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

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Brain networks, resting state functional connectivity, aging, physical fitness, fMRI, network efficiency

39 **Abstract**

40

41 We investigated sex differences in the association between a measure of physical health,  
42 cardiorespiratory fitness (CRF), and brain function using resting state functional connectivity  
43 fMRI. We examined these sex differences in the default, frontoparietal control, and cingulo-  
44 opercular networks, assemblies of functionally connected brain regions known to be impacted by  
45 both age and fitness level. Forty-nine healthy older adults (29 female) were scanned to obtain  
46 measures of intrinsic connectivity within and across these three networks. We calculated global  
47 efficiency (a measure of network integration), and local efficiency (a measure of network  
48 specialization) using graph theoretical methods. Across all three networks combined local  
49 efficiency was positively associated with CRF, and this was more robust in male versus female  
50 older adults. Further, global efficiency was negatively associated with CRF, but only in males.  
51 Our findings suggest that in older adults, associations between brain network integrity and  
52 physical health are sex-dependent. These results underscore the importance of considering sex  
53 differences when examining associations between fitness and brain function in older adulthood.

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61 Abbreviations: cardiorespiratory fitness (CRF); resting state functional connectivity (RSFC);  
62 highest density intervals (HDI)

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65 Physical exercise improves brain physiology, structure, and function in older adulthood  
66 (14, 46). Exercise has been shown to influence neural growth factors and enhance processes such  
67 as angiogenesis, synaptogenesis, and neurogenesis (16; but see 74). These changes are also  
68 measurable at a systems level, impacting cortical structure and function (25; 55).  
69 Cardiorespiratory fitness (CRF), a measure of physical fitness indexing oxygen consumption and  
70 transport (42), has been associated with greater grey matter volume and density in frontal and  
71 parietal cortices as well as increased hippocampal volumes (12; 24; 37; 85). These changes are  
72 associated with higher cognitive functioning, particularly in domains most susceptible to age-  
73 related decline, including executive functioning and memory (14; 85).

74 Cardiorespiratory fitness is also related to changes in the functional architecture of the  
75 brain measured at rest (84). Estimates of resting-state functional connectivity (RSFC)  
76 characterize coherent patterns of intrinsic neural activity in the absence of explicit task demands.  
77 RSFC measures have been used to study brain health both in typical and atypical aging (20).  
78 RSFC is thought to reflect repeated patterns of coherent neural oscillatory activity reinforced  
79 across time and thus provides a stable, neurophysiological marker of brain function (6; see 78 for  
80 a review). Thus, measures of RSFC are useful neural markers for assessing the impact of  
81 systemic lifestyle influences, such as CRF, on brain function. Further, RSFC measures are  
82 readily obtained in older adult populations and have been shown to be both replicable (7, 43),  
83 and reliable (73; 88).

84 RSFC is altered in normal aging (e.g. 13; 30; 31) and these changes appear to target  
85 functional connectivity within and between networks associated with higher-order cognitive  
86 functioning (30; 31). The default, frontoparietal control, and cingulo-opercular networks have  
87 been particularly implicated (30; 31). The default network consists of the ventromedial PFC,

88 posterior cingulate and retrosplenial cortex, inferior parietal lobule, lateral temporal cortex,  
89 dorsomedial PFC and the hippocampal formation among others (9). This network is implicated  
90 in internally-focused cognitive processes (8; 41). The frontoparietal control network is composed  
91 of anterior and dorsolateral PFC, anterior inferior parietal lobule, anterior cingulate, and insular  
92 cortices and is associated with intrinsic (i.e. top down) cognitive control processes (22; 80).  
93 Finally, the cingulo-opercular network (22), which encompasses anterior insula/operculum,  
94 thalamus, and the dorsal anterior cingulate cortex, is associated with sustaining cognitive set as  
95 well as external or salience-driven (i.e. bottom-up) attentional processing. Common age-related  
96 changes across these networks include reduced within, or local, connectivity and increased  
97 between, or more global, connectivity (40). More broadly, aging is associated with greater  
98 overall network integration and reduced functional segregation, as well as reduced connectivity  
99 within networks (13; 30; 31; 75; 84).

100 Functional connectivity of the default, frontal-parietal, and cingulo-opercular networks is  
101 also modulated by fitness and activity levels in older adulthood (81; 82; 84). CRF has been  
102 positively associated with global efficiency, a measure of network integration and *distributed*  
103 processing and negatively associated with local efficiency, a measure of within network  
104 segregation and *regional* specificity across the whole brain (48, and see 68, for a review of  
105 network measures). These findings suggest that greater CRF is associated with increased  
106 network integration and reduced segregation between networks in older adults (48). However,  
107 the evidence remains equivocal. Local, or less-distributed, processing has also been positively  
108 associated with exercise levels (44; 45).

