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Differential associations of engagement in physical activity and estimated cardiorespiratory fitness with brain volume in middle-aged to older adults

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Abstract

Previous work has confirmed the benefits of aerobic exercise for brain aging, however mechanisms underlying these effects remain unclear. Two measures of exercise, time spent in moderate-to-vigorous physical activity (MVPA) and cardiorespiratory fitness (CRF), may reflect different pathways linking activity to brain health. Using data from the UK Biobank, the largest sample combining neuroimaging and objectively measured MVPA available to date ($n=7148$, $n_{\text{male}}=3062$, $n_{\text{female}}=4086$; age= 62.14 ± 7.40 years), we found that, when adjusted for covariates including MVPA, CRF was positively associated with overall gray matter volume (FDR $p=1.28E-05$). In

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contrast, when adjusted for covariates including CRF, MVPA was positively associated with left and right hippocampal ($FDR\ p_{left}=0.01$; $FDR\ p_{right}=0.02$) volumes, but not overall gray matter volume. Both CRF and MVPA were inversely associated with white matter hyperintensity lesion loads ($FDR\ p_{CRF}=0.002$; $p_{MVPA}=0.02$). Our results suggest separable effects of engagement in exercise behaviors (MVPA) and the physiological effects of exercise (CRF) on structural brain volumes, which may have implications for differential pathways linking exercise and brain benefits.

Keywords

Exercise; VO_{2MAX} ; MRI; Hippocampus; Gray Matter

Recent work has shown that aerobic exercise is associated with beneficial effects on brain structure and cognitive function, especially in older adults (Colcombe and Kramer 2003; Colcombe et al. 2006; Erickson et al. 2014; Hillman et al. 2008; Voss et al. 2011). This key finding suggests that modifiable lifestyle behaviors may alter the trajectory of cognitive decline associated with both healthy aging, and neurodegenerative disease (Burns et al. 2008; Kramer et al. 2006; Raichlen and Alexander 2014). However, the mechanisms underlying these effects remain unclear. Both genetic and environmental influences on exercise participation (Klimentidis et al. 2018), as well as on the physiological response to exercise (Bouchard et al. 2015) have been described. Understanding which aspects of physical activity (PA) are important in modifying brain structure and function represents an important step in determining how exercise can enhance outcomes in cognitive aging.

Researchers have traditionally measured engagement in exercise using two variables: time spent in moderate-to-vigorous intensity physical activity (MVPA) and cardiorespiratory fitness (CRF: maximum oxygen consumption during exercise or VO_{2max}). While these measures are related, they track potentially dissociable aspects of physiology (Blair et al. 2001). In general, CRF is increased by long-term participation in MVPA, and is a measure of the accumulated effects of exercise participation on physiology (Blair et al. 2001). Thus, CRF is, in part, an outcome of engaging in MVPA, whereas MVPA is best considered a health-related behavior. However, studies of familial resemblance of aerobic capacity have shown that approximately 50% of the variation in intrinsic CRF (CRF not due to direct engagement in PA) is heritable, and there is a range of heritability of CRF responses to MVPA (Bouchard et al. 2015). Thus, in individuals engaged in the same amount and type of MVPA, CRF values may diverge, reflecting genetic differences. In this way, associations between CRF or MVPA and brain structure may differ, and the resulting differences may help us better understand the underlying mechanisms linking exercise to brain health.

In previous work, CRF has generally shown more consistent associations with the volume of brain structures in older adults compared with measures of time spent in MVPA (Erickson et al. 2014). This has been particularly the case in studies examining total gray matter volume (Gordon et al. 2008; Gow et al. 2012) and the volume of the hippocampus in adults across the lifespan (Erickson et al. 2014; Firth et al. 2018). While recent studies also suggest that white matter volume and the volume of white matter hyperintensities (WMH), reflecting

lesion load, are related to both CRF and PA in older adults, MVPA seems to have a more consistent, significant effect on white matter compared with CRF (Burzynska et al. 2014; Sexton et al. 2016). Finally, there is some evidence that these measures have dissociable effects on the brain, with one recent study showing that the effects of MVPA on WMH are unrelated to CRF (Burzynska et al. 2014), while another found significant effects of CRF on brain functional connectivity distinct from MVPA (Voss et al. 2016).

