## RESEARCH ARTICLE

# Sex differences in the relationship between cardiorespiratory fitness and brain function in older adulthood

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[1]*Department of Psychology, York University, Toronto, Ontario, Canada;* [2]*Laboratory of Brain and Cognition, Montreal Neurological Institute, Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada; and* [3]*Departments of Psychiatry and Psychology, McGill University, Montreal, Quebec, Canada*

**Dimech CJ, Anderson JA, Lockrow AW, Spreng RN, Turner GR.** Sex differences in the relationship between cardiorespiratory fitness and brain function in older adulthood. *J Appl Physiol* 126: 1032–1041, 2019. First published January 31, 2019; doi:10.1152/japplphysiol.01046.2018.—We investigated sex differences in the association between a measure of physical health, cardiorespiratory fitness (CRF), and brain function using resting-state functional connectivity fMRI. We examined these sex differences in the default, frontoparietal control, and cingulo-opercular networks, assemblies of functionally connected brain regions known to be impacted by both age and fitness level. Healthy older adults (*n* = 49; 29 women) were scanned to obtain measures of intrinsic connectivity within and across these 3 networks. We calculated global efficiency (a measure of network integration) and local efficiency (a measure of network specialization) using graph theoretical methods. Across all three networks combined, local efficiency was positively associated with CRF, and this was more robust in male versus female older adults. Furthermore, global efficiency was negatively associated with CRF, but only in males. Our findings suggest that in older adults, associations between brain network integrity and physical health are sex-dependent. These results underscore the importance of considering sex differences when examining associations between fitness and brain function in older adulthood.

**NEW & NOTEWORTHY** We examined the association between cardiorespiratory fitness and resting state functional connectivity in several brain networks known to be impacted by age and fitness level. We found significant associations between fitness and measures of network integration and network specialization, but in a sex-dependent manner, highlighting the interplay between sex differences, fitness, and aging brain health. Our findings underscore the importance of considering sex differences when examining associations between fitness and brain function in older adulthood.

aging; brain networks; fMRI; network efficiency; physical fitness; resting-state functional connectivity

## INTRODUCTION

Physical exercise improves brain physiology, structure, and function in older adulthood (14, 45). Exercise has been shown to influence neural growth factors and enhance processes such as angiogenesis, synaptogenesis, and neurogenesis (16; but see 73). These changes are also measurable at a systems level,

impacting cortical structure and function (25, 54). Cardiorespiratory fitness (CRF), a measure of physical fitness indexing oxygen consumption and transport (41), has been associated with greater gray matter volume and density in frontal and parietal cortices as well as increased hippocampal volumes (12, 24, 36, 84). These changes are associated with higher cognitive functioning, particularly in domains most susceptible to age-related decline, including executive functioning and memory (14, 19, 84).

CRF is also related to changes in the functional architecture of the brain measured at rest (83). Estimates of resting-state functional connectivity (RSFC) characterize coherent patterns of intrinsic neural activity in the absence of explicit task demands. RSFC measures have been used to study brain health both in typical and atypical aging (20). RSFC is thought to reflect repeated patterns of coherent neural oscillatory activity reinforced across time and thus provides a stable, neurophysiological marker of brain function (6; also see Ref. 77 for a review). Thus, measures of RSFC are useful neural markers for assessing the impact of systemic lifestyle influences, such as CRF, on brain function. Furthermore, RSFC measures are readily obtained in older adult populations and have been shown to be both replicable (7, 42) and reliable (72, 87).

RSFC is altered in normal aging (e.g., 13, 30, 31), and these changes appear to target functional connectivity within and between networks associated with higher-order cognitive functioning (30, 31). The default, frontoparietal control, and cingulo-opercular networks have been particularly implicated (30, 31). The default network consists of the ventromedial prefrontal cortex (PFC), posterior cingulate and retrosplenial cortex, inferior parietal lobule, lateral temporal cortex, dorsomedial PFC, and the hippocampal formation, among others (9). This network is implicated in internally focused cognitive processes (8, 40). The frontoparietal control network is composed of anterior and dorsolateral PFC, anterior inferior parietal lobule, anterior cingulate, and insular cortices and is associated with intrinsic (i.e., top down) cognitive control processes (22, 79). Finally, the cingulo-opercular network (22), which encompasses anterior insula/operculum, thalamus, and the dorsal anterior cingulate cortex, is associated with sustaining cognitive set as well as external or salience-driven (i.e., bottom up) attentional processing. Common age-related changes across these networks include reduced within, or local, connectivity and increased between, or more global, connectivity (39). More broadly, aging is associated with greater overall network

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integration and reduced functional segregation, as well as reduced connectivity within networks (13, 30, 31, 74, 83).