109 There is evidence for a relationship between RSFC and CRF in older adulthood and  
110 evidence of sex differences in functional brain aging. Yet sex differences in the relationship

111 between CRF and brain function in older adulthood have not been investigated. Older males and  
112 females show differential benefits in cognitive performance associated with exercise and fitness  
113 levels. Studies with a greater proportion of female participants report greater cognitive gains  
114 (14). A recent meta-analysis reported greater exercise-related cognitive benefits in females (4).  
115 Yet the neural basis of sex differences in the relationship between fitness and brain function in  
116 older adults has not been directly explored.

117 To address this gap, here we investigate sex-differences in the impacts of CRF on RSFC  
118 in older adults. We examine this relationship specifically focusing on three higher-order  
119 association networks (13) that have been most reliably associated with changes both in aging and  
120 fitness levels: the default network, frontoparietal control network and cingulo-opercular network.  
121 We hypothesize that local, or greater within network, connectivity would be associated with  
122 higher CRF levels in older adults (44; 45). As there are no studies investigating sex differences  
123 in the association between RSFC and CRF, we are unable to pose specific hypotheses. However,  
124 greater exercise-related cognitive benefits have been observed in older females (4). This suggests  
125 that patterns of functional brain activity associated with better cognitive performance, i.e.  
126 increased local efficiency, should be more reliably observed in females.

127

## 128 **1. Methods**

### 129 **1.1. Participants**

130 Fifty-one older adults participated in this study and were recruited from the community in  
131 Ithaca, New York. All participants were healthy, over the age of 60, with normal or corrected-to-  
132 normal visual acuity, and no history of psychiatric, neurological, or other medical illness that  
133 could compromise cognitive functions. In addition to the inclusion criteria noted above,

134 participants were required to have Geriatric Depression Scores equal to or less than 9 (i.e. within  
135 the 'normal' range; 87), as well as Mini-Mental State Exam scores of greater than 25 (26) to be  
136 eligible. Two participants were excluded at this point due to elevated scores on the Geriatric  
137 Depression measure, resulting in a final sample of forty-nine older adults (age mean= 67.25 y;  
138 SD= 5.44; years of education = 17.06 y; SD = 2.77; 29 women). All procedures performed in the  
139 studies were approved by the Institutional Review Board at Cornell University and are in  
140 accordance with the ethical standards described in the 1964 Helsinki declaration and its later  
141 amendments, or comparable ethical standards. Participants gave written informed consent in  
142 accordance with the Institutional Review Board of Cornell University.

143

## 144 **1.2. Cardiorespiratory Fitness Assessment**

145 Our CRF metric was derived using a formula developed by Jurca and colleagues (47).  
146 This formula takes a participant's height, weight, age, sex, resting heart rate, and self-reported  
147 physical activity level to derive a CRF score in metabolic equivalents (1 metabolic equivalent=  
148  $3.5 \text{ ml O}_2 \text{ uptake} \cdot \text{kilograms of body mass}^{-1} \cdot \text{minutes}^{-1}$ ). The metabolic equivalent values  
149 derived from the formula have been validated in a population of older adults (58) and  
150 significantly correlated with explicitly recorded metabolic equivalent values from the maximal  
151 graded exercise test and with CRF estimates derived from submaximal field-testing. The formula  
152 was further validated by McAuley and colleagues and significantly correlated with a physician-  
153 supervised maximal exercise test and a 1-mile timed walk (60). The authors also reported that  
154 formula-derived CRF estimates were significantly correlated with cognitive function,  
155 hippocampal volume, and memory complaints consistent with the timed walk and exercise-  
156 derived fitness measures (60). Height and weight were obtained during the MRI safety protocol

157 at time of scanning and were self-reported In accordance with previous studies using this  
158 measure (47; 58; 60), participants self-reported their level of physical activity given a scale of 1-  
159 5 with predetermined descriptions as outlined in the original protocol by Jurca and colleagues  
160 (47). For example, an activity level of 3 requires participation in aerobic exercise (such as brisk  
161 walking, swimming, or jogging) at a comfortable pace for 20-60 minutes per week (47). While  
162 this self-report component may impact the reliability of the measure (65) our approach is  
163 consistent with earlier validation studies (58; 60). Resting heart rate was obtained using Biopac  
164 Systems Software obtained during resting-state MRI scanning (© 2017 BIOPAC Systems Inc.)