Here, we examine exercise and brain structure using data from the UK Biobank, the largest sample collected to date that includes neuroimaging data, objective measures of MVPA from wearable accelerometers, and data needed to estimate CRF in the same large cohort of middle-aged to older adults. A recent study has shown that objectively measured PA from accelerometry data in a smaller release of UK Biobank data was significantly associated with total gray matter volume, and left and right hippocampal volumes (Hamer et al. 2018), however, no study to date has examined CRF and MVPA simultaneously in a sample this large. Since the UK Biobank included a graded exercise test only in a relatively small subset of individuals with available neuroimaging scans, and since methods used did not generate a direct measurement of VO_{2max} (the gold standard for measuring CRF), we use a previously validated non-exercise estimate of VO_{2max} that has been linked to brain and general health benefits (Jurca et al. 2005; McAuley et al. 2011; Stamatakis et al. 2012), which we further evaluated in the UK Biobank sample. By using CRF and MVPA data from the same cohort, we believe this analysis will provide a strong foundation for determining whether these different measures exert shared or separable effects on brain structure.

METHODS

Sample

The UK Biobank is a large prospective cohort study of approximately 500,000 adults aged 40–69 at initial enrollment and living in the United Kingdom (UK) (Sudlow et al. 2015). Over 9 million individuals registered with the National Health Service (NHS) who were age 40–69 and lived within 25 miles of one of the 22 assessment centers, were invited by mail to participate in the UK Biobank (Allen et al. 2012; Fry et al., 2017; Sudlow et al. 2015). These centers were dedicated spaces located throughout the UK in England, Wales, and Scotland, and in varied settings to achieve socioeconomic and rural/urban heterogeneity (Fry et al., 2017). There were no exclusion criteria based on health, although volunteers were required to attend an assessment center in order to participate (Fry et al., 2017). The North West Multicentre Research Ethics Committee, the National Information Governance Board for Health & Social Care, and the Community Health Index Advisory Group provided ethical approval for the UK Biobank Study (<http://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=200>), and all participants provided written informed consent. Table 1 provides demographic data for the sample included in this study (note that this is a subsample of the full cohort that includes brain imaging [see below] and ranges in age from 45–80).

Neuroimaging

A subset of the UK Biobank participants (~100,000) are currently being invited to take part in extensive imaging tests that included MRI scans of the brain. At the time we began this

study, a smaller group of individuals had participated and had data publicly available for variables of interest discussed below (~20,000). Detailed methods are described elsewhere (Miller et al. 2016), and are available online for the imaging protocols (<http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=2367>) and in the Brain Imaging Documentation (<http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1977>). Briefly, MR imaging was performed on a Siemens Skyra 3T system with a 32-channel RF receive head coil (Alfaro-Almagro et al. 2018; Miller et al. 2016). Volumetric 3D MPRAGE scans with 1mm isotropic resolution, 256 mm field-of-view, 208×256×256 matrix, and TI/TR = 880/2000 ms were acquired in sagittal orientation. To obtain volumes of WMH, T2 FLAIR scans were acquired with 3D SPACE, 1.05×1×1 mm resolution, 192×256×256 matrix, and TI/TR = 1800/5000 ms in sagittal orientation. Brain tissue segmentation and spatial normalization were performed using freely available FSL software (Miller et al. 2016). Initial quality control (QC) procedures, applied to remove non-usable MRI scans from the available UK Biobank data, have been previously described (Alfaro-Almagro et al. 2018). As part of the publicly available dataset, the UK Biobank also includes five MRI QC measures for the available processed brain images. We additionally excluded 801 participants with structural MRI scan values greater than 3 standard deviations away from the mean of any of the five QC metrics provided by the UK Biobank (fields 25731–25735).

