

**SEX DIFFERENCES IN THE INFLUENCE OF BRAIN AND LIFESTYLE
FACTORS ON NEUROCOGNITIVE AGING**

CHRISTINA J. VAN DEN BRINK

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Abstract

Declines in executive functioning (EF) are a hallmark of neurocognitive aging, rendering difficulties in activities of daily living and functional independence. In the face of rapid demographic shifts, optimizing brain health and preserving these functions is a societal priority. Much research has focused on the impact of exercise, brain structure, and brain function on neurocognitive aging, yet their relative predictive weights had not been evaluated. Further, the impact of sex differences on interactions between exercise and brain health, and the association with cognitive aging, had not yet been investigated. Fifty-one older adults (age range: 60 to 83) participated in this study evaluating the outcome of cardiorespiratory fitness (CRF), prefrontal cortex volume, and global efficiency of functional brain networks on EF. A stratified, multiple hierarchical regression was performed to identify the best predictors of EF for each sex. For females, a model containing solely CRF served as the best predictor of EF. After accounting for CRF and network efficiency, prefrontal cortex volume also emerged as a significant, positive predictor of EF for females. In contrast, a model containing both CRF and network efficiency best predicted EF in males. For males, global efficiency within the default network, a collection of brain regions associated with off-task behaviors, was associated with poorer EF performance. These results demonstrate that CRF and metrics of structural and functional brain health in older adulthood are independently associated with EF in a sex-dependent manner. The findings emphasize the importance of considering sex differences in the design of future neurocognitive interventions.

Keywords: executive functions, neurocognitive aging, cardiorespiratory fitness, global efficiency, default network, sex differences

This thesis is dedicated to my parents.

For your enduring support, tireless encouragement, and unwavering belief,
I am profoundly thankful.

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Introduction

Executive functioning (EF) plays a decisive role in shaping our personhood, enabling flexible interaction with the environment in a goal-directed manner. EF is an umbrella term for a set of mental functions such as attention, planning, set-shifting and inhibition, and are particularly susceptible to age-related decline (Buckner, 2004). These declines manifest in forgetfulness, disorganization, and problem solving difficulties (Levine et al., 2007), and are associated with functional impairment (Brandt et al., 2010; Cahn-Weiner, Malloy, Boyle, Marran & Salloway, 2000; Royall, Palmer, Chiodo & Polk, 2004). Unsurprisingly, EF are some of the most important cognitive functions for personal autonomy (Workman et al., 2000).

Given the growing burden of age-related diseases impacting cognition and the absence of proven pharmacological interventions, research is increasingly focusing on methods by which to delay the onset of dementias and other age-related (AR) changes, such as declining EF. For example, a delay in Alzheimer's onset of even one year is estimated to spare 9.2 million cases by 2050 (Brookmeyer, Johnson, Ziegler-Graham & Arrighi, 2006). Considering this, an emerging focus has been placed upon modifiable factors, such as lifestyle behaviours, that may mitigate age-related cognitive decline. Given their marked impact (e.g. contributing to nearly half of Alzheimer's Disease cases; Barnes & Yaffe, 2011), the influence of modifiable lifestyle factors on brain health and cognition is an exigent area of inquiry.

In addition to supporting the ongoing metabolic needs of the brain, lifestyle behaviors, such as fitness and nutrition, can alter brain structure (e.g. volume and cortical density; Burns et al., 2008; Gordon et al., 2008) and function (e.g. neural network

reorganization; Voss et al., 2010b; Voss et al., 2013), thus serving as prophylactic interventions, buffering against age-related neurological changes. The exact nature by which lifestyle behaviours alter the brain, whether this is manifest as structural or functional brain changes, as well as the degree to which lifestyle may contribute to enhanced cognitive performance, has yet to be fully investigated (Hillman, Erickson & Kramer, 2008). Elucidating the relationship between lifestyle, brain changes, and cognition will provide a more holistic picture of neurocognitive aging; garnering a better characterization of the process and an ability to tailor interventions accordingly.

Neurocognitive Aging

Neurocognitive aging can be characterized by changes along (at least) three domains: behavioral performance (i.e., cognition), brain structure, and brain function. Importantly, age-related changes across domains may be independent. This suggests that an intervention targeting one domain (e.g., structure) may not translate into others (e.g., behavior), emphasizing the importance of understanding how age-related changes in behavior, brain structure, and function interact, and the factors that may influence these interactions (e.g., lifestyle choices).

Behavioural changes. Age-related decreases in performance have been extensively documented in cognitive tasks (Grady et al., 1998; Schacter, Savage, Alpert, Rauch, & Albert, 1996; Davis et al., 2009), occurring across various cognitive domains, such as working memory (Babcock & Salthouse, 1990), episodic memory (Stark, Yasa & Stark, 2010), EF (Fisk & Sharp, 2004), and perceptual processing (Lindenberger, Scherer, & Baltes, 2001). Cognitive domains such as implicit memory and vocabulary are well-preserved, however, suggesting that aging may affect the brain, and resultant

cognition, in non-uniform ways (Park & Reuter-Lorenz, 2009). Several theories posit that declining EF, such as inhibition (Zacks & Hasher, 1988) or working memory (Park et al., 1996), underlie the changes most often associated with aging. That is, controlled processing (i.e. EF) works in a top-down fashion, orchestrating a wide range of mental functions. Impairments at this level, then, result in a reduced capacity to inhibit distraction, leaving individuals more susceptible to automatic, bottom-up processes and reliant on environmental cues (Park & Reuter-Lorenz, 2009). Given the top-down nature of EF, it is not surprising that declines in this domain are associated with difficulties in daily living and functional independence (Workman et al., 2000). For this reason, EF was selected as our primary outcome measure in this study with the goal of identifying lifestyle (cardiorespiratory fitness) and brain (structure and function) factors most predictive of EF in older adulthood.

Structural changes. With increasing age, the brain undergoes a series of characteristic changes such as reductions in total volume, loss of grey matter (GM) and reductions in the integrity of white matter (WM) tracts (Gunning-Dixon, Brickman, Cheng & Alexopoulos, 2009; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003; Salat et al., 2009). GM loss is most prominent in the prefrontal cortex (PFC), but also occurs in temporal and parietal cortices (Hedden & Gabrielli, 2004; Raz & Rodrigue, 2006; Resnick et al., 2003; Salat et al., 2004; Tisserand et al., 2002). This frontal degeneration underlies impaired performance on tasks of EF (Alvarez & Emory, 2006; Fjell & Walhovd, 2010). For example, PFC volume is associated with performance on the Wisconsin Card-Sorting Task, a measure of set-shifting (Gunning-Dixon & Raz, 2003).

While structural declines may be associated with reduced brain activity (Brassen

et al., 2009; Rajah et al., 2011), the two are not mutually inclusive (e.g. Daselaar et al., 2015). Changes in function can be indicative of structural alterations but can also reflect other neural processes such as neurovascular coupling - that is, the degree of activation and associated blood flow required. For that reason, metrics of brain function and structure may not coincide spatially or temporally (Zatorre, Fields & Johansen-Berg, 2012). As such, there is an increasing need to evaluate both metrics of brain health, as well as external factors, to accurately characterize brain alterations underpinning neurocognitive changes (Sala-Llonch, Bartres-Faz, & Junque, 2015).

Functional changes. Executive functioning has been conceptualized as an emergent property of distinct brain regions working together in the service of goal-directed cognition (Spreng, Sepulcre, Turner, Stevens & Schacter, 2013). Preferential declines in EF suggest, then, that aging may have its most profound effects on behaviors reliant on multiple brain regions, resulting from impaired network integration. Indeed, network connectivity changes are associated with memory and EF performance (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Sala-Llonch et al., 2015; Wang et al., 2010). Network properties may therefore be particularly appropriate markers indexing age-related decline.

Network efficiency is one metric that has been associated with specific cognitive changes (Gong et al., 2009). Global efficiency (GE) is a metric of network integration, describing interactions between local communities of nodes at a network-level (Achard & Bullmore, 2007; Rubinov & Sporns, 2010). With age, GE decreases (Achard & Bullmore, 2007; Ajilore, Lamar & Kumar, 2014; Fischer, Wolf, Scheurich & Fellgiebel,

2014; Wen et al., 2011), having its most prominent effects in frontal and temporal regions (Achard & Bullmore, 2007, but see: Gong et al., 2009; Song et al., 2014).

Estimates of network efficiency have been associated with performance on cognitive tasks, suggesting that these metrics constitute meaningful markers of neurocognition. Network connectivity in superior frontal and posterior cingulate regions, for instance, is positively associated with EF (Wen et al., 2011). Further, structural GE (measured via WM tracts) is associated with higher IQ (Li et al., 2009). Such associations may be age and modality specific. For example, while structural GE was associated with EF in younger adults, this failed to replicate in older adults (Fischer et al., 2014). Considering that structural networks may not correspond directly to functional patterns (Damoiseaux & Greicius, 2009; Honey et al., 2009), further investigation into the association between functional network metrics and cognition is warranted.

At rest, patterns of brain activity can be reliably dissociated. Two networks, the default network (DN) and the frontoparietal control network (FPCN), demonstrate AR alterations and associated AR cognitive declines (Andrews-Hanna et al., 2007; Sambatoro et al., 2010). The DN is a network of brain regions that comprises the ventromedial PFC, the posterior cingulate and retrosplenial cortex, the inferior parietal lobule, the lateral temporal cortex, the dorsomedial PFC and the hippocampal formation (Buckner, Andrews-Hanna & Schachter, 2008). Because of its high resting metabolic rate (Langbaum et al., 2009), the DN is particularly vulnerable to aging (Buckner, 2004; Gusnard, Akbudak, Shulman & Raichle, 2001).

Functional connectivity within the DN decreases with age (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Ferreira & Busatto, 2013; Sambatoro et al., 2010) and is

associated with declining memory, executive functions, and processing speed (Andrews-Hanna et al., 2007; Sambatoro et al., 2010). Beyond resting connectivity, the DN demonstrates particular vulnerability to age-related changes in intranetwork connectivity (Chen et al., 2011; Hedden et al., 2009) and modularity, with decreases in both GE and local efficiency (Song et al., 2014). These decreases may, in turn, underlie the cognitive declines seen in mild cognitive impairment and Alzheimer's Disease (Sorg et al., 2007). DN internetwork connectivity also declines with age and this, along with alterations in the salience network (which serves to integrate processed sensory information, autonomic feedback and cognitive control; Seeley et al., 2007), is associated with cognitive decline (Onoda, Ishihara & Yamaguchi, 2012).

The FPCN includes the anterior and dorsolateral PFC, anterior inferior parietal lobule, anterior cingulate, and insular cortices (Vincent, Kahn, Snyder, Raichle & Buckner, 2008). The FPCN is anchored in the PFC, which plays an integral role in executive control because of its ability to integrate information from the external environment with internally-stored representations (Miller, 2000). The FPCN modulates network interactions (Vincent et al., 2008). By flexibly coupling and decoupling with other networks (Seeley et al., 2007; Spreng et al., 2013; Spreng, Stevens, Chamberlain, Gilmore & Schachter, 2010; Vincent et al., 2008), the FPCN ensures that the appropriate network is engaged for the task at hand. Like the DN, this network also shows AR reductions in resting state functional connectivity (rsFC) (Andrews-Hanna et al., 2007; Betzel et al., 2014; Madden et al., 2010; Zhang et al., 2014).

In summary, network efficiency is a metric of network integration (Rubinov & Sporns, 2010), representing the efficiency of functional connectivity within a network in

a single measure. The DN and FPCN were selected as our networks of interest in this study given their demonstrated AR changes in network connectivity (Andrews-Hanna et al., 2007; Betzel et al., 2014; Damoiseaux et al., 2008; Ferreira & Busatto, 2013; Madden et al., 2010; Sambatoro et al., 2010; Zhang et al., 2014) that are associated with changes in cognition (Andrews-Hanna et al., 2007; Sambatoro et al., 2010), particularly EF (Crossley et al., 2013; Seely et al., 2007).