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### 166 **1.3.Neuroimaging**

#### 167 **1.3.1. Structural imaging acquisition, preprocessing and analysis**

168 Anatomical scans from the Cornell MRI Facility were acquired on a GE750 Discovery  
169 series 3T scanner with a T1-weighted volumetric MRI magnetization prepared rapid gradient  
170 echo (repetition time (TR)=2500ms; echo time (TE)=3.44ms; flip angle (FA)=7°; 1.0mm  
171 isotropic voxels, 176 slices). Anatomical scans were acquired during one 5m25s run with 2x  
172 acceleration with sensitivity encoding. Structural data were corrected for non-uniform intensities,  
173 affine-registered to Montreal Neurological Institute (MNI) atlas (15) and skull-stripped using  
174 Freesurfer (Athinoula A. Martinos Center for Biomedical Imaging, Harvard University,  
175 Cambridge, MA, USA).

#### 176 **1.3.2. Functional imaging acquisition, preprocessing and analysis**

177 Multi-echo functional images were acquired during two 10m 06s resting-state scans.  
178 Participants were instructed to keep their eyes open, blinking and breathing normally. Multi-echo  
179 fMRI is a data acquisition sequence developed to enhance the blood oxygenation level (BOLD)

180 contrast (50; 51). This method uses multiple echoes obtained at different echo times (TEs)  
181 corresponding to different T2\* weighted tissue relaxation rates (52). After recombining the echo-  
182 times, independent components analysis is used to remove noise components (i.e. originating in  
183 white matter, CSF, movement, etc.) which are now more readily identifiable due to the greater  
184 signal contribution from the varying TEs. This procedure, known as multi-echo independent  
185 components analysis or ME-ICA, can render up to fourfold increases in the temporal signal-to-  
186 noise ratio (52). Resting-state functional scans were acquired using a multi-echo echo planar  
187 imaging (ME-EPI) sequence with online reconstruction (TR=3000ms; TE's=13.7, 30, 47ms;  
188 FA=83°; matrix size=72x72; field of view (FOV)=210mm; 46 axial slices; 3.0mm isotropic  
189 voxels) with 2.5x acceleration with sensitivity encoding.

190 Preprocessing was conducted with ME-ICA version 2.5 (50; 51)  
191 (<https://afni.nimh.nih.gov/pub/dist/src/pkundu/meica.py>). The full ME-ICA preprocessing  
192 procedure has been described previously (76). Following ME-ICA, we identified nuisance  
193 components using a semi-automated procedure. This involved conducting a probabilistic  
194 independent components analysis (5) via multivariate exploratory linear decomposition into  
195 independent components (MELODIC) version 3.14, part of FSL (FMRIB's Software Library,  
196 [www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)) to isolate and extract remaining noise components following the ICA  
197 pre-processing.

198 Based on previous evidence of age-associated declines in RSFC (13; 30; 40; 84) or  
199 fitness-related modulation of network integrity (81; 82; 84), the default, cingulo-opercular, and  
200 frontoparietal control networks were selected *a priori* as our networks of interest. We used  
201 previously defined regions of interest based on a resting state cortical parcellation (38). This  
202 parcellation was derived using resting state data and has 333 ROIs, providing sufficient



203 resolution to capture individual differences prominent in aging (27), and to avoid compromising  
204 sensitivity and blurring regional boundaries when networks are decomposed into simpler  
205 parcellations (64). Connectivity analyses were conducted using the Matlab-based Brain  
206 Connectivity Toolbox (68; 69; <http://www.brain-connectivity-toolbox.net/>). For a detailed  
207 description of this procedure, see Rubinov and Sporns (68; 69).

208 Pre-processed resting data were co-registered with the MNI-transformed anatomical scan  
209 within subjects. We identified the three *a priori* selected networks corresponding to 105 regions  
210 of interest (38; 41 default, 24 frontoparietal, and 40 cingulo-opercular nodes). Regions  
211 corresponding to these networks are illustrated in Figure 1. Time courses were extracted for each  
212 region of interest and a node-wise correlation matrix was created. The matrices were thresholded  
213 using a cost density function (averaged over a range of 0.10-0.3, steps of .01). These values were  
214 used to calculate our topological parameters of interest.

215

216 [INSERT FIGURE 1 HERE]

217

### 218 **1.3.3. Functional connectivity metrics**

219 To measure the integrity of functional brain networks we used graph theoretical  
220 measures. Graph theory depicts the brain as a set of interacting nodes and edges. In a functional  
221 dataset, ‘nodes’ represent brain regions and ‘edges’ represent the strength of functional coupling  
222 between those regions (10; 68). Examining the temporal nature of cross-correlations in the  
223 BOLD signal between nodes allows us to index the intrinsic functional architecture of the brain  
224 (68).