For the present study, we used publicly available data for the following variables chosen due to previous links with exercise engagement (Erickson et al. 2014; Gordon et al. 2008; Gow et al. 2012; Sexton et al. 2016): gray matter volume (field ID: 25006), white matter volume (field ID: 25008), left and right hippocampus volume (field ID: 25019 [L] & 25020 [R]), and total volume of WMH (field ID: 25781). With the exception of WMH, all brain structural data were normalized for head size by multiplying the variable of interest by the scale factor provided by the UK Biobank for each participant (field ID: 25000). This scale factor for head size adjustment is determined as the amount of warping needed to spatially transform T1 scans into a common stereotaxic space. WMH values were expressed as a proportion of Total Intracranial Volume (TIV). An estimate of TIV was computed in native brain space by combining the grey, white, and cerebrospinal fluid segments for each of the volumetric T1 MRI brain scans (Alexander et al. 2012) using Statistical Parametric Mapping software (SPM12; Wellcome Department of Imaging Neuroscience, London, UK). There was a strong inverse association between the scale factor and TIV ($F[1,7298]=8.844e+04$, $r^2=0.92$, $p<2.2e-16$). Since the WMH data were skewed, we log transformed WMH as a proportion of TIV for analyses.

Physical Activity

Physical activity was measured using wearable accelerometers in a subset of the UK Biobank sample (~100,000). In this group, participants wore Axivity AX3 triaxial accelerometers on their dominant wrist for up to seven days (Doherty et al. 2017). Accelerometer data were captured at 100 Hz with a range of $\pm 8g$ (Doherty et al. 2017). Data processing prior to public release followed methods previously developed to capture activity levels via accelerometry (da Silva et al. 2014; Doherty et al. 2017; Sabia et al. 2014; van Hees et al. 2011). Briefly, following accelerometer signal calibration, average accelerometer vector magnitude was calculated over 5-second epochs. Non-wear time was identified as

periods of 60 minutes or more in which all three accelerometer axes had values less than 13 milli-gravities (mg) (Doherty et al. 2017). This non-wear time was imputed using data points from similar time but different days (Doherty et al. 2017). Here, we included subjects that passed the UK Biobank data quality criteria of individuals having at least three days of wear time, as well as having data present in every one-hour period of each day. Following Hildebrand et al. (2014), we then identified time spent in moderate-to-vigorous physical activity (MVPA) as the fraction of wear time in which accelerometer readings were greater than 100 mg. We separately calculated time spent in moderate physical activity (MPA) and vigorous physical activity (VPA) using a threshold of 425 mg for VPA (see Hildebrand et al., 2014). While MVPA is the key variable of interest as a behavioral measure of exercise, we also calculated time spent in light physical activity (LPA) and time spent in sedentary behaviors (SB), calculated following thresholds recommended by Hildebrand et al. (2014, 2017). Results for these behavioral variables are presented in Supplementary Materials.

Cardiorespiratory Fitness Test Measurement

A subset of UK Biobank participants (~95,000) at the baseline examination was invited to perform a fitness test. Participants engaged in an exercise test on a cycle ergometer (eBike, Firmware v1.7) while wearing a 4-lead ECG (CAM-USB 6.5, Cardiosoft v6.51). This test consisted of six minutes of activity in subjects who were deemed healthy enough to participate in exercise testing (Orini et al. 2017). Health risk was assessed for each participant and the two lowest assigned categories of risk (category 1 [minimal risk] and category 2 [small risk]) allowed participants to engage in a graded exercise test. In these tests, participants were asked to cycle at a constant workload for two minutes. Following this, resistance was increased gradually over the next four minutes until target workload was achieved (50% of predicted maximum workload for individuals deemed minimal risk, and 35% of predicted maximum workload for individuals deemed small risk [slightly higher than minimal risk]). Participants were included in analyses here only if they were part of the minimal risk group that reached 50% of predicted maximum workload (category 1). Predicted maximum workload was calculated following an age- and sex-based equation (Orini et al. 2017). Exercise tested CRF (eCRF) was calculated following Tikkanen et al. (2018) as:

$$\text{eCRF} = 7 + 10.8 * (\text{workload})/\text{body mass} \quad (1)$$

Non-exercise Cardiorespiratory Fitness Estimate

Given that the overlap between the participants having neuroimaging and accelerometer data with eCRF defined in equation 1 was less than 15% of the available cohort, we calculated a non-exercise estimate of CRF following Stamatakis et al. (2012) to maximize our use of the available neuroimaging data. Researchers who developed this measure performed a validation with an adult UK sample ($r=0.76$ with $\text{VO}_{2\text{max}}$ [$p<0.01$] in Jurca et al (2005; see also Stamatakis et al. 2012). Estimated CRF is calculated using the following equation:

$$\text{CRF} = [\text{sex coefficient} \times 2.78 - (\text{age} \times 0.11) - (\text{BMI} \times 0.17) - (\text{RHR} \times 0.05) + (\text{physical activity level coefficient}) + 21.41] \quad (2)$$