Sex differences in neurocognitive aging. Research suggests that the brain ages in a sexually dimorphic fashion. For example, AR reductions in frontal volumes are greater in men than women (Cowell et al., 1994). Indeed, one consistent finding is that women have greater GM and lower WM volumes than men (Allen, Damasio, Grabowski, Bruss & Zhang, 2003; Goldstein et al., 2001; Filipek et al., 1994; Luders et al., 2005; Tomasi & Volkow, 2012), after correcting for brain size (Gur et al., 1999; Leonard et al., 2008), yielding a greater ratio of GM to WM over the lifespan (Allen et al., 2001; Goldstein et al., 2001). As well, men show more AR atrophy, resulting in increases in cerebrospinal fluid/ventricular volumes (Christiansen et al., 1994) and greater structural declines (Gur et al., 1991; Raz et al., 1997). Sex differences in aging brain structure are not uniformly expressed, however, with some studies finding only regional effects (Raz et al., 2004).

After accounting for metrics of brain structure such as total brain volume, GM, and WM, there is still an effect of sex on functional connectivity, suggesting underlying differences in brain organization (Tomasi & Volkow, 2012). It is hypothesized that sex differences in connectivity develop over the lifespan and may underlie the cognitive advantages ascribed to either sex. Ingallhalikar and colleagues (2014) found that the

female brain is structured to facilitate communication between analytical and intuitive processing modules while males show heightened connectivity between regions subserving perception and coordinated action.

There are sex- and hemisphere-dependent effects on whole brain metrics. One study found that males showed greater clustering (conceptually akin to local efficiency) in the right hemisphere but lower in the left (Tian et al., 2011). The authors speculated that local efficiency may underlie gender-related asymmetries (Tian et al., 2011), yielding differences in cognitive specialization such as phonological processing for females (Hamilton, 2008; Shaywitz et al., 1995) and visuospatial for males (Hamilton et al., 2008; Hiscock et al., 1994; 1995). Indeed, at a whole brain level, women show greater local efficiency than men (Yan et al., 2011).

Sex differences in brain metrics appear most reliably in populations of younger adults, presumably due to the influence of hormones (Witte, Savli, Holik, Kasper & Lanzenberger, 2010). While such findings are more reliably encountered in this demographic, differences have been recognized in older populations as well. Older women show greater GE (Gong et al., 2009) and local efficiency (Yan et al., 2011). Given the paucity of research investigating such differences in older adults, coupled with differences in the network modality (e.g. structural vs. functional efficiency; Tian, Wang, Yan & He, 2011) and methodology (Yan et al., 2011) of previous studies, it is unsurprising that results have been inconsistent and underscores the need for further research.

Neurocognitive aging is a complex phenomenon. Critically, we see that changes are not uniform across the domains of cognition, structure, and function. That is, we can

see discordances between the integrity of brain structure, brain function, and resultant cognition, even within the same regions (e.g., Daselaar et al., 2015). This underscores the importance of selecting intervention targets accordingly. Considering the potential role of modifiable lifestyle factors in mitigating AR changes, we aimed to evaluate to what extent lifestyle affected EF, and how this related to other known predictors of EF, such as brain structure and function.

Fitness and Neurocognitive Aging

Cardiorespiratory fitness (CRF) has been associated with brain structure and function in older adulthood (Voss et al., 2012; Voss et al., 2013a; Colcombe & Kramer, 2003a). Under the domain of lifestyle, CRF has been studied the most extensively and is widely touted as a protective mechanism against neurocognitive aging. For this reason, CRF was selected to represent a modifiable lifestyle behavior in this study.

At a microscopic level, exercise contributes to brain health by way of synaptogenesis, angiogenesis, and the up-regulation of growth factors (for reviews, see Cotman & Berchtold, 2002; Thomas, Dennis, Bandettini & Johansen-Berg, 2012). At a macroscopic level, exercise interventions have been found to yield changes in structural volumes (Alosco et al., 2014), as well as functional connectivity metrics (Voss et al., 2013b), presumably through improving cerebrovascular health (Swain et al., 2003).

Fitness and cognition. CRF is a measure of aerobic capacity, indexing the body's ability to consume and transport oxygen (Hayes, Hayes, Cadden, & Verfaellie, 2013). CRF does not affect all cognitive domains uniformly, having its largest effects on attention and processing speed, EF (Barnes, Yaffe, Satariano & Tager, 2003; Blumenthal et al., 1991; Erickson & Kramer, 2009; Smith et al., 2010), memory (Smith et al., 2010),

as well as estimates of global cognition (Barnes et al., 2003). CRF appears to be particularly beneficial for EF in older adults (Colcombe & Kramer, 2003a; Smiley-Oyen, Lowry, Francois, Kohut & Ekkekakis, 2009).

Though a great deal of research has been conducted, a definitive relationship between fitness and cognition in older adulthood has not been established (e.g. Blumenthal et al., 1989; Etnier, Nowell, Landers & Sibley, 2006). For instance, a Cochrane review incorporating 754 participants did not find significant benefits of aerobic fitness on cognition in older adults (Angevaren, Aufdemkampe, Verhaar, Aleman & Vanhees, 2008). The variability in these findings could be attributed to a host of factors, such as baseline fitness levels (Wray et al., 2006) or, as we investigate here, sample composition, due to sex differences in the effect of CRF.

Fitness and brain structure. Increased fitness is associated with increased GM volume (Burns et al., 2008; Alosco et al., 2014) and greater GM density in frontal and parietal cortices (Gordon et al., 2008; Weinstein et al., 2012). Interestingly, these structural gains occur in brain regions most susceptible to aging, such as the PFC (Gordon et al., 2008; Erickson et al., 2010; Rovio et al., 2010; Bugg & Head, 2011; Voss et al., 2010b) and hippocampus (Erickson, 2009; Head, Singh & Bugg, 2012), and are associated with decreased AR-losses in cortical volume (Colcombe et al., 2003b). The significance of these structural associations, however, is not entirely clear. Some studies have found that brain structure mediates the association between fitness and cognition (e.g. task switching, Verstynen et al., 2012). For example, greater GM volume in the PFC was found to mediate the association between fitness levels and cognitive performance (Weinstein et al., 2012). Others have failed to find an association between structural

improvements and changes in cognition (e.g. the Flanker Task, Verstynen et al., 2012; Voss et al., 2012).

Fitness and brain function. On a network level, exercise is able to modulate cortical plasticity and enhance functional connectivity (Voss et al., 2010b; Voss et al., 2013b). The DN is particularly responsive to fitness-related alterations. For example, long-time athletes show greater cerebral blood flow in areas of the DN (Thomas et al., 2012). Greater fitness is associated with greater rsFC at the whole-brain level, as well as within the DN (Voss et al., 2015). Fitness may also be protective, as higher levels bolster against reduced AR rsFC changes in the DN (Boraxbekk, Salami, Wahlin & Nyberg, 2016). In a 12-month intervention study, fitness was associated with increased connectivity in the FPCN, though these were non-significant trends (Voss et al., 2010b). Interestingly, the study found that increased connectivity in the DN was most associated with EF performance in older adults (Voss et al., 2010a)

Sex differences in CRF and brain health. There is evidence that CRF is able to bolster brain health in areas most susceptible to AR decline. It is important to note, however, that these changes are not necessarily uniform across the sexes - a fact often overlooked in aging research. A meta-analysis suggests that the greatest intervention gains are found in studies with more female participants, suggesting that exercise has its largest behavioural effects on women (Colcombe & Kramer, 2003a). These sex differences, then, may account for inconsistent findings in exercise-related research.

The outcome of CRF may be different between the sexes for a host of reasons. One reason may be that women are found to have higher rates of inactivity at baseline (Barnes & Yaffe, 2011). Interventions may thus demand greater fitness adaptations for

women and yield more changes as a result. Mechanisms of exercise-induced benefits are also sex-dependent. For instance, men show increased exercise-induced improvement in factors related to stroke volume (the amount of blood pumped with each heartbeat) and cardiac output, whereas exercise-induced adaptations in women rely on rate of oxygen extraction by skeletal muscle (Zoeller, 2008).

Sex differences in the impact of exercise can be attributed to fundamental physiological differences in the body's response to exercise. This includes mechanisms such as the autonomic control of vasculature (Fu et al., 2008; Ridout et al., 2010), differences in arterial vasculature (Black et al., 2009; Parker et al., 2008), and exercise-induced cardiovascular adaptations (Spina et al., 1993). Such age-related differences are hypothesized to occur because of age-related changes in sex hormones, varying base levels of fitness, and consequent differential dose-response relationships (Parker, Kalasky & Proctor, 2010).

Current Study

Rationale. The aging brain undergoes characteristic changes in its structural and functional integrity, coinciding with AR cognitive declines. Most notably, there are reductions in PFC volume, decreases in the integrity of functional brain networks associated with controlled processing (i.e. DN and FPCN), and declines in EF. CRF has been found to be neuroprotective, buttressing the brain against degeneration by improving overall brain health. Higher CRF has been associated with less AR decline in brain structure, preserved network connectivity, and preserved performance on metrics of EF. However, the interaction between fitness, brain health, and cognitive preservation remains under-specified.

There is a paucity of literature examining the predictive weight of CRF as a neuroprotective factor when accounting for other metrics of brain health. That is, do the brain changes achieved via fitness present meaningful gains in terms of cognitive outcome? We evaluated the role of CRF as a predictive factor of EF relative to metrics known to associate with cognitive outcome, such as PFC volume and network efficiency. Further, while sex differences have been established in neurocognitive aging and influence the relationship between CRF and cognition, the impact of sex on interactions among CRF, brain, and cognition had yet to be evaluated systematically. To our knowledge, this was the first study to investigate the association among sex, brain function and structure, and CRF as predictors of a specific cognitive capacity - EF.

Research aims. In our study, we were interested in examining factors predicting preserved EF in older adults. Our aims were to: 1) evaluate the relative contributions of CRF, PFC volume and network efficiencies in predicting EF (measured as fluid IQ) in older adults for each sex, and 2) based on the contribution of those factors, identify the most parsimonious level of the model predicting EF for males and females.

Hypotheses. Previous research has demonstrated, with relative consistency, an association between exercise and cognition. While CRF and EF may be associated, the role of brain structure and brain function in mediating this relationship has not been reliably established, suggesting that CRF and brain health may independently contribute to EF. We hypothesize that there will be sex differences at the level of independent predictors, as well in the ‘best fit’ model. Our overarching hypothesis was that CRF, brain structure, and brain function will serve as significant predictors, but in a sex-dependent manner. This can be broken down into four component hypotheses.

Hypothesis 1: Higher CRF will be associated with higher EF in older adults. *Hypothesis 2:* Greater prefrontal volumes will be associated with greater EF. *Hypothesis 3:* Network efficiencies will be positively predictive of EF. *Hypothesis 4:* The associations between CRF, PFC volume and network efficiencies and EF will be larger for females than males.

Our final two hypotheses addressed the secondary objective of the study.

Hypothesis 5: For females, a model containing all of CRF, PFC and network efficiencies will be the best predictor of EF. *Hypothesis 6:* For males, a model containing network function, but not network structure, will account for the most variance in EF.

Summary. Neurocognitive aging is a complex phenomenon. Aging preferentially targets EF, given the integrative nature of these processes, which are heavily reliant on the integrity of structural networks and functional communication between disparate brain regions. Fitness has been posited as a preventative measure against AR declines given its ability to bolster brain health in regions and networks most targeted by aging, such as the PFC, FPCN, and DN. However, the value of CRF as a predictor of EF, and whether it is independently predictive at all, relative to PFC volume and network metrics, has yet to be evaluated. Further, while sex differences are apparent in neurocognitive aging and in the effects of CRF, research has yet to examine how such differences contribute to preserved EF, or indeed, whether they warrant further exploration. By asking these questions, we aimed to identify the best predictors of preserved EF for each sex so as to ultimately identify what factors merit targeting in future neurocognitive intervention

Methods

Participants

Twenty-one males ($M = 67.24$, $SD = 6.46$) and 30 females ($M = 66.07$, $SD = 4.83$) participated in our study. This was a multi-site study conducted at York University (Toronto, Ontario) and at Cornell University (Ithaca, New York). Participants were recruited from the community and participated in a comprehensive cognitive test battery and magnetic resonance image (MRI) scanning. Participants received monetary compensation for their time (equivalent to \$50 for the MRI scan and \$10 CAD per hour). To be eligible for the study, participants had to be: a) over age 60; b) right-handed; and c) a fluent English speaker. Exclusion criteria included any MRI contraindications and/or a history of neurological, neuropsychiatric, or cardiovascular disease. All participants signed an informed consent form and completed an MRI screening procedure before participating in the study. All procedures were approved by the Institutional Review Board of York University and the Institutional Review Board at Cornell University.