Functional connectivity of the default, frontoparietal, and cingulo-opercular networks is also modulated by fitness and activity levels in older adulthood (80, 81, 83). CRF has been positively associated with global efficiency, a measure of network integration and distributed processing, and negatively associated with local efficiency, a measure of within-network segregation and regional specificity across the whole brain (47; see Ref. 67 for a review of network measures). These findings suggest that greater CRF is associated with increased network integration and reduced segregation between networks in older adults (47). However, the evidence remains equivocal. Local, or less-distributed, processing has also been positively associated with exercise levels (43, 44).

There is evidence for a relationship between RSFC and CRF in older adulthood and evidence of sex differences in functional brain aging, yet sex differences in the relationship between CRF and brain function in older adulthood have not been investigated. Older men and women show differential benefits in cognitive performance associated with exercise and fitness levels. Studies with a greater proportion of female participants report greater cognitive gains (14). A recent meta-analysis reported greater exercise-related cognitive benefits in women (4), yet the neural basis of sex differences in the relationship between fitness and brain function in older adults has not been directly explored.

To address this gap, here we investigate sex differences on the impacts of CRF on RSFC in older adults. We examine this relationship specifically focusing on three higher-order association networks (13) that have been most reliably associated with changes both in aging and fitness levels: the default network, frontoparietal control network, and cingulo-opercular network. We hypothesize that local, or greater within-network, connectivity would be associated with higher CRF levels in older adults (43, 44). As there are no studies investigating sex differences in the association between RSFC and CRF, we are unable to pose specific hypotheses. However, greater exercise-related cognitive benefits have been observed in older women (4). This suggests that patterns of functional brain activity associated with better cognitive performance, i.e., increased local efficiency, should be more reliably observed in women.

## METHODS

### Ethical Approval (Human Subjects)

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

### Informed Consent

Written informed consent was obtained from all individual participants included in the study.

### Participants

Fifty-one older adults participated in this study and were recruited from the community in Ithaca, New York. All participants were healthy, over the age of 60, had normal or corrected-to-normal visual acuity, and had no history of psychiatric, neurological, or other medical illness that could compromise cognitive functions. In addition to the inclusion criteria noted above, participants were required to have Geriatric Depression Scores ≤9 (i.e., within the "normal" range; 86) as well as Mini-Mental State Exam scores of >25 (26) to be eligible. Two participants were excluded at this point because of elevated scores on the Geriatric Depression measure, resulting in a final sample of 49 older adults (age mean: 67.25 yr, SD = 5.44; years of education: 17.06 yr, SD = 2.77; 29 women). All procedures performed in the studies were approved by the Institutional Review Board at Cornell University and are in accordance with the ethical standards described in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Participants gave written informed consent in accordance with the Institutional Review Board of Cornell University.

### CRF Assessment

Our CRF metric was derived using a formula developed by Jurca and colleagues (46). This formula takes a participant's height, weight, age, sex, resting heart rate, and self-reported physical activity level to derive a CRF score in metabolic equivalents (1 metabolic equivalent = 3.5 ml $O_2$ uptake·kg body mass$^{-1}$·min$^{-1}$). The metabolic equivalent values derived from the formula have been validated in a population of older adults (57) and significantly correlated with explicitly recorded metabolic equivalent values from the maximal graded exercise test and with CRF estimates derived from submaximal field testing. The formula was further validated by McAuley and colleagues (59) and significantly correlated with a physician-supervised maximal exercise test and a one-mile timed walk. The authors also reported that formula-derived CRF estimates were significantly correlated with cognitive function, hippocampal volume, and memory complaints consistent with the timed walk and exercise-derived fitness measures (59). Height and weight were obtained during the MRI safety protocol at time of scanning and were self-reported. In accordance with previous studies using this measure (46, 57, 59), participants self-reported their level of physical activity given a scale of 1–5 with predetermined descriptions as outlined in the original protocol by Jurca and colleagues (46). For example, an activity level of 3 requires participation in aerobic exercise (such as brisk walking, swimming, or jogging) at a comfortable pace for 20–60 min per week (46). Although this self-report component may impact the reliability of the measure (64), our approach is consistent with earlier validation studies (57, 59). Resting heart rate was obtained using Biopac Systems Software obtained during resting-state MRI scanning (Biopac Systems).

### Neuroimaging

*Structural imaging acquisition, preprocessing, and analysis.* Anatomical scans from the Cornell MRI facility were acquired on a GE750 Discovery series 3T scanner with a T1-weighted volumetric MRI magnetization-prepared rapid gradient echo [repetition time: 2,500 ms; echo time [TE]: 3.44 ms; flip angle: 7°; 1.0 mm isotropic voxels, 176 slices]. Anatomical scans were acquired during one 5-m, 25-s run with ×2 acceleration with sensitivity encoding. Structural data were corrected for nonuniform intensities, affine-registered to Montreal Neurological Institute atlas (15), and skull-stripped using Freesurfer (Athinoula A. Martinos Center for Biomedical Imaging, Harvard University, Cambridge, MA).

