



Cardiorespiratory fitness is positively correlated with cerebral white matter integrity in healthy seniors

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ABSTRACT

High cardiorespiratory fitness (CRF) is an important protective factor reducing the risk of cardiac-related disability and mortality. Recent research suggests that high CRF also has protective effects on the brain's macrostructure and functional response. However, little is known about the potential relationship between CRF and the brain's white matter (WM) microstructure. This study explored the relationship between a comprehensive measure of CRF (VO₂ peak, total time on treadmill, and 1-minute heart rate recovery) and multiple diffusion tensor imaging measures of WM integrity. Participants were 26 healthy community dwelling seniors between the ages of 60 and 69 (mean = 64.79 years, SD = 2.8). Results indicated a positive correlation between comprehensive CRF and fractional anisotropy (FA) in a large portion of the corpus callosum. Both VO₂ peak and total time on treadmill contributed significantly to explaining the variance in mean FA in this region. The CRF–FA relationship observed in the corpus callosum was primarily characterized by a negative correlation between CRF and radial diffusivity in the absence of CRF correlations with either axial diffusivity or mean diffusivity. Tractography results demonstrated that portions of the corpus callosum associated with CRF primarily involved those interconnecting frontal regions associated with high-level motor planning. These results suggest that high CRF may attenuate age-related myelin declines in portions of the corpus callosum that interconnect homologous premotor cortex regions involved in motor planning.

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Introduction

Normal human aging is associated with declines in brain structure and function. Growing evidence suggests that physical activity or exercise training might attenuate some age-related cerebral and cognitive declines (Colcombe et al., 2003; Colcombe and Kramer, 2003; Kramer and Erickson, 2007; van Gelder et al., 2004). In particular, aerobic training has been shown to increase gray matter (GM) volume (Colcombe et al., 2006), reduce GM loss (Colcombe et al., 2003), and attenuate white matter (WM) volume reductions in the corpus callosum (Colcombe et al., 2006). In addition, improvements in cardiorespiratory fitness (CRF) can boost functional activation of frontal cortex in seniors (Colcombe et al., 2004). Collectively, these findings suggest that CRF may offset some declines in the macrostructure and functioning of the aging brain.

While there is a rapidly accumulating body of data suggesting a relationship between CRF and cerebral macrostructure relevant to aging, relatively little is known about the potential relationship between CRF

and the brain's WM microstructure. A greater understanding of this potential relationship is important because microstructural integrity of cerebral WM is required for proper transmission of information between cortical regions. The relatively recent advent of diffusion tensor imaging (DTI) has made it possible to assess the microstructural integrity of the brain's WM tracts *in vivo* (Basser et al., 2000; Basser and Pierpaoli, 1996; Le Bihan, 2003). DTI is sensitized to the random motion of water molecules as they interact within tissues, thus reflecting characteristics of their immediate structural surroundings. In WM, the motion of water molecules is hindered more in directions orthogonal to the main fiber direction than along the fiber, and thus diffusion tends to be anisotropic. Diffusion anisotropy can be measured by DTI by means of fractional anisotropy (FA), an index of overall tissue microstructural integrity (Pierpaoli and Basser, 1996).

To date, only one study has explored the relationship between an objective measure of CRF (determined using peak oxygen consumption measures; VO₂ peak) and WM microstructural integrity using DTI. Marks et al., (*in press*) used a region of interest (ROI) approach to explore the relationship of VO₂ peak and FA in portions of the cingulum in healthy seniors. These authors reported a moderate positive correlation ($r = 0.573$) between VO₂ peak and FA in a middle portion

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of the left cingulum bundle. This ROI-based finding provides preliminary support for a moderate relationship between one component of CRF and WM microstructure in one of the brain's WM tracts. However, several important knowledge gaps remain. One knowledge gap concerns the lack of current understanding about which of the brain's WM tracts are most strongly correlated with CRF. Unbiased voxelwise analyses across the brain's WM can be used to address this knowledge gap.

A second knowledge gap concerns the potential neurobiological bases of a CRF–WM integrity relationship. The diffusion properties of mean diffusivity (MD), radial diffusivity (DR), and axial diffusivity (DA), are thought to reflect different components of WM integrity. For example, MD is dependent on the density of biological barriers, such as cell membranes, and represents the diffusion of water in intra- and extracellular compartments (Beaulieu, 2002; Sen and Basser, 2005). Thus, higher MD values represent increased diffusion suggestive of tissue breakdown, atrophy, and increased brain water content (Pierpaoli and Basser, 1996). Component diffusivities (DR and DA), however, provide more specific information about the integrity of axons and the surrounding myelin sheath. Specifically, increases in DR have been linked with a loss of myelin in multiple sclerosis (Klawiter et al., 2011) and in animal models of experimentally induced myelin loss (Song et al., 2002, 2005), whereas decreases in DA have been linked to axonal damage that is associated with axonal swelling and fragmentation (Concha et al., 2006; Sun et al., 2006).

Thus, one approach to begin to characterize the neurobiological bases of CRF–WM integrity relationships would be to identify correlations between CRF and MD/DR/DA within regions showing a CRF–FA relationship. This approach allows for a more detailed understanding about WM integrity than separate considerations of FA, MD, DR and DA (Assaf and Pasternak, 2008; Burzynska et al., 2010). For example, regions showing a CRF–FA correlation and overlapping CRF–MD or CRF–DA correlations would suggest a relationship between CRF and gross tissue characteristics (Sen and Basser, 2005). In contrast, regions showing a positive CRF–FA correlation and an overlapping negative CRF–DR correlation would suggest a relationship between CRF and myelin integrity (Ciccarelli et al., 2006).