Measures

Fitness. CRF was quantified using an equation-derived non-exercise fitness assessment (Jurca et al., 2005). This formula (which is detailed in Appendix C) takes a participant's height, weight, age, sex, resting heart rate, and self-reported physical activity to derive a CRF score (in metabolic equivalent; MET). The formula has been validated in a group of older adults, significantly correlating with results of a physician-supervised submaximal exercise test and one-mile timed walk (McAuley et al., 2011). Participants self-reported their height, weight, and age. Resting heart rate was obtained from the MRI scanner and by using a Fitbit Charge (San Francisco, California).

Recognizing that lifestyle patterns are often clustered and independently predictive of cognition, we conducted correlational analyses between our predictor variables and a set of covariates. These covariates included physical activity levels, depression, education, and age. These variables, together with hypertension, have been found to account for 46% of global cognition scores (Bowman et al., 2011). For these analyses, physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) Short Form (Booth, 2000), a metric with proven validity and reliability in 12 countries (Booth et al., 2003). The Geriatric Depression Scale (GDS) is a 30-item self-report assessment used to identify depression in the elderly (Sheikh & Yesavage, 1986). Education level was self-reported and coded in accordance with NIH definitions.

Cognition. EF were evaluated using the NIH Toolbox Cognition Battery (NIHTB-CB) for fluid intelligence (NIH Toolbox for Assessment of Neurological and Behavioral Function, 2013; Weintraub et al., 2013). The fluid intelligence score is a composite score of several sub-domains with excellent reliability and validity (Heaton et al., 2014). EF is assessed via the NIHTB Flanker Test of Executive Function-Inhibitory Control and Attention and the NIHTB Dimensional Change Card Sort Test of Executive Function-Cognitive Flexibility. Episodic memory is assessed using the NIHTB Picture Sequence Memory Test of Episodic Memory. Working memory, an integral component of EF, is evaluated using the NIHTB List Sorting Working Memory Test. Finally, the NIHTB Pattern Comparison Processing Speed Test tests for processing speed. Raw scores of each test are processed according to the standardized NIH procedure to derive a composite measure.

Imaging Methods

Structural scans were obtained with a high-resolution, T1-weighted, magnetization-prepared rapid gradient echo (MP-RAGE) sequence. Functional measures were obtained using multi-echo T2-weighted BOLD fMRI to derive metrics of network efficiency over two ten-minute resting sessions. Studying the brain at-rest has several advantages. Resting-state data are easily comparable across studies (Biswal et al., 2010), and have high test-retest reliability (Shehzad et al., 2009; Zuo et al., 2010) and replicability (He et al., 2009). Importantly, these at-rest patterns hold true at-task, suggesting that this intrinsic activity is reflective of the brain's functional architecture (Spreng et al., 2013).

York University. Brain imaging was acquired using a Siemens 3T Magnetom TIM Trio MRI scanner (Siemens Medical Solutions, Erlangen, Germany) with a 32 channel head coil at York University (Toronto, ON). Structural images were obtained with a high-resolution, T1-weighted, multi-planar rapid gradient echo (MP-RAGE) sequence (192 slices; 1.0 mm isotropic voxels; repetition time (TR) = 1900 ms; echo time (TE) = 2.5 ms; TI = 900; flip angle = 9°). Functional scans used a T2*-weighted 2D echo planar imaging (EPI) sequence acquired in the oblique-axial plane (36 axial slices; 3mm isotropic voxels; TR = 3000 ms; TE = 14, 30, 46 ms; flip angle = 83°).

Cornell University. Brain imaging data were acquired using a GE 3T Discovery MR750 MRI scanner (GE Healthcare, Milwaukee, WI) with a 32-channel head coil at the Cornell Magnetic Resonance Imaging facility (Ithaca, New York). Structural images were obtained with a T1-weighted, multi-planar rapid gradient echo (MP-RAGE) sequence (176 slices; 1.0mm isotropic voxels; TR = 7.7 ms; TE = 2.4 ms; flip angle =

7°). Functional scans were acquired with a T2*-weighted EPI pulse sequence (36 axial slices; 3mm isotropic voxels; TR = 3000 ms; TE = 14, 30, 46 ms; flip angle = 83°)

Analyses

Structural MRI preprocessing. Structural data were corrected for non-uniform intensities, affine-registered to Montreal Neurological Institute (MNI) atlas (Collins, Neelin, Peters & Evans, 1994), and skull-stripped using the open-source software Freesurfer (Athinaoula A. Martinos Center for Biomedical Imaging, Harvard University, Cambridge, MA, USA). Functional images were co-registered with their respective anatomical image prior to MNI registration.

Surface reconstruction of the cortex and generation of segmented, cortical volumes were conducted with Freesurfer. The technical details of these procedures are discussed in prior publications (Dale, Fischl & Sereno, 1999; Fischl, Sereno & Dale, 1999; Fischl, Liu & Dale, 2001; Fischl et al., 2002; Fischl et al., 2004a; Fischl et al., 2004b). PFC volumes were derived by aggregating volumes from the caudal middle frontal, lateral orbital frontal, pars opercularis, pars orbitalis, pars triangularis, rostral middle frontal, superior frontal, and frontal pole regions. To control for individual variability in head size and to enable comparison amongst participants, these aggregate volumes were divided by each individual's estimated intracranial volume to obtain a metric of proportion.

Functional MRI preprocessing.

Multi-echo independent components analysis (ME-ICA). Resting data underwent anatomical intensity normalization, skull-stripping, and standard space warp. Functional pre-processing was conducted using ME-ICA (Kundu, Inati, Evans, Luh &

Bandettini, 2012). Briefly, ME-ICA combines MRI sequencing with an independent components analysis (ICA) procedure to improve signal denoising; yielding a more robust estimation of functional connectivity (Kundu et al., 2015). ME-ICA acquires each slice at multiple echo times (TE) to produce an fMRI volume where each voxel has an assigned time series for each TE. A signal delay analysis is then conducted at each voxel distinguishing between TE-dependence and TE-independence. The blood oxygen level dependent (BOLD) signal has a signature T2* decay of signal and is TE-dependent. Artifactual changes (e.g. subject motion or scanner drift) are TE-independent. Then, ICA isolates signal sources into statistical components and TE-dependence analysis classifies these components into BOLD and non-BOLD components. Removing non-BOLD components from the data denoises it, rendering up to four-fold gains in the temporal signal-to-noise ratio of the time series throughout the brain (Kundu et al., 2015). For a more comprehensive description, see Kundu et al. (2012) and Kundu et al. (2015).

Multivariate exploratory linear decomposition into independent components (MELODIC). Following ME-ICA, we identified signal bleed-through from the ventricles and sinuses, likely attributable to declines in white matter integrity occurring with age. We performed a probabilistic independent components analysis (Beckman & Smith, 2004) via MELODIC version 3.14, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) to isolate any remaining noise in our data. The data were processed in the following manner: non-brain voxels were masked; data were de-meaned and variance was normalized at the voxel level. The data were whitened and projected into 36-dimensional subspace using principal components analyses (as per Minka, 2000; Beckmann & Smith, 2004). The data were then decomposed into vectors across spatial

maps and temporal courses in an iterative manner (Hyvarinen, 1999). Component maps were then divided by the standard deviation of the residual noise and thresholded (Beckman, 2004).

Resting state functional brain networks. One method of examining age-related network changes is by using graph theory (Rubinov & Sporns, 2010; Rubinov & Sporns, 2011). Within graph theory, brain graphs depict the brain as an intricate set of interacting nodes and connecting edges. The edges signify the strength of functional coupling between two regions of interest (ROIs), indexing the functional interaction of two regions irrespective of physical distance. Based on their vulnerability to aging and association with performance on executive control tasks, the DN and FPCN were selected *a priori* as our networks of interest. We used previously defined ROIs based on a resting state cortical parcellation (Gordon et al., 2016). This parcellation has 333 ROIs across the brain. The DN accounts for 41 of these nodes while the FPCN accounts for 24. See Figures 1 and 2 for the network connectivity profiles. This parcellation was selected because it was derived using resting state data and had 333 ROIs (exceeding the suggested 200 nodes recommended in order to capture individual differences, which are substantial in aging; Fornito, Zalesky & Bullmore, 2010)

Using the Matlab-based Brain Connectivity Toolbox (CONN; Rubinov & Sporns, 2010; Rubinov & Sporns, 2011; <http://www.brain-connectivity-toolbox.net/>), pre-processed resting data were again co-registered with their MNI-transformed anatomical scan. Using the graph theory function in CONN, the groups of ROIs for the DN and FPCN were entered independently to attain a measure of GE for each network. For a full list of the ROIs used, their labels, and MNI coordinates, see Appendix B.

Network measures of brain systems. Metrics of GE were estimated using CONN. GE indexes the average inverse shortest path length in the network (Latora & Marchiori, 2001). It is inversely related to the characteristic path length (Watts & Strogatz, 1998). Though characteristic path length is the most popular metric of network integration, it is particularly influenced by long paths to the detriment of evaluating short paths (Rubinov & Sporns, 2010), leading to the conclusion that GE is a superior metric of network integration (Achard & Bullmore, 2007).

GE is scaled from zero (lowest efficiency) to one (highest efficiency) where higher GE indicates more efficient communication as a result of shorter path lengths (where there is less possibility of interference). Nodes with high GE have short path distances to other nodes. Similarly, network GE is indicative of the average shortest path distance across all nodes in that network. GE was calculated with Matlab using Dijkstra's algorithm:

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

where d_{ij} is the shortest path (smallest number of edges) between nodes i and j (Dijkstra, 1959)

Statistical analyses. Statistical analyses were conducted using SPSS v. 24.0. A multiple hierarchical regression was conducted to evaluate the relative predictive weight of CRF, prefrontal volume, and DN and FPCN metrics on EF. In order to evaluate sex differences, analyses were stratified by sex. Pearson correlation coefficients were calculated to determine the associations between lifestyle predictor variables (such as depression) and our regression predictors.

Multivariate outliers were identified using the Mahalanobis distance (a measure of how much the value of a case differs in the independent variables from the average of all other cases). Values greater than 12.59 were excluded, which reduced our sample sizes from 23 to 21 for males and 32 to 30 for females. Cook's distance was also employed to identify outliers. Cook's values greater than 1 were identified as outliers but none warranted removal via this method. The assumption of homoscedasticity was checked using residual vs. predicted value plots. The variance was determined to be roughly equal and thus the assumption was presumed to have been met. Data met the assumption of independent errors (Durbin-Watson= 1.97) and normality (for both sexes, residuals clustered around $x = y$ when graphed).

Results

Participant Characteristics

Participant characteristics can be found in Table 1. Sex differences were observed in PFC volume and CRF. PFC proportions were significantly greater ($t(49) = -2.32, p = .025$) in females ($n = 30, M = 7.58, SD = .60$) relative to males ($n = 21, M = 7.21, SD = .50$). Males had significantly greater CRF ($M = 8.96, SD = 1.67$) compared to females ($M = 6.06, SD = 1.45, t(49) = 6.60, p < .001$). There were no sex differences in global efficiencies of the DN ($M_M = .40, SD_M = .04, M_F = .42, SD_F = .05$) or the FPCN ($M_M = .33, SD_M = .04, M_F = .32, SD_F = .05$), or EF ($M_M = 48.50, SD_M = 27.54, M_F = 53.39, SD_F = 23.60$).

Regression Analyses

To evaluate the relative predictive contributions of CRF, PFC volumes, and DN and FPCN efficiency on EF, we implemented a multiple hierarchical regression model.

The analyses were stratified to examine the relative contribution of each factor for each sex (hypothesis 4). CRF was entered at the first level to evaluate its independent impact on EF (hypothesis 1). Considering that CRF has been found to impact networks on a global level, we entered network metrics separately at the second level to examine the independent effect of network efficiency on EF (hypothesis 3). Finally, PFC volumes were added at the final level of the model to examine whether brain structure was associated with EF, independent of network function or CRF (hypothesis 2). The adjusted r-squared was then computed to identify the most parsimonious model (based on the best predictors) for each sex (hypotheses 5 & 6)

Males. In accordance with our first research aim, a multiple hierarchical regression was conducted to evaluate the relative contributions of CRF, PFC proportion, and network efficiencies on EF. Regression coefficients are presented in Table 4. CRF was entered as the sole predictor at the first level of the model and was found not to be a significant predictor of EF ($F(1,19) = 1.26, p = .276, R^2$ for Model 1 = .062). When DN and FPCN efficiency were added at the next level of the model, this significantly increased the predictive value ($F(2, 17) = 9.01, p = .002, \Delta R^2$ for Model 2 = .483). By adding these network metrics, the proportion of EF variance accounted for increased from 6.2% to 54.5%. This effect was driven by GE in the DN ($R^2 = .423$) which was a significant predictor ($p = .001$) whereas FPCN GE was not ($R^2 = .06, p = .153$). Adding brain structure to the model did not significantly increase the proportion of EF variance accounted for ($F(1, 16) = .431, p = .521, \Delta R^2$ for Model 3 = .012). The proportion of variance accounted for by each predictor at each level of the model is illustrated in Figure 3.