, where sex coefficient is 0 for female and 1 for male, age is in years, BMI is body mass index (kg/m^2), RHR is resting heart rate (beats/minute), and physical activity level coefficients are categorized into the following four levels: 1) no physical activity = 0, 2) <1.5 sessions of MVPA per week = 0.39, 3) 1.5 to < 3 sessions of MVPA per week = 0.35, 4) 3–6 sessions of MVPA per week = 0.64, and 4) >6 sessions of MVPA per week = 1.21. Sessions per week of MVPA were calculated by dividing the total minutes per week of self-reported moderate and vigorous activity by 30 minutes using questions from the UK Biobank Touchscreen Assessment. However, data needed to calculate the physical activity level coefficient was missing for nearly 10% of the sample with imaging and accelerometry. Thus, to maintain the large sample size, we calculated CRF without the physical activity level coefficient in equation 2. In addition to increasing the available sample size, this method has the advantage of linking CRF to physiological data only, rather than behavioral variables derived from self-report. In individuals who had data available for the physical activity level coefficient, the difference between using this value in equation 2, and omitting it from equation 2 was small (mean difference = $0.79 \text{ mlO}_2 \text{ min}^{-1} \text{ kg}^{-1} \pm 0.47$).

We validated this estimate by comparing measured CRF from equation 1 with estimated CRF calculated without the physical activity level coefficient. Due to the testing criteria described above, this sample ($n=57,235$; $n_{\text{female}}=31,526$, $n_{\text{male}}=25,709$) was slightly younger (age = 56.1 ± 8.2 years) than the sample used in the imaging analyses (see Table 1). In the sample of individuals that had measured maximum workload from exercise testing, CRF at baseline visit was highly correlated with the maximum workload achieved during the exercise testing session ($F[1, 57233] = 1.901\text{e}+05$, $r^2 = 0.77$, $p < 2\text{e-}16$; Figure 1). This relationship is similar to the comparison between estimated and measured CRF for the UK sample in Jurca et al. (2005; $r^2=0.58$). Results were similar, but slightly weaker, if we include the physical activity level coefficient in the calculation of estimated CRF ($F[1, 48169] = 1.371\text{e}+05$, $r^2 = 0.74$, $p < 2\text{e-}16$).

Based on these analyses, we present results below for CRF calculated without self-reported physical activity levels. Note also that we calculated two estimates of CRF in this sample. The first estimate corresponds to CRF at the time at which maximum workload was measured directly and was used to validate estimated CRF. The second is estimated CRF at the time of brain imaging, and this was the value used in analyses of brain structure. CRF estimated at baseline and at the imaging visit are highly correlated ($F[1, 6975] = 4.562\text{e}+04$, $r^2 = 0.87$, $p < 2\text{e-}16$).

Statistical Analysis

Brain and exercise variables were standardized so that regression coefficients could be compared. We adjusted for the effects of age and sex on all variables except CRF by calculating residuals from regression models with the variable of interest as the dependent variable and age and sex as independent variables. For adjusted MVPA, we also included total accelerometer wear time and the difference in time (fraction of year) between accelerometer wear and brain imaging measurement as independent variables in the regression for calculation of residuals. Since age and sex are included in the calculation of CRF (see equation 2) and therefore intrinsically controlled for, we did not further adjust this

value (Boots et al. 2015). Note that due to the smaller sample sizes discussed above, we did not include exercise-tested CRF (eCRF) in our neuroimaging analysis.

