analysis, and raw score performance descriptive statistics are included in Materials S1.

Individual cognitive tasks were grouped together into four main cognitive domains—fluid intelligence, perceptual speed, vocabulary, and episodic memory—via a Principal Component Analysis (PCA) with Varimax rotation and Kaiser normalization on pre-intervention data. The components were kept consistent for post-intervention data, and *Z*-scores of each task within the component were averaged together to create a cognitive domain composite score. Tasks with cross-loadings of .4 or higher were not included in the composite scores (Letter Set and Shipley Abstraction; Costello & Osborne, 2005). Table 1 demonstrates the component loadings and organization of tasks into cognitive domains. Based on the tasks associated with each component, Component 1 represented Fluid Reasoning, Component 2 represented Vocabulary, Component 3 represented Perceptual Speed, and Component 4 represented Episodic Memory.

2.2.3 | MRI acquisition

An MRI session was conducted before and after the 6-month exercise intervention. All images were acquired during a single session on a 3T Siemens Trio Tim system with a 12-channel head coil. The anatomical scan consisted of a high-resolution T1-weighted MPRAGE image (GRAPPA acceleration factor 2, voxel-size $= 0.9 \times 0.9 \times 0.9\,\mathrm{mm}^3$, TR = 1900 ms, TI = 900 ms, TE = 2.32 ms, flip angle = 9°, FoV = 230 mm). The resting state T2*-weighted images were acquired with a fast echo-planar imaging (EPI) sequence with BOLD contrast (6 min, TR = 2 s, TE = 25 ms,

TABLE 1 Cognitive battery component loadings from Principal Component Analysis (PCA).

	Component			
	1	**2**	**3**	**4**
Spatial Relations	**.844**	.157	.173	.018
Paper Folding	**.732**	.213	.062	.070
Form Boards	**.714**	.172	.229	.017
Matrix Reasoning	**.608**	.370	.246	.227
Task Switching	**.543**	−.250	.001	.374
Letter Set	.442	.417	.426	.044
Word Vocabulary	.044	**.856**	.100	.240
Synonym/Antonym	.159	**.810**	.006	.278
Picture Vocabulary	.324	**.746**	.023	.120
Shipley Abstraction	.480	.519	.402	.061
Letter Comparison	.030	.158	**.842**	.105
Digit-Symbol	.093	−.001	**.827**	.221
Pattern Comparison	.208	.116	**.772**	−.022
Spatial Working Memory	.177	−.043	**.515**	.134
Word Recall	−.103	.288	.162	**.815**
Paired Associations	.157	.118	.181	**.775**
Logical Memory	.236	.315	.098	**.722**

Note: Varimax with Kaiser normalization used for rotation method. Rotation converged in seven iterations. Shading signifies component groupings.

flip angle = 80°, 3.4 × 3.4 mm^2 in-plane resolution, whereas 35 4 mm-thick slices acquired in ascending order with no slice gap, GRAPPA acceleration factor 2).

2.2.4 | MRI preprocessing

Pre-processing was completed using CONN Toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012) (version 19.c) and MATLAB (The MathWorks Inc, Natick, MA, USA; R2018b). The CONN default pipeline included realignment and unwarping (motion distortion also addressed in this stage), slice time correction, outlier identification (framewise displacement >0.9 mm or global BOLD signal changes above five *SD*s), segmentation and normalization into standard Montreal Neurologic Space (MNI) space, and smoothing (6-mm kernel) was applied (Whitfield-Gabrieli & Nieto-Castanon, 2012). For outlier detection, CONN Toolbox used integrated CompCor method (Behzadi et al., 2007), which modeled noise as a voxel-specific linear combination of noise sources and removed cardiac and respiratory effects and subject-specific motion and outlier artifacts (Whitfield-Gabrieli & Nieto-Castanon, 2012). In addition, a temporal band-pass filter (0.008–0.09) was applied. CONN Toolbox also provided integrated artifact detection software called "ART" (www.nitrc.org/projects/artifact_detect). The software created a matrix of outliers that were entered as first-level covariates in CONN. For each voxel, a linear regression was performed to remove the effects of the artifacts from the BOLD time series by assessing the noise from white matter and cerebrospinal fluid, motion parameters and outliers, and constant and first-order linear session effects.

2.3 | Statistical analysis

Statistical procedures were carried out using a combination of SPSS (version 25) and RStudio (version 1.4.1717). The alpha level was set at .05. Chi-squared tests of independence and one-way ANOVAs were performed on demographic data to investigate if there were statistical differences between intervention groups based on race, sex, age, and pre-intervention BMI. Similarly, we performed chi-squared tests of independence and *t* tests to ensure demographic characteristics did not differ from participants who completed the study compared to participants who did not complete the study ($n = 108$). We performed one-way ANOVAs and a linear regression to investigate if sex or age was related to pre-intervention fitness. Lastly, we also performed a one-way ANOVA to determine if pre-intervention CRF differed between groups at baseline.