The adjusted r-squared value was examined to identify the most parsimonious model, accounting for the most variance in EF scores after adjusting for the number of predictors. For males, level two (a model containing CRF and network metrics) was the best model for predicting EF outcomes ($R^2_{\text{adjusted}} = .464$).

In accordance with our second research aim, partial coefficients were obtained to examine sex differences in the predictive value of each factor. These values can be found in Table 4. Simple regression plots illustrating the relationship between each predictor and EF scores for each sex can be found in Figure 4 for CRF, Figure 5 for DN GE, Figure 6 for FPCN GE, and Figure 7 for PFC. Of note, these figures depict simple regressions and thus do not factor in variance accounted for at different levels of the model. However, partial regression coefficients from the hierarchical model are presented in each figure description to convey relationship strength.

Females. To evaluate the relative contributions of CRF, network metrics, and PFC proportion on EF, a multiple hierarchical regression was performed. Regression coefficients can be found in Table 4. For females, the first level of the model containing only CRF accounted for nearly 13% of the variance in EF score ($F(1,28) = 4.00, p = .055, R^2 \text{ for Model 1} = .125$) though this failed to reach significance. Adding brain function to the equation did predict more of the variance in EF, increasing the predictive value from 13% to 20%. However, unlike in the males, this was not significant ($F(2, 26) = 0.31, p = .737, \Delta R^2 \text{ for Model 2} = .020$) suggesting that adding brain function did not significantly increase the predictive value of the model. While adding brain structure did not contribute to the overall strength of the model ($F(1,25) = .09, p = .772, \Delta R^2 \text{ for Model 3} = .003$), PFC volume was found to be a significant predictor of EF in females (p

= .03). Again, the proportion of variance accounted for by each predictor at each level of the model is illustrated in Figure 3.

To identify the most parsimonious level of the model, the adjusted r-squared was computed. A model containing only CRF (i.e. the first level) was the best predictor of EF ($R^2_{\text{adjusted}} = .094$) for females.

Correlational Analyses

Males. Pearson correlation coefficients were calculated to detect associations between lifestyle metrics and our predictor variables. These correlations are reported in Table 2. Body mass index was significantly negatively correlated with CRF ($r = -.54, p = .011$) and education ($r = -.48, p = .029$). The amount of time spent engaged in vigorous activity was significantly associated with CRF ($r = .62, p = .003$) and moderate physical activity ($r = .65, p = .001$). GDS scores, education level, and age were not associated with any of our predictor variables (all $p > .05$).

Females. Correlation tables for females are reported in Table 3. Body mass index was negatively associated with CRF ($r = -.71, p < .001$) and EF ($r = -.37, p = .047$). Scores on the geriatric depression scale were associated with age ($r = .47, p = .011$) suggesting that females tended to show more depressive symptomatology with age. Education level was not associated with any of our predictors (all $p > .05$).

Discussion

The aim of this study was to identify factors predicting neurocognitive aging, specifically EF outcomes. As predicted, we found that the relative predictive weight of brain structure, function, and CRF were markedly different between the sexes (hypothesis 4). CRF trended towards a positive association with EF in females, but was negatively

associated with EF in males. Network metrics were highly predictive of EF performance in males, but not females. Brain structure was a significant predictor of EF in females, but not males, when accounting for brain function and CRF.

The Impact of CRF on EF

As a sole predictor, CRF predicted twice as much variance in EF scores in females than in males. This is in accordance with the general consensus that aerobic exercise may be particularly advantageous for women (Colcombe & Kramer, 2003a; Erickson et al., 2007) and supports our fourth hypothesis. Particularly striking is that the nature of the relationship between CRF and EF in males versus females was reversed. That is, greater CRF was associated with lower EF in males and greater EF in females. This was unexpected. While we did expect the effect to be stronger in females, we hypothesized that greater CRF would be positively associated with EF in both (hypothesis 1).

Females. The relationship between CRF and EF remained steady when brain structure and function were added to the model suggesting that the influence of CRF was not moderated by these factors in females. Considering the widely accepted finding that fitness interventions can yield brain changes (Voss et al., 2010b; Voss et al., 2012; Voss et al., 2015), this finding begs the question of how meaningful such gains are in terms of cognition and, subsequently, whether they should be used as metrics of treatment outcome.

One reason why CRF may be particularly influential in women can be attributed to the presence of estrogens. Specific estrogens, such as estradiol, are neuroprotective and buffer against age-related pathology (Wise et al., 2001; Norbury et al., 2003). Further,

they are cardioprotective (Vitale, Mendelsohn & Rosano, 2009), buttressing the body's response to exercise. Pertinent to this study, estrogens are suggested to enhance the benefits of aerobic activity - acting in a synergistic fashion to promote greater neuroprotection (Berchtold, Kessler, Pike, Adlard & Cotman, 2002; Garcia-Segura, Cardona-Gomez, Chowen & Azcoita, 2000).

In general, older women appear to be more sensitive to the impact of fitness and exercise than men. Physical inactivity is more detrimental to health for women than men (Dunstan et al., 2007; Healy et al., 2008; Blair et al., 1996). The female body also shows an exaggerated response to exercise with age, an effect not seen as prominently in men (Ogawa et al., 1992; Parker et al., 2010). Working from a position of deficiency, then, requires greater exercise-induced adaptations for women to meet the same intervention goals. Indeed, older women show an advantage in exercise-induced gains such as lowered blood pressure (Collier et al., 2008) and mitigating arterial stiffness (Tanaka et al., 2000) in interventions, perhaps for this very reason. This suggests that maintaining comparable levels of CRF for women may be indicative of greater exercise engagement in order to bridge this AR gap. For these reasons, CRF may have a closer relationship with overall brain health in women than men.

Males. Considering the degree to which CRF is being touted as a reliable metric of brain change and neuroprotective potential, its lack of association at the first level of the model in males is striking. While this relationship trended toward significance for females, it was highly insignificant in males. We can suggest several reasons for this sex difference. Higher levels of CRF at baseline may be responsible in part because comparable exercise-induced effects are seen when men start interventions with lower

CRF levels (Wray et al., 2006). Indeed, in our study we saw higher CRF in males. This is in accordance with previous research showing that males have inherently superior cardiac (and cerebrovascular) capacity, which is less effected by age than in women (Matteis, Troisi, Monaldo, Caltagirone & Silverstrini, 1998; Ogawa et al., 1992).

Sex differences in the influence of CRF may also be attributable to innate differences in response to exercise between the sexes (Shephard, 2000). Women have smaller individual muscle fibres resulting in a reduced anaerobic capacity and power compared to men (Miller, Macdougall, Tranopolsky & Sale, 1993; Shephard, 2000). These differences in muscle mass make the female body more suitable for endurance activity, such as running, and the male body to more intensive activity, such as resistance training (Miller et al., 1993; Shephard, 2000). Therefore, men and women may be predisposed to different classes of physical activity and may be primed to receive optimised benefits from those respective activity types.

For this reason, it would be interesting to investigate whether metrics of anaerobic capacity were associated with EF in males. To date, there has been a paucity of research examining the impact of anaerobic activity on neurocognitive aging. Twice weekly resistance training yielded functional changes which were thought to underlie improvements in inhibition responses (Liu-Ambrose, Nagamatsu, Voss, Khan & Handy, 2012) and enhanced EF (Liu-Ambrose et al., 2010). These studies were conducted in samples of women only, however, which impacts their generalizability and our ability to extend these findings to the current study.

Sex has also been found to be a moderator of what aspects of physical activity predict cognitive performance. For example, in one study, walking was predictive of EF

in women, whereas balance and walking were predictive in men (Blankevoort et al., 2013). That CRF may not be an appropriate marker of physical health for males is supported by one study finding that physical activity enhanced metabolic fitness independently of CRF in a sample of predominantly male (80%) runners (Laye et al., 2015).

Network Efficiency and EF

Network efficiency is a global metric of a network's functional integrity (Achard & Bullmore, 2007). Given that network efficiency has been associated with cognitive performance (Wen et al., 2011) and is susceptible to AR alterations (Achard & Bullmore, 2007; Ajilore et al., 2014; Fischer et al., 2014; Wen et al., 2011), we aimed to be the first to examine how such metrics predicted EF in older adults. We hypothesized that global efficiency of both the DN and FPCN would be positively associated with EF in males and females. While network efficiency was found to be predictive of EF, this was in the opposite direction than expected (with greater global efficiency predicting poorer EF performance) in direct contrast to hypothesis 3. Further, unlike we hypothesized, this was only the case for the males and was only in the DN. We will interpret these findings by discussing network differences, sex differences, and the relationship between network efficiency and CRF in turn.

Default network efficiency is negatively associated with EF in males. Network metrics were not significantly associated with EF in females. In males, however, indexes of network function significantly improved predictability, independently accounting for nearly half of EF scores. This effect was driven by GE of the DN, as GE in the FPCN was not significantly predictive on its own. This suggests that the DN may be the most

appropriate network to study when examining network correlates sensitive to neurocognitive aging. The nature of the relationship between DN GE and EF was negative, indicating that greater global efficiency predicted poorer cognitive performance.

That our network findings were in the opposite direction than anticipated (where GE was associated with lower EF) may be attributable to several things. Reducing complex networks to mean network metrics is arguably non-specific (Bassett et al., 2008; Rubinov et al., 2009; Stam et al., 2007; Zhu et al., 2003) and thus may be insensitive (Burdette et al., 2010). As a relatively new metric, the impact of aging on GE is not yet clear. While some studies find reductions in GE within the DN (Achard & Bullmore, 2007; Ajilore, Lamar & Kumar, 2014; Wen et al., 2011), others failed to find an effect (Gong et al., 2009; Song et al., 2014).

Research investigating the relationship between GE and cognition is in its infancy, with only a handful of studies that we are aware of. Wen and colleagues (2011) found that GE was associated with performance in tasks of processing speed and EF, after controlling for age, sex, and education. Of note, that study examined structural, not functional, efficiency. Higher GE has also been found to be associated with higher IQ in young adults (van den Heuvel, Stam, Kahn & Hulshoff Pol, 2009). This association did not carry into a population of older adults in which no significant correlation was found between structural GE and IQ (Fischer et al., 2014).

To understand why decreasing GE might be desirable, a deeper exploration of network metrics is warranted. We intend to examine network modularity in a future study, which may yield insight into why GE is negatively associated with behavioral

outcome. Network modularity is the extent to which a larger network can be decomposed into sub-networks. While high global efficiency reflects strong interactions among remote brain regions, local efficiency is more modularized (Gong et al., 2009). A small-world network is conceptualized as a network with tight, efficient intra-network communication, as well as efficient integration via connector nodes with other distributed networks (Bassett & Bullmore, 2006). Given the modularization of small world networks, these networks are a more cost-effective processing system (Bassett & Bullmore, 2006). Greater modularity is typically seen in healthy young adults (Ferrarini et al., 2009; Meunier et al., 2009), but is subject to age-related changes (Gong et al., 2009).