Our analytical strategy followed Knaeps et al. (2016). For each age- and sex-adjusted brain variable, we calculated regression statistics from the following generalized linear models: 1) model 1: the effects of CRF, 2) model 2: the effects of CRF when adjusted MVPA is included in model 1, 3) model 3: the effects of adjusted MVPA, and 4) model 4: the effects of adjusted MVPA when CRF is included in model 3. We performed these analyses on minimally adjusted models (where only assessment center was included as a covariate) and fully adjusted models, where education, Townsend deprivation index (a continuous and objective measure of socioeconomic deprivation), smoking status, physician diagnosed cardiovascular disease (angina, heart attack, stroke, or hypertension), and physician diagnosed diabetes were included as covariates. Individuals in the final sample currently taking beta-blockers ($n=543$) were removed from analyses due to the effects of beta-blockers on heart rate. We then compared the regression coefficients and significance across the models to determine whether CRF and MVPA have differential effects on brain variables of interest. All p-values were adjusted based on the false discovery rate (FDR) for multiple tests applied to all p-values together. All statistical analyses were performed in R (Team 2016) (version 3.4.0).

RESULTS

Objectively measured MVPA was correlated with CRF, however the association was not strong, as MVPA explains only ~5% of the variation in CRF ($F[1, 90883] = 4272$, $r^2 = 0.05$, $p < 2e-16$) in the full UK Biobank sample (at baseline) with accelerometry available. While this correlation is low, it is similar to other studies comparing objectively measured MVPA with CRF (Cao et al., 2010; Knaeps et al., 2016). The relationship between MVPA and CRF was similar in the sample of individuals that had both accelerometer data and measured fitness from exercise testing ($F[1, 13677] = 589.1$, $r^2 = 0.04$, $p < 2e-16$). The relationship between MVPA and maximum workload during exercise testing (eCRF) was significant, but also weak ($F[1, 13736] = 1020$, $r^2 = 0.07$, $p < 2e-16$).

We examined the association between exercise variables and brain structure in the UK Biobank sample restricted to individuals with accelerometry, neuroimaging, and data needed to calculate CRF at the imaging visit ($n=7148$ for total gray matter, white matter, and hippocampal volumes; $n=6655$ for WMH). Correlations and partial correlations between CRF, MVPA, and brain variables are provided in Supplementary Materials. In a minimally adjusted model (variables adjusted for age, sex, testing center, and, for MVPA, accelerometer wear time and time between accelerometer wear and imaging visit), MVPA was significantly associated with all structural brain variables except for white matter volume when adjusted for multiple testing (Table 2). These associations remained significant even when CRF was included in the models (Table 2). Fully adjusted models (see methods and table for list of covariates; $n=7030$ for white matter, gray matter, and hippocampal volumes; $n=6540$ for WMH) show a similar pattern, with MVPA significantly associated with left and right hippocampal volumes, and WMH with and without inclusion of CRF in the model. However, in fully adjusted models, MVPA is no longer significantly associated

with gray matter volume (Table 2). Other measures of physical activity and inactivity (LPA and SB) did not show significant associations with any brain structural variables (see Supplementary Materials).

In the minimally adjusted model, CRF was not significantly associated with white matter or hippocampal volumes (Table 2), but was significantly associated with total gray matter volume, and WMH. When MVPA was included in the model, CRF remained significantly associated with total gray matter volume and WMH (Table 2). CRF remained significantly associated with gray matter volume and WMH when models were fully adjusted for covariates, with and without inclusion of MVPA (Table 2).

DISCUSSION

Our results show that, in the largest sample measured to date, MVPA and estimated CRF have associations with different aspects of brain structure. When adjusted for covariates, CRF, but not MVPA was significantly associated with overall gray matter volume. In contrast, MVPA, but not CRF, was significantly associated with left and right hippocampal volumes. Both CRF and MVPA were significantly associated with WMH lesion load. While effect sizes are small, based on these results, engagement in physical activity may have beneficial effects on the brain above and beyond the effects related to cardiovascular fitness.