Given the multitude of approaches to analyze resting state functional connectivity data, we chose to use MVPA as a data-driven approach to reduce researcher degrees of freedom. MVPA has demonstrated significant utility in uncovering associations between lifestyle factors and whole-brain patterns of connectivity in older adults (Carp et al., 2011; Morris et al., 2021). MVPA takes each voxel in the brain mask and computes the functional connectivity between that voxel and every other voxel in the brain for each subject individually. Then for that seed voxel, all connectivity maps across subjects are concatenated and further characterized by a lower dimensional eigenpattern score using a singular value decomposition factorization of the connectivity matrix (similar to principal component analysis). This eigenpattern score was then entered into a group-level general linear model to test the null hypothesis that the correlation between pre intervention CRF and change in connectivity pre to post, at this voxel, does not differ from zero. This procedure was then repeated for every voxel in the brain mask sequentially constructing a statistical parametric map characterizing the results of this model across the entire brain. To test our hypothesis across the entire brain, the resulting connectivity maps were corrected for multiple comparisons using traditional nonparametric cluster level inferences (height-level statistical threshold of $p < .001$, cluster threshold of $p < .05$, family-wise error [FWE]-corrected). This approach allowed us to make statistical inferences about the patterns of functional connectivity between any suprathreshold clusters and the rest of the brain. The resultant connectivity pattern represented the correlations between baseline CRF and pre- to post-intervention changes in whole-brain resting-state functional connectivity. To further characterize the patterns of functional connectivity we used the resulting suprathreshold cluster as a seed in a seed-to-voxel analysis. This test was a post-hoc estimate and contains a certain amount of bias yet is considered important to help better elucidate interpretations and build future hypotheses (Nieto-Castanon, 2022). A detailed methodology is provided in a previous publication (Nieto-Castanon, 2022). All results in this study were examined in CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012) using the default pipeline and standard settings for cluster-based inferences based on Gaussian Random Field Theory (Worsley et al., 1996). In all functional connectivity analyses, we controlled for age, sex, mean motion (framewise displacement), and intervention group (Arnold Anteraper et al., 2019).

Because the resultant connectivity pattern from the second level post-hoc analysis fell within two independent resting state functional networks (DMN and DAN—see Section 3), we averaged together their connectivity values separately for each network to create compositive network scores to improve their interpretability and for further exploratory analysis with cognitive function. Accounting for age and sex in the model, linear regressions were performed between CRF and performance on the four cognitive domains prior to intervention, in an attempt to replicate the previously published studies that showed associations between baseline participant factors and cognitive outcomes (Pontifex et al., 2019). Then, linear regressions were performed between pre-intervention CRF and post-intervention cognitive domains (accounting for age, sex, and pre-intervention cognitive data as covariates). As an exploratory aim, to test if functional connectivity change as a function of pre-intervention CRF was related to post-intervention cognition, we performed linear regressions between the composite network scores and any significant relationships between pre-intervention CRF and post-intervention cognition (accounting for age, sex, and pre-intervention cognitive data as covariates).

3 | RESULTS

Table 2 describes participant demographics of the current sample. There were no statistical differences between groups based on race [χ^2 (6, $N=139$) = 7.205, $p = .302$], sex [χ^2 (3, $N=139$) = 0.162, $p = .983$], age [$F(3,135) = .951$, $p = .418$], or pre-intervention BMI [$F(3,135) = .541$, $p = .655$]. There were no demographics differences between participants who completed the study and participants who did not complete the study based on race [χ^2 (2, $N=247$) = 5.544, $p = .63$], sex [χ^2 (1, $N=247$) = 1.824, $p = .177$], age [$t(245) = -1.212$, $p = .227$], pre-intervention BMI [$t(243) = -1.811$, $p = .071$], or pre-intervention CRF [$t(243) = -0.060$, $p = .953$]. For participants who completed the study, pre-intervention fitness was significantly related to sex [$F(1,137) = 19.74$, $p < .001$] and age [$R^2 = .03$, $F(1,137) = 5.73$, $p = .02$]. In this current analysis and subset of participants, no statistically significant differences between intervention group were found in pre-intervention [$F(3,135) = .426$, $p = .735$] or post-intervention CRF [$F(3,135) = 1.376$, $p = .253$]. Thus, intervention groups were collapsed for further analysis. In general, most low-active adults were also low-fit (Table 2).

Using MVPA, greater pre-intervention CRF was correlated with greater changes in patterns of functional connectivity in the right precentral gyrus (MNI coordinates: +40, −20, +62; [$F(10,1330) > 2.98$, k voxels = 44]), which is located in the motor cortex and associated with the Somatosensory Network (Figure 1). We also ran the

TABLE 2 Mean (*SD*) values for participant demographics and fitness data.

	***n* = 139**
Age (years)	65.04 (4.2)
Sex	Female: 71.9% Male: 28.1%
Race	African American: 8.6% Asian: 2.9% Caucasian: 88.5%
Years of education	15.96 (2.85)
Pre-intervention MMSE	28.95 (1.03)
Pre-intervention body mass index (kg/m^2)	30.42 (5.29)
Pre-intervention VO$_2$ peak (mL/kg/min)	19.73 (4.56)