Modular organization reflects functional specialization within the brain (Chan, Park, Savalia, Petersen & Wig, 2014). Conversely, decreases in modularity are associated with age-related dedifferentiation and reflect less specialized, less efficient networks (Meunier et al., 2009). Geerligs et al. (2015) recently investigated AR network reorganisation in the resting networks of older adults and found reduced inter-network connections between functional networks subserving higher-level cognitive processes (like EF). As modularity declined, the FPCN and the DN lost their distinctiveness (Geerligs, Renkin, Saliassi, Maurits & Lorist, 2015). This research supports a growing neurocognitive perspective suggesting that the inability of distinct neural networks to flexibly decouple may contribute to cognitive deficits seen in aging (Spreng & Schachter, 2012; Turner & Spreng, 2015)

Modularity describes a network's functional architecture by incorporating information of global and local efficiency. That is, how efficient a network is at communicating within versus between. By looking at GE, in our study we examined the

first piece - the ‘between’ portion of this equation. It may have been that the negative associations we found between GE and behaviour were not due to maintenance of GE, but were reflecting changes in modularity. That is, if local efficiency was declining but GE was being maintained, this would result in reduced modularity. Indeed, such declines in local efficiency, and modularity, result in a greater processing cost for the brain (Geerligs et al., 2015). Such a shift has been noted where decreased connectivity within a network triggered increased connectivity throughout a larger system (Grady et al., 1999). Chan et al. (2014) interpreted this as a ‘blurring’ of once distinctive systems, yielding impaired cognitive function (and see Spreng, Stevens, Viviano & Schacter, 2016).

GE has only been associated with better cognition in younger (van den Heuvel et al., 2009) not older (Fischer et al., 2014) adults. Together with our findings that GE was associated with poorer EF in males, it is possible that lower GE could be a marker of neurocognitive health. That the nature of the relationship between efficiency and cognition could change directions with age could reflect reorganization in functional networks. Though it hasn’t been examined with respect to GE, AR changes in other metrics of brain function have been associated with positive cognitive performance (Meunier, Achard, Morcom, & Bullmore, 2009; Park & Reuter-Lorenz, 2009), suggesting that functional reorganization may be adaptive.

A study by Heisz and colleagues (2015) demonstrates the value of network reorganization in aging. The authors found that older adults with better cognition showed greater local processing. Of particular note is that this was a distinct neural signature from their younger counterparts. Better cognitive performance was associated with more distributed processing in young adults and more localized processing in older adults

(Heisz et al., 2015). That is, the maintenance of younger connectivity patterns was insufficient to sustain cognitive performance with age (Heisz et al., 2015). This suggests that healthy brain aging may rely more on reorganization than preservation.

Finally, the shift from global to local processing could be adaptive because of structural AR changes. Given that WM declines with age (Madden, Bennett & Song; Salat, 2011; Peters & Rosene, 2003), networks with tight-knit, short distance connections would be more effective in information transfer and be more resilient in the face of anticipated AR WM declines.

Sex differences in the relationship between network efficiency and EF. We observed that GE predicted nearly half of the variance in EF scores for males while accounting for only 2% in females. Considering that GE was not significantly different between males and females in our study, and that females have been found to have greater local efficiency in aging (Gong et al., 2009; Tomasi & Volkow, 2012; Yan et al., 2011), it may be that the ratio of global to local efficiency underlies the sex differences found in network topology. That is, if higher GE occurs in the face of marked reductions in local efficiency, modularity or small-worldness would be decreased.

Previous research has also found sex by hemisphere interactions of network connectivity (Gong et al., 2009; Hamilton, 2008; Tian et al., 2011). Considering that females tend to show the greatest degree of local efficiency with age (Gong et al., 2009; Yan et al., 2011), examining the networks bilaterally may have reduced our ability to detect lateralized specializations between the sexes, possibly accounting for our null-results in females.

Association between CRF and network metrics in males. While CRF and EF were reliably associated in females, the relationship appears to be less direct in males. As a sole predictor, CRF was not associated with cognition. Yet when network metrics were added to the model, CRF became a significant predictor of EF.

The direction of the relationship between CRF and GE is particularly striking. In our sample, higher CRF was negatively correlated with GE in the DN, though this failed to reach significance. Lower GE was significantly associated with vigorous physical activity, however, which was in turn associated with CRF. Given that the relationship between GE and CRF hasn't been examined previously, we can only speculate as to why this negative association might be the case. We can assert that CRF is associated with improved brain health (Colcombe & Kramer, 2003a; Cotman & Berchtold, 2002; Voss et al., 2012). This begs the question, then, whether higher DN GE with aging is also a marker of brain health or if it indicates the opposite. That CRF is only significantly predictive when DN GE is accounted for suggests that greater GE might impede the benefits of CRF to the extent of attenuating the relationship.

These functional network findings are notable for several reasons. Identifying that network efficiency has an impact on the relationship between CRF and EF introduces a new functional metric for consideration in the exercise literature. Moreover, the identification that this relationship may be sex-dependent may account for some of the inconsistencies seen previously in fitness studies (Blumenthal et al., 1989; Etnier, Nowell, Landers & Sibley, 2006). That is, if brain metrics have such an influence on detecting the impact of CRF, and in a sex-dependent manner, it is reasonable to assume

that findings could fluctuate greatly between studies depending on the composition of the research sample (i.e. the proportion of males: females).

Brain Structure is Predictive of EF in Females, but not Males

As expected, PFC volumes were found to be associated with EF in females (hypothesis 2). Contrary to our expectations, this association was not found for both sexes (hypothesis 4). While the association between PFC volume and EF is supported by previous findings (Gunning-Dixon & Raz, 2003; Weinstein et al., 2012), sex differences in this association have not previously been identified. In our sample, there was a significant difference between GM PFC proportion between males and females. Though we didn't look at WM volumes, previous findings suggest that females have a greater proportion of GM to WM (Allen et al., 2003; Goldstein et al., 2001) which may be attributable to sex hormones (Witte et al., 2010). This effect is the opposite in males, who demonstrate a greater WM to GM ratio (Allen et al., 2003; Goldstein et al., 2001). One study examining the relationship between WM lesions and CRF only found a significant association in older men (Sen et al., 2012). Thus, it may be that WM is a more reliable proxy of brain health in males and, subsequently, a more sensitive metric to age-related brain changes.

For women, prefrontal volume was a significant predictor of EF. The association between prefrontal volume and EF is established (Alvarez & Emory, 2006; Fjell & Walhovd, 2010; Gunning-Dixon & Raz, 2003). While greater PFC volumes have been attributed to greater CRF capacity (Gordon et al., 2008; Erickson et al., 2010; Rovio et al., 2010; Bugg & Head, 2011; Voss et al., 2010b), our finding is novel considering that PFC volume was predictive of EF when accounting for CRF. That is, structure was found

to be a predictor of neurocognition independent of fitness level. Further, we did not see a relationship between CRF and PFC volume in females, suggesting that in our sample brain structure was not influenced by CRF. Together, our findings suggest that, in women, prefrontal volume can be used as a marker in neurocognitive aging and it has its influence on neurocognitive health independent of CRF.

Sex Differences in the Determinants of EF - Recommendations

Our secondary research aim was to identify a ‘best fit’ model depicting which factors, together, predicted the greatest amount of variance in EF. We found that the factor composition for these models was different between the sexes, as anticipated. For females, a model containing solely CRF served as the best predictor of executive functioning. This contrasted with our prediction that CRF, PFC volume, and network efficiency would all be incorporated in this model (hypothesis 5). Such a finding is promising, because it suggests that a modifiable factor carries the greatest degree of weight in predicting neurocognitive outcomes for older women. For males, we hypothesized that metrics of brain health would be most associated with EF (hypothesis 6), given that CRF appeared to have its greatest effects in women. In contrast, a model containing CRF and network efficiency was found to be the most parsimonious for males. Based on these findings, we would recommend that future interventions examining EF select their metrics of interest accordingly - electing for network metrics in males, structural metrics in females, and examining CRF for both (paying heed that the nature of the association between CRF and EF is opposite between the sexes).

Future Directions

In this study we examined how metrics of brain structure, function, and CRF predicted EF in older adults. Given our implementation of regression, our analysis was directional. An avenue of future exploration may be to examine the relationship in the opposite direction. That is, to examine the extent to which EF might predict CRF, network connectivity, and brain structure. Theories such as the Temporal Self-Regulation Theory, for example, suggest that EF may predict higher adherence to health behaviours (Hall & Fong, 2007). While health behaviours might be associated with substantial costs in the short term, they have extensive benefits in the long term. The Temporal Self-Regulation theory posits that individuals with greater EF capacity are able to regulate their behaviour to a greater degree, enduring the short-term costs of health-promoting behaviours in order to reap the long-term benefits (Hall & Fong, 2007). Indeed, EF has been found to predict exercise adherence in older adults (McAuley et al., 2011). In another study, EF was found to be more predictive of physical activity than physical activity of EF (Daly, McMin & Allan, 2015).

Another avenue of exploration is to examine metrics of modularity (such as small-worldness) in our sample. Though the association between GE and cognitive performance in older adults is far from clear, our finding that GE is negatively associated with EF is novel and warrants further investigation. We posit that this association is due to reductions in small-worldness, which is known to be a more efficient network topology enhancing cognition (Achard & Bullmoore, 2007). Examining modularity would not only yield further data in which to contextualize our results, but may also serve to enhance our understanding of why we found such stark sex differences in our study. That is, if males

prove to have significant declines in modularity whereas females do not, this may account for why there was such a strong negative effect in the males in our sample.

Limitations

This study is part of an ongoing, long-term data collection project. Once our sample is of sufficient size, we will implement structural equation modeling. Doing so will enable the examination of directionality, covariance, and moderation between our factors of interest. Further, our sample was recruited from the community via a volunteer basis and presents a well-educated, high-performing subset of the larger population. Generalizations should be made accordingly.

We conceptualized EF, brain structure, and brain function using either one or two metrics. While each metric was considered to be representative and supported by the research literature, details were naturally lost when distilling these complex concepts to testable metrics. Fluid IQ is considered to be representative of EF, but given the intricate nature of EF, it is not a perfect characterization (Friedman et al., 2006). We elected to examine the PFC for our structural metric because of its association with CRF and neurocognitive aging. We recognize, however, that our metric of structure constitutes but one region in the face of brain-wide alterations. Further research should profile whole brain metrics of structure in relation to these predictors.

Similarly, reducing brain connectivity to two metrics was a necessary, but simplifying, step. The election of the DN and FPCN as our networks of interest was warranted, given their established declines in aging (Andrews-Hanna et al., 2007; Chen et al., 2011; Madden et al., 2010; Song et al., 2014; Zhang et al., 2014). However, graph theory research has consistently demonstrated a great deal of variability dependent upon a

host of factors such as: whole brain or regional analysis; the number of nodes implemented; whether analyses are conducted across hemispheres or independently in each hemisphere, etc. Future studies should pay heed to these major distinctions in methodology when comparing results.

Several measures used within this study were self-report and thus subjective. We asked participants to self-report their height, weight, and physical activity levels. The IPAQ is also self-report. Though this measure is validated and reliable (Alexander, Bergman, Hagströmer, & Sjöström, 2006; Craig et al., 2003), such avenues of data collection are dependent upon accurate recall, judgment, and are naturally susceptible to biases.

Finally, due to constraints in sample size, it was necessary to scale back the number of predictors included within our model. We elected to use CRF as our ‘modifiable’ lifestyle metric because it is the most common metric of fitness found in the research literature. It should be noted, however, that while changes can be achieved in this measure it may be less conducive to behavioral interventions than other metrics of lifestyle such as physical activity. In fact, CRF is largely predicated by genetic determinants, which account for up to 50% of CRF scores (Bouchard et al., 2011; Pérusse et al., 2001). Targeting changes in physical activity may be more intuitive, and thus tangible, for behavioral interventions. Once our sample is larger, we aim to include IPAQ data in the model to investigate its role as a predictor and potential intervention target.

Conclusion

In our study we examined the relative weights of factors predicting preserved EF in older adults. We found that sex differences were not only present, but played an unequivocal role in determining which factors are most associated with cognition. CRF and PFC volumes were stronger predictors of EF in women than men. In contrast, GE of the DN was a significant determinant of EF performance in men but not women. We found a trend between CRF and EF in women in our study; an association that has been reliably found in previous research. We posit that hormonal interactions may underlie the advantageous benefits of exercise in women, rendering greater health by means of growth factor interactions. We surmise that differences in brain matter composition, particularly pertaining to grey and white matter ratios, may account for sex differences in the influence of brain structure. In our study this was seen in that women had a significantly greater PFC GM proportion than males. Finally, we suggest that the negative association between GE of the DN and EF in males is reflective of a greater alteration at the level of the brain - a reduction in modularity. Our research underscores the importance of considering sex differences in future research examining exercise and neurocognitive aging. Further, in elucidating differential predictive weights of CRF and brain health on cognition, we recommend that neurocognitive interventions tailor their targets accordingly to ensure that intervention gains manifest in meaningful cognitive outcomes. In other words, given that we have shown that brain structure, brain function, and CRF are independently predictive of EF in a sex-dependent manner, we suggest that interventions select their target metric in a similar sex-dependent fashion.