*Functional imaging acquisition, preprocessing, and analysis.* Multi-echo functional images were acquired during two 10-m, 6-s resting-state scans. Participants were instructed to keep their eyes open, blinking and breathing normally. Multi-echo fMRI is a data acquisition sequence developed to enhance the blood oxygenation level contrast (49, 50). This method uses multiple echoes obtained at different TEs corresponding to different T2* weighted tissue relaxation rates (51). After recombining the echo times, independent components analysis is used to remove noise components (i.e., originating in white matter, CSF, movement, etc.) which are now more readily identifiable because of the greater signal contribution from the
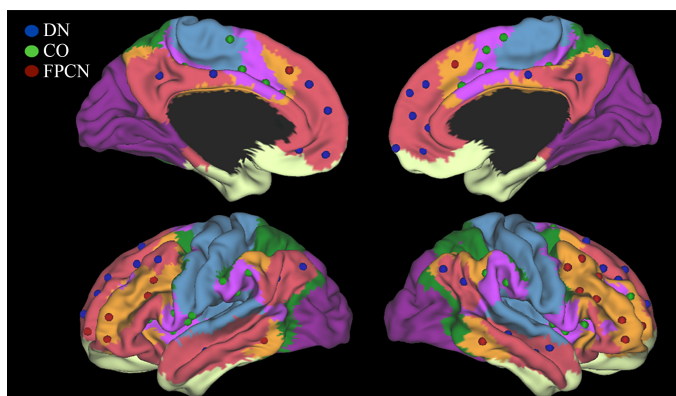
Fig. 1. Visualization of our networks of interest. Regions of interest for the default (DN), cingulo-opercular (CO), and frontoparietal (FPCN) control networks were taken from a resting-state parcellation by Gordon and colleagues (37) and are represented as spheres. For illustrative purposes, regions of interest were superimposed on an overlay (85) to validate functional network assignment. Figure was created using Connectome Workbench (58).

varying TEs. This procedure, known as multi-echo independent components analysis (ME-ICA), can render up to fourfold increases in the temporal signal-to-noise ratio (51). Resting-state functional scans were acquired using a multi-echo echo planar imaging sequence with online reconstruction (repetition time: 3,000 ms; TE: 13.7 ms, 30 ms, and 47 ms; flip angle: 83°; matrix size: 72 × 72; field of view: 210 mm; 46 axial slices; 3.0-mm isotropic voxels) with ×2.5 acceleration with sensitivity encoding.

Preprocessing was conducted with ME-ICA version 2.5 (49, 50) ((https://afni.nimh.nih.gov/pub/dist/src/pkundu/meica.py). The full ME-ICA preprocessing procedure has been described previously (75). Following ME-ICA, we identified nuisance components using a semiautomated procedure. This involved conducting a probabilistic independent components analysis (5) via multivariate exploratory linear decomposition into independent components (MELODIC) version 3.14, part of FSL (FMRIB Software Library, www.fmrib.ox.ac.uk/fsl), to isolate and extract remaining noise components following the ICA preprocessing.

Based on previous evidence of age-associated declines in RSFC (13, 30, 39, 83) or fitness-related modulation of network integrity (80, 81, 83), the default, cingulo-opercular, and frontoparietal control networks were selected a priori as our networks of interest. We used previously defined regions of interest (ROIs) based on a resting-state cortical parcellation (37). This parcellation was derived using resting-state data and has 333 ROIs, providing sufficient resolution to capture individual differences prominent in aging (27) and to avoid compromising sensitivity and blurring regional boundaries when networks are decomposed into simpler parcellations (63). Connectivity analyses were conducted using the Matlab-based Brain Connectivity Toolbox (67, 68; http://www.brain-connectivity-toolbox.net/). For a detailed description of this procedure, see Rubinov and Sporns (67, 68).

Preprocessed resting data were coregistered with the Montreal Neurological Institute-transformed anatomical scan within subjects.

We identified the three a priori-selected networks corresponding to 105 ROIs (37; 41 default, 24 frontoparietal, and 40 cingulo-opercular nodes). Regions corresponding to these networks are illustrated in Fig. 1. Time courses were extracted for each ROI, and a node-wise correlation matrix was created. The matrices were thresholded using a cost density function (averaged over a range of 0.10–0.3, steps of 0.01). These values were used to calculate our topological parameters of interest.

*Functional connectivity metrics.* To measure the integrity of functional brain networks, we used graph theoretical measures. Graph theory depicts the brain as a set of interacting nodes and edges. In a functional data set, "nodes" represent brain regions and "edges" represent the strength of functional coupling between those regions (10, 67). Examining the temporal nature of cross-correlations in the blood oxygenation level signal between nodes allows us to index the intrinsic functional architecture of the brain (67).

To capture changes in overall network connectivity, we derived estimates of global efficiency (to assess network integration or distributed processing) and local efficiency (to assess network segregation or more regional processing specificity). Global efficiency is the average inverse shortest path length in the network (52). In other words, it is derived by examining the connectivity between each node and every other node and averaging the inverse of this measure for all nodes in the network. Global efficiency was calculated using the Brain Connectivity Toolbox (67, 68) and is represented in equation form below:

$$E_{\text{glob}}(i) = \frac{1}{N(N-1)} \sum_{i \neq j} \frac{1}{d_{ij}},$$

where $d_{ij}$ is the shortest path (smallest number of edges) between nodes $i$ and $j$ (21).