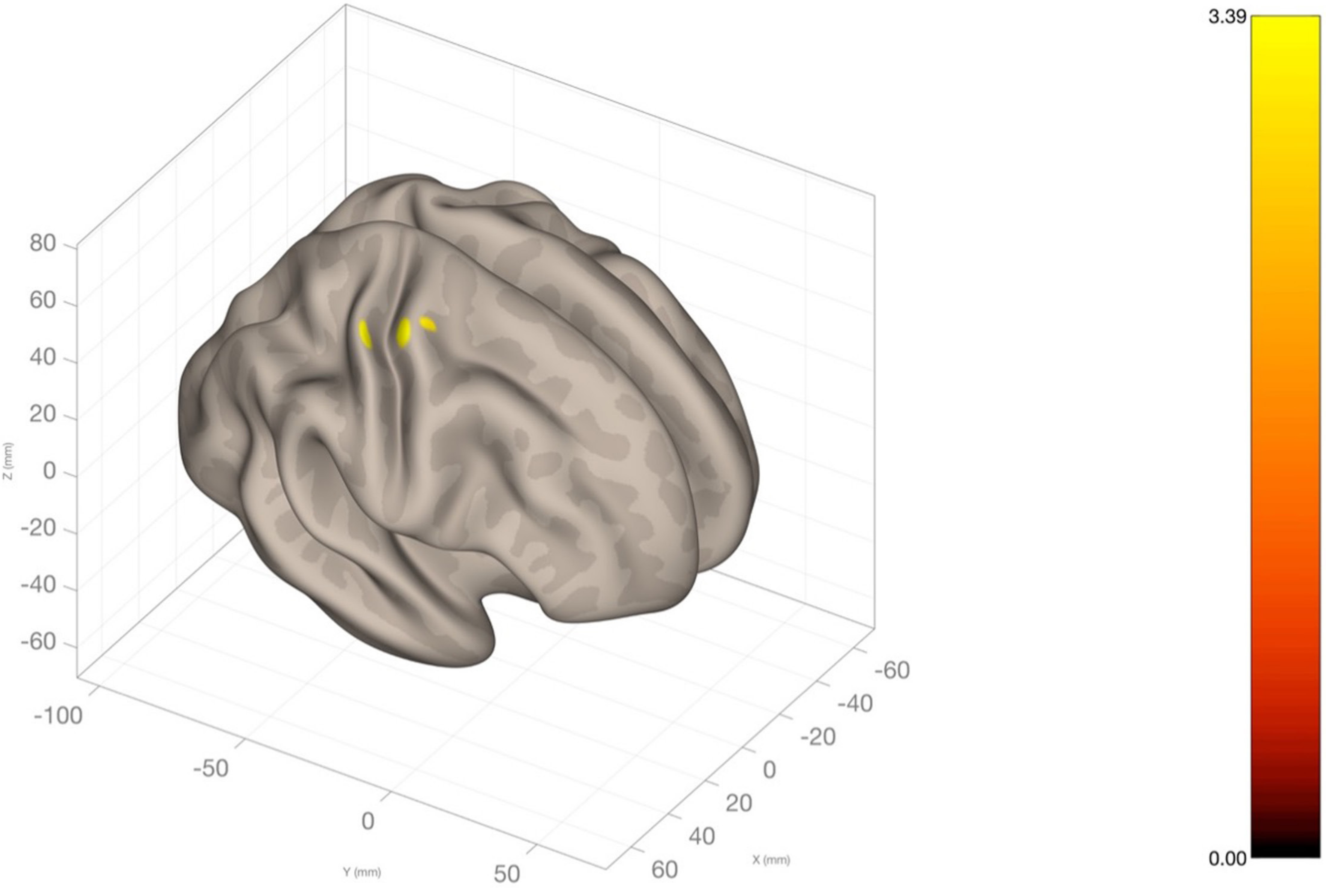
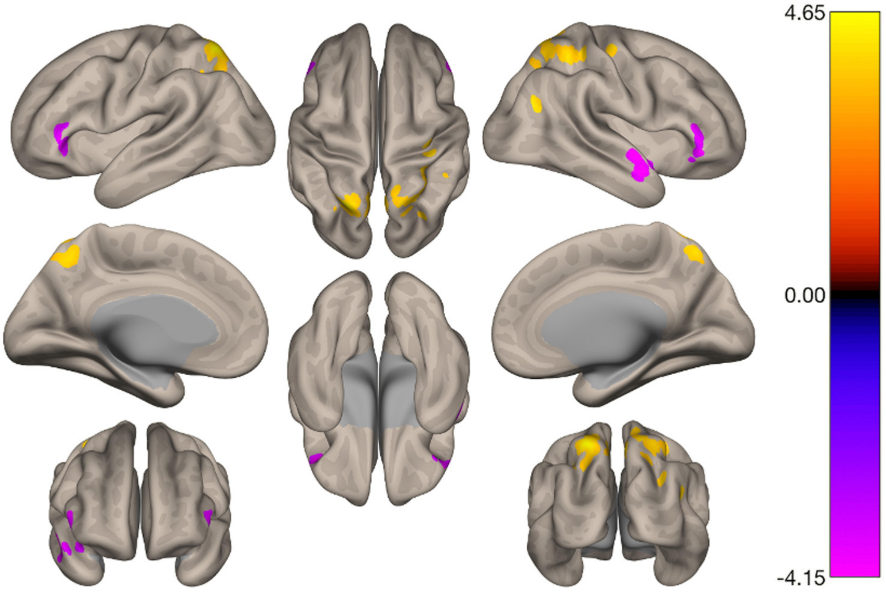


FIGURE 1 Right precentral gyrus cluster resulting from initial voxel-to-voxel MVPA analysis. Color bar indicates *F* statistic.

FIGURE 2 Post-hoc seed-to-voxel analysis revealed increased correlations in the DAN (shown in yellow) and increased anticorrelations in the DMN (shown in purple) with the precentral gyrus seed associated with pre-intervention fitness. Color bar indicates *T* statistic.



MVPA with and without intervention group as a covariate, and there were no statistically significant differences in the results.

Using the precentral gyrus cluster in post-hoc seed-to-voxel analysis, the association between change in functional connectivity in this cluster and pre-intervention CRF was driven by positive correlations with a series of clusters in the Dorsal Attention Network (DAN) and anti-correlations with multiple clusters in the DMN (see Figure 2; Table S3).