Our results differ from previous work that has identified CRF as a key factor influencing structural brain volume, though, with only MVPA significantly predicting hippocampal volumes in multivariate models that include both variables (Bugg et al. 2012; Erickson et al. 2014; Erickson et al. 2011; Szabo et al. 2011). Previous work that has identified a relationship between CRF and hippocampal volume may be capturing the impact of MVPA on this brain structure, and results could be strengthened with objective quantitative measures of this behavior. Thus, it is possible that, while CRF has distinct effects on total gray matter volume, MVPA is a required activity for maintenance of hippocampal volumes, a key region vulnerable to the effects of brain aging and neurodegenerative diseases, like Alzheimer's disease. It is also important to note that neither SB or LPA showed significant associations with brain structure in this sample underscoring the importance of higher intensity activities for linking exercise and the brain. Overall, engagement in MVPA seems to play a prominent role in brain health and future studies of exercise and structural brain volume should include objective measures of exercise engagement when possible.

While our study cannot test hypotheses regarding the mechanisms responsible for these associations, our results suggest the possibility of multiple pathways linking exercise to brain health. A portion of CRF is intrinsic, heritable (measured by familial resemblance), and not altered by exercise participation (Bouchard et al. 2015). In addition, while CRF is also a key measure of how the body responds to exercise training, this response is also determined, in part, by genetic factors (Bouchard et al. 2015). It is possible that our results showing a weak relationship between MVPA and CRF reflect these different components that make up aerobic fitness. This heritable physiological response to exercise training is associated with improved cardiovascular function that includes increased blood flow to the brain, bringing key nutrients and clearing molecules that may affect brain health and risk for

disease (e.g., beta-amyloid) (Ainslie et al. 2008; Brown et al. 2010). Thus, total gray matter volume may be more readily affected by physiological systems that respond to exercise in a way that is altered by underlying genetics (e.g., vascular response to exercise that may enhance cerebral blood flow), as well as longstanding, chronic exposure to physical activity. In this way, total gray matter volume may represent the accumulated effects of MVPA on the cardiovascular system, as well as genetic predispositions for improved vascular health. It is worth noting that MVPA is significantly associated with total gray matter volume when CRF is not included in the model, further supporting the hypothesis that CRF reflects, in part, MVPA-related effects.

In contrast, MVPA as measured here is purely a reflection of participation in exercise behaviors. While engagement in MVPA also leads to increased cerebral blood flow and vascular health (Smith et al. 2010), MVPA is also known to up-regulate the production of BDNF, a protein associated with neurogenesis, neuroprotection, synaptic plasticity, learning, and memory (Intlekofer and Cotman 2013; Marosi and Mattson 2014). In animal models, exercise-induced increases in BDNF are associated with neurogenesis specifically in the hippocampus (Van Praag et al. 2005) and recent work has implicated BDNF in maintenance of white matter (Driscoll et al. 2012; Kennedy et al. 2009; Robinson et al. 2018). Hippocampal volumes may be more sensitive to engagement in MVPA regardless of whether an individual has a propensity to have enhanced CRF due to MVPA. Thus, it is possible that MVPA captures the effects of exercise behavior that do not depend on a strong, long-term cardiovascular response to PA, while CRF better captures aspects of the heritable physiological response to exercise behavior, especially when controlling for MVPA. As with previous studies, the relationship between MVPA and CRF was not strong (see Cao et al., 2010), suggesting that there may in fact be dissociable pathways that can account for the differential effects of MVPA and CRF on brain structure. We believe our analysis sets a strong foundation for more careful work identifying dissociable pathways that generate exercise induced benefits across the brain. We argue that collection of a variety of exercise measures that quantitatively capture both participation and physiological effects will greatly enhance our understanding of links between exercise and the brain.

Finally, our results are consistent with the recently described Adaptive Capacity Model (ACM; Raichlen and Alexander 2017). The ACM suggests that the combination of aerobic physical activity and cognitive challenges experienced during exercise may play an important role in preservation of brain structure during aging (Raichlen and Alexander 2017). In addition to indoor facilities, MVPA is often used during movement across urban or rural landscapes (e.g., during purposeful exercise), requiring a set of cognitive demands that may include hippocampal-dependent memory (Raichlen and Alexander 2017). The stronger relationship of MVPA to most structural brain volume variables compared with CRF in this sample supports the hypothesis that the complex movement of aerobic exercise itself may have benefits for key brain regions, including the hippocampus.