Local efficiency is a measure of functional segregation. Unlike global efficiency, local efficiency measures only the edges connecting direct neighbor nodes and thus quantifies the average efficiency of local subgraphs (52). A network with high local efficiency then describes a topological organization with notable segregated neural processing, which is believed to underlie functional specialization (67). Local efficiency was also calculated in the Brain Connectivity Toolbox and is represented here:

$$E_{\text{local}} = \frac{1}{N_{G_i}(N_{G_i} - 1)} \sum_{j,k} \frac{1}{L_{j,k}},$$

where $N_{G_i}$ is the number of nodes in the subgraph $G_i$. Local efficiencies for each node can be averaged over all nodes to estimate the mean local efficiency of the graph.

### Statistical Analyses

Statistical analyses were conducted in R (version 3.3.2) using the RStanArm package and default settings (76). This software was used to fit two linear Bayesian models using the Markov Chain Monte Carlo algorithm to the data evaluating the impact of CRF of brain network metrics (global and local efficiency were fit separately) for men and women.

Table 1. *Descriptive statistics*

| Variable | Female Mean | Female SD | Male Mean | Male SD | μ Difference | SD Difference | HDI Lower | HDI Upper |
|---|---|---|---|---|---|---|---|---|
| CRF | 6.09 | 0.27 | 9.06 | 0.31 | −2.97 | 0.41 | −3.77 | −2.15 |
| Education | 16.86 | 0.49 | 17.29 | 0.78 | −0.43 | 0.93 | −2.21 | 1.42 |
| Age | 66.28 | 0.94 | 68.37 | 1.52 | −2.08 | 1.79 | −5.57 | 1.44 |
| MMSE | 28.05 | 0.28 | 28.18 | 0.36 | −0.13 | 0.46 | −1.02 | 0.76 |

Difference scores and HDIs refer to Bayesian posterior density estimates of the difference between groups. For mean and SD, CRF values are in metabolic equivalents, and age and education values are in years. CRF, cardiorespiratory fitness; HDI, highest density interval; MMSE, Mini-Mental Status Exam.

Table 2. *Global and local efficiency across networks*

| Variable | Female Mean | Female SD | Male Mean | Male SD | μ Difference | SD Difference | HDI Lower | HDI Upper |
|---|---|---|---|---|---|---|---|---|
| LE All | 0.750 | 0.005 | 0.749 | 0.006 | 0.001 | 0.008 | −0.013 | 0.017 |
| FPCN LE | 0.693 | 0.013 | 0.718 | 0.019 | −0.025 | 0.023 | −0.071 | 0.020 |
| DN LE | 0.711 | 0.008 | 0.721 | 0.006 | −0.010 | 0.010 | −0.030 | 0.008 |
| CO LE | 0.693 | 0.008 | 0.708 | 0.012 | −0.015 | 0.014 | −0.042 | 0.014 |
| GE All | 0.533 | 0.003 | 0.531 | 0.004 | 0.002 | 0.005 | −0.007 | 0.011 |
| FPCN GE | 0.425 | 0.007 | 0.404 | 0.009 | 0.022 | 0.012 | −0.001 | 0.045 |
| DN GE | 0.477 | 0.007 | 0.470 | 0.006 | 0.007 | 0.009 | −0.011 | 0.025 |
| CO GE | 0.477 | 0.006 | 0.479 | 0.007 | −0.003 | 0.009 | −0.020 | 0.016 |

Global and local network statistics are presented by group within and across the networks of interest. Difference scores and HDIs refer to Bayesian posterior density estimates of the difference between groups. CO, cingulo-opercular network; DN, default network; FPCN, frontoparietal control network; GE, global efficiency; GE All, global efficiency for all networks; HDI, highest density interval; LE, local efficiency; LE All, local efficiency for all networks.

For each model, the outcome variable of interest was the network connectivity metric (either local or global efficiency), and the predictors were CRF, sex, and the interaction between CRF and sex. Age and education were included as covariates of no interest. Log$_{10}$ transformations were used to correct variables that did not meet the assumptions for normality before analysis. Evidence for the role of sex was assessed using posterior distributions from each model along with 95% credible intervals and posterior probabilities. This information allows us to determine whether we can reasonably expect to exclude a null finding from our data (i.e., if the 95% credible interval includes 0, we cannot preclude the possibility of no difference). More useful, however, is that posterior distributions can determine exact probabilities for the effect of interest (e.g., "there was an 85% chance that the effect was greater than 0"). Such information is useful, as it helps to quantify the degree of uncertainty in the data.