A third knowledge gap concerns the relationship between brain structure and measures of CRF beyond VO_2 peak. The large majority of studies in this area have used VO_2 peak (assessed either directly or indirectly) because it provides a measure of functional aerobic capacity and is a predictor of cardiac-related events (Kodama et al., 2009; Laukkanen et al., 2004). However, total treadmill exercise time and 1 minute heart rate recovery are also strong predictors of cardiac related events (Ekelund et al., 1988; Hsieh et al., 2009) (Cole et al., 1999; Nishime et al., 2000; Watanabe et al., 2001). In addition, the prognostic accuracy of cardiac-related events increases when these physiological responses are combined in a single fitness score or index (Gulati et al., 2005; Mark et al., 1987; Michaelides et al., 2009; Myers et al., 2008; Shaw et al., 1998). Consequently, the combined use of multiple measures of CRF (VO_2 peak, total time on treadmill, and 1-minute HR recovery) are thought to represent a more comprehensive metric of CRF that reflects functional aerobic capacity and individual differences in physical activity (D'Amore and Mora, 2006). However, little is known about the relationship between a comprehensive measure of CRF and brain structure.

In the present study, we addressed these three knowledge gaps. Specifically, we explored potential relationships between a comprehensive measure of CRF (based on VO_2 peak, total time on treadmill, and 1-minute HR recovery) and FA across the brain's WM using an unbiased voxelwise approach. Next, we determined the relative contributions of each of the physical fitness metrics to voxelwise results. We then explored potential relationships between CRF and MD/DR/DA within regions showing a CRF–FA relationship. Finally, we used tractography methods to determine the anatomical connectivity patterns of WM tract clusters showing a correlation with CRF in the voxelwise results.

Methods

Participants

Thirty-two community dwelling healthy volunteers (19 females) participated in this study (mean age = 64.98 years, $SD = 2.7$). Participants provided written informed consent in a manner approved by the University of Kentucky Institutional Review Board and were monetarily rewarded for participating. Six of these 32 participants (1 male) were excluded from the study. Of these six participants, one terminated the exercise test early due to difficulty swallowing and leg pain and another demonstrated prolonged ventricular bigeminy resulting in supervising physician termination of the exercise test for safety reasons. The remaining 4 participants were excluded because they failed to achieve VO_2 peak (described below).

The 26 remaining participants (14 females) ranged in age from 60 to 69 (mean age = 64.79 years, $SD = 2.8$). Participants met all criteria for participating in a magnetic resonance imaging (MRI) study. Exclusion for the MRI study included history of a major head injury and/or concussion, neurological disorder (e.g., stroke, seizure), or the presence of metal fragments and/or metallic implants that could cause bodily injury or disrupt the magnetic field. All participants also met all criteria for participating in a graded exercise test. Exclusion for the graded exercise test included a diagnosis of any major medical conditions (e.g., heart, lung, or kidney), a history of uncontrolled high blood pressure, uncontrolled diabetes, a history of heart complications (e.g., heart murmur or coronary artery disease), pulmonary dysfunction (e.g., severe asthma, chronic obstructive pulmonary disease, emphysema), or orthopedic limitations (e.g., foot, knee, or hip problems) that would result in bodily injury or limit performance. A modified version of the Physical Activity Readiness Questionnaire (PAR-Q) was used to screen participants prior to participation in the study. Additionally, physician clearance was obtained for each participant.

The Hollingshead Two-Factor Index of Social Position (ISP) was used as a measure of socioeconomic states (SES; (Hollingshead, 1958). The ISP is based on an individual's occupation and highest level of formal education. It is calculated by assigning numeric values, from 1 to 7, to an individual's occupation and education. Lower values represent higher earning occupations and more years of education. Scores are then weighted by multiplying by 7 (occupation) and 4 (education). Values are then summed to produce a social index.

Cardiorespiratory fitness assessment

All participants completed a physician-supervised maximal graded exercise test to assess VO_2 peak. Total time on treadmill and 1-minute HR recovery were also collected. The exercise test was conducted at the University of Kentucky's Clinical Research Development and Operations Center's (CR-DOC) Functional Assessment and Body Composition Core Laboratory using an indirect calorimetry system with integrated 12-lead electrocardiogram (ECG; Sensormedics Vmax229 metabolic cart; Yorba Linda, CA). A multistage stepwise treadmill protocol, including 3-minute stages, was used to assess CRF. Briefly, each participant started at a treadmill speed of 2.2 miles per hour (mph) and a 0% grade (incline). The treadmill speed was increased by 0.4 mph at the beginning of each 3-minute stage. Treadmill grade was increased by 2% at the beginning of the third stage and continued to increase by 2% at the beginning of each successive stage.

Continuous heart rate and dynamic heart function was measured and monitored via 12-lead ECG. Oxygen consumption was measured breath-by-breath and later averaged over minute intervals and expressed relative to body weight (ml/kg/min) during the test and recovery period. Manual blood pressure and rating of perceived exertion (RPE; using the modified Borg Scales; (Borg, 1970) were collected at the end of each 3-minute stage. All tests were terminated upon participant reported volitional fatigue, the presence of any absolute or relative

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