Next, as an exploratory analysis, we investigated if functional connectivity change as a function of individual differences in pre-intervention CRF was related to any aspects of intervention-induced changes in cognition. Given their functional similarities (Thomas Yeo et al., 2011), the connectivity values between the precentral gyrus cluster and all clusters within the DAN and the DMN, respectively, were averaged together to create two composite network scores for use in subsequent analyses. Results suggested that increased anti-correlations in the DMN were associated with post-intervention perceptual speed performance ($\beta = -.58$, $t(134) = -2.12$, $p = .03$), indicating that individuals who had stronger anti-correlations in the DMN performed better on perceptual speed-related tasks (Figure 3).

4 | DISCUSSION

While previous research has suggested that CRF is neuroprotective in older adults, many questions regarding the specific role of CRF on cognitive and brain health remain. To test if individual differences in pre-intervention CRF were related to changes in functional connectivity, we performed a data-driven MVPA. Our results demonstrated that pre-intervention CRF levels were positively associated with patterns of functional connectivity change in the right precentral gyrus, gained over 6 months of participation in a four-arm randomized controlled trial of exercise in a group of older adults. While we originally hypothesized that the MVPA would reveal data-driven results in the DMN, it was the right precentral gyrus that we identified as showing changes in connectivity patterns associated with pre-intervention CRF. The right precentral gyrus and the motor cortex have been associated with CRF in previous literature. For example, compared to rest, a high-intensity exercise intervention enhanced primary motor cortex plasticity, increased cortico-motor excitability, increased glutamatergic facilitation, and reduced GABAergic inhibition following intermittent theta burst stimulation (iTBS; Andrews et al., 2020). Additionally, volume in the precentral gyrus was found to mediate the relationship between CRF and Stroop task interference (Weinstein et al., 2012). Another study investigating individual differences found that higher CRF was associated with greater brain activation in the motor cortex during dual-task processing (Wong et al., 2015). While the physiological brain mechanisms that underlie the relationship between CRF and cognition remain somewhat elusive, the importance of the precentral gyrus in this relationship is becoming clear, and our current results add to this literature by showing how baseline CRF relates to longitudinal changes in precentral gyrus functional connectivity.

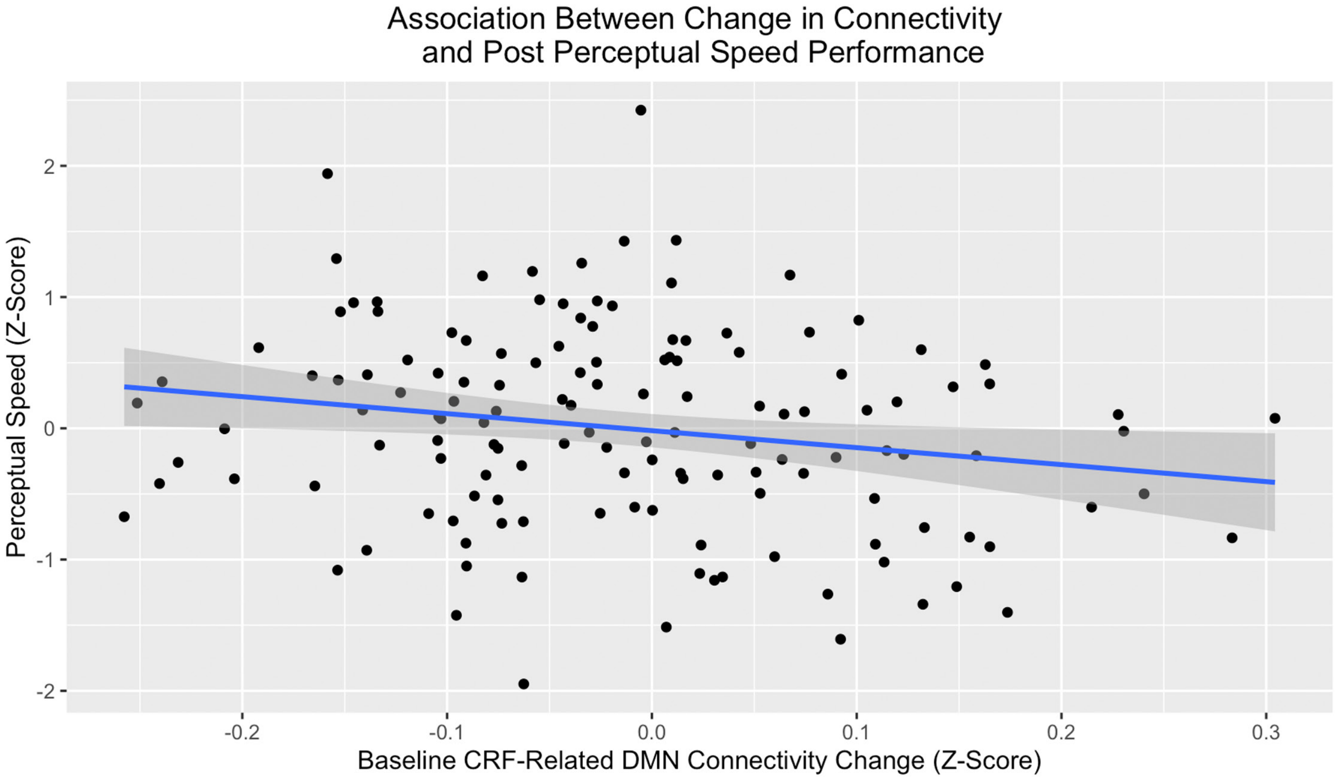


FIGURE 3 Increased anti-correlations between the DMN and the precentral gyrus seed as a function of pre-intervention fitness was associated with better performance on tasks related to perceptual speed.