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Tables

Table 1. Participant Characteristics

	<i>N</i>	Range	Min	Max	<i>M</i>	SD
Males						
<u>Age</u>	21	23	60	83	67.24	6.46
<u>GDS</u>	21	15	0	15	2.81	3.61
<u>Education</u>	21	11.5	13	24.50	17.76	3.30
<u>BMI</u>	21	17.44	20.65	38.09	27.01	4.85
<u>Physical Activity</u>						
Vigorous MET-minutes	21	5040	0	5040	1211.43	1473.07
Moderate MET-minutes	21	3360	0	3360	1224.76	1166.86
Walking MET-minutes	21	3960	198	4158	1419.79	1037.00
<u>Smoking</u>						
Never	13					
Former	7					
Current	1					
Females						
<u>Age</u>	30	21	60	81	66.07	4.83
<u>GDS</u>	30	20	0	20	4	4.09
<u>Education</u>	30	10	10	22	15.98	2.44
<u>BMI</u>	30	20.88	19.11	39.99	26.61	5.32
<u>Physical Activity</u>						
Vigorous MET-minutes	30	6720	0	6730	977.33	1853.33
Moderate MET-minutes	30	4200	0	4200	815.33	1139.43
Walking MET-minutes	30	8910	0	8910	1861.20	1770.61
<u>Smoking</u>						
Never	21					
Former	8					
Current	1					

Table 4. Multiple Hierarchical Regression Coefficients

Variable	<i>B</i>	<i>SE(B)</i>	<i>p</i>	95% CI
<u>Males</u>				
<u>Model 1</u>				
CRF	-4.12	3.67	.276	(-11.80, 3.56)
<u>Model 2</u>				
CRF	-8.43	2.89	.010	(-14.53, -2.34)
FPC_GE	-161.54	108.12	.153	(-389.66, 66.58)
DN_GE	-517.39	125.47	.001	(-782.10, -252.68)
<u>Model 3</u>				
CRF	-8.78	2.99	.010	(-15.11, -2.45)
DN_GE	-513.89	127.73	.001	(-784.67, -243.11)
FPC_GE	-146.81	112.25	.209	(-384.76, 91.14)
ProplatPFC	6.34	9.65	.521	(-14.13, 26.80)
<u>Females</u>				
<u>Model 1</u>				
CRF	5.76	2.88	.055	(-.14, 11.66)
<u>Model 2</u>				
CRF	4.91	3.15	.131	(-1.56, 11.38)
FPC_GE	-59.77	91.52	.519	(-247.90, 128.35)
DN_GE	-59.64	97.87	.548	(-260.81, 141.53)
<u>Model 3</u>				
CRF	4.88	3.21	.141	(-1.73, 11.48)
DN_GE	-63.25	100.39	.534	(-270.02, 143.51)
FPC_GE	-69.48	98.88	.489	(-273.13, 134.17)
ProplatPFC	24.98	10.47	.030	(2.79, 47.17)

Note.

Males. R^2 for Model 1 = .06, $F(1,19) = 1.26$, $p = .276$, R^2 for Model 2 = .55, ΔR^2 for Model 2 = .48, $F(2, 17) = 9.01$, $p = .002$, R^2 for Model 3 = .56, ΔR^2 for Model 3 = .012, $F(1, 16) = .43$, $p = .521$

Females. R^2 for Model 1 = .13, $F(1,28) = 4.00$, $p = .055$, R^2 for Model 2 = .15, ΔR^2 for Model 2 = .02, $F(2, 26) = 0.31$, $p = .737$, R^2 for Model 3 = .15, ΔR^2 for Model 3 = .003, $F(1,25) = .09$, $p = .772$

Figures

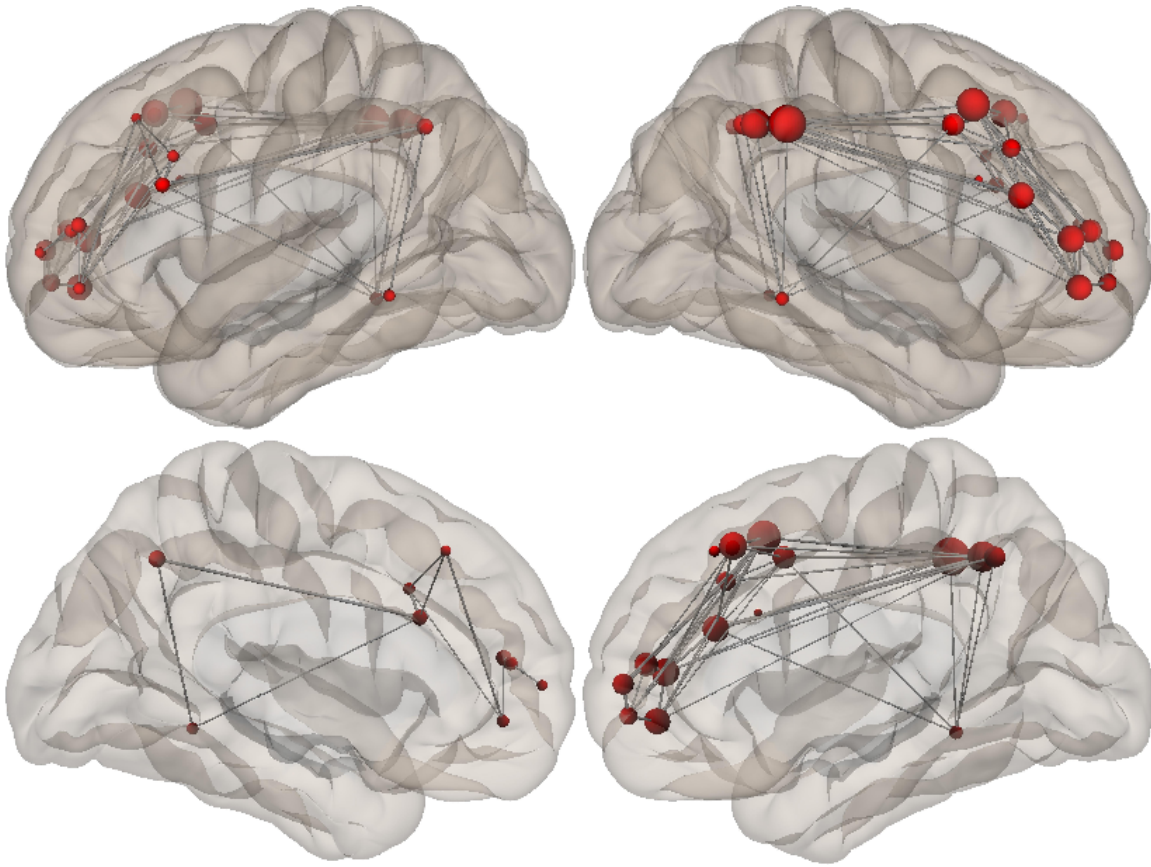


Figure 1. Connectivity profile of the Frontoparietal Control Network derived using the Brain Connectivity Toolbox (Rubinov & Sporns, 2010; Rubinov & Sporns, 2011)

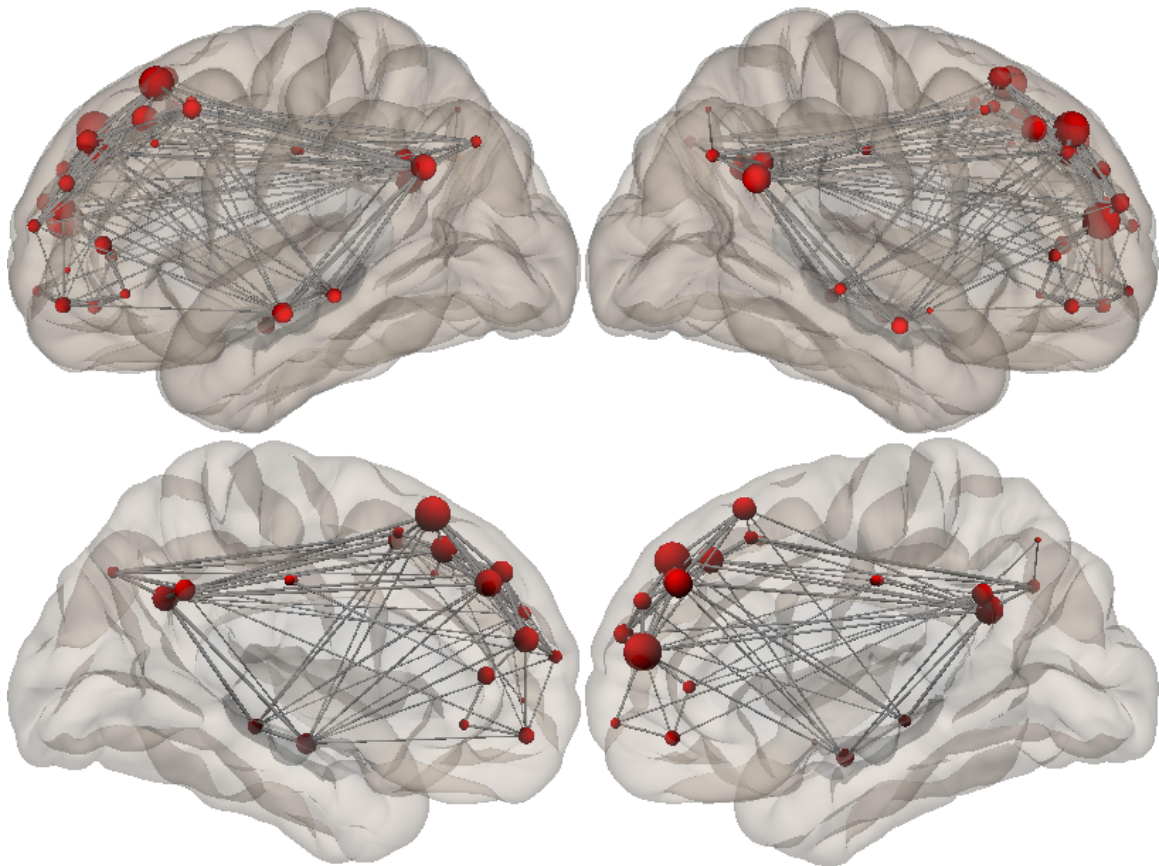


Figure 2. Connectivity profile of the Default Network derived using the Brain Connectivity Toolbox.