## RESULTS

### Behavior

A summary of the demographic and behavioral data can be found in Table 1. We report Bayesian estimates of the posterior difference between groups (i.e., a Bayesian *t*-test) along with 95% credible highest density intervals (HDIs). Posterior credible intervals excluded zero for only one estimate. First, men had higher CRF levels than women (μ difference: −2.97; 95% HDI: −3.77, −2.15), corresponding to an effect size of $d = -2.2$. There were no sex differences in self-reported physical activity levels, education levels, or intelligence quotient (credible intervals included 0, and all effect sizes < ±0.45). Descriptive statistics for
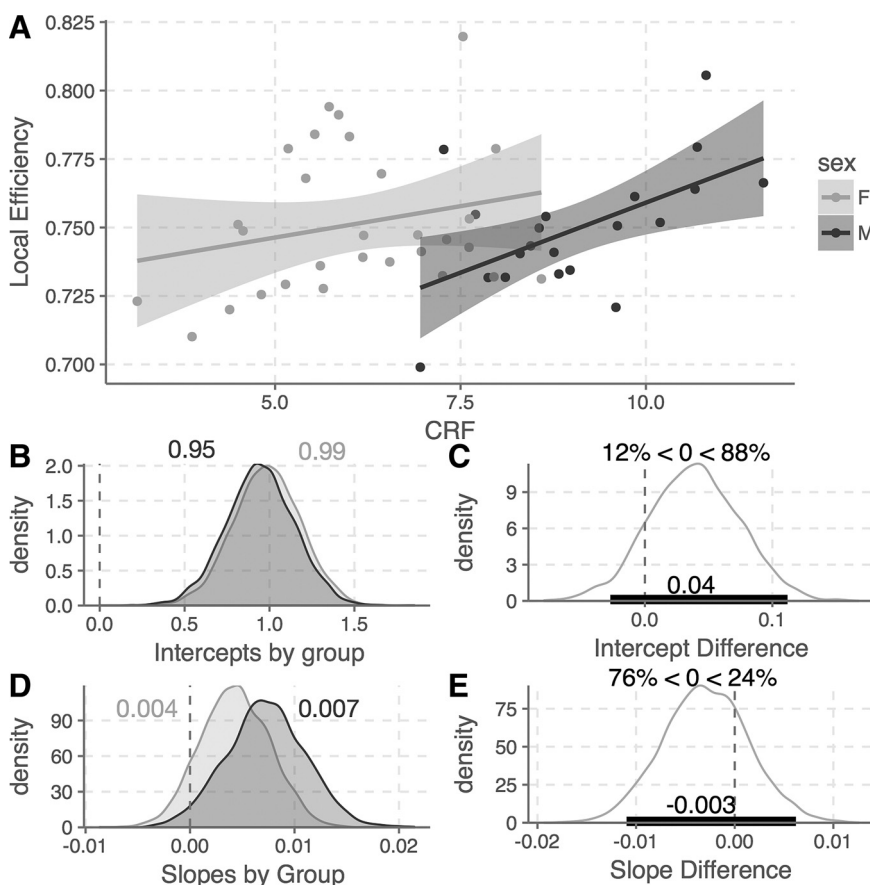


Fig. 2. Bayesian linear model of the relationship between CRF and local efficiency by sex. *A*: linear relationship between CRF and local efficiency by group (shaded regions represent standard errors). *B*: posterior distributions of intercepts for each group (F, M). Numbers appended to the plot are the median posterior density values. *C*: posterior difference between the group intercepts, along with a 95% credible interval and posterior probabilities (i.e., there is an 88% probability that women have higher local efficiency values than men). *D*: posterior distributions for the model slopes by group. *E*: posterior difference as described above for the intercepts. CRF, cardiorespiratory fitness; F, female; M, male.

network efficiencies are available in Table 2. Men and women did not reliably differ on any of these network metrics (all 95% HDIs include 0).

*CRF and Network Connectivity*

Global efficiency and local efficiency were computed for nodes within the three networks of interest (the default, frontoparietal control, and cingulo-opercular networks). Age and education were included as covariates in all graph theory analyses.

*Local efficiency.* As described earlier, we first ran a Bayesian linear model predicting local efficiency with sex as the between-groups variable, CRF as a continuous predictor variable, and age and education as controls (Fig. 2). The main effect of CRF was not reliably different from zero [$b = 0.004$, 95% HDI ($-0.002$, $0.010$)], nor was the main effect of sex [$b = -0.04$, 95% HDI ($-0.11$, $0.03$)], though in this case there was an 88% posterior probability that women had higher local efficiency values than men (Fig. 2*B*). The interaction between sex and CRF (i.e., the difference of slopes) did not reliably differ by sex [$b = 0.003$, 95% HDI ($-0.005$, $0.01$)], though again, posterior probabilities suggest that men are 76% more likely than women to have a stronger positive relationship between CRF and local efficiency.