Our study has several strengths. First, this is the largest study to date to simultaneously examine objective measures of MVPA, data to estimate CRF, and structural brain volumes. Second, our CRF variable has been validated in previous studies (Stamatakis et al. 2012), and is highly correlated with a measure of aerobic fitness performed in the UK Biobank

(Fig. 1). Our study does have some limitations that point to areas for future work. Significantly, CRF was not directly *measured* in a large sample of individuals with overlapping MRI data. In addition, the direct measurement of CRF used in the UK Biobank is not the gold standard for assessing aerobic fitness (VO_{2max}). While estimated CRF is strongly correlated with measured aerobic fitness from an exercise test, it still reflects an estimate and future work should focus on objective measures of CRF to include in large scale epidemiological studies. A final limitation of the use of estimated CRF is that age is a component of the equation used, and therefore cannot be included in models as a variable of interest (e.g., to examine interaction effects of age and CRF). Additionally, our study is based on cross-sectional data for a cohort of middle-aged to older adults and, while we included covariates in our fully adjusted models that account for health and socioeconomic status, there are other factors that may influence brain structure and are not accounted for in this analysis. Studies evaluating the effects of MVPA and CRF on brain structure and function in samples with a wider age range and the inclusion of more covariates, as well as in longitudinal studies and randomized controlled trials are needed to fully evaluate causal relationships. Finally, while our results suggest that CRF and MVPA may be associated with different pathways of action on the brain, we were not able to directly measure either vascular or neurogenic mechanisms in this dataset. Our study forms the foundation for future work examining the difference between engagement in physical activity and the physiological response to activity. Direct measures of molecular mechanisms associated with CRF and MVPA in human and animal models will help us better understand how best to prescribe exercise as a beneficial behavior for targeted brain regions that may be preferentially vulnerable to aging or neurodegenerative disease.

CONCLUSIONS

Structural brain volume is influenced by both CRF and MVPA in middle-aged to older adults, ages 45 – 80, however engagement in exercise seems to play a more important role in maintenance of brain volume. This result is promising since individual response of CRF to purposeful exercise varies greatly and is at least partially genetically determined (Bouchard et al. 2015). While some aspects of exercise-induced brain benefits may be linked to this underlying genetic predisposition, our results suggest that engagement in MVPA may have a distinct impact on the hippocampus, a key brain structure implicated in memory-decline in both aging and in neurodegenerative disease. Although a causal connection is not possible based on our cross-sectional study, our results do suggest that individuals who engage in more MVPA, regardless of their CRF, may derive brain benefits by enhancing hippocampal volume. Thus, investigations of mechanisms linking exercise and the brain may require the exploration of multiple pathways to improve brain health, and individual cardiorespiratory response to exercise may not determine the full extent of effects of exercise on the brain. While we recommend caution in over-interpreting our results due to small effect sizes, these findings suggest that precision medicine initiatives, and future intervention studies, should consider differences in both behavior and physiological markers of exercise effects in relation to the brain to identify optimal exercise prescriptions for brain health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Relationship between estimated CRF and exercise-tested CRF (eCRF) in the UK Biobank.

Data here represent the full sample of individuals at the baseline exam who underwent measured fitness testing and had workload increased during the test (see text for further explanation). Exercise-tested CRF (eCRF) is calculated using equation 1.

Table 1.

Participant characteristics

Variable	Female (n=4086)		Male (n=3062)	
	mean/percent	sd	mean/percent	sd
Age (years)	61.58	7.26	62.89	7.53
MVPA (fraction of wear time)	0.081	0.032	0.076	0.032
MPA	0.078	0.031	0.072	0.030
VPA	0.003	0.004	0.003	0.005
Wear time (days)	6.66	0.63	6.69	0.65
CRF (METs)	6.58	1.35	9.27	1.28
BMI	26.00	4.72	26.80	3.84
Resting heart rate	72.74	11.61	68.93	12.31
Townsend Deprivation Index	-2.08	2.59	-2.00	2.67
<i>Education</i>				
College or University degree	44%		48%	
<i>Smoking</i>				
Never	64%		58%	
Previous	31%		35%	
Current	5%		7%	
<i>Chronic disease</i>				
Doctor diagnosed CVD	21%		29%	
Doctor diagnosed diabetes	3%		6%	

Note: MVPA is moderate to vigorous physical activity measured from accelerometers. MPA is moderate activity and VPA is vigorous activity. CRF is estimated cardiorespiratory fitness in metabolic equivalent units (METs). CVD is cardiovascular disease.