225 To capture changes in overall network connectivity we derived estimates of global  
226 efficiency (to assess network integration or distributed processing) and local efficiency (to assess  
227 network segregation or more regional processing specificity). Global efficiency is the average  
228 inverse shortest path length in the network (53). In other words, it is derived by examining the  
229 connectivity between each node and every other node and averaging the inverse of this measure  
230 for all nodes in the network. Global efficiency was calculated using the Brain Connectivity  
231 Toolbox (68; 69) and is represented in equation form below:

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

232  
233 where  $d_{ij}$  is the shortest path (smallest number of edges) between nodes  $i$  and  $j$  (21).

234 Local efficiency is a measure of functional segregation. Unlike global efficiency, local  
235 efficiency measures only the edges connecting direct neighbor nodes and thus quantifies the  
236 average efficiency of local subgraphs (53). A network with high local efficiency then describes a  
237 topological organization with notable segregated neural processing, which is believed to underlie  
238 functional specialization (68). Local efficiency was also calculated in the Brain Connectivity  
239 Toolbox and is represented here:

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

240  
241 where  $N_{G_i}$  is the number of nodes in the subgraph  $G_i$ . Local efficiencies for each node can  
242 be averaged over all nodes to estimate the mean local efficiency of the graph.

#### 243 1.4. Statistical analyses

244 Statistical analyses were conducted in R (version 3.3.2) using the rstanarm package and  
245 default settings (77). This software was used to fit two linear Bayesian models using the Markov

246 Chain Monte Carlo algorithm to the data evaluating the impact of CRF of brain network metrics  
247 (global and local efficiency were fit separately) for males and females.

248 For each model, the outcome variable of interest was the network connectivity metric  
249 (either local or global efficiency), and the predictors were CRF, sex, and the interaction between  
250 CRF and sex. Age and education were included as covariates of no interest. Log10  
251 transformations were used to correct variables that did not meet the assumptions for normality  
252 prior to analysis. Evidence for the role of sex was assessed using posterior distributions from  
253 each model along with 95% credible intervals and posterior probabilities. This information  
254 allows us to determine whether or not we can reasonably expect to exclude a null finding from  
255 our data (i.e., if the 95% credible interval includes 0, we cannot preclude the possibility of no  
256 difference). More useful however is that posterior distributions can determine exact probabilities  
257 for the effect of interest (e.g., "there was an 85% chance that the effect was greater than 0").  
258 Such information is useful as it helps to quantify the degree of uncertainty in the data.

259

## 260 **2. Results**

### 261 **2.1. Behavior**

262 A summary of the demographic and behavioral data can be found in Table 1. We report  
263 Bayesian estimates of the posterior difference between groups (i.e. a Bayesian *t-test*) along with  
264 95% credible highest density intervals (HDI). Posterior credible intervals excluded zero for only  
265 one estimate. First, males had higher CRF levels than females ( $\mu$  difference -2.97, 95% HDI: -  
266 3.77, -2.15), corresponding to an effect size of  $d = -2.2$ . There were no sex differences in self-  
267 reported physical activity levels, education levels, or intelligence quotient (credible intervals  
268 included 0, and all effect sizes  $< \pm .45$ ). Descriptive statistics for network efficiencies are

269 available in Table 2. Males and females did not reliably differ on any of these network metrics  
270 (all 95% HDI include 0).

## 271 **CRF and Network Connectivity**

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

### 275 **2.2.1. Local efficiency**

276 As described earlier, we first ran a Bayesian linear model predicting local efficiency with  
277 sex as the between-groups variable, CRF as a continuous predictor variable, and age and  
278 education as controls (see Figure 2). The main effect of CRF was not reliably different from  
279 zero,  $b = 0.004$ , 95% HDI (-0.002, 0.010), nor was the main effect of sex,  $b = -0.04$ , 95% HDI (-  
280 0.11, 0.03) – though in this case there was an 88% posterior probability that women had higher  
281 local efficiency values than men (see Figure 2B). The interaction between sex and CRF (i.e. the  
282 difference of slopes) did not reliably differ by sex,  $b = 0.003$ , 95% HDI (-0.005, 0.01), though  
283 again, posterior probabilities suggest that males are 76% more likely than females to have a  
284 stronger positive relationship between CRF and local efficiency.