As posterior values for each group were included as part of the specification for the original model, these distributions could be extracted and examined separately without the need for post hoc tests. The median posterior slope value for men was 0.007, with a 95% HDI that excluded 0 (0.0003, 0.014); indeed, posterior probabilities suggest a 97% likelihood that the slope value for men is greater than 0, and the posterior $R^2$ value for this group was 0.34. The median posterior slope value for women was lower, 0.004, and had a 95% HDI that included 0 ($-0.002$, $0.011$). For women, the posterior probability that their slope is greater than 0 is 90%, and the posterior $R^2$ value for this group was 0.21. The posterior probability distributions suggest that there is a 75% probability that men had steeper slope values than women, indicating that CRF has a similar positive effect on local efficiency across networks for both sexes but that this association is more robust in men than in women. Critically, the relationship across the groups is weaker than the relationships observed within the groups, resulting in a failure to observe a reliable relationship between CRF and local network efficiency across the full sample (Fig. 3).

*Global efficiency.* Next, we ran a similar Bayesian linear model predicting global efficiency. The model was defined as above, but with global efficiency as the outcome. As with local efficiency, the main effect of CRF was not reliably different from 0 [$b = -0.002$, 95% HDI ($-0.006$, $0.001$)]. There was a marginal main effect of sex [$b = 0.031$, 95% HDI ($-0.007$, $0.07$)]. This was associated with a 94% likelihood that men have higher global efficiency values than women (Fig. 4). The interaction between CRF and sex again was marginally reliable [$b = -0.003$, 95% HDI ($-0.008$, $0.002$]; however, the posterior probability that men had a steeper negative slope than women was 90%. Given the posterior probability values, we again examined the posterior slope distributions separately by sex. Men had a median posterior slope value of $b = -0.005$ with a 95% HDI of ($-0.0092$, $-0.00094$) and a posterior $R^2$ value of 0.35, suggesting that for this group the slope was
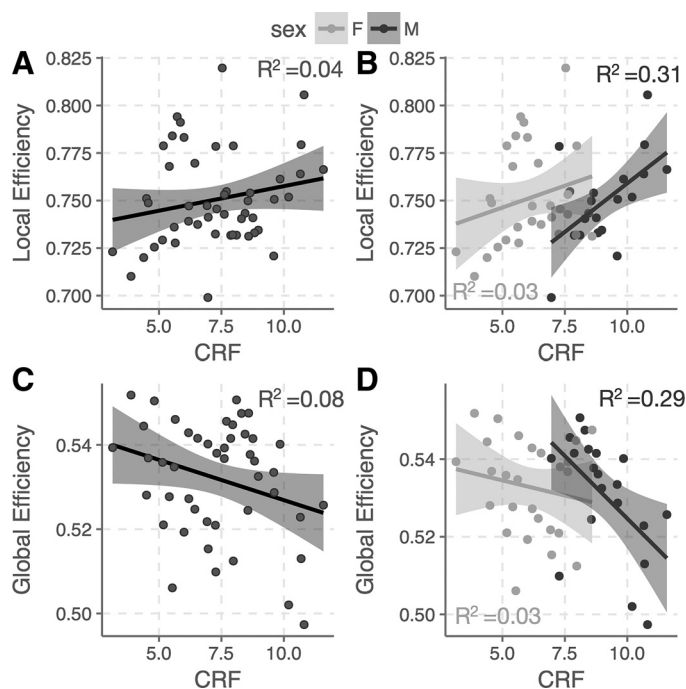


Fig. 3. Illustration of the relationship between CRF and network efficiencies demonstrating Simpson's paradox. *A*: relationship between CRF and local efficiency which, when combined across sexes, is not reliably different from zero (shaded regions represent standard errors). *B*: same relationship between CRF and local efficiency which, when stratified, is reliably different from zero in males. *C* and *D*: same effect as applied to global efficiency. CRF, cardiorespiratory fitness; F, female; M, male.

reliably different from 0. By contrast, women had a median posterior slope value of $b = -0.002$ with a 95% HDI of ($-0.006$, $0.001$) and a posterior $R^2$ value of 0.27, suggesting a weaker, nonreliable relationship for this group.