Table 2.

Regression statistics for associations between exercise variables and brain structure.

brain variable	CRF				MVPA						
	IV	β	95% CI	p	FDR p	IV	β	95% CI	p	FDR p	
Model 1	Volume of white matter	1	-0.003	-0.027,0.02	0.77	0.811	3	0.025	0.002,0.048	0.033	0.058
	Volume of white matter	2	-0.008	-0.031,0.016	0.524	0.582	4	0.026	0.003,0.05	0.028	0.051
	Volume of gray matter	1	0.062	0.039,0.085	1.40E-07	2.80E-06	3	0.03	0.007,0.053	0.012	0.022
	Volume of gray matter	2	0.059	0.036,0.082	8.27E-07	9.13E-06	4	0.021	-0.003,0.044	0.086	0.133
	Vol. of hippocampus (l.)	1	0.013	-0.01,0.036	0.27	0.36	3	0.04	0.017,0.063	7.655E-04	0.003
	Vol. of hippocampus (l.)	2	0.007	-0.017,0.03	0.563	0.608	4	0.039	0.015,0.062	0.001	0.004
	Vol. of hippocampus (r.)	1	0.013	-0.01,0.036	0.265	0.36	3	0.035	0.012,0.058	0.003	0.008
	Vol. of hippocampus (r.)	2	0.008	-0.016,0.031	0.515	0.582	4	0.034	0.011,0.057	0.005	0.011
	Total volume of WMH	1	-0.066	-0.09,-0.042	5.45E-08	2.18E-06	3	-0.051	-0.075,-0.027	3.01E-05	1.72E-04
	Total volume of WMH	2	-0.06	-0.084,-0.036	1.28E-06	1.02E-05	4	-0.042	-0.066,-0.017	7.68E-04	0.003
Model 2	Volume of white matter	1	0.003	-0.021,0.027	0.798	0.819	3	0.025	0.001,0.048	0.041	0.068
	Volume of white matter	2	-0.001	-0.025,0.024	0.964	0.964	4	0.025	0.001,0.048	0.042	0.068
	Volume of grey matter	1	0.059	0.036,0.083	9.13E-07	9.13E-06	3	0.016	-0.007,0.039	0.176	0.26
	Volume of grey matter	2	0.058	0.034,0.082	1.91E-06	1.28E-05	4	0.008	-0.016,0.031	0.521	0.582
	Vol. of hippocampus (l.)	1	0.013	-0.011,0.037	0.289	0.373	3	0.034	0.011,0.058	0.004	0.011
	Vol. of hippocampus (l.)	2	0.008	-0.016,0.032	0.518	0.582	4	0.033	0.01,0.057	0.006	0.013
	Vol. of hippocampus (r.)	1	0.016	-0.008,0.039	0.202	0.289	3	0.033	0.01,0.057	0.005	0.013
	Vol. of hippocampus (r.)	2	0.011	-0.013,0.035	0.38	0.475	4	0.032	0.008,0.056	0.009	0.018
	Total volume of WMH	1	-0.049	-0.074,-0.025	7.15E-05	3.57E-04	3	-0.038	-0.062,-0.014	0.002	0.006
	Total volume of WMH	2	-0.045	-0.069,-0.02	3.73E-04	0.002	4	-0.031	-0.056,-0.007	0.011	0.022

Note: IV (independent variables) are: 1) CRF, 2) CRF + MVPA, 3) MVPA + CRF, Model 1 is a minimally adjusted model, where the brain variables are residuals from a regression model that includes age and sex, and the full model includes assessment center as a covariate. Model 2 is calculated in the same way as Model 1, however covariates also include smoking status, education level, physician diagnosed CVD, physician diagnosed diabetes, and Townsend deprivation index. The scale factor was used to adjust for head size in analyses of white matter volume, gray matter volume, and hippocampal volumes, $n=7148$ ($n=7030$ for fully adjusted models). Total volume of WMH was expressed as a proportion of TIV for analyses, $n=6655$ ($n=6540$ for fully adjusted models). FDR p is p-value adjusted for multiple testing.