In an exploratory analysis, we found an association between the specific patterns of functional connectivity of the pre-central gyrus (namely anti-correlations between the precentral gyrus and several clusters within the DMN) and post-intervention performance on cognitive tasks measuring perceptual speed. This finding aligns with previous research that has shown that long-term engagement in PA (one modifiable lifestyle factor related to CRF) modifies age-related differences in the DMN. For example, greater PA levels over a 10-year period were related to stronger connectivity in the posterior DMN, larger gray matter volume of the PCC, and higher perfusion rate within the PCC (Boraxbekk et al., 2016). Similarly, in a cross-sectional study that included older and younger adults, greater age was associated with lower DMN functional connectivity, but older adults with higher levels of CRF demonstrated DMN functional connectivity comparable to that of younger adults (Voss et al., 2010). Extending beyond connectivity, changes in brain function related to CRF have previously been shown to influence cognition. For example, in an observational longitudinal study, poorer CRF at baseline was associated with greater decline on the Mini-Mental Status Examination (MMSE) and other cognitive tests related to attention, executive function, verbal memory, and verbal fluency during a 6-year follow-up (Barnes et al., 2003). Lastly, several exercise interventions have found that increases in CRF are linked to improvements in executive function (Kramer et al., 1999), motor function and auditory attention (Angevaren et al., 2008), and psychomotor speed (Spirduso, 1980). Our findings highlight the important role of CRF in brain function and cognition following an exercise intervention and suggest that individual differences in baseline characteristics (such as CRF) may prime some participants for benefit following exercise.

Expanding upon previous cross-sectional research (Won et al., 2021), the main finding of this study was that higher pre-intervention CRF was related to greater change in the patterns of functional connectivity of the precentral gyrus in the context of a 6-month exercise intervention. This is especially impactful for the field, as it is the first study to our knowledge to conclude the positive priming effects of CRF on longitudinal exercise-related functional connectivity change in healthy older adults. We have demonstrated that in this sample of low-active and lower-fit older adults, even small variations in fitness can affect intervention-related changes in resting-state functional connectivity and cognition. Based on this novel finding, future research should attempt to identify a potential threshold or range of CRF that maximizes cognitive benefit, particularly in older age, to reduce cognitive decline. This could be achieved through moderation analyses to test for a specific range of CRF at which the relation between the intervention assignment change in cognition/brain metrics becomes non-significant (D'Alonzo, 2004).

There are several limitations to address in the study. First, the initial MVPA cluster found in the right precentral gyrus is considered “small” by field standards, at only 44 voxels. Despite the small size, the cluster was found in accordance with the current best practice of cluster-based thresholding in fMRI analysis (Woo et al., 2014). Second, our sample was moderately homogeneous, consisting of majority Caucasian (88.5%) and female (71.9%) participants. Although there were no statistical differences between groups based on sex, race, age, BMI, or CRF level, we recognize our sample bias, and encourage future research to recruit from more diverse communities. Furthermore, because participants were low-active and generally low-fit, results may differ with a sample of participants with normally distributed fitness. In addition, only participants who self-reported a low-active lifestyle (participating in ≤2 days of PA per week) were eligible to participate. However, these inactivity levels are similar to trends in the US (Watson et al., 2016), which may have recently been further exacerbated by COVID-19 social restrictions (Zieff et al., 2021). A limitation in the exploratory analysis was that we did not account for multiple comparisons when investigating effects between the two networks and cognitive domains.

In conclusion, the findings suggest that in our sample of low-active older adults, those with higher CRF at baseline were more likely to experience changes in functional connectivity important for cognitive improvements as a result of participating in a randomized controlled trial of exercise for 6 months. These results are important for sustaining public health, as maintaining a physically active lifestyle is easily accessible, economically efficient, and effective in preventing and minimizing cognitive decline. By promoting health behaviors, like PA and structured exercise, we are best poised to maintain and sustain cognitive and brain health during the later stages of the lifespan.

AUTHOR CONTRIBUTIONS

Katherine M. Lloyd: Conceptualization; formal analysis; investigation; methodology; writing – original draft. **Timothy P. Morris:** Formal analysis; methodology; writing – review and editing. **Sheeba Anteraper:** Formal analysis; methodology; writing – review and editing. **Michelle Voss:** Supervision; validation; writing – review and editing. **Alfonso Nieto-Castanon:** Formal analysis; methodology; writing – review and editing. **Susan Whitfield-Gabrieli:** Supervision; validation; writing – review and editing. **Jason Fanning:** Data curation; project administration; writing – review and editing.

Neha Gothe: Data curation; project administration; writing – review and editing. **Elizabeth A. Salerno:** Data curation; project administration; writing – review and editing. **Kirk I. Erickson:** Supervision; validation; writing – review and editing. **Charles H. Hillman:** Supervision; validation; writing – review and editing. **Edward McAuley:** Conceptualization; funding acquisition; project administration; supervision; validation; writing – review and editing. **Arthur Kramer:** Conceptualization; funding acquisition; project administration; supervision; validation; writing – review and editing.

ACKNOWLEDGMENTS

The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. Results of the present study do not constitute endorsement by ACSM. We acknowledge the significant contributions made by all co-authors. Dr. Katherine Lloyd contributed to the conceptualization, formal analyses, methodology, and writing of the original draft. Dr. Timothy Morris, Dr. Alfonso Nieto-Castanon, and Dr. Sheeba Anteraper contributed to the formal analyses and methodology. Dr. Jason Fanning, Dr. Neha Gothe, and Dr. Elizabeth Salerno contributed to intervention implementation, data processing, and analyses. Dr. Michelle Voss, Dr. Susan Whitfield Gabrieli, Dr. Kirk Erikson, Dr. Charles Hillman, Dr. Edward McAuley, and Dr. Arthur Kramer served as active advisors and collaborators in all aspects of the analyses and interpretation of the data and results of the study. Dr. Edward McAuley and Dr. Arthur Kramer conceptualized, designed, and executed the original study and obtained funding from the NIH/NIA for the multi-year intervention study. All co-authors assisted in reviewing and editing the manuscript.