**DISCUSSION**

CRF is frequently cited as a modifiable lifestyle factor that is associated with brain health in older adulthood (11, 41, 80, 82). This study investigated the relationship between CRF and RSFC and how these associations differ for men and women. Across the default, frontoparietal control, and cingulo-opercular networks, CRF levels were positively associated with local network efficiency, a measure of regional connectedness, and negatively associated with global efficiency, a measure of overall network integration. However, these associations were less reliable across the entire participant sample (Fig. 3). These findings reflect the Simpson's paradox (34), wherein associations within groups are lost when combined into a single sample. This result speaks directly to the importance of considering sex in research that examines relationships between exercise and brain function. Analyses by sex revealed a positive relationship between CRF and local network efficiency and a negative relationship with global efficiency, but these associations were only reliably observed for men. Women showed a similar overall pattern, with positive associations between CRF and local efficiency and negative associations with global efficiency; however, the associations were weaker and were not reliably different from zero. The results show that physical fitness is related to functional connectivity of the brain
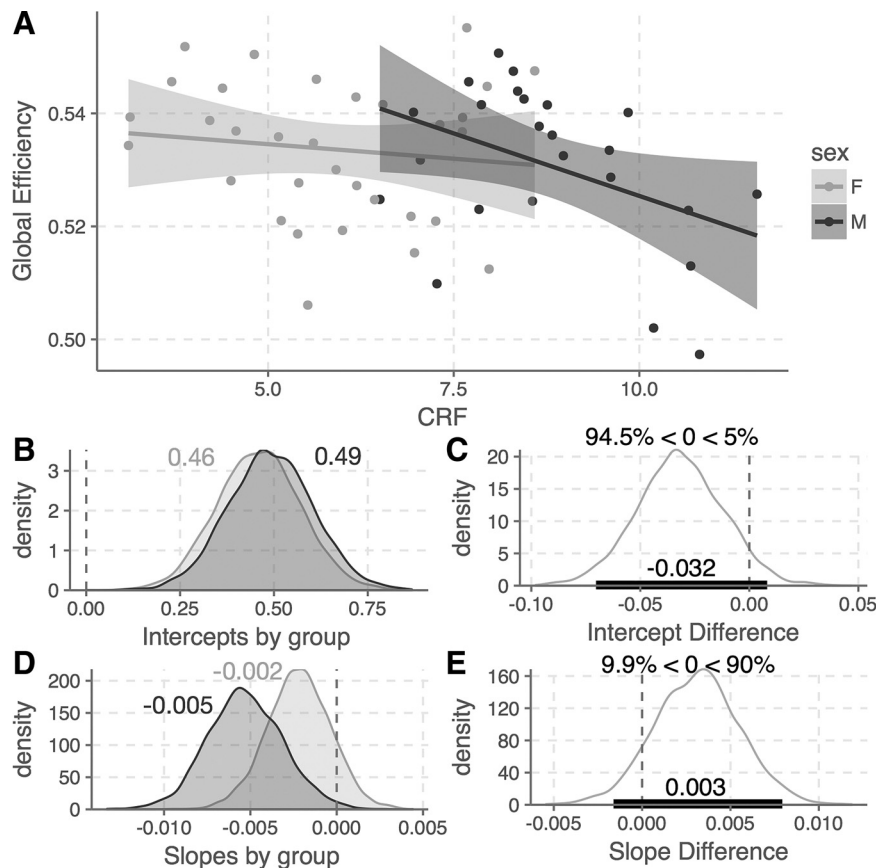
Fig. 4. Bayesian linear model of the relationship between CRF and global efficiency by sex. *A*: linear relationship between CRF and global efficiency by group (shaded regions represent standard errors). *B*: posterior distributions of intercepts for each group (F, M). Numbers appended to the plot are the median posterior density values. *C*: posterior difference between the group intercepts, along with a 95% credible interval and posterior probabilities (i.e., there is a 94% probability that men have higher global efficiency values than women). *D*: posterior distributions for the model slopes by group. *E*: posterior difference as described above for the intercepts. CRF, cardiorespiratory fitness; F, female; M, male.

in older adults during the resting state; however, these associations are sex-specific.

Older adults who are more physically fit have greater local efficiency among functionally connected brain regions and show stronger connections within discrete brain networks (83). This trend toward greater local efficiency in fit older adults contrasts with typical age-related shifts from local to more global efficiency, signaling increasingly dedifferentiated network connections with age (13, 20, 30, 39, 60, 75). In this context, the findings of the current study and others (e.g., 43) suggest that remaining physically fit may help to sustain a "younger" network architecture into later life. Furthermore, these associations may be neuroprotective, as greater local processing has been associated with better executive functioning (3, 43) in older adults and is positively predictive of cognitive gains following both cognitive training (2, 29) and exercise interventions (3).

Our findings of an association between CRF and increased local efficiency differ from that of a recent report by Kawagoe and colleagues (47). In their study, lower local efficiency and greater global efficiency was observed for more fit older adults. This efficiency pattern was also associated with better cognitive functioning, which the authors interpreted as a fitness-related pattern of compensatory network changes. Although they did not stratify their sample by sex, potentially masking the sex differences we report here, other methodological differences may have contributed to these divergent findings. We examined network efficiencies within and among three a priori-identified associative networks with a denser array of functionally defined nodes in contrast to a whole brain, structurally

defined node array (47). These differences in network identification may have enhanced our capacity to identify network-specific associations between RSFC and fitness levels. Furthermore, unlike a network compensation account (47), our findings are consistent with studies suggesting that decreased local, or segregated, network organization and increased global, or dedifferentiated, networks are associated with age-related decline (20, 38, 74). However, given the correlational nature of the study, further work will be necessary to determine the causal impact of CRF in later life. Specifically, it will be important to investigate whether CRF promotes a more "young-like" functional architecture or a compensatory pattern of dedifferentiated network connectivity. Furthermore, although the focus of this study was to elucidate sex differences in the impact of CRF on brain function specifically, the role of network efficiency as a mediator between CRF and cognitive functioning is an important future direction.