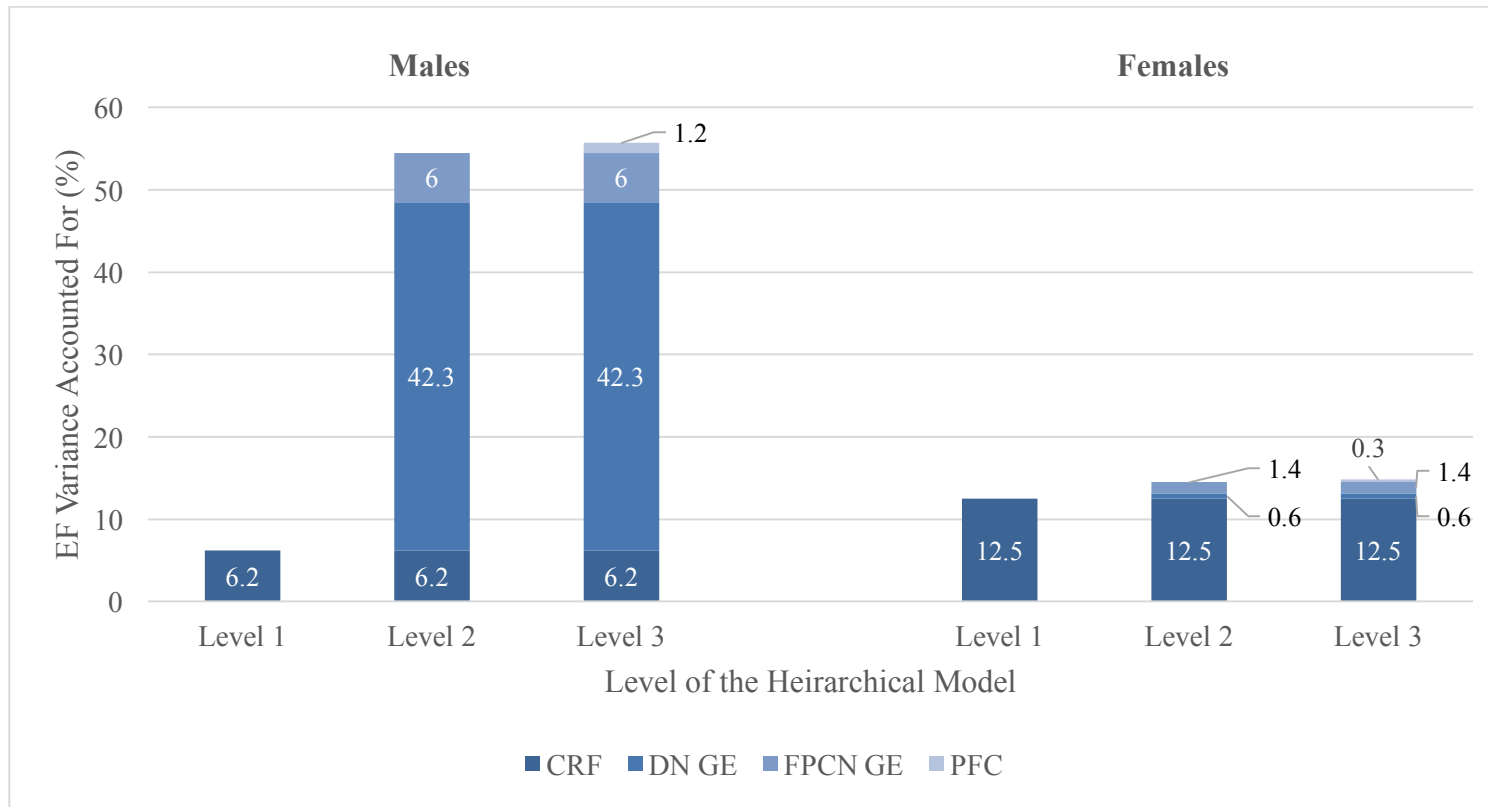


Figure 3. Percentage of EF variance accounted for as a function of model level and sex. For males, a model containing network metrics and CRF (level 2) accounts for the most variance in EF ($R^2_{\text{adjusted}} = .46$). For females, the first level containing only CRF as a predictor is the best model of EF ($R^2_{\text{adjusted}} = .09$).

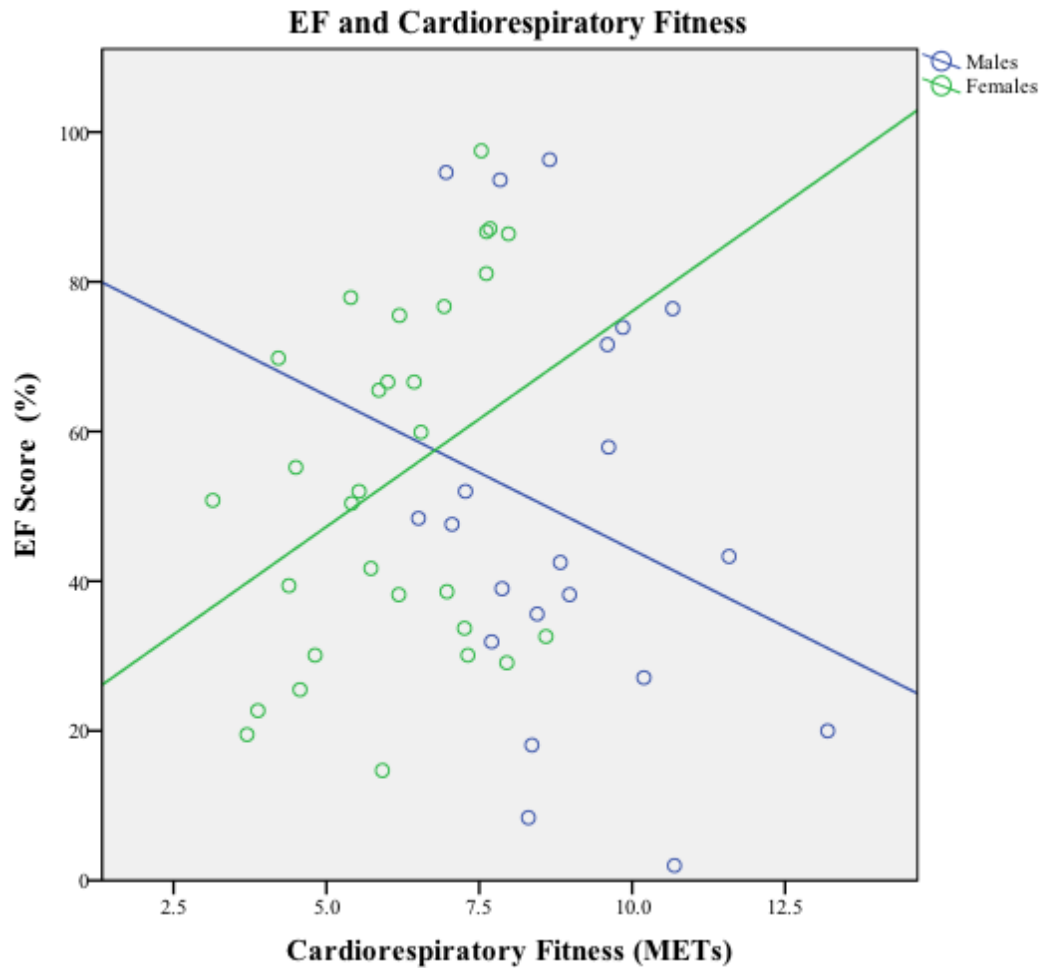


Figure 4. The relationship between EF and CRF in older adults. Males show a negative relationship ($B = -4.12$) where lower EF is associated with higher CRF. In contrast, females demonstrate a positive relationship ($B = 5.76$) where greater CRF is associated with greater EF.

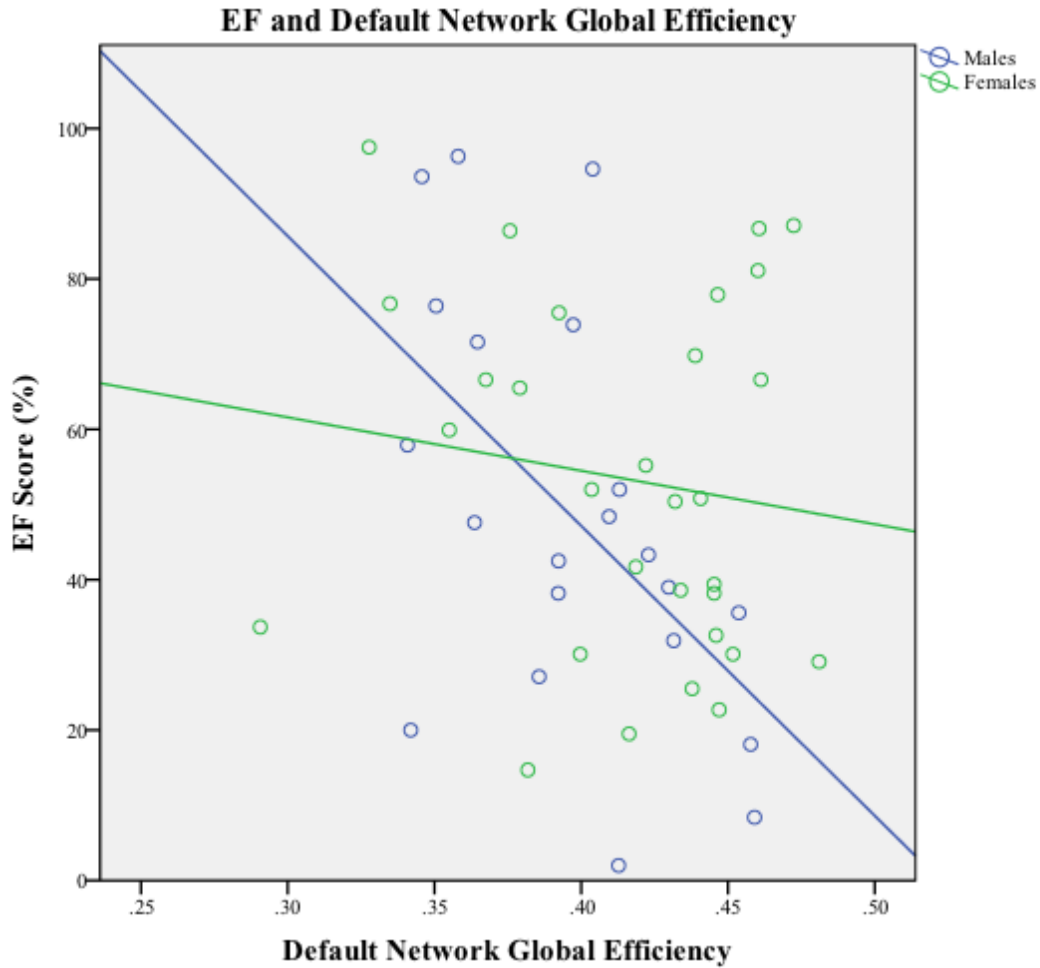


Figure 5. Simple regression illustrating the relationship between DN GE and EF. In our model, after accounting for CRF, males demonstrate a strong, negative relationship ($B = -517.39$) while females demonstrate a tempered, negative relationship ($B = -59.64$).

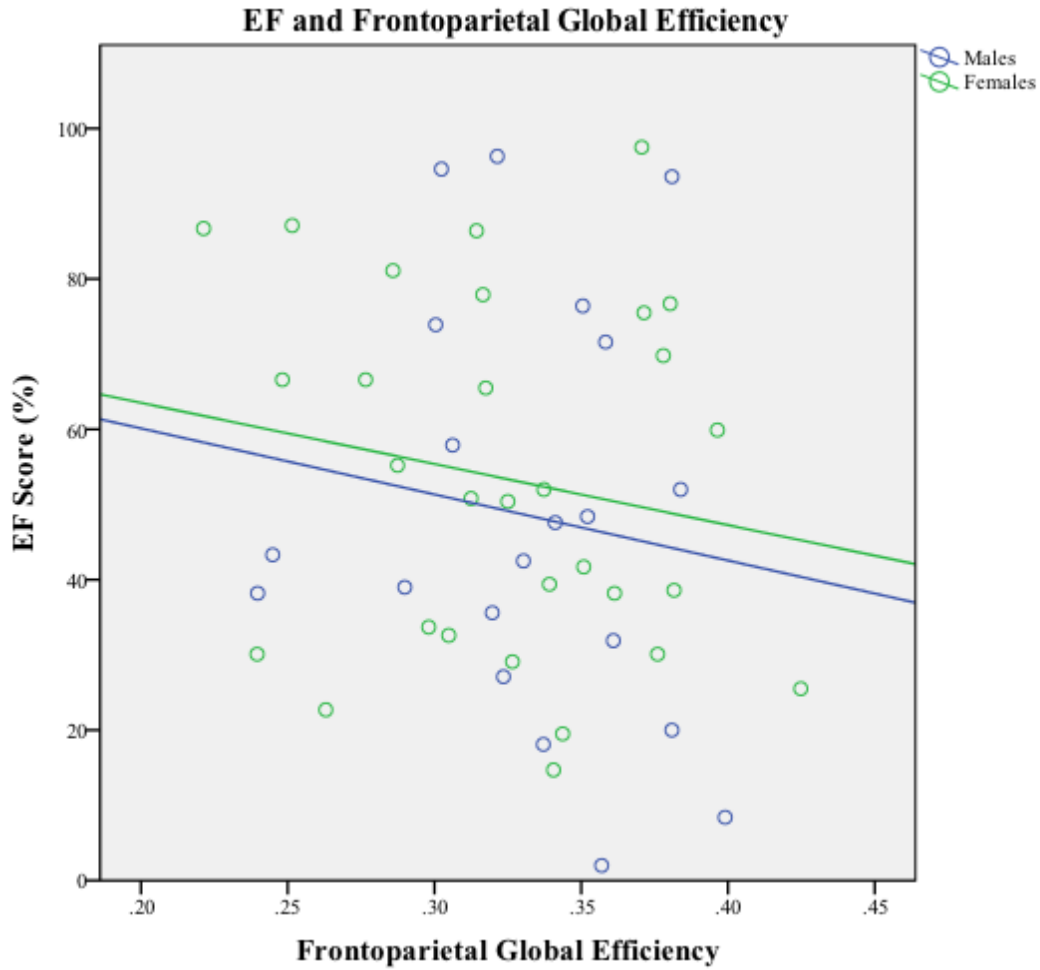


Figure 6. Simple regression demonstrating the relationship between EF and FPCN GE in older adults. In our model, after accounting for CRF, FPCN GE is negatively associated with EF in males ($B = -161.54$) as well as in females ($B = -59.77$)