285

286 [INSERT FIGURE 2 HERE]

287

288 As posterior values for each group were included as part of the specification for the  
289 original model, these distributions could be extracted and examined separately without the need  
290 for post-hoc tests. The median posterior slope value for males was 0.007, with a 95% HDI that  
291 excluded 0, (0.0003, 0.014), indeed, posterior probabilities suggest a 97% likelihood that the

292 slope value for males is greater than 0, and the posterior  $R^2$  value for this group was 0.34. The  
293 median posterior slope value for females was lower, 0.004, and had a 95% HDI which included  
294 0, (-0.002, 0.011). For females, the posterior probability that their slope is greater than zero is  
295 90%, and the posterior  $R^2$  value for this group was 0.21. The posterior probability distributions  
296 suggest that there is a 75% probability that males had steeper slope values than females  
297 indicating that CRF has a similar positive effect on local efficiency across networks for both  
298 sexes, but that this association is more robust in males than in females. Critically, the relationship  
299 *across* the groups is weaker than the relationships observed *within* groups, resulting in a failure  
300 to observe a reliable relationship between CRF and local network efficiency across the full  
301 sample (Figure 3).

302

303 [INSERT FIGURE 3 HERE]

304

### 305 **2.2.2. Global efficiency**

306 Next, we ran a similar Bayesian linear model predicting global efficiency. The model  
307 was defined as above, but with global efficiency as the outcome. As with local efficiency, the  
308 main effect of CRF was not reliably different from 0,  $b = -0.002$ , HDI (-0.006, 0.001). There  
309 was a marginal main effect of sex,  $b = 0.031$ , 95% HDI (-0.007, 0.07). This was associated with  
310 a 94% likelihood that males have higher global efficiency values than females (see Figure 4).  
311 The interaction between CRF and sex again was marginally reliable,  $b = -0.003$ , 95% HDI (-  
312 0.008, 0.002), however the posterior probability that males had a steeper negative slope than  
313 females was 90%. Given the posterior probability values, we again examined the posterior slope  
314 distributions separately by sex. Males had a median posterior slope value of  $b = -0.005$  with a

315 95% HDI of (-0.0092, -0.00094) and a posterior  $R^2$  value of 0.35 suggesting that for this group,  
316 the slope was reliably different from zero. By contrast, females had a median posterior slope  
317 value of  $b = -0.002$  with a 95% HDI of (-0.006, 0.001), and a posterior  $R^2$  value of 0.27  
318 suggesting a weaker, non-reliable relationship for this group.

### 319 **3. Discussion**

320 CRF is frequently cited as a modifiable lifestyle factor that is associated with brain health in  
321 older adulthood (11; 42; 81; 83). This study investigated the relationship between CRF and  
322 RSFC, and how these associations differ for males and females. Across the default, frontoparietal  
323 control, and cingulo-opercular networks, CRF levels were positively associated with local  
324 network efficiency, a measure of regional connectedness, and negatively associated with global  
325 efficiency, a measure of overall network integration. However, these associations were less  
326 reliable across the entire participant sample (Figure 3). These findings reflect the Simpson's  
327 paradox (35), wherein associations within groups are lost when combined into a single sample.  
328 This result speaks directly to the importance of considering sex in research examining  
329 relationships between exercise and brain function. Analyses by sex revealed a positive  
330 relationship between CRF and local network efficiency and a negative relationship with global  
331 efficiency, but these associations were only reliably observed for males. Females showed a  
332 similar overall pattern, positive associations between CRF and local efficiency and negative  
333 associations with global efficiency, however, the associations were weaker and were not reliably  
334 different from 0. The results show that physical fitness is related to functional connectivity of the  
335 brain in older adults during the resting state, however, these associations are sex-specific.

336 Older adults who are more physically fit have greater local efficiency among functionally  
337 connected brain regions and show stronger connections within discrete brain networks (84). This

338 trend towards greater local efficiency in fit older adults contrasts with typical age-related shifts  
339 from local to more global efficiency, signaling increasingly dedifferentiated network connections  
340 with age (13; 20; 30; 40; 61; 76). In this context, the findings of the current study and others (e.g.  
341 44) suggest that remaining physically fit may help to sustain a ‘younger’ network architecture  
342 into later life. Further, these associations may be neuroprotective as greater local processing has  
343 been associated with better executive functioning (3; 44) in older adults and is positively  
344 predictive of cognitive gains following both cognitive training (2; 29) and exercise interventions  
345 (3).