Future research will also be necessary to more fully elucidate sex differences in the relationship between CRF and brain function. As we observed here, sex-dependent associations exist between CRF and RSFC in brain networks that are most susceptible to change with age and fitness levels. It is well established that brain structure and function are sexually dimorphic (1, 18, 32, 33, 55, 56, 78). These sex differences persist into older age and have been observed during the resting state. In this context, sex differences might also be expected in the relationship between RSFC and CRF in later life. Our findings suggest that this is indeed the case. Men, but not women, showed reliable and robust associations between CRF and measures of network connectivity in older adults. This sex

difference is consistent with reports of sex-dependent associations, favoring men, in the relationship between fitness levels and peripheral physical and central nervous system function in older adults (65, 66, 71; also see Refs. 28 and 61 for reviews). However, to our knowledge, these sex differences have not previously been investigated at the level of large-scale cortical networks.

An obvious next question is why this CRF and RSFC association was only reliable for men in our sample. We hypothesized effects favoring women given research demonstrating stronger associations between fitness and cognition in women (4). However, it is important to reiterate that previous studies have not examined sex differences on the impact of fitness at the level of brain function (but at the level of overt cognition). Thus, we are the first to investigate (and interpret) sex differences in this domain. Based on our results, we suggest that the stronger association observed in men is the result of a more rapid shift toward global efficiency among these associative brain networks in men versus women. Age-related declines in brain structure and function are known to occur more rapidly in men, particularly among association regions and related brain networks, which were the focus of the current study (62, 88). Consistent with this interpretation, we observed tendencies for lower measures of local efficiency (88% likelihood) and greater global efficiency (94% likelihood) in men versus women in our sample. Sex differences in the trajectory of age-related changes, with men showing a more rapid shift toward less localized network organization, suggest that lifestyle factors such as physical fitness levels may have a relatively greater impact on the preservation of more differentiated brain networks in older men. Although much research has investigated age and sex as factors in network neuroscience research, these have rarely been investigated within a single study (70). The current findings argue for careful consideration of sex as a factor in future research investigating the determinants and implications of changes in the organization of functional brain networks in older adulthood.

Notably, we did not see sex differences in reported physical activity level in this study, providing greater evidence that the differences seen between sexes are attributable to physiological attributes associated with CRF (i.e., the sum of other components of the CRF equation, including resting heart rate and body mass index) as opposed to systematic differences in physical activity reporting (which are known to occur between the sexes; 48). It should also be noted that we cannot exclude the possibility of a sex-specific reporting bias in our CRF metric. The formula utilizes self-reported height and weight information to calculate body mass index. Although the information was gathered as part of the MRI safety protocol, in which it would be in the participant's interest to provide an accurate report, a sex-dependent bias in reporting these measures is possible (15a).

Furthermore, although our total sample size is generally consistent with similar studies, individual difference studies typically require large cohorts. To help mitigate this limitation, the neuroimaging methods employed in the study (e.g., the use of ME-ICA) served to ensure stronger signal-to-noise ratio for obtained neuroimaging data (i.e., a fourfold increase in signal-to-noise ratio). Furthermore, our use of Bayesian statistics served to minimize the influence of statistical outliers and

enabled us to report probabilities (and thereby quantify uncertainties) in the data.

Although our findings identified sex differences in the association between fitness level and brain function in older adulthood, further research will be necessary to reconcile these findings with previous cognitive neuroscience investigations (47) as well as neurocognitive studies identifying stronger associations between CRF and cognitive functioning in women (4). Unfortunately, myriad methodological differences often preclude direct comparisons among studies in the field. Perhaps the most limiting of these involves discrepancies in the measurement of physical fitness. Differences include the use of self-report versus objective measures (69), as well as the operationalization of physical activity and physical fitness (53, 83). Furthermore, investigating sex differences in this functional domain is complicated by other sex-based differences such as the impact of hormonal replacement therapy (16, 17, 23). Although these challenges are endemic to the field, our findings that CRF is associated with brain function in a sex-dependent manner underscores the importance of considering sex as a factor when studying associations between exercise and brain health in older adulthood. Rapid increases in the popularity of exercise as an intervention to promote brain health in later life presents an urgent need to overcome these methodological challenges toward the goal of building a coherent body of research to inform evidence-based public health initiatives.

## DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

## AUTHOR CONTRIBUTIONS

C.J.D. and G.R.T. conceived and designed research; C.J.D. and A.W.L. performed experiments; C.J.D. and J.A.E.A. analyzed data; C.J.D., J.A.E.A., R.N.S., and G.R.T. interpreted results of experiments; C.J.D. and J.A.E.A. prepared figures; C.J.D., J.A.E.A., and G.R.T. drafted manuscript; C.J.D., J.A.E.A., A.W.L., R.N.S., and G.R.T. edited and revised manuscript; C.J.D., J.A.E.A., A.W.L., R.N.S., and G.R.T. approved final version of manuscript.

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