FUNDING INFORMATION

This work was supported by funding from the National Institute on Aging (NIA) at the National Institutes of Health (NIH) (R37 AG025667) and funding from Abbott Nutrition (C4712) to A.F. Kramer and E. McAuley.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Katherine M. Lloyd https://orcid.org/0000-0001-9122-6117

REFERENCES

Anderson, N. D., & Craik, F. I. (2017). 50 years of cognitive aging theory. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences*, *72*(1), 1–6. https://doi.org/10.1093/geronb/gbw108

Andrews, S. C., Curtin, D., Hawi, Z., Wongtrakun, J., Stout, J. C., & Coxon, J. P. (2020). Intensity matters: High-intensity interval exercise enhances motor cortex plasticity more than moderate exercise. *Cerebral Cortex*, *30*(1), 101–112. https://doi.org/10.1093/cercor/bhz075

Andrews-Hanna, J. R. (2012). The brain's default network and its adaptive role in internal mentation. *The Neuroscientist*, *18*(3), 251–270. https://doi.org/10.1177/1073858411403316

Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R., & Buckner, R. L. (2010). Functional-anatomic fractionation of the brain's default network. *Neuron*, *65*(4), 550–562. https://doi.org/10.1016/j.neuron.2010.02.005

Angevaren, M., Aufdemkampe, G., Verhaar, H., Aleman, A., & Vanhees, L. (2008). Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database of Systematic Reviews*, (2). https://doi.org/10.1002/14651858.CD005381.pub2

Arnold Anteraper, S., Guell, X., D'Mello, A., Joshi, N., Whitfield-Gabrieli, S., & Joshi, G. (2019). Disrupted cerebrocerebellar intrinsic functional connectivity in young adults with high-functioning autism Spectrum disorder: A data-driven, whole-brain, high-temporal resolution functional magnetic resonance imaging study. *Brain Connectivity*, *9*(1), 48–59. https://doi.org/10.1089/brain.2018.0581

Balke, B., & Ware, R. W. (1959). *The present status of physical fitness in the air force*. USAF School of Aviation Medicine Randolph AFB. https://doi.org/10.21236/ADA036235

Barnes, D. E., Yaffe, K., Satariano, W. A., & Tager, I. B. (2003). A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. *Journal of the American Geriatrics Society*, *51*(4), 459–465. https://doi.org/10.1046/j.1532-5415.2003.51153.x

Behzadi, Y., Restom, K., Liau, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage*, *37*(1), 90–101. https://doi.org/10.1016/j.neuroimage.2007.04.042

Boraxbekk, C. J., Salami, A., Wahlin, A., & Nyberg, L. (2016). Physical activity over a decade modifies age-related decline in perfusion, gray matter volume, and functional connectivity of the posterior default-mode network-a multimodal approach. *NeuroImage*, *131*, 133–141. https://doi.org/10.1016/j.neuroimage.2015.12.010

Bouchard, C., Malina, R. M., & Pérusse, L. (1997). *Genetics of fitness and physical performance* (pp. 1–12). Human Kinetics.

Bouchard, C., Sarzynski, M. A., Rice, T. K., Kraus, W. E., Church, T. S., Sung, Y. J., Rao, D., & Rankinen, T. (2011). Genomic predictors of the maximal O_2 uptake response to standardized exercise training programs. *Journal of Applied Physiology*, *110*(5), 1160–1170. https://doi.org/10.1152/japplphysiol.00973.2010

Carp, J., Park, J., Polk, T. A., & Park, D. C. (2011). Age differences in neural distinctiveness revealed by multi-voxel pattern analysis. *NeuroImage*, *56*(2), 736–743. https://doi.org/10.1016/j.neuroimage.2010.04.267

Colcombe, S. J., Erickson, K. I., Raz, N., Webb, A. G., Cohen, N. J., McAuley, E., & Kramer, A. F. (2003). Aerobic fitness reduces brain tissue loss in aging humans. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, *58*(2), 176–180. https://doi.org/10.1093/gerona/58.2.m176

Costello, A. B., & Osborne, J. (2005). Best practices in exploratory factor analysis: Four recommendations for getting the most from your analysis. *Practical Assessment, Research, and Evaluation*, *10*(1), 7. https://doi.org/10.7275/jyj1-4868

D'Alonzo, K. T. (2004). The Johnson-Neyman procedure as an alternative to ANCOVA. *Western Journal of Nursing Research*, *26*(7), 804–812. https://doi.org/10.1177/0193945904266733

Damoiseaux, J. S., Beckmann, C., Arigita, E. S., Barkhof, F., Scheltens, P., Stam, C., Smith, S., & Rombouts, S. (2008). Reduced resting-state brain activity in the "default network" in normal aging. *Cerebral Cortex*, *18*(8), 1856–1864. https://doi.org/10.1093/cercor/bhm207

Davenport, M. H., Hogan, D. B., Eskes, G. A., Longman, R. S., & Poulin, M. J. (2012). Cerebrovascular reserve: The link between fitness and cognitive function? *Exercise and Sport Sciences Reviews*, *40*(3), 153–158. https://doi.org/10.1097/JES.0b013e3182553430

de Jager, C. A., Budge, M. M., & Clarke, R. (2003). Utility of TICS-M for the assessment of cognitive function in older adults. *International Journal of Geriatric Psychiatry*, *18*(4), 318–324. https://doi.org/10.1002/gps.830