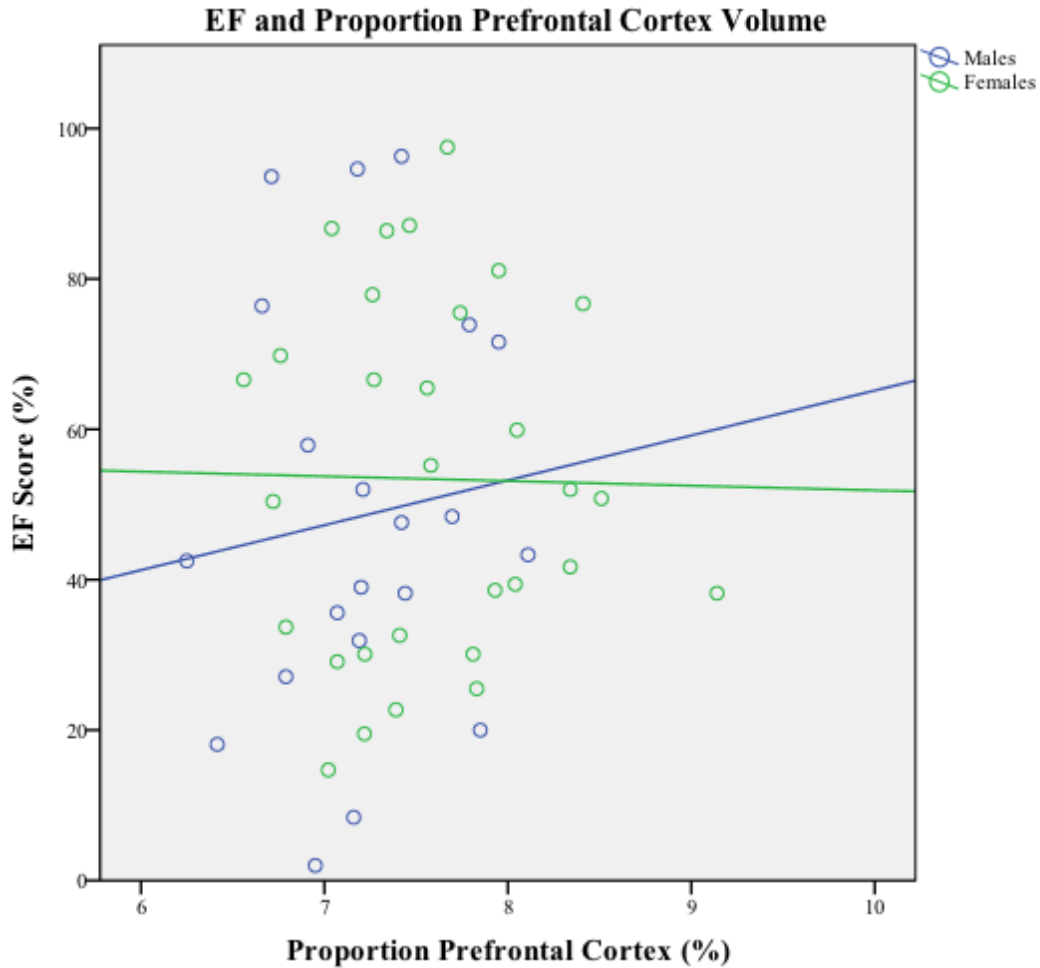


Figure 7. Simple regression illustrating the relationship between PFC proportion and EF score. Importantly, in our hierarchical model females show a much stronger relationship ($B = 24.98$) than males ($B = 6.34$) suggesting that PFC proportion is a stronger predictor of EF, in females, when accounting for network metrics and CRF.

Appendix A

Acronyms

AR	Age-related
BOLD	Blood Oxygen Level Dependent
CRF	Cardiorespiratory Fitness
DN	Default Network
EF	Executive Functions
EPI	Echo Planar Imaging
rsFC	Resting State Functional Connectivity
FPCN	Fronto-parietal Control Network
GDS	Geriatric Depression Score
GE	Global Efficiency
GM	Grey Matter
ICA	Independent Components Analysis
IPAQ	International Physical Activity Questionnaire
MP-RAGE	Magnetization-prepared Rapid Gradient-echo
MRI	Magnetic Resonance Imaging
NIHTB-CB	NIH Toolbox Cognition Battery
PFC	Prefrontal Cortex
TE	Echo Time
TR	Relaxation Time
WM	White Matter

Appendix B

DN and FPCN regions of interest based on parcellation by Gordon et al. (2016)

Network	Region of interest (ROI)	MNI coordinates		
		X	Y	Z
DN	L Precuneus	-11.2	-52.4	36.5
DN	L Superior Frontal Gyrus	-11.7	26.7	57
DN	L Angular Gyrus	-47.2	-58	30.8
DN	L Medial Frontal	-5.6	42.2	35.1
DN	L Posterior Cingulate	-1.7	-17.7	39.1
DN	L Dorsal Prefrontal	-19.5	30.1	45.5
DN	L Posterior Superior Parietal	-39.3	-73.9	38.3
DN	L Frontal Pole	-27.5	53.6	0
DN	L Medial Frontal Gyrus	-5.9	54.8	-11.3
DN	L Anterior Cingulate	-6.8	38.2	-9.4
DN	L Middle Temporal Gyrus	-63.2	-28.7	-7.2
DN	L Inferior Temporal Gyrus	-53.1	-11.4	-16
DN	L Medial Prefrontal	-15.9	48.6	37.2
DN	L Superior Frontal Gyrus	-19.5	56.3	27.5
DN	L Rostral Medial Frontal Gyrus	-6.5	54.7	18.1
DN	L Superior Frontal Gyrus	-15.7	64.7	13.7
DN	L Caudate	-6	22.9	6.3
DN	L Middle Frontal Gyrus	-26.2	26.6	38.8
DN	L Middle Frontal Gyrus	-29.3	16.8	50.7
DN	L Middle Frontal Gyrus	-41.7	16.1	47.5
DN	R Precuneus	12.3	-51.6	34.5
DN	R Superior Frontal Gyrus	11.9	21.9	59.9
DN	R Anterior Cingulate	7.7	44.1	5.5
DN	R Posterior Cingulate	3	-19.6	37.9
DN	R Superior Frontal	21.9	21	46.2
DN	R Inferior Parietal	48.9	-53	28.6
DN	R Superior Temporal Gyrus	62.5	-25.6	-5.5
DN	R Precuneus	7.4	-69.3	49.9
DN	R Inferior Parietal Sulcus	46.5	-67.3	36.2
DN	R Medial Prefrontal	4.8	65.1	-7.1
DN	R Ventromedial Prefrontal	7.2	48.4	-10.1
DN	R Middle Temporal Gyrus	57.5	-7.4	-16.4
DN	R Middle Frontal Gyrus	21	32.8	42.1
DN	R Superior Frontal Gyrus	21.4	42.8	35.1
DN	R Frontal Pole	16	61	19.8
DN	R Dorsomedial Prefrontal	8.2	53.8	14
DN	R Superior Medial Frontal	5.9	54.9	29.4
DN	R Dorsolateral Prefrontal	13.8	46.7	42.1
DN	R Medial Frontal Gyrus	6.8	44.5	34.8
DN	R Middle Frontal Gyrus	30.6	18.9	48.7

DN	R Superior Temporal Gyrus	54.4	1.1	-12.9
FPCN	L Dorsolateral Prefrontal	-38.1	48.8	10.5
FPCN	L Fusiform Gyrus	-55.9	-47.7	-9.3
FPCN	L Superior Frontal Gyrus	-5.5	29.3	44
FPCN	L Lateral Orbitofrontal	-40.3	50.4	-4.8
FPCN	L Superior Parietal	-34.1	-61	42.4
FPCN	L Dorsolateral Prefrontal	-43	19.4	33.5
FPCN	L Inferior Frontal	-40.2	23.6	23.3
FPCN	L Frontal Pole	-21.3	63.1	1.9
FPCN	L Ventrolateral Prefrontal	-28.6	50.9	10.1
FPCN	R Inferior Parietal	47.9	-42.5	41.5
FPCN	R Anterior Prefrontal	38.1	45.9	7.7
FPCN	R Inferior Temporal	59.7	-41	-10.9
FPCN	R Medial Superior Frontal	7	25.7	47.3
FPCN	R Middle Frontal Gyrus	42.8	48.3	-5.1
FPCN	R Inferior Parietal	41.5	-53.5	44
FPCN	R Intraparietal Sulcus	35.7	-56.7	45.2
FPCN	R Dorsolateral Prefrontal	37.8	28.7	35.6
FPCN	R Middle Frontal Gyrus	41.8	29.1	21.6
FPCN	R Lateral Prefrontal	38.6	18.8	25.5
FPCN	R Superior Frontal Gyrus	28.4	57	-5.1
FPCN	R Frontal Pole	23.5	59.1	4.9
FPCN	R Anterior Prefrontal	30.9	52.2	9.9
FPCN	R Superior Frontal	42.4	19.5	48.2
FPCN	R Precentral Sulcus	38.9	9.6	42.7

Appendix C

Non-exercise Fitness Assessment as per Jurca et al. (2005)

STEP 1

Physical Activity Score: Choose one activity category that best describes your usual pattern of daily physical activities, including activities related to house and family care, transportation, occupation, exercise and wellness, and leisure or recreational purposes.

	Score
Level 1: Inactive or little activity other than usual daily activities.	0.00
Level 2: Regularly (≥ 5 d/wk) participate in physical activities requiring low levels of exertion that result in slight increases in breathing and heart rate for at least 10 minutes at a time.	0.32
Level 3: Participate in aerobic exercises such as brisk walking, jogging or running, cycling, swimming or vigorous sports at a comfortable pace or other activities requiring similar levels of exertion for 20 to 60 minutes per week.	1.06
Level 4: Participate in aerobic exercises such as brisk walking, jogging or running at a comfortable pace or other activities requiring similar levels of exertion for 1 to 3 hours per week.	1.76
Level 5: Participate in aerobic exercises such as brisk walking, jogging or running at a comfortable pace, or other activities requiring similar levels of exertion for over 3 hours per week.	3.03

STEP 2**Estimate MET level of Cardiorespiratory Fitness**

Enter 0 for women or 1 for men	_____	x 2.77	=	_____	minus
Enter age in years	_____	x 0.10	=	_____	minus
Enter body mass index	_____	x 0.17	=	_____	minus
Enter resting heart rate	_____	x 0.03	=	_____	plus
Enter physical activity score from step 1	_____	x 1.00	=	_____	plus
Constant					18.07
					=
Estimated MET value				_____	

Appendix D

International Physical Activity Questionnaire.
Short Last 7 Days Self-Administered version. Revised August 2002.

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

1. During the last **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

_____ days per week

_____ No vigorous physical activities

Skip to question 3

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

_____ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

_____ **days per week**

_____ No moderate physical activities

Skip to question 5

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**

_____ **minutes per day**

_____ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you have done solely for recreation, sport, exercise, or leisure.

5. During the last **7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

_____ No walking

Skip to question 7

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

_____ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during **the last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the last 7 days, how much time did you spend sitting on a week day?

_____ **hours per day**

_____ **minutes per day**

_____ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.

Appendix E

International Physical Activity Questionnaire Short Form Scoring Protocol

Continuous Score

Expressed as MET-min per week: MET level x minutes of activity x events per week

MET levels	<i>Sample Calculation</i> MET-min/week for 30 min episodes, 5 times/week
Walking = 3.3 METs	$3.3 \times 30 \times 5 = 495$ MET-min/week
Moderate Intensity = 4.0 METs	$4.0 \times 30 \times 5 = 600$ MET-min/week
Vigorous Intensity = 8.0 METs	$8.0 \times 30 \times 5 = 1,200$ MET-min/week

Guidelines for Data Processing and Analysis of the International Physical Activity Questionnaire (IPAQ) - Short Form, Version 2.0. April 2004. Retrieved from:
http://www.institutferran.org/documentos/scoring_short_ipaq_april04.pdf