346 Our findings of an association between CRF and increased local efficiency differ from  
347 that of a recent report by Kawagoe and colleagues (48). In their study, lower local efficiency, and  
348 greater global efficiency was observed for more fit older adults. This efficiency pattern was also  
349 associated with better cognitive functioning which the authors interpreted as a fitness-related  
350 pattern of compensatory network changes. While they did not stratify their sample by sex,  
351 potentially masking the sex-differences we report here, other methodological differences may  
352 have contributed to these divergent findings. We examined network efficiencies within and  
353 among three *a priori* identified associative networks with a denser array of functionally defined  
354 nodes in contrast to a whole brain, structurally-defined node array (48). These differences in  
355 network identification may have enhanced our capacity to identify network- specific associations  
356 between RSFC and fitness levels. Further, unlike a network compensation account (48), our  
357 findings are consistent with studies suggesting that decreased local, or segregated, network  
358 organization and increased global, or dedifferentiated, networks are associated with age-related  
359 decline (20; 39; 75). However, given the correlational nature of the study, further work will be  
360 necessary to determine the causal impact of CRF in later life. Specifically, it will be important to

361 investigate whether CRF promotes a more ‘young-like’ functional architecture or a  
362 compensatory pattern of dedifferentiated network connectivity. Further, while the focus of this  
363 study was to elucidate sex differences in the impact of CRF on brain function specifically, the  
364 role of network efficiency as a mediator between CRF and cognitive functioning is an important  
365 future direction.

366 Future research will also be necessary to more fully elucidate sex differences in the  
367 relationship between CRF and brain function. As we observed here, sex-dependent associations  
368 exist between CRF and RSFC in brain networks most susceptible to change with age and fitness  
369 levels. It is well established that brain structure and function are sexually dimorphic (1; 18; 33;  
370 34; 57; 79). These sex differences persist into older age and have been observed during the  
371 resting state. In this context, sex differences might also be expected in the relationship between  
372 RSFC and CRF in later life. Our findings suggest that this is indeed the case. Males, but not  
373 females, showed reliable and robust associations between CRF and measures of network  
374 connectivity in older adults. This sex difference is consistent with reports of sex-dependent  
375 associations, favoring males, in the relationship between fitness levels and peripheral physical  
376 and central nervous system function in older adults ( 66; 67; 72, and see 28; 62 for reviews).  
377 However, to our knowledge, these sex differences have not previously been investigated at the  
378 level of large-scale cortical networks.

379 An obvious next question is why this CRF and RSFC association was only reliable for  
380 males in our sample. We hypothesized effects favoring females given research demonstrating  
381 stronger associations between fitness and cognition in females (4). However, it is important to  
382 reiterate that previous studies have not examined sex differences in the impact of fitness at the  
383 level of brain function (but at the level of overt cognition). Thus, we are the first to investigate



384 (and interpret) sex differences in this domain. Based on our results, we suggest that the stronger  
385 association observed in males is the result of a more rapid shift towards global efficiency among  
386 these associative brain networks in males versus females. Age-related declines in brain structure  
387 and function are known to occur more rapidly in males, particularly among association regions  
388 and related brain networks which were the focus of the current study (63; 89). Consistent with  
389 this interpretation we observed tendencies for lower measures of local efficiency (88%  
390 likelihood) and greater global efficiency (94% likelihood) in males versus females in our sample.  
391 Sex-differences in the trajectory of age-related changes, with males showing a more rapid shift  
392 towards less localized network organization, suggest that lifestyle factors such as physical fitness  
393 levels may have a relatively greater impact on the preservation of more differentiated brain  
394 networks in older males. While much research has investigated age and sex as factors in network  
395 neuroscience research, these have rarely been investigated within a single study (71). The  
396 current findings argue for careful consideration of sex as a factor in future research investigating  
397 the determinants and implications of changes in the organization of functional brain networks in  
398 older adulthood.

399         Notably, we did not see sex differences in reported physical activity level in this study,  
400 providing greater evidence that the differences seen between sexes are attributable to  
401 physiological attributes associated with CRF (i.e. the sum of other components of the CRF  
402 equation including resting heart rate and body mass index) as opposed to systematic differences  
403 in physical activity reporting (which are known to occur between the sexes; 49). It should also  
404 be noted that we cannot exclude the possibility of a sex-specific reporting bias in our CRF  
405 metric. The formula utilizes self reported height and weight information to calculate BMI. While  
406 the information was gathered as part of the MRI safety protocol, where it would be in the

407 participant's interest to provide an accurate report, a sex-dependent bias in reporting these  
408 measures is possible (36).

409 Further, while our total sample size is generally consistent with similar studies, individual  
410 difference studies typically require large cohorts. To help mitigate this limitation, the  
411 neuroimaging methods employed in the study (e.g. the use of ME-ICA) served to ensure stronger  
412 signal-to-noise ratio for obtained neuroimaging data (i.e. a four-fold increase in SNR). Further,  
413 our use of Bayesian statistics served to minimize the influence of statistical outliers and enabled  
414 us to report probabilities (and thereby quantify uncertainties) in the data.