Deary, I. J., Corley, J., Gow, A. J., Harris, S. E., Houlihan, L. M., Marioni, R. E., Penke, L., Rafnsson, S. B., & Starr, J. M. (2009). Age-associated cognitive decline. *British Medical Bulletin*, *92*(1), 135–152. https://doi.org/10.1093/bmb/ldp033

Dennis, E. L., & Thompson, P. M. (2014). Functional brain connectivity using fMRI in aging and Alzheimer's disease. *Neuropsychology Review*, *24*(1), 49–62. https://doi.org/10.1007/s11065-014-9249-6

Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Hu, L., Morris, K. S., White, S. M., Wójcicki, T. R., McAuley, E., & Kramer, A. F. (2009). Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus*, *19*(10), 1030–1039. https://doi.org/10.1002/hipo.20547

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., Kim, J. S., Heo, S., Alves, H., & White, S. M. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(7), 3017–3022. https://doi.org/10.1073/pnas.1015950108

Gauthier, C. J., Lefort, M., Mekary, S., Desjardins-Crépeau, L., Skimminge, A., Iversen, P., Madjar, C., Desjardins, M., Lesage, F., & Garde, E. (2015). Hearts and minds: Linking vascular rigidity and aerobic fitness with cognitive aging. *Neurobiology of Aging*, *36*(1), 304–314. https://doi.org/10.1016/j.neurobiolaging.2014.08.018

Gordon, B. A., Rykhlevskaia, E. I., Brumback, C. R., Lee, Y., Elavsky, S., Konopack, J. F., McAuley, E., Kramer, A. F., Colcombe, S., Gratton, G., & Fabiani, M. (2008). Neuroanatomical correlates of aging, cardiopulmonary fitness level, and education. *Psychophysiology*, *45*(5), 825–838. https://doi.org/10.1111/j.1469-8986.2008.00676.x

Hafkemeijer, A., van der Grond, J., & Rombouts, S. A. (2012). Imaging the Default Mode Network in aging and dementia. *Biochimica et Biophysica Acta*, *1822*(3), 431–441. https://doi.org/10.1016/j.bbadis.2011.07.008

Kramer, A. F., Hahn, S., Cohen, N. J., Banich, M. T., McAuley, E., Harrison, C. R., Chason, J., Vakil, E., Bardell, L., Boileau, R. A., & Colcombe, A. (1999). Ageing, fitness and neurocognitive function. *Nature*, *400*(6743), 418–419. https://doi.org/10.1038/22682

Matthews, P. M., & Jezzard, P. (2004). Functional magnetic resonance imaging. *Journal of Neurology, Neurosurgery & Psychiatry*, *75*(1), 6–12.

Mellow, M. L., Goldsworthy, M. R., Coussens, S., & Smith, A. E. (2020). Acute aerobic exercise and neuroplasticity of the motor cortex: A systematic review. *Journal of Science and Medicine in Sport*, *23*(4), 408–414. https://doi.org/10.1016/j.jsams.2019.10.015

Morris, T. P., Chaddock-Heyman, L., Ai, M., Anteraper, S. A., Castanon, A. N., Whitfield-Gabrieli, S., Hillman, C. H., McAuley, E., & Kramer, A. F. (2021). Enriching activities during childhood are associated with variations in functional connectivity patterns later in life. *Neurobiology of Aging*, *104*, 92–101. https://doi.org/10.1016/j.neurobiolaging.2021.04.002

Nieto-Castanon, A. (2022). Brain-wide connectome inferences using functional connectivity MultiVariate pattern analyses (fc-MVPA). *PLoS Computational Biology*, *18*(11), e1010634. https://doi.org/10.1371/journal.pcbi.1010634

Pontifex, M. B., McGowan, A. L., Chandler, M. C., Gwizdala, K. L., Parks, A. C., Fenn, K., & Kamijo, K. (2019). A primer on investigating the after effects of acute bouts of physical activity on cognition. *Psychology of Sport and Exercise*, *40*, 1–22. https://doi.org/10.1016/j.psychsport.2018.08.015

Salthouse, T. A., & Ferrer-Caja, E. (2003). What needs to be explained to account for age-related effects on multiple cognitive variables? *Psychology and Aging*, *18*(1), 91–110. https://doi.org/10.1037/0882-7974.18.1.91

Spirduso, W. W. (1980). Physical fitness, aging, and psychomotor speed: A review. *Journal of Gerontology*, *35*(6), 850–865. https://doi.org/10.1093/geronj/35.6.850

Szabo, A. N., McAuley, E., Erickson, K. I., Voss, M., Prakash, R. S., Mailey, E. L., Wojcicki, T. R., White, S. M., Gothe, N., Olson, E. A., & Kramer, A. F. (2011). Cardiorespiratory fitness, hippocampal volume, and frequency of forgetting in older adults. *Neuropsychology*, *25*(5), 545–553. https://doi.org/10.1037/a0022733

Tarumi, T., Gonzales, M. M., Fallow, B., Nualnim, N., Pyron, M., Tanaka, H., & Haley, A. P. (2013). Central artery stiffness, neuropsychological function, and cerebral perfusion in sedentary and endurance-trained middle-aged adults. *Journal of Hypertension*, *31*(12), 2400–2409. https://doi.org/10.1097/HJH.0b013e328364decc