415 While our findings identified sex-differences in the association between fitness level and  
416 brain function in older adulthood, further research will be necessary to reconcile these findings  
417 with previous cognitive neuroscience investigations (48) as well as neurocognitive studies  
418 identifying stronger associations between CRF and cognitive functioning in females (4).  
419 Unfortunately, myriad methodological differences often preclude direct comparisons among  
420 studies in the field. Perhaps the most limiting of these involves discrepancies in the measurement  
421 of physical fitness. Differences include the use of self-report versus objective measures (70), as  
422 well as the operationalization of physical activity and physical fitness (54; 84). Further,  
423 investigating sex-differences in this functional domain is complicated by other sex-based  
424 differences such as the impact of hormonal replacement therapy (16; 17; 23). While these  
425 challenges are endemic to the field, our findings that CRF is associated with brain function in a  
426 sex-dependent manner underscores the importance of considering sex as a factor when studying  
427 associations between exercise and brain health in older adulthood. Rapid increases in the  
428 popularity of exercise as an intervention to promote brain health in later life presents an urgent

429 need to overcome these methodological challenges, towards the goal of building a coherent body  
430 of research to inform evidence-based public health initiatives.  
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711 **Tables**  
712

713 **Table 1. Descriptive Statistics**

Variable	Female Mean	Female SD	Male Mean	Male SD	mu difference	sd difference	HDI lower	HDI upper
CRF	6.09	0.27	9.06	0.31	-2.97	0.41	-3.77	-2.15
PA	8.43	0.17	8.73	0.21	-0.30	0.27	-0.83	0.22
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

714  
715 Difference scores and Highest Density Intervals (HDI) refer to Bayesian posterior density  
716 estimates of the difference between groups. CRF = cardiorespiratory fitness, PA = physical  
717 activity, MMSE = Mini-Mental Status Exam.

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719  
720 **Table 2. Global and local efficiency across networks**

Variable	Female Mean	Female SD	Male Mean	Male SD	mu 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

721  
722 Global and local network statistics are presented by group within and across the networks of  
723 interest. Difference scores and Highest Density Intervals (HDI) refer to Bayesian posterior  
724 density estimates of the difference between groups. LE = local efficiency, GE = global  
725 efficiency, LE All = local efficiency for all networks, GE All = global efficiency for all  
726 networks. FPCN = fronto-parietal control network, DN = default network, CO = cingulo-  
727 opercular network

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729

730 **Figure Captions**

731

732 **Figure 1.** Visualization of our networks of interest. Regions of Interest for the default, cingulo-  
733 opercular and frontoparietal control networks were taken from a resting state parcellation by  
734 Gordon and colleagues (38) and are represented as spheres. For illustrative purposes, regions of  
735 interest were superimposed on an overlay (86) to validate functional network assignment. Figure  
736 was created using Connectome Workbench (59).

737

738 **Figure 2.** Bayesian linear model of the relationship between CRF and local efficiency by gender.  
739 Figure 2a illustrates the linear relationship between CRF and local efficiency by group (shaded  
740 regions represent standard errors). Figure 2b show posterior distributions of intercepts for each  
741 group (F, M). The numbers appended to the plot are the median posterior density values. The  
742 posterior difference between the group intercepts can be seen in Figure 2c along with a 95%  
743 credible interval and posterior probabilities (i.e. there is an 88% probability that women have  
744 higher local efficiency values than men). Figures 2d plots the posterior distributions for the  
745 model slopes by group and figure 2d plots the posterior difference as described above for the  
746 intercepts.

747

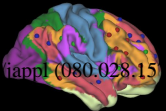
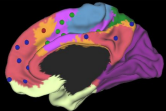
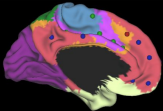
748 **Figure 3.** Illustration of the relationship between CRF and network efficiencies demonstrating  
749 Simpson's paradox. Figure 3a illustrates the relationship between CRF and local efficiency  
750 which, when combined across genders, is not reliably different from zero (shaded regions  
751 represent standard errors). Figure 3b shows the same relationship between CRF and local  
752 efficiency which, when stratified, is reliably different from zero in males. Figures 3c and 3d  
753 demonstrate the same effect as applied to global efficiency.

754

755 **Figure 4.** Bayesian linear model of the relationship between CRF and global efficiency by  
756 gender. Figure 4a illustrates the linear relationship between CRF and global efficiency by group  
757 (shaded regions represent standard errors). Figure 4b show posterior distributions of intercepts  
758 for each group (F, M). The numbers appended to the plot are the median posterior density values.  
759 The posterior difference between the group intercepts can be seen in Figure 4c along with a 95%  
760 credible interval and posterior probabilities (i.e. there is a 94% probability that men have higher  
761 global efficiency values than women). Figures 4d plots the posterior distributions for the model  
762 slopes by group and figure 4d plots the posterior difference as described above for the intercepts.

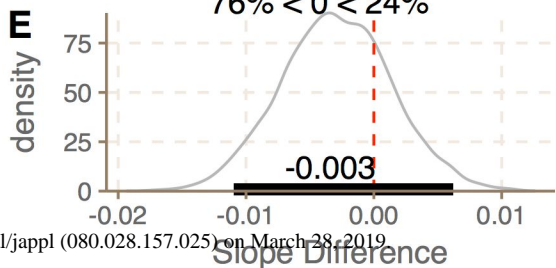
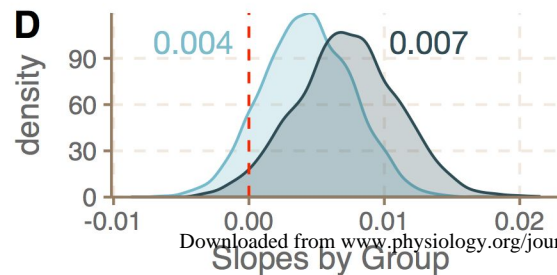
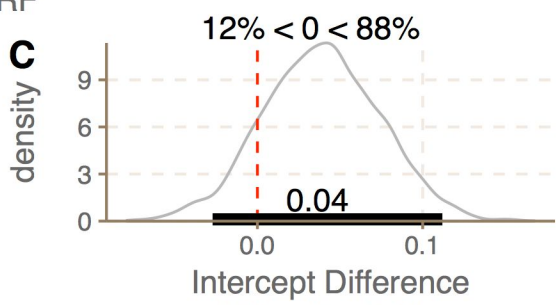
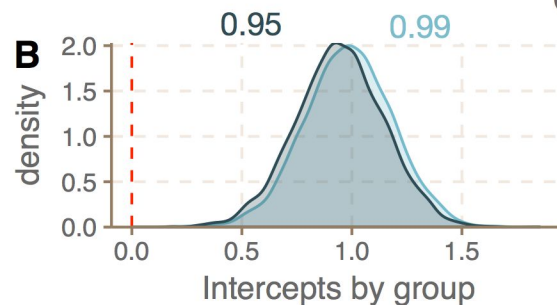
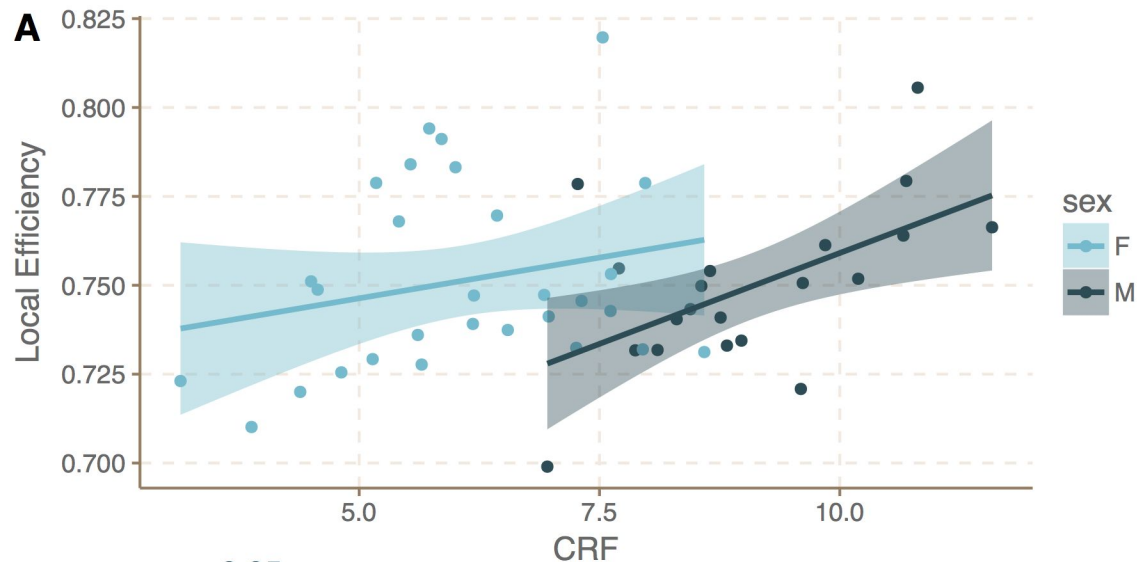
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