Thomas Yeo, B., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zöllei, L., & Polimeni, J. R. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*(3), 1125–1165. https://doi.org/10.1152/jn.00338.2011

Tomasi, D., & Volkow, N. D. (2012). Aging and functional brain networks. *Molecular Psychiatry*, *17*(5), 549–558. https://doi.org/10.1038/mp.2011.81

Van Dijk, K. R., Hedden, T., Venkataraman, A., Evans, K. C., Lazar, S. W., & Buckner, R. L. (2010). Intrinsic functional connectivity as a tool for human connectomics: Theory, properties, and optimization. *Journal of Neurophysiology*, *103*(1), 297–321. https://doi.org/10.1152/jn.00783.2009

Voss, M. W., Erickson, K. I., Prakash, R. S., Chaddock, L., Malkowski, E., Alves, H., Kim, J. S., Morris, K. S., White, S. M., & Wójcicki, T. R. (2010). Functional connectivity: A source of variance in the association between cardiorespiratory fitness and cognition? *Neuropsychologia*, *48*(5), 1394–1406. https://doi.org/10.1016/j.neuropsychologia.2010.01.005

Voss, M. W., Vivar, C., Kramer, A. F., & van Praag, H. (2013). Bridging animal and human models of exercise-induced brain plasticity. *Trends in Cognitive Sciences*, *17*(10), 525–544. https://doi.org/10.1016/j.tics.2013.08.001

Voss, M. W., Weng, T. B., Burzynska, A. Z., Wong, C. N., Cooke, G. E., Clark, R., Fanning, J., Awick, E., Gothe, N. P., & Olson, E. A. (2016). Fitness, but not physical activity, is related to functional integrity of brain networks associated with aging. *NeuroImage*, *131*, 113–125. https://doi.org/10.1016/j.neuroimage.2015.10.044

Watson, K. B., Carlson, S. A., Gunn, J. P., Galuska, D. A., O'Connor, A., Greenlund, K. J., & Fulton, J. E. (2016). Physical inactivity among adults aged 50 years and older—United States, 2014. *Morbidity and Mortality Weekly Report*, *65*(36), 954–958. https://doi.org/10.15585/mmwr.mm6536a3

Weinstein, A. M., Voss, M. W., Prakash, R. S., Chaddock, L., Szabo, A., White, S. M., Wojcicki, T. R., Mailey, E., McAuley, E., & Kramer, A. F. (2012). The association between aerobic fitness and executive function is mediated by prefrontal cortex volume. *Brain, Behavior, and Immunity*, *26*(5), 811–819. https://doi.org/10.1016/j.bbi.2011.11.008

Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connectivity*, *2*(3), 125–141. https://doi.org/10.1089/brain.2012.0073

Wilmore, J., & Costill, D. (1994). *Physiology of sport and exercise* (pp. 161–238). Human Kinetics Books.

Won, J., Callow, D. D., Pena, G. S., Gogniat, M. A., Kommula, Y., Arnold-Nedimala, N. A., Jordan, L. S., & Smith, J. C. (2021). Evidence for exercise-related plasticity in functional and structural neural network connectivity. *Neuroscience & Biobehavioral Reviews*, *131*, 923–940. https://doi.org/10.1016/j.neubiorev.2021.10.013

Wong, C. N., Chaddock-Heyman, L., Voss, M. W., Burzynska, A. Z., Basak, C., Erickson, K. I., Prakash, R. S., Szabo-Reed, A. N., Phillips, S. M., & Wojcicki, T. (2015). Brain activation during dual-task processing is associated with cardiorespiratory fitness and performance in older adults. *Frontiers in Aging Neuroscience*, *7*, 154. https://doi.org/10.3389/fnagi.2015.00154

Woo, C. W., Krishnan, A., & Wager, T. D. (2014). Cluster-extent based thresholding in fMRI analyses: Pitfalls and recommendations. *NeuroImage*, *91*, 412–419. https://doi.org/10.1016/j.neuroimage.2013.12.058

Worsley, K. J., Marrett, S., Neelin, P., Vandal, A. C., Friston, K. J., & Evans, A. C. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. *Human Brain Mapping*, *4*(1), 58–73. https://doi.org/10.1002/(SICI)1097-0193(1996)4:1<58::AID-HBM4>3.0.CO;2-O

Yesavage, J. A. (1988). Geriatric depression scale. *Psychopharmacology Bulletin*, *24*(4), 709–711.

Zieff, G., Bates, L. C., Kerr, Z. Y., Moore, J. B., Hanson, E. D., Battaglini, C., & Stoner, L. (2021). Targeting sedentary behavior as a feasible health strategy during COVID-19. *Translational Behavioral Medicine*, *11*(3), 826–831. https://doi.org/10.1093/tbm/ibaa101

Zoeller, R., Stout, J., O'kroy, J., Torok, D., & Mielke, M. (2007). Effects of 28 days of beta-alanine and creatine monohydrate supplementation on aerobic power, ventilatory and lactate thresholds, and time to exhaustion. *Amino Acids*, *33*, 505–510. https://doi.org/10.1007/s00726-006-0399-6

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Data S1.

How to cite this article: Lloyd, K. M., Morris, T. P., Anteraper, S., Voss, M., Nieto-Castanon, A., Whitfield-Gabrieli, S., Fanning, J., Gothe, N., Salerno, E. A., Erickson, K. I., Hillman, C. H., McAuley, E., & Kramer, A. F. (2023). Data-driven MRI analysis reveals fitness-related functional change in default mode network and cognition following an exercise intervention. *Psychophysiology*, *00*, e14469. https://doi.org/10.1111/psyp.14469